



**Novel
neurotechnologies:**
intervening in the brain

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Novel neurotechnologies: intervening in the brain

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1. to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;
2. to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;
3. in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

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Foreword

During the last 50 years life expectancy in the UK has increased by about 10 years, so that the average age at death is now 85 for men and 89 for women. While this is good news, one result has been that the incidence of neurological disorders such as Alzheimer's disease has increased disproportionately, since this affects about one person in six over the age of 80 (as compared with only one in fourteen among those over 65). And while the increase in life expectancy is partly due to medical advances, treatments for disorders like Alzheimer's have not advanced at the same rate as those for other common diseases. Nonetheless our understanding of the brain has improved dramatically in recent years, in part because of the development of fMRI scanners which produce the familiar striking images of brain activity and provide suggestive hints concerning the basis of neurological disorders. Neuroscience has thus become a central area for biomedical research, and with it there are now new methods of treating neurological disorders and new lines of research which, it is hoped, will lead to further treatments.

In this report we focus on the new methods which involve interventions in the brain, some requiring invasive physical intrusions into the brain, others relying on methods of interacting with the brain from outside, typically by exposing the brain to electromagnetic fields. Some of these 'novel neurotechnologies', as we call them, are still at an early experimental stage (such as the introduction of human neural stem cells into the brain), while others build on existing techniques (such as deep brain stimulation) to provide treatments of further neurological and psychiatric disorders, which at present lack safe and effective treatments.

It is not the aim of this report to provide a detailed clinical assessment of the safety and efficacy of these novel technologies; instead we aim to provide a reflective assessment of the ethical and social issues that are raised by their development and use. The reason for undertaking this task is that because these technologies involve interventions in the brain, the organ which furnishes us with the capacities that underpin our existence, personal and social, interventions here are liable to affect our lives in the most intimate and fundamental ways. So while the aim of these interventions is to meet the need for neurological and psychiatric therapies, there is always the risk of damaging side-effects, as the troubled history of lobotomy indicates. And despite recent advances in neuroscience, this risk has to be taken seriously because of the limited knowledge of the ways in which these new technologies affect the brain.

Thus the situation here is one in which great needs are matched by great uncertainty, and in our report we take this situation as the starting point for our ethical assessment of these technologies. We then identify certain fundamental interests at stake here, such as safety, autonomy, trust and equity, and also discuss the complex social and economic circumstances which affect the development of these technologies, where promising research needs substantial support before devices can be brought into use in the clinic. To bring all these points together we suggest that the social and ethical issues here are best organised by identifying the key values, the 'virtues', that one would ideally like to see exemplified in the practices and institutions of those who develop, regulate and use these technologies. We suggest that these virtues are inventiveness in the research and development of technologies that meet the needs of patients; responsibility in early trials and applications of them; and humility in acknowledging the uncertainties that accompany their use, especially when dealing with patients and carers. Thus among other things we recommend that the procedure for gaining consent from patients should include an opportunity for counselling about the risks and benefits inherent in a proposed treatment; that there should be better ways of gathering systematic data from trials and experimental treatments than appears to be the case at present; and that within the present regulatory system there should be a greater effort to ensure that regulations address patients' needs by supporting innovation that provides access to safe and effective therapies.

At the end of the report we turn to two further topics, - non-therapeutic applications of these neurotechnologies for the purpose of gaming, cognitive enhancement and military uses; and the representation in the media of biomedical research, including in particular the representation of these

novel neurotechnologies. These topics raise rather different issues from those considered so far. Although the non-therapeutic uses appear exciting at first, we suggest that the truth is, so far, rather more mundane; but that this is a field which nonetheless merits continuing attention, particularly because of the lack of knowledge about the long-term effects of regular use of the relevant neural devices. When considering the role of the media we feel that we can draw on two of our fundamental values, responsibility and humility. Despite the nexus of commercial, institutional and personal interests which tempt journalists and media agencies to add a pinch of hype to their reports of these new technologies, exaggeration of their potential benefits and under-reporting of risks do not contribute to a public culture in which there can be a responsible understanding of these technologies.

It has been a challenge and a privilege to work on this report for the Nuffield Council on Bioethics. We have had the benefit of advice from those who responded to our consultation and from others who have come forward to help us; and I have learnt a great deal from my expert colleagues on the working party who have all contributed enormously to this report. I would like also to thank the Secretariat of the Nuffield Council on Bioethics, including Alena Buyx and Varsha Jagadesham, who assisted us so ably in the early stages of our work. But most of all, thanks are owed to our project leader, Emily Postan, who kept us going and provided important drafting and intellectual input, and our research officer, Rosie Beauchamp, without whom the report could never have been completed.

A handwritten signature in blue ink that reads "Thomas Baldwin". The signature is written in a cursive, slightly slanted style.

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Terms of reference

1. To identify and consider the ethical, legal and social issues that arise from the use of novel neurotechnologies to intervene in the human brain in both clinical practice and non-medical settings.
2. To explore ethical issues from the communication and representation of neuroscientific research to intervene in the brain in the media and by researchers.
3. To draft a report and make recommendations for research, policy, governance and public engagement.

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Executive summary

1. In this report we consider the ethical, legal and social issues that arise from the use of novel neurotechnologies. We address these issues primarily in the context of the therapeutic applications of these technologies, because it is here that there is the greatest potential for social benefit and where research and practical uses are most advanced.
2. Illness or injury that results in damage to the brain and its functions can lead to serious disorders that affect memory, cognition, movement, or consciousness or cause conditions such as chronic pain. The brain has a limited capacity to repair damaged tissue, although new functional connections may be formed. The novel neurotechnologies discussed in this report all have the potential – which is in some cases yet to be fully demonstrated – to address some of the distressing and disabling effects of brain damage by intervening in the functions of the brain itself.
3. The ethical dimensions of the development and uses of these technologies, however, extend beyond the contexts of clinical research and patient care. We also consider the economic pressures and regulatory controls that shape and challenge the development pathways and commercial availability of novel neurotechnologies, and the social impacts of their representation by researchers and the non-specialist media. We also give consideration to the potential non-therapeutic applications of these technologies.

Chapter 1: Introduction

4. The neurotechnologies addressed in this report are those used in transcranial brain stimulation (TBS), deep brain stimulation (DBS), brain-computer interfaces (BCIs) and neural stem cell therapies. These are not exhaustive of every neurotechnology in use or under investigation today. We limit our discussion to those that intervene in the brain itself and that, because of their relative novelty, have not yet been subject to extensive bioethical commentary.
5. Our discussion begins by setting these ‘novel neurotechnologies’ in their historical context. Although those we discuss in this report are new, attempts to repair or alter brain function through surgery or electrical stimulation have a long, and sometimes troubled, history. During the twentieth century these methods were largely supplanted by use of pharmacological interventions. However, as these interventions have not always been as successful as had been hoped, attention is increasingly turning to new developments in neurostimulation techniques, and now also to stem cell therapies, for those conditions that remain intractable to other methods of treatment.

Chapter 2: Intervening in the brain: current understanding and practice

6. Our report focuses upon the following four categories of novel neurotechnologies. None of these technologies provides a cure for neurological or mental health disorders, but they could ameliorate symptoms, or fulfil assistive roles in ways that help improve patients’ quality of life.
 - **Transcranial brain stimulation** refers to a group of non-invasive neurotechnologies, which stimulate the brain either by inducing an electrical field using a magnetic coil placed against the head (transcranial magnetic stimulation (TMS)), or by applying weak electrical currents via electrodes on the scalp (transcranial direct current stimulation (TDCS) and transcranial alternating current stimulation (TACS)). These technologies have been used as research tools, but their therapeutic applications are increasingly being explored, the most established application is in treating drug-resistant depression. The exact mechanisms by which TBS achieves its therapeutic effects are still being researched.

- **Deep brain stimulation** also alters the functioning of brain cells and neural networks by using electrical currents, but in this case the stimulation is delivered by electrodes implanted deep in the brain. Therapeutic uses of DBS include the treatment of movement disorders, such as those associated with Parkinson's disease, and of neuropathic pain. There is also considerable research activity exploring its use to treat a wide range of psychiatric disorders. The exact mechanisms by which DBS achieves its therapeutic effects are unknown.
 - **Brain-computer interfaces (BCIs)** use electrodes (either implanted in the brain, or resting on the scalp) to record users' brain signals which are then translated into commands to operate computer-controlled devices. By actively producing brain signals, users can control these devices. BCIs could in principle assist users to communicate, control prostheses or wheelchairs, support rehabilitation, or facilitate detection of consciousness – making these technologies potentially useful to those with paralysis. Therapeutic uses of BCIs are still confined to research contexts, in which non-invasive techniques are most prevalent.
 - **Neural stem cell therapy** involves the injection of stem cells into the brain in order to repair damage caused by acute events such as stroke or neurodegenerative conditions such as Alzheimer's disease. Although this technique could have substantial therapeutic potential, neural stem cell therapies are still at an early phase of development; the first clinical trials in humans in the UK are now being undertaken. The precise ways in which stem cell grafts may assist in repairing lost brain tissue are not known, but these could include direct replacement of lost cells or stimulating repair by the brain itself.
7. In discussing the ethical and social implications of these technologies, their potential therapeutic benefits must be considered alongside any unintended harms associated with their use. Non-invasive neurotechnologies pose the fewest risks to patients. Invasive neurotechnologies requiring neurosurgery (such as DBS or neural stem cell therapies), pose greater risks, including infection and bleeding associated with surgery itself, and potential unintended physiological and functional changes in the brain resulting from the implanted electrodes or stem cells. DBS can also be associated with complex unintended effects on mood, cognition and behaviour.

Chapter 3: Economic drivers of innovation

8. There are few effective treatments for many serious neurological and mental health disorders and therefore a significant degree of unmet need. Moreover, the high global incidence of these disorders generates considerable costs to national economies, not only through direct health care costs but also in lost productivity. The novel neurotechnologies we consider in this report offer potential routes to meeting these needs, but pathways to innovative and effective treatments must negotiate ethical and economic challenges.
9. Economic factors present both opportunities and constraints that shape the innovation pathways of novel neurotechnologies. This is especially so because even where initial research is publically funded, development of research into clinical products will often depend on commercial organisations with obligations to generate profits and shareholder value. For a number of reasons, therefore, it cannot be assumed that this putative area of economic opportunity will translate directly into the provision of therapeutic products where need is most pressing.
10. Private companies and investors are likely to focus on technologies that offer the greatest potential for financial return on investment, thus favouring those that target large or valuable markets. This threatens to divert investment away from potentially less profitable 'low tech' approaches to care, or treatments to address rarer neurological conditions. It may also leave the needs of those in less affluent parts of the world ill-served. Further challenges to equitable access arise from the fact that, even if the early production costs of the neurotechnologies fall, the wider costs of specialist care associated with their use will remain high in many cases. This raises the further risk that patients might travel to access more affordable treatment in countries with potentially less well-regulated systems of protection.

11. Large pharmaceutical companies might seem to be potential sources of investment in the field of novel neurotechnologies, when the limits of public funding are reached. However, their recent withdrawal from psychopharmaceutical research suggests that they have been discouraged by the complexity and costs of developing effective neurological interventions. The long, complex and costly development and regulatory pathways (associated with innovation in stem cell based technologies in particular) can be seen as economically too risky by private investors, such as venture capitalists, who look for swift returns on their investment. The development pathways of many novel neurotechnologies are, therefore, vulnerable to the ‘valley of death’ – where (often small) businesses fail due to a lack of funding to support them through the lengthy process of translating research into commercially viable products.
12. These kinds of challenges in obtaining funding can impose particular pressures on developers to pursue practices that secure greater market share and swifter returns on investment, but (in the field of medical devices in particular) they might also shape innovation pathways and practices in ways that do not best meet patients’ needs for access to safe and effective therapies. These practices might include: exploiting regulatory routes that do not require manufacturers to conduct clinical investigations prior to placing their device on the market; developing therapeutically superfluous consumable elements of otherwise reusable devices; engaging in patent disputes to impede competitors; or offering incentives to clinicians to trial particular products, thus introducing potential conflicts of interest.
13. The economic drivers and constraints on the development of novel neurotechnologies highlight the ethical importance of proportionate regulatory oversight that encourages innovation, but which helps direct responsible research, development and investment towards the production of safe and effective products that meet genuine patient needs. However, effective regulation alone is unlikely to be sufficient to secure equitable access to affordable therapies; incentives for innovative and responsible research, and funding mechanisms to support lengthy development trajectories, will also be needed.

Chapter 4: Ethical Framework

14. The brain has a special status in human life that distinguishes it from other organs. Its healthy functioning plays a central role in the operation of our bodies, our capacities for autonomous agency, our conceptions of ourselves and our relationships with others – and thus in our abilities to lead fulfilling lives. This means that the novel neurotechnologies we consider in this report, each of which intervenes in the brain, raise ethical and social concerns that are not raised to the same extent by other novel biomedical technologies.
15. The ethical framework we construct to navigate these concerns is built up in three stages:
 - **Foundational principles:** A tension between need and uncertainty lies at the foundation of our framework. On one hand given the suffering caused by brain disorders and an absence of other effective interventions, there is a need for therapeutic applications of neurotechnologies. On the other hand there is uncertainty about benefits and risks of these technologies, due not only to their novelty but also to the lack of comprehensive understanding of how the brain works. The special status of the brain therefore provides both a reason to exercise **beneficence** by intervening when injury or illness causes brain disorders, and a reason for **caution** when we are uncertain what the effects of doing so will be.
 - **Interests:** In articulating the implications of the principles of beneficence and caution in the context of developing and using novel neurotechnologies, we identify a cluster of five interests that warrant particular attention. These encompass not only protection against the potential **safety** risks of interventions, but also those interests associated with unintended impacts on **privacy** and the promotion of **autonomy** both in treatment-specific decisions and in the wider context of patients’ lives. There are also important public interests in **equity** of

access to the products of innovation, the preventing of stigma and protecting and promoting public understanding and **trust** in novel neurotechnologies.

- **Virtues:** Finally we suggest that, in seeking to protect and promote these interests, there are three virtues which are especially relevant to guiding the practices of actors across a wide range of settings and applications of novel neurotechnologies. These virtues are: **inventiveness**, which may be exercised through, amongst other means, technological innovation and by identifying ways to provide wider access to therapies; **humility**, which entails acknowledging the limits of current knowledge and of our capacities to use technologies to alleviate the harms of brain disorders; and **responsibility**, which is exemplified by pursuit of robust research practices and refraining from exaggerated or premature claims for these technologies.

16. These virtues are helpful because they characterise the kinds of attitudes and practices that should be exemplified by those engaged in the development, funding, use, regulation and promotion of novel neurotechnologies, and fostered and supported by the institutions within which they work. All three steps of this framework provide the tools we use to assess the practices and oversight mechanisms examined in subsequent chapters.

Chapter 5: Patients and participants: governing the relationships

17. The care of patients and research participants who undergo interventions using novel neurotechnologies presents the most immediate context in which to apply our ethical framework. Care does not only amount to administering safe interventions; it also entails promoting patients' and participants' autonomy and protecting them from psychological and social harms, minimising unrealistic expectations and guarding against privacy infringements.
18. Uncertainty about the long-term and unintended effects of intervening in the brain using novel neurotechnologies, a lack of alternative treatments for some neurological disorders, and the fact that many neurotechnologies address conditions that impair patients' decision-making capacities, all present challenges to responsible endeavours to support decision-making and informed consent by patients and participants and those close to them. Professional humility is particularly relevant here. Experimental therapies should not be characterised as offering a patient's 'last best hope' unless this is justified. We recommend that independent counselling, which acknowledges uncertainty, should be an essential part of treatment referral pathways (paragraph 5.9).
19. The lack of clear evidence of risks and benefits of some interventional techniques also presents challenges to responsible clinical decision-making. The National Institute for Health and Care Excellence's (NICE) Interventional Procedures Guidance (IPG) provides valuable advice to healthcare providers on clinical decision-making and oversight by drawing together the best available evidence. We recommend that compliance with NICE IPG should be mandatory (paragraph 5.24).
20. The NICE guidance and the other oversight mechanisms operating in the NHS will not, however, extend to protecting the interests of patients who use private treatment services. There is a need for professional guidelines that require patients to undergo medical evaluation by a doctor before accessing neurostimulation treatment (paragraph 5.31).
21. Data concerning brain function and neurological health collected by devices such as those delivering DBS or BCIs may be sensitive and stigmatising. We suggest that this, combined with the health risks posed by malfunctions in neurodevices, provides grounds for the Medicines and Healthcare products Regulatory Agency (MHRA) to monitor the vulnerability of neurodevices to interference or data interception (paragraph 5.54).
22. Two important issues arise when considering the responsible protection of research participants' interests. The first is the prospect of sham neurosurgery being used as a placebo control in clinical

trials of neural stem cell therapies. We recommend that research ethics guidance should be provided on this (paragraph 5.41). The second relates to the potentially serious impacts on participants from whom beneficial therapeutic or assistive neurodevices may be withdrawn at the end of a study. Where this is likely to be the case we recommend that submissions to research ethics committees must detail the information and support that will be provided to participants as part of consent procedures and at the conclusion of the study (paragraph 5.45).

23. It is not always possible to draw a neat line distinguishing therapy from research in a field where many novel applications of new technologies take place in the context of experimental treatments. Experimentation may be a necessary and valuable means of exercising inventiveness in this field, but it raises two concerns. First, there is a lack of clarity about whether interventions falling into this grey area should be governed as treatment or research. We recommend that this should be addressed by the provision of professional guidance on responsible conduct in experimental treatment (paragraph 5.60). Second, clinical experience gathered outside formal research studies may not be widely disseminated, thus perpetuating uncertainty. We suggest that publically accessible registers would provide a responsible approach to countering this risk (paragraph 5.63).

Chapter 6: Responsible research and innovation

24. The concept of ‘responsible research and innovation’ (RRI) has been adopted by policy-makers as a way of thinking more systematically about the public benefits of science and technology-based research. The precise definitions and constituent elements of RRI remain matters of debate and can appear abstract, so here we suggest six priorities that apply specifically to RRI in the context of novel neurotechnologies.

- **Clearly identified need:** It is important to justify innovation in terms of its public benefits. In the case of neurotechnologies this means meeting therapeutic need. This highlights the need to resist the technological imperative and the pursuit of novelty for its own sake. It also challenges the value of proliferating products that are indistinguishable in terms of the benefits they bring to patients.
- **Securing safety and efficacy:** Protecting safety is central the pursuit of RRI and to regulatory regimes governing medical technologies. Where the clinical uses of novel neurotechnologies are concerned, their risks can only adequately be assessed relative to their efficacy in delivering therapeutic benefits and the (possibly limited) availability of alternative treatments. This highlights the importance of assessing efficacy as part of the innovation pathway of a product – yet this is not a regulatory requirement for medical devices (such as those used in TBS and DBS) marketed in Europe.
- **Generating robust evidence:** There are both regulatory and methodological reasons why the development of medical devices in particular might not produce the most transparent, robust or balanced body of evidence. These include un-generalisable and dispersed data from small-scale studies, the influence of commercial interests, and methods that encourage the publication of positive, but not disappointing, findings. Alternative methods of linking and disseminating evidence are likely to be needed to address this.
- **Continuous reflexive evaluation:** The development of novel neurotechnologies is unlikely to follow simple linear innovation trajectories. Reflecting upon the directions in which research is (potentially) travelling, and responding to this, can help to guard innovation against lock-in to pathways that do not serve public benefit. It is also an important part of maintaining vigilance for implications of possible unintended dual-use or ‘off-label’ applications of neurotechnologies.
- **Coordinated interdisciplinary action:** Innovation in novel neurodevices, perhaps most markedly BCIs, is often multidisciplinary. Coordination between different disciplines is needed

to protect against potential risks posed by gaps in the collective understanding and oversight of a technology's risks and capabilities. Interdisciplinary collaboration also offers opportunities by introducing diverse visions of potentially fruitful development trajectories.

- **Effective and proportionate oversight:** The tension between need and uncertainty that lies at the foundation of our ethical framework presents a particular challenge to effective regulation and governance of novel neurotechnologies. Responsibility and humility require caution whilst also recognising that failing to pursue interventions also carries risks of extending suffering in the absence of effective treatment. This demands a proportionate approach to supporting innovation while protecting safety; hard-law regulation will not always be the most suitable means of achieving this.

25. This articulation of RRI provides a tool, complementing our ethical framework, which we go on to use to assess the strengths and weaknesses of the regulatory frameworks that govern the commercial availability of novel neurotechnologies. The concept of RRI also acts as an extension of our virtue-guided approach by highlighting the ways in which inventiveness, humility and responsibility should inform the practices and values of those engaged in supporting and pursuing innovation.

Chapter 7: Regulating the technologies

26. The regulatory frameworks that apply to medical devices and to advanced therapeutic medicinal products (ATMPs), such as neural stem cell therapies, govern the entry of the technologies onto the European market, including the clinical investigations preceding this.
27. Using our ethical framework and the elements of responsible research and innovation developed in the preceding chapters we assess whether current regulatory provisions are effective and proportionate given the requirement to protect patients' safety, while also enhancing access to safe and effective therapies. The regimes applying to medical devices and ATMPs share a historical objective of securing a harmonised European market and each is concerned both with supporting innovation while protecting patient safety. However, the regulatory obligations upon manufacturers differ significantly between these two sectors in a number of respects. Concerns regarding effective oversight of medical devices apply especially urgently to invasive neurodevices, as these pose greater risks to patients' safety.
28. Pre-market oversight of medical devices in Europe is decentralised and relatively light-touch (especially for non-invasive devices) in terms of the evidence manufacturers must supply to demonstrate that their products conform to statutory safety and performance requirements. While this may support innovation by limiting regulatory burden, we nevertheless welcome European proposals to narrow the circumstances in which manufacturers can rely on evidence concerning similar devices (rather than conducting new clinical investigations) to demonstrate conformity. We recommend that, since neurodevices intervene in the brain, the case for relying on pre-existing evidence must be particularly sound (paragraph 7.33 and 7.47). We also recommend greater transparency about the basis of all decisions about the conformity of devices with regulatory requirements (paragraph 7.27).
29. Since pre-market scrutiny of neurodevices is light-touch, it is all the more important that post-market surveillance mechanisms are robust. We recommend that these should be strengthened by making it mandatory for clinicians to report adverse events – supported by a scheme to alert them to newly approved devices – and by making all information on adverse incidents and incident trends publically accessible (paragraph 7.55).
30. Uncertainty about the benefits, risks and mechanisms by which some novel neurotechnologies achieve their effects presents one of the central ethical challenges in this field; yet the regulation of medical devices does not itself encourage collection of extensive clinical evidence. In addition to recommending enhanced transparency in the regulatory system (paragraph 7.28), we suggest that collaborative efforts to improve information governance and data linkage by manufacturers,

practitioners and others are needed. Improved evidence on the efficacy (or otherwise) of neurodevices is a particular priority as the regulatory system itself does not currently address this.

31. In contrast to medical devices, the steps required under the multiple regulatory frameworks applying to the licensing of ATMPs as commercial products are many, potentially lengthy and include centralised European authorisation. This complexity and the potentially overlapping roles of the various regulatory bodies involved is a source of concern, particularly given the economic risks that delays pose to companies developing products. Neural stem cell therapies, however, could present significant health risks if they do not perform as expected, so robust regulation is vital. We suggest that a responsible and proportionate approach to oversight should allow an evolution from a mode of protection to one of promotion as the science progresses (paragraph 7.72). We welcome recent developments in the governance of stem cell therapies that aim to streamline and speed up the regulatory and ethical oversight processes involved whilst maintaining rigorous standards for protecting patient safety.
32. There are various routes by which patients with particular needs can access medical devices and ATMPs that are not approved for wider market availability. These are welcome insofar as they may address otherwise unmet needs. However, given the intrinsic vulnerability of patients undergoing more experimental interventions, we raise concerns about the scope of regulatory and ethical oversight of therapies delivered via these routes. Some, such as ‘off-label’, ‘in-house’ and investigative uses of medical devices which are not aimed at commercial applications, may fall outside the regulator’s remit altogether. Even where the supply of some technologies for exceptional or non-routine use is regulated by the MHRA, we suggest that there need to be more thorough mechanisms for collecting and making publically accessible information on approval for these uses and their outcomes (paragraph 7.89).

Chapter 8: Non-therapeutic applications

33. We discuss three areas in which novel neurotechnologies might be used for non-therapeutic purposes: neural enhancement, gaming and military uses.
 - **Enhancement:** A number of small studies using non-invasive neurostimulation report improvements in participants’ performance in laboratory tasks, for example involving memory or language skills, or in their mood that could be construed as ‘enhancements’. However, there is need for great care in extrapolating from small studies conducted under laboratory conditions to lasting real-world effects; the potential use of neurostimulation for neural enhancement is still far from proven.
 - **Gaming:** There are already games on the market claiming to use non-invasive electroencephalography (EEG) based BCI technology, although whether they all actually utilise brain signals is questionable. Nevertheless, there is considerable research activity to develop commercially viable games that are genuinely BCI-controlled. These recreational neurotechnologies overlap with EEG-based neurofeedback ‘games’ that are already being marketed for use as treatments for attention deficit / hyperactivity disorder or that purport to improve capacities such as concentration.
34. Uses of non-invasive neurostimulation or BCIs either for putative ‘enhancement’ purposes or gaming are unlikely to pose serious health risks. Nevertheless, the large number of people targeted by these applications and the lack of any clear associated health benefits mean that it is important to attend to several ethical concerns. In particular, to minimise the pursuit of unnecessary brain interventions, there is a need to ensure the originality and rigour of research investigating non-therapeutic uses in humans (paragraph 8.39) and also to disseminate existing evidence through publically accessible registers (paragraph 8.41).
35. Non-therapeutic applications of neurodevices (such as BCI games and those that purport to offer enhancements) are likely to be used privately and without medical supervision. This places

greater onus on the effective regulation of the devices themselves. We recommend that the European Commission considers designating neurostimulation devices as products that should be regulated under the medical devices regime irrespective of the purpose for which they are marketed (paragraph 8.52).

36. Those marketing neurodevices and services with unsubstantiated or misleading claims about their putative benefits may be exploiting consumers and undermining wider public trust in neurotechnologies. We recommend that there is a need for responsible self-governance by businesses operating in this sector, establishing best practice standards both for the provision of honest and accurate information and for delivering services using neurodevices within parameters of safe use (paragraph 8.59).
37. Given the lack of evidence of the efficacy of these neurotechnologies for enhancement, we do not examine in detail the ethics of human enhancement *per se*. However, two concerns familiar from wider bioethical debates about human enhancement may arise. The first is that pursuit of non-therapeutic innovation might represent an opportunity cost at the expense of investigating applications of greater social value. The second is that, provided some believe that enhancements using neurodevices are realisable, pressure might be exerted on individuals to use these. This latter is a particular concern in children, in whom the effects of neurostimulation or BCIs on the developing brain are not well understood. We recommend that observational research with children who are already using neurotechnologies is needed to address this (paragraph 8.40) and also that advice is issued to teachers and parents about the current evidence of the efficacy of neurofeedback as an educational enhancement tool (paragraph 8.62).
 - **Military:** Novel neurotechnologies have potentially valuable applications in treating physical and psychiatric injuries caused by combat. However, in this chapter our concern is with their non-therapeutic uses, and there are indications from the US that there is considerable investment in non-therapeutic military applications. These include the use of brain-computer interfaces (BCIs) in enhancing fighters' effectiveness by augmenting their perceptual or cognitive capacities, or by permitting neural control of remote weaponry. It is also plausible that BCIs or neurostimulation could be used for interrogation purposes. The existing international conventions outlawing the use of biological and chemical agents in war do not cover the use of neurodevices.
38. We recommend that advice is issued to armed forces highlighting that the use of neurodevices in interrogation would be coercive and illegal under the Geneva Conventions (paragraph 8.84). Military applications of novel neurotechnologies raise particular challenges for research ethics. We suggest that military clinicians can play an important role in protecting the wellbeing of personnel within their own forces who may be subject to professional coercion to participate in experimental uses of neurotechnologies (paragraph 8.87). We further recommend that the education of neuroscientists should include ethical training that draws attention to the dual-use applications of neurotechnologies for military as well as civilian ends (paragraph 8.89).

Chapter 9: Communication of research and the media

39. The novel neurotechnologies discussed in this report attract considerable media attention. We consider issues raised by the reporting and representation of scientific research in the popular and non-specialist media. In particular we look at the representation of novel neurotechnologies and the possible impacts of these representations.
40. The ways in which science and technology are reported and framed in the media may help to shape public understanding and expectations and to influence social norms and the policy and investment landscapes. However, it should not be assumed that media representation determines public attitudes in straightforward or predictable ways.
41. Some of the ways in which science is reported in the media can be attributed to the pressures upon journalists in an increasingly competitive and accelerated media environment. The demands

of this environment can, for example, lead to uncritical reproduction of press releases. Scientists themselves are increasingly engaged in the public communication of science. However, the political and economic pressures on academic researchers to demonstrate the practical and economic impacts of their work can encourage practices that lead to misleading reporting of research evidence through premature emphasis upon commercial applications, or publication bias towards positive or newsworthy findings. These combined factors can contribute to a cumulative spiral of hype.

42. Some of the hallmarks of poor science reporting practices in general are evident in communication about novel neurotechnologies. These include: headlines that misrepresent research, stories that emphasise the benefits of interventions without mentioning risks or longer-term uncertainties, speculation and extrapolation beyond the evidence and lack of contextual balance in the use of compelling images or personal stories.
43. Social media might be assumed to provide a more direct connection between scientific researchers and the public and an outlet for personal stories. Indications are, however, that content about novel neurotechnologies on social media platforms is significantly populated by commercial and academic organisations promoting therapeutic services and innovations.
44. Using the media to promote research into novel neurotechnologies may encourage investment and foster inventiveness, but hype can also be harmful. For example, it may offer false hope to patients and those close to them by failing to alert them to the limits or risks of current technological capabilities. This in turn may undermine their abilities to make informed, autonomous treatment choices. Wider risks include loss of public trust in these technologies and engendering misplaced conceptions that individuals are reducible to their brain functions. Communication practices, therefore, need to exhibit the virtues of humility and responsibility no less than clinical research and care practices do.
45. Responsible communication of the capabilities of novel neurotechnologies should not only include accurate, evidence-based reporting, but it should also take account of the possible personal and social impacts of the (mis)representations of the capabilities of these technologies. These impacts provide a particular ethical dimension of the ways in which novel neurotechnology research is framed by the media. We recommend that the behaviour of researchers, press officers and journalists involved in the communication of novel neurotechnologies should be informed by humility and responsibility, exercised through reflecting on how their representations of these technologies might contribute to cumulative hype. Points on which to reflect include: vigilance for institutional pressure to hype; the need to contextualise compelling, but potentially misleading, images; attention to use of language that might prematurely imply availability of effective treatments; and recognition that novel neurotechnologies may not be the preferred therapeutic route for every eligible patient (paragraph 9.72).
46. In addition to research institutions and journalists, we recommend that two further groups of actors should reflect on their role in practices that might drive hype: policy makers and higher education funding councils in framing the value of research in relation to the impact agenda (paragraph 9.73); and commercial enterprises in seeking to attract investment and promote their products (paragraph 9.74).

Conclusions

47. This report draws together a number of diverse neurotechnologies that differ in several ethically relevant respects. They encompass both physically invasive and non-invasive technologies, devices and stem cell products; some alleviate symptoms or assist users, while others offer non-therapeutic applications; some are already in use, while others are still undergoing investigation. The development and uses of these neurotechnologies engages a wide variety of actors and oversight of their activities involves a complex and sometimes overlapping network of professional ethical norms, governance frameworks and statutory regulations.

48. Despite this diversity, one central feature remains: these technologies intervene in the human brain, the healthy functioning of which plays a central role in our capacities for leading fulfilling lives, for sustaining both our senses of ourselves and our personal relationships. We do not argue that the ethical issues raised by novel neurotechnologies that intervene in the brain are necessarily unique or exceptional. Nevertheless, the significance of the brain in human existence does give us both a powerful reason to intervene when illness or injury damages its functions, and a reason to pause before intervening without good evidence that it will be safe and beneficial to do so. This tension, and the consequent need to steer a proportionate path between providing access to treatments whilst exercising caution, provides the foundation for our ethical framework. It is a tension that is also echoed in the cross-cutting ethical themes that we identify in the concluding chapter of the report. In particular:
- We recognise that novel treatments will often have to be explored through experimental interventions. This creates particular obligations to safeguard those patients rendered vulnerable by incapacity or constrained choices, who are most likely to be candidates for more experimental therapies.
 - This is a field marked by uncertainty and hype. Decisions taken by professionals and patients to use novel neurotechnologies must be based on the best available evidence of their benefits and risks. Achieving this demands responsible communication that is open about the limits of our current understanding of efficacy and risk, while maintaining trust in these technologies. It must also be underpinned by collaborative approaches to capitalise more effectively on existing evidence.
 - In focusing upon therapies that intervene in the brain, we must not to lose sight of the fact that neurological disorders and methods of treating them affect the whole person and their personal relationships. In assessing the benefits and risks of these neurotechnologies we must therefore attend to the outcomes that patients themselves value and look also to the wider social and psychological impacts of their use.
49. Many of the neurotechnologies we have discussed are currently available only to those participating in research, or as expensive interventions offered when others have failed. Our hope is that, in time, safe and effective neurotechnologies will emerge, which will be cheaper, easier to use, and more widely available. The considerable unmet needs of patients with some of most serious and intractable neurological and mental health disorders, combined with the challenges of securing funding for the development of new therapies, provide ethical imperatives to support inventiveness in this field. However, uncertainties about the longer term and unintended impacts of intervening in the brain need to be acknowledged. The first priority for responsible oversight must be the protection of patients' safety and wellbeing. We believe that through proportionate regulation we can better promote innovation that delivers safe and effective technologies.

Chapter 1

Introduction

Chapter 1 - Introduction

- 1.1 The number of people in the UK with serious neurological and mental health disorders is large and rising steadily as life expectancy increases. For example, in the UK there are currently around 127,000 people with Parkinson's disease¹ and approximately 800,000 with dementia (mainly with Alzheimer's disease).² In addition, brain damage from stroke is the leading cause of disability in the UK.³ Conditions associated with old age will increase as populations age; and this poses a problem not only for high income countries such as the UK, but also increasingly for low- and middle-income countries. Other groups of people with serious neurological disorders may also include those who are partially or fully paralysed due to spinal cord injury and those with conditions that cause varying degrees of paralysis, such as motor neurone disease. In Chapter 3 we provide more detail about the number of people affected by neurological and mental health disorders (see paragraphs 3.10 to 3.15).
- 1.2 We have become very familiar in recent decades with a range of pharmaceutical interventions into the brain, from over-the-counter painkillers, to prescription drugs to treat psychiatric disorders and even illegal mind-altering drugs such as LSD and ecstasy. But we are less familiar with physical interventions into the brain: those which use electrical currents or magnetic fields to stimulate neurological functions or that record brain signals to control external devices, or those that use stem cells to attempt to repair damaged brain tissue. These are the types of interventions we term 'novel neurotechnologies' in this report (see paragraph 1.12)
- 1.3 While the social and ethical issues concerning psychopharmaceutical drugs have been discussed and debated at great length⁴ – although by no means resolved – there has been less consideration of novel neurotechnologies. Yet there is considerable interest in exploring the efficacy of such interventions, especially in addressing neurological conditions that are currently untreatable. Diseases for which neurotechnologies are being developed include Parkinson's disease, stroke, and mental health disorders such as depression and obsessive-compulsive disorder (OCD). Their use to assist the daily lives of those paralysed by brain injury is also being explored. As we shall see, these technologies raise some difficult ethical questions, such as how novel treatments can be made available to individuals who would benefit from them without incurring disproportionate risks. In Europe and the United States, there is a developing debate about the ways in which these devices and procedures should best be regulated to ensure safety and efficacy, to guard against false or misleading claims, to encourage responsible innovation and to ensure that the maximum individual and social benefits are realised.

The historical context

- 1.4 Attempts to intervene in the brain are far from new. There is a long history of interventions into the brain for what we would now consider 'medical' reasons, dating from as early as the Palaeolithic period where trepanning – removing a piece of the skull to treat conditions such as epilepsy – was used.⁵
- 1.5 The practice of lobotomy was for a time prevalent in the field of psychiatric neurosurgery. Lobotomy (also known as pre-frontal leucotomy), involved a direct surgical intervention into the brain of those diagnosed with severe mental health disorders, in order to cut or otherwise

¹ Parkinson's UK (2012) *Our plan to cure Parkinson's*, available at: http://www.parkinsons.org.uk/research/our_plan_to_cure_parkinsons.aspx.

² Alzheimer's Society (2013) *What is dementia?*, available at: http://alzheimers.org.uk/site/scripts/documents_info.php?documentID=106.

³ NHS Choices (2012) *Standards for stroke care*, available at: <http://www.nhs.uk/NHSEngland/NSF/Pages/Nationalstrokestrategy.aspx>.

⁴ See, for example, Rose N (2003) Neurochemical selves *Society* **41(1)**: 46-59.

⁵ Harris JC (2004) The cure of folly *Archives of General Psychiatry* **61(12)**: 1187.

destroy certain key regions in the frontal lobes.⁶ This procedure gained widespread popularity after it was developed in 1935 by the Portuguese neurologist Egas Moniz, who later received the 1949 Nobel Prize for medicine for his work in developing this technique. Moniz claimed some remarkable results with this practice, and used it on patients with a wide range of severe mental health disorders from depression to mania; and others, including the British neurologist Sir Wylie McKissock, claimed to be able to replicate these results. The practice became widespread during the 1950s, especially in the United States where it was enthusiastically adopted by the surgeon Walter Freeman. Early reports were optimistic about the results and their implications, as it appeared to offer a way of treating those who were otherwise liable to be confined for years within mental asylums. However, many neurologists expressed doubts about its efficacy, and the procedure was increasingly called into question as evidence emerged of side-effects which left many debilitated by serious brain damage.⁷

- 1.6 Among those who opposed the relative crudity of lobotomy were neurosurgeons who believed that more refined and careful neurosurgical techniques were more appropriate for the treatment of conditions such as epilepsy or neuropsychiatric disorders. Innovations by surgeons such as William Macewen, who developed a technique for the successful removal of brain tumours, contributed to major advances in the field of brain lesioning in the latter part of the 19th Century and the early part of the 20th Century.⁸ This technique, also known as ablative brain surgery, involves cutting lesions in brain tissue. Advances in this field were made possible by parallel innovations. For example, in the early 20th Century the neurosurgeon Harvey Cushing used X-rays to locate brain tumours and the introduction in 1947,⁹ by Ernest Spiegel and Henry Wycis, of a stereotactic apparatus made it possible to direct brain lesions much more accurately by locating and targeting particular areas using measured coordinates.¹⁰ With the use of stereotactic apparatus, research and limited clinical application of ablative brain surgery continued in the United States and Europe despite the damage to the reputation of neurosurgery which followed the public recognition that lobotomy had been a medical disaster.
- 1.7 At the same time, an important new line of research began to be explored in which the localised electrical stimulation of regions of the brain was investigated as an alternative to lesions as a method of treating neurological and mental health disorders. One of the most influential pioneers in this field was the Spanish neuroscientist José Delgado.¹¹ During the 1950s Delgado, who worked mainly in the United States, implanted electrodes in the skulls of patients in a psychiatric hospital and showed that electrical stimulation of their brains could elicit both motor actions and emotional experiences (for example, fear, rage, and lust), depending on the area stimulated. He also carried out extensive research with implanted electrodes in cats and monkeys, showing, for example, that animals that were habitually aggressive to their subordinates could be calmed by stimulation to certain areas of the brain.¹² Delgado's devices were what he termed 'stimoceivers': they could both monitor the electrical activity of the brain and stimulate the brain electrically. This two-way communication opened the possibility of linking information on patterns of neural activity to calculated interventions to modulate that activity. In his 1969 book, *Physical control of the mind: towards a psychocivilized society*,

⁶ Valenstein ES (1986) *Great and desperate cures: the rise and decline of psychosurgery and other radical treatments for mental illness*, Volume 24 (New York: Harper Collins). Leucotomies were only one of a whole set of physical treatments that were used at that time, see: Sargent W, Slater E, Kelly D and Dally P (1972) *An introduction to physical methods of treatment in psychiatry* (Edinburgh: Churchill Livingstone).

⁷ Johnson J (2009) A dark history: memories of lobotomy in the new era of psychosurgery *Medicine Studies* **1(4)**: 367-78.

⁸ Neuroportraits (2011) *William Macewen*, available at: <http://neuroportraits.eu/portrait/william-macewen>.

⁹ Yale Medical History Library (2006) *Harvey Cushing: a journey through his life*, available at: <http://www.med.yale.edu/library/historical/cushing/hopkins.html>.

¹⁰ PL. G (2001) Spiegel and Wycis - the early years *Stereotactic and functional neurosurgery* **77(1-4)**: 11-6.

¹¹ Other important pioneers from this period were Robert Heath, who worked at Tulane University, Carl-Wilhelm Sem-Jacobsen, who worked in Oslo, and Nathalia Bechtereva, who worked in Leningrad. For further discussion, see: Hariz MI, Blomstedt P and Zrinzo L (2010) Deep brain stimulation between 1947 and 1987: the untold story *Neurosurgical Focus* **29(2)**: E1.

¹² See: John Horgan's account in Scientific American, Inc. (2005) *The forgotten era of brain*, available at: <http://www.mesolimbic.com/delgado/brainchips.pdf>.

Delgado downplayed ideas of brain control by ‘evil scientists’, but did suggest that neurotechnology was “on the verge of ‘conquering the mind’” and creating “a less cruel, happier and better man”.¹³ The work became mired in controversy when it was suggested that the technology might be used for controlling potential criminals and reducing homosexual attraction, and Delgado returned to Spain to work on less invasive methods of neural control that anticipated transcranial magnetic stimulation (TMS) (see paragraph 1.12).

- 1.8 Despite these developments in ablative surgery and brain stimulation, attention shifted during the 1960s to new pharmacological compounds such as chlorpromazine (Largactil), L-3, 4-dihydroxyphenylalanine (L-DOPA), and other neuroleptics which appeared to act directly on the underlying neural causes of mental health conditions. As other drugs were developed that seemed to be safe and effective, and were thought to work on the neurotransmitter systems in the brain, the pharmacological route became the preferred approach for acting on the brain.¹⁴ Of course, there were other approaches – psychoanalytic and behavioural, for example – and some direct interventions into the brain were still used – notably electro-convulsive therapy (ECT) for severe depression and neurosurgery for intractable epilepsy – but by the end of the 1970s, biological psychiatry with its focus on treatment with drugs, appeared to prevail.¹⁵ Coupled with the growing use of ‘minor tranquillisers’ such as Valium for managing the problems of everyday life, and the later rise of new generations of drugs for treating depression, panic disorders and much more, the future of psychiatry seemed to lie with pharmacology. This was not only the case with psychiatry; in neurological diseases such as Parkinson’s and Alzheimer’s disease, the chemical route seemed the obvious one to pursue, and commercial companies devoted much effort to developing new drugs to treat disorders of the brain.
- 1.9 However, some of these hopes have been disappointed. Several new drugs turned out to be less effective in the long term than had been anticipated.¹⁶ In addition, due to a lack of new molecules to explore and the advent of generics, which provided a disincentive to the pharmaceutical industry to invest in exploratory drug development, the pipeline of psychiatric drugs slowed. Altogether it has proved difficult to translate the great advances in our knowledge of the brain into new and effective compounds.¹⁷ Doubt has also been cast on the safety and efficacy of some of the drugs that had once seemed the obvious first-line treatment for psychiatric and mental illnesses. Moreover, the chronic nature of many neurological and mental health conditions means that the brain adapts to the drugs (as it would to any intervention) leading to loss of efficacy. Despite growing knowledge of the neurological basis of conditions such as dementia, it has proved especially difficult to develop drugs that do more than slow its development.
- 1.10 One result of this situation has been the impetus to explore altogether new methods of treatment, including the introduction of stem cells into the affected sites in the brain. Another has been the return to techniques for brain intervention which use electrical stimulation, which had, to some degree, been marginalised by psychopharmacology. The central instance of this was the development of deep brain stimulation (DBS), which combined stereotactic techniques from ablative surgery with new technology for brain stimulation involving the insertion of small electrodes into the regions where lesions were used to treat mental health disorders.¹⁸ These surgical techniques have also developed alongside the emergence of new imaging technologies for visualising normal and pathological processes within the living brain, including functional magnetic resonance imaging (fMRI).

¹³ Ibid, at page 71.

¹⁴ Rose N (2003) Neurochemical selves *Society* **41(1)**: 46-59.

¹⁵ NICE (2013) *Depression overview*, available at: <http://pathways.nice.org.uk/pathways/depression>.

¹⁶ Miller G (2010) Is pharma running out of brainy ideas *Science* **329(5991)**: 502-4.

¹⁷ Hyman SE (2012) Revolution stalled *Science Translational Medicine* **4(155)**: 1-5.

¹⁸ DBS was developed in 1987 by the Grenoble team: Benabid AL, Pollak P, Louveau A, Henry S and de Rougemont J (1987) Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease *Applied Neurophysiology* **50(1-6)**: 344-6.

- 1.11 Thus the hope for the future is that the new understanding of these recalcitrant disorders provided by these and other recent developments in neuroscience can be used to inform new therapeutic interventions in the brain. Such interventions could both avoid the perils of the older neurosurgical interventions and provide better treatments than current pharmacological therapies offer.

Novel neurotechnologies in this report

- 1.12 This report focuses on the issues which are most characteristic of interventions that involve new neurotechnologies. It does not discuss the significance of brain imaging techniques such as fMRI, important though these are. Equally, we do not discuss refinements of older surgical techniques, such as the use of ablative radiosurgery or the use of new psychopharmaceuticals. Instead, we concentrate on technologies that are either radically new, or where new knowledge and practices are combined with recently-established technologies to develop novel therapeutic interventions in the brain. Thus this report focuses on the following four categories of technologies:

- **Transcranial brain stimulation**, which encompasses a range of non-invasive interventions using devices to apply either weak electrical fields or electromagnetic pulses to the scalp to affect the brain's neural activity.
- **Deep brain stimulation**, which also uses a device to administer electrical current to stimulate neural activity, but through the use of electrodes that are inserted into the brain directly.
- **Brain-computer interfaces**, which use electrodes (either implanted in the brain, or resting on the scalp) to record brain signals that are translated into commands to operate computer-controlled devices.
- **Neural stem cell therapies**, where stem cells are injected into the brain in order to replace or stimulate regeneration of lost or damaged brain tissue.

- 1.13 Applications of neural stem cell therapies and assistive brain-computer interfaces are still confined to experimental uses and research settings. Transcranial brain stimulation (TBS) techniques have been used as research tools for some time, but are now being translated from the laboratory into clinical practice. DBS has become an established therapy for Parkinson's disease, but its use is now being extended to a number of other conditions. As such, the technologies discussed in this report occupy a spectrum of maturity as emerging therapeutic interventions. We discuss each of these technologies in detail in Chapter 2.

Ethical and social considerations

- 1.14 Our attention is focused on ethical, legal and social issues to which these four categories of novel neurotechnologies give rise. These technologies encompass a wide variety of applications, ranging from highly invasive surgical interventions used to ameliorate the effects of serious brain disorders, to non-invasive brain-computer interfaces (BCIs) that might provide assistance to individuals with impaired motor control. Although this report focuses primarily on therapeutic applications of novel neurotechnologies, non-therapeutic applications in relation to cognitive enhancement, gaming and military applications will also be considered (see Chapter 8).

- 1.15 This report evaluates the potential individual and social benefits and risks arising from the development and use of this diverse range of technologies. This evaluation begins in Chapter 4, with an ethical framework. This focuses solely on therapeutic applications of novel neurotechnologies, as it is here that there is the greatest potential for social benefit, where

research and usage are most advanced and therefore, in our view, where the most pressing and least speculative ethical concerns arise. This is not to say that non-therapeutic applications do not pose their own challenges, but these are sufficiently distinct that we discuss them separately (see Chapter 8).

- 1.16 Ethical issues raised by novel neurotechnologies are not wholly exceptional or unique. However, we suggest that the brain has a special status in founding the capacities and abilities which are central to our existence, and this provides both a reason to intervene – in order to try to restore what has been lost when the brain ceases to function as it should – and a reason for great caution when we are uncertain what the effects of doing so will be. These two competing considerations provide the foundation of our ethical framework.
- 1.17 In articulating what negotiating this tension between need and uncertainty entails in the context of developing and using novel neurotechnologies, we identify a cluster of five interests that warrant particular attention. These include safety, autonomy, privacy, equity and trust. Finally we suggest that, in seeking to protect and promote these interests, three virtues in particular should guide actors across a wide range of settings and applications of novel neurotechnologies. These virtues are inventiveness, humility and responsibility.
- 1.18 Our ethical framework is intended to guide the activities of all actors involved in funding, developing, regulating, using and promoting novel neurotechnologies. In many cases those living with serious neurological or mental health conditions will have few other therapeutic options for treating or ameliorating their conditions other than those potentially offered by novel neurotechnologies. As a result, there are also ethical dimensions to the economic drivers (discussed in Chapter 3) and regulatory frameworks (discussed in Chapter 7) which determine whether these technologies progress from research to marketable commercial applications, since both impact on the availability of, and access to, these technologies. A further social context with significant ethical ramifications is the media presentation, and ‘hying’, of the capabilities and promises of novel neurotechnologies (discussed in Chapter 9).
- 1.19 Our discussions of the social and ethical issues raised by novel neurotechnologies over subsequent chapters adopt the following structure. **Chapter 2** describes in some detail the four categories of neurotechnologies that are the subject of this report. It outlines their state of development on the pathway to therapeutic application, what these applications are, the mechanisms by which they achieve therapeutic (or assistive) effects, and any unintended consequences of their use. **Chapter 3** addresses the demand for, and availability of, therapeutic applications of these technologies in the context of the economic pressures and incentives that influence whether they reach the stage of development that permits them to be marketed for widespread use. This provides the background to our ethical framework, the key elements of which we have outlined above and which are described fully in **Chapter 4**. The chapters that follow the ethical framework consider the contexts in which novel neurotechnologies are developed, used, regulated and promoted. Each applies our framework – and the principles, interests and virtues identified therein – to the practices of a wide range of actors and organisations, and to the mechanisms of oversight that govern and shape them, making recommendations as appropriate.
- 1.20 **Chapter 5** focuses on ethical issues raised by the care of patients using novel neurotechnologies and of participants in clinical research. **Chapter 6** introduces the concept of Responsible Research and Innovation (RRI) and identifies the elements that are of greatest priority for RRI in this field. **Chapter 7** describes different regulatory frameworks applicable in the UK to neurodevices and neural stem cell therapies and applies the values set out in our ethical framework to identify possible gaps, or areas of disproportionate burden, in the current system of oversight. We then widen our scope to look beyond the solely therapeutic applications of these technologies. **Chapter 8** describes the potential for novel neurotechnologies to be applied to enhancement, recreational and military purposes. Finally, in **Chapter 9** we address issues arising from communication about novel neurotechnologies, the harm that misinformation and hype might cause, and the respective responsibilities of researchers and journalists to

communicate with responsibility and humility. **Chapter 10** draws together cross-cutting themes that emerge from the preceding chapters and recommendations arising.

A Freudian ending: man as a “prosthetic god”

- 1.21 In *Civilization and its discontents*, Sigmund Freud famously wrote “Man has, as it were, become a kind of prosthetic God. When he puts on all his auxiliary organs he is truly magnificent; but those organs have not grown on to him and they still give him much trouble at times. [...] Future ages will bring with them new and possibly unimaginably great advances in this field of civilization and will increase man’s likeness to God still more. But in the interests of our present investigation, we will not forget that present-day man does not feel happy in his God-like character.”¹⁹
- 1.22 Some see in neurotechnologies the emergence of new ways for humans to escape the limitations of their bodies and minds, the sub-optimal legacy of our evolved history. These ideas, that humans are ‘hybridising’ with machines, becoming cyborg-like fusions of machine and organism, excite enthusiasm and repugnance in equal measure. Nowhere are they more problematic, and intriguing, than when the human brain and mind are at stake. Neurotechnologies offer us both prospects – to become Delgado’s psychocivilised citizens or to enable us to achieve undreamed levels of control and remediation over the most severe and troublesome medical conditions that affect our species. While much of our report will focus on more prosaic issues of regulation, efficacy, and safety, we will not ignore these more fundamental social and ethical questions raised by the development of these novel neurotechnologies.

¹⁹ Freud S (1961) *Civilization and its discontents* (New York: W.W. Norton & Co.).

Chapter 2

Intervening in the brain:
current understanding and
practice

Chapter 2 - Intervening in the brain: current understanding and practice

Introduction

Chapter 2 - overview

Illness or injury that results in damage to the brain and its functions can lead to serious disorders that affect memory, cognition, movement, or consciousness or cause conditions such as chronic pain. The brain has a limited capacity to repair damaged tissue, although new functional connections may be formed.

The novel neurotechnologies discussed in this report all have the potential – which is in some cases yet to be fully demonstrated – to address some of the distressing and disabling effects of brain damage by intervening in the functions of the brain itself.

Our report focuses upon the following four categories of novel neurotechnologies. None of these technologies provides a cure for neurological or mental health disorders, but they could ameliorate symptoms, or fulfil assistive roles in ways that help improve patients' quality of life.

- **Transcranial brain stimulation (TBS)** refers to a group of non-invasive neurotechnologies, which stimulate the brain either by inducing an electrical field using a magnetic coil placed against the head (transcranial magnetic stimulation (TMS)), or by applying weak electrical currents via electrodes on the scalp (transcranial direct current stimulation (TDCS) and transcranial alternating current stimulation (TACS)). These technologies have been used as research tools, but their therapeutic applications are increasingly being explored, the most established application is in treating drug-resistant depression. The exact mechanisms by which TBS achieves its therapeutic effects are still being researched.
- **Deep brain stimulation (DBS)** also alters the functioning of brain cells and neural networks by using electrical currents, but in this case the stimulation is delivered by electrodes implanted deep in the brain. Therapeutic uses of DBS include the treatment of movement disorders, such as those associated with Parkinson's disease, and of neuropathic pain. There is also considerable research activity exploring its use to treat a wide range of psychiatric disorders. The exact mechanisms by which DBS achieves its therapeutic effects are unknown.
- **Brain-computer interfaces (BCIs)** use electrodes (either implanted in the brain, or resting on the scalp) to record users' brain signals which are then translated into commands to operate computer-controlled devices. By actively producing brain signals, users can control these devices. BCIs could in principle assist users to communicate, control prostheses or wheelchairs, support rehabilitation, or facilitate detection of consciousness – making these technologies potentially useful to those with paralysis. Therapeutic uses of BCIs are still confined to research contexts, in which non-invasive techniques are most prevalent.
- **Neural stem cell therapy** involves the injection of stem cells into the brain in order to repair damage caused by acute events such as stroke or neurodegenerative conditions such as Alzheimer's disease. Although this technique could have substantial therapeutic potential, neural stem cell therapies are still at an early phase of development; the first clinical trials in humans in the UK are now being undertaken. The precise ways in which stem cell grafts may assist in repairing lost brain tissue are not known, but these could include direct replacement of lost cells or stimulating repair by the brain itself.

In discussing the ethical and social implications of these technologies, their potential therapeutic benefits must be considered alongside any unintended harms associated with their use. Non-invasive neurotechnologies pose the fewest risks to patients. Invasive neurotechnologies requiring neurosurgery (such as DBS or neural stem cell therapies), pose greater risks, including infection and bleeding associated with surgery itself, and potential unintended physiological and functional changes in the brain resulting from the implanted electrodes or stem cells. DBS can also be associated with complex unintended effects on mood, cognition and behaviour.

- 2.1 This chapter offers an overview of the structure and function of the brain, and the principles behind brain responses to external intervention. We outline the possible therapeutic uses of four categories of novel neurotechnologies: non-invasive neural stimulation, invasive neural stimulation, brain-computer interfaces (BCIs) and neural stem cells. We also provide an overview of the current evidence of the risks and benefits of these applications. Here we restrict the discussion of risks to those directly associated with the application of the technologies, such as the side-effects of repeated brain stimulation, or the risks from brain surgery. Wider questions relating to ethical issues and societal effects are addressed in each of the subsequent chapters. Non-therapeutic applications of novel neurotechnologies are discussed in Chapter 8.

Organisation of the brain

- 2.2 The brain is the most sophisticated and complex organ in the body. The largest and most striking brain structure is the cerebrum, divided into two hemispheres, which are encased within the skull and protected from direct outside influence other than by the neural pathways carrying information from sensory organs (mainly via the spinal cord and brainstem) or through hormonal influences mediated via the blood supply.²⁰
- 2.3 There are approximately 100 billion neurons in the brain, residing in a complex network of non-neuronal cells, called glia. While there are ten times more glia cells than neurons, it is the neurons that are responsible for sensing changes in the environment, communicating these changes to other neurons, and commanding the body's responses to them. Neurons are specialised in complex ways to fulfil particular functions: the number, length and pattern of extensions (axons and dendrites) that extend from their cell bodies; the connections they make with other neurons; the neurotransmitters that they release to pass on information; and the surface channels and receptors, selectively sensitive to particular chemicals. These are just some of the features that distinguish individual neurons. Glia appear more uniform, though they too contribute to information-processing in individual ways. The three main types of glia are astrocytes, which regulate the chemical environment between neurons; oligodendrocytes which provide electrical insulation; and microglia, the resident immune cells of the brain, which clean up debris and react to disruptions in brain homeostasis such as those caused by brain damage.²¹
- 2.4 Neuroscientists study the brain at many different levels. Using the neuron as the basic building block of brain function, neuroscientists can apply a reductionist approach and study the detailed cell biology of the neuron, its genetic machinery, molecular signalling and biophysical properties. Alternatively, they may take a wider approach and study the way in which neurons form circuits and networks for communication, integration and modulation of information through electrical and chemical signalling, or even monitor activity as it relates to whole regions of the brain. This final approach can range from the detailed analysis of a simple memory circuit in the sea slug *Aplysia*, to the broader inferences of human brain function using advanced recording and imaging techniques in conscious subjects. Some neuroscientists do not focus upon the brain itself, but rather upon the cognitive, social and behavioural outcomes of brain function. The current view of most neuroscientists is that there needs to be a combined molecular, cellular, circuit and systems, and cognitive approach, together with an understanding of human behaviour and social interaction, if we are to better understand brain function.
- 2.5 Neurons conduct information by means of electrical signals. This is not simply a passive conductance along nerve fibres, but rather an active process which means that the signals, or 'action potentials', are of fixed size and duration and do not diminish over distance. Information is coded by the frequency of action potentials (or 'firing frequency' as it is commonly called), but also by the number and distribution of neurons that are firing. Action potentials are initiated in the brain by the passage of ions across the neuronal cell membrane through specialised channels. This normally occurs through the release of neurotransmitters from other neurons,

²⁰ Bear MF, Connors BW and Paradiso MA (2006) *Neuroscience: exploring the brain* (Lippincott: Williams & Wilkins); Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA and Hudspeth AJ (2012) *Principles of neural science*, 5th Edition (London: McGraw-Hill Medical).

²¹ Bear MF, Connors BW and Paradiso MA (2006) *Neuroscience: exploring the brain* (Lippincott: Williams & Wilkins); Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA and Hudspeth AJ (2012) *Principles of neural science*, 5th Edition (London: McGraw-Hill Medical).

connected through specialised junctions, called synapses, or by physical means, such as by light falling upon the retina.²²

- 2.6 The brain has evolved such that neurons assemble into clear ‘grey matter’ nuclei, which have their own anatomical names (such as the thalamus or the basal ganglia) and which can be seen deep within the brain using magnetic resonance neuroimaging techniques or with the naked eye in post-mortem brains. This efficient organisation forms the basis of a broad regional specialisation of function and is likely to speed up communication. Nerve fibres entering or leaving these nuclei are also identifiable as ‘white matter’ bundles or tracts which form key routes of communication between brain nuclei. Covering the whole surface of the brain is a convoluted, layered sheet of grey matter, which has a thickness of two-to-three millimetres in man, but with a surface area of several hundred square centimetres.²³ This is the cerebral cortex, one of the most important parts of the human brain responsible for perception of sensations, voluntary movement, learning, speech, cognition and emotional control.
- 2.7 The cerebral cortex is broadly divided into specialised regions (sensorimotor, visual, auditory, olfactory) as well as those for high-level perceptual analysis of faces, places, bodies, visually presented words, and thinking about another person’s thoughts.²⁴ Many cortical regions have multiple integrating and analytic properties, and so, despite many popular accounts, regions cannot be simply ascribed to a single function. Furthermore, many brain nuclei control less obvious, but equally important, functions: for example, hormonal and autonomic functions such as cardiovascular control. Many human experiences, such as the perception of pain, have sensory, emotional and autonomic components (entailing bodily responses that are separate from the brain) and do not involve a single cortical area, but rather involve a spatial and temporal pattern of activity in multiple brain regions that are also activated in other contexts, such as fear.²⁵ The complexities of cortical circuitry are immense and neuroscientists are encompassing new fields of neuroinformatics, or network science, together with more traditional biological approaches to try and understand the functional connections within and between cortical regions and between the cortex and the deep brain nuclei.²⁶

Brain damage

Box 2.1: Terminology

There are several terms to describe the different types of damage that can befall the brain, and various other terms to describe the elements that comprise the brain’s response, or the response that might be elicited by therapeutic agents.

Brain injury is often used synonymously with brain damage, although more typically it would be used to refer to the damage that might follow traumatic brain injury or a stroke, rather than that following infection or disease. It is typically associated with impairment or disability.

Neurodegeneration refers to the progressive loss of structural integrity and functional capacity in individual nerve cells associated with specific disorders. Parkinson’s disease, Alzheimer’s disease, multiple sclerosis and Huntington’s disease are examples of neurodegenerative disorders in which specific populations of neurons undergo such change.

Brain repair is a term often used in two different contexts. The first relates to a natural process of repair undertaken by the body following brain damage that involves the immune and circulatory systems as well as neural tissue itself. This process seeks to limit damage by facilitating the survival and repair of the brain cells that can be saved, and inducing the death and removal of those that cannot. The second refers to a therapeutic approach that seeks to aid this natural process. This therapeutic repair might involve **neuroprotection**, which seeks to aid the survival and recovery of damaged nerve cells, or **neurotrophism**, whereby the growth of nerve cells, or their processes, is encouraged. More ambitiously, it might aspire to **brain reconstruction**, a true regenerative medicine of the brain, in which new brain cells would be formed, and connected appropriately to the host brain. This might involve enhanced **neurogenesis**, namely the

²² Bear MF, Connors BW and Paradiso MA (2006) *Neuroscience: exploring the brain* (Lippincott: Williams & Wilkins); Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA and Hudspeth AJ (2012) *Principles of neural science*, 5th Edition (London: McGraw-Hill Medical).

²³ Shipp S (2007) Structure and function of the cerebral cortex *Science* **297**(1): 443-9.

²⁴ Kanwisher N (2010) Functional specificity in the human brain: a window into the functional architecture of the mind *Proceedings of the National Academy of Sciences* **107**(25): 11163–70.

²⁵ Tracey I (2008) Imaging pain *British Journal of Anaesthesia* **101**(1): 32-9.

²⁶ Shipp S (2007) Structure and function of the cerebral cortex *Science* **297**(1): 443-9.

generation of new neurons from endogenous neural stem cells, or the grafting of exogenous cells or other factors.

Brain damage is a generic term used to describe the destruction of brain tissue that occurs as a consequence of injury, infection, or disease. Typically, this damage is associated with a functional impairment or disability. In this report, the term 'brain damage' is used as a general term for the destruction of brain tissue due to any cause leading to disability.

- 2.8 Like other bodily organs, the brain and spinal cord are subject to damage caused by injury, infection, or disease. Many of these types of damage are quite common, and together they are responsible for some of the most intractable medical conditions. The most serious include traumatic brain injury (TBI), which follows an impact to the skull;²⁷ stroke, where damage results from the interruption of the blood supply to the brain;²⁸ and a range of neurodegenerative disorders, such as Parkinson's disease or Alzheimer's disease, where populations of brain cells undergo degenerative change.²⁹ Whatever the cause of the brain damage, there are two particular consequences. First, neurons are lost.³⁰ This can be a diffuse loss, such as happens in Alzheimer's disease, or the complete loss of a particular area of brain, which can occur following a stroke. Specific populations of neurons may also be targeted by disease processes, such as the midbrain dopaminergic neurons lost in Parkinson's disease, the spinal and cortical motor neurone in motor neuron disease, or spinal inhibitory neurons in neuropathic pain.³¹ In other conditions, for example Batten's disease, almost every nerve cell can be affected. Similarly, the loss can be acute as in TBI or stroke, or chronic and progressive as in Alzheimer's disease. Whatever the specifics, however, lost neurons cannot generally be replaced. The second consequence of damage is that the connections between brain cells are lost.³² A central example of this is spinal cord injury, where typically a fall or a motor vehicle accident causes damage to the spinal column. Consequently the connection between the brain and the spinal cord is partly or completely severed, and both sensation and control of muscles are lost or reduced significantly.
- 2.9 When nerve cells are lost or connections severed, there is an impact on brain function. The set of functions served by a particular neuron population or specific neural pathway become compromised. The brain plays an irreducible role in the maintenance and performance of our bodies, including controlled movements and autonomic functions, as well as thoughts, emotions, memories and behaviour. When the brain is damaged through illness or injury and its functions fail, there can be devastating personal consequences. The misery and stress of living with a damaged brain, the loss of memory and cognition in dementia, the lack of controlled movement in Parkinson's disease, the relentlessness of neuropathic pain, and the hopelessness of depression can profoundly change the lives of the individuals affected and those close to them.
- 2.10 The unfortunate fact is that loss of brain function is often permanent and progressive. Thus, while small lesions in brain may be compensated for by 'rewiring' or remyelination, neurons in the adult brain do not repair themselves if damaged.³³ An important feature of central nervous tissue is that it has a very limited capacity to reverse either the loss of cells or connectivity. While some 'lower' vertebrates such as frogs and fish have the capacity to rebuild damaged

²⁷ Headway (2013) *What happens in a TBI?*, available at: <https://www.headway.org.uk/What-happens-in-a-TBI.aspx>.

²⁸ NHS Choices (2012) *Stroke*, available at: <http://www.nhs.uk/Conditions/Stroke/Pages/Introduction.aspx>.

²⁹ Prusiner SB (2001) Neurodegenerative diseases and prions *New England Journal of Medicine* **344**(20): 1516-26.

³⁰ Nixon RA and Yang D-S (2012) Autophagy and neuronal cell death in neurological disorders *Cold Spring Harbor Perspectives in Biology* **4**(10): 1-23.

³¹ Laguna Goya R, Tyers P and Barker R (2008) The search for a curative cell therapy in Parkinson's disease *Journal of the Neurological Sciences* **265**(1): 32-42; Rothstein JD (2009) Current hypotheses for the underlying biology of amyotrophic lateral sclerosis *Annals of Neurology* **65**(1): S3-S9; Bráz JM, Sharif-Naeini R, Vogt D *et al.* (2012) Forebrain GABAergic neuron precursors integrate into adult spinal cord and reduce injury-induced neuropathic pain *Neuron* **74**(4): 663-75.

³² Silver J and Miller JH (2004) Regeneration beyond the glial scar *Nature Reviews Neuroscience* **5**(2): 146-56.

³³ Rossi F and Cattaneo E (2002) Neural stem cell therapy for neurological diseases: dreams and reality *Nature Reviews Neuroscience* **3**(5): 401-9.

brain tissue, mammals do not.³⁴ Unlike other organs, such as the skin, which renews and repairs itself by cell division throughout life, the process of neurogenesis, or neuronal birth, is largely restricted to the fetal and neonatal brain (with some notable exceptions in specific brain regions³⁵).³⁶ Therefore, if neurons die or connections are lost through trauma or disease, they will be replaced only minimally. If this loss is major, then the functional consequences are likely to be profound and intractable. This is seen very clearly in paraplegics following spinal cord damage or in the chronic disability following a serious stroke.

- 2.11 However, the normal, healthy brain is capable of considerable ‘plasticity’ – that is, the capacity to continuously shift its functional connectivity. While it was once thought that neuronal connections were fixed and that functional adaptation in the adult nervous system was severely limited, evidence now suggests that new brain connections are continuously forming and reforming.³⁷ Indeed, the dynamics we most associate with normal brain function – cognition, memory, and learning – are almost certainly a reflection of the brain’s plasticity. The functional status of patients with traumatic brain injury can therefore improve following rehabilitative treatment involving repeated practice and relearning tasks. The mechanisms underlying this plasticity are unclear, but are likely to result from the strengthening of neuronal connections from remaining, undamaged neurons through activity-dependent processes.³⁸
- 2.12 Limited functional restoration can be brought about by rehabilitative therapies following brain damage and this indicates that neuronal circuits in the brain do have some capacity for change.³⁹ Nonetheless, no rehabilitative therapy used on its own has yet had more than an ameliorative effect on the consequences of either neuron loss, or the loss of connections between neurons. This is the area of unmet medical need that novel neurotechnologies are seeking to address.

Addressing brain damage using neurotechnology

- 2.13 In the following sections, we examine the current state of the art in four categories of neurotechnologies that offer potential treatment – albeit often temporary relief rather than a cure – or therapeutic assistance to individuals who have neurological and mental health disorders as a result of injury or illness. These categories are: transcranial brain stimulation (TBS), deep brain stimulation (DBS), brain-computer interfaces (BCIs) and neural stem cell therapies. These technologies share the feature that they all, in different ways, intervene in the brain itself – where ‘intervention’ is understood in terms of an action undertaken to bring about an effect in the brain.
- 2.14 Neurostimulation devices and BCIs are thought to work – at least in part – through activating and modulating existing networks in the brain. In damaged brains, our understanding of activity-dependent synaptic plasticity has provided good rationale for attempting to enhance the function of remaining, undamaged neurons through external brain stimulation.⁴⁰ Neural stem cell therapies, meanwhile, aim to replace lost neurons by inserting stem cells into damaged brain

³⁴ Bonfanti L and Peretto P (2011) Adult neurogenesis in mammals—a theme with many variations *European Journal of Neuroscience* **34(6)**: 930-50, at page 944.

³⁵ These are the hippocampus and the sub-ependymal zone.

³⁶ Bonfanti L and Peretto P (2011) Adult neurogenesis in mammals—a theme with many variations *European Journal of Neuroscience* **34(6)**: 930-50.

³⁷ Holtmaat A and Svoboda K (2009) Experience-dependent structural synaptic plasticity in the mammalian brain *Nature Reviews Neuroscience* **10(9)**: 647-58.

³⁸ *Ibid*, at 651.

³⁹ Komitova M, Johansson BB and Eriksson PS (2006) On neural plasticity, new neurons and the postischemic milieu: an integrated view on experimental rehabilitation *Experimental Neurology* **199(1)**: 42-55.

⁴⁰ Schulz R, Gerloff C and Hummel FC (2012) Non-invasive brain stimulation in neurological diseases *Neuropharmacology* **64**: 579–87.

regions, which may have the potential to differentiate and replace neurons within networks.⁴¹ This too has a strong scientific rationale.⁴²

- 2.15 In the following discussion it is recognised that it may be artificial to consider the brain in isolation from the rest of the nervous system. In light of this, at several points in this chapter we consider interventions in other regions of the nervous system as part of the context within which we understand the implications of intervening in the brain.

Stimulating the brain

- 2.16 We have described the passage of ions required to trigger action potentials in the brain. The same effect can also be induced by the external application of an electrical current or field to the brain. This is a standard technique used by laboratory neuroscientists when they wish to activate specific neurons and nuclei in the brain in order to explore their functional connections with another region and thus understand a circuit. A further electrode is commonly used to record the pattern of action potentials produced by the electrical stimulation.⁴³
- 2.17 External stimulation of the brain, if applied repetitively, can also have longer term effects on the excitability of neurons, rendering them more or less likely to produce action potentials. This may be due to altered levels of chemicals released from stimulated neurons, such as neurotransmitters and neuromodulators, but also a change in the number of receptors for those chemicals.⁴⁴ A classic example of this is long term potentiation (LTP) or long term depression (LTD), whereby high frequency trains of electrical pulses applied to specific fibre tracts can lead to prolonged changes in synaptic communication between affected neurons, long outlasting the stimulation period, sometimes for months.⁴⁵ Such 'synaptic plasticity' (the ability of activity in neural circuits to alter the subsequent communication between neurons over time) is a fundamental principle of brain function and adds further to the complexity of the system. This ability of neurons to change in the face of either physiological or externally-applied inputs, or structural correlates of this, can be observed by imaging the living brain.⁴⁶ The application of magnetic pulses across the brain can also alter the ability of neurons to produce action potentials and this is likely to be due to synaptic plasticity rather than by direct excitation.⁴⁷
- 2.18 There are a number of risks associated with brain stimulation. Some of this is attributable to the lack of control over what is being stimulated. Neurons can be excitatory or inhibitory (that is, they can excite or inhibit activity in other neurons to which they are connected, depending upon their neurotransmitter content and the ionic environment) and DBS will not discriminate between these.⁴⁸ Much as plasticity following brain damage can be useful (for example, leading to recovery after rehabilitation in stroke patients) or harmful (as in the onset of phantom limb pain following amputation), there is also a risk that activating particular neurons, fibre tracts and circuits might result in, acute or chronic adverse or damaging unintended consequences.

⁴¹ Price J (2011) Reconstructing brains: a biological impossibility? *BioSocieties* **6**(3): 299-322.

⁴² Rossi F and Cattaneo E (2002) Neural stem cell therapy for neurological diseases: dreams and reality *Nature Reviews Neuroscience* **3**(5): 401-9.

⁴³ Newer optogenetic approaches, whereby specific groups of neurons are genetically manipulated to express light-sensitive ion channels, allow stimulation of neurons with laser probes inserted into the brain, rather than with conventional electrodes. See: Han X (2012) Optogenetics in the nonhuman primate *Progress in Brain Research* **196**: 215-33.

⁴⁴ Spitzer NC (2012) Activity-dependent neurotransmitter respecification *Nature Reviews Neuroscience* **13**(2): 94-106.

⁴⁵ Cooke S and Bliss T (2006) Plasticity in the human central nervous system *Brain* **129**(7): 1659-73.

⁴⁶ Berning S, Willig KI, Steffens H, Dibaj P and Hell SW (2012) Nanoscopy in a living mouse brain *Science* **335**(6068): 551

⁴⁷ Funke K and Benali A (2010) Cortical cellular actions of transcranial magnetic stimulation *Restorative Neurology and Neuroscience* **28**(4): 399-417.

⁴⁸ Although TMS and TDCS will. See paragraph 2.32.

Neurons and tracts may also be damaged by local high current densities or mechanical movements.⁴⁹

- 2.19 These risks also extend to the behaviour and function of glial cells. Glial cells may accumulate in the stimulated region and cause neuronal changes. External stimulation of the brain will also alter glial cell function in ways that are poorly understood.⁵⁰ Astrocytes (a category of glial cell) are known to assemble into networks of cells that can propagate calcium waves upon stimulation and form a tripartite synapse together with neuronal synapses playing an active role in neural signalling. Astrocytes are also likely to react to the ‘foreign’ implanted stimulation electrode. Microglia respond to intense neural firing by migrating to the stimulated region and changing their properties to releasing a range of cytokines that can cause neuronal hypersensitivity.⁵¹
- 2.20 We turn now to describing the four categories of novel neurotechnologies that are the focus of this report, starting with techniques for non-invasive neural stimulation.

Transcranial brain stimulation

- 2.21 There are currently three modes of transcranial brain stimulation in use: transcranial magnetic stimulation (TMS); transcranial direct current stimulation (TDCS); and transcranial alternating current stimulation⁵² (TACS).
- 2.22 Stimulation of the brain using currents is not new. The ability to apply electrodes to the scalp and to pass a direct current between them has been available for over a century (direct current stimulation). Stimulation using electromagnetic induction (TMS) is a more recent development.⁵³

Specific procedures in TBS

- 2.23 TMS has been used since 1985 when it was developed to assist in assessing studies of the motor system. In TMS, a coil is placed over the scalp and a large current is passed through the coil, delivering a ‘TMS pulse’, with each pulse lasting less than 1ms. It is this rapid exchange of current that gives TMS the ability to stimulate brain tissue. TMS is best understood in studies of the motor system⁵⁴ and the most common way of assessing its effects is through measuring muscle responses following stimulation to the motor cortex either in research or clinical settings.⁵⁵ In studies of cognition, the effects of TMS are measured in terms of small percentage changes in reaction time, or changes in behavioural performance on psychological tasks – for example, the time taken to complete sentences, recognise faces or add numbers.⁵⁶

⁴⁹ Pilitsis JG, Chu Y, Kordower J *et al.* (2008) Postmortem study of deep brain stimulation of the anterior thalamus: case report *Neurosurgery* **62**(2): E530-E2.

⁵⁰ Vedam-Mai V, van Battum E, Kamphuis W *et al.* (2011) Deep brain stimulation and the role of astrocytes *Molecular Psychiatry* **17**(2): 124-31.

⁵¹ Hathway GJ, Vega-Avelaira D, Moss A, Ingram R and Fitzgerald M (2009) Brief, low frequency stimulation of rat peripheral C-fibres evokes prolonged microglial-induced central sensitization in adults but not in neonates *Pain* **144**(1): 110-8.

⁵² Transcranial alternating current stimulation includes the technique transcranial random noise stimulation (TRNS).

⁵³ Barker AT, Jalinous R and Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex *The Lancet* **325**(8437): 1106-7.

⁵⁴ Amassian V, Stewart M, Quirk G and Rosenthal J (1987) Physiological basis of motor effects of a transient stimulus to cerebral cortex *Neurosurgery* **20**(1): 74-93; Berardelli A, Inghilleri M, Rothwell JC, Cruccu G and M. M (1991) Multiple firing of motoneurons is produced by cortical stimulation but not by direct activation of the descending motor tracts *Electroencephalography & Clinical Neurophysiology* **81**(3): 240-2; Rossini P, Berardelli A, Deuschl G *et al.* (1999)

Applications of magnetic cortical stimulation *Electroencephalography & Clinical Neurophysiology Supplement* **52**: 171-85.

⁵⁵ Deletis V and Bueno De Camargo A (2002) Interventional neurophysiological mapping during spinal cord procedures *Stereotactic and Functional Neurosurgery* **779**(1-4): 25-8.

⁵⁶ Walsh V and Cowey A (1998) Magnetic stimulation studies of visual cognition *Trends in Cognitive Sciences* **2**(3): 103-10; Walsh V and Pascual-Leone A (2003) *Neurochronometrics of mind: transcranial magnetic stimulation in cognitive science* (Cambridge, MA: MIT Press).

- 2.24 TDCS is the application of weak electric fields to the scalp via sponge electrodes. Only a small proportion of the current stimulates brain tissue.⁵⁷ The effects of TDCS, like TMS, are measured in terms of small percentage or reaction time changes in behavioural performance on psychological tasks. The effects of TDCS on the motor system can be assessed by using TMS to measure the sensitivity of muscle responses.⁵⁸
- 2.25 TACS is delivered using the same apparatus as TDCS and the procedures are identical but rather than direct current, alternating current is used. Alternating current entrains cortical activity at specific frequencies.⁵⁹ It is used when examining or manipulating a brain function associated with brain oscillations.⁶⁰
- 2.26 TMS, TDCS and TACS are all simple, non-invasive procedures. The TMS coil or the DC/AC electrodes are placed on the scalp regions overlying the areas to be stimulated. The subject is conscious, no anaesthetic is required and the procedures are rarely uncomfortable. In a typical TMS experiment, a subject will receive between one and ten pulses every few seconds. In some studies, TMS is delivered in high frequency bursts for up to 190 seconds⁶¹ or in low frequency trains (usually 1 Hz) for up to 30 minutes,⁶² with the aim of changing the level of excitability of a brain network. The brain region to be stimulated is located either by using scalp coordinates from electroencephalography (EEG) procedures, which use non-invasive electrodes to pick up areas of brain activity, or by positioning the coil guided by a structural magnetic resonance imaging (MRI) scan of the subject's brain. The TMS coil can also be co-registered with the coordinates of functional MRI studies.⁶³
- 2.27 In a typical DC/AC experiment, subjects will be continuously stimulated for between five and 20 minutes. The electrodes are placed according to the 10-20 EEG system (that is, according to locations measured from the ears or skull landmarks) or, rarely, according to MRI data. During DC/AC, the subject will usually be required to perform a psychological task.

Current therapeutic applications of TBS

- 2.28 The importance of TBS methods lies in their current use as research tools and their potential as therapeutic delivery devices. As research tools, they permit researchers to interfere transiently with brain function and thus attempt to model some effects of brain damage, such as speech difficulties following stroke.⁶⁴ They also permit researchers to attempt to change perceptual experiences⁶⁵ or behavioural choices⁶⁶ to try to understand cognitive systems. Over 3,500 research papers have been published using these methods (mostly TMS) since 1985.⁶⁷

⁵⁷ Nitsche M and Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation *The Journal of Physiology* **527(3)**: 633-9.

⁵⁸ Ibid, at 634.

⁵⁹ Zaehle T, Rach S and Herrmann CS (2010) Transcranial alternating current stimulation enhances individual alpha activity in human EEG *PLoS ONE* **5(11)**: e13766.

⁶⁰ Kanai R, Chaieb L, Antal A, Walsh V and Paulus W (2008) Frequency-dependent electrical stimulation of the visual cortex *Current Biology* **18(23)**: 1839-43; Ridling MC and Ziemann U (2010) Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects *The Journal of Physiology* **588(13)**: 2291-304; Feurra M, Paulus W, Walsh V and Kanai R (2011) Frequency specific modulation of human somatosensory cortex *Frontiers in Psychology* **2(3)**: 1-6.

⁶¹ Huang YZ, Edwards MJ, Rounis E, Bhatia KP and Rothwell JC (2005) Theta burst stimulation of the human motor cortex *Neuron* **45(2)**: 201-6.

⁶² Ibid, at 205.

⁶³ Sack AT, Cohen Kadosh R, Schuhmann T *et al.* (2009) Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods *Journal of Cognitive Neuroscience* **21(2)**: 207-21.

⁶⁴ Stewart L, Walsh V, Frith U and Rothwell J (2001) TMS produces two dissociable types of speech disruption *Neuroimage* **13(3)**: 472-8.

⁶⁵ Silvanto J, Muggleton NG, Cowey A and Walsh V (2007) Neural adaptation reveals state-dependent effects of transcranial magnetic stimulation *European Journal of Neuroscience* **25(6)**: 1874-81.

⁶⁶ Cho SS, Pellecchia G, Ko JH *et al.* (2012) Effect of continuous theta burst stimulation of the right dorsolateral prefrontal cortex on cerebral blood flow changes during decision making *Brain Stimulation* **5(2)**: 116-23.

⁶⁷ From a search conducted by the Working Party on PubMed.

Use of TBS in depression

2.29 TMS and TDCS are both used in drug resistant depression,⁶⁸ and several meta-analyses have concluded that TMS has significant clinical effects.⁶⁹ Additional benefits of TMS over electroconvulsive therapy (ECT), which is the most effective treatment for severe depression, is that TMS does not require anaesthetic, is not associated with memory loss and does not require a seizure to be induced to achieve its effect, all of which are drawbacks of ECT.⁷⁰ Only a small number of TMS stimulation parameters have been tested and it is not possible to predict which patients will benefit from this kind of treatment, but at least one quarter to one third of patients respond positively and more protocols are being tested.⁷¹ The effect size is not negligible and is comparable to any individual antidepressant.⁷² In the UK, the National Institute for Health and Care Excellence (NICE) Interventional Procedures Programme (IPP) has advised that TMS should, at present, only be used for the purposes of researching its efficacy in treating depression.⁷³ TMS has, however, been licensed for use in the United States by the US Food and Drug Administration (FDA).⁷⁴ The use of TDCS in depression has been less extensively studied than TMS, but already a consensus is emerging that TDCS may be beneficial.⁷⁵

Use of TMS, TDCS in other mental health and neurological disorders.

2.30 There are many applications of TBS in mental health and neurological disorders that are at varying levels of scientific and clinical maturity. Many conditions have at least one study making positive therapeutic claims including schizophrenia, Tourette's syndrome, pain, addiction, epilepsy, decision making, memory loss, anxiety disorders, tinnitus, migraine, obsessive compulsive disorders, sleep, movement disorders (dystonia, Parkinson's disease, ataxia) and stroke. The most advanced of these are addiction,⁷⁶ stroke,⁷⁷ and tinnitus.⁷⁸ Work in addiction has shown that people's choices and cravings can be temporarily changed by TDCS.⁷⁹ Trials with stroke patients have shown that some relearning can be moderately accelerated following TDCS.⁸⁰ In tinnitus, TMS has been used to screen patients prior to brain implants and both TDCS and TACS have shown promising results.⁸¹ Even so, there have been no large clinical trials in any of these areas. Studies are usually on small groups of patients and even though some are of high quality, they remain preliminary.

⁶⁸ Lisanby SH, Kinnunen LH and Crupain MJ (2002) Applications of TMS to therapy in psychiatry *Journal of Clinical Neurophysiology* **19(4)**: 344-60; O'Reardon JP, Solvason HB, Janicak PG *et al.* (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial *Biological Psychiatry* **62(11)**: 1208-16; George MS, Lisanby SH, Avery D *et al.* (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial *Archives of General Psychiatry* **67(5)**: 507-16.

⁶⁹ See: Kozel A and George M (2002) Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression *Journal of Psychiatric Practice* **8(5)**: 270-5; NICE (2007) *Transcranial magnetic stimulation for severe depression* available at: <http://www.nice.org.uk/nicemedia/live/11327/38391/38391.pdf>.

⁷⁰ Carney S, Cowen P, Geddes J *et al.* (2003) Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis *The Lancet* **361(9360)**: 799 - 808.

⁷¹ O'Reardon JP, Solvason HB, Janicak PG *et al.* (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial *Biological Psychiatry* **62(11)**: 1208-16.

⁷² *Ibid*, at 1214.

⁷³ NICE (2007) *Transcranial magnetic stimulation for severe depression*, available at: <http://www.nice.org.uk/nicemedia/live/11327/38391/38391.pdf>.

⁷⁴ FDA (2011) *K061053; NeuroStar TMS System*, available at: http://www.accessdata.fda.gov/cdrh_docs/pdf6/K061053.pdf.

⁷⁵ Loo CK, Alonzo A, Martin D *et al.* (2012) Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial *The British Journal of Psychiatry* **200(1)**: 52-9.

⁷⁶ Levasseur-Moreau J and Fecteau S (2012) Translational application of neuromodulation of decision-making *Brain Stimulation* **5(2)**: 77-83, pp79--80.

⁷⁷ Miniussi C, Cappa SF, Cohen LG *et al.* (2008) Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation *Brain Stimulation* **1(4)**: 326-36.

⁷⁸ De Ridder D, De Mulder G, Walsh V *et al.* (2004) Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus *Journal of Neurosurgery* **100(3)**: 560-4.

⁷⁹ Fecteau S, Knoch D, Fregni F *et al.* (2007) Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study *The Journal of Neuroscience* **27(46)**: 12500-5.

⁸⁰ Schlaug G RVND (2008) Transcranial direct current stimulation in stroke recovery *Archives of Neurology* **65(12)**: 1571-6.

⁸¹ Nitsche M and Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation *The Journal of Physiology* **527(3)**: 633-9; De Ridder D, De Mulder G, Walsh V *et al.* (2004) Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus *Journal of Neurosurgery* **100(3)**: 560-4; Fregni F, Marcondes R, Boggio PS *et al.* (2006) Transient tinnitus suppression induced by repetitive transcranial magnetic stimulation and transcranial direct current stimulation *European Journal of Neurology* **13(9)**: 996-1001.

- 2.31 From a clinical perspective, the caveat in all claims surrounding TBS is that these methods have only small, transient effects on the brain. These are impressive, interesting and publishable for experimental scientists but the effects are usually unable to outlast a few seconds and occasionally minutes (TMS), or a few tens of minutes (TDCS). To produce clinical effects, TBS needs to be used as an adjunct to other therapies or delivered every day at intensities and durations greater than those used in experiments (as might be required in the treatment of depression).⁸²

Mechanisms of action of TBS

- 2.32 The exact mechanisms of TMS, TDCS and TACS continue to be investigated. However, there is considerable understanding of the changes that these techniques produce in neuronal pathways in the brain. Unlike other methods of brain study, many of which rely on brain imaging techniques, TBS has an effect on the human brain rather than solely measuring its output. The principles of electromagnetic stimulation that underpin these methods are, however, well understood and electrical currents can be used to selectively activate subpopulations of neurons: excitatory or inhibitory neural systems can be controlled by selecting stimulation polarity frequency or duration.⁸³ In TMS, TDCS and TACS, effects spread beyond the principle site of stimulation. This can mistakenly lead to the belief that the site of stimulation is unknown, but the main effects are usually to be found at the site of stimulation.⁸⁴ In TMS, the spread of current is predictable according to anatomical pathways, while in TDCS and TACS, the spread is less predictable because of current shunted by cerebrospinal fluid. Even here, studies of the motor cortex show that the main effects are under the site of the stimulating electrode and recent advances in multi channel DC stimulation show greater specificity.⁸⁵

TMS

- 2.33 The rapidly changing current used in TMS induces a magnetic field which passes unattenuated through the scalp which, in turn, induces an electrical field in the underlying cortical tissue. This electrical field causes brain cells to be active. So, the name 'magnetic' stimulation is something of a misnomer; the effect is electrical stimulation produced as an example of Faraday's law of electromagnetic induction.⁸⁶ TMS can be delivered in single pulses or multiple pulses, in the latter case to try to extend the effects beyond the period of stimulation and selective stimulation of excitatory or inhibitory neurons is achieved by modifying the time between pulses.⁸⁷ Theta burst TMS delivers several hundred pulses over a few tens of seconds and induces a period of inhibition.⁸⁸ However, the effects of a particular stimulation paradigm on the resting motor threshold when the subject remains relaxed and stationary does not mean that behavioural effects will also be observed. This is important to note when reading claims about transferability to use in the 'real world'. Experimental conditions – where subjects are relaxed, still, or

⁸² O'Reardon JP, Solvason HB, Janicak PG *et al.* (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial *Biological Psychiatry* **62(11)**: 1208-16, at 1214.

⁸³ Werhahn KJ, Kunesch E, Noachtar S, Benecke R and Classen J (1999) Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans *The Journal of Physiology* **517(2)**: 591-7; Sack AT, Cohen Kadosh R, Schuhmann T *et al.* (2009) Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods *Journal of Cognitive Neuroscience* **21(2)**: 207-21; Stagg CJ, Best JG, Stephenson MC *et al.* (2009) Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation *The Journal of Neuroscience* **29(16)**: 5202-6; Jacobson L, Koslowsky M and Lavidor M (2012) tDCS polarity effects in motor and cognitive domains: a meta-analytical review *Experimental Brain Research* **216(1)**: 1-10.

⁸⁴ Walsh V and Pascual-Leone A (2003) *Neurochronometrics of mind: transcranial magnetic stimulation in cognitive science* (Cambridge, MA: MIT Press).

⁸⁵ Datta A, Bansal V, Diaz J *et al.* (2009) Gyri-precise head model of transcranial DC stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad *Brain Stimulation* **2(4)**: 201-7.

⁸⁶ Greiner W and Bromley DA (1998) *Classical electrodynamics*, Volume 1 (Berlin: Springer).

⁸⁷ Kujirai T, Caramia M, Rothwell J *et al.* (1993) Corticocortical inhibition in human motor cortex *The Journal of Physiology* **471(1)**: 501-19.

⁸⁸ Huang YZ, Edwards MJ, Rounis E, Bhatia KP and Rothwell JC (2005) Theta burst stimulation of the human motor cortex *Neuron* **45(2)**: 201-6.

performing a routine task – are likely to be markedly different from those outside the laboratory (see paragraphs 8.12 to 8.14). For example, it is often the case that normal brain activity – for example that associated with talking, writing, and walking – will immediately nullify the measurable effects of TMS, TDCS or TACS. This is in contrast to some of the words used to describe these methods such as ‘zapping’, ‘brain-boosting’ or ‘brain doping’ which suggest large, dramatic and lasting effects on the brain.

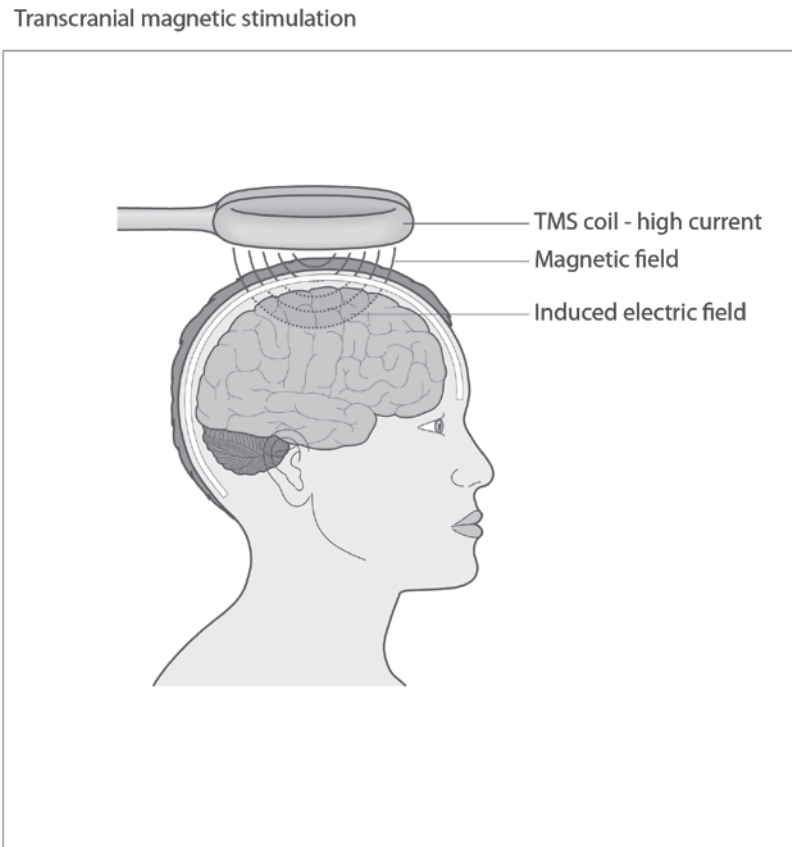


Figure 1: TMS

TDCS and TACS

2.34 Investigation of the effects of static electric fields on neurons *in vivo* have a long history, and rely on the orientation of neurons relative to the induced electric field.⁸⁹ The spatial resolution of DC is a function of voltage-sensitive channels. The main effect of DC is to change firing rates of cells but, unlike TMS, it does not induce spontaneous neural activity. Anodal stimulation causes increases in excitation; cathodal stimulation causes increases in inhibition, reflected in the relative concentrations of GABA and glutamate,⁹⁰ major inhibitory and excitatory neurotransmitters. The currents delivered are usually between 0.5 and 2mA. Approximately half of this current is absorbed by the scalp⁹¹ and most of the rest by cerebrospinal fluid. It is

⁸⁹ Hern J, Landgren S, Phillips C and Porter R (1962) Selective excitation of corticofugal neurones by surface-anodal stimulation of the baboon's motor cortex *The Journal of Physiology* **161(1)**: 73-90.

⁹⁰ Stagg CJ and Nitsche MA (2011) Physiological basis of transcranial direct current stimulation *The Neuroscientist* **17(1)**: 37-53.

⁹¹ Miranda PC, Lomarev M and Hallett M (2006) Modeling the current distribution during transcranial direct current stimulation *Clinical Neurophysiology* **117(7)**: 1623-9.

estimated that for a 2mA current, the density induced in the cortex is approximately $1\mu\text{A}/\text{cm}^2$.⁹² Of all the modern methods for human brain imaging and stimulation, the mechanisms of TDCS are the best understood. AC stimulation is most likely to have an effect via rhythmic stimulation which entrains or enhances endogenous neurophysiologic activity, rather than through polarising brain tissue.⁹³

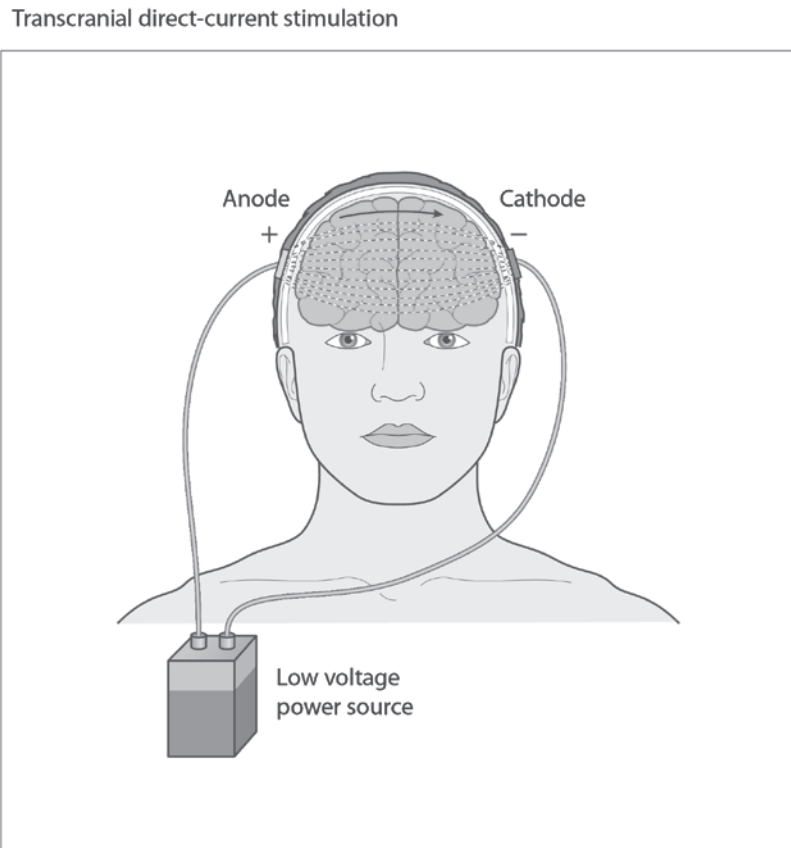


Figure 2: TDCS

Proposed therapeutic applications emerging in the literature

- 2.35 As noted above, the literature in TBS is replete with claims about its possible use in any number of neurological and mental health conditions and enhancement interventions. Whether any of these come to fruition will depend on larger, better controlled studies and with further knowledge of the practicalities of using relevant equipment in therapeutic settings.
- 2.36 The field, however, is poised to make contributions and there are real possibilities in depression, tinnitus, addictive behaviours, stroke rehabilitation, migraine and pain management. However, the more cognitive the functions the weaker the scientific foundations are for them. There are emerging claims of the ability of TBS to improve cognitive functions such as memory in the absence of pathology and at the limits of what might be considered pathology. We return to discuss these in Chapter 8.

⁹² Miranda PC, Faria P and Hallett M (2009) What does the ratio of injected current to electrode area tell us about current density in the brain during tDCS? *Clinical Neurophysiology* **120**: 1183-7.

⁹³ Zaehle T, Rach S and Hermann CS (2010) Transcranial alternating current stimulation enhances individual alpha activity in human EEG *PLoS ONE* **5(11)**: e13766.

- 2.37 Nevertheless, there are simple physical limits to TBS. The use of magnetic fields cannot achieve spatial resolution to target areas of the brain with pinpoint accuracy. Acceptable levels and duration of magnetic pulses will be limited by the comfort of patients. In addition, the delivery of AC or DC currents is limited by the effects of current density and heating of the hair and scalp.

Technology-related risks and potential unintended consequences

- 2.38 There is little danger from the application of TMS or DC/AC currents *per se*. The sensations of participants or patients undergoing TMS will be an experience of an auditory click and a tactile 'tap' under the coil every time a pulse is discharged. They may also experience a transient facial muscle twitch but this is usually avoided. If the motor cortex is stimulated, the participant or patient may experience finger twitches. With TDCS or TACS, they may be aware of a faint tingling sensation under the electrodes. In cognitive experiments with TMS, TDCS or TACS participants are rarely aware of any change in their behaviour or experience.
- 2.39 The major theoretical risk with using TMS is of inducing an epileptic seizure. However, current guidelines and exclusion criteria make this risk extremely small. The number of seizures in individuals without prior history of epilepsy or drugs that reduce their seizure threshold has not reached double figures worldwide since the advent of TMS in 1985. Indeed, all of these cases occurred before the current guidelines came into force.⁹⁴ The greatest danger comes from using these techniques outside their safety limits.
- 2.40 Other unintended consequences associated with inducing brain activity using TBS are also very small. For example, in research settings there are some indications of TMS causing brief interference with memory.⁹⁵ Vigilance for other kinds of cognitive interference has been advised.⁹⁶
- 2.41 A different kind of risk arises from researchers making unsubstantiated claims about what TBS can achieve in the long term, thereby stimulating brains unnecessarily. For example, researchers may make claims that these methods can improve cognitive performance based on small, temporary, but statistically significant laboratory findings that may not be translatable to real-world applications. We return to this topic in Chapter 8.

⁹⁴ Rossi S, Hallett M, Rossini PM and Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research *Clinical Neurophysiology* **120(12)**: 2008-39.

⁹⁵ Horvath JC, Perez JM, Farrow L, Fregni F and Pascual-Leone A (2011) Transcranial magnetic stimulation: a historical evaluation and future prognosis of therapeutically relevant ethical concerns *Journal of Medical Ethics* **37(3)**: 137-43; Rossi S, Hallett M, Rossini PM and Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research *Clinical Neurophysiology* **120(12)**: 2008-39.

⁹⁶ Horvath JC, Perez JM, Farrow L, Fregni F and Pascual-Leone A (2011) Transcranial magnetic stimulation: a historical evaluation and future prognosis of therapeutically relevant ethical concerns *Journal of Medical Ethics* **37(3)**: 137-43, at page 141.

Deep brain stimulation

Specific procedures used for DBS

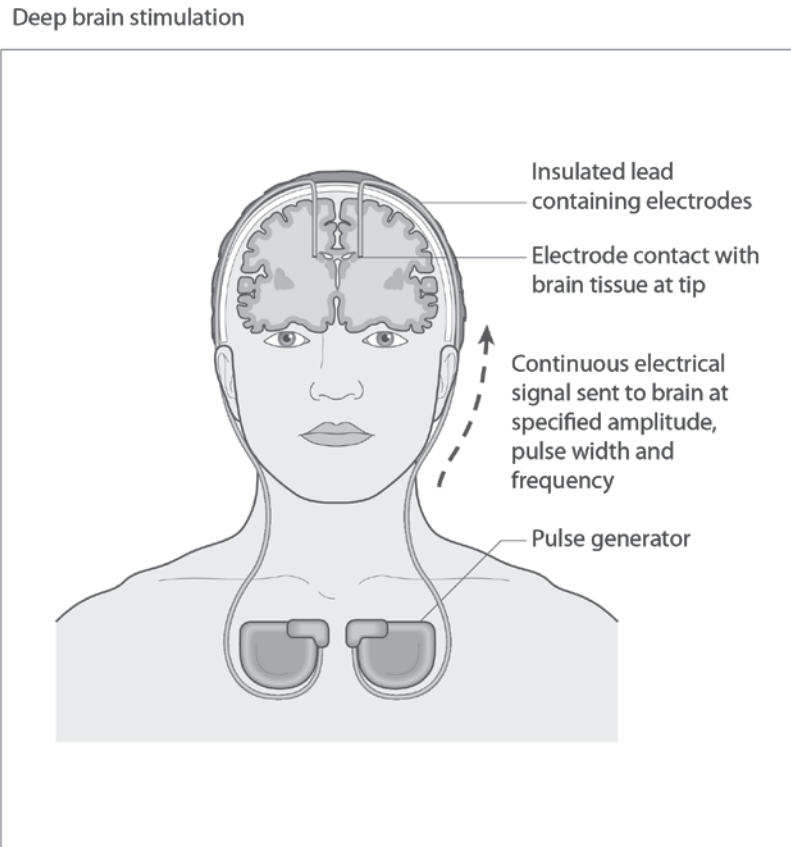


Figure 3: DBS

2.42 Deep-brain stimulation (DBS) was first developed in France in 1987 and evolved out of the ablative, or lesioning, surgeries where neurosurgeons used heat probes to burn and permanently damage small regions of the brain which were malfunctioning.⁹⁷ Now, DBS is the most widely used neurosurgical form of therapeutic brain stimulation.⁹⁸ DBS involves implanting electrode arrays into a deep subcortical brain nucleus using image-guided stereotactic neurosurgical techniques. The particular electrode placement depends on the condition being treated and pulses of current are applied to the affected region in an attempt to correct the functional deficit. DBS electrode leads are connected to battery-driven stimulus generators (IPGs) which are implanted subcutaneously, such that the system is located entirely within the patient's body. Stimulation parameters can be set via a handheld control; typical settings are 60–130 Hz, 60–200 μ s pulse width, and 2–10 volts.⁹⁹

⁹⁷ Hariz MI, Blomstedt P and Zrinzo L (2010) Deep brain stimulation between 1947 and 1987: the untold story *Neurosurgical Focus* **29(2)**: E1.

⁹⁸ Ibid.

⁹⁹ Holtzheimer PE and Mayberg HS (2011) Deep brain stimulation for psychiatric disorders *Annual review of neuroscience* **34**: 289-307.

Current therapeutic applications of DBS

- 2.43 DBS has developed during the past 20 years as a treatment option for several different disorders. Stimulation of specific thalamic nuclei improves tremor control, slowness of movement, gait disturbance, and rigidity in patients with Parkinson's disease, while stimulation of specific regions of the *globus pallidus* relieves primary dystonia (a movement disorder involving sustained muscle contractions). Evidence for the success of this procedure in essential tremor, Parkinson's disease and dystonia has led to further, widespread applications such as for chronic pain, epilepsy, migraine, Alzheimer's disease, and obesity, with variable evidence of improvement.¹⁰⁰ DBS is an elective intervention that is neither life-saving, nor curative. Patients usually choose this method in order to improve their quality of life, which is greatly limited for some due to the illness and the undesired effects of pharmaceutical treatments.¹⁰¹
- 2.44 In the UK, the use of DBS for patients with drug-resistant Parkinson's disease has been assessed by NICE's Interventional Procedures Programme and it is recommended that DBS is performed by a multidisciplinary team including a neurologist, neurosurgeon and psychologist, and is assessed on a patient-by-patient basis.¹⁰² In the United States, DBS that positions electrodes in various basal ganglia has approval from the FDA for essential tremor, Parkinson's disease and dystonia.¹⁰³ Consensus statements provide recommendations to patients, physicians, and other health care providers on DBS for Parkinson's disease.¹⁰⁴
- 2.45 Mood changes have long been reported in studies of DBS for movement disorders and this has led to an enormous interest in the potential use of DBS for mental health disorders, especially treatment-resistant depression and treatment-resistant OCD focussing on a number of different stimulation targets in the brain.¹⁰⁵ Although mental health conditions are among the most difficult to treat, the possibility of a placebo effect cannot be discounted.¹⁰⁶ It has been suggested that before widespread clinical use for these purposes is considered, it will be necessary to replicate early data in larger, placebo-controlled trials.¹⁰⁷
- 2.46 DBS is being used increasingly as an experimental treatment for patients with OCD that is resistant to psychological therapy.¹⁰⁸ In 2009, Medtronic received European marketing approval for the use of their DBS device to treat chronic, severe treatment-resistant OCD¹⁰⁹ although this use has not been considered by NICE, nor is it supported by the charity OCD-UK.¹¹⁰ In 2009, the FDA approved the use of DBS for clinical trials: the decision was based on a study of 26 patients with severe OCD that showed a 40 per cent reduction in symptoms after a year of DBS.

¹⁰⁰ Lyons MK (2011) Deep brain stimulation: current and future clinical applications *Mayo Foundation* **86(7)**: 662-72

¹⁰¹ Glannon W (2009) Stimulating brains, altering minds *Journal of Medical Ethics* **35(5)**: 289-92 at page 292; Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* **2(1)**: 3-13.

¹⁰² NICE (2003) *Deep brain stimulation for Parkinson's disease*, available at: <http://egap.evidence.nhs.uk/deep-brain-stimulation-for-parkinsons-disease-ipp019>.

¹⁰³ Department of Neurology: UNC School of Medicine (2013) *Deep brain stimulation*, available at: http://www.med.unc.edu/neurology/divisions/movement-disorders/copy_of_deep-brain-stimulation.

¹⁰⁴ Bronstein JM, Tagliati M, Alterman RL *et al.* (2011) Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues *Archives of Neurology* **68(2)**: 165-71.

¹⁰⁵ These include the subcallosal white matter, ventral capsule/ventral striatum, nucleus accumbens and sub thalamic peduncle (v) habenula. Holtzheimer PE and Mayberg HS (2011) Deep brain stimulation for psychiatric disorders *Annual review of neuroscience* **34**: 289-307, pp296-8.

¹⁰⁶ Goetz CG, Wu J, McDermott MP *et al.* (2008) Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions *Movement disorders* **23(5)**: 690-9.

¹⁰⁷ Holtzheimer PE and Mayberg HS (2011) Deep brain stimulation for psychiatric disorders *Annual review of neuroscience* **34**: 289-307;

¹⁰⁸ Goodman WK, Foote KD, Greenberg BD *et al.* (2010) Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design *Biological Psychiatry* **67(6)**: 535-42; Denys D, Mantione M, Figeo M *et al.* (2010) Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder *Archives of General Psychiatry* **67(10)**: 1061-68.

¹⁰⁹ Medtronic (2011) *Getting DBS therapy for OCD*, available at: <http://www.medtronic.co.uk/your-health/ocd/getting-a-device/index.htm>.

¹¹⁰ OCD-UK (2011) *Deep brain stimulation*, available at: <http://www.ocduk.org/deep-brain-stimulation>.

Some of the original pioneers of this treatment have expressed severe doubts about this approval and its potential for misuse.¹¹¹ Recent results using DBS in the *nucleus accumbens*¹¹² and *ventral capsule/ventral striatum*¹¹³ in small groups of patients, with stringent criteria for resistance to existing treatments, and blinded design, show significant improvement in some but not all patients with OCD.

- 2.47 DBS is also used for the treatment of neuropathic pain which is resistant to analgesic therapy. NICE recommends that DBS in this context should be carried out by multidisciplinary teams specialising in chronic pain management.¹¹⁴ DBS has not been approved by the FDA for the relief of chronic neuropathic pain, and has variable outcomes in neuropathic pain patients, but appears to have some long-term efficacy for select aetiologies in clinical case series.¹¹⁵ Clinical trials with long term follow-up are required to assess the efficacy of this technique over other treatments.¹¹⁶
- 2.48 Novel applications for DBS are published regularly, based on single case or small group experimental studies including obesity,¹¹⁷ addiction,¹¹⁸ epilepsy,¹¹⁹ Alzheimer's disease, and Alzheimer's-type dementia.¹²⁰ DBS has also been used for Tourette's syndrome,¹²¹ anorexia nervosa¹²² and cluster headache.¹²³ Proof of principle also exists for the use of DBS in minimally conscious states.¹²⁴ Each of these applications are in differing states of evolution and are supported by varying degrees of evidence, but none has a sufficiently strong evidence base to be considered effective at present. Targeting DBS using combined functional magnetic resonance imaging (fMRI) is likely to help increase the precision of this technique. Low-intensity focused ultrasound pulsation (LIFUP) is a new non-invasive brain stimulation method that uses ultrasound focused noninvasively through the skull anywhere within the brain, together with concurrent imaging fMRI. This technique is still in preclinical testing but holds promise.¹²⁵

Mechanism of action of DBS

- 2.49 The exact mechanism of action in DBS is unknown but, as in TBS, reasonable explanations have been proposed on the basis of current neuroscientific knowledge. The main effect is likely to be due to the passage of current in the vicinity of the stimulating electrode, directly exciting local neuronal cell bodies and axons. The effects will depend upon whether these neurons are

¹¹¹ Goodman S (2002) France wires up to treat obsessive disorder *Nature*.

¹¹² Denys D, Mantione M, Figeo M *et al.* (2010) Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder *Archives of General Psychiatry* **67(10)**: 1061-68.

¹¹³ Goodman WK, Foote KD, Greenberg BD *et al.* (2010) Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design *Biological Psychiatry* **67(6)**: 535-42.

¹¹⁴ NICE (2011) *Deep brain stimulation for refractory chronic pain syndromes (excluding headache)*, available at: <http://www.nice.org.uk/nicemedia/live/12803/53588/53588.pdf>

¹¹⁵ Boccard SGJ, Pereira EAC, Moir L, Aziz TZ and Green AL (2012) Long-term outcomes of deep brain stimulation for neuropathic pain *Neurosurgery* **72(2)**: 221-30.

¹¹⁶ Cruccu G, Aziz T, Garcia-Larrea L *et al.* (2007) EFNS guidelines on neurostimulation therapy for neuropathic pain *European Journal of Neurology* **14(9)**: 952-70.

¹¹⁷ Whiting DM, Tomyzc ND, Bailes J *et al.* (2013) Lateral hypothalamic area deep brain stimulation for refractory obesity: a pilot study with preliminary data on safety, body weight, and energy metabolism: clinical article *Journal of Neurosurgery*: 1-8.

¹¹⁸ Luigjes J, van den Brink W, Feenstra M *et al.* (2011) Deep brain stimulation in addiction: a review of potential brain targets *Molecular Psychiatry* **17(6)**: 572-83.

¹¹⁹ Talan J (2013) Five years after DBS, epilepsy outcomes improved *Neurology Today* **13(1)**: 1-5.

¹²⁰ Laxton AW and Lozano AM (2012) DBS for the treatment of Alzheimer's disease and dementias *World Neurosurgery* **12**.

¹²¹ Holtzheimer PE and Mayberg HS (2011) Deep brain stimulation for psychiatric disorders *Annual review of neuroscience* **34**: 289-307.

¹²² Lipsman N, Woodside DB, Giacobbe P *et al.* (2013) Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: a phase 1 pilot trial *The Lancet* **381(9587)**: 1361-70.

¹²³ Messina G, Rizzi M, Cordella R *et al.* (2013) Secondary chronic cluster headache treated by posterior hypothalamic deep brain stimulation: first reported case *Cephalalgia* **33(2)**: 136-8.

¹²⁴ Luigjes J, van den Brink W, Feenstra M *et al.* (2011) Deep brain stimulation in addiction: a review of potential brain targets *Molecular Psychiatry* **17(6)**: 572-83.

¹²⁵ Bystritsky A, Korb AS, Douglas PK *et al.* (2011) A review of low-intensity focused ultrasound pulsation *Brain Stimulation* **4(3)**: 125-36.

inhibitory or excitatory and upon the intensity and frequency of the stimulus pulses.¹²⁶ Furthermore, how effective the DBS is will depend on how excitable the target region is and whether it can be modulated by externally-applied current.¹²⁷ Animal models are used to explore the exact neural network components that are stimulated or modulated by DBS.¹²⁸

Box 2.2: Established therapeutic uses of nerve stimulation – a comparison

The novel technologies we are examining here are not the only methods of stimulating the nervous system used in medicine. Vagal nerve stimulation (VNS) and spinal cord stimulation (SCS) are both established therapeutic methods.

Vagal nerve stimulation is an effective neural stimulation technique in the treatment of therapy-resistant epilepsy. VNS does not directly stimulate the central nervous system but instead activates the brain indirectly by stimulating nerve fibres entering the brainstem through the vagus nerve, which can affect a very broad range of basic brain functions. VNS electrodes are placed by a neurosurgeon in the neck and a cable is fed under the skin to a pulse generator which can be turned on and off by the patient.¹²⁹ Several clinical trials have assessed the efficacy, safety, and tolerance of VNS therapy and as a result it is an approved treatment for medically refractory epilepsy in Europe, the United States, and Canada.¹³⁰ Long-term (12 year) follow up of patients using VNS indicates that its therapeutic effects last for long periods.¹³¹

Spinal cord stimulation is commonly used for conditions which cause intractable chronic pain. These include neuropathic back and leg pain, complex regional pain syndrome, spinal cord injury, and ischemic pain.¹³² NICE has approved SCS for treatment of pain, though it has recommended that this should only be given after the person has been assessed by a specialist team experienced in assessing and managing people receiving treatment with SCS.¹³³ SCS systems are designed to apply low voltage electrical pulses to afferent nerve fibres via an epidural electrode that is implanted surgically or through the skin. This electrode is connected to and powered by a neurostimulator device, which generates electrical pulses and is surgically implanted under the skin. The patient can turn the stimulator on or off and vary the stimulation parameters within physician-set limits by using a hand-held remote control.

These two neurostimulation techniques lie outside the terms of reference of this report because they do not intervene directly in the brain. Nevertheless, they provide an instructive context against which to consider the development trajectory, from research laboratory to clinic, of the neurotechnologies discussed in this chapter. It is notable that although these two methods of neurostimulation are approved and widely used for therapeutic purposes, in two different respects our understanding of them remains partial: there is still a surprising lack of robust data with regard to its effectiveness of SCS in pain treatment; and, while the effectiveness of VNS in treating therapy-resistant epilepsy is well-evidenced, the exact mechanism by which it reduces epileptic seizures is not known. The fact that VNS and SCS are both in clinical use indicates that uncertainties of these kinds need not necessarily present a barrier to their being approved and accepted as widespread methods of treatment.

Proposed therapeutic applications emerging in the literature

2.50 There is enthusiasm in the literature for testing DBS to address a wide range of serious mental health disorders.¹³⁴ Future therapeutic applications will rely on selection of the best possible candidates and the most favourable risk-benefit ratios. In addition, more effort is required to determine the mechanism of action in DBS and hence the rationale for using it on specific patients rather than letting the results 'speak for themselves'. Improvements in the battery and stimulator, tailored stimulation and therapy delivery, and remote monitoring are anticipated over the next few years.

¹²⁶ For example, thalamic DBS usually requires stimulation above 50 Hz and optimally above 100 Hz to suppress tremor, while globus pallidus DBS for dystonia generally requires 60–130 Hz.

¹²⁷ For example, modulation of abnormal oscillatory activity in thalamic and globus pallidus nuclei is a potential target in Parkinson's disease.

¹²⁸ Holtzheimer PE and Mayberg HS (2011) Deep brain stimulation for psychiatric disorders *Annual review of neuroscience* **34**: 289-307.

¹²⁹ Beekwilder J and Beems T (2010) Overview of the clinical applications of vagus nerve stimulation *Journal of Clinical Neurophysiology* **27(2)**: 130-8; NICE (2004) *Vagus nerve stimulation for refractory epilepsy in children*, available at: <http://www.nice.org.uk/nicemedia/live/11078/30908/30908.pdf>.

¹³⁰ Beekwilder J and Beems T (2010) Overview of the clinical applications of vagus nerve stimulation *Journal of Clinical Neurophysiology* **27(2)**: 130-8, at page 130.

¹³¹ *Ibid*, at page 131.

¹³² Hegarty D (2011) Spinal cord stimulation: The clinical application of new technology *Anesthesiology Research and Practice* **2012**, at page 4.

¹³³ NICE (2008) *Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin*, available at: <http://www.nice.org.uk/nicemedia/pdf/TA159Guidance.pdf>.

¹³⁴ Holtzheimer PE and Mayberg HS (2011) Deep brain stimulation for psychiatric disorders *Annual review of neuroscience* **34**: 289-307.

- 2.51 New methods of combining DBS with recording are likely to provide new information about how local neuronal circuits are modified by DBS¹³⁵ as well as offering therapeutic advantages. This technique will be aided by the development of a new generation of multi-channel microprobes for DBS, offering both stimulation and recording capabilities.¹³⁶

Technology-related risks and potential unintended consequences

- 2.52 DBS surgery is a very invasive procedure, which has serious associated risks (see Box 2.3 below). These include intracranial haemorrhage, infection, and complications associated with anaesthesia. In addition, the DBS system could malfunction or break, making replacement of one or more components necessary (see Box 7.4). Repeated minor surgery is also needed to replace the implantable pulse generator.¹³⁷ In experienced clinical hands these risks can be minimised.
- 2.53 Substantial increases in weight, which can lead to obesity and metabolic problems, are one reported unintended effect of DBS treatment for Parkinson's disease.¹³⁸ There are also documented risks of unwanted neuropsychological and neuropsychiatric side-effects of DBS in Parkinson's disease.¹³⁹ These include loss of word fluency, declines in word memory, visuospatial memory, manual dexterity, and working memory in addition to the onset of depression, mania/hypomania, anxiety, apathy and visual hallucinations. There are also some indications that use of DBS of the subthalamic nucleus may be accompanied by alterations in personality traits, such as impulsiveness, in some patients.¹⁴⁰ However, small sample sizes, lack of adequate controls and complexities associated with the combination of DBS and current medication makes these data difficult to interpret.¹⁴¹ Nevertheless, while some of these effects may be treatable and preventable, the incomplete understanding of what exactly is being stimulated and the mechanism of action in DBS makes these a real concern. There is therefore a particular need for great caution in the use of DBS in patients with existing neuropsychological and neuropsychiatric conditions, such as depression.¹⁴² While the effects of DBS are mostly reversible – the stimulation can be turned off if it is not effective or causes too many adverse effects – few follow up studies exist in this area.¹⁴³

¹³⁵ Cleary DR, Raslan AM, Rubin JE *et al.* (2012) Deep brain stimulation entrains local neuronal firing in human globus pallidus internus *Journal of Neurophysiology* **109(4)**: 978-87.

¹³⁶ Fomani AA, Moradi M, Assaf S and Mansour RR (2010) 3D microprobes for deep brain stimulation and recording. In Engineering in Medicine and Biology Society (EMBC), 2010 Annual International Conference of the IEEE, (IEEE), pp. 1808-11.

¹³⁷ Clausen J (2010) Ethical brain stimulation – neuroethics of deep brain stimulation in research and clinical practice *European Journal of Neuroscience* **32(7)**: 1152-62.

¹³⁸ Rieu I, Derost P, Ulla M *et al.* (2011) Body weight gain and deep brain stimulation *Journal of the Neurological Sciences* **310(1)**: 267-70.

¹³⁹ Voon V, Kubu C, Krack P, Houeto JL and Tröster AI (2006) Deep brain stimulation: neuropsychological and neuropsychiatric issues *Movement disorders* **21(s14)**: S305-S27.

¹⁴⁰ Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* **2(1)**: 3-13.

¹⁴¹ *Ibid.*

¹⁴² Glannon W (2009) Stimulating brains, altering minds *Journal of Medical Ethics* **35(5)**: 289-92.

¹⁴³ For a follow up study of DBS see: Oh MY, Abosch A, Kim SH, Lang AE and Lozano AM (2002) Long-term hardware-related complications of deep brain stimulation *Neurosurgery* **50(6)**: 1268-76.

Box 2.3: Complications and side effects of DBS¹⁴⁴

Complications of DBS:

Perioperative risks %

- Haemorrhage 1.3-4
- Epileptic seizures 0.4-2.8
- Pneumonia 0.4-0.6
- Death 0.4
- Liquor leakage 0-0.9

Hardware related problems %

- Infection 2.8-6.1
- Lead migration 5.1
- Lead breakage 5
- Leads needing repositioning 2.3
- Skin erosion 1.3-2.0
- Malfunctioning of pulse generator 0.4-9.7

Side effects of DBS:

Cognitive %

- Speech disturbances 10.8-33
- Memory Impairment 1.1-20
- Dementia 6.1-24.5

Behavioural %

- Aggression 2
- Hypomania 4.2-10.2
- Increased libido/hypersexuality .8
- Apathy 1.3

Psychiatric %

- Depression 1.5-25
- Mania 2-18
- Suicide 0.5-2

Psycho-social %

- Patient's perception of themselves 66
- Familial problems 50-71
- Professional life 0-43

Brain-computer interfaces

General principles

2.54 A brain-computer interface (BCI) involves a connection between the brain and an external device.¹⁴⁵ Their potential practical applications are in assisting, repairing or enhancing sensory-motor functions. Imagined bodily movements, certain kinds of affective states, and moments of focused attention, are associated with the particular patterns of brain signals.¹⁴⁶ A BCI picks up, measures and analyses these brain signals from the user (which are generally consciously invoked, but may alternatively be passively produced) and, by means of a translation algorithm, converts these into information. This information is then used to control the operation of a device in real-time in ways that can reflect the intentions of the user.¹⁴⁷ At present, potential users to whom BCIs offer the most significant therapeutic opportunities are those who have very limited or no control over the movement of their bodies, though the cortical region of their brain concerned with planning such movement remains intact.¹⁴⁸

¹⁴⁴ Clausen J (2010) Ethical brain stimulation – neuroethics of deep brain stimulation in research and clinical practice *European Journal of Neuroscience* **32(7)**: 1152-62.

¹⁴⁵ Here we are chiefly concerned with BCIs where brain signals are used to bring about an effect in the outside world. A distinction may be drawn between BCIs and neuroprostheses, though there is some of overlap between these. A BCI usually connects the brain or nervous system to a device via a computer, while a neuroprosthetic connects the nervous system directly to a device. A BCI also usually involves the outward translation of signals *from* the brain. A neuroprosthetic involves the delivery of sensory signals *to* the brain.

¹⁴⁶ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4(3)**: 1-22, at page 3.

¹⁴⁷ Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* **2**: 187-99, at page 191.

¹⁴⁸ Leuthardt EC, Schalk G, Roland J, Rouse A and Moran DW (2009) Evolution of brain-computer interfaces: going beyond classic motor physiology *Neurosurgical Focus* **27(1)**: 1-21, at page 6; Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Rev Biomed Eng* **2**: 187-99, at page 192.

Non-invasive brain-computer interface / Invasive brain-computer interface

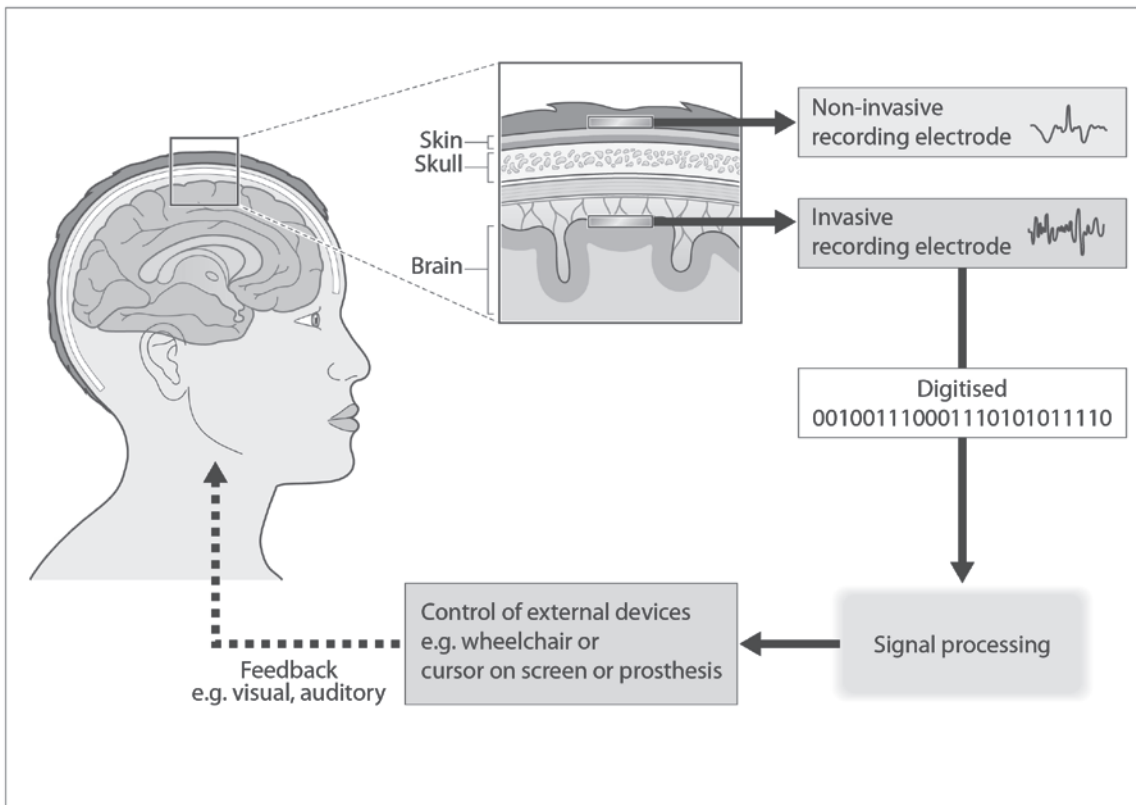


Figure 4: BCI

Procedures involved in brain-computer interfaces

2.55 Brain signals are acquired by a BCI by means of electrodes. BCIs tend to be divided into three categories depending on the type and location of the electrodes used. The type of electrode employed can make a significant difference to success rates with regard to establishing a reasonable contact with a desired area or cell type in the brain and therefore with the precision of the outputs and the amount of control the user has over these. Associated safety concerns also vary depending on where electrodes are located. This is due to the risks of neurosurgery and implanted electrodes that we have already discussed in relation to DBS (see paragraph 2.52).

Non-invasive BCIs

2.56 The most studied BCI techniques are those based on electroencephalography (EEG). As a consequence, the term ‘BCI’ is sometimes mistakenly taken to be synonymous with ‘EEG-based BCI’. This method involves recording brain signals using electrodes positioned on the outside of the user’s scalp. This means there is no need for surgery, with its attendant risks of neural damage and infection. EEG electrodes are also readily available and portable. This means that costs are significantly lower than for the other BCI methods outlined below.

- 2.57 The number of electrodes employed for EEG for experimental and research purposes can vary from a small number (four to six), to the most commonly encountered 26-30, to over 100, where the aim is to achieve even better resolution.¹⁴⁹ Electrodes may be attached directly on the scalp, often using wet gel to improve contact, or attached in fixed position on a cap. Wet electrodes may improve the accuracy of signal transduction, but may also decrease the comfort of the user.¹⁵⁰
- 2.58 Though posing fewer physiological risks from surgery and implanted electrodes than other, more invasive, BCI methods, EEG is not without its disadvantages. Facial muscle contractions or electrical appliances can interfere with the acquisition of brain signals.¹⁵¹ The spatial resolution of EEG can also be poor. The amount of user-training required varies greatly, from as little as one or two hours to some sources reporting as many as 20 to 50 30-minute sessions.¹⁵² The rate and depth of learning depends greatly on the specific intervention, the nature, and extent of brain damage and the patient's level of function.

Invasive BCIs

- 2.59 The method that permits the highest resolution recording of brain signals, and therefore affords the user the greatest level of control, involves the surgical implanting of microelectrodes directly into the cortical layers of the brain at a depth of 1.5-3mm in order to record the signals from individual neurons.¹⁵³ By increasing the number of recording sites over the area of a single implant, signals from neighbouring neurons and nerve fibres can be collected.¹⁵⁴ As signals in the brain are in general not determined by individual neuronal activity, it is often necessary to observe the inhibition of neighbouring neurons. Recording at multiple sites may be achieved by the use of shaft electrodes of electrode arrays.¹⁵⁵
- 2.60 A shaft electrode improves the likelihood of interfacing with the desired cortical area, as multiple electrode sites are concatenated onto a single needle-like shaft making it possible to target several layers of tissue at once, permitting measurement of an area spanning approximately 1.6 mm.¹⁵⁶ Meanwhile, multi-electrode arrays, in which multiple electrodes are packaged in one device, allow measurement from multiple nerves and give access to lateral neuronal interaction, permitting the pinpointing of neural activity and observation of several colonies.¹⁵⁷

Box 2.4: BCI research in non-human primates

Often in this field, non-human experiments have paved the way for future human studies. Perhaps most notable in recent years has been the relationships found between the electrical responses of single motor cortex neurons in rhesus monkeys and the direction in which the monkeys moved their arms.¹⁵⁸ More recently, a series of experiments has shown how, using electrode implants, brain activity in rhesus monkeys could be decoded to reproduce reaching and grasping movements in a robotic arm.

¹⁴⁹ Trejo LJ, Rosipal R and Matthews B (2006) Brain-computer interfaces for 1-D and 2-D cursor control: designs using volitional control of the EEG spectrum or steady-state visual evoked potentials *IEEE Transactions on Neural Systems and Rehabilitation Engineering* **14(2)**: 225-9.

¹⁵⁰ Tanaka K, Matsunaga K and Wang HO (2005) Electroencephalogram-based control of an electric wheelchair *IEEE Transactions on Robotics*, **21(4)**: 762-6.

¹⁵¹ Leuthardt EC, Schalk G, Roland J, Rouse A and Moran DW (2009) Evolution of brain-computer interfaces: going beyond classic motor physiology *Neurosurgical Focus* **27(1)**: 1-21, at page 4.

¹⁵² *Ibid*, at page 4.

¹⁵³ *Ibid*, at page 6.

¹⁵⁴ Spiers A, Warwick K, Gasson M and Ruiz V (2006) Issues impairing the success of neural implant technology *Applied Bionics and Biomechanics* **3(4)**: 297-304, at page 300.

¹⁵⁵ *Ibid*, at page 300.

¹⁵⁶ *Ibid*, at page 299.

¹⁵⁷ *Ibid*, at page 300.

¹⁵⁸ Georgopoulos AP, Lurito JT, Petrides M, Schwartz AB and Massey JT (1989) Mental rotation of the neuronal population vector *Science* **243(4888)**: 234-6.

This research was successful in getting the monkeys to operate the arm.¹⁵⁹ Other recent successes include Macaca mulatta monkeys tracking visual targets on a computer screen¹⁶⁰ and enabling a monkey to feed itself with small food chunks which it picked up by means of a robot arm controlled by its own brain signals.¹⁶¹

Partially invasive BCIs

2.61 Partially invasive BCIs are positioned surgically inside the skull but rest on the brain rather than being implanted into it. They therefore have a higher spatial resolution in comparison with non-invasive BCIs, but usually less than that of invasive BCIs. Determining the correct level of resolution depends on the type of information to be captured and the use to which it is put. For the most part the practical method in this category is electrocorticography (ECoG) which measures signals in a similar way to the method used by electroencephalography EEG (the flat electrodes are positioned in a small plastic casing which is placed adjacent to the cortex).¹⁶² In many ways, the method is a compromise solution: there is the possibility of infection due to surgery, but less damage is inflicted to the cortex as there is no forced insertion.¹⁶³ There has been limited investigative use of partially invasive ECoG BCIs in humans;¹⁶⁴ studies have related chiefly to invasive monitoring of the onset of seizures in patients with intractable (uncontrollable) epilepsy, rather than in relation to impaired motor control.¹⁶⁵

Feedback

2.62 It is possible for users of BCIs to practice and improve the exercise of imagining movements in a way that gives rise to signals associated with the desired effect.¹⁶⁶ Irrespective of which method of BCI is used, therefore, it is necessary for the user to receive feedback to indicate to them when their imagined movements have resulted in the desired device output.¹⁶⁷ BCI interfaces with the brain are usually uni-directional, and feedback is invariably received through outputs recognised by normal sensory means. That is, users rely on sight, hearing or touch to ascertain if their desired outcome is achieved. However, in the future, it may be possible for two or more implants in different parts of the brain to provide a direct neural feedback loop (see Box 2.5).

Practical applications of BCIs

2.63 At present, BCIs are primarily investigated with a view to being used to support individuals whose motor functions are severely impaired because of stroke, motor neurone disease, spinal cord injury, cerebral palsy, or similar conditions, to the extent of being entirely paralysed or having 'locked-in syndrome'.¹⁶⁸ Although, it is not yet clear to what extent patients who are

¹⁵⁹ Lebedev MA, Carmena JM, O'Doherty JE *et al.* (2005) Cortical ensemble adaptation to represent velocity of an artificial actuator controlled by a brain-machine interface *The Journal of Neuroscience* **25(19)**: 4681-93.

¹⁶⁰ Serruya MD, Hatsopoulos NG, Paninski L, Fellows MR and Donoghue JP (2002) Brain-machine interface: instant neural control of a movement signal *Nature* **416(6877)**: 141-2.

¹⁶¹ Velliste M, Perel S, Spalding MC, Whitford AS and Schwartz AB (2008) Cortical control of a prosthetic arm for self-feeding *Nature* **453(7198)**: 1098-101.

¹⁶² Kotchetkov IS, Hwang BY, Appelboom G, Kellner CP and Connolly ES, Jr. (2010) Brain-computer interfaces: military, neurosurgical, and ethical perspective *Neurosurg Focus* **28(5)**: E25, at page 2.

¹⁶³ *Ibid.*, at page 3.

¹⁶⁴ Cahn BR and Polich J (2006) Meditation states and traits: EEG, ERP, and neuroimaging studies *Psychological Bulletin* **132(2)**: 180-211.

¹⁶⁵ Leuthardt EC, Schalk G, Roland J, Rouse A and Moran DW (2009) Evolution of brain-computer interfaces: going beyond classic motor physiology *Neurosurgical Focus* **27(1)**: 1-21, pp. 5-6; Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* **2**: 187-99, at page 189.

¹⁶⁶ Tanaka K, Matsunaga K and Wang HO (2005) Electroencephalogram-based control of an electric wheelchair *IEEE Transactions on Robotics*, **21(4)**: 762-6.

¹⁶⁷ Coyle D, Carroll A, Stow J *et al.* (2012) Enabling Control in the minimally conscious state in a single session with a three channel BCI. In 1st international DECODER Workshop, (Paris: 1st international DECODER Workshop).

¹⁶⁸ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4(3)**: 1-22, at page 2.

wholly locked-in can be assisted by BCIs.¹⁶⁹ Therapeutic applications of BCIs offer users access to means of communication, independent locomotion and increased control over their environment. Their use, therefore, has the potential to improve users' quality of life, independence and self esteem significantly.¹⁷⁰

- 2.64 Therapeutic uses of BCIs are still at an investigative stage due to the significant technical support generally needed for users to learn to operate them. This means that their practical uses are, for the most part, limited to research environments.¹⁷¹ However, some more basic EEG-based devices are marketed directly to consumers for recreational and putatively educational purposes by healthy users (see Chapter 8). In this section, we outline only some of the most promising therapeutic applications of BCIs emerging in research and experimental settings. As we have noted, most research into therapeutic applications of BCIs to date are conducted using non-invasive EEG-based devices.¹⁷²

Applications of invasive BCIs

- 2.65 Invasive BCIs have only been used in investigative settings, with much of this research involving non-human primates (see Box 2.4). However, research is being conducted increasingly with human subjects. The first study to implant shaft electrodes into the motor cortex in a human was published in 2000. In this study, a patient, who had suffered a stroke resulting in paralysis, was able to learn to move a cursor on a computer screen by thinking about various movements (initially movements of his hand).¹⁷³ Eventually, no abstraction (using imagined hand movement) was needed; the patient was able to move the cursor simply by thinking about doing so. This permitted him to carry out tasks using the computer, including writing.¹⁷⁴ Another research subject was able to operate connected technology (for example, a light switch).¹⁷⁵ Subsequent clinical studies using a flat array implanted in the motor cortex region of the brain have enabled users with tetraplegia to operate robotic arms to pick up and manipulate objects.¹⁷⁶ One user was able to lift a coffee cup and drink independently through a straw.¹⁷⁷ A recent study reported that, for the first time, a human participant had performed better than non-human primates in research activities such as these.¹⁷⁸ The user's ease of manipulation of the device in this study may be due to the use of a 'shared control' function – meaning that the robot arm's movement is determined not only by the user's intentions (derived from their brain signals) but also by additional environmental information collected by the BCI, for example about the robot's position.¹⁷⁹

¹⁶⁹ Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* **2**: 187-99, at page 192.

¹⁷⁰ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4(3)**: 1-22, at page 5.

¹⁷¹ *Ibid*, at page 7.

¹⁷² Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* **2**: 187-99, at page 189.

¹⁷³ Kennedy PR, Bakay RA, Moore MM, Adams K and Goldwaithe J (2000) Direct control of a computer from the human central nervous system *IEEE Transactions on Rehabilitation Engineering*, **8(2)**: 198-202

¹⁷⁴ Kennedy PR, Kirby MT, Moore MM, King B and Mallory A (2004) Computer control using human intracortical local field potentials *IEEE Transactions on Neural Systems and Rehabilitation Engineering* **12(3)**: 339-44.

¹⁷⁵ Kennedy P, Andreasen D, Ehirim P *et al.* (2004) Using human extra-cortical local field potentials to control a switch *Journal of Neural Engineering* **1(2)**: 72-7.

¹⁷⁶ Donoghue JP, Nurmikko A, Friehs G and Black M (2004) Development of neuromotor prostheses for humans *Supplements to Clinical neurophysiology* **57**: 592-606.

¹⁷⁷ Hochberg LR, Serruya MD, Friehs GM *et al.* (2006) Neuronal ensemble control of prosthetic devices by a human with tetraplegia *Nature* **442(7099)**: 164-71; Hochberg LR, Bacher D, Jarosiewicz B *et al.* (2012) Reach and grasp by people with tetraplegia using a neurally controlled robotic arm *Nature* **485(7398)**: 372-5.

¹⁷⁸ Collinger JL, Wodlinger B, Downey JE *et al.* (2012) High-performance neuroprosthetic control by an individual with tetraplegia *The Lancet* **381(9866)**: 557-64.

¹⁷⁹ Courtine G, Micera S, DiGiovanna J and del R Millán J (2013) Brain-machine interface: closer to therapeutic reality? *The Lancet* **381(9866)**: 515-7, at page 516.

Box 2.5: Invasive BCIs in the peripheral nervous system

In 2002, the 100 electrode BrainGate array was implanted into the peripheral nervous system (at the wrist) of Professor Kevin Warwick at the Radcliffe Hospital, Oxford. Through the implant, Professor Warwick was able to use neural signals to operate various pieces of technology directly (e.g. driving a wheelchair and controlling the grip of a robot hand, obtaining realisable feedback from the fingertips via the same implant). As part of the experimentation, Professor Warwick's nervous system was plugged into the internet in Columbia University, New York and he controlled a robotic hand in England by using feedback.¹⁸⁰ The same type of implant was subsequently, used in the kinds of studies referred to in paragraph , this time planted in the neural cortex of participants.

Electrodes implanted in the peripheral nervous system have also been used to investigate bi-directional interfacing through a single implant source. Studies carried out in this way using a human subject have shown how motor signals can be used to control a robot hand with direct sensory feedback being provided through the implant to indicate the force directly applied by the hand.¹⁸¹

Applications of non-invasive (EEG-based) BCIs

- 2.66 Three broad categories of clinical applications of BCIs using EEG have been identified: assistive technologies – for example to support communication, movement control, environmental control and locomotion; neurorehabilitation; and the potential detection of awareness in patients with severe brain damage.
- 2.67 **Assistive technologies:** Restoring communication in locked-in patients has, so far, been the main focus of BCI research.¹⁸² Several types of EEG-based systems have been explored and those using three kinds of brain signals have been used in research with human participants.¹⁸³ These have used slow cortical potential, sensorimotor rhythms, and P300 event-related potential (ERP) signals. BCIs that rely on the first two of these categories of signals require the user to actively control their brain activity, for example by imagining movement, to produce signals that can then be translated into, for example, the movement of a cursor on a screen. The third kind of signal is 'passively' produced by the brain in response to significant stimuli. Thus, for example, BCIs that rely on these might allow a user to spell a word on a computer by recording the P300 ERP signals that are produced by the user's brain when they recognise the letter they wish to select from a randomly presented display.¹⁸⁴
- 2.68 Several studies have been published which investigate the development of an EEG-based BCI-controlled wheelchair for paralysed individuals.¹⁸⁵ BCI-driven wheelchairs carry intrinsic safety concerns because of the risk of injury if control is lost.¹⁸⁶ Further work is needed to establish their practical safety and utility. Methods of 'shared control principle' are being explored to provide added usability in circumstances where precise (and therefore potentially demanding) control of a device such as a wheelchair would be required.¹⁸⁷ This principle involves the user

¹⁸⁰ Warwick K, Gasson M, Hutt B *et al.* (2003) The application of implant technology for cybernetic systems *Archives of Neurology* **60(10)**: 1369-73.

¹⁸¹ *Ibid.*

¹⁸² Kubler A, Kotchoubey B, Kaiser J, Wolpaw JR and Birbaumer N (2001) Brain-computer communication: unlocking the locked in *Psychological Bulletin* **127(3)**: 358-75.

¹⁸³ Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* **2**: 187-99, at page 193.

¹⁸⁴ *Ibid.*, at page 193.

¹⁸⁵ Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Rev Biomed Eng* **2**: 187-99; Tanaka K, Matsunaga K and Wang HO (2005) Electroencephalogram-based control of an electric wheelchair *IEEE Transactions on Robotics*, **21(4)**: 762-6.

¹⁸⁶ Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* **2**: 187-99, pp.196-7.

¹⁸⁷ Millan JDR, Renkens F, Mourino J and Gerstner W (2004) Noninvasive brain-actuated control of a mobile robot by human EEG *IEEE Transactions on Biomedical Engineering* **51(6)**: 1026-33.

producing high-level commands and the computer undertaking low-level commands needed to execute these instructions.¹⁸⁸

- 2.69 It is envisaged that, by affording means for controlling their environment, BCI technology could be applicable to individuals who have severe motor disabilities and are housebound. A study involving both healthy users and those with severe motor disabilities indicated that, using EEG-based interfaces, users were able to operate household devices (including lights, a front-door opener and a motorised bed) in a simulated home environment with an average of 60-75 per cent accuracy.¹⁸⁹
- 2.70 Movement control is another key area for EEG research. Having learnt how to control an electrically-driven hand orthosis (an externally applied brace) using EEG signals, a tetraplegic user was then able to open and close his paralysed hand using this orthosis.¹⁹⁰
- 2.71 **Neurorehabilitation:** There is interest in the use of BCI systems to help ‘relearn’ motor function in those individuals in whom this has been impaired by disease or injury.¹⁹¹ BCI-assisted neurorehabilitation makes use of the individual’s own muscles (in contrast to those noted in paragraph 2.67 to 2.70 above, which make use of a device to carry out the action). One mechanism of BCI-based neurorehabilitation uses EEG to record brain signals (for example, those associated with limb movement) and feed these back to the user, thus affording the opportunity for them to modulate their brain activity. This has assisted stroke patients to gain control over specific brain activity.¹⁹² Another type of approach uses robotics to assist the movement of, for example, a limb – on the basis that such movement will lead to improved independent user control of that movement.¹⁹³ EEG has also been used to enable a quadriplegic participant to learn to carry out simple hand movement tasks by means of stimulation through embedded nerve controllers.¹⁹⁴
- 2.72 **Detection of awareness:** Early studies suggest that EEG might be used to detect awareness in patients for whom it is not otherwise possible to ascertain whether, for example, they are in a minimally conscious state or are ‘locked-in’ but retain cognitive functions. In these studies, participants are asked to imagine moving parts of their bodies in order to move an onscreen icon towards a target.¹⁹⁵ It has been suggested that inferences of, for example, a participant’s capacity to understand language or maintain attention, might be drawn cautiously from the percentage of successfully-guided icons.¹⁹⁶ Real-time sensory feedback is thought to be

¹⁸⁸ Luna P (2011) Controlling machines with just the power of thought *Lancet Neurology* **10(9)**: 780-1, at page 2.

¹⁸⁹ Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* **2**: 187-99. [Original study is reported in Cincotti F, Mattia D, Aloise F *et al.* (2008) Non-invasive brain-computer interface system: towards its application as assistive technology *Brain Research Bulletin* **75(6)**: 796-803]. The participants in this study had spinal muscular atrophy or Duchenne Muscular Dystrophy.

¹⁹⁰ Pfurtscheller G, Muller-Putz G, Schlogl A *et al.* (2006) 15 years of BCI research at Graz university of technology: current projects *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, **14(2)**: 205-10.

¹⁹¹ Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* **2**: 187-99, at page 197.

¹⁹² Prasad G, Herman P, Coyle D, McDonough S and Crosbie J (2009) Using motor imagery based brain-computer interface for post-stroke rehabilitation. In 4th International IEEE/EMBS Conference on Neural Engineering, 2009. NER '09. , Akay M, ed. (Antalya, Turkey: 4th International IEEE/EMBS Conference on Neural Engineering), pp. 258-62.; Ang KK, Guan C, Chua KSG *et al.* (2011) A large clinical study on the ability of stroke patients to use an EEG-based motor imagery brain-computer interface *Clinical EEG and Neuroscience* **42(4)**: 253-8 Caria A, Weber C, Brötz D *et al.* (2011) Chronic stroke recovery after combined BCI training and physiotherapy: a case report *Psychophysiology* **48(4)**: 578-82; Ang KK, Guan C, Chua KSG *et al.* (2011) A large clinical study on the ability of stroke patients to use an EEG-based motor imagery brain-computer interface *Clinical EEG and Neuroscience* **42(4)**: 253-8.

¹⁹³ Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* **2**: 187-99, at page 197.

¹⁹⁴ Cochlin University of Science and Technology (2008) *Brain-computer interface*, available at: <http://www.123seminaronly.com/Seminar-Reports/006/28708676-Brain-Computer-Interface.pdf>.

¹⁹⁵ Coyle D, Carroll A, Stow J *et al.* (2012) Enabling Control in the minimally conscious state in a single session with a three channel BCI. In 1st international DECODER Workshop, (Paris: 1st international DECODER Workshop).; Cruse D, Chennu S, Chatelle C *et al.* (2011) Bedside detection of awareness in the vegetative state: a cohort study *The Lancet* **378(9809)**: 2088–94.

¹⁹⁶ Cruse D, Chennu S, Chatelle C *et al.* (2011) Bedside detection of awareness in the vegetative state: a cohort study *The Lancet* **378(9809)**: 2088–94. Claims made by Cruse *et al* are queried in Goldfine AM, Bardin JC, Noirhomme Q *et al.* (2013) Reanalysis of “Bedside detection of awareness in the vegetative state: a cohort study” *The Lancet* **381(9863)**: 289-91.

particularly important for engaging and encouraging participants with impaired consciousness in these activities.

Reported technology risks and unintended consequences of BCIs

- 2.73 A recent review of BCI technologies observed that there are few studies which are investigating the unintended effects of regular BCI use on the brain, and that there is little consensus amongst researchers about what the unintended risks (or benefits) might be.¹⁹⁷ Here we provide a brief overview of the unintended risks or benefits raised most frequently.
- 2.74 The advantages invasive and partially invasive BCIs offer in terms of the accurate acquisition of brain signal are accompanied by several disadvantages that make them unsuitable, at present, for long-term therapeutic use.¹⁹⁸ Specifically, because they are implanted in brain tissue, they cause local neural and vascular damage and introduce an increased risk of infection. This damage also tends to precipitate reactions in other brain cells, which can cluster around the electrode interfering with the reliable acquisition of signals.¹⁹⁹ The invasive nature of the procedure also precludes easy repositioning of electrodes in response to evidence of locations that would permit better control of the device by the user.²⁰⁰ In common with other interventions using implanted electrodes, there are risks associated with neurosurgery (see paragraph 2.52) and risks of connecting wires acting as aerials and interfering with the operation of the device.²⁰¹ Interference and errors in interpretation of brain signals may cause difficulties for users which may be particularly acute for locked-in users, where there are no secondary means (for example eye blinks) by which it may be ascertained whether the operation of a device represents their actual intentions.²⁰²
- 2.75 With regards to non-invasive EEG-based BCIs there may be a risk due to the inherent plasticity of the brain, of changing brain structure and functioning since these BCIs employ a highly repetitive use of certain pathways. However, in assessing this as a risk, it should be borne in mind that any kind of external influence, such as learning a new skill, can bring about such changes.²⁰³ As we note at paragraph 2.58, one current disadvantage of non-invasive EEG-based BCIs is the time and effort that users must invest in learning how to generate motor imagery signals that will control a device. The performance of users is affected by fatigue (sometimes caused by the significant demand on the user's attention), distraction and the progression of any underlying illness. A key aim of BCI research is to achieve more efficient ways of controlling devices.²⁰⁴

¹⁹⁷ Future-BNCI (2012) *Future BNCI: a roadmap for future directions in brain / neuronal computer interaction research*, available at: http://future-bnci.org/images/stories/Future_BNCI_Roadmap.pdf, at page 181.

¹⁹⁸ Guger C, Bin G, Gao X *et al.* (2011) State of the art in BCI research: BCI award 2010, in *Recent Advances in Brain-Computer Interface Systems*, R. F-R (Editor) (Online: InTech); Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* **2**: 187-99, at page 196.

¹⁹⁹ Leuthardt EC, Schalk G, Roland J, Rouse A and Moran DW (2009) Evolution of brain-computer interfaces: going beyond classic motor physiology *Neurosurgical Focus* **27(1)**: 1-21, at page 5.

²⁰⁰ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4(3)**: 1-22, at page 8.

²⁰¹ Spiers A, Warwick K, Gasson M and Ruiz V (2006) Issues impairing the success of neural implant technology *Applied Bionics and Biomechanics* **3(4)**: 297-304.

²⁰² Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4(3)**: 1-22, at page 9.

²⁰³ *Ibid.*, pp.6-7.

²⁰⁴ Daly I, Nasuto SJ and Warwick K (2011) Single tap identification for fast BCI control *Cognitive neurodynamics* **5(1)**: 21-30; G. Prasad, McGinnity TM, Leng G and Coyle D (2010) On-line identification of self-organizing fuzzy neural networks for modelling time-varying complex systems, in *Evolving intelligent systems: methodology and applications*, Angelov P, Filev DP, and Kasabov N (Editors) (Hoboken, New Jersey: Wiley-IEEE Press).

Neural stem cell therapies

General principles

2.76 Stem cells are of interest for regenerative medicine because they have the potential to regenerate tissue lost as a consequence of disease or injury. This tissue loss can be acute, as when someone has a stroke, or it can be chronic, as with slow degenerative disease such as Parkinson's disease or Alzheimer's disease. These are the most disabling of disorders, yet current therapies are able to do little to restore lost brain cells. Since stem cells have the capacity to generate neural cells, it is possible they could be used to engineer a replacement of the lost cells, a so-called 'neuron replacement therapy' (NRT). There are multiple types of stem cell (see Box 2.6), each with different potentials, but many stem cells can generate neural cells, and so could, in theory, be used for this approach to brain repair.

Box 2.6: Types of stem cells

Stem cells are defined as cells with two seminal properties. First, they have the potential to generate a range of other cell types. Second, they are self-replicative, that is they have the capacity to generate more stem cells like themselves. There are multiple types of stem cells, and they are classified according to the range of cell types they can generate, and their origin.²⁰⁵

Adult stem cells (or somatic stem cells) are found in the mature organism. They are referred to as 'multipotential' because they can generate all the different cell types that make up a tissue (although, in specific cases, the actual range of cell types they generate might be quite limited). So, for example, bone marrow stem cells generate all blood cell types: red blood cells, lymphocytes, macrophages, etc. They are self-replicative, which ensures that the stem cell population itself does not become depleted. This is important because the capacity to generate blood is crucial for the entire lifetime of the organism. Other examples of adult stem cells are found in the skin, connective tissue, blood vessels, and the nervous system.²⁰⁶

Embryonic stem cells (ES cells) are derived from embryos. They differ from adult stem cells in a number of important regards. First, they are 'pluripotent', that is they can generate all the different types of cells in the body. Second, they are artificial in the sense that they only exist stably in tissue culture. Pluripotent cells in the embryo itself are transient. An important breakthrough in stem cell biology was the discovery of technologies to keep these cells perpetually in culture.²⁰⁷

Induced pluripotent cells (iPSCs) are indistinguishable from ES cells in most regards. They are pluripotent and stable in culture. They differ, however, in being derived from adult cells. Using a technology called 'reprogramming', cells can be taken from skin, hair, or blood and changed into pluripotent stem cells.²⁰⁸ This discovery has transformed stem cell technology, since anyone's stem cells can effectively be created 'in a dish' from a simple tissue biopsy and without any need to manipulate embryos.

Therapeutic approaches and mechanisms of action

2.77 As we have noted (see paragraph 2.10), unlike blood and skin, the brain does not replace lost neurones naturally, except in two locations in the brain where there are resident stem cell populations (the hippocampus and the sub-ependymal zone) or where specific glial progenitor populations exist. Two possibilities arise for inducing neuron replacement: either endogenous brain stem cells could be induced to replace lost cells, possibly by treatment with drugs or electrical stimulation; or stem cells could be grafted into the damaged brain in the hope that they might generate new brain tissue. The first of these approaches is still at an early stage of development, but the engraftment strategy has a long history. As far back as the 1980s, neural cells were transplanted into damaged brain tissue (first of animals, then in patients) in attempts

²⁰⁵ Watt FM and Driskell RR (2010) The therapeutic potential of stem cells *Philosophical Transactions of the Royal Society B: Biological Sciences* **365(1537)**: 155-63.

²⁰⁶ NIH (7 June 2012) *What are adult stem cells?*, available at: <http://stemcells.nih.gov/info/basics/pages/basics4.aspx>.

²⁰⁷ Zhang SC, Wernig M, Duncan ID, Brustle O and Thomson JA (2001) In vitro differentiation of transplantable neural precursors from human embryonic stem cells *Nature Biotechnology* **19(12)**: 1129-33.

²⁰⁸ Takahashi K and Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors *Cell* **126(4)**: 663-76.

to relieve neurodegenerative conditions such as Parkinson's or Huntington's disease.²⁰⁹ The cells for these initial studies were not stem cells, but were taken from aborted human fetuses. Researchers took fetal midbrain cells and injected them into the brains of people with Parkinson's disease.²¹⁰ The efficacy of this approach remains controversial, but the early studies appeared to provide 'proof-of-concept' that patients improved clinically following this cellular therapy, and that injecting cells into the brain was apparently safe.

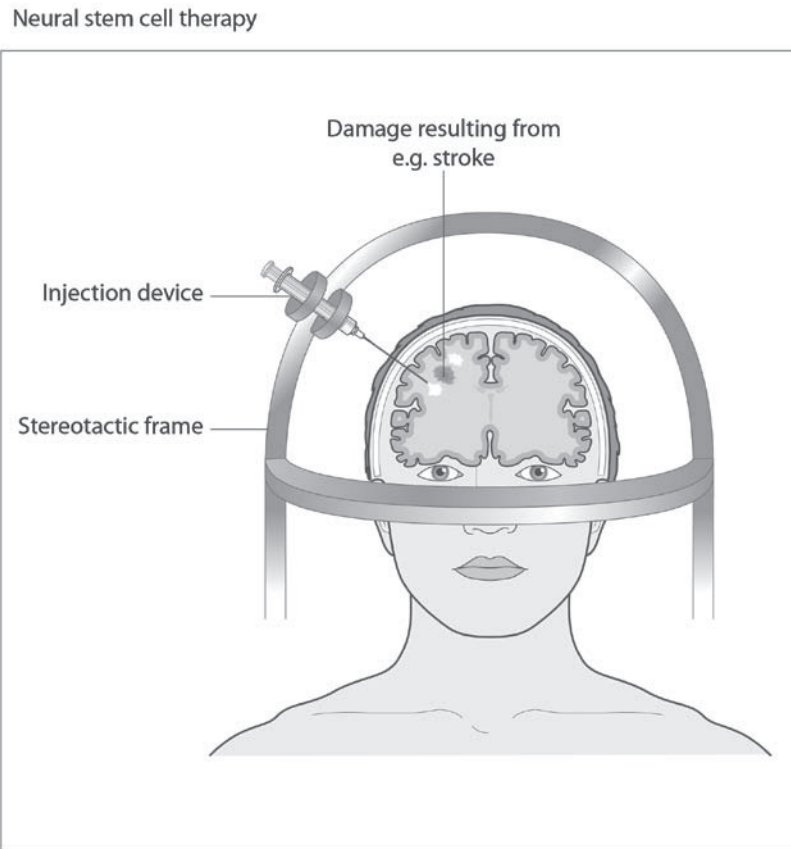


Figure 5: Neural stem cell therapy

2.78 However, these initial 'fetal grafts' were limited by variable outcomes, ethical concerns, and logistical difficulties. Furthermore, doubts about efficacy meant that, for some years, attention instead turned to gene therapy approaches.²¹¹ More recently, however, other sources of cells have emerged through the development of stem cell therapies for neurological conditions by a number of private companies. A small number of these therapies have either entered (or are close to entering) clinical trials.²¹² These involve human cells derived either from fetal brain, or somewhat surprisingly, other adult stem cell sources. Bone marrow stem cells, mesenchymal²¹³ stem cells, and olfactory stem cells are all in various stages of pre-clinical development.²¹⁴ No

²⁰⁹ Dunnett SB, Bjorklund A and Lindvall O (2001) Cell therapy in Parkinson's disease-stop or go? *Nature Reviews Neuroscience* **2**(5): 365-8.

²¹⁰ Ibid.

²¹¹ Eberhardt O and Schulz JB (2004) Gene therapy in Parkinson's disease *Cell and Tissue Research* **318**(1): 243-60.

²¹² Pollock K, Stroemer P, Patel S *et al.* (2006) A conditionally immortal clonal stem cell line from human cortical neuroepithelium for the treatment of ischemic stroke *Experimental Neurology* **199**(1): 143-55.

²¹³ These are stem cells derived from organ connective tissues that can differentiate into many but not all types of cell.

²¹⁴ Lindvall O and Kokaia Z (2010) Stem cells in human neurodegenerative disorders—time for clinical translation? *The Journal of Clinical Investigation* **120**(1): 29-40.

cells derived from pluripotent stem cells are currently in the clinic, but this development is clearly in progress.²¹⁵

- 2.79 In evaluating progress, it is useful to distinguish between various categories of potential neural stem cell therapies. The first wave of potential therapies have now either reached clinical trials or are in advanced pre-clinical phases.²¹⁶ These therapies are mostly derived from adult or foetal stem cells, either from the brain or another somatic tissue. These cells appear to have a very limited capacity for NRT, and their efficacy results from their ‘neurotrophic’ properties – that is, rather than predominantly replacing the lost cells in neural circuits, they work by *enhancing* the function of the cells that remain. Their mode of action, however, is not clear; they seem to have a ‘bystander’ effect, whereby they enhance capacity of the brain to repair, without themselves contributing cells to brain structure.²¹⁷ The cells also induce the host brain to make more blood vessels, to modulate its immune responses, and to augment the activity of the host’s own stem cell activity,²¹⁸ but precisely *how* these effects bring about efficacy is not resolved.
- 2.80 If this first wave of therapeutics confirms its initial promise, it is likely to be followed by subsequent developments in which these same cells (or others very like them) are reformulated to improve their performance. For example, neural stem cells can be combined with other components such as artificial matrices or other bioactive molecules to enhance and direct their integration into brain tissue.²¹⁹ Such ‘neuro-scaffolds’ are intrinsically more invasive, but could substantially enhance the therapeutic potential of stem cells. None of these approaches necessarily involve true NRT, but attempts to generate new neural tissue do continue – possibly with cells derived from pluripotential ES or iPS cells – in a genuine ‘regenerative medicine’ for the brain, and may well reach the clinic. However, these technologies will face logistical issues, all of which need to be overcome before these products can safely move from the laboratory bench to clinical practice. These include: how the founder cells will be collected and stored; determining the appropriate quality assurance criteria for such products; and delivering cells to an operating theatre in a controlled and timely fashion.

Current status of neural stem cell therapies

- 2.81 The collective terminology of ‘neural stem cell therapy’, which began with the relatively simple concept of neural cell replacement, has expanded into multiple approaches including those employing the bystander effect, whereby the brain’s own capacities for repair are enhanced, and other ill-defined modes of action. The first potential therapies are presently in Phase I clinical trials in stroke and spinal cord injury.²²⁰ The PISCES stroke trial is currently the most advanced in the UK. An interim report from this Phase I safety trial of fetal-derived human neural stem cells recently reported a modest but significant improvement in a number of clinical parameters in the first nine patients cohort treated.²²¹ These represent modest improvements in

²¹⁵ Robinton DA and Daley GQ (2012) The promise of induced pluripotent stem cells in research and therapy *Nature* **481(7381)**: 295-305; Okano H, Nakamura M, Yoshida K *et al.* (2013) Steps toward safe cell therapy using induced pluripotent stem cells *Circulation Research* **112(3)**: 523-33.

²¹⁶ For example: Neuralstem Inc (17 April 2013) *Neuralstem receives FDA approval to commence phase II stem cell trial in amyotrophic lateral sclerosis*, available at: <http://investor.neuralstem.com/phoenix.zhtml?c=203908&p=irol-newsArticle&ID=1807567&highlight=>; ReNeuron (2013) *Clinical trials in disabled stroke patients*, available at: <http://www.reneuron.com/the-piscs-clinical-trial-in-disabled-stroke-patients>.

²¹⁷ Lindvall O and Kokaia Z (2010) Stem cells in human neurodegenerative disorders—time for clinical translation? *The Journal of Clinical Investigation* **120(1)**: 29-40.

²¹⁸ Martino G, Bacigaluppi M and Peruzzotti-Jametti L (2011) Therapeutic stem cell plasticity orchestrates tissue plasticity *Brain* **134(6)**: 1585-7.

²¹⁹ Bible E, Chau DYS, Alexander MR *et al.* (2009) Attachment of stem cells to scaffold particles for intra-cerebral transplantation *Nature protocols* **4(10)**: 1440-53.

²²⁰ ReNeuron (2012) *ReNeuron receives DSMB clearance to progress to higher dose in stem cell clinical trial in disabled stroke patients: first patient treated in this higher dose cohort*, available at: <http://www.reneuron.com/press-release/reneuron-receives-dsmb-clearance-to-progress-to-higher-dose-in-stem-cell-clinical-trial-in-disabled-stroke-patients-first-patient-treated-in-this-higher-dose-cohort>.

²²¹ ReNeuron (28 May 2013) *Interim data from clinical trial of ReNeuron’s stem cell therapy for stroke to be presented at leading stroke conference. Longer term data continue to show good safety profile and evidence of sustained reductions in neurological impairment and spasticity*, available at: <http://www.reneuron.com/press-release/interim-data-from-clinical-trial-of>

limb motility and the ability to conduct activities associated with daily living. Evaluation of this positive outcome is difficult, however, since in this Phase I trial there was no control group and the extent of the placebo effect could not be assessed. This trial has reported no cell-related or immunological adverse events, which is broadly in line with the earlier ‘fetal graft’ studies. However, at present there is no way to know whether more long-term issues might arise.

- 2.82 The fact that the PISCES stroke study has reached clinical trials means that a number of the logistical problems (for example, demonstrating efficacy in a rodent model²²²) have been overcome to the satisfaction of regulators, though there may still be issues around the ‘scale-up’ required to generate enough product to treat a substantial number of patients. The extent to which the sponsors of these trials have a tractable business model also remains unresolved. The clinical data are currently very limited, so it is still too early to know whether these therapies will deliver effective forms of treatment. Nonetheless, should the safety profile remain encouraging, a Phase II trial (to evaluate effectiveness) is expected to commence in 2013. This will be a pivotal moment for stem cell therapies in the brain. We might also expect to see the start of the second wave of optimised or ‘better-engineered’ variants to follow. If these attempts fail, there will be a considerable disincentive to pursue more adventurous approaches.
- 2.83 The technical progress of true NRT is more difficult to map. It is likely to impact more fundamentally on brain structure, and thus be both more effective and more invasive. Pluripotent stem cells (ES and iPS cells) are potentially much more powerful than the ‘multipotential’ adult stem cells. Although multipotential neural stem cells can generate neurons and glia, they seem to have limited ability to build brain tissue *per se*; that is to generate all the appropriate cell types, in appropriate proportions, and combine them together to form functioning brain tissue. This seems to be why they are less useful for NRT than initially anticipated. If lost brain tissue is really to be reconstructed in, for example, a stroke patient, then this true histogenesis (the ability to develop into different kinds of tissues) will be required. Some biotechnologists anticipate that ES and iPSC cells may have this histogenic potential, in which case a true regenerative medicine of the brain might become a reality.²²³
- 2.84 No such advanced approach has yet gained regulatory approval for clinical trials, but several reports of preclinical studies suggest that such therapeutics are plausible. The likely first target is Parkinson’s disease. Investigators have enabled human pluripotent cells to generate dopaminergic neurons, which showed efficacy when grafted into animal models of Parkinson’s disease.²²⁴ Whether this approach will be taken to the clinic is currently unclear. This therapy would be an example of the simplest form of NRT—a single neuronal cell type inserted into host brain tissue. More ambitious therapies, combining multiple cell types, or even whole tissue regeneration, still seem some way off.

Technology-related risks

- 2.85 The technologies currently in clinical trials have identified risks. Once transplanted, the cells are difficult to remove. Unlike a conventional drug, stem cell treatment cannot simply be discontinued if side effects arise. In addition, the stem cells will have been engineered to allow them to expand in culture, but to stop growing in the host brain. If this switch fails, the cells

reuron-s-stem-cell-therapy-for-stroke-to-be-presented-at-leading-stroke-conference-longer-term-data-continue-to-show-good-safety-profile-and-evidence-of-sustained-reductions-in-neurologica.

²²² Pollock K, Stroemer P, Patel S *et al.* (2006) A conditionally immortal clonal stem cell line from human cortical neuroepithelium for the treatment of ischemic stroke *Experimental Neurology* **199**(1): 143-55.

²²³ Espuny-Camacho I, Michelsen KA, Gall D *et al.* (2013) Pyramidal neurons derived from human pluripotent stem cells integrate efficiently into mouse brain circuits in vivo *Neuron* **77**(3): 440-56. Due to their ability to form any of the tissue and organ cell types of the human body, as well as their ability to grow indefinitely, pluripotent stem cells may not be considered suitable for direct implantation. Instead a therapy would consist of derivatives of pluripotent cells.

²²⁴ Studer L (2011) Derivation of dopaminergic neurons from pluripotent stem cells *Progress in Brain Research* **200**: 243-63.

might start to regrow and form a tumour.²²⁵ Alternatively, if newly formed neurons are inadequately integrated into the host, they could become the foci of intractable pain²²⁶ or epileptic seizures.

- 2.86 More advanced technologies, as they emerge, could raise risks not limited to those affecting physical health. The brain, more than any other tissue, is associated with the characteristics and traits that make us the individuals that we are. We now know that there is enormous diversity between different individuals in terms of cortical areas and their connectivity, which raises the question as to how a piece of generic, reconstructed brain would fit within existing structures and connections. It has been suggested that it is not possible to rule out effects on behaviour, mood and cognition arising from neural stem cell grafts or newly-formed neurons.²²⁷ However, it should be noted that, if these were to occur, it is thought that this might follow from the unpredictable consequences of the growth of new neurons and the establishment of new neural networks, rather than the highly implausible importation of personality traits with a neural stem cell graft; such complex traits are not characteristics of individual cells.²²⁸

Delivering therapeutic applications

- 2.87 At the start of this chapter, we outlined the effects that brain damage may have on the individual, including loss of motor control, autonomic functions, memory or other cognitive functions, alterations in mood and behaviour, and the profound distress that may accompany these. Potential effects such as these provide reason enough to try to intervene to alter the brain therapeutically. However, our ability to treat such problems with conventional drugs or non-pharmacological rehabilitative therapies is limited, due in part to our incomplete understanding of underlying mechanisms in the brain, and also the increasingly apparent inadequacies of pharmaceutical interventions. Novel neurotechnologies offer new avenues for addressing conditions such as these and, if successful, may relieve considerable suffering either by offering symptomatic relief to patients or by restoring their means of interacting with the world around them; however, they do not yet offer life-saving treatment or cures.
- 2.88 As is clear from the descriptions of the four categories of novel neurotechnologies described in this chapter, their development is, to varying degrees, at investigatory stages: DBS and TBS are established techniques, though there is a drive to understand their potential applications beyond those conditions for which they are currently indicated, while neural stem cell therapies and assistive BCIs are still in their infancy. The current state of scientific understanding and technological capabilities of these technologies is only one part of delivering effective therapeutic interventions. Equally essential to their development is the resources and support to conduct basic research and to translate this into safe and practical applications that meet the needs of those living with neurological and mental health conditions. In the Chapter 3 we look at the role of economic drivers and obstacles to the development of novel neurotechnologies and consider the forces that shape these.

²²⁵ Goldring Chris EP, Duffy Paul A, Benvenisty N *et al.* (2011) Assessing the safety of stem cell therapeutics *Cell Stem Cell* **8(6)**: 618-28, at page 620.

²²⁶ Hofstetter CP, Holmström NA, Lilja JA *et al.* (2005) Allodynia limits the usefulness of intraspinal neural stem cell grafts; directed differentiation improves outcome *Nature Neuroscience* **8(3)**: 346-53, at page 346.

²²⁷ Duggan PS, Siegel AW, Blass DM *et al.* (2009) Unintended changes in cognition, mood, and behavior arising from cell-based interventions for neurological conditions: ethical challenges *American Journal of Bioethics* **9(5)**: 31-6.

²²⁸ *Ibid.*, at page 33.

Chapter 3

Economic drivers of
innovation

Chapter 3 - Economic drivers of innovation

Chapter 3 - overview

There are few effective treatments for many serious neurological and mental health disorders and therefore a significant degree of unmet need. Moreover, the high global incidence of these disorders generates considerable costs to national economies, not only through direct health care costs but also in lost productivity. The novel neurotechnologies we consider in this report offer potential routes to meeting these needs, but pathways to innovative and effective treatments must negotiate ethical and economic challenges.

Economic factors present both opportunities and constraints that shape the innovation pathways of novel neurotechnologies. This is especially so because even where initial research is publically funded, development of research into clinical products will often depend on commercial organisations with obligations to generate profits and shareholder value. For a number of reasons, therefore, it cannot be assumed that this putative area of economic opportunity will translate directly into the provision of therapeutic products where need is most pressing.

Private companies and investors are likely to focus on technologies that offer the greatest potential for financial return on investment, thus favouring those that target large or valuable markets. This threatens to divert investment away from potentially less profitable 'low tech' approaches to care, or treatments to address rarer neurological conditions. It may also leave the needs of those in less affluent parts of the world ill-served. Further challenges to equitable access arise from the fact that, even if the early production costs of the neurotechnologies fall, the wider costs of specialist care associated with their use will remain high in many cases. This raises the further risk that patients might travel to access more affordable treatment in countries with potentially less well-regulated systems of protection.

Large pharmaceutical companies might seem to be potential sources of investment in the field of novel neurotechnologies, when the limits of public funding are reached. However, their recent withdrawal from psychopharmaceutical research suggests that they have been discouraged by the complexity and costs of developing effective neurological interventions. The long, complex and costly development and regulatory pathways (associated with innovation in stem cell based technologies in particular) can be seen as economically too risky by private investors, such as venture capitalists, who look for swift returns on their investment. The development pathways of many novel neurotechnologies are, therefore, vulnerable to the 'valley of death' – where (often small) businesses fail due to a lack of funding to support them through the lengthy process of translating research into commercially viable products.

These kinds of challenges in obtaining funding can impose particular pressures on developers to pursue practices that secure greater market share and swifter returns on investment, but (in the field of medical devices in particular) they might also shape innovation pathways and practices in ways that do not best meet patients' needs for access to safe and effective therapies. These practices might include: exploiting regulatory routes that do not require manufacturers to conduct clinical investigations prior to placing their device on the market; developing therapeutically superfluous consumable elements of otherwise reusable devices; engaging in patent disputes to impede competitors; or offering incentives to clinicians to trial particular products, thus introducing potential conflicts of interest.

The economic drivers and constraints on the development of novel neurotechnologies highlight the ethical importance of proportionate regulatory oversight that encourages innovation, but which helps direct responsible research, development and investment towards the production of safe and effective products that meet genuine patient needs. However, effective regulation alone is unlikely to be sufficient to secure equitable access to affordable therapies; incentives for innovative and responsible research, and funding mechanisms to support lengthy development trajectories, will also be needed.

Background

- 3.1 This chapter describes some of the economic factors that shape the development and deployment of novel neurotechnologies for therapeutic purposes. We suggest that these economic factors produce both opportunities for, and constraints upon, the development of novel neurotechnologies, and can in some circumstances provide perverse incentives, directing the pathways of development in ways that do not match the needs of health services, or of patients.
- 3.2 We begin by locating these economic factors in relation to estimates of need, by considering the prevalence of those conditions that these new technologies might treat or ameliorate. These conditions clearly indicate the considerable degree of what is often termed 'unmet need', that is to say, the prevalence of many widespread neurological and mental health conditions that are not yet adequately addressed by available therapeutic options. This also suggests that there is

a potentially large market for innovative neurotechnologies to address these conditions, and that the kinds of technologies that we are considering in this report might have an important part to play although, as we discuss, it would be a mistake to think that this is simply a matter of providing better technological solutions. We consider the ways in which novel neurotechnologies might be brought from the laboratory – where research is often publicly funded – into therapeutic practice, a process of product development that is largely, if not exclusively, undertaken in the private and for profit sector.

- 3.3 After a general account of the ‘political economy’ of the neurotechnology industry, we consider three interrelated issues. First, do the characteristics of the market encourage or inhibit the development of innovative and effective neurotechnologies to the stage where they are available to those who need them? Here we suggest that there are major hurdles that have to be overcome if a truly innovative neurotechnology industry is to flourish. These differ among the various neurotechnologies considered in this report, and pose particular issues for the commercialisation of therapies involving neural stem cells. Second, are there characteristics of the market that drive the development of valuable neurotechnologies in ways that do not best meet the interests of prospective patients in receiving safe and effective therapies? We suggest that there are indeed a number of troubling practices, though many of these may not be unique to neurotechnological innovation. Third, we ask whether the market form itself generates ethical dilemmas concerning who will have access to the products of innovation. Here, we point in particular to the familiar gulf between promises and delivery that characterise this area, and highlight key issues of equity and justice.

Economic drivers and access to therapies

- 3.4 Why should a report on the ethical and social issues entailed in novel neurotechnologies that intervene in the brain give an important role to these economic considerations? There are a number of reasons, and we introduce them briefly in the following paragraphs.
- 3.5 Research and development in this area, as in the contemporary life sciences more generally, takes place within a global bioeconomy,²²⁹ where research and product development is shaped by decisions that are made by public and private actors about investment priorities.²³⁰ Given the “path dependent” character of knowledge production and product development, these decisions shape patterns of research and development in a quite fundamental way.²³¹ Such decisions are, of course, not based simply on an assessment of the scientific elegance or excellence of the research. They are made, explicitly or implicitly, on the basis of assumptions and expectations as to which problems are most important or exciting to explore (and which are either less important or less amenable to solution), which pathways are likely to be most productive, which outcomes are likely to be of most benefit, and so forth.²³² In the field of biomedical research, those expectations and anticipations could lead to public funding bodies giving priority to supporting the investigation of particular problems or diseases at the expense of others,²³³ and to particular solutions rather than others. Where research is funded by commercial companies or venture capitalists, decisions are shaped by expectations as to the research and development that will deliver products – or shareholder value – to ensure a return on capital

²²⁹ Rose quotes the OECD definition of the bioeconomy as ‘that part of economic activities “which captures the latent value in biological processes and renewable bioresources to produce improved health and sustainable growth and development.”’ Rose N (2007) *The politics of life itself: biomedicine, power, and subjectivity in the twenty-first century* (NJ: Princeton University Press), p32. Original can be found at <http://www.oecd.org/futures/long-termtechnologicalsocietalchallenges/thebioeconomyto2030designingapolicyagenda.htm>.”

²³⁰ Ibid, at page 80.

²³¹ See: Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, pp.18-9.

²³² Rose N (2007) *The politics of life itself: biomedicine, power, and subjectivity in the twenty-first century* (NJ: Princeton University Press), pp 31-39.

²³³ Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf.

invested within a specific timeframe. These expectations may lead to an emphasis on high-tech, product-based solutions to tractable problems, where intellectual property rights (IPR) may be exploited and where the market is large and sufficiently resourced, rather than on low-tech, more affordable, but less profitable solutions; or, more complicated and risky explorations of potential solutions to more difficult problems.

- 3.6 Where investment is at stake, and potential profits are to be achieved, the emphasis on translation and commercialisation may generate the appetite for innovation that is needed if new products are to be created that would effectively address market demands; that is to say, the demands of those with needs for treatments that will alleviate their conditions.²³⁴ But it may also lead to premature claims about likely benefits, and this is especially significant where products are sold directly to consumers. Further, even where research in a laboratory situation seems to show that a particular invention may generate significant therapeutic benefits, and early stage finance is obtained to create a small commercial company to develop the product, there are many financial hurdles to overcome in bringing it to market. These include crossing the gulf between obtaining relatively small sums of short term funding for small scale research and development and obtaining much larger and longer term funding to scale up to commercial development (see paragraphs 3.41 to 3.47).²³⁵ Indeed, it has been suggested that private investors are increasingly interested in companies with products in later stage development, where the required funding may be greater but the risks are smaller.²³⁶
- 3.7 In this chapter, we also comment on a number of other potentially problematic issues arising from the political economy on novel neurotechnologies, which threaten the pursuit of responsible research and innovation practices. These issues include the incentive for manufacturers of devices to utilise any available means to speed products through the regulatory system and onto the market (see paragraphs 3.55 to 3.59), given the need to show a return on investment and the limited periods of market exclusivity afforded by many intellectual property rights. Other issues that have been raised in relation to medical devices in general, but which also may have implications for neurotechnologies specifically, include potential financial links and close relationships between manufacturers and clinicians who play a role in the uptake of technologies and in reporting on the results of their clinical use (see paragraphs 3.66 to 3.70).²³⁷
- 3.8 By exploring the nature of the economic drivers and constraints that operate on the development pathways of novel neurotechnologies, the kinds of challenges that must be confronted if innovation is to deliver access to safe, effective and affordable therapies can be appreciated. In order to understand more fully the ethical and social challenges posed by the aspects of the political economy outlined above, we first need to examine commercial imperatives that surround the development of novel neurotechnologies and the problems of securing sufficient investment to support their translation from basic research to marketable products, particularly where innovation trajectories entail uncertain risks and target markets may be small or otherwise less lucrative.

Assessing need

- 3.9 We argue here that there is a great and urgent need for innovative approaches to address the multiple problems of neurological disorders, and to develop better therapeutic approaches to tackle many mental health disorders that are currently inadequately treated by psychopharmaceuticals. Obtaining a clear picture of what this need looks like at a local and

²³⁴ In the area of pharmaceuticals, commercial incentives can stimulate imitation rather than innovation, as in the creation of 'me too' drugs to tap into a market that has already been opened by the products produced by a rival manufacturer.

²³⁵ House of Commons Science and Technology Committee (2013) *Bridging the valley of death: improving the commercialisation of research*, available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/348/348.pdf>.

²³⁶ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 374.

²³⁷ Wilmshurst P (2011) The regulation of medical devices *British Medical Journal* **342:d2822**.

global level and assessing to what extent novel neurotechnologies might realistically address the needs of various groups, however, can be difficult. In this section, we bring together the available evidence to outline the extent of need.

3.10 We begin by considering some recent estimates of the economic cost (conventionally termed ‘burden’) of brain disorders. The term ‘burden’ is used to describe not only the actual economic cost of treating those affected by these conditions but also other associated costs, for example those of welfare payments and loss of productivity. These figures should be treated with caution for a number of reasons:

- figures often include many conditions that are not currently considered as potentially treatable by novel neurotechnologies;
- the term brain disorders has come to be used by some bodies to cover both mental health and neurological disorders – misleadingly implying that the only pathway to therapy for conditions from anxiety to addiction²³⁸ lies in acting on the brain; and
- the estimates are often generated by organisations that have an interest in overestimation, because large numbers can be used rhetorically to stress the need for further investment in their own area of research. We observe below how such figures are deployed by neurotechnology market research companies (see paragraphs 3.18 to 3.20).

Indeed, without underplaying the significance of these estimates, we also note that they aim to have ‘performative’ consequences through shaping the direction of policy and investment. It is therefore unsurprising that, while some claim that these figures highlight the urgent need for action, others argue that they tend to overestimate necessary levels of public investment.²³⁹

3.11 Estimates of the economic cost of neurological diseases and mental health disorders vary widely. In 2001, the World Health Organization (WHO), perhaps set the pattern for subsequent estimates of previously under-recognised worldwide prevalence of mental health disorders in its report *Mental health: new understanding, new hope*. The report stated:

“By the year 2020, if current trends for demographic and epidemiological transition continue, the burden of depression will increase to 5.7 per cent of the total burden of disease, becoming the second leading cause of DALYs (disability adjusted life years) lost. Worldwide it will be second only to ischemic heart disease for DALYs lost for both sexes. In the developed regions, depression will then be the highest ranking cause of burden of disease.”²⁴⁰

Furthermore, in 2007, the WHO estimated that 6.8 million people die every year as a result of a neurological disorder, and that up to one billion people worldwide are affected.²⁴¹

3.12 There have also been a series of other reports by NGOs, professional organisations and commercial companies, many of which attempted to estimate the cost of such disorders. For example, in 2002, the Society for Neuroscience estimated that the annual direct cost of

²³⁸ Gustavsson A, Svensson M, Jacobi F *et al.* (2011) Cost of disorders of the brain in Europe 2010 *European Neuropsychopharmacology* **21(10)**: 718-79, at page 720.

²³⁹ Estimates of the size and burden of psychiatric disorders have been particularly controversial, with disputes focused on the methodology of generating estimates. See: Regier DA, Kaelber CT, Rae DS *et al.* (1998) Limitations of diagnostic criteria and assessment instruments for mental disorders: implications for research and policy *Archives of General Psychiatry* **55(2)**: 109-20.

²⁴⁰ World Health Organization (2001) *The world health report 2001: mental health: new understanding, new hope*, available at: http://www.who.int/whr/2001/en/whr01_en.pdf, at page 30.

²⁴¹ World Health Organisation (2007) Neurological disorders affect millions globally, available at: <http://www.who.int/mediacentre/news/releases/2007/pr04/en/index.html>

neurological and mental health disorders in the US exceeded \$548 billion.²⁴² According to data compiled by the market research organisation NeuroInsights and the lobbying body Neurotechnology Industry Organization, the annual economic burden of brain-related illness in the US exceeds \$1.4 trillion.²⁴³ To put this into perspective, the American Cancer Society estimated the overall costs of cancer in the US in 2010 to be \$263.8 billion,²⁴⁴ while the economic burden of pre-diabetes and diabetes in the US in 2007 has been estimated at \$218 billion.²⁴⁵

- 3.13 A report by the European Brain Council (EBC) recently estimated the total cost of brain disorders in Europe to be €798 billion in 2010. Direct healthcare costs constituted 37 per cent (€295 billion) and 23 per cent (€183.5 billion) for direct non-medical costs. The remaining 40 per cent (€319 billion) were indirect costs associated with patients' production losses.²⁴⁶ Analogous estimates have been made in the US:²⁴⁷ according to estimates made in 2007, migraine was the most common neurological disorder in the US population affecting 35 million people. Stroke was the second most common neurological disorder and affected a total of 541,000 people each year (75% of whom were aged 65 or over) with a prevalence in the US population of 2,956,000. The next most common disorder was Alzheimer's disease with an annual incidence of 468,000, and almost 2.5 million people living with the disorder. Parkinson's disease affected 349,000 people, with 59,000 new cases each year.²⁴⁸
- 3.14 The figures for migraine are just one element in the more general 'empire of pain' that seems to affect so many in advanced industrial societies: thus the Medical Expenditure Panel Survey (MEPS) estimated that approximately 100 million adults in the US are affected by chronic pain, including joint pain or arthritis. The survey also estimated that persistent pain costs the US economy between \$560 and \$635 billion annually.²⁴⁹ Statistics published by the National Institutes of Health (NIH) state that the costs of persistent pain exceed the economic costs of the six most costly major diagnoses, namely cardiovascular diseases (\$309 billion), neoplasms (\$243 billion), injury and poisoning (\$205 billion), endocrine, nutritional and metabolic diseases (\$127 billion), digestive system diseases (\$112 billion), and respiratory system diseases (\$112 billion).²⁵⁰

²⁴² NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 35.

²⁴³ *Ibid.*, at page 35.

²⁴⁴ Christakis P (2011) Bicentennial: the birth of chemotherapy at yale: bicentennial lecture series: surgery grand round *Yale Journal of Biology and Medicine* **84(2)**: 169-72, at page 169.

²⁴⁵ Dall TM, Zhang Y, Chen YJ *et al.* (2010) The Economic burden of diabetes *Health Affairs* **29(2)**: 297-303.

²⁴⁶ Gustavsson A, Svensson M, Jacobi F *et al.* (2011) Cost of disorders of the brain in Europe 2010 *European Neuropsychopharmacology* **21(10)**: 718-79, at page 720.

²⁴⁷ The research was carried out by US National Institutes of Neurological Disorders and Stroke/National Institutes of Health and the National Center for Chronic Disease Prevention and Health & Promotion/Centers for Disease Control and Prevention.

²⁴⁸ Hirtz D, Thurman D, Gwinn-Hardy K *et al.* (2007) How common are the "common" neurologic disorders? *Neurology* **68(5)**: 326-37, at page 332.

²⁴⁹ Gaskin DJ and Richard P (2012) The economic costs of pain in the United States *The Journal of Pain* **8(13)**: 715-24, p715

²⁵⁰ *Ibid.*, at page 723.

Box 3.1: UK estimates for people affected by neurological and mental health conditions

We can make some rough estimates of the numbers of people in the UK that might benefit from the novel neurotechnologies that we discuss in this report.

- There are more than one million stroke survivors in the UK, 300,000 of which are living with moderate or severe disabilities.²⁵¹
- In the UK, 127,000 people are thought to have Parkinson's disease.²⁵²
- 800,000 are living with Alzheimer's disease and other forms of dementia.²⁵³
- 100,000 people have multiple sclerosis (MS).²⁵⁴
- Dystonia is thought to affect at least 70,000 people.²⁵⁵
- Epilepsy affects around 600,000 people. However, approximately one third of patients do not respond to medication, continuing to experience seizures.²⁵⁶
- Around 500,000 people (aged 16-74) live with long term disabilities as a result of traumatic brain injury.²⁵⁷
- Approximately 40,000 individuals in the UK are living with a traumatic spinal cord injury.²⁵⁸
- Four adults in every 100 over the age of 40 are affected by essential tremor.²⁵⁹
- One in 100 people are affected by Tourette's syndrome.²⁶⁰
- OCD affects approximately 12 people in 1,000.²⁶¹
- Approximately one in 1,000 experience cluster headaches.²⁶²
- About 12 people per 100,000 are affected by Huntington's disease.²⁶³
- 5,000 people are thought to have motor neurone disease.²⁶⁴
- Anorexia is thought to affect approximately 2,000 people in the UK.²⁶⁵
- In 2008-2009 4,211 weight loss procedures were carried out on the NHS.²⁶⁶
- It has been estimated that treatment-resistant depression – usually defined as when at least two trials with antidepressants from different pharmacologic classes do not produce a significant clinical improvement – occurs in 15-33 per cent of people with depression.²⁶⁷
- Neuropathic pain occurs in three to eight per cent of individuals in industrialised countries.²⁶⁸
- Chronic pain “of moderate to severe intensity” occurs in 13 per cent of adults in the UK and seriously affects the quality of their social and working lives.²⁶⁹

²⁵¹ BBC News Health (1 May 2012) *Stroke survivors "being denied best recovery chance"*, available at: <http://www.bbc.co.uk/news/health-17893433>.

²⁵² Parkinson's UK (2013) *What is Parkinson's?*, available at: <http://www.parkinsons.org.uk/about-parkinsons/what-is-parkinsons.aspx>.

²⁵³ Alzheimer's Society (2013) *What is dementia?*, available at: http://alzheimers.org.uk/site/scripts/documents_info.php?documentID=106.

²⁵⁴ NHS Choices (2012) Multiple sclerosis, available at: <http://www.nhs.uk/conditions/Multiple-sclerosis/Pages/Introduction.aspx>.

²⁵⁵ The dystonia society (2012) *About dystonia*, available at: <http://www.dystonia.org.uk/index.php/about-dystonia>.

²⁵⁶ Central Manchester University Hospital (2012) *Surgery boost for children with drug-resistant epilepsy*, available at: <http://www.cmfh.nhs.uk/media-centre/latest-news/surgery-boost-for-children-with-drug-resistant-epilepsy.aspx>.

²⁵⁷ The United Kingdom Acquired Brain Injury Forum (2004) *Prevalence*, available at: <http://www.ukabif.org.uk/information/data/55-prevalence>.

²⁵⁸ National Guidelines (2008) *Chronic spinal cord injury: management of patients in acute hospital settings*, available at: http://www.spinal.co.uk/userfiles/Professionals_Portal/RCP_SCI_Guidelines.pdf, at page 1.

²⁵⁹ NHS Choices (2011) *Tremor (essential)*, available at: [http://www.nhs.uk/conditions/Tremor-\(essential\)/Pages/Introduction.aspx](http://www.nhs.uk/conditions/Tremor-(essential)/Pages/Introduction.aspx).

²⁶⁰ NHS Choices (2011) *Tourette's syndrome*, available at: <http://www.nhs.uk/conditions/Tourette-syndrome/Pages/Introduction.aspx>.

²⁶¹ NHS Choices (2012) *Obsessive compulsive disorder*, available at: <http://www.nhs.uk/Conditions/Obsessive-compulsive-disorder/Pages/Introduction.aspx>.

²⁶² NHS Choices (2011) *Cluster headaches*, available at: <http://www.nhs.uk/conditions/cluster-headaches/Pages/Introduction.aspx>.

²⁶³ NHS Choices (2012) *Huntington's disease*, available at: <http://www.nhs.uk/conditions/Huntingtons-disease/Pages/Introduction.aspx>.

²⁶⁴ Motor Neurone Disease Association (2013) *Journalist's guide to MND*, available at: <http://www.mndassociation.org/news-and-events/news-room/journalists-guide-to-mnd>.

²⁶⁵ House of Commons Hansard (9 March 2009) *Parliamentary questions: eating disorders*, available at: <http://www.publications.parliament.uk/pa/cm200809/cmhansrd/cm090309/text/90309w0028.htm>.

²⁶⁶ National Institute of Clinical Excellence (2012) *New weight-loss operation: NICE encourages more research*, available at: <http://www.nice.org.uk/newsroom/pressreleases/NewWeightLossOperationNICEEncouragesResearch.jsp>. As noted at paragraph 2.54 above, there are studies investigating the use of DBS to treat obesity.

²⁶⁷ See, for example, Little A (2009) *Treatment-resistant depression* *American Family Physician* **80(2)**: 167-72.

²⁶⁸ Ashton JC and Milligan ED (2008) *Cannabinoids for the treatment of neuropathic pain: clinical evidence* *Current opinion in investigational drugs (London, England: 2000)* **9**: 65.

²⁶⁹ Based on 46,394 people within 15 European countries and Israel who took part: Breivik H, Collett B, Ventafriidda V, Cohen R and Gallacher D (2006) *Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment* *European Journal of Pain* **10(4)**: 287-333.

- 3.15 The figures we cite in Box 3.1 above can give only approximate figures for the numbers of people in the UK who are in need of access to effective treatments to ameliorate neurological and psychiatric disorders. These disorders are, at the very least, disruptive to their lives and the lives of their families and, at the most, are severely disabling, leading to incapacity and death. It is also clear that these conditions have major social and economic consequences, although as we have noted, estimates of the costs of such disorders should be treated with caution.
- 3.16 The conditions aggregated in assessments of need such as those cited above are of different orders, with different causes. One EBC report has argued that “[b]oth lay persons and professionals are typically unaware of the commonalities and the shared mechanisms of ‘brain disorders’²⁷⁰ in which it includes depression, schizophrenia, anxiety disorders, drug dependence, dementia, epilepsy and multiple sclerosis (MS). However, framing these diverse conditions in this way, could be misleading to the extent that it implies that the pathway to understanding and treating all of them lies in solely the brain, hence accentuating the potential role for technologies that intervene directly in the brain. While some disorders, such as Parkinson’s disease, clearly arise from neurological damage located in the brain, the causal pathways for others, such as obesity, are more complex, and the centrality of the brain as the key target for intervention is less certain, and often disputed. Similarly, while some of these conditions have no available and effective treatments, others (for example, several mental health disorders), respond to available pharmaceuticals in various degrees, and may respond even better to cognitive therapy or social interventions.
- 3.17 Two points remain clear, however. The first is that the perceived size of the potential market for products to address these disorders provides significant financial incentives for companies to develop products to meet these needs. The second is that these companies have to engage in and understand the complex process required to turn developments that work in laboratory situations or in small-scale medical interventions into products that are available on the market, that will be accepted by medical practitioners, and will be purchased by those who commission health services, or, in some circumstances, by patients themselves. The processes of how these aims may be achieved, and the difficulties in achieving them, are discussed below.

Estimating neurotechnology markets

- 3.18 Assessments of the value of biotechnology markets – specifically the revenue generated by biotechnology companies – are produced by a number of organisations, including governments, international organisations and private market research companies. According to one estimate, the value of the global biotechnology market in 2011 was \$281.7 billion, which will rise by over 60 per cent by 2016 to an estimated \$453.3billion.²⁷¹ The majority of the biotechnology industry is based in the US, but China, India, Japan, Brazil, and EU countries are also developing biotechnology markets.²⁷²
- 3.19 It is generally held that the most lucrative part of the global biotechnology market is that concerned with medicine and health care. According to one estimate, in 2008 this section generated 69 per cent of the market’s overall value.²⁷³ Another forecast concluded that “[t]he medical technology market is estimated to be worth £150-70 billion worldwide with growth rates

²⁷⁰ Wittchen HU, Jacobi F, Rehm J *et al.* (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010 *European Neuropsychopharmacol* **21(9)**: 655-79, at page 656.

²⁷¹ Biotechnology: Global Industry Guide (2012) *Biotechnology: global industry guide*, available at: http://www.researchandmarkets.com/reports/41522/biotechnology_global_industry_guide.

²⁷² Abuduxike G and Aljunid SM (2012) Development of health biotechnology in developing countries: can private-sector players be the prime movers? *Biotechnology Advances* **30(6)**: 1589-601; Neurotechnology Industry Organization (2009) *Neurotech clusters 2010: leading regions in the global neurotechnology industry 2010 - 2020*, available at: http://www.neurotechindustry.org/images/Neurotech_Clusters_2010_Report.pdf.

²⁷³ Highbeam Business (2009) *Global - biotechnology (industry overview)*, available at: <http://business.highbeam.com/437189/article-1G1-206253164/global-biotechnology>.

forecast at ten per cent per annum over the next five to six years and a market size approaching £300 billion by 2015.”²⁷⁴

3.20 NeuroInsights has stated that the 2011 market for neurodevices for therapeutic use generated estimated revenues of \$8.63 billion (8.1% growth). “This compares to \$7.98 billion (13% growth) in 2010, \$7.06 billion (15% growth) in 2009, and \$6.1 billion (18.6% growth) in 2008.”²⁷⁵

3.21 In light of these estimates, the belief in the potential value that can be generated by neurotechnologies has consequences for the direction of research and development. A significant amount of basic research is conducted in universities and funded with grants from research councils and charitable foundations. Even this area is now subject to requirements to realise value in terms of intellectual property,²⁷⁶ and to have an ‘impact’, by translating research into treatments or products to enhance health and generate wealth.²⁷⁷ There are partnerships between universities and industry,²⁷⁸ with industry playing a role in funding basic research and training of neuroscientists,²⁷⁹ as well as supporting research into products that are closer to being launched on the market.

3.22 When public bodies estimate the ‘burden’ of brain disorders, they frequently couple this estimate of ‘costs’ with potential ‘benefits’ (the economic returns that can be generated by fulfilling unmet medical needs). For example, the Department for Business, Innovation and Skills, in a report published jointly with the Department of Health, argues that:

“The expected ageing of the UK’s population will continue to boost market opportunities for regenerative medicine products as well as increase cost pressures on health care providers. There are also large and growing unmet medical needs, for example neurodegenerative diseases (including Parkinson’s disease), stroke and heart failure that currently have no significant therapeutic options and are therefore only managed palliatively.”²⁸⁰

3.23 The Nuffield Council on Bioethics’ report on *Emerging biotechnologies* draws attention to the ‘growth agenda’ that dominates publicly funded research, noting that the promotion of economic growth has featured centrally in the aims of research councils for a number of years.²⁸¹ The Council’s report cites a number of examples, including the Treasury’s *Science and innovation framework 2004-2014* which begins by stating that “[h]arnessing innovation in Britain is key to improving the country’s future wealth creation prospects.”²⁸² This focus on economic motivation is echoed in the *Strategy for UK Life sciences* which, as the Council’s *Emerging biotechnologies*

²⁷⁴ Department for Business Innovation and Skills, UK Trade and Investment and Department of Health (2011) *Strength and opportunity 2011: the landscape of the medical technology, medical biotechnology, industrial biotechnology and pharmaceutical sectors in the UK*, available at: <http://www.bis.gov.uk/assets/biscore/innovation/docs/s/11-p90-strength-and-opportunity-2011-medical-technology-sectors.pdf>, at page 10.

²⁷⁵ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 18

²⁷⁶ The Royal Society (2012) *Science as an open enterprise*, available at: http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/projects/sape/2012-06-20-SAOE.pdf, at page 47.

²⁷⁷ HM Treasury (2006) *A review of UK health research funding*, available at: <https://www.bioin.or.kr/upload/industry/1192426342312.pdf>, pp.3-4; UK Evaluation Forum (2006) *Medical research: assessing the benefits to society*, available at: http://www.wellcome.ac.uk/stellent/groups/corporatesite/@msh_publishing_group/documents/web_document/wtx031817.pdf, at page 5.

²⁷⁸ For example: NIHR Imperial BRC (2011) *Industry partners*, available at: <http://imperialbrc.org/our-partners/industry-partners>.

²⁷⁹ Amara SG, Grillner S, Insel T, Nutt D and Tsumoto T (2011) Neuroscience in recession? *Nature Reviews Neuroscience* **12(5)**: 297-302, pp.297-8.

²⁸⁰ Department of Health and Department for Business Innovation and Skills (2011) *Taking stock of regenerative medicine in the United Kingdom*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32459/11-1056-taking-stock-of-regenerative-medicine.pdf, at page 7.

²⁸¹ Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, pp.117-20.

²⁸² HM Treasury (2004) *Science and innovation investment framework 2004-2014*, available at: http://www.hm-treasury.gov.uk/d/spend04_sciencedoc_1_090704.pdf, at page 5.

report observes, is notable for the way in which it “corrals the whole area of medical research (on which it is almost exclusively focused) into the guiding objective of generating economic benefit.”²⁸³ The Council’s report also argued that priorities have become excessively narrowed by economic considerations which are inevitably tied to speculations about future benefits which are themselves shaped by the promises and predictions that are encouraged by public research funding systems.²⁸⁴ Research, whether conducted in the public or the private domain or in partnerships between these, may increasingly be viewed as ‘promissory’ in nature: the policy and funding environments place increasing expectations on researchers to promise benefits, and research is increasingly shaped by these promises.²⁸⁵

Promises and problems in neurotechnology markets

3.24 In the promissory political economy of neurotechnologies, expectations of the potential for developments in neurotechnologies play a crucial role in developing the market. Hence market scoping companies such as IMS and NeuroInsights, claim to help commercial companies identify and estimate key potential markets for their products.²⁸⁶ Such estimates are ‘performative’ as they help to bring these new markets into existence by encouraging their commercial exploitation. For example, NeuroInsights estimates that almost half the global patient population is “unserved” and that “The unserved market represents neurotechnology’s enormous, long-term market opportunity. Examples of indications in this segment include cures for Alzheimer’s disease, chronic addiction and age-related sensory disorders (such as hearing loss).”²⁸⁷ We can see echoes in these commercial forecasts of the kind of foresight activities, estimating the prevalence and costs of disease, conducted by the public bodies such as the WHO (see paragraph 3.11).

Box 3.2: Neuro-lobbying in the US

In the US, the neurotechnology industry forms a powerful lobby group. For example, the National Neurotechnology Initiative, which comprises over 100 companies, was formed to coordinate and accelerate neurotechnology research, support entrepreneurship, and improve the effectiveness and efficiency of the FDA neurotechnology approval process.²⁸⁸ In 2009, it lobbied Congress for incentives for the neurotechnology industry in the form of a National Neurotechnology Initiative Act.²⁸⁹ It argued that “[f]or \$200 million – three percent of the current NIH brain and nervous system research and development budget – the NNTI Act will dramatically increase the speed and number of treatments and cures for brain and nervous system illnesses, disorders and injuries. It coordinates research for increased efficiency, and leverages private sector innovation.” The Initiative also proposed the establishment of “a research center to conduct studies on the ethical, legal and social implications of neurotechnology, addressing issues such as its appropriate use in the criminal justice system, or enhancement of soldier and civilian mental capabilities (\$10 million).”²⁹⁰ The legislation failed to gather sufficient support and did not proceed, but lobbying continues with hopes for success at a future session.²⁹¹

3.25 If incentives to innovate in this field are framed purely in terms of likely financial return on investment, it is clear that economic considerations – such as the capacity of health care organisations or individuals to afford to purchase products – will steer development towards the

²⁸³ Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, at page 120.

²⁸⁴ Ibid.

²⁸⁵ Hedgecoe A (2004) *The politics of personalised medicine: pharmacogenetics in the clinic* (Cambridge: Cambridge University Press), at page 17.

²⁸⁶ NeuroInsights (2012) *The neurodiagnostics report 2012: brain imaging, biomarkers and neuroinformatics*, available at: <http://www.neuroinsights.com/marketreports/neurodiagnosticsreport.html>. These reports often cost several thousand dollars to purchase, indicating their potential value to their target audience of investors,

²⁸⁷ NeuroInsights (2010) *Neurotechnology industry reports revenues of \$143.1 billion in 2009*, available at: <http://www.neuroinsights.com/neurotech2010release.html>, at page 21.

²⁸⁸ Neurotechnology Industry Organization (2011) *Neurotechnology Industry Organization: homepage*, available at: <http://www.neurotechindustry.org/>.

²⁸⁹ Neurotechnology Industry Organisation (2012) *About the Neurotechnology Industry Organization*, available at: <http://www.neurotechindustry.org/aboutnio.html>.

²⁹⁰ NeuroInsights (2010) *Neurotechnology industry reports revenues of \$143.1 billion in 2009*, available at: <http://www.neuroinsights.com/neurotech2010release.html>, at page 39.

²⁹¹ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights)

health care needs of the developed world, and within that, to specific population groups. Such market-based shaping of technology development raises particular issues of equity and justice. For example, Alzheimer's disease and other age-related conditions offer tempting potential markets, and the development of effective treatments promises significant benefits for both industry and national economies; however, there is significant unmet need for people with rare and complex neurological conditions, such as motor neurone disease, locked-in syndrome and end-stage Parkinson's disease. In the case of medicines for rare conditions, various options have been tried. For example, some companies create successful business models for rare conditions, based on setting very high costs for their products,²⁹² although a more familiar route is via the designation of 'orphan disease' status for conditions affecting fewer than five per 10,000 (in Europe).²⁹³ For such conditions, EU legislation seeks to encourage innovation with incentives including ten years of market exclusivity; protocol assistance and access to centralised procedure at the European Medicines Agency; reduction in fees such as those for pre-authorisation activity; and free scientific advice.²⁹⁴ Neurological devices for smaller populations face less costly manufacturing and regulation (see Box 7.6), but may struggle to demonstrate efficacy to potential buyers without larger clinical trials, an issue which is compounded by small patient populations.

- 3.26 Even though some novel neurotechnologies such as deep brain stimulation (DBS) have proven effective for relatively common conditions such as Parkinson's disease, the question remains whether they will be available to the majority of patients who have such conditions. Considerations such as cost and the need for ongoing skilled medical attention and surveillance bring into question whether the widespread use of such novel neurotechnologies will be possible in the foreseeable future. For example, while stroke is a major global health problem, the WHO recommends that stroke is best addressed in primary care settings as this is the only point of access the majority of sufferers have to medical treatment.²⁹⁵ It is, of course, possible that as efficacy of a particular neurotechnology product is demonstrated and production volume increases, its price will fall and the size of the market will increase, as evidenced by conventional economics. By definition, the 'novel' neurotechnologies that we discuss in this report have not reached this point. However, even when those technologies are mature, the realities of health care systems and funding in the global south may well mean that, for the vast majority, these treatments will remain out of reach, and that in developing countries, the availability of these treatments will follow a familiar and inequitable path.

Securing funding to pursue innovation

- 3.27 The dilemma we are faced with is this: emphasising the global incidence of neurological disease, the very large numbers of persons affected and the high personal, familial and national costs they entail, may help to raise the profile of these disorders, and therefore opportunities for commercial exploitation. It may also stimulate those who, aware of unmet needs, seek to exploit desperate patients. The challenge for those seeking to develop such neurotechnologies in clinically appropriate ways remains that of seeking funds for research and development of neurotechnologies that, in the short term at least, are unlikely to be widely available. It is in this light that we can consider whether the current political economy of neurotechnologies encourages the development of devices that address unmet needs, both in relation to common conditions such as stroke and Parkinson's disease, and in relation to rarer conditions. We will

²⁹² Novas C (2008) Patients, profits and values, in *Biosocialities, Genetics and the Social Sciences: Making Biologies and Identities*, Gibbon S, and Novas C (Editors) (London: Taylor Francis), pp 136-152.

²⁹³ Taruscio D, Capozzoli F and Frank C (2011) Rare diseases and orphan drugs *Annali dell'Istituto Superiore di Sanità* **47(1)**: 83-93.

²⁹⁴ *Ibid*, at page 85. The introduction of value-based pricing (VBP) may also provide further incentives for the development of products for smaller patient populations in the future. VBP is a proposal for changing the way that the UK prices and reimburses new medicines. Price will be linked to an assessment of the value of a new medicine to the NHS.

²⁹⁵ World Health Organization (2007) *Neurological disorders: a public health approach*, available at: http://www.who.int/mental_health/neurology/chapter_3_a_neuro_disorders_public_h_challenges.pdf, at page 178.

see that even where market incentives appear to be significant because potential demand is high, it is often difficult to obtain funding of an appropriate scale and duration to bring products to market. This challenge is even more pronounced in relation to rarer conditions, although there are examples of investors or companies who focus on relatively small market opportunities where it is commercially viable.²⁹⁶

Public and third sector funding

- 3.28 In the case of stem cell therapies and regenerative medicine, funding from public sources and third sector organisations has been particularly significant in Europe and North America. They are viewed by some national governments, including the UK government, as key areas of opportunity for economic growth.²⁹⁷ However the practical considerations associated with the regulation and production of products based on living cells may be perceived as investment risks that present challenges to private funding models.²⁹⁸
- 3.29 In the UK, regenerative medicine generally has seen significant public funding over the last ten years (over £200 million since 2003).²⁹⁹ A joint report by the Department for Business, Innovation and Skills and the Department of Health entitled *Taking stock of regenerative medicines in the United Kingdom*, argues for investment in the development of regenerative medical techniques, especially therapies for stroke and Parkinson's disease in light of potential economic savings which could offset growing costs of public health care for an ageing population.³⁰⁰ In the US in 2004, Californian voters approved *Proposition 71: the California stem cell research and cures initiative*, which meant that \$3 billion (funded by the sale of public bonds) would be made available over 10 years for the creation of the California Institute for Regenerative Medicine (CIRM) and the funding of stem cell research.³⁰¹
- 3.30 However, much of the burden for funding research into regenerative medicine has fallen on third sector organisations. It has been argued by Rare Diseases UK that “[m]ajor national funders do not include research into rare disease as a priority and are often reluctant to support such research because of a perceived lack of impact on the burden of disease and expected limited cost-effectiveness due to the small number of affected people.”³⁰² It has often fallen to charities to fund research into rare diseases that offer less attractive markets to commercial companies, and do not have the economic impact to attract large amounts of public funding. For example, the Association of Medical Research Charities (AMRC) estimates that in 2008-9 UK charities invested approximately £3.6 million in rare disease research.³⁰³ According to the AMRC the third sector invested approximately £38 million in regenerative medicine research from 2005-2009.³⁰⁴ Indeed, of the £60 million of grants made by Parkinson's UK,³⁰⁵ it has invested over

²⁹⁶ Genzyme (2012) *Our treatment areas*, available at: <http://www.genzyme.co.uk/treatment-areas.aspx>.

²⁹⁷ Gov.UK (2012) *Speech by the Chancellor of the Exchequer, Rt Hon George Osborne MP, to the Royal Society*, available at: <https://www.gov.uk/government/speeches/speech-by-the-chancellor-of-the-exchequer-rt-hon-george-osborne-mp-to-the-royal-society>; Department of Health and Department for Business Innovation and Skills (2011) *Taking stock of regenerative medicine in the United Kingdom*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32459/11-1056-taking-stock-of-regenerative-medicine.pdf.

²⁹⁸ Department of Health and Department for Business Innovation and Skills (2011) *Taking stock of regenerative medicine in the United Kingdom*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32459/11-1056-taking-stock-of-regenerative-medicine.pdf, at page 22.

²⁹⁹ *Ibid*, at page 22.

³⁰⁰ *Ibid*, at page 7.

³⁰¹ Adelson JW and Weinberg JK (2010) The California stem cell initiative: persuasion, politics, and public science *Journal of Information* **100**(3): 446-51.

³⁰² Rare Disease UK (2011) *Improving lives optimising resources: a vision for the UK Rare Disease Strategy*, available at: <http://www.raredisease.org.uk/documents/RD-UK-Strategy-Report.pdf>, at page 23.

³⁰³ *Ibid*, at page 23.

³⁰⁴ Department of Health and Department for Business Innovation and Skills (2011) *Taking stock of regenerative medicine in the United Kingdom*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32459/11-1056-taking-stock-of-regenerative-medicine.pdf, at page 27.

³⁰⁵ Parkinson's UK (2012) *Our plan to cure Parkinson's*, available at: http://www.parkinsons.org.uk/research/our_plan_to_cure_parkinsons.aspx.

£1.7 million in stem cell research.³⁰⁶ Figures provided by the Medical Research Council (MRC), show that approximately £500,000 has been invested in neural stem research between 2007 and 2012.³⁰⁷ A further search for “neural stem cells” via the European PubMed Central “Grant lookup tool”³⁰⁸ identifies that the Wellcome Trust have registered research projects that amount to over £2.5 million in this area. However, even the significant public and third sector investments outlined here have not yet been sufficient to bring neural stem cell therapies to market.³⁰⁹ While these are significant sums for public and charitable organisations, they are very small compared to the historical investments of large pharmaceutical companies in the development of drugs which target the central nervous system.

- 3.31 The public sector has also invested in neurotechnological devices though these sums are very small compared with those invested in research and development by commercial companies. Figures provided by the MRC show that approximately £3 million and £1 million have been invested in DBS and TMS/TDS respectively. The European PubMed Central “Grant Lookup Tool” also indicates that Wellcome Trust has invested close to £1.5 million in TMS/TDCS. The European Commission spent approximately €38 million on ten projects based on BCI-related systems between 2007 and 2013,³¹⁰ and in the US the Department of Defense and the Department of Veterans’ Affairs have invested in BCI with the hope that research in this area will improve the quality of life for war veterans who have lost limbs.³¹¹

Large pharmaceutical and medical technology companies

- 3.32 Historically, large pharmaceutical and medical technology companies have been relied on to bring new therapies to market. However, recent withdrawal of multinational pharmaceutical companies such as GlaxoSmithKline and AstraZeneca³¹² from research into the brain suggests that there needs to be a paradigm shift away from such funding and development models for neurotechnologies. High hopes were placed in the therapeutic possibilities that would be opened up by the emergence of the field of neuroscience in the 1960s. However, while some new pharmaceuticals for mental health and neurological conditions have proved to be effective, few new drug targets or therapeutic mechanisms of real significance have been identified for more than four decades.³¹³ According to Steven Hyman, former Director of the US National Institute of Mental Health, despite the large unmet need and the growing markets for treatments for mental health disorders, these financial drivers have not proved sufficient to overcome the “very difficult scientific terrain.”³¹⁴
- 3.33 One major problem that has been experienced by pharmaceutical companies in developing their drug pipeline has been that compounds that appear promising in laboratory experiments – often with animal models – have not proved successful in clinical trials with humans.

³⁰⁶ Data on file at NCOB received from Parkinson’s UK. Parkinson’s UK, personal communication, 19.19.2012.

³⁰⁷ Data on file at NCOB received from Medical Research Council MRC *personal communication*, 16.01.2013.

³⁰⁸ European PubMed Central (2013) *Grant lookup tool*, available at: <http://europepmc.org/GrantLookup/>.

³⁰⁹ Economic factors are of course not the only constraints on complex biological products reaching the market. In Chapter 2 (paragraph 2.80) we review some of the scientific issues that must first be resolved and in Chapter 7 (paragraphs 7.60 to 7.72) we review the regulatory framework that determines the marketability of these products.

³¹⁰ Future BNCI (2012) *Future BNCI: A Roadmap for Future Directions in Brain / Neuronal Computer Interaction Research*, available at: http://future-bnci.org/images/stories/Future_BNCI_Roadmap.pdf, at page 24.

³¹¹ Brown University (2012) *People with paralysis control robotic arms using brain-computer interface*, available at: <http://news.brown.edu/presreleases/2012/05/braingate2>.

³¹² The Guardian (13 June 2011) *Research into brain disorders under threat as drug firms pull out*, available at: <http://www.guardian.co.uk/science/2011/jun/13/research-brain-disorders-under-threat>.

³¹³ Hyman SE (2012) Revolution stalled *Science Translational Medicine* **4(155)**: 1-5, at page 1.

³¹⁴ *Ibid*, at page 3. Both the EU and the US have recently announced major long term investments in human brain mapping programmes, designed, in part, to provide alternative approaches to the use of animal models in the trialling of therapeutic interventions into the brain, which may provide effective alternatives able to capture these complex neural properties and explore mechanisms of action in ways that facilitate translation.

“The best recognized obstacles to effective clinical translation in psychiatry include the complexity of the brain and the associated challenge of connecting levels of analysis from molecules to cells, synapses, circuits, and thence to higher cognition, emotion, regulation, and executive function.”³¹⁵

These difficulties in translation from the laboratory to clinical application in psychopharmaceuticals illustrate a general problem for the funding and longer term support of neurotechnology. Investment in psychopharmaceuticals from the 1960s was based on widely accepted hypotheses as to the mode of action of the drugs, linked to hypotheses about the neurobiological basis of the conditions that they sought to treat.³¹⁶ These hypotheses – even if they now appear partial, at best – guided research and development. However, there is still little understanding of how some neurotechnological interventions achieve their intended therapeutic effects (for example, see paragraph 2.49) and this has consequences for the development and refinement of the technologies.

- 3.34 Nonetheless, it has been suggested that the difficulties encountered in the development of novel psychopharmaceuticals opens new opportunities for those developing devices.³¹⁷ Historically, neurodevices have been better supported by bigger companies than stem cells. Several major companies – including Medtronic,³¹⁸ St. Jude Medical,³¹⁹ and Boston Scientific³²⁰ – have made significant investments in start-ups and have successfully brought products to market, including those used in DBS. In 2009 it was estimated that over 60,000 people worldwide had received DBS.³²¹ DBS accounts for about one sixth of the neuromodulation devices market with an estimated global volume of \$3 billion in 2010.³²² There are indications that pharmaceutical companies are beginning to consider increasing investment in neurotechnologies of the sort that we are discussing in this report.³²³
- 3.35 In the context of stem cells, some pharmaceutical companies have, to date, begun to invest in cell-based therapies, although not yet in the neurological area.³²⁴ However large companies have, for the most part, shown a reluctance to invest in stem cell research and have, instead, preferred to observe the field to monitor if any potentially viable products emerge.³²⁵ While successful developments in neural stem cell therapies may lead to lucrative buy-outs from these companies later in development pathways, this does not address the initial costs of basic research and development or those of transitional research.

³¹⁵ Ibid, at page 3.

³¹⁶ Healy D (1997) *The antidepressant era* (Harvard: Harvard University Press).

³¹⁷ Neurotech Business Report (2011) *Drop in pharma R&D for CNS opens door for devices* available at: http://www.neurotechreports.com/pages/CNS_Pharma_R&D_Funding_Decline.html.

³¹⁸ Medtronic (2013) *Deep brain stimulation for movement disorders*, available at: <http://professional.medtronic.com/pt/neuro/dbs-md/index.htm#.UbG3H-dwprR>.

³¹⁹ At a conference organised by J. P. Morgan in 2011, “St. Jude Medical CEO Dan Starks touted the company’s 11% top-line growth. In neuromodulation, Starks said the company has a leadership position in Japan with its Eon Mini device [a very small implantable pulse generator (IPGs) for chronic pain management] and that SJM would be first to market with neuromodulation system to treat migraine.” Neurotech business report (2011) *Neurotech executives report progress at J.P. Morgan healthcare conference* available at: http://www.neurotechreports.com/pages/2011_JP_Morgan_Healthcare_Conference_Neurotech.html.

³²⁰ In 2011, Boston Scientific CEO Ray Elliott reported that his company “had lots of IP and two opportunities to compete in the hypertension neuromodulation space, which he sees as a \$5 billion business by 2020. The approaches include stimulation of baroreceptors and renal nerves... he touted the company’s Vercise DBS system, which is currently undergoing clinical trials in Cologne...”. See: Ibid.

³²¹ Ponce FA and Lozano AM (2010) Chapter 16 - Deep brain stimulation: state of the art and novel stimulation targets, in *Progress in brain research*, Anders B, and Cenci MA (Editors) (Elsevier).

³²² Christen M and Müller S (2012) Current status and future challenges of deep brain stimulation in Switzerland *Swiss Medical Weekly* **142(w13570)**: 1-8, at page 2.

³²³ Gewin V (2008) Brain work *Nature* **426**: 276-7; The Lundbeck Foundation (2011) *The Lundbeck Foundation 2011 annual report*, available at: <http://www.lundbeckfoundation.com/media/LF11-12UK.pdf>, at page 30.

³²⁴ See, for example, Bloomberg (8 December 2010) *Cephalon buys mesoblast stake, drug rights in potential \$2 billion deal*, available at: <http://www.bloomberg.com/news/2010-12-08/cephalon-buys-20-stake-in-mesoblast-rights-to-adult-stem-cell-therapies.html>.

³²⁵ Parson A (2006) The long journey from stem cells to medical product *Cell* **125(1)**: 9-11.

Venture capital

- 3.36 Venture capital (VC) is a key source of funding for the development of novel neurotechnologies.³²⁶ There has already been significant investment from venture capitalists in this field, and it has been estimated that in 2011, this amounted to over \$1.63 billion.³²⁷ Approximately \$646 million (52%) of this neurotechnology funding was in neurodevice companies at the late stages of development.³²⁸ However, during a factfinding meeting, it was suggested to the Working Party that the large amount of VC investment in this area is due to smaller companies – in which venture capitalists had already invested – lacking exit capability, and thus retaining their dependence on VC funding, rather than due to an increase in the number of ideas or companies in which to invest.³²⁹ The standard route for the progress of novel neurotechnological products from early stage research to scaled-up production and marketing is via acquisition by a large company. It was suggested that the reason VC investment remains high may be explained by, in these cases, the difficulty of establishing intellectual property meaning that they were not attractive acquisition targets for large medical device companies.³³⁰
- 3.37 While VC investment – with its willingness to take risks in the hope of large returns – can potentially play a key role in addressing unmet need, it can also make developers highly dependent on the decisions of the investor. Investors may wish to steer developments into areas with which they are more familiar, or where they consider that the market is more mature or offers more opportunities; if the scientists and researchers who initiate the start-up company are unable or unwilling to move in this direction, future investment may be curtailed.³³¹ Such decisions, in favour of a developed and established market rather than a new and risky one, may undermine the need for innovation in this area, and instead focus development on small improvements in familiar technologies, rather than on novel approaches.
- 3.38 Investment in non-therapeutic products could potentially have positive repercussions for the development of BCI technologies that might also be applied to therapeutic or assistive purposes. BCI companies Neurosky and Emotiv, both of whom focus on entertainment and performance BCIs, in 2010, received over \$10 million in VC funds.³³² The prospects for the therapeutic market could grow significantly as more capable and practical systems are developed.³³³ However, in the near future, assistive BCIs are likely to remain available to only a small number of people³³⁴ meaning that companies developing assistive BCIs may find it difficult to attract VC funding.
- 3.39 In contrast to neurodevices, private and VC investment has been deterred by the particular challenges of bringing stem cell based therapies to market.³³⁵ In addition to general problems associated with translating advances in brain research into therapeutic applications, neural stem cell products, unlike novel neurodevices, have to satisfy stringent regulatory criteria that apply to ‘advanced therapeutic medicinal products’ (ATMPs), which are similar to those that

³²⁶ Ernst & Young (2012) *Beyond borders: global biotechnology report 2012*, available at: [http://www.ey.com/Publication/vwLUAssets/Beyond_borders_2012/\\$FILE/Beyond_borders_2012.pdf](http://www.ey.com/Publication/vwLUAssets/Beyond_borders_2012/$FILE/Beyond_borders_2012.pdf), at page 39.

³²⁷ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 22.

³²⁸ *Ibid.*

³²⁹ Factfinding meeting on industry and investment, 16 February 2012.

³³⁰ Factfinding meeting on industry and investment, 16 February 2012; NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 256.

³³¹ Factfinding meeting on industry and investment, 16 February 2012.

³³² Future BNCI (2012) *Future BNCI: A Roadmap for Future Directions in Brain / Neuronal Computer Interaction Research*, available at: http://future-bnci.org/images/stories/Future_BNCI_Roadmap.pdf, at page 107.

³³³ Frances J. R. Richmond and Gerald E. Loeb (2012) Dissemination: getting BCIs to people who need them, in *Brain-Computer Interfaces: Principles and Practice*, Wolpaw J, and Wolpaw EW (Editors) (New York: Oxford University Press), at page 349.

³³⁴ *Ibid.*

³³⁵ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 377. See also footnote 309 above.

apply to traditional pharmaceuticals.³³⁶ Furthermore, the need to satisfy the assessment by the specialised ethics committee, the Gene Therapy Advisory Committee (GTAC). These factors have, historically, had the potential to cause delays for product research and development (see paragraphs 7.70 to 7.71 for further discussion).

- 3.40 In comparison to pharmaceutical products and most neurodevices, investors are also confronted by the prospect of high costs of manufacturing neural stem cell therapies. Laborious manufacturing processes, batch testing, shipping costs, shelf life, staff turnover and patentability of products all contribute to a rise in production costs which effectively reduce profit margins.³³⁷ Venture capitalists are also reluctant to invest in technologies that have extended development trajectories³³⁸ (for example, those extending over more than ten years); this category of investor rarely sees a product through to market and is far more likely to seek a trade sale, an option which is currently limited due to factors such as the financial crisis and lower budgets in the pharmaceutical industry.³³⁹

The valley of death

- 3.41 A major problem that affects start-up companies has become known as the ‘valley of death’. This term refers to the difficulty of carrying through research and development from spun-out academic research to commercially-viable innovation.³⁴⁰ In part, these difficulties result from the significant escalation of costs involved in developing, scaling-up and trialling biomedical products, combined with high attrition rates for new products. The problem typically occurs when small spin-out companies find themselves unable to fund further development and potential investors are unwilling to bear the substantial risk involved for the anticipated returns. These potential investors may be large firms who wish to acquire stock or smaller companies with valuable intellectual property in the same field, or they may be venture capitalists. The Nuffield Council’s earlier report on *Emerging biotechnologies* (referring to pharmaceutical companies) noted that:

“It is possible, in principle, for venture capital to bridge this gap but it is hard and/or unacceptable in practice, because venture capitalists demand a very large stake in return for their investment. There may be specific reasons for the limitations of venture capital in the UK, but the problem is clearly worldwide. The exorbitant terms of venture capital funding arise from their perception of risk (which depends on their understanding of the technology and the market).”³⁴¹

- 3.42 Venture capitalists may also show increasing reluctance to invest in biotechnologies owing to historically poorer-than-expected returns and external economic conditions. In particular, they may perceive earlier translational stages of development to be too risky and prefer to invest at a later stage, when products are closer to market and the risks are perceived as lower.³⁴²

³³⁶ MHRA (2013) *How we regulate advanced therapy medicinal products*, available at: <http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/Aboutadvancedtherapymedicinalproducts/index.htm>.

³³⁷ Parson AB (2008) Stem cell biotech: seeking a piece of the action *Cell* **132(4)**: 511-3; Working Knowledge: Harvard Business School (2011) *Funding unpredictability around stem-cell research inflicts heavy cost on scientific progress*, available at: <http://hbswk.hbs.edu/item/6601.html>; Malik N (2012) Allogeneic versus autologous stem-cell therapy *BioPharm International* **25(7)**: 36-40

³³⁸ Parson AB (2008) Stem cell biotech: seeking a piece of the action *Cell* **132(4)**: 511-3, at page 511.

³³⁹ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 394.

³⁴⁰ House of Commons Science and Technology Committee (2013) *Bridging the valley of death: improving the commercialisation of research*, available at: <http://www.publications.parliament.uk/pa/cm/201213/cmselect/cmsctech/348/348.pdf>, at paragraph 9.

³⁴¹ Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, at page 164.

³⁴² NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), p374.

- 3.43 Recently, the problem posed by the valley of death has been discussed by the UK Parliament's Science and Technology Select Committee.³⁴³ The Committee heard evidence from several people, including Sir David Cooksey, author of the Cooksey Report.³⁴⁴ In his evidence, he remarked:

“[I]n order to make the valley of death crossable you need to have finance to do it in the first place... If you look today at the successful venture capital firms, they are the ones that are investing at the later stages of the process, as the company comes up the other side of the valley of death, and the real problem is getting from there to where you see the growth beginning to take place.”³⁴⁵

- 3.44 In a well-known example from the US, Geron (a US-based biopharmaceutical company) sought permission from the FDA to begin a clinical trial of a therapy using human embryonic stem cells (hESCs) to treat spinal cord injury. The process of gaining approval for the trial took several years,³⁴⁶ with Geron required to submit a 21,000-page application to the FDA.³⁴⁷ This trial aimed only to test the *safety*, rather than the *efficacy* of the therapy, and involved injecting cells into the spinal cord of between eight and ten individuals.³⁴⁸ The trial began in October 2010, but by July 2011, after treating just four patients, Geron announced that it had abandoned the trial on financial grounds:³⁴⁹ the projected returns from investment in stem cell research – which was high risk, at early stages, and therefore quite distant from the market – were less than those anticipated from investing the same resources in therapies that were closer to market applications. This decision was understandable in the context of the company's obligations to its shareholders, however it resulted in the termination of a potentially important clinical application.
- 3.45 As the Geron example shows, costs incurred at the preclinical/clinical interface can be vast, especially for companies which, like Geron, seek to develop genuinely innovative technologies in a heavily-regulated field such as stem cells. In other areas of neurotechnology research, however, some small neurodevice companies have had success in bridging the gap. For example Neuronetics developed the first repetitive transcranial magnetic stimulation³⁵⁰ (rTMS) device (NeuroStar TMS Therapy[®]) to be licensed by the FDA in 2008 for use to treat depression in the US. So far, 270 of these devices, each of which is worth \$70,000, have been sold.³⁵¹ In the UK the NHS National Institute for Health Research's Healthcare Technology Co-operatives operates with the specific aim of encouraging collaborations between industry, patients, charities and academic researchers to develop new medical devices and technology-dependent interventions to address areas of serious illness and unmet need for NHS patients.³⁵²
- 3.46 As the problems of translation at the preclinical/clinical interface have been increasingly recognised, measures have been introduced in the UK to try to alleviate this situation. These include the £180 million Biomedical Catalyst funding programme operated by the Medical

³⁴³ House of Commons Science and Technology Committee (2013) *Bridging the valley of death: improving the commercialisation of research*, available at:

<http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/348/348.pdf>.

³⁴⁴ HM Treasury (2006) *A review of UK health research funding*, available at:

<https://www.bioin.or.kr/upload/industry/1192426342312.pdf>

³⁴⁵ House of Commons Science and Technology Committee (2011) *Bridging the valley of death: improving the commercialisation of research*, available at:

<http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/348/348vw.pdf>, at Ev40.

³⁴⁶ The New York Times (23 January 2009) *FDA approves a stem cell trial* available at:

http://www.nytimes.com/2009/01/23/business/23stem.html?_r=0.

³⁴⁷ Nature Newsblog (18 October 2012) *Former Geron execs bid for abandoned stem cell programme*, available at:

<http://blogs.nature.com/news/2012/10/former-geron-execs-bid-for-abandoned-stem-cell-program.html>.

³⁴⁸ The New York Times (23 January 2009) *FDA approves a stem cell trial* available at:

http://www.nytimes.com/2009/01/23/business/23stem.html?_r=0.

³⁴⁹ The Guardian Online (15 November 2011) *Geron abandons stem cell therapy as treatment for paralysis*, available at:

<http://www.guardian.co.uk/science/2011/nov/15/geron-abandons-stem-cell-therapy>.

³⁵⁰ rTMS, refers to a variant of TMS, repetitive transcranial magnetic stimulation.

³⁵¹ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 283.

³⁵² NIHR (2008) *Healthcare technology co-operatives*, available at: <http://www.nihr.ac.uk/infrastructure/Pages/HTCs.aspx>.

Research Council (MRC) and the Technology Strategy Board (TSB) with the aim of helping small and medium sized enterprises (SMEs) and academics with innovative products to bridge the translational gap.³⁵³ The similarly aimed Cell Therapy Catapult has a core grant of £70 million from the TSB.³⁵⁴ While these funds are significant, are not sufficient to cover the funding gap that currently faces biomedical initiatives that are unable to obtain private funding to take them through this stage in the translation process. Hence, in the current situation, it is likely that many potentially useful novel neurotechnologies at the research stage, or in development by start-up companies, will fail because they cannot negotiate ‘the valley of death’. This seems particularly true in the field of stem cell research, where costs are high, and the risks for investors are often perceived as formidable.

- 3.47 The ability for companies to bridge the valley of death is a source of concern in the context of this report not because of the survival of these enterprises themselves, but because the failure of promising therapeutic innovations to translate into marketable products affects the well-being of patients who lack other therapeutic products. Despite the expectations and anticipations that characterise the market for novel neurotechnologies, it is by no means clear that the market, as it is currently structured, has proved the best mechanism for bringing therapeutic technologies to the clinic. We suggest that the combined effects of the complexity of the brain, lack of incentives where patient populations are small, the perceived risks of investment in stem cell technologies, navigating regulatory requirements, the focus of public investment on economic benefit and the short-termism of VC, mean that the market mechanism runs the risk of combining exaggerated promises with failure to deliver.

Market-driven development and the need for safe and effective treatment

- 3.48 So far in this chapter, we have looked at different approaches to characterising unmet need and at how the novel neurotechnology market strives, to varying degrees of success, to address this need. Where funding *is* secured, there is usually an associated imperative to make a profit in a specific timeframe. A number of familiar techniques are used to monetise innovations in neurotechnology, some of which have significant social and ethical implications; it is to these that we now turn. While our main geographical focus in this report is on the UK, it is relevant here to discuss some US examples, given the key role that the US plays in the research and development of novel neurotechnologies.

Intellectual property

- 3.49 One of the main ways that commercial companies may derive revenue from a product or process, by protecting market share from potential competitors, and displaying a product’s viability to potential funders, is through exercising intellectual property rights (IPR).³⁵⁵ Mechanisms of protection include patents, trade secrets, design rights, regulatory data protection or marketing exclusivity.³⁵⁶ There are significant differences between different intellectual property (IP) regimes in different regions. For example, in Europe, surgical, therapeutic or diagnostic instruments or devices can be patented, but novel methods for

³⁵³ The £180 million Biomedical Catalyst is operated jointly by the MRC and TSB, with the intention of providing support to life science opportunities arising in the UK. See: Medical Research Council (2012) *Biomedical catalyst: developmental pathway funding scheme (DPFS)*, available at: <http://www.mrc.ac.uk/Fundingopportunities/Grants/DPFS/index.htm>.

³⁵⁴ Cell Therapy Catapult (2013) *The cell therapy catapult: the UK’s initiative to accelerate the development of cell therapies*, available at: http://www.cirm.ca.gov/sites/default/files/files/about_cirm/04_Mount_CriticalPathWorkshop.pdf, at page 8.

³⁵⁵ For example CellFactors, a UK biotechnology company founded in 1997 had IP in both the US and in Europe on its method to produce and immortalise human neural stem cell lines. It raised a total of £7 million to develop this work over seven years, and passed a number of pre-clinical milestones, but was unable to attract further funding, and went into administration in 2004. See: BioSpace (2005) *CellFactors plc enters administration*, available at: <http://www.biospace.com/News/1-enters-administration/16873420>.

³⁵⁶ IP issues relating to biotechnologies are discussed in more detail in Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, pp.156-61.

treatment cannot. However, in the US, it is possible to patent a procedure, thus associating neurotechnology with a medical application.³⁵⁷

- 3.50 Stem cell therapies again pose specific issues, distinct from neurodevices, that may deter investors and thus hinder the pathway to clinical applications. In 2011, the Court of Justice of the European Union ruled that patenting products derived from human embryos was prohibited in Europe, and this would apply to neural stem cells derived from such material, although not to those developed by other means (such as iPS).³⁵⁸ However, the German Federal Court has already narrowed this prohibition (within its own jurisdiction) to products that *directly* entail the destruction of embryos.³⁵⁹ Further, there may be more effective options than patents by which developers can protect market share. The chief purpose of a patent is to prevent competition from generic products, but it will be virtually impossible for a stem cell therapy to receive regulatory approval as a 'generic' due to the near impossibility of showing that the second product is bioequivalent to the original.³⁶⁰ In addition, the valuable intellectual assets in this field are as likely to be located in the processes of manufacturing products as in the cell lines themselves. Aspects of these processes could themselves be patentable, but much of the value may well be the technical 'know-how' which is amenable to protection as confidential trade secrets and regulatory exclusivity afforded by statute to new medicinal products.³⁶¹ Finally, the originator of a cell line should be able to exert control as a result of appropriate terms of access of the physical cell line itself. It is thus too early to evaluate the effect of the European Court of Justice ruling on the development of neurotechnologies based on stem cells.
- 3.51 In contrast, where neurodevices are concerned, patents are likely to remain a relevant form of protection of IPR. In the UK, patent rights last for up to 20 years and make it illegal for anyone except the owner or someone operating under licence from the owner, to use, make, import or sell the invention in the country where the patent is in force.³⁶² Unlike ATMPs, medical devices are likely to have shorter development periods and be subject to rapid incremental modifications. This can be both a boon and a limitation for the use of patent rights. Shorter development periods mean that rights may be secured more quickly; in contrast, mere incremental modifications might not meet the stringent requirements for patentability which include the need to show that an invention is 'novel' and embodies an 'inventive step', that is, it is an advance in the field that would be a non-obvious advance to a relevant expert.³⁶³ For

³⁵⁷ In *Mayo v Prometheus* 132 S Ct 1289 (2012), the Supreme Court ruled that a patent for a method of drug delivery was non-patentable as an example of natural law: "[T]he claims inform a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately. For these reasons we believe that the steps are not sufficient to transform un-patentable natural correlations into patentable applications of those regularities." Jeffer Mangels Butler & Mitchell LLP (2012) *Mayo collaborative services, , dba mayo medical laboratories, et al., petitioners v. prometheus laboratories, Inc*, available at: <http://www.jmbm.com/docs/mayovprometheus.pdf>, at page 11.

³⁵⁸ InfoCuria: Case-law of the Court of Justice (2011) *Oliver Brüstle v Greenpeace e.V. (C-34/10)*, available at: <http://curia.europa.eu/juris/document/document.jsf?text=&docid=111402&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=1520913>. This decision does not impact the patentability of therapies based on autologous cells or other allogeneic cells, nor does it affect the patentability of hESC therapies outside Europe. See: Harmon SH, Laurie G and Courtney A (2013) Dignity, plurality and patentability: the unfinished story of *Brüstle v Greenpeace* *European Law Review* 92-106.

³⁵⁹ BioNews (3 December 2012) *German court upholds Brüstle patent as valid*, available at: http://www.bionews.org.uk/page_222080.asp.

³⁶⁰ House of Lords Select Committee on Science and Technology (2012) *Regenerative medicine*, available at: <http://www.parliament.uk/documents/lords-committees/science-technology/RegenerativeMedicine/ucST271112ev8.pdf>, at page 3.

³⁶¹ These may include regulatory data exclusivity. See: Article 10 of the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. For orphan drug designation, see: European Medicines Agency (2010) *Orphan incentives*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000393.jsp.

³⁶² Intellectual Property Office (2011) *Patents: basic facts*, available at: <http://www.ipo.gov.uk/p-basicfacts.pdf>, at page 6.

³⁶³ *Ibid.*, at page 8.

these reasons, design rights (which do not have such exacting requirements) might be more effective for neurodevice developers.³⁶⁴

- 3.52 Some of the limits of patent law can be seen, for example, with TMS and TDCS, which are underpinned by simple physics, and which make use of components that have been in the public domain for many years. Since the potential to exploit IP is often a priority for investors, some argue that the inability to protect IP makes it difficult for companies, especially smaller ones, to attract funding to develop their products and bring them to market, or to become attractive targets for acquisition by larger companies. It also means that research on product development is inadequately protected, and innovations can be made use of by other, particularly larger, competing companies.³⁶⁵
- 3.53 The fact that many components of a medical device may not be the novel inventions of the developer, but long-established technologies, or used under licence from other patent holders, sometimes leads companies to seek other ways to introduce elements that will secure them market share. For example, some companies may make minor modifications to their product which, while therapeutically unnecessary, can provide the basis for a patent application.³⁶⁶ Unlike pharmaceuticals, there are rarely consumables associated with devices, and indeed, unlike pharmaceuticals, a single device may be used to treat many patients over an extended period of time without generating additional revenue for the company. Developers may also seek to incorporate therapeutically superfluous consumable elements into a technology to enable the company to generate funds from repeated sales.³⁶⁷ While this might be regarded as cynical, it may actually provide some of the necessary conditions for the financial survival of the company in question. It therefore has an understandable economic rationale in a highly competitive field. Nevertheless, it is not always clear that it provides patient benefit.
- 3.54 In established medical technology markets, such as those for cardiac stents and valves, for spinal surgical implants, or for artificial joints, very small modifications are often made in the search for products that can claim greater efficacy.³⁶⁸ This characteristic of the medical device market is one reason for the high number of patent disputes. Companies are frequently involved in lawsuits claiming that others have infringed their patents on these minor improvements, with lawsuits used either to seek compensation or to delay the marketing of competitors' products.³⁶⁹ Such lawsuits often continue for many years with multiple appeals used to overturn rulings, and numerous countersuits; they rarely drive one of the parties out of the market, and often end with one of the parties paying large sums in compensation, and the parties subsequently collaborating as owners and licensees.³⁷⁰ These characteristics of the device market are hardly conducive to innovation by small companies, which are constantly open to predation by larger companies, which can afford to pay any compensation that is awarded.³⁷¹

³⁶⁴ Design Rights are the legal protection that permit those who hold them to prevent others from copying the three dimensional shape or configuration of an original design.

³⁶⁵ Brown N and Webster A (2004) *New medical technologies and society: reordering life* (Cambridge: Polity).

³⁶⁶ Factfinding meeting on industry and investment, 16 February 2012.

³⁶⁷ Factfinding meeting on industry and investment, 16 February 2012. An example was cited at this meeting, which noted that Neuronetics included a consumable plastic shield in its TMS device to enable it to claim patent protection: while this may appeal to patient or physician concerns about hygiene, it does not improve the performance of the device.

³⁶⁸ For example see: Frey M, Manchikanti L, Benyamin R *et al.* (2009) Spinal cord stimulation for patients with failed back surgery syndrome: A systematic review *Pain Physician* **12**: 379-97, at page 380; Mohandas A and Foley K (2010) Medical devices: adapting to the comparative effectiveness landscape *Biotechnology Healthcare* **7(2)**: 25-8.

³⁶⁹ JSDUPRA Law News (2012) *Medical device industry remains a hotbed for non-compete litigation*, available at: <http://www.jdsupra.com/legalnews/medical-device-industry-remains-a-hotbed-33002/>; Non-Compete and Trade Secrets (2013) *Mediating non-compete disputes in the medical device industry*, available at: <http://www.noncompetenews.com/post/2013/03/17/Mediating-Non-Compete-Disputes-in-the-Medical-Device-Industry.aspx>.

³⁷⁰ For example, see: Bloomberg (21 September 2011) *Medtronic wins \$101 million award from NuVasive over spinal device patents*, available at: <http://www.bloomberg.com/news/2011-09-20/medtronic-nuvasive-infringed-each-other-s-patents-jury-finds.html>.

³⁷¹ Perhaps the best know case is that of the LA surgeon, Dr. Michelson, whose patent disputes with Medtronic resulted, after four years, in a \$1.35 billion award paid by Medtronic to Dr. Michelson in 2005: £550 million to settle the lawsuit, plus \$800 million to acquire the patents. The New York Times (April 23, 2005) *Medtronic to pay \$1.35 billion to inventor*, available at: http://www.nytimes.com/2005/04/23/business/23medronic.html?_r=1&.

Exploiting regulatory measures – medical devices

- 3.55 Delays in gaining market approval may have significant impact on profits as well as reducing ‘first mover’ advantage in a highly competitive market, given the time limit on patents and the rapid rate at which incremental innovation in the device sector can progress. This may be a particular issue for start-up companies funded by VC, where the timeframe for recovery of investment is usually a few years. This creates incentives for companies to use the fastest available routes to market which make the least amount of demands on companies to provide evidence or, indeed, to conduct their own, costly, clinical investigations.
- 3.56 As we discuss in more detail in Chapter 7, the regulatory system for medical devices in Europe entails relatively (in comparison to that in the US, for example) light touch pre-market requirements for evidence. It does not oblige manufacturers to produce data demonstrating a device’s efficacy before it may be placed on the market.³⁷² There is some anecdotal evidence that this may attract device manufacturers to enter the market in Europe first, rather than undertake the more onerous pre-market approval process in the US,³⁷³ which uses a procedure analogous to new pharmaceuticals, requiring valid scientific evidence (usually based on clinical trials) that demonstrates both safety and efficacy.³⁷⁴
- 3.57 Moreover, devices classed as medium risk under the European Medical Devices Directive (such as those delivering TMS) can be approved without additional clinical investigations if a similar ‘predicate’ device is already on the market.³⁷⁵ Approval can be granted if the manufacturer can provide literature showing that their device’s safety and performance are substantially equivalent to the existing device that already has market approval.³⁷⁶ A similar ‘predicate’-based route is also available under the US FDA premarket notification system for devices considered to be lower risk: a process often referred to as 510(k).³⁷⁷ In the context of the US system, which generally requires efficacy data, 510(k) is seen to be particularly lenient. One criticism levelled at the 510(k) route in the US is that termed “predicate creep”, by which devices can be approved through claiming they have the ‘same intended use’ as other devices that were themselves approved via substantial equivalence, leading to the expansion of reasonable equivalence.³⁷⁸
- 3.58 While these routes may be in manufacturers’ immediate economic interests, and potentially enable devices to be made available to patients more swiftly, they could also be criticised for placing the interests of the market above patients’ safety and their need for effective interventions.³⁷⁹ These routes might also encourage an approach to product development that fails to foster innovations that bring additional benefits to patients. It has been suggested that investors might be particularly attracted to the development of devices that, by reason of their similarity to products already on the market, could demonstrate compliance with regulatory

³⁷² Cohen D and Billingsley M (2011) Europeans are left to their own devices *British Medical Journal* **342:d2748**: 1-7, at page 2.

³⁷³ Medtronic (2012) *Grand designs – how to take your medical device innovation from patent to production*, available at: http://www.medtronic-eureka.com/innovation-articles/making-it-happen/patent_to_production.

³⁷⁴ FDA (2013) *Overview of device regulation*, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/overview/default.htm#pma>.

³⁷⁵ Annex 5 of the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (MDD).

³⁷⁶ Cohen D and Billingsley M (2011) Europeans are left to their own devices *BMJ* **342:d2748**, at page 2; European Commission (2009) *Clinical evaluation: a guide for manufacturers and notified bodies*, available at: http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_1rev_3_en.pdf, at page 8.

³⁷⁷ US Food and Drug Administration (2009) *510(k) clearances*, available at: <http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/510kclearances/default.htm>.

³⁷⁸ Hines JZ, Lurie P, Yu E and Wolfe S (2010) Left to their own devices: breakdowns in United States medical device premarket review *PLoS Medicine* **7(7)**: e1000280, at page 4.

³⁷⁹ Cohen D and Billingsley M (2011) Europeans are left to their own devices *BMJ* **342:d2748**.

requirements and so reach market without the need for additional pre-market testing.³⁸⁰ This raises the possible risk that the availability of predicate routes, and the willingness of manufacturers to exploit them, could have a chilling effect on the kinds of innovation that might fill the most important gaps in the market for genuinely novel devices that address unmet patient needs.

- 3.59 In the US, the Humanitarian Device Exemption (HDE) is a regulatory route intended to incentivise innovation to address unmet need through the development of devices for the treatment or diagnosis of diseases that affect fewer than 4,000 people in the US per year. An HDE application made to the FDA does not require any evidence that the device is effective for its intended purpose, but must convince the FDA that the device does not pose an “unreasonable or significant” risk and that the potential benefit outweighs the risk.³⁸¹ However, concerns have been raised in the US about misuse of the HDE; particularly where it was invoked for a DBS device intended to treat OCD. It is questionable whether OCD can be considered an ‘orphan’ condition when the population of people affected by the disorder in the US far exceeds 4,000.³⁸² Moreover, it has been observed that the HDE effectively removes the requirement for a device to undergo clinical trials and may be seen to be enabling the manufacturer to access patients, rather than providing patients with access to therapies grounded in sound scientific evidence.³⁸³
- 3.60 The regulatory routes described above are intended to support innovation by reducing requirements for pre-market evidence and thus seeking to make development trajectories swifter and less costly. This might serve to make a therapeutic product more attractive to investors and help it to reach market – and patients – more swiftly (or at all). However, this is not a desirable outcome unless it also provides sufficient protection to patients’ interests in accessing treatments that have been demonstrated to be safe (and, ideally, effective) by robust clinical evidence. This serves to illustrate the point that difficulties faced by developers in securing sufficient funds to bring a product to market are not the only kind of challenge to patients accessing the kinds of treatment they need. This produces a dilemma: how can the need to stimulate innovation to provide much needed therapeutic products be reconciled with ensuring that patients’ wider interests in the safety and efficacy of these products are protected? We discuss the efficacy and proportionality of the regulation of medical devices in Europe and the US in more detail in Chapter 7.

Selling devices to the NHS

- 3.61 Regulatory approval is prerequisite for monetising devices and medicines, but it is not sufficient. One of the most important ways of capitalising on a novel technology is by ensuring successful sales within a healthcare market. This can be particularly difficult for technologies that are expensive, such as ATMPs, or that lack comprehensive efficacy data, as is the case for most novel devices.
- 3.62 NICE’s technology appraisals make recommendations relating to the use within the NHS of new and existing medicines and treatments.³⁸⁴ The NHS is unlikely to provide medicines that are not recommended by NICE. One of the major barriers to neural stem cell therapies (once any are

³⁸⁰ Royal Academy of Engineering and The Academy of Medical Sciences (2013) *Establishing high-level evidence for the safety and efficacy of medical devices and systems* available at: http://www.raeng.org.uk/Medical_devices_and_systems.pdf, at page 17.

³⁸¹ US Food and Drug Administration (2012) *Humanitarian Device Exemption*, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm>.

³⁸² Fins estimates that there are 440,000-660,000 people with chronic, severe and treatment-resistant OCD. See: Fins JJ, Mayberg HS, Nuttin B *et al.* (2011) Misuse of the FDA Humanitarian Device Exemption in deep brain stimulation for obsessive-compulsive disorder *Health Affairs* **30(2)**: 302-11, at page 304.

³⁸³ *Ibid*, at page 306.

³⁸⁴ NICE technology appraisals are only relevant for the NHS in England and Wales. See: NICE (2012) *About technology appraisals*, available at: http://www.nice.org.uk/aboutnice/whatwedo/abouttechnologyappraisals/about_technology_appraisals.jsp.

licensed) being made available through the NHS is that such treatments are likely to be expensive due to manufacturing complexity, resource requirement, high labour costs and timescales. To justify such an expense, NICE will require returns such as life-changing treatment or cure.³⁸⁵ Attempts are being made to provide some recourse for both developers and potential users of novel medicines, which could potentially include stem cell therapies. For example, in 2012 the MHRA launched a public consultation on an Early Access Scheme for Medicines in the UK. The intention of the scheme is to create a more “progressive regulatory environment” while also providing earlier access to treatments for people with serious life threatening or debilitating illnesses.³⁸⁶ However, the MHRA estimate that based on eligibility criteria, it is unlikely that more than one or two medicines each year will become available via an early access route.³⁸⁷

- 3.63 Unlike medicines, which require significant data from clinical trials before being granted a licence, medical devices are available for purchase and use in the NHS with comparatively little research data, which can make them less amenable to early assessment by NICE’s evidence-based technology appraisals. Alternative assessment options include NICE’s Medical Technologies Evaluation Programme (MTEP) for new or innovative technologies; if the technology receives a positive assessment, NICE encourages its use through guidance (although unlike technology appraisals, it does not *oblige* provision). However, MTEP still requires significant amounts of data and, to date, has only published 13 pieces of guidance.³⁸⁸
- 3.64 In the absence of NICE guidance, interventional procedures³⁸⁹ are often adopted in a haphazard way. A recent study found that, in most cases, the introduction of such technologies was initiated by clinicians,³⁹⁰ a further study notes that hospitals often buy novel devices *directly* from the manufacturer without the knowledge of NHS commissioners.³⁹¹ The consequence for patients is that access to expensive novel neurotechnologies has been variable between NHS Trusts. For example, people with the same indications for Parkinson’s disease will not necessarily have been afforded the same DBS treatment throughout the NHS.

Box 3.3: Specialised Services Commissioning Innovation Fund

In December 2011, *Innovation Health and Wealth*³⁹² announced the introduction of the Specialised Services Commissioning Innovation Fund (SSCIF). The fund is intended to provide a clear pathway for novel technologies to enter the NHS where there is not yet sufficient evidence available to justify full commissioning of the technology. The fund will be launched in the summer of 2013 with funding of £50-5m until April 2014. Applications will be online, with Clinical Reference Groups³⁹³ assessing their viability.

³⁸⁵ Very expensive drugs that lead to only a few months of extra life are unlikely to be recommended by NICE: this has led to high profile controversies, especially in relation to drugs for late stage cancer. See: BBC (2 February 2012) *NICE: Prostate cancer drug too costly for NHS*, available at: <http://www.bbc.co.uk/news/health-16838825>; NICE (2013) *Breast cancer treatment not value for money says draft NICE guidance*, available at: <http://www.nice.org.uk/newsroom/pressreleases/BreastCancerTreatmentNotValueMoney.jsp>.

³⁸⁶ MHRA (2012) *Consultation on a proposal to introduce an early access to medicines scheme in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/websiteresources/con173756.pdf>.

³⁸⁷ MHRA (2012) *Earlier market access for medicines in the UK: impact assessment*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/websiteresources/con173758.pdf>, at page 22.

³⁸⁸ NICE (2013) *Medical Technologies Evaluation programme*, available at: <http://www.nice.org.uk/aboutnice/whatwedo/aboutmedicaltechnologies/medicaltechnologiesprogramme.jsp>.

³⁸⁹ Interventional procedures are technologies used for diagnosis or treatment involving an incision, puncture, entry into the body cavity or the use of electromagnetic radiation.

³⁹⁰ Lourenco T, Grant AM, Burr JM and Vale L (2011) The introduction of new interventional procedures in the British National Health Service—A qualitative study *Health Policy* **100**(1): 35-42, at page 38.

³⁹¹ Health Service Journal (22 February 2012) *Embracing new technologies can drive innovation in healthcare services*, available at: <http://www.hsj.co.uk/resource-centre/best-practice/qipp-resources/embracing-new-technologies-can-drive-innovation-in-healthcare-services/5041593.article?sm=5041593>.

³⁹² NHS (2011) *Innovation, health and wealth: accelerating adoption and diffusion in the NHS*, available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_134597.pdf.

³⁹³ NHS Commissioning Board (2013) *Clinical reference groups for specialised services: a guide for clinicians*, available at: <http://www.england.nhs.uk/wp-content/uploads/2013/01/crg-guide.pdf>.

- 3.65 Apart from concerns about equity of access, the lack of a clear pathway for the introduction of novel devices militates against best practice (such as systematic and comprehensive data collection) and ensuring that clinicians build their experience of the device by treating lots of patients. Such pitfalls may be intensified in the case of novel treatments for neurological diseases, where patients' desperation makes them exceptionally vulnerable to the promise of a novel or experimental treatment. However, in April 2013, NHS England took responsibility for specialised services³⁹⁴ (previously commissioned by 10 Specialised Commissioning Groups). One outcome of this more centralised approach will be the intention to reduce variation in the availability of services, including those novel technologies used to treat neurological and mental health conditions.

“[D]rugs/devices will only be funded if they are endorsed within a national clinical commissioning policy and the patient meets the agreed criteria. Those excluded drugs/devices that are either not NICE approved and/or endorsed within a national clinical commissioning policy can be considered via an individual funding request. However, where the intervention relates to a cohort, a business case will be required. Excluded drugs/devices recommended within a NICE IPG and/or guideline will not be routinely funded unless endorsed within a national clinical commissioning policy.”³⁹⁵

Conflicts of interest

- 3.66 The role of clinicians in the development of devices raises particular concerns that do not arise to the same extent in the context of pharmaceuticals, largely because the development of medical devices is far more reliant on clinicians' experience. In this context, particular attention has focused on the close financial links between the companies and clinicians and surgeons, especially those carrying out clinical trials.³⁹⁶ Clinicians are often involved in the conceptualisation, invention, and development of devices, and frequently advise companies on the further development of a device into a commercial product. They often act as enthusiastic promoters for these devices.³⁹⁷ Links between clinicians and companies may be strengthened by the provision of educational grants from those companies to enable further device development, which the company in turn hopes to develop into an improved marketable product. Moreover, far more than with pharmaceuticals, the success of a device relies on training and surgical skill to ensure intended clinical outcomes and hence market authorisation. Indeed, clinicians are often dependent on industry to produce the devices that they wish to use in their research.³⁹⁸
- 3.67 However, conflicts of interest in relation to non-neurotechnological medical devices have been highlighted by a number of researchers and doctors. Thus, for example, consultant cardiologist Peter Wilmschurst has argued that:

“...technical skills allow some clinicians to appreciate a gap in the market and conceive a design. They may have built and tested prototypes... They may have done initial *in vivo* animal or human trials. They or their employing hospital often owns the patent for the device and gets royalties for its sale. They may have

³⁹⁴ There are four factors that will determine whether NHS England commissions a service as a prescribed specialised service: 1) The number of individuals who require the service; 2) The cost of providing the service or facility; 3) The number of people able to provide the service or facility; and 4) The financial implications for Clinical Commissioning Groups (CCGs) if they are required to arrange for provision of the service or facility.

³⁹⁵ NHS Commissioning Board (2012) *Prescribed specialised services: commissioning intentions for 2013/14*, available at: <http://www.commissioningboard.nhs.uk/files/2012/11/comm-int.pdf>, pp.28-9.

³⁹⁶ La Violette PA (2007) Medical devices and conflict of interest: unique issues and an industry code to address them *Cleveland Clinical Journal of Medicine* **74(Sup2)**: S26-8.

³⁹⁷ Cohen D (2011) Out of joint: the story of the ASR *British Medical Journal* **342**:d2905.

³⁹⁸ Fins JJ, Schlaepfer TE, Nuttin B *et al.* (2011) Ethical guidance for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic deep brain stimulation *Journal of Neural Engineering* **8(3)**: 1-6, at page 2.

founded a company to develop the device or sold or leased the rights to a commercial company.”³⁹⁹

Further, Wilmshurst argues that, following the granting of a licence, doctors act as part of the “company’s marketing arm”, cascading skills to other doctors to increase the take up of the device in question, acting as “paid investigators in clinical trials” of the devices and, in return, receiving shares in the company that they are investigating.⁴⁰⁰ It has been suggested that the sums that clinicians can generate by these means, in some cases, amount to millions of dollars.⁴⁰¹ Related research has claimed that, in some cases, direct payments have been made by manufacturers to clinicians for the use of their devices;⁴⁰² in some cases clinicians may be reluctant to report complications that arise from the use of the devices for reasons that include a fear of damaging their relations with the manufacturers.⁴⁰³

- 3.68 In the context of neurodevices, the relatively small market intensifies the monopolistic environment and hence the potential for pressures to be exerted on clinicians by industry.⁴⁰⁴ Similar risks of conflicts of interest have been examined in relation to DBS; in particular, it has been argued that, where DBS is concerned the situation is exacerbated by the semi-monopolistic relations that obtain between the small number of investigators and small number of companies involved.⁴⁰⁵
- 3.69 Other authors, however, have cast doubt on the extent of these conflicts as applied to neurotechnologies. One article explores the relations between the industry and neurosurgeons, in the light of the criticisms that “surgeon-held patents and royalties incentivise surgeon loyalty, influencing decision making as to which devices are used intraoperatively.”⁴⁰⁶ On the basis of a search of US patent records and the physician payment registries of the largest device makers, the authors of this article found that 147 neurosurgeons (three per cent of the total of 4,868 recognised by the appropriate professional body) held a total of 582 patents and that the royalties expected to be paid to neurosurgeons in 2010 amounted to a little over \$13 million (the lowest payment was a mere \$7,000 while the largest was \$8.261 million). They concluded that, despite public and legislative concerns, in this area at least, the conflicts of interest were limited.⁴⁰⁷ Nonetheless, clearly for some neurosurgeons, they may be significant.
- 3.70 Whether or not neurosurgeons are making profits from inappropriate relations with industry, the potential for mismanagement of conflicts of interest is clearly a significant issue in the medical devices industry. In relation to neurotechnologies that intervene in the brain, the situation is more worrying because, in addition to shaping the developmental pathways in perverse ways, such conflicts of interest may result in devices being brought into clinical use without objective and impartial assessments of safety and efficacy. The difficulties may be exacerbated by the vulnerability brought about by some neurological and mental health conditions, and the potential for overselling the therapeutic benefits of the devices in question to patients who have few, if any, other options.

³⁹⁹ Wilmshurst P (2011) The regulation of medical devices *British Medical Journal* **342**:d2822, at page 1.

⁴⁰⁰ *Ibid.*, at page 1.

⁴⁰¹ *Ibid.*, at page 1.

⁴⁰² Cohen D (2011) Out of joint: the story of the ASR *British Medical Journal* **342**:d2905, at page 1,118.

⁴⁰³ *Ibid.*, at page 1,119.

⁴⁰⁴ Fins JJ, Schlaepfer TE, Nuttin B *et al.* (2011) Ethical guidance for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic deep brain stimulation *Journal of Neural Engineering* **8**(3): 1-6, at page 2.

⁴⁰⁵ Fins JJ and Schiff ND (2010) Conflicts of interest in deep brain stimulation research and the ethics of transparency *The Journal of Clinical Ethics*, **21**(2): 125.

⁴⁰⁶ Babu MA, Heary RF and Nahed BV (2012) Device innovation in neurosurgery: controversy, learning, and future directions *Neurosurgery* **70**(4): 789-5.

⁴⁰⁷ *Ibid.*

Obstacles to accessing treatment

3.71 At the start of this chapter, we illustrated the high and global incidence of disorders that novel neurotechnologies seek to treat. The challenges to securing investment to bring a product to market described earlier in this chapter account for some of the reasons that many who might benefit from novel neurotechnologies do not currently have access to them. However, we cannot assume that investment alone would deliver the neurotechnologies to meet the needs of all of those living with neurological and mental health disorders in a global context. The cost of delivering treatment using many of these technologies presents a further obstacle to access. It is likely, at least for the time being, that even if products *do* secure funding to reach the market, they will be expensive. Approximate indications of the cost of treatments using the neurotechnologies considered in this report are given in Box 3.4.

Box 3.4: Approximate cost of treatments using novel neurotechnologies

DBS: In 2011, the East of England Specialised Commissioning Group (SCG) estimated the average cost of DBS was £33,000 per patient (including surgery, hospital stay and follow-up) and that their eligible disease population was approximately 27, taking the annual cost up to about £891,000 *per annum*. East of England was one of ten specialised groups commissioning DBS (now commissioned by NHS England), and the cost of DBS for Parkinson's disease across England can therefore be estimated as approximately £9 million *per annum*.⁴⁰⁸

Neural stem cell therapies: There are currently no neural stem cell therapies available in the UK and costs are likely to reflect long lead-times for manufacturing and licensing arrangements. NeuroInsights report that companies developing neural stem cell products cite the cost of neurodevices (\$30,000-\$100,000) as a reasonable price point for future stem cell treatments.⁴⁰⁹

TMS: In the US, Neuronetics' TMS device costs approximately \$70,000.⁴¹⁰ A typical course of outpatient TMS therapy involves 20 to 30 sessions, occurring five days a week over a four-to-six-week period. The cost varies from approximately \$300 to \$600 per session.⁴¹¹

BCI: Non-invasive BCIs for therapeutic or assistive purposes are likely to be closer to commercial application than those which are invasive. Multiple factors dictate the price of non-invasive BCIs, including types of electrodes (whether these are active, passive, wet or dry), signal quality, impedance checks, and software. Expensive laboratory systems with higher numbers of electrodes and good signal quality are estimated to cost between \$6,000-14,000.⁴¹² This, however, does not include the personnel costs associated with training of and support for users. Invasive BCIs will inevitably be considerably more expensive, not least because of the costs of neurosurgery.

3.72 Development of neurotechnologies is not, of course, limited to high-income countries. For example there is both research and development of DBS in China and India,⁴¹³ with clinical use of the technology in an increasing number of cases, largely for Parkinson's disease and some other movement disorders.⁴¹⁴ The development of neurotechnology industries in emerging economies and the routinisation of production of neurodevices are likely to contribute to incremental cost reductions. However, the expense of treatment using many of these neurotechnologies is not due only to costs associated with the development and marketing of products themselves.

⁴⁰⁸ NHS East of England Specialised Commissioning Group (2010) *Commissioning policy on the use of deep brain stimulation for Parkinson's disease, tremor and dystonia*, available at: <http://www.derbycitypct.nhs.uk/UserFiles/Documents/DocumentsDownloads/policies/P037V1%20EMSCG%20Policy%20for%20DBS%20V1.pdf>.

⁴⁰⁹ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 236.

⁴¹⁰ NeuroInsights (2010) *Neurotechnology industry reports revenues of \$143.1 billion in 2009*, available at: <http://www.neuroinsights.com/neurotech2010release.html>, at page 283.

⁴¹¹ *Ibid*, at page 283.

⁴¹² Future BNCI (2011) *A Roadmap for Future Directions in Brain / Neuronal Computer Interaction Research*, at page 217.

⁴¹³ Functional Neurosurgery: Jaslok Hospital (2012) *About Dr. Paresh*, available at: <http://www.neurologicalsurgery.in/about-dr-paresh/>; The Times of India (9 February 2011) *City docs try alternate cure for Parkinson's disease*, available at: http://articles.timesofindia.indiatimes.com/2011-02-09/mumbai/28541185_1_subthalamic-nucleus-deep-brain-stimulation-parkinson.

⁴¹⁴ Hu WH, Zhang K, Meng FG, Ma Y and Zhang JG (2012) Deep brain stimulation in China: present and future *Neuromodulation: Technology at the Neural Interface* **15(3)**: 251-9.

- 3.73 Unlike pharmaceuticals, treatment costs associated with many novel neurotechnologies will not drop dramatically with the expiry of IPR. Treatment using most novel neurotechnologies discussed in this report requires the continuing presence of medical personnel and is almost always administered in a hospital or clinical setting. For example, in the case of DBS, medical intervention does not stop at the initial highly-skilled surgery needed to situate electrodes and battery packs, but continues with regular medical follow-up care which is required to check that the technology is functioning as it should, to vary stimulation parameters.⁴¹⁵ Discrepancies in the cost of delivering treatments such as DBS may lead to people from higher income countries travelling abroad to access cheaper treatment options; there is some evidence of hospitals already positioning themselves for such a market.⁴¹⁶
- 3.74 Where neural stem cell therapies are concerned, while production methods used to develop and manufacture these products may eventually become more routine and reduce costs, this currently remains a distant prospect. High costs of treatment could mean that even if some therapies *do* reach the market, they may not be available in the UK through the NHS. The barriers in terms of affordability are clearly even more profound in low- and middle-income countries.
- 3.75 The lure of novel treatments, with their promise of cutting-edge medical innovation to address conditions that are currently untreatable, means that the possible incentives for patients to access cross-border treatment may not be limited to cost considerations alone. At the time of writing, no neural stem cell therapies have been approved for commercial use in the UK, Europe or the US, although some therapies are in the clinical trial phase.⁴¹⁷ This gives some people living with currently untreatable conditions a strong impetus to travel abroad to access treatments in other jurisdictions.⁴¹⁸ There is already a market for unregulated and unproven stem cells therapies. There is significant evidence that unproven treatments, in particular those claiming to use stem cells to treat stroke and Parkinson's disease, are being offered in unlicensed and unregulated clinics in countries such as China and India, exploiting the desperation of patients both within and from outside those regions.⁴¹⁹ While the outcomes of such interventions are rarely reported in scientific journals, those offering the treatments often make bold claims of efficacy.⁴²⁰ Undoubtedly, these developments raise concerns in those regions themselves; for example, in China, there have been several attempts to develop regulations to curb unlicensed stem cell treatments.⁴²¹ However these characteristics of the developing transnational market for neural stem cell therapies do not only raise challenges for regulation; they also have the possibility of driving the development of novel neurotechnologies in a direction that does *not* meet wider public need.

⁴¹⁵ Fins JJ (2009) Deep brain stimulation, deontology and duty: the moral obligation of non-abandonment at the neural interface *Journal of Neural Engineering* **6(5)**: 1-4.

⁴¹⁶ Dr. Dheeraj Bojwani (2012) *Deep brain stimulation in India*, available at: <http://www.dheerajbojwani.com/deep-brain-stimulation-therapy-low-cost-advantages-India.html>.

⁴¹⁷ ReNeuron (2013) *Clinical trials in disabled stroke patients*, available at: <http://www.reneuron.com/the-pisces-clinical-trial-in-disabled-stroke-patients>; Neurogeneration (2009) *Groundbreaking paper publishes long term results of a successful phase I clinical trial using autologous neural stem cells to treat Parkinson's disease*, available at: <http://neurogeneration.com/pdf/NGNPress021609.pdf>.

⁴¹⁸ For example, see: China Medical Tourism (2012) *China medical tourism brain injury stem cell therapy 3 clip*, available at: <http://www.youtube.com/watch?v=Lpre3UoObKs>.

⁴¹⁹ Barclay E (2009) Stem-cell experts raise concerns about medical tourism *The Lancet* **373(9667)**: 883-4; Murdoch CE and Scott CT (2010) Stem cell tourism and the power of hope *The American Journal of Bioethics* **10(5)**: 16-23; Cohen CB and Cohen PJ (2010) International stem cell tourism and the need for effective regulation: part I: stem cell tourism in Russia and India: clinical research, innovative treatment, or unproven hype? *Kennedy Institute of Ethics Journal* **20(1)**: 27-49.

⁴²⁰ See, for example, the claims made in ChinaStemCellNews *8 SCI survivors talk improvements* available at: <http://stemcellschina.com/>.

⁴²¹ New Scientist (11 January 2012) *China attempts to halt unproven stem cell therapies*, available at: <http://www.newscientist.com/blogs/shortsharpscience/2012/01/china-halts-new-stem-cell-tria.html>; McMahon D and Thorsteinsdóttir H (2010) Lost in translation: China's struggle to develop appropriate stem cell regulations *Scripted* **7(2)**: 283-94.

Box 3.5: Stem cell tourism

The size of the unregulated neural stem cell market is difficult to estimate and is based largely on self-reporting by clinics providing treatments. For example, Beike Biotech, a Chinese clinic specialising in neurological disorders, claims to have treated over 3,000 patients at its 24 hospital clinics in China: its website appeals directly to potential medical tourists, and contains videos of patients claiming remarkable therapeutic effects for their therapies which have not been validated by clinical trials.⁴²² ACT, from Turks and Caicos, and Emcell, from Ukraine, claim to have treated over 700 and over 2,000 patients, respectively.⁴²³

Research conducted on the websites of 19 clinics advertising stem cell therapies, including those based in China, India, Ukraine, Philippines, and Dominican Republic, concluded that the portrayal of stem cell medicine on provider websites was optimistic and unsubstantiated by peer-reviewed literature.⁴²⁴

An observational study of the stem cell treatment of spinal cord injury in Beijing concluded that the “procedures observed did not attempt to meet international standards for either a safety or efficacy trial. In the absence of a valid clinical trials protocol, physicians should not recommend this procedure to patients.”⁴²⁵

- 3.76 It seems unlikely that neurotechnologies will provide a comprehensive and affordable answer to the increasing global incidence of neurological and mental health disorders in the near future. The economic drivers and constraints upon the development of novel neurotechnologies present considerable challenges to ensuring that products are available in ways that are consonant with the values of equitable access in response to urgency of need. This may, in turn, raise the risk that desperate patients will be attracted by the promises made for cheap treatments in inadequately regulated jurisdictions.

Concluding remarks

- 3.77 In this chapter, we have described the national and global extent of the neurological and mental health conditions for which there are, currently, few good, effective, and economically viable forms of treatment, and which novel neurotechnologies might hope to address. We have then examined the extent to which the current ‘economy’ of novel neurotechnologies – that is to say the financial and economic factors that shape their development – facilitates or hampers their development in ways that can meet these needs. We have identified a number of characteristics of the current innovation landscape which are obstacles to such developments: features which do not always stimulate innovation, do not always direct research and development to the areas of greatest global need, and which sometimes appears to militate against research and innovation that meet the interests of patients in accessing safe and effective therapies.
- 3.78 We have argued that, despite much discussion of the problems of funding the development of biotechnologies, there remain major difficulties in innovators bringing their potentially valuable products through from early stage development to marketable products, in particular across the difficult terrain that has been colloquially termed ‘the valley of death’. While this funding gap has been widely recognised, the costs in bridging the gap between early, small scale and short term technological development and the subsequent scaling up of effective innovations to meet market requirements, are often very great, as some of our examples have shown. Private investors are often reluctant to commit funds over the long periods that may be required, and it is difficult to imagine public funders committing to decade-long financing of inherently risky developments.

⁴²² Beike Biotech *Mom hopes stem-cell treatment will give her child the gift of sight*, available at: http://beikebiotech.com/index.php?option=com_content&view=article&id=388:mom-hopes-stem-cell-treatment-will-give-her-child-the-gift-of-sight&catid=5:beike-in-the-news&Itemid=5.

⁴²³ Lau D, Ogbogu U, Taylor B *et al.* (2008) Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine *Cell Stem Cell* **3(6)**: 591-4, at page 591.

⁴²⁴ *Ibid.*

⁴²⁵ Dobkin BH, Curt A and Guest J (2006) Cellular transplants in china: observational study from the largest human experiment in chronic spinal cord injury *Neurorehabilitation and Neural Repair* **20(1)**: 5-13, at page 5.

- 3.79 This then presents the challenge of how to create an economic landscape that favours inventiveness and innovation in products that meet the needs that we have identified. This will require identifying means for commercial enterprises to access secure medium term funding for product development. It remains an open question as to what the source of this kind of funding might be. For example, is the withdrawal of large pharmaceutical companies from CNS drug development indicative a more general problem of market failure that only long-term and sustained public investment can resolve?
- 3.80 While it may not be possible to specify the precise sources of sufficiently secure funding, it is clear that whatever form it takes, this needs to support, rather than disincentivise, innovation pathways that have patients' interests in securing access to safe, effective therapies as a central priority. As we have suggested, patients' interests may be undermined by innovations, the primary aim of which is to secure first mover advantage and market share by the exploitation of regulatory routes that do not necessitate the highest standards of pre-market clinical evidence, and by financial incentives to test particular technologies that may compete with clinicians' duties towards their patients. Nor should securing investment in innovation rely upon, or encourage, hype and premature and exaggerated promises as the current situation does. While many of these problems are not unique to neurotechnologies, the fact that we still know so little about how neural processes are affected by interventions such as DBS, gives us special cause for reflection. There is an important role here for large public health providers, like the NHS, regulators, such as the MHRA, and non-departmental public bodies such as NICE, in managing and stimulating the innovation landscape according to public norms of efficacy and value.
- 3.81 Given the global nature of some of the conditions we have discussed (including stroke, dementia, and chronic pain) and given the cost and complexity of some of the neurotechnological interventions discussed in this report, the immediate reality is that even where novel neurotechnologies have been proven to be safe and effective, they are likely to be available only to the wealthy few. The challenge remains as to whether novel neurotechnologies can be developed in such a way that maximises equity of access globally as well as locally.
- 3.82 In Chapter 7, we return to many of the topics we have introduced here as part of our assessment of the regulatory systems operating in the UK and Europe. We ask how these systems may operate in effective and proportionate ways to support innovation and the entry into the market of much needed therapies, while protecting patients' safety and well-being in ways that are appropriate to novel technologies that intervene in the brain. As part of this discussion we also consider how the market may not be the only means to access treatment using novel neurotechnologies and review the means by which treatments for single, or small groups, of patients are regulated (see paragraphs 7.73 to 7.82).
- 3.83 Before examining the regulatory landscape, we turn first to the task of identifying which ethical considerations are key to guiding the practices of all actors involved in funding, developing, regulating, using and promoting neurotechnologies and to providing safe and effective therapies to address unmet health needs. As such, the ethical framework we provide in Chapter 4 supplies not only a means of assessing the values and interests that are crucial to the clinical care of patients and research participants, it also provides a guide to understanding what constitutes responsible research and innovation in the field of novel neurotechnologies, and thus what obligations fall on those who fund and pursue innovation under the pressures and constraints we have identified in this chapter.

Chapter 4

Ethical Framework

Chapter 4 - Ethical Framework

Chapter 4 – overview

The brain has a special status in human life that distinguishes it from other organs. Its healthy functioning plays a central role in the operation of our bodies, our capacities for autonomous agency, our conceptions of ourselves and our relationships with others – and thus in our abilities to lead fulfilling lives. This means that the novel neurotechnologies we consider in this report, each of which intervenes in the brain, raise ethical and social concerns that are not raised to the same extent by other novel biomedical technologies.

The ethical framework we construct to navigate these concerns is built up in three stages:

- **Foundational principles:** A tension between need and uncertainty lies at the foundation of our framework. On one hand given the suffering caused by brain disorders and an absence of other effective interventions, there is a need for therapeutic applications of neurotechnologies. On the other hand there is uncertainty about benefits and risks of these technologies, due not only to their novelty but also to the lack of comprehensive understanding of how the brain works. The special status of the brain therefore provides both a reason to exercise **beneficence** by intervening when injury or illness causes brain disorders, and a reason for **caution** when we are uncertain what the effects of doing so will be.
- **Interests:** In articulating the implications of the principles of beneficence and caution in the context of developing and using novel neurotechnologies, we identify a cluster of five interests that warrant particular attention. These encompass not only protection against the potential **safety** risks of interventions, but also those interests associated with unintended impacts on **privacy** and the promotion of **autonomy**, both in treatment-specific decisions and in the wider context of patients' lives. There are also important public interests in **equity** of access to the products of innovation, the preventing of stigma and protecting and promoting public understanding and **trust** in novel neurotechnologies.
- **Virtues:** Finally we suggest that, in seeking to protect and promote these interests, there are three virtues which are especially relevant to guiding the practices of actors across a wide range of settings and applications of novel neurotechnologies. These virtues are: **inventiveness**, which may be exercised through, amongst other means, technological innovation and by identifying ways to provide wider access to therapies; **humility**, which entails acknowledging the limits of current knowledge and of our capacities to use technologies to alleviate the harms of brain disorders; and **responsibility**, which is exemplified by pursuit of robust research practices and refraining from exaggerated or premature claims for these technologies.

These virtues are helpful because they characterise the kinds of attitudes and practices that should be exemplified by those engaged in the development, funding, use, regulation and promotion of novel neurotechnologies, and fostered and supported by the institutions within which they work. All three steps of this framework provide the tools we use to assess the practices and oversight mechanisms examined in subsequent chapters.

Introduction

- 4.1 The brain has a special status in human life which implies that interventions upon this organ provoke concerns not raised to the same extent by other novel biomedical technologies or interventions. Our development of an ethical framework for these interventions starts from a consideration of the reasons we have for valuing our brains and the related imperatives for intervening when the brain ceases to function as it should due to injury or illness. We observe that the combination of the imperative to alleviate the harms resulting from brain damage and the limits to our understanding of how this may be effectively achieved gives rise to a particular tension between need and uncertainty.
- 4.2 Need and uncertainty find their natural ethical counterparts in the principles of beneficence and caution. The requirement to strike a balance between these is at the heart of the ethical framework set out here. However, we recognise that beneficence and caution are only general signposts; therefore we develop our ethical framework through a set of interests that mediate between these principles. The interests that capture the chief considerations relevant to the novel neurotechnologies discussed here are safety, autonomy, privacy, equity, and trust. Each of these interests is of fundamental value and importance to each of us, and requires special attention in the context of novel neurotechnologies.
- 4.3 We recognise that a list of principles and interests does not suffice for an ethical framework that seeks to provide guidance in balancing the demands of need and uncertainty. In this shifting dynamic, conflicting interests will often require recourse to practical judgement. Therefore we

also establish the virtues that actors in this field – those who research, develop, administer, use, fund, market, govern, and communicate the capacities of novel neurotechnologies – should exemplify in their professional conduct. In some cases, these also apply to patients and research participants with whom the technologies are used. As a third step in our ethical framework, we suggest that the virtues of inventiveness, humility and responsibility are those most pertinent to guiding ethical practice in the development and therapeutic uses of novel neurotechnologies.

- 4.4 We have constructed this framework on the premise that the most pressing ethical challenges are raised by therapeutic applications of novel neurotechnologies. This does not mean that non-therapeutic applications (in this report we consider those for enhancement, recreational, and military purposes) fail to raise relevant ethical considerations. We discuss these applications separately in Chapter 8 for two reasons: either because, where neurotechnologies are used for military purposes, the ethical issues raised are markedly distinct; or because, even where the ethical framework described in this chapter may be applied in contexts of non-therapeutic uses for enhancement or recreational purposes, the circumstances of use and the actors involved are sufficiently distinct to merit a separate analysis.
- 4.5 Before introducing the principles and interests, and the virtues associated with supporting their promotion and protection in the field of novel neurotechnologies, we will first address what we mean by the ‘special status of the brain’ in order to elucidate the fundamental personal interest that drives ethical concerns in this area.

The special status of the brain

- 4.6 The human brain is the organ of the human species that most profoundly distinguishes us from all other species, including other primates. It is an extraordinary network of neuronal structures, containing nearly 100 billion neurons, whose connections somehow underpin the capacities that are central to our lives. As we outline in the following paragraphs, it is the foundation of human existence – personal, sub-personal and interpersonal. This gives us reason enough to attach particular value to the brain, and to appreciate the profound concerns that surround interventions that act directly upon it.

Brain, mind and body

- 4.7 The processes by which mental functions are enabled by the brain remain largely unknown. Brain research has made enormous progress over the past five decades, but at present we have no comprehensive models of this structurally complex and functionally-dynamic system. The precise relations between mind and brain, between mental states and brain-states, are notoriously disputed but, for the purposes of this report, it is not necessary to take sides in this ancient debate. The broad dependence of human mental capacities, such as perception, thought, memory, feeling, and agency upon our brains, is now taken for granted.
- 4.8 A central aspect of the brain’s special status comes from its role as the organ through which the body as a whole is controlled. Our embodiment is an essential dimension of our existence, of our capacities for perception and action, for language and emotion. Since the brain is central to the management of this somatic existence, it provides the basis for the sense we have of ourselves as a material and historical presence in the world. We learn from neuroscience, particularly from the study of brain injuries, that this sense of ourselves is founded upon non-conscious processes in the brain that both prepare materials for conscious experience and manage the body’s routine autonomic systems – for example, breathing, digestion or sexual arousal – which are the basis of our embodied existence. Hence these non-conscious processes, as much as our conscious processes, make a significant contribution to the ways in which we see ourselves and are seen by others, to the maintenance of our independence and our relationships.

Identity and autonomy

- 4.9 The brain receives special attention because, for each of us, it is uniquely associated with ‘me’; with our subjective self-conception and capacity to develop and exercise this conception through our actions, pursuits and relationships with others. In many cultures (though not all), a high value is placed on the development of this individualised sense of oneself. This is associated with the belief that developing and realising this identity through the course of one’s life and relationships with others is a central aspect of living a fulfilling human life. Brain damage can, however, threaten this ideal of self-realisation, since injury or disease has the potential to disrupt this possibility at the most fundamental level by interfering with the capacity to form and maintain a connected sense of oneself over time. For example, where people with dementia experience serious memory loss this may, to varying degrees, impact on their own sense of their identity.⁴²⁶
- 4.10 Personal identity is closely bound up with our sense of autonomy. As autonomous agents, we are able to act for reasons that we ourselves identify with and endorse rather than, for example, following habits or instructions from others without reflection. We value our capacity to exercise this kind of rational control over our actions and to exhibit a degree of consistency of character, in part because this is the central means through which we develop our own sense of ‘who we are’ and the personalities by which others recognise us. This is particularly true where we act from desires and beliefs that we think of as ‘authentic’ or ‘true to ourselves’ - yet some serious neurodegenerative illnesses and mental health disorders have the potential to create a separation between precisely these kinds of motivations and an individual’s behaviour.⁴²⁷ Even where cognitive or affective functions are not damaged, serious movement disorders and conditions such as locked-in syndrome undermine autonomy in the most basic way, by preventing individuals from communicating or putting their desires into action.
- 4.11 Our intention is not to talk as if personal identity and autonomy are capacities of an individual existing in isolation. This is, of course, not the case. Our abilities to frame lives of our own are not merely dependent on the functions of our individual embodied brains, but are sustained by relationships with others. We develop a sense of our own identity through our dealings with others and we exercise our autonomy in the context of lives which we share with them. These relationships run very deep and should be seen as an essential dimension of the individual self.⁴²⁸ An adequate ethical framework must be sensitive to this interdependence of persons.

⁴²⁶ This is not to suggest that memory loss and its effect on self-perception make those with dementia any less deserving of respect as persons and in the context of others’ ethical and legal obligations to them. The Nuffield Council on Bioethics’ previous report on dementia explores these questions in depth, emphasising the importance of not stigmatising those living with this condition and that it is possible to live a fulfilling life with dementia. See: Nuffield Council on Bioethics (2009) *Dementia: ethical issues*, available at: <http://www.nuffieldbioethics.org/sites/default/files/Nuffield%20Dementia%20report%20Oct%2009.pdf>, at page 30.

⁴²⁷ See, for example, NICE (2006) *Dementia: supporting people with dementia and their carers in health and social care*, available at: <http://www.nice.org.uk/nicemedia/live/10998/30318/30318.pdf>, at page 4; and Dworkin R (1994) *Life’s dominion: an argument about abortion, euthanasia, and individual freedom* (New York: Vintage Books), pp224-5. Unlike Dworkin, however, we do make further inferences here from the authenticity of choices, to the rights of individuals with severe dementia.

⁴²⁸ See, for example, Mackenzie C and Stoljar N (2000) Introduction, in *Relational autonomy: feminist perspectives on autonomy, agency, and the social self*, Mackenzie C, and Stoljar N (Editors) (New York: New York: Oxford University Press). For discussion of relational autonomy in the context of respecting the interests of those with dementia see: Nuffield Council on Bioethics (2009) *Dementia: ethical issues*, available at: <http://www.nuffieldbioethics.org/sites/default/files/Nuffield%20Dementia%20report%20Oct%2009.pdf>, at paragraph 2.53.

Box 4.1: Neuroscience and free will⁴²⁹

The idea that human beings – of a certain age and not affected by illness or disorder – are agents capable of autonomy is central to prevailing western ideas of the person. However, we should note that some contemporary neuroscientists have questioned these beliefs. They argue that laboratory experiments on volition have shown that the brain prepares for an action – and in a sense has ‘decided’ on that action – before an individual is conscious of that intention. Many go on to argue that these results have implications beyond the laboratory, to decisions in everyday life, that much decision making takes place below the level of conscious awareness, and that our sense of conscious deliberation and choice is illusory. If this is the case, they suggest, agency and thus autonomy are illusory. This conclusion can, however, be disputed, as it depends on the extrapolation of results from highly simplified laboratory situations. While there is no reason to doubt that the brain does take the lead in preparing us for action, it does not follow that we do not also have a capacity for conscious deliberation and action which builds upon our sub-intentional acts. For the purposes of our argument here, therefore, we shall assume that our current conceptions of agency and autonomy are not radically undermined by neuroscience and that, fictional or not, beliefs in agency and autonomy are crucial to our sense of self, and real in their effects in social relationships.

Grounding our ethical framework: need and uncertainty

Why intervene in the brain?

- 4.12 The crucial role of the brain in the functioning of the mind, the body, and the development of self conceptions and autonomous agency makes it clear why neurological disorders and other conditions with a neurobiological basis threaten such profound and distressing personal consequences. Damage to the brain can rob individuals of their ability to participate fully in life by affecting the individual’s mood, capacity for organised action, their awareness of themselves and others, and their memory. Chronic pain and movement disorders such as dystonia are enervating and interfere with everyday activities. Equally, where brain disease or injury affects the body’s autonomic systems, even when higher functions are largely unaffected, life can become very difficult. People who have lived active lives find themselves dependent on others in ways that are difficult to manage. Neurological and mental health conditions can also be a source of social stigma, embarrassment, and social isolation.⁴³⁰
- 4.13 Damage to the brain has the potential to disrupt the life history of a self that has emerged, grown and changed over time, as well as the imagined futures of this self. An evolving and dynamic identity is a normal and appropriate response to new experiences, but where changes in identity result instead from illness or injury they may be the cause of confusion and alienation.⁴³¹ Sometimes the condition itself may mean these changes are not appreciable by the individual herself or himself, but the effects on those with whom they share their lives may be no less distressing. Neurological and mental health disorders can profoundly affect relationships with family members and others close to them. Where relationships become ones of dependence, this can transform the lives of those who accept the responsibility for care, bringing domestic upheaval, social isolation and economic burdens. These personal impacts collectively provide powerful motives for seeking to alleviate these effects where possible.
- 4.14 Neurological and mental health conditions are also liable to present significant challenges for wider society. As we outline in Chapter 3, the global incidence and costs of disorders affecting the brain are considerable. The development and application of novel neurotechnologies plays a vital role in a society that values equal participation and equal access to life’s goods for all its citizens. Therapeutic applications also have the potential to contribute to the public good by

⁴²⁹ See, for example, Libet B, Gleason CA, Wright EW and Pearl DK (1983) Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential) The unconscious initiation of a freely voluntary act *Brain* **106(3)**: 623-42 and Haggard P (2008) Human volition: towards a neuroscience of will *Nature Reviews Neuroscience* **9(12)**: 934-46.

⁴³⁰ See, for example, Jacoby A, Snape D and Baker GA (2005) Epilepsy and social identity: the stigma of a chronic neurological disorder *The Lancet Neurology* **4(3)**: 171-8; Nuffield Council on Bioethics (2009) *Dementia: ethical issues*, available at: <http://www.nuffieldbioethics.org/sites/default/files/Nuffield%20Dementia%20report%20Oct%2009.pdf>, at page 59.

⁴³¹ Baylis F (2011) “I am who I am”: on the perceived threats to personal identity from deep brain stimulation *Neuroethics*: 1-14.

minimising those individual and social harms arising from disorders or diseases of the brain, and by so doing, contributing to both individual and collective well-being and prosperity.⁴³²

- 4.15 As described in Chapter 2, it is a distinctive feature of the brain that it has only a limited capacity to heal itself. This is not to say that some recovery from stroke or brain injury is impossible. Our growing understanding of brain plasticity suggests that both the physical architecture and the internal organisation of the brain is modulated throughout our lives (see paragraphs 2.10 to 2.12). In some circumstances, rehabilitation can assist the brain in ‘rewiring’ itself, thereby recovering some or most lost function. Nevertheless, in many cases, where there is severe damage to the brain or progressive degeneration, it may only be possible to repair or alleviate this to a limited extent through medical interventions. While some existing surgical procedures or pharmacological therapies are available, there are few effective interventions at present. The increasingly pessimistic outlook for pharmacological options to address many mental health disorders is just one example of this gap.⁴³³

Therapeutic need and the principle of beneficence

- 4.16 There is therefore a *need* for effective treatments in this area that gives sufficient grounds for asserting that the familiar bioethical principle of beneficence – that is, the principle underpinning the responsibility to do good where possible – applies here. In the present context this principle attaches to the good achievable through promoting biomedical research, providing treatments, and seeking to improve upon neurotechnologies which could help to alleviate serious neurological and mental health disorders for which alternative effective interventions are not available. The kinds of novel neurotechnologies discussed in this report offer promising therapeutic avenues. At present they do not represent cures, but the possible impacts of these interventions on the health and quality of life for individuals (and their families), for whom there are few or no other therapeutic options, should not be underestimated. For example, assistive BCIs offer ‘locked-in’ users perhaps their only opportunities to interact with the world. DBS and non-invasive neurostimulation, meanwhile, can be targeted to mitigate the debilitating symptoms of chronic pain, depression or movement disorders that remain resistant to other forms of therapy.
- 4.17 As we have seen in Chapter 3, a significant obstacle to meeting need is securing funding to bring these technologies to market and to attempt to achieve, as far as possible, equitable access to the products of research and innovation. While beneficence is most obviously a principle that gives responsibilities to those with authority to direct public resources in this area (for example, in the UK, this will mean national governments, research funding councils, and the NHS), it is by no means limited to these authorities. For example, this duty will also extend to researchers, clinicians, and regulators. It extends also to other parties who are in a position to support innovation, for example through private funding. Each of these parties may be seen as a bearer of a duty to meet the needs of those who lack access to effective interventions. However, the obligation to ‘do good’ through the development and administration of therapeutic interventions in the context of neurotechnologies is importantly constrained, not only by economic obstacles to making these products widely available and the opportunity costs of doing so, but also by a responsibility to exercise caution in light of the persistent uncertainty about the possible consequences of intervening in the brain.

Why we face uncertainty

- 4.18 For many of the technologies discussed in this report, the balance between the therapeutic benefits of intervening in the brain and the risks of doing so remains unclear. This is, therefore, a chief concern for this report. The ‘novel’ nature of these technologies means that evidence

⁴³² Foresight (2008) *Mental capital and wellbeing: making the most of ourselves in the 21st century*, available at: http://www.bis.gov.uk/assets/biscore/corporate/migratedD/ec_group/116-08-FO_b.

⁴³³ Hyman SE (2012) Revolution stalled *Science Translational Medicine* **4(155)**: 1-5.

which addresses this lack of clarity is often unavailable, in particular in relation to longer-term unintended effects. Novelty is not the only reason for uncertainty, however; our knowledge about how the brain works is still strikingly limited. While neuroscience has made immense strides forward in recent decades, and we have gained much knowledge – for example, in respect of particular neural processes – the complexity of the brain as a whole and the dynamics of its relations with its bodily and external environment, is still largely beyond scientific understanding. As we observed in the Chapter 2, the precise mechanism by which some interventions (even those, such as DBS, that have been in use for several decades) achieve their therapeutic effects remains unknown. It is also the case that some of the unintended effects associated with novel neurotechnologies include psychosocial impacts – for example, to a user’s personality or sense of self – that are still poorly understood. There is little systematic research into or documentation of such effects, not least because their inherently subjective nature makes them harder to quantify than physiological risks.⁴³⁴

- 4.19 While uncertainty, *prima facie*, requires that more research is conducted to fill evidence gaps, the ethical conduct of research itself relies on an understanding that participants will not be exposed to unnecessary risk, but this assurance is precisely what remains uncertain. There are also practical obstacles to gathering a robust body of evidence needed to address uncertainty. Conventional routes to evidence gathering, such as large scale randomised controlled trials (RCTs), may be unavailable or unsuitable in this content. The kinds of serious neurological and mental health disorders for which novel neurotechnologies are indicated mean that limited numbers of individuals are eligible to participate in these kinds of studies. This may require evidence to be generated through experimental treatment, which itself raises significant ethical issues and the conduct of which needs to be guided by the appropriate consideration of patients’ interests, as described further below and in Chapter 5.
- 4.20 The ethical challenges presented by uncertainty do not pertain to knowledge of risks alone; it is equally important that the *benefits* of intervening are well understood. Understanding of such benefits, however, is incomplete for some of the neurotechnologies with which we are concerned. For example, as medical devices are not required to prove efficacy to receive marketing approval in Europe, pursuing evidence of efficacy will not always be a high priority for those with a commercial interest.⁴³⁵ Even if, as in the case of non-invasive neurostimulation, risks are considered low, given the special status of the brain even less serious risks must be counterbalanced by clear indications of effectiveness in comparison with other therapeutic options if their use is to be supportable.
- 4.21 A distinct, but no less important, factor contributing to uncertainty about the long-term ratio of benefits-to-risks of any particular novel neurotechnology is the prospect of ‘dual use’⁴³⁶ and spin-off developments. In this report, we seek to avoid speculation about the ethical implications of future applications of neurotechnologies that are unsubstantiated by current evidence. Nevertheless, it is important to reflect upon plausible future applications to understand the ethical implications of a technology’s development trajectory. While the ethical issues raised by future uses of technologies inevitably remain obscure, there is current evidence that the non-invasive neurodevices are particularly amenable to non-therapeutic applications - we consider these in detail in Chapter 8.

⁴³⁴ Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* **2(1)**: 3-13, pp.5-6.

⁴³⁵ Campbell B (2012) How to judge the value of innovation *British Medical Journal* **344:e1457**: 1-2.

⁴³⁶ ‘Dual use’ is the phrase used to describe the possibility of a technology being applied to hostile ends (in this case, as well as therapeutic) ends.

Uncertainty and the principle of caution

- 4.22 In bioethics, the principle of beneficence is often accompanied by a corresponding principle of non-maleficence, closely connected to the Hippocratic duty to ‘do no harm’. This duty applies to all areas of medical practice and research, but carries a particular imperative where interventions in the brain are concerned because of the brain’s special status in our lives. The history of such interventions, as described at the start of this report, shows clearly how terrible damage can be inflicted upon patients by clinicians, albeit by those who operate with the best of intentions. The possibility that new and current treatments may harm patients cannot be excluded.⁴³⁷ The obligation to avoid harm requires an ongoing commitment to develop a robust body of evidence, attention to the needs and vulnerabilities of particular individuals, and a willingness to reflect upon and review clinical practices and the development trajectories of these technologies. We may think of this as the ‘principle of caution’.
- 4.23 The principle of caution might be taken to require evidence of the absence of risk before research involving humans or treatment is employed, along the lines of ‘strong’ versions of the precautionary principle often invoked in public health and environmental policy contexts (see paragraph 6.25). But here we take the precautionary principle to be too restrictive where there is also a duty to promote research and find effective treatments. To argue for inaction or to set disproportionately high regulatory hurdles for innovation is itself ethically problematic: in the face of clear suffering and unmet need, the precautionary principle runs the risk of stifling the development of new neurotechnologies. The ‘principle of caution’ we adopt here recommends a less restrictive standard of behaviour, one which is tempered by the recognition that some risks, and some uncertainty about risks, may be tolerated where technologies could make a significant contribution both to individual patients and to the public good.

Developing the framework through interests

- 4.24 Beneficence and caution constitute the fundamental signposts of an ethical framework that is sensitive to the needs and uncertainties that are characteristic of therapeutic applications of neurological interventions. In navigating between these two (sometimes conflicting) ethical dimensions, a set of interests emerge as requiring particular attention, given what we have noted about the special status of the brain, the state of development of the neurotechnologies under consideration, and the conditions for which these technologies are used. We outline these interests – safety, autonomy, privacy, equity, and trust – in the paragraphs that follow.

Safety

- 4.25 The unintended effects of therapeutic uses of novel neurotechnologies include their potentially harmful impacts on patients’ health and brain functions. As observed in Chapter 2, these kinds of impacts vary between the different technologies. We do not repeat them in full here, but note that they are pertinent to any ethical consideration of neurotechnologies because of the importance of the healthy functioning of the brain to so many aspects of human life.
- 4.26 The concerns here relate chiefly to implanted neurotechnologies where the potential for harm is greatest. The risks associated directly with surgery to implant electrodes or stem cells (such as tissue damage, bleeding or infection) are considered relatively low compared with other more invasive forms of neurosurgery.⁴³⁸ However, the enduring implantation of foreign objects in the brain itself carries risks. Inadequately integrated cell grafts could give rise to pain.⁴³⁹ Where neurotechnologies work by stimulating the brain, it can be difficult to predict precisely what is

⁴³⁷ In Chapter 2 we outline some of the chief technology-related risks and unintended consequences associated with these technologies and we discuss a wider range of psychological and social impacts in this chapter.

⁴³⁸ For example, the surgical removal of brain tumours may be considered more physically invasive and risky.

⁴³⁹ Hofstetter CP, Holmström NA, Lilja JA *et al.* (2005) Allodynia limits the usefulness of intraspinal neural stem cell grafts; directed differentiation improves outcome *Nature Neuroscience* **8(3)**: 346-53, at page 346.

being stimulated.⁴⁴⁰ Possible consequences of neural stimulation can include seizures (though these are rare),⁴⁴¹ weight gain,⁴⁴² and disruption to cognitive functions (we consider these unintended cognitive and behavioural effects in the next section).⁴⁴³ In contrast to pharmaceutical therapies where treatment can usually be stopped if a patient suffers adverse effects, surgical interventions may not be reversible to the same degree. Electrical stimulation can be varied or switched off, but transplanted stem cells may not be easily removed.

- 4.27 It is not possible to assess the degree to which caution requires a patient to be protected from unintended health risks in isolation from an appreciation of the expected therapeutic benefits (and how these compare with the risk/benefit ratio of other treatment options). It is the responsibility of those developing and using these technologies, as well as those regulating their activities, to ensure there is adequate evidence that any risks are not disproportionate to benefits. However, as we have observed, for many of the technologies with which we are here concerned, this evidence is still being accrued.

Autonomy

- 4.28 We have already discussed the value we place on personal autonomy (understood as the capacity to act for reasons that we ourselves identify with and endorse), and have indicated the ways in which this capacity can be threatened by damage to the brain. There are two different (though not unconnected) ways in which ethical concerns arise in respect of autonomy in the context of the development and use of novel neurotechnologies. The first of these relates to the discussion at the start of this chapter regarding the value many of us place on being able to behave in ways that reflect our understandings of who we are, and the negative impacts of brain disease or injury upon this. The relevant ethical concerns here relate to the role of therapeutic neurotechnologies in restoring – or possibly disrupting – an individual’s capacity to exercise their autonomy and identity *as a result of intervening in the brain*. The second context in which neurotechnologies raise autonomy concerns relates to the importance of respecting patients’ and research participants’ opportunities for self-determination through informed consent in the *conduct of research, experimental treatment or treatment*. We will discuss these two issues in turn.

The impact of neurotechnologies on autonomy and identity

- 4.29 As we have observed at the start of this chapter, the effects of disease or injury affecting the brain often go beyond poor physical health to impact upon individuals’ capacities to formulate motives or to act in ways that reflect who they are. Novel neurotechnologies that repair or counteract the effects of damage to the brain therefore potentially offer not only health benefits, but also significant improvements in quality of life by improving cognitive capacities and mood, or by substituting lost motor control in ways that increase individuals’ autonomy and restore their capacities to develop, and to express, their sense of their own identity. We do not accept here the suggestion that reliance on, for example, assistive BCI technology or neurostimulation *in itself* diminishes autonomy. Autonomy is not a capacity exercised in isolation, but is rather dependent on our social and physical environments and tools. As tools, therapeutic applications of novel neurotechnologies may rather be seen as potentially autonomy-enhancing. However, responsible research and clinical practice cannot proceed on the simple assumption that the relationship between these technologies and capacities for autonomy and self-realisation is straightforwardly positive; the reality is more complex.

⁴⁴⁰ See paragraph 2.18.

⁴⁴¹ See: Rossi S, Hallett M, Rossini PM and Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research *Clinical Neurophysiology* **120(12)**: 2008-39.

⁴⁴² Rieu I, Derost P, Ulla M *et al.* (2011) Body weight gain and deep brain stimulation *Journal of the Neurological Sciences* **310(1)**: 267-70.

⁴⁴³ Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* **2(1)**: 3-13.

- 4.30 The first reason for this complexity is that the potential therapeutic benefits exist in tension with, and must be weighed against, the possibility that neurotechnologies may also have unintended negative impacts upon autonomy and identity. As we observe in Chapter 2, there is evidence – particularly in relation to treatment of with Parkinson’s disease – that the use of DBS can have effects on a patient’s mood, behaviour and cognition.⁴⁴⁴ In some cases, aggression, depression or mania can be amongst these effects and result in measurable alterations in personality. However, it may be difficult to distinguish changes due to neurostimulation *alone* from the effects of the progress of the illness itself and any associated changes to drug regimes.⁴⁴⁵ These kinds of unintended psychological and social effects are well documented for DBS used in Parkinson’s disease, but similar concerns also arise in relation the use of DBS to treat mental health disorders such as depression or OCD.⁴⁴⁶ Though there is no evidence of similar behavioural effects from neural stem cell therapies, commentators have suggested this possibility cannot be wholly dismissed.⁴⁴⁷
- 4.31 A second layer of complexity is introduced because the evidence of these kinds of unintended risks of therapeutic interventions is no more amenable to a straightforward practical and ethical response than the evidence of potential benefits. Notwithstanding what has been said earlier in this chapter about the value of authentic, autonomous action as an important aspect of human well-being, personality and behavioural changes cannot be construed as unequivocal harms that clinicians should seek to avoid at any cost.⁴⁴⁸ As is perhaps most obvious in the case of serious mental health disorders, changing a patient’s sense of herself or himself and behaviour might be precisely the desired therapeutic outcome. Furthermore, when faced by the seemingly impossible choice between leaving debilitating physical or psychiatric symptoms untreated, or a degree of lost cognitive capacity and behavioural control (as unintended consequences of treatment), the latter option might be preferable for some patients (see Box 4.2).

Box 4.2: Choosing motor control over capacity

One case, much discussed in the bioethics literature, demonstrates several aspects of the complex ethical challenges presented by treatment using DBS.⁴⁴⁹

In this instance, a 62-year-old man had been treated for Parkinson’s disease using DBS. This had been effective in alleviating some of the illness’s serious motor symptoms that would otherwise have been so severe as to confine him to bed. It also led, however, to his being admitted to hospital three years into his treatment in a manic state, the consequences of which were “chaotic behaviour, megalomania, serious financial debts and mental incompetence”.⁴⁵⁰ Changing the parameters of his stimulation restored his capacities for insight and reflection, but his physical incapacity returned. There was no middle ground between these symptomatic extremes. Whilst in a competent non-manic state, this individual voluntarily chose to proceed with a level of neurostimulation that controlled his severe movement disorder and thus allowed him to undertake for himself the routine activities of daily life, even though this meant committal to a psychiatric hospital due to his mania.

This case illustrates some of the serious possible unintended effects of DBS that are closely linked to self-conception and autonomy, and the potential challenges to obtaining informed consent to treatment when the intervention itself can interfere with relevant decision-making capacities. It also highlights the importance, in delivering care, of attending to patients’ own perceptions of what constitutes the best (or least-bad) treatment outcome and, from a public health perspective, of recording patient-reported outcomes as an essential part of building a better understanding of the risks and benefits of DBS. Similar issues are brought to life by the sociologist Helmut Dubiel’s memoir of receiving DBS

⁴⁴⁴ Ibid, at page 9.

⁴⁴⁵ Ibid, at page 5. The observation of these effects is highly variable between patients and between studies.

⁴⁴⁶ Glannon W (2009) Stimulating brains, altering minds *Journal of Medical Ethics* **35(5)**: 289-92, at page 290.

⁴⁴⁷ Duggan PS, Siegel AW, Blass DM *et al.* (2009) Unintended changes in cognition, mood, and behavior arising from cell-based interventions for neurological conditions: ethical challenges *American Journal of Bioethics* **9(5)**: 31-6.

⁴⁴⁸ Baertschi B (2009) Intended changes are not always good, and unintended changes are not always bad--why? *The American Journal of Bioethics* **9(5)**: 39-40; Baylis F (2011) “I am who I am”: on the perceived threats to personal identity from deep brain stimulation *Neuroethics*: 1-14.

⁴⁴⁹ Leentjens A, Visser-Vandewalle V, Temel Y and Verhey F (2004) Manipulation of mental competence: an ethical problem in case of electrical stimulation of the subthalamic nucleus for severe Parkinson’s disease *Nederlands Tijdschrift voor Geneeskunde* **1489(28)**: 1394-8; also discussed in Glannon W (2009) Stimulating brains, altering minds *Journal of Medical Ethics* **35(5)**: 289-92 and Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* **2(1)**: 3-13.

⁴⁵⁰ Leentjens A, Visser-Vandewalle V, Temel Y and Verhey F (2004) Manipulation of mental competence: an ethical problem in case of electrical stimulation of the subthalamic nucleus for severe Parkinson’s disease *Nederlands Tijdschrift voor Geneeskunde* **1489(28)**: 1394-8.

treatment for Parkinson's disease, where he notes the difference between his surgeons' criteria for determining that his neurosurgery had been a "complete success" and his own experience of distressing unintended effects, including those upon his mood and voice.⁴⁵¹

- 4.32 A responsible approach to supporting prospective users of novel neurotechnologies, which could have both positive and detrimental impacts on autonomy and identity, must seek to accommodate the complexity outlined here. This must be managed as part of a commitment to sensitive, ongoing communication with patients, and those close to them, which takes account of both the needs of the particular patient and the general duty of informed consent. We turn now to consider the ethical challenges posed by novel neurotechnologies for informed consent itself.

Autonomy and decision-making

- 4.33 The requirement for informed consent is widely considered as the 'gold standard' for the protection of patients' and research participants' autonomy. Nevertheless, the limitations of informed consent as the principal means of protecting autonomy are widely recognised and are not unique to use of neurotechnologies.⁴⁵² This notwithstanding, the nature of these technologies and the conditions they address mean that particular challenges come into sharp focus. These relate to: the experimental status and uncertainty about the longer term and unintended effects of some therapeutic interventions; the vulnerability and potential incapacity of patients with serious neurological or mental health disorders; and the possibility, that we noted in Chapter 3, that some clinicians may have vested economic interests in pursuing certain kinds of intervention (see paragraph 3.66 to 3.70).
- 4.34 Where definitive information about the risks and benefits of intervening in the brain using a particular neurotechnology is not available, this presents a *prima facie* hurdle to securing informed consent. However, clinicians and researchers may nevertheless take responsible steps to assist individuals to make meaningful, autonomous choices to undergo such interventions where there is clear therapeutic need. These include being open about uncertainties, about current understandings of what constitutes a good outcome, and about how neurotechnological interventions compare with other more established therapeutic options. This is a particular imperative where an individual's desperation for any chance to relieve their suffering might dispose them to overlook the possibility of poor outcomes. It is also important that investigators are vigilant to the risk of consent being given under a 'therapeutic misconception' – that is, the not uncommon belief of participants that, whatever they have been told as part of consent procedures, treatment of their individual health needs will be part of the aims and outcomes of the study.⁴⁵³ The possibility of this misconception raises particular concerns about managing the expectations and supporting the needs of participants in experimental studies to whom beneficial interventions may not be available beyond the end of the investigation.⁴⁵⁴
- 4.35 The final point to note here engages ethical concerns relating to both decision-specific autonomy and a more far-reaching capacity for autonomy and self-realisation in all aspects of life. Assistive BCIs and neural stem cell therapies that are intended for use by individuals with impaired cognitive capacities, or those who retain cognitive functions but cannot communicate

⁴⁵¹ Dubiel H (2009) *Deep within the brain: living with Parkinson's disease*, 2009 Edition (New York: Europa).

⁴⁵² See, for example, O'Neill O (2002) *Autonomy and trust in bioethics* (Cambridge: Cambridge University Press); Manson NC and O'Neill O (2007) *Rethinking informed consent in bioethics* (Cambridge: Cambridge University Press).

⁴⁵³ For further discussion of the therapeutic misconception, see: Appelbaum PS, Roth LH, Lidz CW, Benson P and Winslade W (1987) False hopes and best data: consent to research and the therapeutic misconception *The Hastings Center Report* **17(2)**: 20-4.

⁴⁵⁴ As might be the case if, for example, the technology is not licensed for use outside investigational settings, or requires unaffordable ongoing clinical support for its continued use.

their wishes (for example as a result of locked-in syndrome),⁴⁵⁵ raise particular challenges. For each of these groups, novel neurotechnologies could offer, respectively, the potential to partially restore cognitive functions; or, using assistive technologies, the ability to interact with the world and communicate their wishes. These outcomes could restore a degree of autonomy. However, neither group is able to give valid consent ‘upfront’ in relation to the undertaking of a potentially risky intervention that would permit this to happen.

- 4.36 Legal provisions in the UK permit decisions to be made on behalf of those who lack capacity, provided certain conditions are met (these are discussed in more detail in Chapter 5). Where decision-making is delegated to another person(s), or ‘proxy’, the legal threshold for the lawfulness of any intervention is that the chosen path is judged to be in the ‘best interests’ of the patient or participant. However, some applications of novel neurotechnologies, where it is not yet possible to be sure of any benefit to patients (for example, the use of BCIs with locked-in patients) present a particular challenge to demonstrating whether they are in the patients’ best interests.⁴⁵⁶ This can leave proxy decision-makers in a quandary about whether and how to proceed from a legal standpoint. From an ethical point of view the alternative (of never pursuing research or experimental treatments with patients who cannot themselves give consent) is disproportionately cautious. It serves neither the needs of these individuals nor the wider public good, as it risks excluding serious neurological and mental health conditions from the scope of the quest for effective interventions. The best interests test must be recognised for the nuanced judgement-call that it is, despite any paucity of evidence.

Privacy

- 4.37 BCI devices function by obtaining and transmitting digital data about the brain activity of their users. It is conceivable that, in the future, implanted neurodevices, such as those used in DBS, might also record patients’ brain activity to enhance their therapeutic functions by, for example, predicting tremors.⁴⁵⁷ Our current understanding of the brain means that data about brain activity does not permit the content of someone’s thoughts to be ‘read’.⁴⁵⁸ Nevertheless, while popular conceptions persist that the brain’s activities are especially associated with ‘who we are’, the direct and automated collection of data on brain activity by neurodevices, or external interference with the functioning of these devices, may be seen as intrusions into an individual’s private domain.
- 4.38 Sensitivities may also arise insofar as information collected from neurodevices can be obtained and used to identify someone as undergoing treatment, or reveal their abnormal brain activity, particularly where this indicates a stigmatising neurological or mental health condition, or could otherwise be used for discriminatory purposes. Responsible clinical and research practices should protect patients’ and research participants’ informational privacy by ensuring they understand and agree to the collection of sensitive personal data by neurodevices and by providing adequate safeguards to protect confidential information derived from these. We return to discuss the legal restrictions in the processing of personal data in Chapter 5.
- 4.39 Neurodevices are also potentially vulnerable to malfunctioning, or to illegitimate information interception, due either to accidental signal interference or malware infections via devices’

⁴⁵⁵ Even incomplete locked-in syndrome may leave someone with means of signalling too weak to be taken as indications of valid consent – see: Haselager P, Vlek R, Hill J and Nijboer F (2009) A note on ethical aspects of BCI *Neural Networks* **22(9)**: 1352-7, at page 1354.

⁴⁵⁶ *Ibid.*

⁴⁵⁷ Lempka SF and McIntyre CC (2013) Theoretical analysis of the local field potential in deep brain stimulation applications *PLoS ONE* **8(3)**: e59839.

⁴⁵⁸ Limited exceptions might be BCIs that record brain signals associated with the user’s registering an external stimulus or with a change in affective state, which could potentially reveal what it was that piqued the user’s attention or crudely be seen as betraying a user’s mood. See, for example, Martinovic I, Davies D, Frank M *et al.* (2012) On the feasibility of side-channel attacks with brain-computer interfaces. In *Usenix Security Symposium 2012*, (Bellevue, WA).

wireless connections.⁴⁵⁹ At present, there is no evidence of malware affecting neurodevices specifically, but it has been suggested the increasing complexity of all medical devices makes illegitimate interception of information more likely.⁴⁶⁰ The adoption of measures to protect devices against external interference is an ethical matter not simply for reasons of safety; there may also be wider impacts on users' private lives. Where those who depend on devices for managing serious symptoms, mobility or communication are unable to control (or lack confidence in) how their device functions, this may undermine their self-reliance and jeopardise the satisfactory integration of the device into their self-conceptions. Such concerns may render these technologies burdensome or alien rather than enabling.⁴⁶¹

Equity

- 4.40 The principle of beneficence requires the provision of treatments that alleviate suffering caused by brain-related disorders and, as such, may be seen to extend to a requirement to provide wide access to those treatments. However, this will not always be possible. Instead, the aim must be to offer the best treatment that is reasonably available and affordable in the circumstances that prevail, which raises issues of distributive justice.
- 4.41 In Chapter 3, we outlined the high national and global incidence of the kinds of neurological and mental health disorders that these neurotechnologies seek to treat (see paragraphs 3.11 to 3.15). Some disproportionately affect persons who are vulnerable, due to age, socio-economic status, and exposure to dangerous or toxic environments. Indeed, the problems posed by brain disorders might be seen to present more significant challenges in less developed regions, where they may carry significant stigma and where public health infrastructure and access to treatments for such disorders are very limited.
- 4.42 Various structural factors create significant barriers to accessing treatments, especially in the developing world: we noted in Chapter 3 that the costs of delivering treatment using many of these technologies are and will remain high. Despite the great need for effective treatments for neurological and mental health disorders, without further resources and interventions it is likely that, in the short to medium term, these new treatments will be available only to the citizens of wealthy states, and then only to some of them. It is therefore desirable that research scientists, technologists, funders and industry partners should work together to develop ways of making access to novel neurotechnologies a more realistic possibility for those who need and desire them, by making them cheaper, easier to use, and more widely available. Given the difficulties discussed in Chapter 3 in relying on current market mechanisms to bring new products into use, this goal is likely to require the development of alternative funding models and closer relationships between science, industry and non-governmental organisations.
- 4.43 There are also other, more local, problems of justice associated with neurological and mental health disorders and their treatment which merit action of a different kind. Some individuals will have difficulty finding meaningful and valued social engagements, due, in part, to the nature of the disorders themselves, but also because of the stigma that accompanies these disorders, which generates fear, anxiety, and lack of understanding. The relationships between the use of novel neurotechnologies, social stigma and discrimination may well be complex. Treatment itself can be a cause of embarrassment or discrimination, particularly while these interventions remain novel. Paradoxically, however, neurotechnologies that support some individuals' capacities to be 'more normal' might be seen as inherently discriminatory – and exacerbating

⁴⁵⁹ Maisel WH and Kohno T (2010) Improving the security and privacy of implantable medical devices *New England Journal of Medicine* **362(13)**: 1164-6, United States Government Accountability Office: Report to Congressional Requesters (2012) *Information security of active medical devices*, available at: <http://www.gao.gov/assets/650/647767.pdf>.

⁴⁶⁰ United States Government Accountability Office: Report to Congressional Requesters (2012) *Information security of active medical devices*, available at: <http://www.gao.gov/assets/650/647767.pdf>, at page 17.

⁴⁶¹ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4(3)**: 1-22, pp.8-9.

misunderstanding and discrimination – against those who continue to live with neurological and mental health disorders. All relevant stakeholders should work steadfastly to combat social stigma and discrimination against individuals with brain-related disorders and their families on a societal level, in the interest of equity and justice.

Trust

- 4.44 Brain disease and damage present frightening prospects because they threaten many capacities central to our leading fulfilling lives. As more of us live longer and experience age-related conditions such as stroke or dementia, more of us have a stake in technologies that offer treatments for such conditions. Accounts of the therapeutic promise of novel neurotechnologies in both academic publications and the mainstream media are compelling. It is, therefore, all the more important that trust is preserved through responsible and transparent practices in publication and reporting.
- 4.45 There are strong economic incentives for researchers and the neurotechnology industry to emphasise the translational value of their findings in order to secure public funding and private investment. Those seeking to market products to healthcare providers or directly to consumers have an incentive to expand the therapeutic applications of novel neurotechnologies. Indeed, novel neurotechnologies occupy a field characterised almost as much by what we do not know as that which we do. Hype is likely to result in a loss of trust and confidence if its promises are not sustained in practice.⁴⁶² Despite the understandable motives for optimistic claims and projects, the pressure to secure scarce resources to fund costly development paths, there is a need to build and maintain trust if there are to be long-term scientific and economic gains. This is best achieved through development trajectories that are based on the most robust clinical evidence and transparent communication of this evidence by those involved in conducting, funding and regulating innovation in novel neurotechnologies.
- 4.46 Trust is not only an overarching economic and scientific interest; it is also an ethical demand grounded in relationships with patients. Representations of research findings in the mainstream media that underplay potential risks or extrapolate beyond that which is supported by available evidence are more than just regrettable exaggerations. Hype may also perpetuate popular reductive misconceptions of the brain and our abilities to understand and influence its functions.⁴⁶³ More acutely, however, it also carries the risk that the hopes of potential patients and their families will be raised without justification. As well as threatening disappointment and distress, this creates particular problems for informed consent. The challenges facing clinicians and researchers in conveying the limits of current knowledge to secure valid consent, outlined above, are compounded where their efforts to secure patients' realistic understanding of the efficacy and risks of the neurotechnology in question must operate against a background of overheated expectations. We discuss these issues of responsible communication of research by the media in more detail in Chapter 9.

Putting principles and interests into practice: a virtue-guided approach

- 4.47 The ethical framework outlined so far is grounded in the principles of beneficence and caution as ethical foundations that correspond to the overarching tension between uncertainty and need in the context of novel neurotechnologies. These foundations give rise to a set of interests: safety, autonomy, privacy, equity and trust, which are elaborated above. However, it is clear that the complex network of technologies, therapeutic applications, risks and benefits in the field of novel neurotechnologies means that it is insufficient to lay out a set of principles and interests

⁴⁶² Schlaepfer TE, Lisanby S and Pallanti S (2010) Separating hope from hype: some ethical implications of the development of deep brain stimulation in psychiatric research and treatment *CNS Spectrums* **15**(5): 285-7.

⁴⁶³ Gilbert F and Ovadia D (2011) Deep brain stimulation in the media: over-optimistic portrayals call for a new strategy involving journalists and scientists in ethical debates *Frontiers in Integrative Neuroscience* **5**(16): 1-6.

and expect their practical application to be obvious. This is particularly so because the need for, and uncertainty about, the development and uses of these technologies exist in mutual tension. This is an area of competing priorities in which ‘doing what is right’ is not simply a matter of following rules, but frequently requires the exercise of informed practical judgement.

- 4.48 Moreover, this is not a unified or static ethical landscape. As the discussion in this chapter has emphasised, a potentially wide range of actors is involved in the development and use of novel neurotechnologies. An adequate ethical framework must, therefore, remain open to the diverse contexts faced by these actors in a variety of settings, and guide them through the fundamental tension between seeking to do good while navigating uncertainty. Furthermore, in an emerging area of biotechnology such a framework must also be able to respond to fresh evidence of the capabilities of these neurotechnologies and to changing social attitudes to what they offer.
- 4.49 In light of these considerations, our ethical framework is reinforced by the introduction of virtues as means of guiding the practical application of the principles and interests we have already identified. We suggest that a virtue-guided approach is appropriate in this context for several reasons. A virtue-guided approach is particularly (though perhaps not uniquely) well-suited to accommodating the kind of flexibility and balance between need and uncertainty that our framework requires. Intrinsic to virtue ethics is the idea that, in doing the right thing, we must apply practical judgement to identify a response that is appropriate and proportionate to the particular circumstances at hand. Virtue ethics is also associated with supporting the efforts of each of us to ‘flourish’; that is, to pursue the most fulfilling and rich lives we can. We are concerned here with interventions that impact on lives in deeply personal and pervasive ways. The imperative is to attend to potential recipients of neurotechnological interventions not merely as the owners of damaged brains, but as whole individuals with particular values, life plans, and relationships.
- 4.50 Each of these features highlights the value of a virtue-guided approach where sensitivity to particular circumstances is so important. An emphasis upon virtue does not overlook the importance of ‘doing the right thing’, but encourages us to look to the wider moral landscape of perceptions, priorities, and values in which actions are located. This inclusivity captures some important intuitions about what makes someone, for example, a good clinician or a good friend who is well-equipped to recognise and respond to the needs of individuals with serious brain illness or injury in a way that attending to duties or outcomes alone might not. We explore further the central tenets of virtue ethics and some challenges to these in Box 4.3 below.
- 4.51 The virtues we highlight here for particular attention are *inventiveness*, *humility* and *responsibility*. These are intended to complement, rather than replace, the all-purpose virtues that are characteristic of almost any decent human life and society (see Box 4.3).⁴⁶⁴ Instead, we seek to identify those whose practice is especially important in the development and use of novel neurotechnologies. These virtues are not exercised in the abstract, but conceived of as guiding reasoned and evidence-based judgement that attends to the principles and interests we have identified as part of this framework. These principles and interests help define the meaning of the virtues as applied in this field, and set limits to their scope.
- 4.52 In this report, we are chiefly concerned with the attitudes and conduct of those acting in their professional capacities. Though virtue ethics is normally associated with the moral characters of individuals, our use of the virtues here is not intended to preclude or minimise the role of communities and institutions. Organisations ought, through their functions and norms, seek not only to support and facilitate virtuous behaviours, but also to foster amongst their members

⁴⁶⁴ Indeed, on many views, all moral virtues are mutually supporting and it would not be possible to exercise responsibility, humility or inventiveness appropriately in the absence of, for example, kindness or prudence. The idea that the virtues are ‘unified’ in this sense may be found in Aristotelian ethics and some contemporary writers: see, for example, Wolf S (2007) Moral psychology and the unity of the virtues *Ratio* 20(2): 145-67.

virtuous ways of seeing and understanding situations. Virtues may also be thought of as the qualities that support practices aimed at achieving that which is valuable and worthwhile, in particular shared endeavours⁴⁶⁵ such as patient care, or innovation to meet therapeutic needs. Even where, for example, regulatory and governance regimes pre-empt the exercise of personal virtue, it would still be desirable for the intentions underlying these to motivate and instil the virtues in the professional practices of those they govern. The three virtues we highlight here do not, however, all apply equally to every actor or practice involved in the development and use of novel neurotechnologies. In the following paragraphs and subsequent chapters, we provide some illustrations of how we might see each applying chiefly to professional practices and, in some circumstances, to patients themselves.

Box 4.3: Virtue ethics

Virtue ethics is an approach to addressing questions about how we should live and conduct ourselves that places particular emphasis on moral character. It is most closely associated with the Aristotle's ethics,⁴⁶⁶ but is also connected with elements of eastern philosophies and Christian ethics. For some time, virtue ethics was overshadowed in western ethical traditions – and in bioethics in particular – by two other approaches: deontology (according to which an action is right if it accords with a moral rule); and consequentialism (in which the right action is that with the best outcome). However, virtue-based approaches are now regaining greater prominence.⁴⁶⁷

According to traditional virtue ethics, a person is good if they possess and exercise particular character traits (virtues), while lacking others (vices). 'Virtue', as used in this way, does not carry the term's everyday connotations of piety or abstinence. Virtues are instead understood as those characteristics of people, and their actions and attitudes, which are a necessary part of 'flourishing' or living well. This is not simply a matter of leading an enjoyable life, but a worthwhile one. This worth is not determined on wholly subjective or superficial grounds, but by the kinds of things that are held to be important in the groups and traditions to which we belong.⁴⁶⁸

Insofar as perspectives on what constitutes a good life can change, there is room for variation amongst the kinds of virtues that are seen as important. Nevertheless, there tends to be agreement about some key virtuous characteristics, for example: kindness, justice, courage, generosity and prudence. Each of these can be seen as contributing not only to an individual's own life 'going well', but to the impact they have on others' lives and thus as underpinning the shared endeavours and mutually supportive relationships that are central to a good life. Virtues can, therefore, be seen as the characteristics of collective undertakings and practices of communities and need not be construed individualistically.

One prominent criticism of virtue ethics is that it is (too) concerned with what sort of people we should *be*, rather than what we should *do*.⁴⁶⁹ Moreover, it is objected, virtue ethics provides neither guidance about *how* to go about doing the 'right thing', nor the means to resolve conflicts between competing demands.⁴⁷⁰ These criticisms may be seen as particularly problematic for the application of virtue theory to bioethics, where the challenge tends to be determining the right things to do, often in the face of hard choices.

The response from many virtue ethicists is that it is possible to give a virtue-based account of what makes an action right and thus provide guidance on how to behave.⁴⁷¹ However, doing the right thing is often not straightforward or formulaic, but requires practical judgement. Such judgement cannot be codified in simple rules, but depends upon life experience and education through which appropriate ways of seeing and understanding are developed. Right actions are those that are done from the kinds of perceptions and motives that a good person would have in similar circumstances. This is not equivalent to acting out of duty. Instead, acting in a kind way, for example, entails doing so because a person values kindness, and recognises and is moved by distress in others, and because they understand how they could (or just as importantly, could not) usefully do something to alleviate this. Adopting a virtue-based approach, it is argued, equips us no less well to navigate difficult dilemmas than trying to accommodate conflicting moral duties or decide between which of two comparably terrible outcomes to avert.⁴⁷²

The ethical framework we have developed in this chapter reflects an approach where the virtues are seen as vital to navigating the tension between the principles of beneficence and caution, and in seeking to promote and protect the key interests outlined in the previous sections.

⁴⁶⁵ See, for example, MacIntyre I (1996) *After virtue: a study in moral theory*, 2nd Edition (London: Duckworth), at Chapter 15.

⁴⁶⁶ Ross D (2009) *The Nicomachean ethics* (Oxford: Oxford University Press).

⁴⁶⁷ Hursthouse R (2012) Virtue ethics. In *The Stanford Encyclopedia of Philosophy*, Zalta EN, ed. (The Stanford Encyclopedia of Philosophy).

⁴⁶⁸ MacIntyre I (1996) *After virtue: a study in moral theory*, 2nd Edition (London: Duckworth).

⁴⁶⁹ Loudon RB (1984) On some vices of virtue ethics *American Philosophical Quarterly* **21**(3): 227-36.

⁴⁷⁰ Oakley J (2001) Chapter 10: A virtue ethics approach in *A companion to bioethics*, Kuhse H, and Singer P (Editors) (Oxford: Wiley-Blackwell).

⁴⁷¹ See, for example, Hursthouse R (1991) Virtue theory and abortion *Philosophy & Public Affairs* **20**(3): 223-46.

⁴⁷² *Ibid.*

Inventiveness

- 4.53 Novel neurotechnologies are attempts to advance understanding and provide urgently-needed treatments for some of the most distressing disorders of contemporary life. What is required from research scientists and clinicians who are working towards new therapies in this area is a willingness to develop new products and techniques, or to explore new uses of existing technologies to find new ways of confronting sometimes familiar problems – in short, a creative inventiveness that moves forward the standard of treatment.
- 4.54 As we have observed in Chapter 3, the development trajectory of many potentially useful applications of these technologies and their successful translation from laboratory to market is vulnerable to structural funding gaps. Inventiveness might be exercised by researchers, funders and patient activist groups to explore novel funding models that permit new technologies to cross the ‘valley of death’.⁴⁷³ However, creativity directed chiefly at attracting investment rather than meeting the most pressing patient needs, or attending inadequately to accompanying interests, is not the virtue we intend here. Inventiveness is not just a matter of doing something new, which perhaps turns out to be beneficial but might also jeopardise patients’ safety, autonomy or sense of self, or exploit their trust. Rather, it concerns helping to develop genuinely beneficial therapies that can be applied in ways that promote equitable access.
- 4.55 Inventiveness amongst clinicians and service providers can help to extend the benefits of these technologies to those with profound therapeutic needs, but who lack the opportunity or resources to access licensed treatments. Sometimes clinicians will be in a position to offer more experiential treatments to patients in such circumstances. Indeed, patients and those close to them may themselves exhibit inventiveness (coupled with impressive courage and altruism) by volunteering to participate in investigations of this kind (or by finding new ways of living with serious disorders). Respect for patients’ autonomy in these circumstances demands absolute clarity about when the relationship involved is one of treatment (where patients’ therapeutic needs are primary), or one of research (directed chiefly at wider public benefits). Inventiveness does not justify unsystematic experimentation or offering interventions in the absence of robust evidence, however great a patient’s needs. The principle of caution constrains its exercise, as do the corollary virtues of responsibility and humility.

Humility

- 4.56 Humility in the context of novel neurotechnologies refers to the acknowledgment of the limitations of our understanding of the brain and our current capacities to cure or remove all suffering associated with brain disease or damage. The virtue of humility goes beyond merely enacting the duty of caution and suggests a need for conscientious deliberation (even within oneself) about the right action in a given situation with due attention to protection of the interests at stake. For example, it is premature to think we can intervene precisely to control a particular brain function or state without unknown or unpredictable short, medium or long term consequences for other brain functions. A profound appreciation of the unknown consequences of intervening on the brain, particularly using physically invasive technologies, means that clinical practices may need to proceed in incremental steps. This is especially true where risks include unintended effects on complex mental functions such as cognition, emotion and intention and thus impact upon patients’ autonomy or sense of self.
- 4.57 These risks also serve as a reminder that the ‘novelty’ of novel neurotechnologies should not lead to the neglect of the possibility of other, effective, cheaper and more transportable technologies and practices to support those with these disorders. Humility importantly tempers

⁴⁷³ The concept of the ‘valley of death’ refers to the funding gap in product development where a company needs investment to develop a prototype, but has not yet reached the point at which it can secure funding on the basis of a commercially viable product. We discuss this problem in more detail in Chapter 3 at paragraph 3.41 to 3.47.

inventiveness by cautioning against the technological imperative – the drive to develop high-tech solutions to the problems of brain disorders in order to demonstrate technical prowess rather than better and more accessible treatments.

- 4.58 Humility also builds on the interests of trust and autonomy to instil a mutual appreciation that patients and medical professionals occupy different roles, with different levels of access to power and knowledge, recognising that it is difficult for each to know the needs, obligations and commitments of the other. Establishing and preserving trust requires that medical professionals endeavour to gain empathetic understanding of the experiences of patients who live with neurological and mental health disorders and of the situation of those on whom they depend. Professional humility will sometimes require respecting the choices of competent patients to expose themselves to the unavoidable risks of treatment. At the same time, patients and those close to them need to have an appreciation of a doctor's difficult and uncertain position in a situation where a patient has a condition for which there might be no approved or safe treatment. Thus the virtue of humility suggests that patients' entitlement to the best care be exercised with an awareness of constraints under which medical professionals and researchers necessarily operate.

Responsibility

- 4.59 A responsible approach to the development and use of novel neurotechnologies is one that strives to strike a proportionate balance between the competing demands of the principles at the heart of our framework: beneficence and caution. The virtue of responsibility requires that, even where much is unknown, those involved in the research and development of novel neurotechnologies need to be able to articulate the justifications for their endeavours. Responsibility and accountability, as applied to the protection and promotion of each of the interests we have identified in this framework, may be enforced through regulatory measures, but they are also fostered through a commitment to self-governance and ethical reflexivity and accountability among the researchers, and within the communities and organisations that contribute to the development and application of novel neurotechnologies. Responsibility thus requires attention to the ethical formation of researchers themselves, especially where this takes place in a climate where short term gains and economic benefits are often valued above longer term, public values.
- 4.60 The virtue of responsibility also connects with the social responsibilities of researchers, medical professionals and regulators as members of democratic communities in which the costs of brain-related diseases and the hope of new treatments are collective interests. Therefore, this virtue requires those developing and exploring the applications of these technologies to consider how to achieve the translation of their work into the public sphere in a way that meets pressing therapeutic needs and contributes to the interest of equity. This entails the close engagement of various communities – commercial interests, patients and families, policy-makers, other researchers and laypersons – in order to address two central obstacles in this field: the limited evidence of efficacy, and longer-term and unintended effects on one hand, and the challenges of securing sufficient investment to translate innovation into widely available therapeutic applications on the other.
- 4.61 Responsibility precludes those involved in developing novel neurotechnologies (and their application) from making exaggerated claims, but rather allowing this field room to develop appropriate paradigms and to ensure that technologies are as fully formed and well evaluated as possible before they are widely implemented. This virtue is particularly pertinent in countering the pressures on those developing new technologies to overstate the capacities, or underplay the risks and limitations, of novel neurotechnologies to attract funding or to enter the market as swiftly as possible. Failures to exercise this kind of responsibility – whether in academic publications, the popular media, or marketing activities – raise unsustainable expectations,

exploit the trust of patients and those close to them, threaten disappointment and undermine autonomy and informed consent.⁴⁷⁴

- 4.62 Finally, patients and those close to them can also play a role in ensuring that high quality evidence and treatments are translated into the public domain. This role includes treatment compliance and regular communication and follow-up with doctors. This is not to suggest that the virtue of responsibility requires that patients should be unquestioning or compliant in their roles. Rather, it is to assert their interests in autonomy and their potential for agency. A paternalistic or overly protective view of patients can overlook the activities and responsibilities that these stakeholders willingly take on in research, when they are able and enabled to do so.

Concluding remarks

- 4.63 The ethical priorities outlined here provide a framework to guide the activities of all parties involved in the development and use of novel neurotechnologies in the context of both research and treatment. This framework is action-guiding in three complementary ways. First, it establishes the central ethical imperative for action: to provide reasonably safe and effective treatment or assistance for those living with the effects of brain disease and injury for which other effective interventions are not available. Secondly, recognising that this imperative exists alongside a responsibility to avoid harm from uncertain and unintended effects, we have suggested that ethical conduct must navigate a tension between need and uncertainty. We suggest that, in doing this, the interests that come into play include safety, autonomy, privacy, equity, and trust. Finally, we have proposed that three virtues – inventiveness, humility and responsibility – capture the values and perspectives that should be exemplified in activities that seek to protect and promote these interests, whilst permitting actors room to respond to particular circumstances and negotiate the tension between uncertainty and need.
- 4.64 Amongst other aims, regulation and governance mechanisms can help to guide and institutionalise ethical conduct. In the next three chapters, we turn to consider the regulatory and governance landscape in which the development and uses of novel neurotechnologies operate. The ethical framework set out here provides an important benchmark against which to assess current approaches to regulating the development, marketing and clinical uses of novel neurotechnologies to determine where there might be problems and deficiencies and to help us to construct normative recommendations about how these could be addressed. In Chapter 5, we look at the governance of relationships between professionals and those undergoing interventions in treatment and research contexts. In Chapters 6 and 7, we turn to consider the regulation of the technologies themselves, asking first what responsible research and innovation looks like with respect to these technologies and then interrogating the formal regulatory frameworks that operate in this field.

⁴⁷⁴ Gilbert F and Ovadia D (2011) Deep brain stimulation in the media: over-optimistic portrayals call for a new strategy involving journalists and scientists in ethical debates *Frontiers in Integrative Neuroscience* 5(16): 1-6.

Chapter 5

Patients and participants:
governing the
relationships

Chapter 5 - Patients and participants: governing the relationships

Chapter 5 - overview

The care of patients and research participants who undergo interventions using novel neurotechnologies presents the most immediate context in which to apply our ethical framework. Care does not only amount to administering safe interventions; it also entails promoting patients' and participants' autonomy and protecting them from psychological and social harms, minimising unrealistic expectations and guarding against privacy infringements.

Uncertainty about the long-term and unintended effects of intervening in the brain using novel neurotechnologies, a lack of alternative treatments for some neurological disorders, and the fact that many neurotechnologies address conditions that impair patients' decision-making capacities, all present challenges to responsible endeavours to support decision-making and informed consent by patients and participants and those close to them. Professional humility is particularly relevant here. Experimental therapies should not be characterised as offering a patient's 'last best hope' unless this is justified. We recommend that independent counselling, which acknowledges uncertainty, should be an essential part of treatment referral pathways (paragraph 5.9).

The lack of clear evidence of risks and benefits of some interventional techniques also presents challenges to responsible clinical decision-making. The National Institute for Health and Care Excellence's (NICE) Interventional Procedures Guidance (IPG) provides valuable advice to healthcare providers on clinical decision-making and oversight by drawing together the best available evidence. We recommend that compliance with NICE IPG should be mandatory (paragraph 5.24).

NICE guidance and the other oversight mechanisms operating in the NHS will not, however, extend to protecting the interests of patients who use private treatment services. There is a need for professional guidelines that require patients to undergo medical evaluation by a doctor before accessing neurostimulation treatment (paragraph 5.31).

Data concerning brain function and neurological health collected by devices such as those delivering deep brain stimulation (DBS) or using brain-computer interfaces (BCIs) may be sensitive and stigmatising. We suggest that this, combined with the health risks posed by malfunctions in neurodevices, provides grounds for the Medicines and Healthcare products Regulatory Agency (MHRA) to monitor the vulnerability of neurodevices to interference or data interception (paragraph 5.54).

Two important issues arise when considering the responsible protection of research participants' interests. The first is the prospect of sham neurosurgery being used as a placebo control in clinical trials of neural stem cell therapies. We recommend that research ethics guidance should be provided on this (paragraph 5.41). The second relates to the potentially serious impacts on participants from whom beneficial therapeutic or assistive neurodevices may be withdrawn at the end of a study. Where this is likely to be the case we recommend that submissions to research ethics committees must detail the information and support that will be provided to participants as part of consent procedures and at the conclusion of the study (paragraph 5.45).

It is not always possible to draw a neat line distinguishing therapy from research in a field where many novel applications of new technologies take place in the context of experimental treatments. Experimentation may be a necessary and valuable means of exercising inventiveness in this field, but it raises two concerns. First, there is a lack of clarity about whether interventions falling into this grey area should be governed as treatment or research. We recommend that this should be addressed by the provision of professional guidance on responsible conduct in experimental treatment (paragraph 5.60). Second, clinical experience gathered outside formal research studies may not be widely disseminated, thus perpetuating uncertainty. We suggest that publically accessible registers would provide a responsible approach to countering this risk (paragraph 5.63).

Introduction

- 5.1 When addressing the ethical use of therapeutic applications of novel neurotechnologies, the first line of concern is the care of those individuals who undergo interventions using these. Care does not only amount to administering effective therapeutic interventions; it also entails protecting and promoting the autonomy of these individuals, safeguarding their health and well-being, protecting their privacy and refraining from building unsustainable hope. In this chapter we examine the role played by regulation and governance in shaping practices that protect these interests in the context of the relationships between patients or research participants, and the clinicians and researchers responsible for their care.

- 5.2 Many of these neurotechnologies are still under development, and even the more established technology of deep brain stimulation (DBS) is subject to exploration for new therapeutic applications. In these exploratory stages of a technology's development, there are often grey areas in which it is not possible to make a clear practical or ethical separation between research and treatment – although legal frameworks and professional guidance are sometimes premised on the assumption that this is possible. We return in the final section of this chapter to consider issues raised by this separation. Research participants will frequently be patients, and clinicians will usually be central to research teams. Many of the considerations dealt with here apply across the spectrum of users of neurotechnologies – from participants in clinical trials, through recipients of experimental treatment, to users of more established therapies – and pertain to the professional responsibilities of clinicians and researchers. For these reasons, in this chapter we are concerned with the care of both patients and research participants, and often talk of them together.
- 5.3 The care needs of individuals who use different technologies will be diverse and the exchanges and negotiations in their relationships with professionals will be shaped by the uncertainty inherent to many emerging applications of neurotechnologies. Our ethical framework supplies us with a normative map to guide our understanding and evaluation of professional practices in this area in light of individuals' interests and wider public benefits. This then assists in determining where ethically-informed governance can play a valuable role in engendering or enforcing these practices and outcomes. This allows us to assess where there may be gaps in current legal provisions or professional guidance and to make recommendations where we judge that there might be ethical grounds for different approaches or additional support.

Decision-making, consent and autonomy

- 5.4 Obtaining consent from prospective patients or research participants for the use of novel neurotechnologies that intervene in the brain is one important aspect, although not the sole means, of respecting their autonomy. In law, consent is required for a clinician or a researcher to have physical contact with a patient or participant if it is not to constitute the common law offence of battery.⁴⁷⁵ In health research contexts more widely, consent is an ethical requirement and may be a legal obligation, as in the regulations governing clinical trials in the UK.⁴⁷⁶ In much professional guidance, such as that issued by the General Medical Council (GMC), the requirement is for 'valid consent', meaning that which meets all three criteria of being sufficiently informed, voluntary, and given by an individual with decision-making capacity.⁴⁷⁷ Failure to obtain valid consent, especially in respect of ensuring the individual is sufficiently informed, may be grounds for a finding of negligence in law.⁴⁷⁸
- 5.5 As we observed in constructing our ethical framework, there are (to varying degrees) a number of impediments to meeting the criteria for valid consent in respect of current applications of novel neurotechnologies in treatment and health-related research. These arise chiefly from continued uncertainty – perhaps further clouded by hype in the popular media – about the efficacy and risks of some of these technologies, and the desperation and hope experienced by some patients (and those close to them) with neurological or mental health conditions that have proved resistant to other forms of treatment.⁴⁷⁹ These factors present challenges to professionals' responsible efforts to ensure that, as far as possible, patients and participants have a sufficiently full and realistic understanding of proposed interventions and that they are

⁴⁷⁵ See, for example, *Chatterton v Gerson* [1981] QB 432 and *Appleton v Garrett* [1995] 34 BMLR 23.

⁴⁷⁶ Medicines for Human Use (Clinical Trials) Regulations 2004.

⁴⁷⁷ General Medical Council (2010) *Good practice in research and consent to research*, available at: http://www.gmc-uk.org/Research_guidance_FINAL.pdf_31379258.pdf, at page 8.

⁴⁷⁸ See, for example, *Chester v Afshar* [2004] UKHL 41, [2005] 1 AC 134.

⁴⁷⁹ Bell E, Mathieu G and Racine E (2009) Preparing the ethical future of deep brain stimulation *Surgical Neurology* **72(6)**: 577-86, at page 580.

making choices free from external pressures, even where these pressures are well-meaning. In some instances, it might not be possible to achieve valid consent to the satisfaction of ethically or legally required standards. Securing valid consent cannot, however, mean eliminating all influences of desperation or hope. If the conditions of capacity, sufficient information, and absence of constraint can be achieved, professionals may have to exercise humility by stepping back from making paternalistic judgements about whether patients' or participants' choices are the 'right' ones. A further challenge to achieving consent that is especially marked (although not unique) in this field arises from the close link between many neurological disorders and impaired decision-making and decision-communicating capacities (we return to this issue in paragraphs 5.11 to 5.14).

- 5.6 Underlying these dilemmas is the practical question of whether a paradigm of decision-making and consent based upon a one-to-one clinician-patient or researcher-participant relationship and a single moment of consent is sufficient to protect the latter parties' wider interests in determining what happens to them and how they live their lives.⁴⁸⁰ Despite an evolution over recent decades that has seen the kind of information provision required in the UK under common law evolve from what doctors would typically tell to what a reasonable patient would want to know,⁴⁸¹ consent to treatment is still largely equated with the moment when patients assent to a course of action proposed by their doctor. Similarly, the legal framework governing conduct in clinical research establishes a regulatory requirement for a signed consent form, thus focusing on professionals' responsibilities for the steps preceding its signing.⁴⁸² There are undoubtedly care teams that operate best practice procedures and engage patients in detailed discussions both before and after interventions, nevertheless, these legal frameworks reflect, and perhaps even perpetuate, models of practice that place chief emphasis upon securing and recording a *particular moment* of agreement.⁴⁸³
- 5.7 A 'one-off and one-to-one' model of consent as underscored by legal obligations may be unsuitable in contexts characterised by uncertainty, desperation and hype. This is perhaps particularly so where decision-making pertains to invasive novel neurotechnologies involving commitments to long-term interventions; where interventions may be accompanied by deeply personal unintended impacts upon identity, behaviour, and personal relationships (such as some patients experience with DBS);⁴⁸⁴ or where interventions are experimental and of uncertain benefits (such as in the use of assistive brain-computer interfaces (BCIs)). The value of permitting prospective patients sufficient opportunity to explore in depth the possible implications of undergoing treatment with an invasive neurotechnology is underlined by the following perspective from one individual interviewed as part of the preparation of this report:

“When they [the clinicians] mention what the [DBS] operation involves it's very hard to understand exactly what it means, even though I would usually consider myself capable in this respect. I had asked all the questions that you would expect to ask

⁴⁸⁰ Cambridge University Press (2001) *Autonomy and trust in bioethics*, available at: <http://catdir.loc.gov/catdir/samples/cam033/2002073521.pdf>, pp.18-9; Manson NC and O'Neill O (2007) *Rethinking informed consent in bioethics* (Cambridge: Cambridge University Press).

⁴⁸¹ *Pearce v United Bristol Healthcare NHS Trust* (1999) 48 BMLR 118.

⁴⁸² Part 1 to Schedule 1(3) of the Medicines for Human Use (Clinical Trials) Regulations 2004. Although these regulations are not legally binding in research that is not a clinical trial, as a matter of policy they provide the benchmark for best practice in the ethical conduct of health research in the UK. See: NHS Health Research Authority (2012) *Standard operating procedures*, available at: <http://www.nres.nhs.uk/nres-publications/publications/standard-operating-procedures/>, v5.1, at page 14.

⁴⁸³ For example, judgments such as that in *Chester v Afshar* [2004] UKHL 41; [2004] 3 W.L.R. 927 highlight that doctors may be found liable for negligence in failing to support patients' autonomy through information provision, but nevertheless make information provision prior to consent the focus of the standard of care on which this negligence is determined. See: Laurie G and Postan E (2012) Rhetoric or reality: what is the legal status of the consent form in health-related research? *Medical Law Review*.

⁴⁸⁴ Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* **2(1)**: 3-13, at page 5.

relating to the risks and what was involved – but there are only so many questions you can ask.”⁴⁸⁵

- 5.8 Responsible professional practice and humility require clinicians to be open about the limits of current knowledge and the therapeutic benefits that a patient can expect. These virtues also require that clinicians recognise a distinction between those aspects of decisions for which their professional expertise provides the best guide, and where patients and participants would additionally benefit from the advice and support of non-clinical counsellors or from individuals who have undergone similar therapies. These sources of additional support could help in negotiating an uncertain landscape and decisions that may be more personal than clinical in nature. As we noted in Chapter 4, sometimes this may involve making difficult choices to prioritise health gains at the expense of other aspects of quality of life (see paragraph 4.31). The same interviewee we quoted in the previous paragraph also highlighted the potential value of talking to individuals with personal experience of these kinds of treatment:

“One way I felt I could give something back would be to talk to people and relatives before they have the [DBS] operation. Doctors can say what they have to say but it’s a totally different matter to have the operation. When I was in hospital for the first time this year there was a man in the bed next to me with cluster headaches who was waiting to have the operation. He overheard that I had had the operation and wanted to know more about it. I showed him my x-rays and I was able to explain a few things. One of the nurses said that it had made all the difference to the patient, to meet someone who was alive after the operation...”⁴⁸⁶

- 5.9 Given the uncertainty about the long-term unintended effects of some (particularly invasive) neurotechnologies, and the potential personal ramifications of these, prospective patients and those close to them are likely to benefit from counselling, which would complement information provided by clinicians. **We recommend that those responsible for commissioning specialised services for the NHS in each of the UK countries make it a requirement that, where treatments involving invasive neurostimulation (and, in the future, neural stem cell therapies) are provided, patients must be offered the opportunity to receive independent counselling from suitably qualified professionals about the implications of these treatments. Features of this counselling should include:**

- That it is offered as part of the referral pathway before consent is given; this would be in addition to, rather than a replacement for, the provision of clinical information supporting informed consent.
- It should also be distinguished from any parallel provision of therapeutic counselling for patients with mental health disorders.
- The counselling services recommended here would be analogous in delivery and aims to NHS genetic counselling services to the extent that they should: be delivered by a member of an interdisciplinary health care team; be non-directive; provide information suitable to patients’ individual circumstances and treatment options; and provide support to family members and others close to and caring for the patient.⁴⁸⁷
- Decision making is often a collective enterprise involving both patients and those close to them. Extending counselling to those close to the patient will be valuable in meeting these

⁴⁸⁵ Factfinding meeting with Richard Smith, DBS patient, 20th November 2012.

⁴⁸⁶ Factfinding meeting with Richard Smith, DBS patient, 20th November 2012.

⁴⁸⁷ NHS Choices (2012) *What is genetic counselling and do I need a genetic counsellor?*, available at: <http://www.nhs.uk/chq/Pages/2370.aspx>; EuroGentest (2011) *What is EuroGentest?*, available at: <http://www.eurogentest.org/index.php?id=160>.

individuals' own support needs, and in helping to protect patients from pressures to undertake interventions, even where such pressures are well-intended.⁴⁸⁸

- 5.10 Obtaining legally valid consent for interventions using novel neurotechnologies is a key step in the conduct of ethically robust professional practice, but it is only the first step. It does not obviate the need for professional practices to respect individuals' autonomy throughout a treatment or research relationship, nor the need to safeguard parallel interests in, for example, safety and privacy. Ongoing discussion and information provision, beyond any initial consent process, would allow patients, participants and those close to them to adjust their expectations or reassess their participation in light of emerging understandings of the efficacy and risks of an intervention. This is illustrated, for example, by the significance of permitting users of DBS to be able to self-calibrate the levels of stimulation delivered,⁴⁸⁹ or BCI users to control the way their device works,⁴⁹⁰ in recognition of the role that these devices may play in users' concepts of their own bodies and their capacity to control their behaviour and express their identities.

Decision-making and incapacity

- 5.11 Many of the therapeutic or assistive neurotechnologies we consider in this report are intended for use by patients with neurodegenerative disorders or brain injuries that affect their capacity to exercise their own autonomy. In the UK, several different legal regimes permit decisions to be made, and consent given, on the behalf of patients who lack capacity to make or to communicate their own decisions.⁴⁹¹ In this context it is crucial to be able to distinguish whether an intervention constitutes research, routine treatment, or the kind of experimental intervention that is seen as an incapacitated individual's 'last best hope' for treatment, as different rights, responsibilities and potential liabilities follow as a result.
- 5.12 In the UK, the Mental Capacity Act 2005 and the Adults with Incapacity (Scotland) Act 2000 permit treatment decisions to be made on behalf of incapacitated adults, provided these are made in their 'best interests'.⁴⁹² Best interests are to be assessed by taking account of all considerations affecting the patient's condition, of which medical or carer perspectives are only two components.⁴⁹³ In deciding what a patient's best interests might be, clinicians must consult those with a lasting power of attorney before treatment is given. Even if no such individual has been appointed, any prior expressed wishes of the patient must be taken into account and those with a legitimate interest in the patient's welfare must be consulted if practically possible.
- 5.13 Adults who lack capacity have the right in law to take part in research, provided stringent safeguards are in place.⁴⁹⁴ The relevant legislation prescribes a risk-benefit analysis insofar as the research must be concerned with the treatment of the condition from which the person suffers, the research cannot be carried out on a consenting population, and that there must be a potential to benefit the person without disproportionate burden (or, if the only outcome is generalisable knowledge about the condition, then there must be negligible risk and any

⁴⁸⁸ Bell E, Mathieu G and Racine E (2009) Preparing the ethical future of deep brain stimulation *Surgical Neurology* **72**(6): 577-86, at page 581.

⁴⁸⁹ Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* **2**(1): 3-13, at page 9.

⁴⁹⁰ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4**(3): 1-22, pp. 14-5.

⁴⁹¹ In England and Wales Section 3 of the Mental Capacity Act 2005 applies and the law in Scotland is set out in Section 1(6) of the Adults with Incapacity (Scotland) Act 2000. In Northern Ireland decision-making about medical treatment is governed by the common law, though the Northern Ireland Assembly is currently considering the introduction of a Mental Capability Bill.

⁴⁹² Section 4 of the Mental Capacity Act 2005; Part 5 of the Adults with Incapacity (Scotland) Act 2000. The Scottish legislation does not use the terminology of 'best interests' but rather in terms of 'safeguarding or promoting' health and 'benefit'; the practical consequences of this are unlikely to be significant.

⁴⁹³ See, for example, *Re A (medical treatment: male sterilisation)* [2000] 1 FLR 549 for a particularly clear articulation of the considerations.

⁴⁹⁴ See, for example, sections 30-4 of the Mental Capacity Act 2005 and Section 51 of Adults with Incapacity (Scotland) Act 2000.

intrusion must not be unduly invasive or restrictive).⁴⁹⁵ There are obligations to make reasonable attempts to consult family members and carers and any view they express that, in their opinion, the person would not want to be involved, must be respected. It is unlawful to proceed with research outside these parameters. The distinction between research and treatment is, however, not always clear in this context. For example, the Mental Capacity Act 2005 states that "...treatment that [the patient] has been receiving as part of the project [does not have to be] discontinued if [the researcher] has reasonable grounds for believing that there would be a significant risk to [the patient's] health if it were discontinued."⁴⁹⁶

- 5.14 It has been suggested that the only acceptable uses of invasive neurotechnologies are those in which there is a reasonable, evidence-based expectation of considerable benefit to the patient, and that this benefit clearly outweighs any risks.⁴⁹⁷ However, as we have observed for some of the neurotechnologies we have considered – for example, the use of invasive BCIs by patients with locked-in-syndrome or in a minimally conscious state – it may be extremely difficult to give a straightforward assessment of benefit, therefore making any robust risk-benefit analysis impossible.⁴⁹⁸ Applications of novel neurotechnologies such as these present a serious problem for all parties involved in making decisions on behalf of individuals who lack capacity, as it may not be clear whether and how the best interests test can be met. Where there is dispute about whether an experimental treatment would be in a patient's best interests, this will be referred to the courts where a decision will be made by a judge.⁴⁹⁹ This route may be taken in instances of a patient's 'last best hope' – that is, where patients find themselves in desperate circumstances where the likely impacts of the few (or only) remaining options for therapeutic or assistive interventions are themselves unknown or doubtful.

Experimental therapies and 'last best hope'

- 5.15 In the case of *Simms v Simms and Another*, the parents of two teenagers in advanced stages of variant Creutzfeldt-Jakob disease sought court authority for a 'treatment' that had never been tried in humans (though had shown moderate success in animal models). In this case, the High Court applied the best interests test to allow treatment on the basis that no medical witness would rule out the possibility that some benefit might accrue. It was relevant that there remained no other option but death and there was no significant risk of the intervention further harming the patients. This raises the question of the ethics of last best hope scenarios.⁵⁰⁰ While, from a legal perspective, a court is the ultimate arbiter, this is often a pronouncement made retroactively.⁵⁰¹ This is not helpful to those facing decisions at the coalface on a daily basis. There is, nonetheless, a suggestion from this case that the desperate nature of the circumstances changes the ethical considerations and that desperation alone should not be taken as a reason to exclude highly experimental interventions. Perhaps the most important feature from a regulatory perspective is who should be responsible for taking such decisions if the court route is not practicable, and on what basis?⁵⁰² In *Simms*, the court relied on a "responsible body of medical opinion"; taking this benchmark from the criterion applied to determine medical negligence.⁵⁰³ It may, however, be questioned whether such a decision

⁴⁹⁵ These are the English and Welsh provisions. The Scottish position is similar but in some sense stricter; for example, the research must be "likely to produce a real and direct benefit" or if only generalisable knowledge can be generated, then there must be "no foreseeable risk, or only minimal foreseeable risk": section 51 of the Adults with Incapacity (Scotland) Act 2000.

⁴⁹⁶ Section 33(6) of the Mental Capacity Act 2005.

⁴⁹⁷ Haselager P, Vlek R, Hill J and Nijboer F (2009) A note on ethical aspects of BCI *Neural Networks* **22(9)**: 1352-7.

⁴⁹⁸ *Ibid*, at page 1354.

⁴⁹⁹ See, for example, *Simms v Simms and Another* [2003] 2 WLR 1465.

⁵⁰⁰ See also: *An NHS Trust v HM* [2004] Lloyd's Reports Medical 207 and *EP v Trusts A, B and C* [2004] Lloyd's Reports Medical 211.

⁵⁰¹ Although not in the case of *Simms v Simms* since a declarator was sought about whether it would be lawful to proceed.

⁵⁰² Price D (2005) Remodelling the regulation of postmodern innovation in medicine *International journal of adaptive control and signal processing* **1(2)**: 122-41.

⁵⁰³ This is the 'Bolam test', *Bolam v Friern Hospital Management Committee* [1957] 1 WLR 582. See: Laing J (2003) Incompetent patients, experimental treatment and the 'bolam test' *Medical Law Review* **11(2)**: 237-41.

ought to be left to the medical profession alone, given that best interests may be construed differently by different parties and that it seems desirable that input is received from as many quarters as possible.

- 5.16 While the *Simms* case did not concern one of the novel neurotechnologies we discuss in this report, the circumstances of last best hope are exemplified by instances where patients with locked-in syndrome have already lost, or fear losing, the ability to move and are offered experimental invasive BCIs in an effort to restore or preserve their only opportunity for communication.⁵⁰⁴ However, not all neurological disorders present such stark choices. The best interests test may be welcomed to the extent that it does not preclude individuals – whose neurological disorders have severely impaired their consciousness, cognitive capacities or motor skills – from partaking in potentially beneficial interventions. Nevertheless, humility warns against applying this test in a short-termist or cavalier way. This is particularly true where the absolutism implied by ‘last best hope’ itself may be questionable. Many conditions for which therapeutic or assistive neurotechnologies are indicated are chronic but not fatal, so it may be inappropriate to talk in terms of *last* best hope. It is also relevant to consider to what ‘best hope’ refers, when we are not in the tragic circumstances of imminent death with which the *Simms* case was concerned. Moreover, exercising responsibility and humility entails recognising that extending hope by offering treatment options of uncertain value (even if these delay death) may itself be contrary to the interests of patients and those close to them. This is particularly important in view of the desperate circumstances in which some patients and their families might find themselves, as illustrated by the Dementia Services Development Centre’s response to the Working Party’s public consultation:

“...we recognize how desperate some of the families and individuals with dementia are, and we can see that they might be tempted to undertake risky or dangerous interventions to escape from the horror of their situation.”⁵⁰⁵

- 5.17 In order to protect and uphold trust by ensuring that risks and benefits are appropriately understood by those with delegated legal responsibility for making care decisions on behalf of incapacitated patients, responsibility and humility require that clinicians draw a distinction between experimental therapies that genuinely represent someone’s last best hope, and those that might better be characterised as the ‘*latest new hope*’, in the absence of other effective interventions. It is no less important that clinicians also avoid the inappropriate presentation of novel, experimental therapies as last best hope in situations where patients are competent to make their own treatment decisions.

Protection from harm to health and well-being

- 5.18 In Chapter 2, we outlined the potential unintended risks to health associated with therapeutic applications of novel neurotechnologies. These technologies do not share a single profile in terms of potential risks, but rather occupy a broad spectrum from the least invasive, such as electroencephalography-based (EEG) BCIs, to the most, such as DBS, invasive BCIs and neural stem cell therapies, which require neurosurgery, with attendant risks of infection, bleeding and unintentional damage to, or stimulation of, neural tissue and neural functions. Though the risks of these invasive technologies may be considered relatively low compared with other kinds of more drastic neurosurgery (for example, surgery to remove brain tumours), the special status of the brain nevertheless means that protecting against harm arising from treatment and research uses of these technologies is particularly important. Given the role of the brain not only in the healthy functioning of our minds as well as our bodies, this encompasses not only physical impacts but also those affecting behaviour and individuals’ experiences of themselves.

⁵⁰⁴ Haselager P, Vlek R, Hill J and Nijboer F (2009) A note on ethical aspects of BCI *Neural Networks* **22(9)**: 1352-7.

⁵⁰⁵ Dementia Services Development Centre, University of Stirling, responding to the Working Party’s consultation.

Treatment contexts

- 5.19 In treatment relationships, the protection of patients from harm is secured by the fundamental ethical principle of non-maleficence, corresponding to the principle of caution in our ethical framework (see paragraph 4.22), and by the common law of medical negligence. An approach to pursuing novel interventions that exemplifies all three virtues of responsibility, humility and inventiveness is not one that seeks to avoid risks at any cost, but strives for a proportionate balance between potential risks and benefits. Nevertheless, clinicians must proceed with great caution in pursuing experimental therapies where there are evidence gaps regarding their safety and efficacy. The law regarding medical negligence in the UK is founded upon the legal duty of care that doctors owe to their patients. Broadly speaking, treatment is negligent where it departs from the standard of care expected by “a responsible body of medical opinion” (the so-called ‘Bolam test’)⁵⁰⁶ and causes the patient a legally recognised form of physical or psychiatric harm. This last element could mean that redress under negligence law might not be available if unwanted behavioural or cognitive effects are not classed as psychiatric harms.
- 5.20 As we have seen in the *Simms* case discussed in the previous section, the Bolam test does not necessarily preclude the pursuit of more experimental therapeutic interventions where there might not yet be an established opinion.⁵⁰⁷ This is significant, given the investigative status of many interventions involving novel neurotechnologies. Decisions about whether to pursue experimental therapies will be a matter for clinicians’ professional judgement, although they can also draw on good practice guidance from the GMC,⁵⁰⁸ the advice of local ethics committees within their hospital or health authority⁵⁰⁹ and *Interventional Procedures Guidance* (IPG) issued by the National Institute for Health and Care Excellence (NICE).⁵¹⁰ There is an irony here that the most experimental interventions are likely to be carried out on some of the most vulnerable patients. This places all the more emphasis on professionals exercising the virtue of responsibility in deciding whether interventions can be justified in terms of being of genuine benefit to the patient.⁵¹¹ As we discuss in the final section of this chapter, distinguishing when experimental treatment crosses over into what should be more properly regarded as ‘clinical research’ (to which different governance measures apply) may not always be a straightforward matter.

NICE Interventional Procedures Programme

- 5.21 The National Institute for Health and Care Excellence (NICE) is charged, *inter alia*, with reviewing the evidence and approving new interventional procedures for use in the NHS under the *Interventional procedures programme* (IPP).⁵¹² The aim of guidance issued under the IPP is to assess the safety and efficacy of a procedure, whether it works well enough for routine use or whether special arrangements are needed for patient consent, clinical governance and research when it is used in the NHS.⁵¹³ This safety dimension makes the IPP’s focus distinct from NICE’s role in evaluating the cost-effectiveness of health technologies, for example under the *Technology appraisals and medical technologies evaluation* programmes. It also means that

⁵⁰⁶ *Bolam v Friern Hospital Management Committee* [1957] 1 WLR 582.

⁵⁰⁷ *Simms v Simms and Another* [2003] 2 WLR 1465.

⁵⁰⁸ GMC (2013) *Good medical practice*, available at: http://www.gmc-uk.org/guidance/good_medical_practice.asp.

⁵⁰⁹ For example, Imperial College Healthcare NHS Trust (2012) *Clinical ethics committee*.

⁵¹⁰ For example, NICE (2003) *Deep brain stimulation for Parkinson's disease*, available at: <http://egap.evidence.nhs.uk/deep-brain-stimulation-for-parkinsons-disease-ipg019>.

⁵¹¹ In December 2012 Lord Saatchi, as a member of the House of Lords, introduced a proposal for a ‘Medical Innovation Bill’ that would aim to codify ‘responsible innovation’ to offer protection to doctors pursuing innovative treatment in the absence of evidence-based treatments: House of Lords (2012) *Medical Innovation Bill*, available at:

<http://www.publications.parliament.uk/pa/bills/lbill/2012-2013/0061/20130061.pdf>.

⁵¹² NICE (2013) *Interventional procedures*, available at: <http://www.nice.org.uk/guidance/ip/index.jsp>.

⁵¹³ NICE (2011) *About interventional procedures*, available at:

http://www.nice.org.uk/aboutnice/whatwedo/aboutinterventionalprocedures/about_interventional_procedures.jsp.

NICE does not recommend that procedures *must* be used, but instead gives the conditions under which innovative procedures can be introduced safely for patients and clinicians.

- 5.22 Although anyone may notify NICE of a procedure for assessment, it is most often clinicians who do so. The process for gathering evidence to produce an IPG involves specialist advisors, an independent advisory committee and public consultation.⁵¹⁴ Many of the procedures considered will be new, but where these involve medical devices they will only be assessed by NICE where such a device is licensed to be marketed for that purpose in the UK. Several novel neurotechnologies have been considered under the IPP.⁵¹⁵ One example of this is the IPG on DBS for refractory epilepsy, which was considered in January 2012. The guidance states that:

“The evidence on the efficacy of deep brain stimulation (DBS) for refractory epilepsy is limited in both quantity and quality. The evidence on safety shows that there are serious but well-known side effects. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.”⁵¹⁶

In view of these caveats, the guidance lays out procedures to be followed by clinicians, including: informing clinical governance leads in the NHS trust; patient selection and management by multidisciplinary teams; ensuring that patients and their carers understand the uncertainty about the procedure’s safety and efficacy; and auditing and reviewing clinical outcomes of all patients. The IPG also encourages the pursuit of further research.⁵¹⁷

- 5.23 The NICE IPP reflects the virtue of responsibility in that it embodies a step-by-step precautionary approach while laying out clearly the duties of practitioners when involving patients in such procedures. Evidence of efficacy and of adverse or negative outcomes (including inefficacy) must be gathered and shared as robustly as possible. The IPP also embodies inventiveness in that it seeks to encourage innovation by welcoming all appropriate forms of evidence as to the efficacy and safety of procedures. While the quality of this evidence is crucial for NICE, its sources are not limited to the results of randomised controlled trials (RCTs). Observational data such as case studies and registers will often form a more appropriate evidence base for identifying features such as device failure or other longer term adverse events that would not arise during the normally limited time period of an RCT. Specialist advisors’ knowledge of the use of procedures in clinical practice is also an important component of the assessment by the NICE IPP, as are patients’ own experiences and views on the relative benefits and risks of the procedure. The resulting guidelines are reviewed as new evidence emerges.

- 5.24 The role of a centralised body such as NICE in considering evidentiary and consent issues, and in providing uniform guidance on how to proceed with appropriate caution, is clearly to be welcomed. However, while the practical application of its guidance is largely down to local level decision-makers such as commissioners and clinicians, it can only go so far in ensuring good patient outcomes. **It is essential that NICE continue to work with stakeholders, including patients, to maximise usefulness of *Interventional procedures guidance (IPG)* and its application in real life settings. At present, compliance with NICE IPG is voluntary. We recommend that compliance with NICE IPG should be made compulsory within the NHS and that the Care Quality Commission (CQC) is assigned the role of inspecting NHS trusts (and boards) to ensure compliance.**

⁵¹⁴ NICE (2012) *Developing NICE interventional procedures*, available at: http://www.nice.org.uk/aboutnice/howwework/developingniceinterventionalprocedures/developing_nice_interventional_procedures.jsp.

⁵¹⁵ NICE (2013) *Published interventional procedures*, available at: <http://www.nice.org.uk/guidance/ip/published/index.jsp?p=off>.

⁵¹⁶ NICE (2012) *Deep brain stimulation for refractory epilepsy*, available at: <http://www.nice.org.uk/nicemedia/live/12775/57916/57916.pdf>.

⁵¹⁷ Ibid.

5.25 The NICE IPP fulfils an important function by providing a framework for clinicians and commissioners to refer to when using novel neurotechnologies. Even so, IPGs cover procedures in *general* terms; they do not address the efficacy or safety of devices made by particular manufacturers, nor can they reflect the significant differences to patient outcomes that may be made by the techniques of individual clinicians. As we discuss in paragraphs 5.61 to 5.66 and further in Chapter 7, there is a broad need, particularly in respect of neurodevices, to encourage better collection and sharing of information on clinical experiences of using novel neurotechnologies.

Private provision of treatment services

5.26 It might be assumed from our discussion thus far that therapeutic uses of novel neurotechnologies will be administered by clinicians or other health care professionals working for the NHS. However, this will not always be the case; treatments may, of course, be provided through private medical care. They might also be offered outside the formal healthcare sector, by private therapists without medical training. Unlike prescription drugs, there are no regulatory restrictions upon who can administer treatment using licensed neurodevices and where these treatments can be sold.⁵¹⁸

5.27 The NICE IPG on the use of TMS in severe depression advises that, in view of uncertainty about the clinical efficacy of this treatment (at the parameters of delivery that have been studied thus far) TMS for depression should be only performed in *research* to investigate its efficacy using different parameters of neurostimulation.⁵¹⁹ In accordance with this guidance, there appear to be no NHS hospitals which formally offer TMS services for depression in the UK. However, several TMS devices are licensed for this purpose in Europe, and it is possible that treatment is being offered where equipment and expertise are available in research institutes and at the request of private practitioners. There are indications that private businesses are operating to meet a demand for provision of TMS and rTMS⁵²⁰ to treat depression.⁵²¹ As we discuss further in Chapter 8, at least one private company offers TBS services directly to consumers with the suggestion that this “can help” in depression, stroke and migraine.⁵²² Box 5.1 below provides one example rTMS being offered in a private healthcare setting.

Box 5.1: The London Psychiatry Centre⁵²³

The London Psychiatry Centre website claims that it is only clinic in the UK offering rTMS for depression. The website describes rTMS as “a highly effective and safe intervention to help overcome treatment-resistant Depression” and “safe middle step in cases which do not respond to antidepressants, but before considering ECT”. The information provided by their website notes that there is a “very small” risk of suffering a seizure, but it also includes the potentially obfuscatory claim that “since the only thing entering your body is pure energy, rTMS is free from the many side effects associated with antidepressant medications”.

The treatment plan outlined by the centre offers five sessions of just over half an hour per week and the Centre’s website suggests that an average treatment will last four weeks – the total cost of which is given as six thousand pounds.

⁵¹⁸ The Medicines Act 1968 and Prescription Only Medicines (Human Use) Order 1997 cover the sale, use and production of medicines, including prescribing rights. Neurodevices are not medicines and are not covered by these statutes.

⁵¹⁹ NICE (2007) *Transcranial magnetic stimulation for severe depression* available at: <http://www.nice.org.uk/nicemedia/live/11327/38391/38391.pdf>.

⁵²⁰ rTMS, refers to a variant of TMS, repetitive transcranial magnetic stimulation.

⁵²¹ The London Psychiatry Centre (2011) *rTMS*, available at: <http://www.psychiatrycentre.co.uk/our-services/repetitive-transcranial-magnetic-stimulation-rtms/>; Neuradaptix (2012) *Using TMS to treat depression*, available at: <http://www.neuradaptix.com/>.

⁵²² Biofeedback & Neurofeedback in York (2012) *Transcranial direct current stimulation*, available at: <http://www.york-biofeedback.co.uk/neurofeedback/tcds.aspx>.

⁵²³ The London Psychiatry Centre (2011) *rTMS*, available at: <http://www.psychiatrycentre.co.uk/our-services/repetitive-transcranial-magnetic-stimulation-rtms/>.

- 5.28 The use of rTMS and TMS in private settings raises clear issues regarding the regulation and protection of patients' interests. In considering what kinds of restrictions should be placed on the private provision of services involving non-invasive neurotechnologies, it is important to attend to the need for proportionate oversight. Whether existing oversight is adequate is likely to depend on what categories of provider are involved. Private doctors are bound by professional ethical norms and principles of common law and those who are licensed by the GMC will also be bound by associated guidance. However, oversight of safe and ethical practice may be less stringent than that entailed by the codes of practice applying to NHS employees. The oversight and accountability of private practice, for example in respect of the long-term follow-up of patients or reporting an adverse event, is unclear. If interventions are administered by, or under the instructions of, a doctor or in a health care setting, the GMC and the CQC could use their powers to sanction fraudulent or unsafe use by the professionals or services that fall within their respective remits.⁵²⁴ If, for example, a doctor were to use a licensed medical device 'off-label'⁵²⁵, the GMC would be concerned to know that this was based on honest beliefs of sound evidence that this was in the 'patient's' best interests and that the patient had been provided with sufficient information to support informed consent. However, where an intervention is non-invasive and considered low risk, the GMC would be unlikely to sanction doctors offering poorly evidenced interventions.⁵²⁶
- 5.29 Where services are delivered wholly outside the medical sphere, the restrictions on what service providers can and cannot do becomes even less clear. For example, many of the guarantees that patients can expect within medical settings regarding standards of diagnosis, information provision, and consent procedures cannot be assumed to apply. It is not clear from the website of the private clinic described in Box 5.1 above what category of practitioner will actually *deliver* treatment, what training they have received to carry out these procedures, and what referral route(s) would be accepted. These omissions raise questions about ensuring that this kind of treatment is safe and suitable for individual patients. The website of one UK-based company reflects a responsible approach by stating that patients will only be able to access their services on the referral of a medical professional, that treatment will be discontinued if "there are any adverse experiences or there is no discernible improvement", and that the "referring physician" must confirm that the prospective patient does not have other risk factors.⁵²⁷
- 5.30 Where there are no other effective treatments available for severe conditions such as depression, it might be disproportionate to outlaw the private provision of neurostimulation services – especially while providers of more poorly evidenced alternative therapies are permitted to operate. However, harm to *physical* health is not the only category of potential risk that is relevant for the users of such services. For example, fraudulent (or even unknowingly useless) provision of interventions may also exploit vulnerable individuals and irresponsibly sustain hope. As we note above, service providers who are not doctors will not be bound by the same professional duties as clinicians to protect privacy and confidentiality. The potential risks are also not restricted to individual harm. Whilst public awareness and understanding of these technologies is still evolving, poorly performed or poorly explained uses may also undermine trust in therapies that, when delivered under appropriate protocols, could deliver valuable outcomes.
- 5.31 In view of these considerations, we judge that the greatest risk to patients' health and well-being arises from the provision of services by private providers without medical qualifications who operate outside the governance structures of the health service or professional medical ethics.

⁵²⁴ CQC (2010) *Essential standards of quality and safety*, available at: http://www.cqc.org.uk/sites/default/files/media/documents/gac_-_dec_2011_update.pdf.

⁵²⁵ The expression 'off-label' is most commonly used in relation to prescription drugs where it refers to the practice of prescribing drugs for conditions, in categories of patients, or at doses other than those for which it has been licensed. Here it is used to refer to analogous practice in respect of medical devices. The regulations governing medical devices in Europe prohibit manufacturers' *marketing* devices for uses other than those for which approval has been obtained, but do not prohibit these 'off-label' uses. For further discussion, see Chapter 7.

⁵²⁶ Fact-finding meeting with the GMC, 20 September 2012.

⁵²⁷ Neuradapix (2012) *Using TMS to treat depression*, available at: <http://www.neuradapix.com/>.

We recommend that the relevant professional bodies, including the Association of British Neurologists and the Royal College of Psychiatrists, should work together to issue a set of guidelines to establish a benchmark for responsible professional standards in the delivery of non-invasive neurostimulation treatments. These guidelines should state those categories of neurostimulation treatment that should only be provided by a suitably qualified professional, following clinical evaluation of a patient by a doctor. The aim is to ensure that neurostimulation treatments are provided only where there are appropriate clinical indications and where individual risk factors have been assessed.

Direct-to-consumer advertising

- 5.32 A final issue to consider where neurotechnologies such as TMS are offered by private providers is that of direct-to-consumer (DTC) advertising. The websites referenced in paragraph 5.27 are written in a style that suggests their target market is prospective patients themselves, indicating that DTC marketing of services using neurotechnologies is an emerging area of commerce. This raises the question of what regulation in this arena might look like and who would regulate it. It is noteworthy that none of the EU Directives regulating the entry of medical devices onto the market (which we consider in more detail in Chapter 7) covers advertising. It is also worthwhile observing that companies could offer their treatment services from bases anywhere in the world, and as such their advertising efforts might fall under a different jurisdiction.
- 5.33 The issues raised here are similar to those addressed by the Nuffield Council's 2010 report on *Medical profiling and online medicine*, which considered the regulatory challenges relating to DTC marketing of, amongst other services, body scanning.⁵²⁸ In that context the Council concluded that harms did not appear sufficiently serious to justify a restriction on sales of these services. Rather, what was required was more *accurate* information for consumers on their utility and value. With regards to a DTC body scan, the Council recommended: i) independent research on the impact and effects on individuals of DTC body imaging performed as a health check; ii) appropriate regulation of services; iii) better provision of information; and iv) good professional medical practice in the public healthcare system.⁵²⁹ There are clear parallels here with the direct marketing of TBS and TMS services. As far as these non-invasive neurotechnologies are understood, the health risks are not sufficient to seek to prohibit the advertising of private services, but there *is* a need for greater efforts to inform potential customers and professionals alike. The level of action that is most likely to have a beneficial effect is that targeted at the professional or service provider and which emphasises the importance of accessing these services via the appropriate medical referral routes. The virtue of responsibility suggests that, while efforts to develop a better evidence base and to inform users are necessary, it is not clear that efforts to go beyond this in an attempt to control DTC marketing would be effective or practical.

Research contexts

- 5.34 It is a central principle of ethical research practice, as established by international guidelines such as the Declaration of Helsinki, that the well-being of the individual research subject takes precedence over other interests.⁵³⁰ This does not mean that research involving novel neurotechnologies must be risk-free, but that potential harm to participants must be

⁵²⁸ Nuffield Council on Bioethics (2010) *Medical profiling and online medicine: the ethics of 'personalised healthcare' in a consumer age*, available at: [http://www.nuffieldbioethics.org/sites/default/files/Medical%20profiling%20and%20online%20medicine%20-%20the%20ethics%20of%20personalised%20healthcare%20in%20a%20consumer%20age%20\(Web%20version%20-%20reduced\).pdf](http://www.nuffieldbioethics.org/sites/default/files/Medical%20profiling%20and%20online%20medicine%20-%20the%20ethics%20of%20personalised%20healthcare%20in%20a%20consumer%20age%20(Web%20version%20-%20reduced).pdf).

⁵²⁹ Ibid, at page 166.

⁵³⁰ See, for example, World Medical Association (2008) *WMA declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/>, Principle 6.

proportionate to the benefits and carefully managed.⁵³¹ In the UK this principle is reflected in the combination of practice guidance, statutory regulation, and ethical oversight that governs health research involving, or impacting upon the care of, NHS patients. Each of the countries in the UK has published a research governance framework for health and social care (or ‘community care’ in Scotland).⁵³²

- 5.35 The scientific value of all proposed health research involving or impacting on the care of NHS patients is subject to scrutiny and research proposals are assessed by Research Ethics Committees (RECs).⁵³³ Protection of the health and well-being of participants in clinical trials of medicines is regulated in the UK by the Medicines for Human Use (Clinical Trials) Regulations 2004 under the authority of the responsible licensing body, the Medicines and Healthcare products Regulatory Agency (MHRA). Though most research involving neurodevices will not take place as clinical trials, but rather small studies, the clinical governance requirements of these regulations applies to all research involving patients – although as a matter of policy rather than strict law.⁵³⁴ Novel neurotechnologies do not present any particular challenges to the application of these governance measures that seek to secure the safety and well-being of research participants, except in one area: the ethical status of sham neurosurgery as placebo in the control arm of clinical trials.

Sham surgery as placebo control

- 5.36 The purpose of sham surgery is to provide a control arm for double-blinded RCTs of medical interventions involving surgery. These are clinical research trials in which neither the participants nor the investigators are told which of the participants have received the active treatment under investigation or a ‘control’ against which the effects of this will be compared. Sham surgery is used as a control in some trials to exclude the possibility that any observed benefits (or harms) are attributable to the placebo effects of surgery alone.⁵³⁵ A number of clinical neurosurgical trials for Parkinson’s disease in the US have used this form of placebo control.⁵³⁶ The research protocol for the control group has commonly been to drill holes in the outer layer of the skull, but not to inject cells into the brain itself.⁵³⁷
- 5.37 In the context of this report, the issue of sham neurosurgery arises particularly in the context of RCTs of neural stem cell therapies.⁵³⁸ The only clinical trial of neural stem cells in the UK to

⁵³¹ Department of Health (2005) *Research governance framework for health and social care: second edition*, available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962, at page 8.

⁵³² Ibid; Scottish Executive Health Department (2006) *Research governance framework for health and community care*, available at: <http://www.cso.scot.nhs.uk/publications/ResGov/Framework/RGFEdTwo.pdf>; Welsh Assembly Government (2012) *Research and governance framework for health and social care in Wales: second edition*, available at: <http://wales.gov.uk/docs/dhss/publications/governance/090929researchen.pdf>; Research & Development Office (2006) *Research and governance framework for health and social care* available at: http://www.dhsspsni.gov.uk/research_governance_framework.pdf.

⁵³³ Department of Health (2005) *Research governance framework for health and social care: second edition*, available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962, at pages 13 and 41.

⁵³⁴ Ibid, at page 13; NHS Health Research Authority (2012) *Standard operating procedures*, available at: <http://www.nres.nhs.uk/nres-publications/publications/standard-operating-procedures/>, at page 14.

⁵³⁵ In the context of surgery, the term ‘placebo’ has slightly different connotations from its use in drug trials. In the latter a placebo will be inactive – for example involving a sugar pill, any effects of which can be assumed to be psychological (though no less significant for this). However, in surgery, the sham procedures are in a sense *real* surgery with associated physiological effects. The control is therefore not strictly against a wholly inactive procedure, but rather one that is active, but which omits the element of the treatment under investigation.

⁵³⁶ Swift T and Huxtable R (2011) The ethics of sham surgery in Parkinson’s disease: back to the future? *Bioethics*: 1-11.

⁵³⁷ Ibid, at page 1.

⁵³⁸ In the case of sham-controlled DBS research, the considerations are somewhat different. Participants are unlikely to be subject to the risks of surgery without the possibility of gaining any therapeutic benefit from receiving the active intervention. There may be a control arm of the research protocol, in which the neurostimulation is sham, but the surgery itself will be real. Barring unforeseen complications, a functioning DBS device will be implanted and a cross-over research protocol will be used so that participants who do not receive stimulation will do so later in the study. Galpern WR, Corrigan-Curay J, Lang AE *et al.* (2012) Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations *The Lancet Neurology* **11(7)**: 643-50, at page 644.

date has not involved sham surgery.⁵³⁹ However, as more trials progress to Phase II, at which efficacy is tested with larger cohorts, the greater the chance that this method of placebo control could be considered.

- 5.38 The Declaration of Helsinki permits placebo controlled trials, provided there is no current proven intervention that may be used as control, or a placebo is needed to assess efficacy.⁵⁴⁰ Sham controlled trials of neural stem cells, for example to restore damaged neural tissue in stroke or Parkinson's disease patients, may fulfil these criteria. This methodology nevertheless raises a profound ethical dilemma.⁵⁴¹ On one hand, it could be the most robust method of ascertaining efficacy of invasive interventions for serious conditions. Even though alternative control methods exist, these may fail to distinguish which effects are due to the surgery rather than the active treatment.⁵⁴² On the other hand, it has been suggested that sham surgery is "arguably the riskiest and most invasive type of active placebo".⁵⁴³ As such, its use runs contrary to the Declaration's further provisions that participants' well-being takes precedence over other considerations and that "extreme care" should be taken to ensure that the control group are not be subject to "serious or irreversible harm".⁵⁴⁴ This possible harm arises not only from incisions or drilling. Participants in the sham control group may also be subject to brain scans, anaesthesia, immunosuppressant drugs and other interventions associated with surgery and follow-up.⁵⁴⁵
- 5.39 Decisions about whether sham surgery is an ethically defensible part of the development of novel neurotechnologies in the UK will be made by Research Ethics Committees and there is unlikely to be one straightforward answer. The virtue of responsibility – to participants or to the wider public interest in delivering effective therapies – occupies each side of this dilemma. The acceptability of sham surgical controls will therefore be distilled into an assessment of the risks and benefits in any particular study and whether participants can be said to give valid consent for exposure to risks that cannot be eliminated.
- 5.40 Patients may exhibit both altruism and the virtue of inventiveness by participating in RCTs, but it is important to consider whether those with few or no therapeutic options outside the chances offered by participating are truly making a free choice. It has been suggested that the prevalence and tenacity of the therapeutic misconception amongst research participants (that irrespective of what they are told, they will receive beneficial treatment) also threatens informed consent. Similarly, active attempts by surgical teams to conceal the sham nature of control procedures may be viewed as an unethical degree of deception of participants.⁵⁴⁶
- 5.41 Recommendations have been made as to how the risk-benefit ratio of sham surgery may be improved, including permitting it to be used only when a trial has a sufficiently strong scientific

⁵³⁹ A summary of the protocol for the PISCES trial may be found on the NIH clinical trials database: ClinicalTrials.gov (2013) *Pilot Investigation of Stem Cells in Stroke (PISCES)*, available at: <http://clinicaltrials.gov/ct2/show/NCT01151124?term=stem+cells+and+stroke&rank=6>.

⁵⁴⁰ World Medical Association (2008) *WMA declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/>, Principle 32.

⁵⁴¹ For further discussion, see, for example, Macklin R (1999) The ethical problems with sham surgery in clinical research *The New England journal of medicine* **341(13)**: 992-6; Dekkers W and Boer G (2001) Sham neurosurgery in patients with Parkinson's disease: is it morally acceptable? *Journal of Medical Ethics* **27**: 151-6; Galpern WR, Corrigan-Curay J, Lang AE *et al.* (2012) Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations *The Lancet Neurology* **11(7)**: 643-50.

⁵⁴² Galpern WR, Corrigan-Curay J, Lang AE *et al.* (2012) Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations *The Lancet Neurology* **11(7)**: 643-50, at page 646.

⁵⁴³ Swift T and Huxtable R (2011) The ethics of sham surgery in Parkinson's disease: back to the future? *Bioethics*: 1-11, at page 8.

⁵⁴⁴ World Medical Association (2008) *WMA declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/>, Principles 6 and 32

⁵⁴⁵ Swift T and Huxtable R (2011) The ethics of sham surgery in Parkinson's disease: back to the future? *Bioethics*: 1-11, at page 1.

⁵⁴⁶ Macklin R (1999) The ethical problems with sham surgery in clinical research *The New England journal of medicine* **341(13)**: 992-6.

rationale; when the sham procedure is the least invasive possible while maintaining uncertainty; where information provision is thorough; and when participants will have opportunities (all being well) to receive active interventions after the trial.⁵⁴⁷ It is notable that no professional bodies in the UK have issued guidance on the consideration and weighing of criteria such as these. We suggest that this represents a significant gap and that the production of such guidance ought to be prepared in time to inform the progression of UK clinical trials of neural stem cell therapies to Phase II in which efficacy is assessed. **We recommend that – to support decision-making by clinical investigators, sponsors and Research Ethics Committees – the Health Research Authority (HRA) should develop guidance on the kinds of circumstances in which sham neurosurgery may, or may not, be an appropriate part of clinical investigations, and what post-trial obligations should hold in respect of participants assigned to the sham arm of trials.**

Managing wider psychological, behavioural and social impacts

- 5.42 The goals of minimising harm to patients and participants, and providing them with the best advice about the likely impacts of undertaking neurotechnological interventions rely on the presumption that the information necessary to achieve this will be available. One area in which this poses a particular problem is in the assessment of the unintended cognitive, emotional and behavioural consequences of treatment, which could have significant effects on individuals' conception of themselves and relationships with people close to them. These kinds of effects are currently of greatest concern in relation to the use of DBS. As we have noted, these effects are poorly understood and present a complex picture, in part because their incidence varies between patients and also because disease progression and pharmacological therapies can contribute similar effects (see paragraphs 2.53 and 4.31).⁵⁴⁸ A further crucial factor is that objective measures of these consequences fail to capture arguably the most important element; not simply whether these effects occur, but whether they are experienced as welcome or unwelcome by patients themselves. The following personal account was received in response to the Working Party's public consultation.

"I have been pulled up by the DBS...My mood has improved from base-line but I think I have a way to go yet, I experience a lot more anxiety (usually over silly little things) now than before. I usually only get about 3 hours sleep a night, my short term memory is bad and I lack concentration which makes reading very difficult... I am not sure whether these were totally pre-existing but I am sure there are ways around them... DBS has given me the most important thing – HOPE."⁵⁴⁹

The view expressed by this respondent, an individual who had received DBS to treat depression, illustrates the multifaceted nature of a patient's own experience of the outcomes and unintended effects of treatment. It has been argued that, where it is possible to obtain them, qualitative patient-reported outcome measures (those that patients rather than clinicians judge to be most significant) provide an essential part of the evidence puzzle.⁵⁵⁰ For this reason, we suggest that capturing patient reported outcome measures should be one important aim of the registers of clinical experiences that we recommend at paragraph 5.63.

- 5.43 Patient and participant selection is a central element of the responsible conduct of treatment and research involving invasive neurotechnologies such as DBS; for example, to ensure that those involved are those best equipped to tolerate surgery and manage their own postoperative

⁵⁴⁷ Galpern WR, Corrigan-Curay J, Lang AE *et al.* (2012) Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations *The Lancet Neurology* **11(7)**: 643-50, at page 646.

⁵⁴⁸ Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* **2(1)**: 3-13, at page 6.

⁵⁴⁹ An anonymous respondent, responding to the Working Party's consultation.

⁵⁵⁰ Mathieu G, Bell E and Racine E (2011) Subjective Outcomes Measurement and Regulatory Oversight for Deep Brain Stimulation in Parkinson's Disease *AJOB Neuroscience* **2**: 16-8.

care. Neuropsychological factors may be particularly important in making such assessments,⁵⁵¹ and considerations such as supportive home environments are also relevant. Securing the psychological well-being of individuals post-intervention will also depend on the efforts of professionals to manage the expectations of patients, participants and those close to them through the kind of counselling to which we refer above (see paragraph 5.9). This requires transparency about the therapeutic limits of the intervention, for example that a neurotechnology offers alleviation of symptoms rather than a cure and also about the possibility (when participating in research) of being assigned to a placebo control group.

- 5.44 One area of particular concern is the ‘non-abandonment’ of patients and research participants following treatment, or at the conclusion of a study.⁵⁵² The removal of beneficial therapeutic technologies at the end of research studies could impact significantly on the health and quality of life of participants who may have come to depend on them.⁵⁵³ This is particularly true where there are no effective alternative therapeutic or assistive options available, as is so often the case with the neurotechnologies that are the subject of this report. This problem may be particularly acute for assistive BCIs which are currently only available in research contexts.

Box 5.2: The experience of a family participating in BCI research

The following extracts are from an interview conducted with the parents of a young man, whose official diagnosis is the minimally conscious state although recent evidence from BCI based awareness assessment (along with his family’s own observations over 12 years) would suggest that the young man is more than just minimally conscious and perhaps in a total locked-in state. The young man has been participating in a follow on (post assessment) BCI research programme to determine if he can learn to modulate brain activity to produce a communication channel through BCI. The extracts below highlight the generosity and commitment of individuals who participate in research and that of their families, as well as the difficult circumstances that might arise at the conclusion of the research:

“BCI is our huge hope really... This is our only hope of informed communication with [our son]... So it’s hugely important... and, as such, we would pay towards funding of it if we thought it was going to help.”

“I’ve told [our son] “this is your life’s work now. You have the opportunity to work with [the scientist] to advance this technology which hopefully will be of benefit to you and to a lot of other people as well. This is your work. [The scientist] needs you as much as you need [the scientist].” I just keep saying those kinds of things to him. What effect that has – I don’t know. But hopefully he can take some kind of benefit from it, some worth and some self esteem.”

Fact finding meeting with Eoin, Eddie and Karen O’Mahony, 7 December 2012

- 5.45 The Declaration of Helsinki states that ethical research practice entails offering participants access to treatments identified as beneficial by the study.⁵⁵⁴ However, neurodevices such as assistive BCIs present particular challenges to securing continued access. Unlike many pharmaceuticals, neurodevices may require significant support for their continued use. Even if resources for such support were available, the continued use of devices may be precluded by intellectual property rights, or regulatory approval that extends to only to non-research uses.⁵⁵⁵ Nevertheless, the virtue of responsibility requires that researchers have in place appropriate arrangements to protect participants’ quality of life at the end of a study. The HRA currently provides framework guidelines for NHS RECs on ethical and practical issues of care after research.⁵⁵⁶ These refer to the position of the 2005 Nuffield Council on Bioethics report *The*

⁵⁵¹ Bell E, Mathieu G and Racine E (2009) Preparing the ethical future of deep brain stimulation *Surg Neurol* **72**: 577-86, at page 579.

⁵⁵² Fins JJ (2009) Deep brain stimulation, deontology and duty: the moral obligation of non-abandonment at the neural interface *Journal of Neural Engineering* **6**(5): 1-4.

⁵⁵³ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4**(3): 1-22, at page 10.

⁵⁵⁴ World Medical Association (2008) *WMA declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/>, Principle 33.

⁵⁵⁵ For example, in the UK a device that has been notified to the Medicines and Healthcare products Regulatory Agency for use in a clinical investigation need not have a CE mark, without which it cannot be placed on the market: MHRA (2013) *Clinical trials for medical devices*, available at: <http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm>.

⁵⁵⁶ HRA (2012) *Care after research*, available at: http://www.nres.nhs.uk/applications/guidance/guidance-and-good-practice/?1307152_entryid62=148568.

ethics of research related to healthcare in developing countries, that “researchers should endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee.”⁵⁵⁷ We reiterate here our position from this earlier report and **recommend that researchers should provide, as part of their submissions to RECs, exit strategies for circumstances in which they are unlikely to be in a position to provide patients with continued use of neurodevices beyond the conclusion of the study.** These strategies should be proportionate to the harm (or loss of benefit) to participants from withdrawal of the device. At minimum, these submissions should include what participants will be told as part of consent procedures about access to treatment beyond the study’s duration, and details of arrangements to offer appropriate counselling and support at the study’s conclusion. **We further recommend that the HRA guidance on care after research includes explicit recognition of the issues raised by the withdrawal of access to assistive technologies.**

Privacy and data protection

Protection of personal information

- 5.46 Clinical care teams or researchers have legitimate reasons for accessing or sharing data collected from neurodevices and wider health information about those using novel neurotechnologies in order to deliver good care, or to support health research in the public interest. However, as we observed in our ethical framework, this raises concerns about the collection and handling of such information in order to protect the privacy of the patients and research participants from whom it is obtained (see paragraphs 4.37 to 4.39).
- 5.47 In the UK, there are a number of legal frameworks that, *inter alia*, offer protection to individuals’ personal health information. These include: the common law regarding confidentiality of patient information; the protection of privacy and autonomy under the right to respect for ‘private life’ under Article 8 of the Human Rights Act 1998;⁵⁵⁸ and the Data Protection Act 1998 (DPA).⁵⁵⁹ These are underpinned by professional guidance from bodies such as the GMC,⁵⁶⁰ MRC⁵⁶¹ and, within NHS trust or boards, by the Caldicott Guardians.⁵⁶² We do not suggest here that identifiable personal information pertaining to, or obtained from, the use of novel neurotechnologies is exceptional in the context of these legal frameworks which provide sound protection for individuals’ informational privacy – it is, and should be, treated like any other sensitive health-related information. However, there are some aspects relating to their collection and use that warrant attention.
- 5.48 Doctors have a professional duty of confidence, which extends to other professionals in health care environments. Confidentiality and privacy may also be ascribed in law on the basis of an individual’s reasonable expectations, given the nature of the information in question and the circumstances in which it is divulged.⁵⁶³ Under the DPA 1998, certain principles must be observed with respect to the processing (which includes storage, use and disclosure)⁵⁶⁴ of personal data. Personal data are those from which a living person to whom they relate (the ‘data subject’) can be identified either directly, or in combination with “other information which is in

⁵⁵⁷ Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries*, available at: <http://www.nuffieldbioethics.org/sites/default/files/Ethics%20of%20research%20related%20to%20healthcare%20in%20developing%20countries%20l.pdf>, at paragraph 9.31.

⁵⁵⁸ See, for example, *Campbell v Mirror Group Newspapers* [2004] 2AC 457, [2004] 2 All ER 995.

⁵⁵⁹ Data Protection Act 1998.

⁵⁶⁰ General Medical Council (2009) *Confidentiality*, available at: http://www.gmc-uk.org/static/documents/content/Confidentiality_0910.pdf.

⁵⁶¹ Medical Research Council (2011) *Data and tissues tool kit*, available at: <http://www.dt-toolkit.ac.uk/home.cfm>.

⁵⁶² NHS (2013) *Caldicott guardians*, available at: <http://www.connectingforhealth.nhs.uk/systemsandservices/infogov/caldicott>.

⁵⁶³ *Campbell v Mirror Group Newspapers* [2004] 2AC 457, [2004] 2 All ER 995 and Mason J and Laurie G (2011) *Law and medical ethics*, 8th Edition (Gosport, Hampshire: Oxford University Press), at page 182 (paragraph 6.22).

⁵⁶⁴ Section 1(1) of the Data Protection Act 1998.

possession of, or is likely to come into the possession of, the data controller”.⁵⁶⁵ These include restrictions on how these are obtained, the duration and security of their retention, and how they will be used.⁵⁶⁶ Health-related personal data are classed as ‘sensitive’ under this legislation, meaning that certain further restrictions to apply its lawful storage and use.⁵⁶⁷

- 5.49 Under the DPA 1998, sensitive personal data may be used lawfully for research purposes, including those beyond any research for which they were originally collected. This use is permitted provided that this does not underpin decisions regarding particular individuals or risk substantial damage or distress to them, and that individuals will not be identifiable from the research outputs.⁵⁶⁸ The need to build a robust body of evidence about efficacy and risks of neurotechnologies to address ongoing uncertainty in the field of novel neurotechnologies means that research uses of patient data (including linkage between data sets held by different organisations) are likely to be of particular value. However, vigilance to protect patients’ informational privacy is warranted here as the relatively small numbers of individuals being treated with some categories of novel neurotechnologies at present mean that they may be more readily identifiable, even from anonymised data. This risks exposing individuals to distress or discrimination and also potentially exposes researchers to liability for unlawful data processing.⁵⁶⁹ There is a need for particular attention where data are shared internationally (as would be particularly valuable in creating rich multinational registry resources), as the DPA 1998 requires that personal data are not shared outside the European Economic Area unless an adequate level of protection can be ensured in those jurisdictions.⁵⁷⁰
- 5.50 Distinct issues are raised by neurodevices that collect sensitive health information directly from patients. The automated nature of collection, storage or transmission of data by devices presents difficulties for identifying a single definitive point or purpose of ‘data collection’ at which it can be confirmed that the patient has understood and agreed to potential uses. This could pose a challenge to obtaining sufficiently informed and specific consent to processing these data.⁵⁷¹ Although consent is not always required for the lawful processing of sensitive personal data under the DPA 1998, it may nevertheless be the means by which its privacy or confidentiality can be determined.⁵⁷² If patients or participants have not clearly understood, or agreed to, particular uses of automatically collected personal data – for example, the extent to which these might be shared within care or research teams – not only could their privacy be undermined, but professionals could be liable for unlawful disclosures. This has particular salience in the context of BCIs where it has been noted that research teams are large and represent diverse professions.⁵⁷³ Where data collection is automated and clinical care or research teams are large, there is an additional challenge in identifying the data controller, who

⁵⁶⁵ Section 1(1) of the Data Protection Act 1998.

⁵⁶⁶ Schedule 1 to the Data Protection Act 1998.

⁵⁶⁷ Section 2 of the Data Protection Act 1998.

⁵⁶⁸ Section 33 of the Data Protection Act 1998.

⁵⁶⁹ See, for example, *Common Services Agency v Scottish Information Commissioner* [2008] UKHL 47.

⁵⁷⁰ Principle 8, Schedule 1 to the Data Protection Act 1998.

⁵⁷¹ The data subject’s consent is only one of the possible grounds for the lawful processing of sensitive personal data under the Data Protection Act 1998. It is not necessary for the data to be used for ‘medical purposes’, including medical research, when undertaken someone bound a duty of confidentiality equivalent to a health professional (Schedule 3 to the Data Protection Act 1998). Under the terms of the proposed reforms to European data protection law, however, a requirement has been added for consent to be both ‘specific’ and ‘explicit’ (Regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation) 2012/0011 (COD) draft Article 4.8. See further: Recitals 25, 38 and 41 on the requirement that consent be ‘explicit’).

⁵⁷² For example, establishing what a patient was told about how their data would be handled, and what they agreed to, could be key to determining whether there has been an unlawful breach of confidentiality, or if their right to respect for private life under Article 8 of the HRA 1998 has been infringed. Broadly speaking, under the common law of confidentiality, it is unlikely to be lawful for clinicians or researchers to share health information about which there is a reasonable expectation of privacy or confidentiality, unless the individual has assented to its wider disclosure or it this is otherwise authorised or justified – for example, by a Court holding that the disclosure is in the public interest, or because there is appropriate ethical and statutory oversight for its use in research.

⁵⁷³ Haselager P, Vlek R, Hill J and Nijboer F (2009) A note on ethical aspects of BCI *Neural Networks* **22(9)**: 1352-7, at page 1355.

holds responsibility for ensuring the lawful processing of data under the DPA 1998, and ensuring they understand the extent of their legal responsibilities.⁵⁷⁴

- 5.51 In practical terms, a lack of clarity about the potential liabilities of professionals for unauthorised disclosure of information could impact upon the care of patients and participants. The virtues of inventiveness and responsibility both point to the value of sharing health data amongst those responsible for ensuring patients' safety and well-being and in the wider public interest in using these as part of health-related research. Yet if clinical teams or researchers are unsure about what they may lawfully do with patient data, or are deterred from sharing them by fear of legal liability, this may infringe the interests of current and future users of novel neurotechnologies by inhibiting the optimal flow of information and placing unnecessary obstacles in the way of much needed research.

Securing neurodevices against interference

- 5.52 Personal information might, as suggested in our ethical framework, not only be collected from neurodevices for legitimate reasons, there is a possibility – albeit somewhat speculative at present – that sensitive information may be vulnerable to unauthorised interception through hacking or wireless transmission. This is related to a potential parallel problem of accidental or malicious interference with the functioning of neurodevices. Inventiveness would suggest that one means of preventing these kinds of infringements of privacy would be for manufacturers to respond by designing technical protections (such as user-authorisation checks) into medical devices.⁵⁷⁵ However, responsibility also requires weighing up the risks and benefits of technical solutions for users of these technologies. For example, greater encryption of data might enhance information security, but use more power, thus requiring more frequent surgery (with its attendant risks) to replace battery packs.⁵⁷⁶ Obligations to improve the protection against unauthorised interference should be proportionate to how critical a device's safe functioning is to patients' well-being.⁵⁷⁷ DBS and assistive BCI technologies might not be life-preserving in a literal sense, but their safe functioning could be critical to the quality of life of individuals with debilitating movement disorders or paralysis.
- 5.53 Since it is not yet clear how serious or widespread the potential threats from unauthorised access to devices might be to the private lives of those using them, it is challenging to assess how pressing the need is for regulators to act to address any gaps in protection from potential risk. Expert advice provided to the US Government Accountability Office about the informational security of active implantable medical devices (although not specifically neurodevices) is that the threat is sufficiently plausible and serious that the US Food and Drug Administration (FDA) ought to develop a plan for “enhancing its review and surveillance of medical devices as technology evolves [to] incorporate the multiple aspects of information security”.⁵⁷⁸ It was suggested this should include increasing the FDA's focus on manufacturers' role in mitigating security risks and the role of post-market surveillance to identify possible information security problems.
- 5.54 At present, the European Directive which governs the marketing of active implantable medical devices requires that devices must not compromise the safety or health of patients or other users.⁵⁷⁹ The safety considerations listed in the Directive include “risks connected with

⁵⁷⁴ Section 1(1) of the Data Protection Act 1998.

⁵⁷⁵ Maisel WH and Kohno T (2010) Improving the security and privacy of implantable medical devices *New England Journal of Medicine* **362**(13): 1164-6, at page 1165.

⁵⁷⁶ United States Government Accountability Office: Report to Congressional Requesters (2012) *Information security of active medical devices*, available at: <http://www.gao.gov/assets/650/647767.pdf>, at page 21.

⁵⁷⁷ Maisel WH and Kohno T (2010) Improving the security and privacy of implantable medical devices *New England Journal of Medicine* **362**(13): 1164-6, at page 1165.

⁵⁷⁸ United States Government Accountability Office: Report to Congressional Requesters (2012) *Information security of active medical devices*, available at: <http://www.gao.gov/assets/650/647767.pdf>, at page 35.

⁵⁷⁹ Article 2 of the Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States relating to active implantable medical devices (AIMD).

reasonably foreseeable environmental conditions such as magnetic fields, external electrical influences, [and] electrostatic discharge”, which covers some sources of accidental interference, and instructions for use must also include advice about such risks.⁵⁸⁰ Particular attention is also required for the proper functioning of the device’s software.⁵⁸¹ The Directive does not, however, address directly the risks of malicious hacking or of unauthorised data interception. **We recommend that the MHRA monitors the vulnerability of neurodevices to accidental, unauthorised or malicious interference, especially where these could impair health, undermine patients’ confidence in their devices, or lead to the interception of sensitive personal data about health or neural activity. Appropriately anonymised records of any such incidents should be made publically accessible.**

Experimental treatment

- 5.55 Underlying the discussion in this chapter thus far is an assumption that, where the governance frameworks, or professional norms, underlying treatment and research relationships diverge, it will be possible to determine which of these applies in any particular instance. In truth, this may not always be a straightforward matter. Many of the investigational uses of novel neurotechnologies take place as experimental interventions with patients.⁵⁸² This, rather than larger or more formal research studies, may often be the more appropriate approach, given the small numbers of individuals eligible to participate in investigations for rare conditions (for example, identification of cognitive activity in patients in minimally conscious states), where there is uncertainty about risks, or where there is limited evidence on which pursue the kind of hypothesis-driven research protocol needed for an RCT. Nevertheless, this raises a question, namely: what is the appropriate dominion in which to regulate investigation occupying this intermediate area of investigation: treatment or research?
- 5.56 It is questionable whether all such exploratory activities occupy the realm of research. Research implies a predetermined protocol, with a clearly defined end-point and which results in generalisable knowledge and understanding.⁵⁸³ Experimentation, by contrast, is a more *ad hoc*, speculative endeavour, usually calibrated by a particular subject’s responses and not beholden to a rigid protocol.⁵⁸⁴ The difference may also be reduced to a question of *intention*. Research in general is not chiefly concerned with the research participant’s own health and is instead about improving the wider scientific knowledge base. Experimental treatment, in contrast, is usually more concerned with the therapeutic benefits to the person upon whom the experiment is being conducted. In its recent judgment in the case of *Walker-Smith v GMC* the High Court confirmed that establishing the clinician’s intention is key to determining whether they have strayed beyond the boundaries of treatment into research.⁵⁸⁵ The court further acknowledged that:

“[W]hen a clinician departs in a significant way from standard or accepted practice entirely for the benefit of a particular individual patient, and with consent, the

⁵⁸⁰ Annex 1, Part 1 (8-15) of the Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States relating to active implantable medical devices.

⁵⁸¹ Article 16(9) of the Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States relating to active implantable medical devices. For example, claims that a device is compliant with the essential requirements of the Directive must be supported by descriptions of how the software is protected from accidental or unauthorised change.

⁵⁸² See, for example, Synofzik M, Fins JJ and Schlaepfer TE (2012) A neuromodulation experience registry for deep brain stimulation studies in psychiatric research: rationale and recommendations for implementation *Brain Stimulation* **5(4)**: 653-5, at page 653. This is particularly apparent for the medical devices sector: Factfinding meeting with clinicians, 16 February 2012.

⁵⁸³ Department of Health (2005) *Research governance framework for health and social care: second edition*, available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962, at page 3.

⁵⁸⁴ Mason J and Laurie G (2011) *Law and medical ethics*, 8th Edition (Gosport, Hampshire: Oxford University Press), at page 611(19.05).

⁵⁸⁵ *Walker-Smith v General Medical Council* [2012] EWHC 503 (Admin), at paragraph 186.

innovation need not constitute research, though it may be described as an experiment in the sense that it is novel and un-validated.”⁵⁸⁶

If highly experimental interventions “need not constitute research”, this exposes a possible regulatory lacuna whereby investigatory procedures are governed under the legal and professional frameworks that set the standards for which appropriate and lawful clinical care – which, in the UK, are chiefly a matter of common law – that are quite distinct from the protocols that apply to research. Clinical trials in the UK are subject to statutory regulation which is increasingly providing the benchmark for all health-related research involving patients.⁵⁸⁷

- 5.57 It might seem unsatisfactory that the question of which regulatory framework applies in particular situation is determined solely by the subjective intention(s) of the clinician. While proposed health research involving or impacting on the care of NHS patients must not only be approved by a REC, but also exposed to peer review,⁵⁸⁸ decisions about treatment depend on the judgements and professional norms of clinicians without any prior requirement for external scrutiny. This disparity raises particular concerns where there are potential conflicts of interest that might remain unexposed in a treatment paradigm, but must be declared according to the research ethics standards established by the Clinical Trials Regulations.⁵⁸⁹
- 5.58 Financial interests are not the only possible source of conflicts of interest to which clinicians might be subject. They might equally have intellectual or reputational investment in gathering evidence through pursuing new and experimental applications of neurotechnologies. Therefore while the inventiveness of researchers and clinicians is essential to the development of novel therapies, this needs to be qualified by the virtue of responsibility, lest the pursuit of innovation and knowledge threaten to overshadow clinicians’ obligation first to protect the health and well-being of the patient. Clinicians are likely to be found guilty of serious professional misconduct and struck off if, while purporting to offer *treatment*, their intention is actually to undertake *research*.⁵⁹⁰ Corresponding concerns might also arise where investigations of therapeutic or assistive technologies are categorised as research. In particular, these may arise in relation to ambiguities in the extent of the duty of care owed to research participants by researchers – for example regarding their responsibilities to promote participants well-being beyond the scope of the a research protocol (as discussed at paragraph 5.44 to 5.45).
- 5.59 It seems inappropriate that so much should rest on category allocation when the core interests at stake remain the same, particularly from the perspective of the person who is subject to intervention.⁵⁹¹ While so much of the development of the therapeutic applications of novel neurotechnologies takes place in the realm of experimental treatment, our ethical framework suggests that there is a need for clear and specific ethical guidance on how clinicians and investigators should navigate this difficult boundary in a way that is responsible, without stifling inventiveness. The MRC has developed an *Experimental medicine toolkit* for use in small-scale, academic-led studies in humans.⁵⁹² This provides valuable sources of advice on the development of protocols, risk assessment and the dissemination of findings. However, as its focus is on academic studies, it may not be seen to apply to, or capture, the full range of

⁵⁸⁶ Ibid, at paragraph 12. This passage from the judgment directly quotes the Royal College of Physicians’ guidance (January 1990) “Research involving patients”.

⁵⁸⁷ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use; NHS Health Research Authority (2012) *Standard operating procedures*, available at: <http://www.nres.nhs.uk/nres-publications/publications/standard-operating-procedures/>, v5.1.

⁵⁸⁸ Department of Health (2005) *Research governance framework for health and social care: second edition*, available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962, at page 13.

⁵⁸⁹ Part 1(1) of Schedule 3 to the Medicines for Human Use (Clinical Trials) Regulations 2004.

⁵⁹⁰ GMC (2013) *Good practice in research and Consent to research*, available at: http://www.gmc-uk.org/static/documents/content/Good_practice_in_research_and_consent_update_17_4_13.pdf.

⁵⁹¹ Compare with the observations in Oberman M and Frader J (2003) Dying children and medical research: access to clinical trials as benefit and burden *American Journal of Law and Medicine* **29(2-3)**: 301-17.

⁵⁹² MRC (2012) *Experimental medicine tool kit*, available at: <http://www.em-toolkit.ac.uk/home.cfm>.

experimental interventions conducted with single, or very few, patients in treatment rather than academic contexts.

5.60 **We recommend that the GMC, the HRA and the MRC work together to produce guidance for clinicians pursuing experimental therapies. This would address lacunae between the regulation of research and treatment, with the aim of ensuring that experimental interventions are pursued in a responsible way that protects patients' interests, while supporting inventiveness through the generation of new knowledge in the public interest.** The recommended guidance would adopt the best features of each of the treatment and research governance paradigms, while seeking to eliminate the worst. What this might mean in practice is that:

- the primacy of patient interests is imported from the treatment paradigm, entailing a duty of care that persists beyond the period of experimentation.
- Unlike clinical trials, experimental treatments taking place in this middle-ground cannot be expected to meet the requirements for large numbers of participants, control groups, or double blinding of participants and investigators.
- They can, however, be expected to be grounded in an evidence base that is appropriate to the (necessarily) exploratory context.
- The pursuit of an intervention solely because it putatively represents a patient's 'last best hope' is likely to be too cavalier to justify an experimental intervention.
- A responsible approach imported from the clinical research paradigm would, therefore, recommend adopting clear investigatory protocols, including means of assessing efficacy and risk, as well as methods of recording and sharing findings.
- Humility recommends independent ethical oversight of these protocols and practices.

We suggest that this guidance might usefully build on the MRC's *Experimental medicine toolkit*.

Registers of clinical experiences

5.61 A further implication of many investigatory applications of novel neurotechnologies taking place in treatment settings rather than as part of formal research is that clinical experience of the efficacy and risks of these technologies, and the benefits and adverse events associated with their use, is lost. There is an absence of mechanisms to capture and share the outcomes of single-patient interventions or small observational or pilot studies. As we explore further in Chapter 7, the regulatory systems operating in the UK are ill-equipped to capture information on (or simply do not require reporting of) the kinds of experimental or single-patient uses of medical devices and stem cell therapies with which we are concerned here, or their outcomes. The outcomes from these kinds of interventions, particularly negative or non-positive findings, are also less likely to be published in peer reviewed journals.⁵⁹³ The risk is that, if clinical experiences are shared only in *ad hoc* ways through, for example, journals or professional networks such as conferences, the reach of this information will remain narrow and elite. There is an addition risk that outcomes could be misleading or meaningless when taken out of context.

5.62 This report recognises that uncertainty about the efficacy, unintended effects and mechanisms of action of many of the novel neurotechnologies discussed here is a key ethical issue. There is a need for greater transparency and accessibility of evidence to ensure the safety and well-

⁵⁹³ Schlaepfer TE and Fins JJ (2010) Deep brain stimulation and the neuroethics of responsible publishing *The Journal of the American Medical Association* **303**(8): 775-6, at page 775.

being of patients and research participants, and to also make the best use of existing knowledge to underpin robust research practices and support innovation. The exercise of all three virtues, responsibility, humility, and inventiveness, requires that the professions conducting experimental and investigational treatments adopt new means for capturing and sharing their own clinical experiences. There are a number of calls in the academic literature for registers to be established to capture this kind of evidence – particularly where it is generated outside of formal clinical trials.⁵⁹⁴ Many of these focus upon DBS, but we suggest that the value of registers would extend to the other categories of neurotechnologies we discuss in this report.

5.63 **Therefore, we recommend that professional bodies, such as the Association of British Neurologists and the Society of British Neurological Surgeons and the Royal College of Psychiatrists, work with each other and with relevant patient groups and charities to establish registers (where these do not already exist), or to improve the quality, accessibility and profile of those which already exist. These registers would gather data on clinical experiences of treatments using novel neurotechnologies, record the outcomes of these interventions, and make these publically available.**

5.64 As these registers would potentially encompass a range of different technologies and clinical uses, it is not possible to be prescriptive about their exact form or scope. However, we suggest that essential features would include:

- independent oversight to ensure the impartiality of registered data;
- robust mechanisms for protecting patient confidentiality;
- academic involvement to ensure the quality of data;
- dedicated curatorship, to ensure that the data collected is of a kind that is useful and informative to the intended users of the register, and collected and presented in ways that facilitates comparisons and meta-analyses of aggregate data;
- recording negative or inconclusive findings as well as positive treatment outcomes;⁵⁹⁵ and
- capturing patient-reported outcomes as part of building a comprehensive picture of benefits and risks that includes subjective experiences (see paragraph 5.42 above).⁵⁹⁶

5.65 We anticipate that registers of this kind will not only be useful to clinicians and researchers seeking to give the best advice to their patients or participants and to avoid pursuing futile or disproportionately risky interventions (and thus unnecessary interventions to individuals’ brains), but will also be valuable to patients (or their family and carers) in making treatment decisions and thus also to those delivering counselling services we recommended at paragraph 5.9. Other users of these registers might include NICE, regulators and ethical review committees, each of whom have an interest in providing effective oversight, proportionate to the best current understanding of risks and benefits. This wide range of potential users should inform decisions regarding the information collected and the presentation of outputs. In accordance with recent recommendations by the Royal Society for the pursuit of open science, the aspiration should be for these registers to provide outputs that, wherever possible, are “accessible, intelligible, assessable and usable” to a non-specialist public audience, with patients’ needs particularly in

⁵⁹⁴ Mathieu G, Bell E and Racine E (2011) Subjective outcomes measurement and regulatory oversight for deep brain stimulation in Parkinson's disease *AJOB Neuroscience* **2(1)**: 16-8; Schermer M (2011) Ethical issues in deep brain stimulation *Frontiers in Integrative Neuroscience* **5(17)**: 1-5; Synofzik M, Fins JJ and Schlaepfer TE (2012) A neuromodulation experience registry for deep brain stimulation studies in psychiatric research: rationale and recommendations for implementation *Brain Stimulation* **5(4)**: 653-5.

⁵⁹⁵ Synofzik M, Fins JJ and Schlaepfer TE (2012) A neuromodulation experience registry for deep brain stimulation studies in psychiatric research: rationale and recommendations for implementation *Brain Stimulation* **5(4)**: 653-5.

⁵⁹⁶ Mathieu G, Bell E and Racine E (2011) Subjective outcomes measurement and regulatory oversight for deep brain stimulation in Parkinson's disease *AJOB Neuroscience* **2(1)**: 16-8.

mind.⁵⁹⁷ These might initially cover data collected in the UK, but an aspiration to create connections with international registers would be valuable.

- 5.66 We recognise that the establishment and maintenance of data repositories of this kind are resource-intensive and that adequate resourcing is essential to their utility and longevity.⁵⁹⁸ In view of the potential breadth of their utility in research, innovation, regulation, and health care delivery, costs might appropriately be met by a number of organisations including the research councils or the Wellcome Trust in the UK, or by European research and innovation funds. Financial support might also be sought from commercial partners in the neurodevice and regenerative medicine industries, provided there is robust independent oversight.

Concluding remarks

- 5.67 Therapeutic applications of novel neurotechnologies do not present unique or exceptional concerns for the ethical conduct of relationships of care in treatment and research contexts. However, examination of the governance mechanisms that apply to these relationships through the filter of our ethical framework highlights some areas of concern which, while not unique to this field, are nonetheless important in protecting the interests of patients and participants. These include the limits of legally required consent procedures and the assessment of patients' best interests in light of the limits of current knowledge of efficacy and risks – which is particularly pressing in relation to delegated decision-making, determinations of when experimental treatment is justified when few other options are available, and sham neurosurgery. There is also a need for greater attention to harm beyond impacts on physical health, including impacts on wider well-being, privacy and autonomy. As befits a context in which approaches must remain responsive to individual patients' and participants' different needs and experiences, our recommendations relate to the provision of professional guidance rather than more rigid regulatory measures. Although these recommendations are necessarily directed at the organisations responsible for the governance of clinical care and health research respectively, we suggest that while so much investigation in this field takes place in the realm of experimental treatment, it is essential that there is uniformity between professional practices in these domains, wherever possible.
- 5.68 Having considered the 'frontline' of the use of novel neurotechnologies in this chapter, in Chapter 7 we turn to consider the regulatory frameworks that license these technologies for use. Before we do so, however, in Chapter 6 we address broader questions of *where* priorities lie for governance in this context by offering a definition of what constitutes 'responsible research and innovation' (RRI) when framed specifically with novel neurotechnologies in mind.

⁵⁹⁷ The Royal Society (2012) *Science as an open enterprise*, available at: http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/projects/sape/2012-06-20-SAOE.pdf, at page 14

⁵⁹⁸ House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK*, available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/163/163.pdf>, at page 32(73).

Chapter 6

Responsible research and
innovation

Chapter 6 - Responsible research and innovation

The concept of ‘responsible research and innovation’ (RRI) has been adopted by policy-makers as a way of thinking more systematically about the public benefits of science and technology-based research. The precise definitions and constituent elements of RRI remain matters of debate and can appear abstract, so here we suggest six priorities that apply specifically to RRI in the context of novel neurotechnologies.

- **Clearly identified need:** It is important to justify innovation in terms of its public benefits. In the case of neurotechnologies this means meeting therapeutic need. This highlights the need to resist the technological imperative and the pursuit of novelty for its own sake. It also challenges the value of proliferating products that are indistinguishable in terms of the benefits they bring to patients.
- **Securing safety and efficacy:** Protecting safety is central the pursuit of RRI and to regulatory regimes governing medical technologies. Where the clinical uses of novel neurotechnologies are concerned, their risks can only adequately be assessed relative to their efficacy in delivering therapeutic benefits and the (possibly limited) availability of alternative treatments. This highlights the importance of assessing efficacy as part of the innovation pathway of a product – yet this is not a regulatory requirement for medical devices (such as those used in TBS and DBS) marketed in Europe.
- **Generating robust evidence:** There are both regulatory and methodological reasons why the development of medical devices in particular might not produce the most transparent, robust or balanced body of evidence. These include un-generalisable and dispersed data from small-scale studies, the influence of commercial interests, and methods that encourage the publication of positive, but not disappointing, findings. Alternative methods of linking and disseminating evidence are likely to be needed to address this.
- **Continuous reflexive evaluation:** The development of novel neurotechnologies is unlikely to follow simple linear innovation trajectories. Reflecting upon the directions in which research is (potentially) travelling, and responding to this, can help to guard innovation against lock-in to pathways that do not serve public benefit. It is also an important part of maintaining vigilance for implications of possible unintended dual-use or ‘off-label’ applications of neurotechnologies.
- **Coordinated interdisciplinary action:** Innovation in novel neurodevices, perhaps most markedly BCIs, is often multidisciplinary. Coordination between different disciplines is needed to protect against potential risks posed by gaps in the collective understanding and oversight of a technology’s risks and capabilities. Interdisciplinary collaboration also offers opportunities by introducing diverse visions of potentially fruitful development trajectories.
- **Effective and proportionate oversight:** The tension between need and uncertainty that lies at the foundation of our ethical framework presents a particular challenge to effective regulation and governance of novel neurotechnologies. Responsibility and humility require caution whilst also recognising that failing to pursue interventions also carries risks of extending suffering in the absence of effective treatment. This demands a proportionate approach to supporting innovation while protecting safety; hard-law regulation will not always be the most suitable means of achieving this.

This articulation of RRI provides a tool, complementing our ethical framework, which we go on to use to assess the strengths and weaknesses of the regulatory frameworks that govern the commercial availability of novel neurotechnologies. The concept of RRI also acts as an extension of our virtue-guided approach by highlighting the ways in which inventiveness, humility and responsibility should inform the practices and values of those engaged in supporting and pursuing innovation.

Introduction

- 6.1 In this chapter and the next we apply our ethical framework to the challenges generated by the *development* of novel neurotechnologies themselves. On the basis of this framework we may understand that the central goal of innovation in this field is to deliver therapeutic technologies to those who need them. This is tempered by caution to avoid harm to these individuals and to avoid intervening in the brain unnecessarily, or where evidence of efficacy or unanticipated consequences remain unclear. The various actors involved in the development of these technologies must exercise the virtue of responsibility by striking a balance between these twin imperatives. Here we chiefly focus on the activities of those directly engaged in funding, conducting, and steering research and innovation endeavours. However, it is not possible to draw a definitive line around this class of actors. For example, as Chapter 5 makes plain, much exploration of therapeutic applications of these technologies will take place in experimental treatment contexts, making many clinicians ‘developers’ too.

6.2 The approach we appeal to in this chapter is based around the concept of ‘Responsible research and innovation’ (RRI). There is increasing support amongst policy makers for a systematic approach to RRI as a practical lens through which states and actors are encouraged to think about technology development. It has notably been adopted as a key cross-cutting theme under the prospective EU Framework for Research and Innovation “Horizon 2020”.⁵⁹⁹ The critical discourse surrounding the aims and component aspects of RRI is still evolving and subject to debate.⁶⁰⁰ For this reason, component elements of various RRI frameworks vary. They nevertheless share a common emphasis upon the achievement of public benefits through science and technology-based research. This entails securing ethically sound and scientifically robust research objectives, conduct, and governance.⁶⁰¹ RRI can be viewed as being as much about fostering practices and cultures amongst those engaged in supporting and pursuing innovation as a concern with appropriate regulatory and governance structures. The engagement of publics in determining what the desirable ends of research are, and how innovation processes can achieve these, is also often seen as a crucial part of responsible practice.⁶⁰²

RRI in the context of novel neurotechnologies

6.3 In Chapter 3, we highlighted how funding gaps in the development trajectories of neurotechnologies from laboratory to commercial product – and the resultant economic pressures upon developers – might drive innovation practices (particularly in relation to neurodevices) towards those that focus upon swift financial returns, potentially at the expense of meeting the public interest in safe, effective, and well-evidenced therapies. Attention to the demands of RRI can play an important role in characterising how developers’ intentions should be refocused. RRI should not, however, be understood as antithetical to profitable commercial activities. A recent report prepared for the European Commission emphasised that early consideration of an RRI approach in a field of innovation can help to ensure that research funding is not wasted and to identify developing fruitful markets that meet social needs.⁶⁰³

6.4 The concept of RRI, as often construed, remains rather generic, pegged at a level of abstraction that permits them to be applied across different contexts and different technologies. Our purpose in this chapter is to establish what this concept looks like in the context of the novel neurotechnologies with which we are concerned, to make it more concrete and thus of practical use both to those conducting and funding research and to those involved in governing this field by guiding the discharge of their responsibilities. In the context of this report, understanding what is entailed by RRI can, alongside our ethical framework, provide us with the tools to assess the strengths and weaknesses of existing approaches to regulating the development of neurotechnologies and their entry onto the market.

⁵⁹⁹ European Commission: Research and Innovation (2013) *Horizon 2020*, available at: http://ec.europa.eu/research/horizon2020/index_en.cfm?pg=home&video=none. See also: European Commission: DG Research and Innovation (2011) *A report on responsible research & innovation*, available at: http://ec.europa.eu/research/science-society/document_library/pdf_06/rri-report-hilary-sutcliffe_en.pdf.

⁶⁰⁰ European Commission: DG Research and Innovation (2011) *A report on responsible research & innovation*, available at: http://ec.europa.eu/research/science-society/document_library/pdf_06/rri-report-hilary-sutcliffe_en.pdf; Owen R, Macnaghten P and Stilgoe J (2012) Responsible research and innovation: from science in society to science for society, with *Society Science and Public Policy* **39(6)**: 751-60.

⁶⁰¹ Von Schomberg R (2013) A vision of responsible innovation [forthcoming], in *Responsible Innovation*, Owen R, Heintz M, and Bressant J (Editors) (London: John Wiley).

⁶⁰² For example, Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf includes an in-depth discussion of how public discourse may shape normative propositions about the direction and governance of innovation.

⁶⁰³ European Commission (2013) *Options for strengthening responsible research and innovation*, available at: http://ec.europa.eu/research/science-society/document_library/pdf_06/options-for-strengthening_en.pdf.

6.5 We suggest the following six elements as priorities for the RRI of novel neurotechnologies. These are derived from the discussions of this report up to this point: the current state of the art of these technologies; the economic forces operating upon their development; and our ethical framework:

- Clearly identified need
- Securing safety and efficacy
- Generating robust evidence
- Continuous reflexive evaluation
- Coordinated interdisciplinary action
- Effective and proportionate oversight

Clearly identified need

6.6 Recent debates regarding synthetic biology have suggested that researchers in that field must be able to justify their endeavours in terms of what they hope to achieve and their beliefs about how they will get there. Those supporting research (for example through funding, institutional ethical approval, or policy) also need to look beyond technical excellence to ask what social good an emerging technology serves.⁶⁰⁴ These questions are equally relevant to the pursuit of innovation in novel neurotechnologies.

6.7 Unwarranted intervention in the human body is always hard to defend, but this is particularly true of the brain. Our ethical framework construes ‘need’ in this context in terms of a therapeutic priority to alleviate the suffering of those living with the effects of neurological or mental health disorders. Inventiveness is a virtue when directed at these ends, while remaining mindful of the enduring uncertainties of intervening. RRI of novel neurotechnologies entails being able to justify innovation in these terms.

6.8 Of course, this does not mean that the pursuit of foundational research, for which a need for particular translational applications cannot yet be clearly articulated, is excluded. However, the criterion of ‘clearly identified need’ provides a valuable benchmark against which to assess the relative merits, in terms of social value, of any predictable directions to which such research could be applied. This could be of use, for example, in weighing up the respective opportunity costs of pursuing divergent research questions or development pathways where resources such as professional expertise or facilities are limited. A precept that challenges developers and funders to attend to need warns both against pursuing the merely novel and the largely imitative. On one hand it questions the wisdom of following the technological imperative, where existing therapeutic interventions might be more effective or accessible. On the other hand, it highlights the lack of value in adding to a proliferation of similar technologies, distinguished only by superfluous or trivial modifications that serve manufacturers’ economic interests rather than patients’ needs.⁶⁰⁵

Securing safety and efficacy

6.9 RRI must deliver safe neurotechnologies as outputs – this much might seem self-evident. It is nonetheless important to draw attention to safety in order to be able to pose questions about what its significance is in practice.

6.10 Safety is one of the key considerations of the regulatory regimes governing whether neurodevices or neural stem cell therapies receive approval to be marketed in the UK and the rest of Europe. However, as we note in Chapter 3, regulatory routes are available that permit

⁶⁰⁴ Biotechnology and Biological Sciences Research Council (BBSRC) and the Engineering and Physical Sciences Research Council (EPSRC) (2010) *Synthetic biology dialogue*, available at: <http://www.bbsrc.ac.uk/web/FILES/Reviews/1006-synthetic-biology-dialogue.pdf>, pp. 7-9.

⁶⁰⁵ Von Schomberg R (2013) A vision of responsible innovation [forthcoming], in *Responsible Innovation*, Owen R, Heintz M, and Bressant J (Editors) (London: John Wiley), at page 5.

medical devices to receive marketing approval on the basis of safety and performance evidence relating to previously approved devices.⁶⁰⁶ These may be attractive to manufacturers by removing the delay and costs of the need to demonstrate safety through clinical studies. However, unless it can be adequately demonstrated that the device in question and that to which the existing evidence pertains are sufficiently similar in function and effect, exploiting these routes represents a failure in the protection of patients' interests and in transparency, which runs contrary to responsible innovation.

- 6.11 Moreover, considerations of safety must be assessed in relation to the degree of any likely benefit that can be expected and the nature of any foreseeable risks. This means that information about the *efficacy* of an intervention in delivering purported therapeutic benefits will be a crucial part of determining whether safety – once established below a certain threshold – is of an acceptable level. In meeting therapeutic need and protecting patients from unnecessary harm, it is therefore important that the oversight mechanisms determining the availability of these technologies look beyond safety as an isolated consideration. Where regulations governing neurotechnologies do not require demonstration of efficacy⁶⁰⁷ – as in the European regulation of neurodevices – this could be seen as an important gap in being able to understand safety in its proper context (see paragraph 7.17).

Generating robust evidence

- 6.12 The development of neurotechnologies must proceed on the *basis* of the best available evidence to minimise risks to research participants. Humility and responsibility counsel that, where there are evidence gaps, these must be acknowledged and accounted for throughout the development pathway. It is just as important that the processes of innovation also *generate* robust evidence; not least to satisfy the conditions of demonstrating the two conditions of RRI outlined in the preceding sections by demonstrating that neurotechnologies are effective, meet therapeutic needs and do so without posing disproportionate risks. The availability of such evidence is also essential to support autonomous decision-making by patients and research participants (and therefore their valid consent), and to ensure that interventions in the brain only occur when there are scientifically and methodologically sound grounds for doing so. The virtue of inventiveness drives this pursuit of knowledge, but must be matched by responsible practices with respect to conducting research and reporting findings.
- 6.13 There is a *prima facie* hurdle to gathering robust scientific evidence in the field of novel neurotechnologies. As we have already noted, the kinds of serious neurological and mental health disorders for which novel neurotechnologies are indicated will often mean that limited numbers of individuals are eligible to participate in large-scale research studies such as randomised controlled trials (RCTs) (see paragraph 5.55). We explore further in Chapter 7 why RCTs may not be best suited to the characteristics development pathways for medical devices in particular (see 7.37 to 7.38). Clinical investigations of neurotechnologies will therefore often proceed through small scale studies and experimental treatment rather than large clinical trials. However, a landscape of small dispersed investigations may not be best suited to gathering a consolidated body of knowledge upon which to assess the promises and risks of these technologies. Dispersed experimental findings, and indeed unanticipated adverse events, may not be published or widely disseminated, and even where they are, studies with small numbers of participants and varying protocols can generate un-generalisable data.
- 6.14 Further considerations arise from possible threats to research and publishing integrity that may result from the sheer novelty of these fields of research and the kind of hype that might be

⁶⁰⁶ European Commission (2009) *Clinical evaluation: a guide for manufacturers and notified bodies*, available at: http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_1rev_3_en.pdf; Cohen D and Billingsley M (2011) Europeans are left to their own devices *British Medical Journal* **342:d2748**: 1-7, at page 2.

⁶⁰⁷ Cohen D and Billingsley M (2011) Europeans are left to their own devices *British Medical Journal* **342:d2748**: 1-7, at page 2.

driven by competition for investment and funding that we have already discussed in Chapter 3. The need to attract funding perhaps inevitably leads to overstatement of the capacities and benefits of technologies under development. Commercial interests may further militate against transparency by seeking to treat studies as commercially confidential or by blurring the lines between impartial clinical investigation and sponsored use of medical devices by paid clinicians (see paragraphs 3.66 to 3.70). Particular methodological and reporting practices may contribute to this hype. For example, there is an acknowledged problem of suppression of negative findings from clinical trials sponsored by pharmaceutical companies.⁶⁰⁸ It has also been suggested that there is a particular risk of bias towards the reporting of positive results in the field of neurostimulation research.⁶⁰⁹ This is thought to arise because the ongoing lack of clarity about exactly *how* neurostimulation achieves its effect encourages the publication of *any* incidental positive results, even if these were not part of the original research protocol and findings relating to the primary aims of the study were not positive. There is also anecdotal evidence that, in some research studies of non-invasive brain-computer interfaces (BCIs), participants who are found not to produce the requisite or kinds of readable brain signals will be excluded from the research sample at an early stage.⁶¹⁰ The exclusion of ‘non-responders’ means that resultant findings may be more positive than they might otherwise have been about participants’ capacities to control computer commands.

- 6.15 These practices run contrary to the ideals of RRI by failing to represent the true capacities and promise of neurotechnologies. It is, therefore, crucial that exclusions of participants, the original hypothesis being tested, disappointing negative findings, and commercial interests are made explicit in published research. Open science is now widely recognised as an important route towards supporting innovation that serves the public good.⁶¹¹ The registers of clinical experience that we recommended in Chapter 5 would help to contribute to this, and in Chapter 7, we consider the need for enhanced information governance in respect of neurodevices.

Continuous reflexive evaluation

- 6.16 RRI also requires that those pursuing or supporting research lift their eyes above the narrow focus upon a particular application of neurotechnology to ask first whether it will offer real advantages over existing therapies, and second what spin-off developments from a technology might be anticipated. Addressing these questions may help to avoid ‘lock in’ to a development trajectory that might not deliver socially beneficial ends.⁶¹² They may also help to illuminate the intermeshed nature of therapeutic technologies and their potential non-therapeutic applications – for example, the use of BCI-controlled games for both pure recreational activities and as useful tools to maintain the interest and engagement of users during the training phase of therapeutic or assistive uses of BCIs. This may be of particular value in assisting developers to anticipate, and if necessary protect against, the possible dual-uses of technologies for both benign and hostile ends. We discuss the issues raised by non-therapeutic applications in more detail in Chapter 8.

⁶⁰⁸ This has led to a campaign for all trials to be registered and their full methods and results reported: All Trials (2013) *All trials registered: all results reported*, available at: <http://www.alltrials.net/>. Lexchin JR (2005) Implications of pharmaceutical industry funding on clinical research *The Annals of Pharmacotherapy* **39**(1): 194-7.

⁶⁰⁹ Schlaepfer TE and Fins JJ (2010) Deep brain stimulation and the neuroethics of responsible publishing *The Journal of the American Medical Association* **303**(8): 775-6.

⁶¹⁰ See, for example, Friedrich EVC, Scherer R, Sonnleitner K and Neuper C (2011) Impact of auditory distraction on user performance in a brain-computer interface driven by different mental tasks *Clinical Neurophysiology* **122**(10): 2003-9; Höhne J, Schreuder M, Blankertz B and Tangermann M (2011) A novel 9-class auditory ERP paradigm driving a predictive text entry system *Frontiers in Neuroscience* **5**(99): 1-10; Horki P, Solis-Escalante T, Neuper C and Müller-Putz G (2011) Combined motor imagery and SSVEP based BCI control of a 2 DoF artificial upper limb *Medical & Biological Engineering & Computing* **49**(5): 567-77; Popescu F, Fazli S, Badower Y, Blankertz B and Müller K-R (2007) Single trial classification of motor imagination using 6 dry EEG electrodes *PLoS ONE* **2**(7): 1-5.

⁶¹¹ The Royal Society (2012) *Science as an open enterprise*, available at:

http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/projects/sape/2012-06-20-SAOE.pdf.

⁶¹² See: Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, pp.16-17.

- 6.17 Challenging developers of neurostimulation devices to consider possible new directions for these technologies might seem unnecessary in a field of research where new neural targets for stimulation and new clinical indications are continually being sought for existing devices. But these might still be viewed as following a linear approach to anticipating opportunities and risks. Technology ‘foresight’ exercises alone are unlikely to be sufficient to anticipate potential directions of development because complex neurotechnologies can be expected to follow multifaceted and non-linear innovation trajectories.⁶¹³ This is likely to encompass a variety of actors, any of whom may assume the role of enactor of innovation development and uptake.⁶¹⁴ RRI of neurotechnologies require a truly reflexive approach to ongoing evaluation in which alternative development pathways are recognised and humility is exercised through a willingness to change direction in light of emerging evidence.⁶¹⁵ Humility is also required to recognise the developers and regulators cannot be alone in determining the direction of innovation; responsiveness to public views and values is an essential part of any evaluation.⁶¹⁶ The value of reflexive evaluation does not end at the point at which a neurotechnological application receives regulatory approval to enter the market, but endures with the responsibility to respond to unexpected adverse effects or emerging ‘off-label’ uses.
- 6.18 It is important not to overlook the role that regulatory or governance oversight can themselves play in helping to shape or constrain the trajectory of innovation in a technological sphere. The one-dimensional view that technology itself is the principal driver of change has long since been abandoned.⁶¹⁷ In recent decades, we have come to understand that science, technology and society co-produce our technological futures, greatly complicating the task but also giving us better insight into the kinds of considerations that must be taken into account if we are to plan better for such futures.⁶¹⁸ *Legal* foresighting has been defined as “the identification and exploration of possible and desirable future legal or quasi-legal developments aimed at achieving valued social and technological ends.”⁶¹⁹ It is, however, a nascent discipline: law can have an important role to play in the social-shaping exercise that foresighting encourages, but humility teaches us that it should be seen as only one element in the armoury of possible social responses.

Coordinated interdisciplinary action

- 6.19 It is tempting portray researchers in a particular field of technological development as a single cohesive community. This is rarely true, and the field of neurotechnology is no exception. Innovation in BCIs is particularly notable for its interdisciplinarity, spanning (but not limited to) engineers, neurosurgeons and psychologists.⁶²⁰ From an RRI perspective, this poses a set of risks associated with the “fragmentation in the understanding of the overall picture.”⁶²¹ This

⁶¹³ ‘Foresight’ here refers to an evidence based, future-directed approach to analysing the potential opportunities and risks posed by an emerging technology in order to inform policy. See, for example, Martin BR and Irvine J (1989) *Research foresight: priority-setting in science* (London: Pinter); Georghiou L (1996) The UK technology foresight programme *Futures* **28(4)**: 359-77.

⁶¹⁴ Fraunhofer Institute for Systems and Innovation Research (2003) *Annex 3: integrating technological and social aspects of foresight in europe (ITSAFE)*, available at: <http://www.supra.ed.ac.uk/Publications/annex3.pdf>; Swierstra T and Rip A (2007) Nano-ethics as NEST-ethics: patterns of moral argumentation about new and emerging science and technology *Nanoethics* **1(1)**: 3-20.

⁶¹⁵ STEPS Working Paper 32. Brighton: STEPS Centre (2009) *Direction, distribution and diversity! Pluralising progress in innovation, sustainability and development*, available at: <http://anewmanifesto.org/wp-content/uploads/stirling-paper-32.pdf>.

⁶¹⁶ Owen R, Macnaghten P and Stilgoe J (2012) Responsible research and innovation: from science in society to science for society, with society *Science and Public Policy* **39(6)**: 751-60, at page 755.

⁶¹⁷ SUPRA (2003) *ITSAFE project: intergrating technological and social aspects of foresight in Europe*, available at: http://www.supra.ed.ac.uk/Publications/ITSAFE_FINAL_REPORT.pdf, pp. 16-8.

⁶¹⁸ Jørgensen MS, Jørgensen U and Clausen C (2009) The social shaping approach to technology foresight *Futures* **41(2)**: 80-6.

⁶¹⁹ Laurie G, Harmon SH and Arzuaga F (2012) Foresighting futures: law, new technologies, and the challenges of regulating for uncertainty *Law, Innovation and Technology* **4(1)**: 1-33, at page 3.

⁶²⁰ Haselager P, Vlek R, Hill J and Nijboer F (2009) A note on ethical aspects of BCI *Neural Networks* **22(9)**: 1352-7, at page 1355.

⁶²¹ *Ibid.*, at page 1355.

potentially leads to gaps in a global understanding of the technology’s capabilities, creates challenges for assigning responsibility (for example, for obtaining informed consent), threatens the effective dissemination of information (both within teams and to the media), and thus presents obstacles to assessments of efficacy and safety.⁶²² In addition, uncertainties generated by divergent development trajectories and the priorities and vision of diverse actors make directing regulatory and governance responses all the more challenging. Governance approaches that support all the elements of RRI that we outline here need to speak to many different actors and to unite their diverse endeavours under the common aim of promoting the well-being of those who will use the technologies.

- 6.20 However, this diversity is also valuable insofar as it offers multiple perspectives from which reflexive evaluation and the identification of valuable research directions may be undertaken, and should be embraced.⁶²³ There can also be significant value in different groups of actors working together to deliver outcomes that might not be so readily achieved in isolation. For example, collaborative, interdisciplinary efforts to gather and disseminate information might help to fill important evidence gaps in understanding the capabilities and unintended effects of neurodevices.

Effective and proportionate oversight

- 6.21 Here we understand ‘oversight’ to include a range of measures, including regulatory regimes, the common law, and governance approaches such as professional codes of conduct. There is a wealth of literature and debate on what is meant by ‘regulation’ and ‘governance’ in the context of biotechnologies.⁶²⁴ It is not possible to explore the contours of this in any depth in this report but the broad definition adopted here is that oversight encompasses systems or approaches of directing or influencing behaviours in science and innovation trajectories towards desirable public goods and away from undesirable social outcomes.
- 6.22 Before we turn our attention in Chapter 7 to the specific questions of how the regulatory framework that applies to novel neurotechnologies measures up against the elements of RRI outlined above, it will be useful first to consider the more fundamental matter of what good governance and regulatory approaches themselves look like in the context of these technologies. Our ethical framework is a valuable guide to addressing this question. The role for ethical analysis in the context of regulation and governance is in providing common language and the means to reflect critically on the processes involved, and to evaluate them relative to our core social values. The aspiration towards good governance and regulation in this area is an ethical issue because failures or limitations in these regimes will impact very seriously and negatively on core human and social interests.

Responsible oversight in a context of uncertainty

- 6.23 A well-functioning regulatory system would be expected to deliver safe innovations in a timely fashion and with a minimum of regulatory burden so long as considerations of safety and proportionality are met. As we have noted, a key hurdle here to assuring safety is uncertainty surrounding the unintended and long-term risks of novel neurotechnologies.
- 6.24 Regulators constantly face uncertainty about the future. It has been posited that society’s diverse feelings about new technologies – whether they are greeted with fear or hope – depends to some degree on “how confident we feel about our ability to regulate them and, indeed, on how we react to the prospect of being regulated by them” and that negotiating mixed

⁶²² Ibid, at page 1355; Mak JN and Wolpaw JR (2009) Clinical applications of brain-computer interfaces: current state and future prospects *IEEE Reviews in Biomedical Engineering* 2: 187-99 pp. 197-8.

⁶²³ Stirling A (2011) Pluralising progress: from integrative transitions to transformative diversity *Environmental Innovation and Societal Transitions* 1(1): 82-8.

⁶²⁴ See, for example, Lyall C, Smith J and Papaioannou T (2009) *The limits to governance: the challenge of policy-making for the new life sciences* (Farnham: Ashgate Publishing Limited).

perceptions of promise and threat is not an easy task for regulators.⁶²⁵ This then demands the question of *how* society can regulate in circumstances of uncertainty, especially when this coexists in tension with need and in competition with hype. We have suggested that uncertainty gives rise to a principle of caution; that we should be circumspect as to the paucity of evidence about longer-term and unintended effects of intervening in the brain when proceeding with neurotechnological development. This recommends an approach to regulation that instantiates this principle. Crucially, however, is not precisely the same as adopting the *precautionary principle* itself.

- 6.25 The precautionary principle is a central feature of European regulatory frameworks and many national systems.⁶²⁶ It is considered to sit “at the heart of medical and public health theory and practice and is an underpinning to many our current environmental and public health policies”.⁶²⁷ The precise definition of the precautionary principle is a contested matter. Some readings frame it as an approach to risk management.⁶²⁸ It is intended to allow actors and governments to proceed when faced with an absence of conclusive or unambiguous scientific knowledge about likely risks associated with a particular development, initiative, new project or product.
- 6.26 However, as we have already noted in introducing the principle of caution in Chapter 4 (see paragraph 4.23), the precautionary principle is often constructed in ways that may be seen to stifle innovation and be overly restrictive. A common criticism is that it fails to take account of the harms of *inaction* – in this context, the harms of failing to deliver effective therapeutic interventions.⁶²⁹ In contrast, an approach based in the principle of caution and the virtue of humility acknowledges that there are limits to evidence based approaches to scientific and policy development. The challenge of uncertainty arises not only from a lack of evidence, but also ambiguities in that which is available to us. As the National Institute for Health and Care Excellence (NICE), has observed: “All evidence requires interpretation as evidence alone cannot determine the content of a recommendation”.⁶³⁰ This leads to a conclusion that both scientific and non-scientific values should form part of decision-making when faced with uncertainty about how best to proceed.⁶³¹ Moreover, the virtue of responsibility also requires approaching innovation in a way that avoids lock-in and leaves open the possibility of reversibility or adopting a different path.

⁶²⁵ Bekou O and Murphy T (2010) Editorial *Human Rights Law Review* **10(4)**: 597-9, at page 597.

⁶²⁶ Annex III to the *European Council Resolution on the Precautionary Principle*, SN 400/00 ADD 1 20 EN, at paragraphs 24-5. See also: European Court of Justice Case C–236/01, *Monsanto Agricoltura Italia SpA and Others v Presidenza del Consiglio dei Ministri and Others*, ECR 2003 I–08105 (133), in which the ECJ stated that the principle is “...an integral part of the decision-making process leading the adoption of any measure for the protection of human health.”

⁶²⁷ Tickner J and Kriebel D (2006) The role of science and precaution in environmental and public health policy, in *Implementing the precautionary principle: perspectives and prospects*, Fisher E, Jones JS, and Schomberg Rv (Editors) (Cheltenham: Edward Elgar Publishing Limited). See also: Kopelman LM, Resnick D and Weed DL (2004) What is the role of the precautionary principle in the philosophy of medicine and bioethics? *The Journal of Medicine and Philosophy* **29(3)**: 255-8.

⁶²⁸ For example, according to Principle 15 of the Rio Declaration on Environment and Development (1992), “In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation”.

⁶²⁹ See, for example, Sunstein CR (2002) The Paralyzing principle *Regulation* **25**: 32-7.

⁶³⁰ NICE (2009) *Methods for the development of NICE public health guidance (second edition)*, available at: <http://www.nice.org.uk/media/2FB/53/PHMethodsManual110509.pdf>, at page 118.

⁶³¹ The Nuffield Council on Bioethics’ report ‘*Public health: ethical issues*’ addressed the role and value of precaution when the evidence for proceeding with particular policies is incomplete, fragmented or contested. Preference was given to the term ‘precautionary approach’ rather than ‘precautionary principle’, in recognition of the fact that multiple principles and considerations must be taken into account. See: Nuffield Council on Bioethics (2007) *Public health: ethical issues*, available at: <http://www.nuffieldbioethics.org/sites/default/files/Public%20health%20-%20ethical%20issues.pdf>, at page xviii. The emphasis on the principle of caution we adopt in the present report is similarly motivated.

Proportionality in a context of need

- 6.27 Caution alone cannot be the only guide to effective regulation. The concept of need that lies at the heart of our ethical framework, and the associated virtue of inventiveness, draw our attention to the risk that too much regulatory burden or governance in these processes can stifle research and innovation or create unacceptable delays, thus potentially denying access to treatment or assistance. A responsibility for proportionate oversight is owed to all parties affected by the development of novel neurotechnologies. This means not only patients, but also researchers, innovators, manufacturers and those with a wider economic interest in the design and delivery of safe and effective new inventions. The regulatory system must work well for all: it must not only be safe and effective, but it must also be efficient and proportionate to the risks and benefits involved. An inefficient and overly-burdensome regulatory system is not in anyone's interests and is unethical as a result.
- 6.28 Moreover, in an area of technological development that is characterised by uncertainty, efforts to control research and clinical practices must themselves instantiate humility in recognising that the optimal path will not always be obvious. One key aspect of this will be recognising the limits of what can be achieved by top-down regulation and identifying those areas where professional groups of actors may more usefully govern their own activities according to the relevant virtues and interests at stake.

Box 6.1: Regulatory principles

Three regulatory principles may be seen as relevant to achieving effective and proportionate oversight.

Proportionality is a central feature of European and domestic regulatory practice.⁶³² It provides an important safeguard against regulatory burden by requiring that the content and form of any particular action or policy must not go beyond what is necessary to achieve the regulatory objective, which must itself be proportionate to the benefits, risks, and alternative courses of action.⁶³³ This principle, therefore, also speaks against unjustified overlap between regulatory and governance regimes – for example, in clinical research where research ethics approval, regulatory compliance, good clinical governance and both product and device regimes must all be satisfied.

Subsidiarity relates to the question of who has responsibility for acting where multiple actors have competence at various strata of regulation and lines of accountability are unclear. It has particular salience in the European context, The European Commission has clarified that, where the European Union (EU) and Member States share competence, the principle of subsidiarity establishes a presumption in favour of the Member States taking action.⁶³⁴ This is relevant in the field of novel neurotechnologies, where Member States and the EU share competence in respect of the regulation of medical devices and advanced therapeutic medicinal products. The EU has sought to achieve harmonisation in these fields in response to its twin aims of ensuring safety and proper functioning of the internal market. In Chapter 7, we consider whether these aims might be inadequate to meet priorities in respect of novel neurotechnologies, leaving areas where the UK might consider acting to fill any regulatory gaps.

Regulatory orientation is concerned with the transparency and clarity of regulatory objectives. One caricature is that regulatory regimes are burdensome bureaucracies more concerned with form-filling than the advancement of human knowledge and well-being. In reality, regulators are committed to reducing burden and to the twin objectives of protecting research participants and patients while promoting scientific advancement. However, there is only so much that states can achieve alone through regulatory regimes if there is not commitment and buy-in from the communities being regulated. Early and sustained dialogue and interaction with stakeholders can help to ensure that regulation is most effectively oriented to predict, shape and protect against harms from possible directions of development.⁶³⁵

⁶³² Article 5 of the Official Journal of the European Union (2012) *The treaty on European Union*, available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2012:326:FULL:EN:PDF>; EUROPA (2012) *Glossary: proportionality principle*, available at: http://europa.eu/legislation_summaries/glossary/proportionality_en.htm.

⁶³³ European Commission (2010) *Report from the commission on subsidiarity and proportionality (18th report on better lawmaking covering the year 2010)* available at: http://ec.europa.eu/governance/better_regulation/documents/com_2011_0344_en.pdf.

⁶³⁴ *Ibid.* pp.1-2.

⁶³⁵ Fins JJ, Schlaepfer TE, Nuttin B *et al.* (2011) Ethical guidance for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic deep brain stimulation *Journal of Neural Engineering* **8(3)**: 1-6.

Humility and limits of regulation

- 6.29 Even once the principles listed in Box 6.1 have been taken into account, the suitability of hard law and top-down, command-and-control response to fill regulatory gaps might still be questioned. Responsibility, and liability for harmful outcomes, can be attributed through law and regulatory frameworks and this can serve to foster a compliance culture where regulatory requirements become the main drivers of processes. While it is important that regulation embodies clear lines of accountability, this can have the unlooked-for consequence of creating burdensome bureaucracy and can result in losing sight of the underpinning ethical objective and values of the regime to deliver safe and effective products efficiently.

- 6.30 Humility counsels against a presumption that introducing more law or further layers of regulatory oversight is always the most appropriate response to any concerns we might have about the ethical and social impacts of novel neurotechnologies. This is particularly so in the context of the provision of novel neurotechnologies for therapeutic purposes. Knee-jerk, rapid regulatory responses can not only be ineffective but can prevent the emergence of the kinds of evidence and experience that are necessary to conduct an appropriate assessment of the advent and acceptability of a new technology. It also challenges us to consider when regulation is appropriate at all, and in whom this power ought to be vested.

- 6.31 In some circumstances, governance approaches (rather than regulation) will offer the most appropriate paradigm within which to respond to any concerns we might have about the conduct of research and innovation in the field of neurotechnology. The distinction between regulation and governance is not rigid; they overlap both in form and function. Nevertheless, governance from within a profession or community of professions involved in the development of new technologies offers some advantages over the external imposition of regulations. This is due to the fact that it permits responsible research and innovation to be undertaken as a collective endeavour, built upon iterative, flexible, reflective and consensual approaches that seek to engage actors at all stages of the innovation trajectory, regardless of the path that is taken.

- 6.32 In Chapter 7, we address the specific questions of whether the existing regulatory regimes that apply to medical devices and to stem cell therapies meet criteria for effective and proportionate oversight. In doing so, we ask, in particular, whether these regimes foster the kinds of practices and outcomes that we have identified as priorities for RRI in the field of novel neurotechnologies.

Chapter 7

Regulating the
technologies

Chapter 7 - Regulating the technologies

Chapter 7 - overview

The regulatory frameworks that apply to medical devices and to advanced therapeutic medicinal products (ATMPs), such as neural stem cell therapies, govern the entry of the technologies onto the European market, including the clinical investigations preceding this.

Using our ethical framework and the elements of responsible research and innovation developed in the preceding chapters we assess whether current regulatory provisions are effective and proportionate given the requirement to protect patients' safety, while also enhancing access to safe and effective therapies. The regimes applying to medical devices and ATMPs share a historical objective of securing a harmonised European market and each is concerned both with supporting innovation while protecting patient safety. However, the regulatory obligations upon manufacturers differ significantly between these two sectors in a number of respects. Concerns regarding effective oversight of medical devices apply especially urgently to invasive neurodevices, as these pose greater risks to patients' safety.

Pre-market oversight of medical devices in Europe is decentralised and relatively light-touch (especially for non-invasive devices) in terms of the evidence manufacturers must supply to demonstrate that their products conform to statutory safety and performance requirements. While this may support innovation by limiting regulatory burden, we nevertheless welcome European proposals to narrow the circumstances in which manufacturers can rely on evidence concerning similar devices (rather than conducting new clinical investigations) to demonstrate conformity. We recommend that, since neurodevices intervene in the brain, the case for relying on pre-existing evidence must be particularly sound (paragraph 7.33 and 7.47). We also recommend greater transparency about the basis of all decisions about the conformity of devices with regulatory requirements (paragraph 7.27).

Since pre-market scrutiny of neurodevices is light-touch, it is all the more important that post-market surveillance mechanisms are robust. We recommend that these should be strengthened by making it mandatory for clinicians to report adverse events – supported by a scheme to alert them to newly approved devices – and by making all information on adverse incidents and incident trends publically accessible (paragraph 7.55).

Uncertainty about the benefits, risks and mechanisms by which some novel neurotechnologies achieve their effects presents one of the central ethical challenges in this field; yet the regulation of medical devices does not itself encourage collection of extensive clinical evidence. In addition to recommending enhanced transparency in the regulatory system (paragraph 7.28), we suggest that collaborative efforts to improve information governance and data linkage by manufacturers, practitioners and others are needed. Improved evidence on the efficacy (or otherwise) of neurodevices is a particular priority as the regulatory system itself does not currently address this.

In contrast to medical devices, the steps required under the multiple regulatory frameworks applying to the licensing of ATMPs as commercial products are many, potentially lengthy and include centralised European authorisation. This complexity and the potentially overlapping roles of the various regulatory bodies involved is a source of concern, particularly given the economic risks that delays pose to companies developing products. Neural stem cell therapies, however, could present significant health risks if they do not perform as expected, so robust regulation is vital. We suggest that a responsible and proportionate approach to oversight should allow an evolution from a mode of protection to one of promotion as the science progresses (paragraph 7.72). We welcome recent developments in the governance of stem cell therapies that aim to streamline and speed up the regulatory and ethical oversight processes involved whilst maintaining rigorous standards for protecting patient safety.

There are various routes by which patients with particular needs can access medical devices and ATMPs that are not approved for wider market availability. These are welcome insofar as they may address otherwise unmet needs. However, given the intrinsic vulnerability of patients undergoing more experimental interventions, we raise concerns about the scope of regulatory and ethical oversight of therapies delivered via these routes. Some, such as 'off-label', 'in-house' and investigative uses of medical devices which are not aimed at commercial applications, may fall outside the regulator's remit altogether. Even where the supply of some technologies for exceptional or non-routine use is regulated by the Medicines and Healthcare products Regulatory Agency, we suggest that there need to be more thorough mechanisms for collecting and making publically accessible information on approval for these uses and their outcomes (paragraph 7.89).

Introduction

- 7.1 As is so often the case in the realm where ethics and novel technologies meet, there is little that is absolutely novel. Interventions in the brain are not new and, as the examples of psychosurgery considered in Chapter 1 illustrate, the challenges and criticisms raised about such techniques in the 1970s continue to have resonance today for many invasive

neurotechnologies.⁶³⁶ In regulatory terms, the enduring challenge is not so much about uncovering entirely unexplored issues; rather, it is about dealing with the vagaries of regulatory systems that have grown up over many years and in ensuring that they remain responsive to emerging developments. If the regulatory response to any given technological development is not outright prohibition, then the task becomes more nuanced in identifying how far and how well existing regulatory mechanisms capture an emergent technology, address adequately the range of technical, social and ethical issues associated with its adoption, and delivers the said technology safely and efficiently to its users. Where systems are found to function sub-optimally, then regulatory reform should follow.

- 7.2 The focus of this chapter is the regulatory regimes that determine whether neurodevices on one hand, and neural stem cell therapies on the other, are licensed to be marketed and used for the treatment of humans. These regimes impact on whether, and for what purposes, a neurotechnology may be made available and also set the conditions that shape both the investigatory routes followed by developers and post-market oversight. Our first step is to map the landscape of these regimes and the responsible authorities involved. It is a complex picture that has grown up over a number of years and involves actors and agencies at multiple levels. We then turn to a sector-specific analysis, considering whether these regulatory regimes raise any concerns about the effective and proportionate oversight of novel neurotechnologies in three distinct sectors: non-invasive devices, invasive devices and neural stem cell therapies.

Applying our ethical framework

- 7.3 The ethical framework developed in Chapter 4 serves here as the normative template through which to view these regulatory systems and to determine whether the controls they provide are appropriate. The present chapter considers the virtues from the regulators' perspective. The central question that we address here is whether regulatory approaches currently in place support practices that instantiate the virtues in ways that promote the key interests at stake. In the context of regulation of new technologies, the central interest is meeting unmet therapeutic need through the delivery of safe and effective innovations. This means that responsible regulatory approaches must attend not only to the needs of patients, research participants and those responsible for their care, but also to the pressures upon innovators, manufacturers and those with a wider economic interest in the design and delivery of new inventions. The interests of patients in the availability of safe and effective treatments coincide with the inventiveness and economic interests of those marketing them. However, the respective interests of these two groups may diverge in regard to the degree and nature of regulatory oversight that best serves them. As we describe in Chapter 6, when our ethical framework is applied to the concept of Responsible Research and Innovation (RRI), it reveals certain priorities that act as benchmarks against which any regulatory regime can be measured.
- 7.4 First and foremost, effective regulation must deliver safe neurotechnologies. Regulation must be effective in protecting the interests of those using these technologies, but also proportionate. Considerations of safety must be proportionate to the actual risks involved – as far as these can be determined – and any assessment must also be relative to the degree of any likely benefits that can be expected. An inefficient, slow or burdensome system that presents a barrier to the availability of effective innovations is not in the interests of patients. However, where wholly new neurotechnologies with limited histories of clinical use and potentially significant effects on brain functions are concerned, it is also vital that regulatory oversight is thorough.
- 7.5 One essential element of securing safety and making assessments of proportionality is the availability of high quality and transparent evidence of the risks and benefits of each technology.

⁶³⁶ Fins JJ (2003) From psychosurgery to neuromodulation and palliation: history's lessons for the ethical conduct and regulation of neuropsychiatric research *Neurosurgery Clinics of North America* **14(2)**: 303-19, at page ix-x.

A robust regulatory system is one that not only grounds its decision-making in high quality evidence and is responsive to changes in this evidence; it must also be one that incentivises generation of evidence and a culture of openness around its accessibility and use. Considerations of subsidiarity are also relevant here, that is, the question of which authorities are best placed to discharge regulatory responsibilities. This is particularly important in the European context where both national and European agencies have roles to play. International and national bodies must have an appropriate division of labour; equally, there should not be any undue overlap between the function of regulatory or professional bodies: good clinical practice and good research practice must function together. Finally, it must be recalled that there are limits to what can be achieved through regulation and that RRI is also supported by grass-roots and collaborative practices of all those involved in the innovation, marketing and use of new technologies.

- 7.6 A well-functioning regulatory system would be expected to deliver the innovations needed in a timely fashion and with a minimum of regulatory burden so long as considerations of safety and proportionality are met. In this chapter, we consider the particular challenges in achieving proportionality in the context of regulating novel neurotechnologies.

Surveying the regulatory landscape

- 7.7 This section offers a brief overview of the regulatory environments that apply to the novel neurotechnologies discussed in this report. Broadly, there are two regulatory spheres: medical devices and advanced therapeutic medicinal products (ATMPs). These are not neuro-specific, but apply to all medical devices and ATMPs. The devices used to administer transcranial brain stimulation (TBS) or deep brain stimulation (DBS) and in brain-computer interfaces (BCIs) are classed as medical devices where they are used, *inter alia*, for diagnostic, monitoring or treatment purposes or in the modification of a physiological process.⁶³⁷ Neural stem cell therapies are regulated as ATMPs.⁶³⁸ Regulation in the European context is thus a complex web of intersecting laws, standards, guidelines and regulatory authorities operating at European and national levels. Paragraphs 7.8 to 7.22 provide an overview of these.

European level

- 7.8 The European Union (EU) has legislated in both regulatory spheres of medical devices and ATMPs.

Medical devices

- 7.9 Three Directives regulate medical devices, respectively concerning:

- medical devices *per se*;⁶³⁹
- active implantable medical devices;⁶⁴⁰ and
- *in vitro* diagnostic medical devices.⁶⁴¹

- 7.10 Only the first two are pertinent to the technologies we are concerned with in this report. All of these Directives are now subject to proposals for reform (see Box 7.1 below).⁶⁴² The relevant

⁶³⁷ A full definition of a medical device may be found in: MHRA (2011) *Bulletin no. 17: medical devices and medicinal products*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007498.pdf>.

⁶³⁸ European Medicines Agency (2011) *Advanced therapies*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0; European Medicines Agency (2011) *Reflection paper on stem cell-based medicinal products* available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500101692.pdf.

⁶³⁹ Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (MDD).

⁶⁴⁰ Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States on the approximation of the laws of the Member States relating to active implantable medical devices.

⁶⁴¹ Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices.

UK implementing legislation for the original Directives is found in the Medical Devices Regulations 2002, as amended. This transposed the provisions of the Directives into domestic law and is designed to bring the UK into line with the objectives of the Directives.⁶⁴³ The historical purpose of the three Directives has been to remove technical barriers to trade by harmonising safety and manufacturing requirements for medical devices across Europe. The emphasis is now placed upon safeguarding public health by supporting innovation, whilst ensuring the safety of the products that reach the market. This means that manufacturers must demonstrate conformity with the essential requirements as set out in the relevant Directive. Once conformity has been established, devices may then carry the CE mark. There is considerable economic incentive for manufacturers of medical devices to receive CE marking - once products have a CE mark, they must be allowed to circulate freely in the European internal market.

ATMPs

7.11 Similar objectives (of supporting innovation and harmonisation while protecting patient safety) underlie European law regulating ATMPs. The UK legislation giving effect to the European ATMP Regulation came into force on 19 August 2010.⁶⁴⁴ However, under the ATMP Regulation, ATMPs which are intended to be placed on the market in the European Community are subject to a *centralised* European authorisation procedure. The Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA) is responsible for preparing a draft opinion on the quality safety and efficacy of ATMPs for which marketing authorisation is sought. The opinion of CAT is then submitted to the EMA's Committee for Medicinal Products for Human Use (CHMP) for final approval.⁶⁴⁵

Harmonisation across Europe

7.12 A high degree of harmonisation exists with respect to the regulation of devices and ATMP regulation in Europe; at least as a matter of strict law. However, only ATMPs are subject to a centralised authorisation procedure. The EU has shared competence with Member States in a number of related areas beyond the specific regulation of devices and products. For example, it has sought to bring harmonisation to clinical research through the Clinical Trials Directive⁶⁴⁶ and the Tissues and Cells Directive. However, as we discuss below, harmonisation is not absolute. There is variability between Member States in the performance of Notified Bodies (the independent accredited organisations responsible for independently assessing conformity for all but low risk devices with regulatory requirements) and in the implementation of procedures that permit the production of ATMPs for on a non-routine basis for small numbers of patients. Furthermore, even when an ATMP has received pan-European marketing authorisation, matters such as labelling and reimbursement must still be dealt with at state level.

⁶⁴² Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁶⁴³ Later revisions to the MDD and AIMD are specified in Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market. These changes were transposed into UK law by Medical Devices Amendment Regulations SI 2008 No 2936.

⁶⁴⁴ Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending directive 2001/83/EC and regulation (EC) no 726/2004; MHRA (2010) *Guidance on the UK's arrangements under the hospital exemption scheme*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>.

⁶⁴⁵ MHRA (2013) *How we regulate advanced therapy medicinal products*, available at: <http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/Aboutadvancedtherapymedicinalproducts/index.htm>.

⁶⁴⁶ Now subject to a proposal for a new Clinical Trials Regulation, see: Proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (17 July 2012).

National level

- 7.13 Member States of the EU are obliged to implement Directives and to give direct effect to European Regulations. They are at liberty to regulate above and beyond these measures but they must, as a minimum, adopt these measures.
- 7.14 A common feature of the regulatory architecture is the need for Member States to establish a national Competent Authority to discharge regulatory duties at a local level (and liaise with European agencies). In the UK, the Competent Authority ensuring implementation of the relevant European laws is the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA (and its equivalents in other Member States) acts as the pivotal regulator in both spheres affecting neurotechnologies. Its roles and powers are, however, limited by the regulatory objectives that it is designed to deliver, as dictated by the relevant European laws.
- 7.15 With respect to medical devices, the MHRA duties as Competent Authority include:⁶⁴⁷
- enforcing compliance of CE marked devices with regulations
 - monitoring and designating the 'Notified Bodies' that conduct conformity assessments;
 - registration of manufacturers of primarily low risk devices;
 - assessing notifications for clinical investigations; and
 - authorising the use of non-CE marked medical devices on humanitarian grounds and for custom-made purposes.
- 7.16 With respect to ATMPs, the MHRA is the supervisory authority for UK manufacturers or importers of those ATMPs that are centrally authorised at EU level. The MHRA's duties as Competent Authority in the UK include:⁶⁴⁸
- authorisation of clinical trials of ATMPs at a national level;
 - active involvement in the European system for authorisation of ATMPs by providing two members for CAT;
 - the provision of scientific advice at a European and national level;
 - authorisation of UK sites for manufacture and importation of ATMPs that are 'investigational medicinal products' (those to be used in a clinical trial); and
 - authorisation of UK sites where ATMPs are manufactured (this applies both to ATMPs authorised for the wider market and to products manufactured under the regulatory provisions permitting non-routine supply to single, or small numbers, of patients – the 'hospital exemption' and 'Specials' arrangements).

Requirements for evidence of efficacy

- 7.17 An important feature distinguishing the regulation of devices from ATMPs is the question of efficacy. Where ATMPs are concerned, the MHRA is required by law to establish their safety, quality and efficacy (in the same way as other medicinal products such as drugs). However, there is no parallel requirement for medical device manufacturers to demonstrate their products' efficacy. MHRA is only concerned with the safety, manufacturing quality, and performance of devices.
- 7.18 The difference between performance and efficacy may be understood as follows. A device will meet the criterion of performance if it operates as described (for example, that it administers an

⁶⁴⁷ Department of Health (2012) *Poly implant prothèse (PIP) silicone breast implants: review of the actions of the medicines and healthcare products regulatory agency (MHRA) and department of health*, available at: <http://www.meddevicesupplychain.com/public/06-12-MHRA.pdf>, at page 112.

⁶⁴⁸ MHRA (2013) *How we regulate advanced therapy medicinal products*, available at: <http://www.mhra.gov.uk/Howweregulate/Advancedtherapy Medicinalproducts/Aboutadvancedtherapy Medicinalproducts/index.htm>; MHRA (2013) *Scientific advice for licence applicants*, available at: <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Informationforlicenceapplicants/Otherusefulservice sandinformation/Scientificadviceforlicenceapplicants/CON009534>.

electrical current through electrodes at xHz per second). Evidence of efficacy, meanwhile, would require demonstrating that the device achieved a particular outcome (for example, that it alleviates tremor in Parkinson’s disease patients). The practical consequence of this distinction is that while useless and dangerous devices clearly would not be approved as a matter of risk-benefit analysis, the MHRA does not require evidence that a medical device will deliver a particular therapeutic outcome for users or improve on the efficacy of similar devices on the market. It may not always be possible to make a sharp distinction between evidence of performance and efficacy. However, as the exact mechanisms of action are still often unknown for many neurostimulation devices (such as those used in DBS) and outcomes will depend to a great extent on the skills of surgeons implanting them, there is an inferential gap from performance to efficacy of devices which means that these two terms cannot be read as synonymous.

Scope and limits of regulatory oversight

- 7.19 Alongside a concern for safeguarding public health, the second key focus for both of these regulatory regimes is whether a device or product is being developed with a view to introduction on the market. The regulatory driver here stems from the original objective of the EU, namely to create and maintain a single economic market. This means that the historical motive for regulating in this area has been to pave the way to market as much as to address concerns of safety for patients.
- 7.20 The practical consequence of this is that the MHRA has regulatory responsibility for only some kinds of activities involved in the clinical investigation or uses of novel neurotechnologies, but only where these are part of a pathway to marketing the product. For example, the MHRA must be notified when a pre-clinical assessment or a clinical investigation is to be conducted to obtain evidence prior to placing a medical device on the market.⁶⁴⁹ If, however, a device is manufactured by a health care establishment and only used on their *own* patients, the manufacturer is exempt from compliance with the medical device regulations.⁶⁵⁰ Similarly, it is not necessary for clinicians using CE marked devices for ‘off-label’ uses (uses other than those for which the device holds CE marking) to notify the MHRA, unless these uses are intended to be a pathway to marketing the device for this new purpose (see paragraphs 7.49 to 7.51 below).
- 7.21 Where regulatory agencies *are* engaged, there usually follows significant additional oversight. For example, clinical investigations involving medical devices that do not carry the CE-mark, and are intended for eventual market use, fall under the Medical Devices Regulations 2002 and require approval from the MHRA, which may take up to 60 days. For clinical investigations to proceed, approval must also be sought from an ethics committee appointed by the National Research Ethics Service (NRES).⁶⁵¹ For ATMPs involving cell therapies derived from stem cell lines, input is also required in the UK from the Gene Therapy Advisory Committee (GTAC) where there is an intention to market these products (we discuss this in further detail at paragraphs 7.70 to 7.72).
- 7.22 The significance of this is that, despite high levels of harmonisation in Europe, the regulatory regimes do not cover, to the same degree, all instances of innovation, experimental treatments or *ad hoc* investigations (which are a common feature of neurotechnology development),

⁶⁴⁹ MHRA (2012) *Guidance for manufacturers on clinical investigations to be carried out in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf>, at page 6.

⁶⁵⁰ MHRA (2010) *In house manufacture*, available at: <http://www.mhra.gov.uk/Howweregulate/Devices/Inhousemanufacture/index.htm>. The removal of this exemption for devices manufactured and used in-house is one of the proposed changes under the revisions to European legislation: Article 4 of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁶⁵¹ MHRA (2013) *Clinical trials for medical devices*, available at: <http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm>.

although these may threaten patient safety. The close relationship between the intention to market a device or ATMP, and the degree of regulatory oversight this invites, raises questions about whether proportionality and appropriate regulatory orientation is achieved in the regulation of medical devices and ATMPs. We explore the consequences of this potentially uneven patchwork of regulatory oversight at paragraphs 7.49 to 7.51 and 7.73 to 7.89.

Box 7.1: Proposed revision of European legislation on medical devices

In September 2012, the European Commission produced proposals to address a number of matters arising in relation to the regulation of medical devices, predominantly in response to rapid changes in medical device technology.⁶⁵² At the time of writing, the MHRA (alongside the Competent Authorities of other Member States) is liaising with the Commission on these proposals.⁶⁵³ If adopted as they currently stand, some of the key changes of relevance to this report will include:

- Increasing transparency of the system by requiring, *inter alia*: manufacturers to register clinical investigations; manufacturers to improve information to the public about devices, to include details of warnings and precautions; the newly configured centralised European ‘Eudamed’ database in which this information is recorded to be made publically accessible.
- Strengthening criteria for clinical evaluation, for example by introducing ‘common technical specifications’ for safety and performance requirements; by requiring manufacturers to nominate a sponsor and to publish a summary of safety and performance evaluations for high-risk devices; and by requiring manufacturers to pursue post-market clinical follow-up strategies.
- Removing the full exemption of devices manufactured and used in-house by health care institutions from obligations to comply with the medical devices regulations (although some aspects of exemption will remain, including any requirement to record a summary of safety and performance on the centralised European database).
- Increasing oversight and audit of Notified Bodies, while also clarifying their duties and allowing joint assessments of Notified Bodies with other Member States and the European Commission.
- Requiring implantable and higher risk devices to undergo additional scrutiny for conformity by a new centralised European expert committee.
- Establishing an EU portal to which adverse events must be reported for automatic onwards transmission to competent authorities.

Sector-specific considerations

7.23 Having outlined the mechanisms by which the availability of novel neurotechnologies is regulated we now turn to assess the suitability of these regimes as they operate in the UK. The approach in this section will be to consider how the priorities we have established for RRI in this field and our ethical framework can assist in assessing the adequacy of current regulatory provisions and whether recommendations for reform are necessary. In doing, so we remain mindful of the need for effective and proportionate oversight and the possibility that regulatory burden may be no less detrimental to meeting therapeutic need and protecting patients’ safety than regulatory gaps. The following analysis divides the neurotechnologies with which we are concerned into three categories that capture the shared clusters of concerns that arise in respect of each. This division is based on the degree of invasiveness of a technology from the patient’s or research participant’s perspective: more invasive technologies are likely to carry higher risks and require tighter regulation. These sectors are: non-invasive neurodevices; invasive neurodevices; and neural stem cell therapies.

Non- invasive neurodevices

7.24 Transcranial magnetic stimulation (TMS) provides an illustration of some of the challenges posed by non-invasive neurodevices and associated technologies (though much of what we

⁶⁵² Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁶⁵³ MHRA (2013) *New legislation on medical devices*, available at: <http://www.mhra.gov.uk/Howweregulate/Devices/NewLegislationonMedicalDevices/>.

discuss in this section applies equally to transcranial brain stimulation (TBS) and non-invasive BCI devices). TMS devices currently have European market approval (CE marking) for use in, for example, the treatment of drug-resistant major depressive disorder in adults⁶⁵⁴ and neuropathic chronic pain.⁶⁵⁵ The European regulatory procedures involve assigning a medical device (marketed for a particular purpose) to one of four classes (see Box 7.2 below); these determine which regulatory pathway will be followed. Classification depends on a number of factors, including likely length of use, invasiveness (surgical or otherwise), whether the device is implantable or active, and whether the device also contains a therapeutic substance.⁶⁵⁶ TMS devices are non-invasive, but they are also “active” and are intended to “administer energy”.⁶⁵⁷ They are, therefore, likely to be assigned to one of the two ‘medium risk’ categories. Whether they are assigned to Class IIa or Class IIb will depend on how hazardous their use is considered to be in view of the purpose for which they are intended, and the mode of action by which the manufacturer intends this to be achieved.⁶⁵⁸

Box 7.2: Risk-based classification of medical devices in Europe

- **Class I** – generally regarded as low risk
- **Class IIa** – generally regarded as medium risk
- **Class IIb** – generally regarded as medium risk
- **Class III** – generally regarded as high risk

These classifications are established by the European Medical Devices Directive.⁶⁵⁹ These classifications determine the level of regulatory control proportionate to the degree of risk associated with the device and, therefore, the kind of conformity assessment the manufacturer and Notified Body must undertake in order for the device to receive a CE mark.⁶⁶⁰ Non-invasive medical devices will often fall under Class I. However, the particular functions of the kinds of active neurodevices with which we are concerned in this report will also engage particular additional rules under the Directive that place them in a medium risk class. For example ‘active therapeutic devices’ that administer or exchange energy (including electrical or magnetic energy), or those that perform a diagnostic function by monitoring physiological processes will be placed in Class IIa. If they perform these functions in a potentially hazardous way or are used in critical conditions they may be placed in Class IIb.

7.25 It is likely that TBS devices would be similarly assigned to Class II. Non-invasive BCI devices used for assistive purposes might also be assigned to a ‘moderate risk’ class insofar as they are judged to be used to “monitor physiological processes”.⁶⁶¹ This means that regulatory controls of all such non-invasive neurodevices are relatively light touch. Despite the fact that these devices are not classified as ‘high risk’, questions about the adequacy of regulatory oversight do arise, as we now go on to discuss.

Effective and proportionate oversight: the role of Notified Bodies

7.26 A central feature of the European regulatory system is the role played by Notified Bodies. These are independent agencies accredited by national regulators (such as the MHRA) to make judgments about the conformity of moderate and high risk devices to the criteria laid down in

⁶⁵⁴ PR Newswire (4 June 2012) *Neuronetics, inc. receives ce mark approval for neuroStar TMS therapy*, available at: <http://www.prnewswire.com/news-releases/neuronetics-inc-receives-ce-mark-approval-for-neurostar-tms-therapy-156965925.html>.

⁶⁵⁵ BioTuesday (2 July 2012) *Brainsway gets ce mark to treat neuropathic chronic pain*, available at: <http://biotuesdays.com/2012/07/02/brainsway-gets-ce-mark-to-treat-neuropathic-chronic-pain/>.

⁶⁵⁶ See: Annex IX of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁶⁵⁷ MHRA (2011) *Bulletin no. 10: the classification rules*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007495.pdf>.

⁶⁵⁸ European Commission (2010) *Guidelines relating to the application of the Council directive 93/42/EEC on medical devices*, available at: http://ec.europa.eu/health/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf.

⁶⁵⁹ Article 9 and Annex IX of the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.

⁶⁶⁰ MHRA (2011) *Bulletin no. 10: the classification rules*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007495.pdf>.

⁶⁶¹ *Ibid.*

legislation.⁶⁶² Importantly, however, the European system is one of self-certification. For Class II devices (as well as Class III and ‘active implantable’ devices), this means that a manufacturer will work with a Notified Body to satisfy itself that their device meets minimum requirements of performance and safety.⁶⁶³ The MHRA does no more than oversee and audit the processes. The decision to assign these classifications falls to manufacturers and Notified Bodies, acting in accordance with rules and guidance; the MHRA only becomes involved with the decision-making process when there is disagreement between these parties.⁶⁶⁴ Notified Bodies are responsible for verifying the correct classification (and therefore the correct regulatory pathway) and whether sufficient evidence has been provided to support this. If these verifications are made, the manufacturer can attach the CE-mark.

7.27 There are currently 76 Notified Bodies in Europe operating in the field of medical devices, of which six are in the UK.⁶⁶⁵ It has been suggested that this decentralised system has sped up the approval process, but it has also been criticised for lacking transparency.⁶⁶⁶ These bodies do not publish the basis of their decisions regarding the conformity of a device with legal requirements for performance and safety, and do not make publically available the information on which it was based.⁶⁶⁷ This is because Notified Bodies consider themselves to be ‘clients’ of manufacturers, and so under no obligation to disclose information that could be commercially sensitive and covered by the law of commercial confidentiality.⁶⁶⁸ There are also concerns about variable standards between Notified Bodies across Europe. This is particularly worrying given that manufacturers have discretion to decide to which notifying body they will submit their data. In addition, there is little systematic Europe-wide monitoring of devices once they enter the market. If a device must later be removed from the market, it is the responsibility of the Notified Body to alert the national competent authority (the MHRA in the UK). Following the PIP breast implant controversy, the European Health and Consumer Policy Commissioner called for tighter controls on Notified Bodies.⁶⁶⁹ These are now echoed in the European Commission’s proposed reforms to the regulation of medical devices.⁶⁷⁰ **We welcome these proposals, but suggest that in the interests of transparency there is still a pressing need for the evidential bases on which Notified Bodies reach compliance decisions to be a matter of public record.**

7.28 The lack of transparency in the European system arguably perpetuates the scarcity of evidence upon which patients, health professionals, and public health services can take decisions about the uptake and use of medical devices. However, in 2013, the European Commission announced the establishment of a voluntary European Health Technology Assessment (HTA) network that will enable “easier sharing of HTA knowledge concerning devices and other health technologies among Member States” and “...make it easier for health decision-makers to identify which new devices can contribute to efficiency gains and improved services.”⁶⁷¹ The

⁶⁶² European Commission: Enterprise and Industry (2012) *Notified bodies*, available at:

http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=13.

⁶⁶³ MHRA (2008) *Bulletin No. 4: conformity assessment procedures*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007492.pdf>.

⁶⁶⁴ MHRA (2011) *Bulletin no. 10: the classification rules*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007495.pdf>.

⁶⁶⁵ European Commission: Enterprise and Industry (2012) *Notified bodies*, available at:

http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=13.

⁶⁶⁶ Cohen D and Billingsley M (2011) Europeans are left to their own devices *British Medical Journal* **342:d2748**: 1-7, at page 2.

⁶⁶⁷ *Ibid*

⁶⁶⁸ Fraser AG, Daubert J-C, Van de Werf F *et al.* (2011) Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform: report of a policy conference of the European Society of Cardiology *European Heart Journal* **32(13)**: 1673-86, at page 1684.

⁶⁶⁹ European Commission (2012) *Medical devices: European Commission calls for immediate actions - tighten controls, increase surveillance, restore confidence*, available at: http://europa.eu/rapid/press-release_IP-12-119_en.htm.

⁶⁷⁰ Articles 28 to 40 of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁶⁷¹ European Commission (2012) *Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions: safe, effective and innovative medical devices and in vitro diagnostic medical devices for the benefit of patients, consumers and healthcare professionals* available at: http://ec.europa.eu/health/medical-devices/files/revision_docs/com_2012_540_revision_en.pdf, at paragraph 3.3.

European Databank on Medical Devices (Eudamed),⁶⁷² which captures information on medical devices for the benefit of regulators, is not currently accessible to the public. Transparency is also likely to be improved by forthcoming European regulatory changes. The European Commission's proposals include making key aspects of an expanded and newly configured Eudamed publically accessible and enhancing the range of data it contains, including that on clinical investigations.⁶⁷³ **We welcome these proposed changes and the extent to which they would enhance the transparency of the European system. However, we suggest to the European Commission that Eudamed should aspire to a similar degree of transparency as that which operates in the US Food and Drug Administration (US FDA), the body charged with regulating medical devices in the US.** The FDA operates a publically accessible database through which information on, for example, approved medical devices and incident reports, can be searched and accessed.

Effective and proportionate oversight: pre-market evidence requirements

- 7.29 The regulation of medical devices in Europe may be characterised as one that is relatively light touch in terms of pre-market scrutiny when compared, for example, with that operating in the US. Indeed, the European regime has been described as one that relies "...more on postmarketing surveillance than it does on premarket testing."⁶⁷⁴ Like the European system, the US FDA is also responsible for overseeing the safety of products and market access regimes and also adopts an approach whereby regulatory requirements become increasingly stringent in proportion to the level of risk. However, in contrast, the FDA operates a highly centralised system, which brings both benefits and challenges. The US system has advantages in terms of transparency of the evidence on which decisions are based.⁶⁷⁵ A register is maintained of all devices and this includes details of the intended use and pre- and post-market evaluations. Unlike the European system, before medical devices can be marketed under the US system, it is usually necessary to demonstrate that they are not only safe, but also *effective*.⁶⁷⁶
- 7.30 There are examples of medical devices being denied approval in the US, despite prior-approval in the EU.⁶⁷⁷ The apparently more stringent compliance standards in the US system that might be seen, *prima facie*, as offering better protection to prospective patients' interests than the European system. However, the US system is regarded as scoring less well in terms of alacrity. Delays and bureaucracy in the US system may be also seen as threatening patient safety insofar as they postpone access to therapies.⁶⁷⁸ These factors can mean that market costs are correspondingly high thus creating further barriers to access. However, accounts of such delays are mixed; one published literature review suggests that, in general, approval times under the US and European systems are comparable for all but high-risk devices.⁶⁷⁹ Nevertheless, anecdotal evidence suggests that manufacturers of some types of medical devices (for

⁶⁷² European Commission: Consumer Affairs (2011) *European databank on medical devices*, available at: <http://ec.europa.eu/consumers/sectors/medical-devices/market-surveillance-vigilance/eudamed/>.

⁶⁷³ Article 27 of the European Commission (2012) *Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012)*.

⁶⁷⁴ Cohen D and Billingsley M (2011) Europeans are left to their own devices *BMJ* **342**:d2748, at page 5.

⁶⁷⁵ House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK* available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/163/163.pdf>, at paragraph 37.

⁶⁷⁶ It is not necessary to demonstrate effectiveness under the US Humanitarian Device Exemption described further in Box 7.5.

⁶⁷⁷ Cohen D and Billingsley M (2011) Europeans are left to their own devices *BMJ* **342**:d2748, at page 4. For example, in 2007 Medtronic's device 'Chronicle', an implantable device designed to measure and record haemodynamic variables was approved for market authorisation in Europe but was refused by the FDA due to "lack of clinical effectiveness".

⁶⁷⁸ House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK* available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/163/163.pdf>, at paragraph 44.

⁶⁷⁹ Kramer DB, Xu S and Kesselheim AS (2012) How does medical device regulation perform in the United States and the European Union? A systematic review *PLoS Medicine* **9**(7): e1001276. Note, however, the authors acknowledge the potential limits of data in the literature, especially where studies have not been peer reviewed.

example, DBS devices) may increasingly seek to enter the market in Europe *first* for this reason.⁶⁸⁰

- 7.31 Devices assigned to Class II under the European Medical Devices Directive, such as those delivering TMS, will not necessarily require manufacturers to pursue their own clinical investigations. Approval can also be granted on the basis of literature alone, provided the literature pertains to an established device already on the market which the manufacturer can demonstrate is 'equivalent' to the new device in terms of "technology, critical performance, design, principles of operation, biological safety, population involved, conditions of use and clinical purpose".⁶⁸¹ This regulatory route is attractive to manufacturers because it entails less onerous evidence requirements, thus potentially offering a faster and less costly route to market and more time to exercise time-limited intellectual property rights (IPRs). As we noted in Chapter 3, a similar system operates in the US under the so-called '510(k)' or premarket notification route (see paragraph 3.57). The FDA has attracted criticism for permitting what has been viewed as inappropriate use of the 510(k) route (see Box 7.3). In the UK, the Chief Executive of the MHRA has expressed the view that it is "critical" to reduce the extent to which manufacturers are able to rely on substantial equivalence.⁶⁸² The criterion of equivalence may be seen as particularly ill-suited to the assessment of neurodevices as their benefits and risks depend crucially on the region of the brain that is stimulated, not solely on the performance of the device itself.⁶⁸³

Box 7.3: Market notification using predicate devices in the US

Under regulations operated by the FDA, low and moderate risk devices may receive a license to be marketed in the US by submitting a 'premarket notification' (also known as a 510(k)) without having to follow the most stringent pathway of 'premarket approval' (PMA). The 510(k) route requires manufacturers to demonstrate that: "the device to be marketed is at least as safe and effective, that is substantially equivalent, to a legally marketed device... that is not subject to PMA".⁶⁸⁴ As we observed in Chapter 3, the 510(k) 'premarket notification' pathway is attractive to neurotechnology companies wishing to reach the market as quickly as possible, and concerns have been raised about whether the 510(k) route strikes an appropriate balance between public safety and market access.

A device is substantially equivalent to a legally marketed device under 510(k) if it has both the same intended use and the same technological characteristics. There may also be substantial equivalence if the device has the same intended use but different technological characteristics compared with the legally marketed device, as long as the device does not raise new questions of safety and efficacy. In the case of *Medtronic, Inc. v. Lohr* (concerning a cardiac pacemaker cleared by the 510(k) process) a regulatory expert noted that: "A determination of 'substantial equivalence' by [the] FDA does not signify an agency endorsement of the safety and effectiveness of the device but is merely a clearance to market."⁶⁸⁵

In 2007, Neuronetics Inc. sought 510(k) clearance for its NeuroStar rTMS device to treat drug resistant depression on the basis that the TMS device was substantially equivalent to electroconvulsive therapy (ECT). In relation to the fact that the FDA had originally required not only that Neuronetics demonstrate that rTMS treatment was favourable and comparable to ECT, but that any reduction in effectiveness of the former was counter-balanced by a reduction in risk, the President of the National Research Center for Women & Families observed that: "It is not clear how that qualifies a product for the 510(k) process."⁶⁸⁶ In this instance, the FDA Advisory Panel found that the risk-benefit profile of the rTMS device was not

⁶⁸⁰ Medtronic (2012) *Grand designs – how to take your medical device innovation from patent to production*, available at: http://www.medtronic-eureka.com/innovation-articles/making-it-happen/patent_to_production.

⁶⁸¹ MHRA (2012) *Guidance for manufacturers on clinical investigations to be carried out in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf>, at paragraph 12.

⁶⁸² House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK* available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/163/163.pdf>, at paragraph 29.

⁶⁸³ Fins JJ, Mayberg HS, Nuttin B *et al.* (2011) Misuse of the FDA Humanitarian Device Exemption in deep brain stimulation for obsessive-compulsive disorder *Health Affairs* **30(2)**: 302-11, at page 304.

⁶⁸⁴ FDA (2010) *Premarket notification (510k)*, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm>. Note that a legally marketed device is "a device that was legally marketed prior to May 28, 1976... for which PMA is not required, or a device which has been reclassified from Class III to Class II or I, or a device which has been found SE through the 510(k) process".

⁶⁸⁵ Fins JJ, Mayberg HS, Nuttin B *et al.* (2011) Misuse of the FDA Humanitarian Device Exemption in deep brain stimulation for obsessive-compulsive disorder *Health Affairs* **30(2)**: 302-11, pp. 304-5.

⁶⁸⁶ National Research Center for Women & Families (2012) *Statement of Diana Zuckerman, PhD., president, National Research Center for Women & Families at the FDA Advisory Panel meeting, regarding the NeuroStar TMS system for major depression*, available at: <http://center4research.org/public-policy/testimony-briefings-statements/statement-of-diana-zuckerman-phd-president-national-research-center-for-women-families-at-the-fda-advisory-panel-meeting-regarding-the-neurostar-tms-system-for-major-depression/>.

comparable to that of ECT and declined to pass the device on the basis of substantial equivalence. It did, however, grant marketing approval to NeuroStar on the evidence of its own efficacy and safety.⁶⁸⁷ Subsequent transcranial brain stimulation devices may now follow the 510(k) pathway with less controversy, as more closely comparable devices are on the market. For example, in 2013 the Brainsway Deep rTMS System received clearance on grounds of substantial equivalence to be marketed in the US for the treatment of major depression.⁶⁸⁸

With criticisms of the 510(k) process in mind, the FDA asked the US Institute of Medicine (IOM) to evaluate this pathway. The IOM reported in July 2011, finding that the reliance on substantial equivalence could not ensure safety and efficacy, since the majority of devices used as comparators were never themselves evaluated on these criteria. The IOM recommended that, rather than trying to fix an inherently flawed system, the FDA should develop a new framework integrating premarket and post-market regulation.⁶⁸⁹ The IOM added, as an imperative, that the new process should not unduly delay progress or be burdensome.

- 7.32 The absence of the strictest pre-market evidence requirements for non-invasive neurodevices under European regulations might entail less bureaucracy, meaning that therapies may be developed, and thus reach patients, more quickly. However, it could also be criticised for placing the interests of the market above the safety of patients and the associated need for more robust evidence about how these new technologies function.⁶⁹⁰ In the context of devices that intervene in the brain – even if not through surgical means – patient safety and well-being are of primary concern. The virtue of responsibility requires that regulators and manufacturers reflect on the need for robust evidence before neurodevices are allowed to enter the market. Moreover, lighter pre-market regulatory controls are no guarantee that the market alone will deliver the range or quality of products required to meet therapeutic need. As we observe in Chapter 3, the availability of routes to market approval based on equivalence data, and the willingness of manufacturers to exploit these, could potentially inhibit the kinds of innovation that fill the most important gaps in the market for devices that address unmet patient needs, by encouraging more conservative approaches that reproduce similar products.⁶⁹¹ Furthermore, innovation in this field is often conducted by smaller businesses with limited resources. Where demand is limited to the few people with the most intractable and severe manifestations of serious conditions, there may be little financial incentive for companies to pursue (or for investors to support) commercial development of devices. We return to consider how the regulatory system serves the needs of patients for whom there are no suitable devices on the market in paragraphs 7.73 to 7.89.
- 7.33 We recognise that that permitting the provision of data pertaining to ‘equivalent’ products may in some circumstances represent a proportionate approach for some kinds of medical devices and that any efforts to narrow the availability of this route must be mindful of unintended consequences, such as discouraging innovation. Nevertheless, this might not always be a proportionate approach for devices that intervene in the brain. As a responsible regulatory approach, we therefore welcome the MHRA’s position that reliance on equivalence data should be minimised. We also welcome the introduction of more specific criteria for the demonstration of equivalence by the European Commission proposals for revised legislation on medical devices.⁶⁹² **In recognition of the special status of the brain and continued uncertainty regarding the consequences of intervening in it, we recommend to the MHRA that, where equivalence data are relied upon to demonstrate the regulatory conformity of a**

⁶⁸⁷ FDA (2008) *Repetitive transcranial magnetic stimulator for treatment of major depressive disorder*, available at: http://www.accessdata.fda.gov/cdrh_docs/pdf6/K061053.pdf.

⁶⁸⁸ FDA (2013) *Brainsway deep TMS system*, available at: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K122288.pdf.

⁶⁸⁹ The National Academies (29 July 2011) *FDA should invest in developing a new regulatory framework to replace flawed 510(k) medical device clearance process*, available at: <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=13150>.

⁶⁹⁰ Cohen D and Billingsley M (2011) Europeans are left to their own devices *British Medical Journal* **342:d2748**: 1-7.

⁶⁹¹ Royal Academy of Engineering and The Academy of Medical Sciences (2013) *Establishing high-level evidence for the safety and efficacy of medical devices and systems* available at: http://www.raeng.org.uk/Medical_devices_and_systems.pdf, at page 17.

⁶⁹² Annex XIII of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

neurodevice, the condition of equivalence must be satisfied in relation to its effect, not only its purpose, performance and safety. Furthermore, clear justification for approving neurodevices on the basis of equivalence data alone must always be provided and open to public scrutiny.

Obstacles to generating robust evidence

7.34 Effective regulation of devices and products that intervene in the brain should not only proceed on the basis of the best possible evidence of the safety and impacts of these interventions, it should also support the *generation* of this evidence. However, there is a well-acknowledged problem in the medical devices sector of incentivising or generating a rich body of evidence, in particular about the efficacy and long-term unintended impacts of devices.⁶⁹³ This is not only attributable to structural factors such as the relative lack of transparency and decentralisation of the decision-making of Notified Bodies, but also to the absence of any requirement under European regulations for manufacturers to provide evidence of the efficacy of their devices.

7.35 There are, therefore, few incentives for developers and manufacturers to pursue research to build a robust body of evidence about the clinical applications of neurodevices this end. This problem of is well summarised by the Chair of the Medical Technologies Advisory Committee of NICE:

“Medical technologies are often evaluated using limited evidence. This is partly because the regulation of medical devices worldwide does not require as much research data as does the regulation of drugs; partly because new technologies are often developed by small companies that have little experience in research; and partly because new technologies typically reach market early, before many research findings are available.”⁶⁹⁴

Providing a complementary perspective on the same issue, the MHRA has argued that, for a number of reasons, including the rapid and iterative nature of medical device innovation, the vast numbers of devices seeking approval and sporadic or wear-and-tear-related nature of faults, requirements for extensive pre-market clinical research would be ill-suited to regulation in this sector.⁶⁹⁵

7.36 This reveals the limitations of the regulatory system’s own capacity to incentivise and to capture the scientific knowledge of the effects of medical devices and to tackle the persistent problem of uncertainty. This then presents a significant challenge to responsible governance of clinical practices and healthcare provision where neurodevices are involved. A lack of evidence leaves clinicians under-equipped to provide the best advice to patients could hinder informed decision-making by patients and research participants. It also presents a challenge to NICE in drawing on the best and most complete evidence to guide health service purchasing decisions. The virtues of responsibility and inventiveness therefore then demand that a range of actors address the question of what is the most appropriate means of obtaining sufficiently relevant and robust evidence of the safety and benefits of these technologies and work towards this goal.

Limitations of randomised controlled trials

7.37 Randomised controlled trials (RCTs) are often characterised as the gold standard for generating evidence about the effectiveness and risks of health care interventions. Recent evidence submitted to a Congressional debate in the US on medical devices raised the question of why

⁶⁹³ Royal Academy of Engineering and The Academy of Medical Sciences (2013) *Establishing high-level evidence for the safety and efficacy of medical devices and systems* available at: http://www.raeng.org.uk/Medical_devices_and_systems.pdf.

⁶⁹⁴ Campbell B (2012) How to judge the value of innovation *British Medical Journal* **344**:e1457: 1-2, at page 1. See also: Campbell B (2011) NICE medical technology guidance: devices and diagnostics *Heart* **97**(21): 1794-5.

⁶⁹⁵ House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK* available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/163/163.pdf>, at paragraph 28.

clinical trials – which are so central to confirming patient safety in the pharmaceutical sector – are not also required in the medical devices field.⁶⁹⁶ The pharmaceutical sector has been at the vanguard of much regulatory reform, and it is the experience of the UK that the adoption of the European Directive relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use ('the Clinical Trials Directive')⁶⁹⁷ was the catalyst to conduct a wholesale review of research governance. This review ultimately led to the establishment of NRES in 2006 (which in turn became the core function of the Health Research Authority (HRA) established in December 2011). NRES provides central administration for the ethics review service in the UK and seeks to "facilitate and promote robust ethical research".⁶⁹⁸ Much of the framework and procedures of organisations such as the MHRA (and its equivalents in other countries), including the EMA at European level, have been shaped by the clinical trials paradigm.

- 7.38 The arguments are, however, finely balanced as to whether RCTs and the standards of evidence approximating to these are appropriate in the medical devices sector. It is certainly the case that medical devices are far more complex and potentially risky compared to several decades ago when the regulatory regimes were established. On the other hand, there are a number of methodological reasons why RCTs may *not* be a suitable approach in this sector.⁶⁹⁹ The numbers of patients with the most severe and intractable neurological and mental health disorders, for whom these technologies might offer most benefit, are very small, meaning that full-scale control trials might not be possible. Trials using robustly blinded control arms also may not be achievable for the kinds of neurodevices addressed by this report. This is not just because of the ethical challenges posed by sham surgery (as discussed at paragraphs 5.36 to 5.41), but also because even non-invasive stimulation may be detectable by participants. For example, TMS produces a contraction in the muscles of the scalp directly beneath the area of application.⁷⁰⁰ Furthermore, an RCT approach is hypothesis-driven and dependent on an existing evidence base against which to test the hypothesis and from which to inform participants and ethical oversight bodies of likely risks and benefits. Where there is little existing evidence of exactly how a device achieves therapeutic effects or of unintended effects, as is the case with some interventions using neurostimulation, it may not be possible to develop the same kind of research protocol that is needed to conduct a clinical trial.

Alternative sources of evidence

- 7.39 The results of randomised controlled trials do not have a monopoly on valuable evidence of the safety and efficacy. Cochrane Reviews and the development of NICE guidance, both respected evidence-based processes for assessing health care interventions, draw on a much wider range of sources, including patients' experiences.⁷⁰¹ The virtue of inventiveness suggests that an open approach to what constitutes sufficient and appropriate evidence of the safety and efficacy of neurodevices (and embracing incremental approaches to accruing this) would be of value in this sector, provided that mechanisms are in place to gather it and assure its quality. Observational

⁶⁹⁶ University of California, San Francisco (2011) *Testimony of Rita F. Redberg*, available at: http://democrats.energycommerce.house.gov/sites/default/files/image_uploads/RitaRedberg.pdf.

⁶⁹⁷ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. The Directive was implemented in the UK by the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended by SIs 2006/1928, 2006/2984, and 2008/941. There are now proposals for reform: Proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (17 July 2012).

⁶⁹⁸ NRES (2013) *How we work*, available at: <http://www.nres.nhs.uk/about-the-national-research-ethics-service/about-nres/how-we-work/>.

⁶⁹⁹ Royal Academy of Engineering and The Academy of Medical Sciences (2013) *Establishing high-level evidence for the safety and efficacy of medical devices and systems* available at: http://www.raeng.org.uk/Medical_devices_and_systems.pdf.

⁷⁰⁰ Lisanby SH, Kinnunen LH and Crupain MJ (2002) Applications of TMS to therapy in psychiatry *Journal of Clinical Neurophysiology* **19**(4): 344-60, at page 345.

⁷⁰¹ NICE (2012) *How we work*, available at: http://www.nice.org.uk/aboutnice/howwework/how_we_work.jsp.

studies and small scale pilots as well as modelling may also provide potentially useful sources of evidence.⁷⁰² The registers of clinical experience that we recommend at paragraph 5.63 would provide a valuable means of capturing precisely these types of evidence.

7.40 The fragmented nature of top-down regulatory mechanisms in Europe has led to attempts at self-governance amongst practitioners working with TMS and rTMS. One research group has published information on the role of international consensus guidelines in this area, updating previous measures in light of growing evidence from the thousands of healthy volunteers and patients with a range of neurological and psychiatric conditions who have undergone TMS; this has revealed not only better understandings of risk, but also a very low occurrence of seizures (the most serious TMS-related adverse reaction).⁷⁰³ The resultant review of international guidelines encompasses issues of risk and safety and proposes limits for TMS parameters in various clinical circumstances.⁷⁰⁴ A consortium of French scientific societies commissioned a comprehensive literature review of the evidence of safety and efficacy of rTMS,⁷⁰⁵ culminating in a consensus statement from the review group in light of the evidence gathered, including assessments that reported side effects are very low. Many of the recommendations mirror the conclusions of the aforementioned review, but go further by representing the first attempt to establish the therapeutic indications for rTMS.

7.41 These examples of professional initiatives to improve the evidence base of understanding of new technologies are to be lauded. They exemplify the virtues of inventiveness and responsibility in that the science community, on its own initiative, has sought to engage with some of the intractable challenges of neurotechnologies – specifically uncertainty, and the absence of sound evidence. The value of coordinated grassroots efforts to improve the availability of robust scientific evidence of efficacy and longer-term risks of neurodevices is unquestionable. They may not, however, be sufficient on their own, not least because there are no mechanisms to oversee their use by clinicians, and far less to *require* this. This is an example of where it matters very much whether clinical uses of TMS are seen as experimental treatment – and so regulated by clinical standards – or as a form of research, which is more likely to involve independent approval and oversight by ethics bodies. These limitations notwithstanding, other opportunities for generating and sharing robust data could be better exploited. For example, the establishment of the International Medical Devices Regulators Forum (IMDRF) in February 2011, continuing the work of the Global Harmonization Task Force on Medical Devices (GHTF), not only signals a commitment to increased international harmonisation, but also provides an ideal platform for further integration of the regulator and practitioner communities via open stakeholder forums.⁷⁰⁶

Robust evidence through effective information governance

7.42 The diverse means of gathering and making accessible greater quantities of robust data about the efficacy and safety of neurodevices, as described in the preceding paragraphs, are potentially invaluable where the regulatory system does not itself drive the generation of this evidence. However, the risk is that their findings are isolated in diffuse locations, making outputs inaccessible to a wide range of interested parties. A further risk is that diverse methods of recording data preclude their comparability, verifiability, or linkage.

7.43 Existing mechanisms for collecting information about the benefits and risks of neurodevices and their therapeutic applications could be more effectively exploited if an overarching approach to

⁷⁰² Royal Academy of Engineering and The Academy of Medical Sciences (2013) *Establishing high-level evidence for the safety and efficacy of medical devices and systems* available at: http://www.raeng.org.uk/Medical_devices_and_systems.pdf, pp21-2.

⁷⁰³ Rossi S, Hallett M, Rossini PM and Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research *Clinical Neurophysiology* **120**(12): 2008-39.

⁷⁰⁴ *Ibid*, at page 2028.

⁷⁰⁵ Le Faucheur J, André-Obadia N, Poulet E *et al.* (2011) [French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): safety and therapeutic indications] *Neurophysiologie Clinique* **41**(5-6): 221-95.

⁷⁰⁶ IMDRF (2013) *International medical device regulators forum*, available at: <http://www.imdrf.org/>.

information governance were to be adopted in order to facilitate their transparency and linkage. The Royal Society's *Science as an open enterprise* report makes a number of recommendations to meet the public interest in promoting science as an open enterprise.⁷⁰⁷ These include the recommendations that common standards for sharing information should be adopted to make it widely usable and that science journals should require the accessibility of the underlying research data as a condition of publication of an article. In these ways, the self-correcting precepts of scientific endeavour can best operate to allow verifiability of data. We endorse this commitment to openness. There are a number of UK projects that aim to maximise the linkage and utility of NHS patient data, while keeping appropriate scrutiny undiluted. These include the Clinical Practice Research Datalink, the Scottish Informatics Programme and the recently-launched e-Health Informatics Research Centres and Network.⁷⁰⁸ The remits of such initiatives are clearly much wider than neurological health. We suggest that similar efforts to achieve a 'meta-network' between information repositories holding data on the risks and benefits of neurodevices would support the regulatory system by ensuring that oversight is proportionate to the current best evidence, facilitate research and enhance innovation by highlighting areas of unmet need and, ultimately and most importantly, protect patients interests in receiving safe and effective treatments. This network would not itself be a data repository but would extend the reach and value of the data held in any existing information holdings in order to strengthen capability and competitiveness in the development of neurodevices.

- 7.44 Efforts at achieving open approaches to health information governance are necessarily multiplatform, interdisciplinary, and international; they rely on the parallel and collaborative efforts of a number of stakeholders, including funders, regulators, manufacturers, researchers, health care providers, and patients' groups. As the preceding paragraphs suggest, the information sources captured by such a collaboration must extend much wider than data from clinical trials, to encompass evidence from small-scale research studies and experimental approaches to treatment, patient-reported outcomes and post-market surveillance data. The aspiration would be for a meta-network to facilitate linkage between the kinds of clinical experience registries discussed in Chapter 5, but also to extend far beyond these kinds of data to capture those generated in manufacturing, academic, and regulatory contexts including, for example, the newly-purposed centralised European regulatory database for medical devices, Eudamed. In an effort to capture the widest possible body of evidence, international linkage would be an asset. The linking and mining of data in such circumstances raises further questions about how to deliver public benefit through research, while ensuring appropriate protection of privacy in respect of personal data. The Nuffield Council on Bioethics has recently convened a separate Working Party to examine ethical issues in sharing and linking biological data and health records.⁷⁰⁹

Invasive neurodevices

- 7.45 Invasive neurodevices, which in the context of this report include those used to deliver DBS and invasive BCIs, are examples of technologies that involve surgical invasion of the patient's bodily or cerebral integrity to some degree. As we note in Chapter 2 and in our ethical framework, the physical risks of invasive neurodevices extend beyond the surgery itself, to those relating to the long-term implantation of electrodes in the brain, and to the possible unintended psychological and behavioural effects of invasive neurostimulation. As such, these invasive neurotechnologies give rise to inherently more acute concerns about the safety of their use and the need to

⁷⁰⁷ The Royal Society (2012) *Science as an open enterprise*, available at: http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/projects/sape/2012-06-20-SAOE.pdf.

⁷⁰⁸ Clinical Practice Research Datalink (2013) *Welcome to the clinical practice research datalink*, available at: <http://www.cprd.com/intro.asp>; MRC (2013) *Background to the Health Informatics Research Centres* available at: <http://www.mrc.ac.uk/consumption/groups/public/documents/content/MRC009053.pdf>; Scottish Informatics Programme (2012) *Scottish informatics programme*, available at: <http://www.scot-ship.ac.uk/>.

⁷⁰⁹ See: Nuffield Council on Bioethics (2013) *The collection, linking, use and exploitation of biological and health data: ethical issues*, available at: <http://nuffieldbioethics.org/biological-and-health-data>.

exercise responsibility and humility in not intervening in the brain unnecessarily. The concerns we have raised about the effective and proportionate regulation of non-invasive neurodevices and the availability of robust evidence in the previous section therefore apply *a fortiori* to invasive devices.

- 7.46 Under the regulatory regime operating in the UK and the rest of Europe, the invasive neurodevices we discuss in this report are regulated under the Active Implantable Medical Devices Directive (AIMD).⁷¹⁰ According to the AIMD, medical devices are automatically considered to be ‘high risk’. As such, the pre-market regulatory oversight of *invasive* medical devices it is more demanding than that which applies to non-invasive devices, including the pathways for assessing conformity with the legislation. This reflects greater caution commensurate with the greater risks involved.
- 7.47 If the proposals for revised European legislation are implemented without significant deviation from their current form, then it is likely that oversight of higher risk and implantable devices will be further strengthened, for example by requiring that these devices undergo additional scrutiny for conformity by a new centralised European expert committee and that the manufacturers publish a summary of safety and performance evaluations (see Box 7.1 above). **In light of our recommendation at paragraph 7.33 we welcome the European Commission’s legislative proposals which state that, for implantable and high risk devices, demonstration of equivalence with existing devices will “generally not be considered as sufficient justification” for relying on existing clinical data alone.**⁷¹¹ This means that manufacturers who seek to market invasive neurodevices will ‘generally’ have to conduct clinical evaluations of the device for its intended purpose.
- 7.48 However, as we have already observed, whether a device is subject to regulatory scrutiny at all depends chiefly on whether there is an intention to market the device. This could be seen as giving rise to some uneven distribution of regulatory oversight which is a particular concern for invasive devices, which is perhaps most notable in the context of the pursuit of clinical investigations of these devices, as we explore in the following paragraphs.

Effective and proportionate oversight: clinical investigations and experimental treatment

- 7.49 Where a medical device does not have a CE-mark, the MHRA must be notified in advance of clinical investigations of its safety and performance, and the provisions of the relevant Directive will be engaged. The same is true when a clinician modifies a CE-marked device or uses it for a new ‘off-label’ purpose if they anticipate a commercial application of this. In effect, each of these provisions treats such investigations as potential steps on a device’s route to market.⁷¹² The focus of much of the regulatory regime upon the marketability of devices can lead to unlooked-for consequences, as illustrated by an example from a factfinding meeting with clinicians conducted by the Working Party as part of the preparation of this report. In this example, a clinician wanted to hold a trial investigating the use of DBS for the treatment of OCD.⁷¹³ The clinician reached an agreement with a device company such that they would donate the (expensive) equipment for this study. The company agreed to have no involvement in the study (for example, regarding protocol design) because they did not want to become involved with associated regulatory requirements. The clinician reasoned that the trial did not have to be notified to the MHRA, given that there was no company involvement, and that the trial’s aim was solely research-focused. The MHRA disagreed, however, and argued that the company was

⁷¹⁰ Devices for DBS fall under the Active Implantable Medical Devices Directive (AIMD). If a device falls within the terms of the AIMD Directive then, technically, each component belonging to the system is also covered by the AIMD and must comply with its requirement. See: Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States relating to active implantable medical devices.

⁷¹¹ Annex XIII of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁷¹² MHRA (2012) *Guidance for manufacturers on clinical investigations to be carried out in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf>, at paragraphs 14-27.

⁷¹³ Ludvic Zrinzo, contributing to a Factfinding meeting with clinicians, 16 February 2012.

effectively a sponsor as they might use the information in the future to obtain a CE-mark. Thus, if the company donated the equipment, the MHRA would have to be notified and the appropriate regulations engaged. As a result, the industry rescinded its interest and it was necessary for the clinician to raise significant funds for the equipment himself. The irony here is that regulatory attention was attracted not because of a concern about securing patient safety, but because the investigation was viewed by the regulator as a possible route to market.

- 7.50 This example may be contrasted with the situation that applies where there is, unambiguously, *no* intention to market a device on a commercial basis. For example, when a CE-marked device is used off-label or a device is manufactured ‘in-house’ by a health care establishment with the intention to use it only in investigations involving patients in the care of that establishment, the MHRA need not be notified.⁷¹⁴ The realm where such investigations are most likely to happen is that concerning *ad hoc* experimental treatment using these devices, in the absence of any other available therapeutic options. This raises the question of whether there is a regulatory lacuna, one that potentially means that interventions using the least developed devices with the most vulnerable patients occur outside the oversight of the regulator. If the device is used as part of a formal research study then the intervention of a REC might fill this gap. However, if it is used as an investigative treatment, it is likely to be governed by professional medical ethics alone.
- 7.51 Given that patient safety is a primary concern, particularly in the realm of invasive neurodevices, we might question whether the orientation of the current regulatory system is appropriate. The focus upon the prospective marketability of devices fails to capture some of the most pressing concerns arising in the use of these technologies in the early stages of their development trajectories. In light of this, we welcome the proposal of the European Commission to remove the exemption of medical devices manufactured by health care establishments for in-house uses from the requirement to comply with some obligations under the device regulation.⁷¹⁵ It is, however, regrettable that these devices would still be exempt from the requirement to record clinical data or adverse events relating to these on the central European database.⁷¹⁶ The patchwork nature of the regulatory coverage provided by the medical device Directives suggests that there is a need for more clarity on the ethical issues at stake in the investigatory stages of invasive neurodevices and clearer routes of responsibility, accountability, and transparency.

Continuous reflexive evaluation and post-market vigilance

- 7.52 As we have already observed, the European regulatory system may be praised for its relative speed but this might be a product of its relatively light-touch approach to pre-market approval and its non-centralised operation. These aspects, as we have suggested, can be seen as being to the detriment of transparency and of ensuring that devices are approved for market on the basis of the most suitable evidence. Pre-market oversight is more rigorous for invasive devices. However, the risks and negative impacts of patients’ quality of life resulting from equipment failures are also potentially more serious where invasive devices are concerned (see Box 7.4 below). These factors mean that the imperative for effective and enforceable post-market vigilance arrangements is all the stronger. In recognition of the particular challenges to practically and reliably predicting medium and longer-term equipment failures affecting invasive neurostimulation devices through pre-market clinical investigations, and the seriousness of associated risks, the MHRA has produced guidance to manufacturers specifically in relation to

⁷¹⁴ MHRA (2012) *Guidance for manufacturers on clinical investigations to be carried out in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf>, at paragraph 26.

⁷¹⁵ Article 4 of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁷¹⁶ *Ibid.*

their responsibilities for post-market vigilance and adverse-incident reporting for this category of devices.⁷¹⁷

Box 7.4: A personal experience of DBS equipment failures

The following example illustrates the kinds of equipment failures that can affect components of devices used for DBS and the serious consequences these will have for the individual patient. It demonstrates why it is so important that effective use is made of regulatory mechanisms to record, disseminate information about, and respond to such incidents.

“The operation I had in July last year was, in my opinion, a success. But at the end of December/beginning of January (2010-1), I suddenly felt that something wasn’t right. It transpired that one of the two cables running from the battery [in my chest] had severed at the connection with the battery. The doctors didn’t know that yet, they just knew that the current wasn’t reaching the stimulators. The old pain was coming back so at the end of March I went in and had one of the cables replaced. They also tested the other cable and it was fine. But about a week later the other cable severed at the other end. I went back into hospital in July so that both cables could be replaced. By this time the manufacturer had replaced the type of cable with a spiral cord to give it more flexibility... At the end of September (2011) I was “recharging” myself and I noticed that the battery was charging itself initially and then it stopped charging. I reported this immediately and they tested it with two other chargers but it wasn’t working. They wanted to operate straight away but I had too much work on at the office. In the interim I would turn it on when I needed to be in public and turn it off when I didn’t to preserve the battery life. When they replaced the battery they found that the transistor had failed. So that was three bits of hardware that had broken... Of course, we all know with hardware that things do go wrong. But it seems rather hard that things should have gone wrong with me and that I underwent three general anaesthetics in less than six months.”

Factfinding meeting with Richard Smith, DBS patient, 20th November 2012.

- 7.53 Device manufacturers who place medical devices on the market in Europe are legally bound to report adverse incidents (meeting certain criteria) to the national competent authority of the country in which the incident occurred.⁷¹⁸ Manufacturers are also expected to establish systems to monitor trends in expected and foreseeable adverse incidents and to report these trends. Incident reporting by clinicians is not mandatory. National competent authorities can take action at any time and are expected to nominate a single coordinating competent authority in cases of transnational incidents. No centralised body exists, as yet, to assist in the execution of these guidelines. While manufacturers are required to report adverse events to the central European database directly, there is little coordinated action or analysis.⁷¹⁹ Only a few EU Member States provide the majority of reports and safety notices.⁷²⁰ Moreover, there is little evidence of coordinated action by Notified Bodies in policing the system.
- 7.54 The system’s decentralised nature may be seen as preventing regulators, clinicians, and patients from gaining the full picture where the safety of invasive medical devices is concerned. However, a number of changes are included in the proposed revisions to the European legislation. If adopted, these will include obligations on manufacturers to report serious adverse incidents directly to a centralised European database and national regulators similarly to record incidents reported by clinicians centrally.⁷²¹ We welcome EC proposals to centralise the collection of this important information. It is to be hoped that that this will be amongst the information held on Eudamed that is made publically available so that this information can form part of a valuable web of networked evidence that improves understanding of the risks of neurodevices and permits regulatory oversight to be proportionate to the imperative to protect the safety of patients using invasive neurodevices.

⁷¹⁷ Reportable incidents are deterioration or malfunctions that have led or might lead to a serious deterioration in health and include tissue damage and electrical failures in pulse generation; MHRA (2009) *Guidance on the vigilance system for CE-marked medical devices: neurostimulators*, available at: <http://www.mhra.gov.uk/home/groups/dts-bs/documents/publication/con065418.pdf>.

⁷¹⁸ MHRA (2008) *Directives Bulletin no. 3 guidance on the operation of the EU vigilance system in the UK* available at: <http://www.mhra.gov.uk/home/groups/dts-bi/documents/publication/con2033936.pdf>, at page 6.

⁷¹⁹ Kramer DB, Xu S and Kesselheim AS (2012) Regulation of medical devices in the US and European Union *New England Journal of Medicine* **366**(9): 848-55, at page 849.

⁷²⁰ Villarraga ML, Guerin HL and Lam T (2007) Medical device recalls from 2004-2006: a focus on class I recalls *Food & Drug Law Journal* **62**: 581-92.

⁷²¹ Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

7.55 Lessons might be learned from the pharmaceutical sector, where considerable improvements have been secured in the harmonisation of approaches throughout Europe, including the capture of data about adverse events and schemes to deal with gaps in knowledge relating to the effects of newer medicines on populations. One example of this is the MHRA's *Black Triangle Scheme*, according to which newer medicines are denoted by an inverted black triangle symbol.⁷²² Through the use of such schemes, the MHRA and the Commission on Human Medicines (CHM) aim to highlight a medicine's status of being newly-licensed and to prompt reporting of suspected adverse drug reactions (ADRs) by patients and health care professionals. Reporting ADRs to medicines occurs through the *Yellow Card Scheme*, whereby it is a legal requirement for industry to relay all reports to the MHRA for robust assessment.⁷²³ While the MHRA does operate a similar system for clinicians, health and social care workers, and patients to report adverse incidents involving medical devices to the regulator, this is not underpinned by a mechanism for alerting users to particular reasons for vigilance, such as the novelty of a device. **We endorse the House of Commons Science and Technology Committee's recommendation that a *Black Triangle Scheme*, similar to that used in the pharmaceutical sector, be introduced (especially when devices have received marketing approval on the basis of equivalence data) to signal to patients and professionals when an invasive medical devices is newly approved and to encourage incident reporting.**⁷²⁴ **We further recommend to the Medicines and Healthcare products Regulatory Agency that the reporting of adverse incidents involving *all* neurodevices by professionals should be mandatory. Information regarding adverse incidents and incident trend reports should be made publically available.**

The complementary role of the National Institute for Health and Care Excellence (NICE)

7.56 The proposed changes (see Box 7.1) to the European legislation on medical devices system – if adopted – would be an undoubted improvement to the current system, but a number of matters that we have highlighted as concerns here will remain unchanged. While the proposals to make the Eudamed database publically accessible, and to require summaries of safety and performance evidence for high-risk devices to be published, are something of an advance, this falls far short of providing an extensive evidence base across technologies (invasive, non-invasive, low or high risk), such that the fundamental ethical interests in this area can be properly advanced. As we have suggested at paragraphs 7.34 to 7.36, the regulatory system alone is not currently set up to achieve this end.

7.57 In the UK, NICE adds a valuable complementary layer of governance that helps to fill some of the gaps relating to regulatory silence on the efficacy of medical devices and in advancing the body of clinical evidence more widely. As we note in Chapter 5, NICE's Interventional Procedures Programme (IPP) plays an important role in presenting the current state of knowledge regarding how well new procedures work (in the context of known risks).⁷²⁵ 'Interventional procedures' include procedures involving both non-invasive and invasive neurodevices, provided these devices have marketing approval. NICE is in a position to address the current best evidence of how well an intervention works (in a way that the MHRA is not charged with doing), and to provide valuable practical guidance to health care providers on matters such as the provision of additional oversight and informed consent procedures. The NICE IPP also fosters inventiveness by being an important means of introducing innovative procedures into the health service.

⁷²² MHRA (2013) *Black Triangle Scheme – new medicines and vaccines subject to EU-wide additional monitoring*, available at: <http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/BlackTriangleproducts/index.htm>.

⁷²³ MHRA (2013) *Yellow Card: helping to make medicines safer*, available at: <https://yellowcard.mhra.gov.uk/>.

⁷²⁴ The Committee uses different terminology from this report and talks not of "invasive devices" in this context but of "medical implants": House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK* available at: <http://www.publications.parliament.uk/pa/cm201213/cmsselect/cmsstech/163/163.pdf>, at paragraph 67.

⁷²⁵ NICE (2013) *Interventional procedures*, available at: <http://www.nice.org.uk/guidance/ip/index.jsp>.

- 7.58 NICE’s Medical Technologies Evaluation and Technology Appraisals Programmes could also play a useful role in addressing uncertainty about the comparative value of neurodevices in health care – though none of the novel neurotechnologies we discuss in this report has yet been assessed under these programmes. These programmes provide evidence-based assessments to guide (or make recommendations to) the NHS in its commissioning of efficient and cost-effective technologies. They therefore help to fill gaps in terms of enhancing the understanding of the ‘value’ (in terms cost-effectiveness) of particular technologies.⁷²⁶
- 7.59 As part of these core functions, NICE also plays an important role in building the evidence base regarding the benefits and risks of new technologies and enhancing patients’, practitioners’ and regulators’ understandings of these invasive techniques. The advisory committee responsible for overseeing the development of the *Medical technologies guidance* operates a concept of ‘plausible promise’.⁷²⁷ For promising medical technologies, NICE is able to commission and encourage third parties to seek out an evidence base for interventions that seem worthy of further clinical investigations. Independent assessors are used to oversee the integrity of the findings and all recommendation that feature in its guidance are made available to researchers to ensure that uncertainties in important topics considered by NICE influence the research agenda.⁷²⁸ As we note at paragraph 5.23 above, NICE takes an inclusive view of what counts as valuable evidence: information on negative outcomes or inefficacy and the experiences of both experts and patients are included as important parts of the full picture. It is hoped that the recommendations we make in this report in respect of the development of clinical experience registers, and networks for enhanced information governance and data linkage with respect to medical devices, will further support NICE’s work in delivering valuable guidance.

Neural stem cell therapies

- 7.60 In a discussion of regulatory systems based on proportionate risk assessments, the area of neural stem cell therapies represents that in which the health risks are potentially the highest, and the regulatory intervention likely to be at its most intense. This is also the field where regulators have most experience in that, although the technologies here are novel in *themselves*, the regulatory pathways are *not* – following, in large part, the well-established routes for medicinal products. The overarching questions that arise here from our ethical framework are whether the system strikes the right balance between concerns for safety and delivering an effective and proportionate system (notwithstanding the potentially very serious risks involved), and whether the system can effectively support inventiveness so that both investors and patients can benefit from safe innovations in light of considerations of high-costs and small markets.
- 7.61 Two different regulatory pathways may be distinguished in the development of neural stem cell therapies. These may be characterised broadly as that followed by a standardised product developed for widespread market use and that followed by the development of a product on a patient-by-patient basis. Where a patient is treated with stem cells derived from his or her own body (in what is known as autologous transplantation) these cells could, under certain circumstances, be classified as a medicine and subject to regulatory oversight by the MHRA, rather than simply as human tissue (the use of which would be governed under the Human Tissue Act 2004). Autologous cells will only fall outside the sphere of regulation as an ATMP if they have *not* been subject to extensive manipulation. Manipulation is defined widely and includes, for example, cell expansion. However, if manipulated cells are not intended for wider market availability, but only for the treatment of an individual patient, the MHRA will oversee their manufacture under the ‘hospital exemption’ or ‘Specials’ arrangements (described further

⁷²⁶ ‘Value’ in this context is construed by NICE in one of two possible ways: either that it has been demonstrated by sufficient evidence that a more expensive intervention works better than those already available, or the evidence indicates that it works just as well and releases resources back into the public health system.

⁷²⁷ Campbell B (2012) How to judge the value of innovation *British Medical Journal* **344**:e1457: 1-2.

⁷²⁸ NICE (2012) *Research and development*, available at:
<http://www.nice.org.uk/guidance/GuidanceResearchRecommendations.jsp>.

at paragraphs 7.77 to 7.82 below), which effectively free manufacturers from the central authorisation procedure and the need for clinical trials described in the following section.

Steps of development for market use

- 7.62 This section, expanding on the introduction given at the start of this chapter, outlines the regulatory pathway that must be followed by stem cell therapies seeking market approval. No medicines based on stem cell development have yet received authorisation for distribution on the market in the EU. At a European level, matters are overseen by the EMA. In the UK, the primary role of oversight falls to the MHRA. Both agencies have advised and supported companies in development for many years.
- 7.63 In the UK development for market use is currently exemplified by an ongoing clinical trial of a neural stem cell therapy for disabled stroke patients (see paragraph 2.81).⁷²⁹ This trial is being funded by ReNeuron as part of the Pilot Investigation of Stem Cells in Stroke (PISCES) study and is being conducted at the Institute of Neurological Sciences, Glasgow.⁷³⁰
- 7.64 The Department of Health, the MHRA, the GTAC, and other regulatory bodies have developed the *UK Stem Cell Tool Kit*.⁷³¹ This is a reference tool to indicate the regulatory landscape to those involved with stem cell clinical research and manufacture, and who are aiming to develop clinical applications. The kit is applicable to stem cell therapy in general, not only neural cells. The step-by-step account in Box 7.5 below illustrates the complex and incremental development of the regulatory regime. Its complexity helps to explain some of the features of the innovation pathways of these products that we discussed in Chapter 3, including uncertainties about the duration and outcome of regulatory processes and the very high costs involved (which are many times higher than those most medical device manufacturers would face). It also allows us to understand a key difference between the regulatory requirements faced by a new stem cell therapy and neurodevices – as with medicines, but not medical devices, stem cell therapies *do* have to demonstrate efficacy before market approval. This means that it must be shown that the new intervention does no more harm than – and is at least as effective as – treatments that are already available.

Box 7.5: Regulatory pathway for the development of stem cell therapies in the UK

Donation, procurement and testing of stem cells⁷³²

- The donation, procurement and testing of stem cells that are to be used in a medicinal product is covered by the Tissues and Cells Directive 2004/23/EC, for which the Human Tissue Authority (HTA) is the competent authority in the UK.⁷³³ The research establishment involved requires a licence from the HTA to be able to carry out these activities, covering donation, procurement, testing, and processing activities up until the point where a Master Cell Bank has been established, and there is a reasonable expectation of clinical utility in a medicinal product.
- There are also separate requirements relating to the *type* of stem cell. For example, if human embryonic stem cells (hESC) are to be used to derive the stem cell line, a licence must be sought from the Human Fertilisation and Embryology Authority (HFEA). In the case of genetically modified stem cells, the Health and Safety Executive (HSE) must be notified.

⁷²⁹ Webster A, Haddad C and Waldby C (2011) Experimental heterogeneity and standardisation: stem cell products and the clinical trial process *BioSocieties* **6(4)**: 401-19, at page 402.

⁷³⁰ ReNeuron (2013) *Clinical trials in disabled stroke patients*, available at: <http://www.reneuron.com/the-piscs-clinical-trial-in-disabled-stroke-patients>.

⁷³¹ Department of Health (2013) *UK stem cell tool kit*, available at: <http://www.sc-toolkit.ac.uk/home.cfm>.

⁷³² MHRA (2013) *How we regulate advanced therapy medicinal products*, available at: <http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/Aboutadvancedtherapymedicinalproducts/index.htm>.

⁷³³ HTA (2007) *EU tissue and cells directives*, available at: <http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/legislation/eutissueandcellsdirectives.cfm>.

Animal and clinical studies⁷³⁴

- No neural stem cell trial would pass directly to humans. Animal models will be used first. Before the stem cells can be tested in animals to establish their safety and efficacy, there must be dialogue with the MHRA on which animal models will be approved. The research must also be approved by the Home Office Animal Licensing Inspectorate. The stem cells must be expanded in culture, and the facilities in which this occurs must be approved by MHRA Good Manufacturing Practice (GMP) Inspectors. For example, the PISCES neural stem cell trial now underway in Glasgow⁷³⁵ is based on pre-clinical data acquired from the rat MCAo (middle cerebral artery occlusion) model, the most widely accepted animal model of ischaemic stroke.⁷³⁶
- Before a clinical trial can begin, approval by the MHRA Clinical Trials Unit is necessary as the trial will involve somatic cell transfer. Further, as the trial involves a cell therapy derived from a stem cell line,⁷³⁷ GTAC must also give a 'favourable opinion' (see paragraph for further discussion of the changing role of GTAC). The NHS Research and Development Office (NHS R&D) must also give its approval. In case of GM cells stem cell, the HSE must be notified of the trial.

Clinical trials in the context of 'novel' technologies

- With regards to clinical trials of novel technologies, the MHRA's Expert Advisory Group (EAG) must be engaged before starting the trial. EAG's remit includes the duty to advise the Commission on Human Medicines on 'first time in man' (FTIM) studies with new compounds acting (directly or indirectly) via the immune system with a novel target or a novel mechanism of action or having a secondary potential effect on the immune system via a mechanism of action which currently is not well characterised".⁷³⁸ All clinical trials involving humans are regulated in the UK under the Clinical Trials Regulations.

Seeking market approval at European level

- As outlined at paragraph 7.11 above, under the ATMP Regulation, a centralised authorisation procedure applies to those ATMPs that are intended to be placed on the European Community market. The MHRA is the 'supervisory authority' for UK manufacturers or importers of those ATMPs that are centrally authorised.

Effective and proportionate oversight

7.65 There are very few regulatory issues reported in the literature regarding development of neural stem cell therapies for market use. This is unsurprising given that there are, to date, very few instances of clinical trials of neural stem cell therapies. The UK-based PISCES study is the world's first fully regulated clinical trial of a neural stem cell therapy for disabled stroke patients.

7.66 As the level of detail given in Box 7.5 illustrates, the regulatory process for developing neurotechnologies involving biological material and establishing a clinical trial is complex, with many agencies and regulatory bodies playing a role. The path from development to therapy is a long and potentially arduous one, which may raise concerns about regulatory burden in terms of delay and regulatory overlap between the functions of many bodies with responsibility for oversight of this process. Complexities in the regulatory pathways governing neural stem cell therapies matter from an *ethical* perspective because delays in undertaking trials mean delays to subsequent stages of clinical research, manufacture and ultimately to therapeutic products reaching the market. Moreover, neural stem cell therapies may offer perhaps the *only* possible option for treating the serious and debilitating effects of brain damage or disease. The

⁷³⁴ UK Stem Cell Tool Kit: Scenarios (2013) *Therapeutic use of dopaminergic neurons purified from chemically-differentiated human embryonic stem cells*, available at: <http://www.sc-toolkit.ac.uk/scenarios/acelltherapyderivedfromahumanembryonicstemcellline.cfm>.

⁷³⁵ ReNeuron (2013) *Clinical trials in disabled stroke patients*, available at: <http://www.reneuron.com/the-piscs-clinical-trial-in-disabled-stroke-patients>.

⁷³⁶ Pollock K, Stroemer P, Patel S *et al.* (2006) A conditionally immortal clonal stem cell line from human cortical neuroepithelium for the treatment of ischemic stroke *Experimental Neurology* **199(1)**: 143-55; Stevanato L, Corteling RL, Stroemer P *et al.* (2009) c-MycERTAM transgene silencing in a genetically modified human neural stem cell line implanted into MCAo rodent brain *BMC Neuroscience* **10(1)**: 86.

⁷³⁷ "A stem cell line is a permanently established culture of unspecialised cells derived from a single parental cell, or group of parental cells, that can (1) proliferate *in vitro* for a prolonged period when given appropriate nutrition and space and (2) be made to differentiate in culture into more specialised types of cells when given appropriate chemical or molecular cues." See: UK Stem Cell Tool Kit: Glossary (2013) *Serious adverse event/serious adverse reaction*, available at: http://www.sc-toolkit.ac.uk/glossary.cfm?cit_id=0&startLetter=S.

⁷³⁸ MHRA (2013) *Clinical trials expert advisory group of the commission on human medicines*, available at: <http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines/ExpertAdvisoryGroups/ClinicalTrials/index.htm>.

regulatory principles of proportionality, subsidiarity and regulatory orientation are particularly engaged here, given the dense regulatory framework, multiple regulators, and multi-level actions that must be negotiated. Many of these concerns are not unique to *neural* stem cells, but are shared by the wider field of regenerative medicine.

- 7.67 Lengthy and multi-layered regulatory pathways can contribute to economic pressures upon those conducting trials and attempting to bring products to market. Delays in undertaking trials and the preparation of multiple different dossiers of evidence to meet the requirements of different oversight bodies are themselves resource-intensive. The risks associated with this will vary between larger companies and smaller biotech companies. They might, as in the case of Geron (see paragraph 3.44), result in the trials being abandoned and the company deciding to direct its research efforts elsewhere. This not only impacts upon the wider public interest in developing effective therapies, but also potentially causes significant disruption to any existing trial participants. The length of development trajectories in this field may affect investor confidence across the sector, resulting in the ‘valley of death’ phenomenon discussed in Chapter 3 (see paragraphs 3.41 to 3.47). Investors, particularly venture capitalists, may not be attracted to enterprises that still have a long way to go before delivering a marketable product. As a result, smaller companies may not be able to survive delays and uncertainty regarding regulatory approval to progress to clinical trials if they cannot attract funding to bridge the development process from academic laboratory to viable commercial concern.
- 7.68 The perception of regulatory oversight as unduly burdensome is, perhaps inevitably, a matter of perspective. The same requirements that can be framed as costly regulatory hurdles that threaten the existence of small and medium sized enterprises (SMEs) struggling to secure funding to bring useful products to market, can also be seen as unavoidable aspects of ensuring participant and, ultimately, patient safety. For example, in response to the consultation conducted for this report, the Wellcome Trust noted that some in the research community broadly “consider research with neural stem cells to be well regulated in the UK, allowing pioneering work to proceed in a carefully controlled manner.”⁷³⁹
- 7.69 We do not seek here to question the need to proceed with humility and caution in the regulatory oversight of neural stem cell therapies. The justifications for doing so are, of course, that interventions in the brain may carry significant risks to many aspects of patients’ health and well-being if they do not perform as expected. These therapies are highly invasive; biological manipulation potentially presents considerable dangers and in such a new area of innovation, the risk-benefit ratio is still uncertain. However, exercise of the virtue of responsibility through regulatory processes entails that caution is not the only ethical guide to appropriate regulatory orientation where practices need to be kept under review in light of evolving evidence. Furthermore, multiple layers of oversight, although rightly directed at protecting patient safety, could paradoxically risk undermining this very goal. Where no other therapeutic options are available in the UK, this might drive patients to seek treatment in other countries. These could include countries where regulatory oversight is not as robust and treatment practices are less scrupulous (see Box 3.5).

Recent developments in the UK regulatory landscape

- 7.70 A number of changes are taking place in the practical arrangements for the regulation of regenerative medicine (which encompasses neural stem cell therapies) in the UK to reduce regulatory overlap and unnecessary obstacles, and to reduce approval times for ethical review. Measures to improve partnership working between the four regulators with responsibilities in

⁷³⁹ Wellcome Trust, responding to the Working Party’s consultation.

this field are one aspect of this.⁷⁴⁰ These measures include the introduction of joint inspections by the MHRA and HTA of licensed establishments and measures to streamline the information requirements and submission of research applications to the MHRA and GTAC. In addition, in early 2013, the MHRA launched its 'Innovation office' to promote early discussions between the MHRA and organisations involved in developing innovative medicines or medical devices to help the organisations navigate the regulatory process.⁷⁴¹

- 7.71 A further significant development has been the changing oversight and functioning of GTAC. GTAC is the UK national Research Ethics Committee (REC) for clinical trials of gene therapy, ATMPs, and certain other types of research, including those involving stem cell therapies.⁷⁴² GTAC performs an important function in the regulation of clinical investigations of ATMPs, as its members bring particular technical expertise in relevant scientific fields to their determinations. However, its role in the regulatory process had previously been viewed as a possible source of some delay. In the spirit of achieving proportionate governance, the UK Government established the Health Research Authority (HRA) in 2011.⁷⁴³ Since September 2012, GTAC has been one of the RECs within NRES operating within the Health Research Authority (HRA).⁷⁴⁴ The aim is that that these changes will improve the service offered to researchers by providing more timely ethical review by meeting more frequently and operating across a wider geographical area. Indeed, since these changes were introduced in 2012, approval times for ethical review have been significantly reduced, with all studies reviewed within the legal requirement of 90 days. The most recent study was approved in 38 days, (compared with pre-2012 timelines of between 82 and 144 days).⁷⁴⁵ Reviews of applications will now follow NRES Standard Operating Procedures which clearly distinguish the role of the MHRA from that of RECs.
- 7.72 Precisely because neural stem cell therapy is a pioneering field, the current evidence of benefits and risks is limited. Inflexible caution maintained in the face of equivocal evidence may deliver diminishing returns in terms of protecting public health. In view of the need for safe and effective therapies for brain damage there is a need for the regulatory system to support inventiveness so that the evidence can be generated to permit this field of science to move forwards. Proportionate and effective regulation must therefore be flexible enough to accommodate an evolution from protection to promotion. In light of this, **we welcome the recent and ongoing changes to achieve effective collaboration between the regulators responsible for overseeing regenerative medicine in the UK. We would encourage continued dialogue between regulators and researchers, genuine sharing of experiences, and reflexive systems of oversight in order to foster innovation while protecting patient safety.**

Meeting the needs of small patient populations

- 7.73 This final section of this chapter considers an area of the regulatory framework which we have not yet addressed in great detail. That is, oversight of the supply of products to meet the needs of patients that are *not* met by traditional market-driven approaches to innovation. As we have noted in Chapter 3, bringing novel neurotechnologies – particularly neural stem cell therapies – to market may require significant investment. This potentially introduces an economic

⁷⁴⁰ Joint submission from the MHRA, HTA, HFEA and HRA to the House of Lords Select Committee on regenerative medicine: HTA (2013) *HTA responses to consultations*, available at: <http://www.hta.gov.uk/consultations/htaresponsestoconsultations.cfm>.

⁷⁴¹ Joint submission from the MHRA, HFEA, NTA and HRA to the House of Lords Select Committee on regenerative medicine; *Ibid*; MHRA (2013) *Innovation Office*, available at: <http://www.mhra.gov.uk/Howweregulate/Innovation/index.htm>.

⁷⁴² NRES (2013) *Gene therapy and other advanced therapy medicinal products*, available at: <http://www.nres.nhs.uk/applications/approval-requirements/ethical-review-requirements/gene-therapy-and-other-advanced-therapy-medicinal-products/>.

⁷⁴³ Health Research Authority (2013) *Health Research Authority*, available at: <http://www.hra.nhs.uk/>.

⁷⁴⁴ NRES (2013) *New arrangements for the Gene Therapy Advisory Committee (GTAC)*, available at: <http://www.nres.nhs.uk/nres-publications/news/new-arrangements-for-the-gene-therapy-advisory-committee/>.

⁷⁴⁵ Presentation by HRA to MHRA and the London Regenerative Medicine Network (4 April 2013). Health Research Authority (2013) *New GTAC arrangements and experience to-date*, available at: <http://www.hra.nhs.uk/EasysiteWeb/getresource.axd?AssetID=152412&type=Full&servicetype=Attachment>

disincentive to developing products that will find only a small market. There is, therefore, a risk of a gap between what the market (operating without intervention) will supply and the provision of licensed products to meet the therapeutic needs of patients with rare neurological disorders or those that require bespoke therapies. In the UK, there are several regulatory mechanisms in place to facilitate and oversee patients' access to medical devices or to ATMPs that do not have full market authorisation.

Medical devices: exceptional use and custom-made

7.74 Under exceptional circumstances the MHRA has responsibility for authorising the exceptional use of non-CE marked devices on humanitarian grounds; that is, in the interests of single patients. This is provided for under the Medical Devices Regulations 2002,⁷⁴⁶ And applications are typically made on a patient-by-patient basis. The manufacturer has legal responsibility for this, but both the clinician and manufacturer must complete forms that accompany the application (including the identity and medical details of the patient) which is then assessed by the MHRA. The clinician must also declare their opinion that the patient's condition will deteriorate without the use of the device and that the patient has given their explicit consent. The MHRA sets criteria and provides guidance to clinicians and manufacturers for the appropriate use of this exception, the essential criteria being that:

- There are no alternative CE-marked devices available for this treatment; and
- There is evidence that use of the device reduces significantly morbidity and/or mortality, compared with the use of alternative treatments that are available.⁷⁴⁷

7.75 The MHRA also has regulatory oversight of devices designed and built particularly for individual patients. To qualify as 'custom-made', a device must be "manufactured specifically in accordance with a written prescription of a qualified medical practitioner or a professional user" and be intended for the sole use of a particular patient.⁷⁴⁸ Manufacturers of these devices must ensure that their products meet the relevant requirements, including being clearly labelled as fulfilling a restricted purpose, and must register these products with the MHRA. It is unclear to what extent the 'custom-made' route is suitable, or has been used, for the supply of neurodevices.

7.76 These two regulatory mechanisms are not exhaustive of the routes available for individual or small numbers of patients to receive treatment using medical devices. Devices that are manufactured by health care establishments and only used on their own patients are currently exempt from compliance with the medical device regulations.⁷⁴⁹ Clinicians may use licensed devices 'off-label' (although manufacturers may not market devices on the basis of such off-label uses). Provided health care establishments or clinicians do not intend to utilise these as routes to market, the MHRA has no regulatory oversight of medical devices used in these ways. As we have already suggested (see paragraphs 7.49 to 7.51) these regulatory gaps give rise to some concerns about effective oversight. The interests of patients in accessing safe and effective therapies – and indeed the economic interests of manufacturers – are more likely to be best protected if rare neurological conditions can be addressed by devices that are approved for these conditions.

⁷⁴⁶ Regulation 12(5) of The Medical Devices Regulations 2002.

⁷⁴⁷ MHRA (2011) *Application for the exceptional use of non-complying devices*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007502.pdf>.

⁷⁴⁸ MHRA (2006) *Guidance notes for manufacturers of custom made devices*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007515.pdf>, at page 4.

⁷⁴⁹ MHRA (2010) *In house manufacture*, available at: <http://www.mhra.gov.uk/Howweregulate/Devices/Inhousemanufacture/index.htm>. As we have noted (see Box 7.1) there are EC proposals to end the 'in-house' exemption.

Box 7.6: Does the UK require an orphan devices regime?

The question may be raised as to whether the non-market routes described in this section are sufficient to meet unmet patient need or if more could be done to incentivise device manufacturers to develop devices for serious but rare neurological conditions. The economic challenges of bringing therapeutic products to market were discussed in Chapter 3: these are likely to be most acute where demand is low (in terms of numbers of patients) because conditions are rare. Demand in terms of the severity of unmet needs may, however, be significant.

In the pharmaceutical sector, the US and Europe have legislated to address precisely this problem of so-called ‘orphan’ conditions where, without incentives, it is unlikely that the revenue from marketing a medicinal product would cover the investment in its development. In Europe, these conditions must be classed as life-threatening or chronically debilitating and affect no more than five in 10,000.⁷⁵⁰ Incentives include assistance from the EMA in developing protocols, streamlined market authorisation, and ten years market exclusivity. The US also operates a Humanitarian Device Exemption (HDE) for devices addressing conditions affecting fewer than 4,000 people in the US per year.⁷⁵¹ The HDE offers the incentive of removing from the pre-market approval process the requirement to provide evidence of the device’s effectiveness for the intended purpose (although evidence of safety is a requirement).

This might suggest that both patients and manufacturers would benefit from the introduction of an orphan *devices* regime in the UK. However, this underestimates the significant differences between the regulatory requirements for marketing medical devices under European law and those for medicinal products in Europe, or medical devices in the US. As we have seen, in contrast to the latter two systems, pre-market regulation of devices in Europe is relatively ‘light touch’ – for example, there are no requirements for manufacturers to demonstrate efficacy. Furthermore, the MHRA *already* provides advice and support to device manufacturers, and the structure of the regulatory system does not permit market exclusivity provisions. It is difficult, therefore, to see how further incentives could be provided to manufacturers while exercising the virtue of responsibility. Moreover, the barriers to producing devices for small markets are much lower than for medicinal products, as research and development costs for devices are comparatively small and the life cycles of devices tends to be much shorter than those of drugs.

It should also not be overlooked that in the US, the HDE has been subject to criticism. One group of commentators has expressed concern that this simpler, cheaper, and faster approval process – such as that used to approve DBS for the suppression of symptoms of severe OCD – means that devices are not subject to sufficiently rigorous clinical investigation, potentially risking patient safety.⁷⁵² Further concerns arise regarding the potential commercial motivations for manufacturers to pursue the HDE, and that “the humanitarian device exemption is being used to give the device manufacturer access to patients, rather than giving researchers access to subjects, or patients access to sound scientific evidence.”⁷⁵³ Any hypothetical reductions to the (already light) pre-market evidence requirements under European regulations could be vulnerable to a similar criticism that commercial interests have obscured patient interests.

The challenge to device manufacturers operating in the UK, who seek to make economic returns on devices, is more likely to stem from their securing market share when there might be competition from innumerable licensed devices fulfilling similar purposes and where there are only a small number of potential patients. Such challenges will not be solved by regulatory incentives. Instead, the opportunities for manufacturers are likely to come from exercising inventive routes to identify the kinds of devices that would best address unmet therapeutic needs and, working with NICE and the NHS National Institute for Health Research (NIHR), to provide the kinds of evidence of efficacy that would encourage uptake by health care providers. For example, the NIHR Healthcare Technology Co-operatives (HTCs) aim to encourage collaborations between industry, patients, charities, and academic researchers to develop new medical devices and technology-dependent interventions to address areas of serious illness and unmet need for NHS patients.⁷⁵⁴

ATMPs: the hospital exemption and ‘Specials’

7.77 The development of stem cell therapy for a particular patient is possible under the so-called ‘hospital exemption scheme’ which applies to all ATMPs, and which is provided for under the ATMP Regulation and Directive 2001/83/EC. The UK legislation regarding this – and implementing the ATMP Regulation in general – came into force on 19 August 2010. The MHRA has regulatory oversight for the hospital exemption in the UK.

⁷⁵⁰ European Medicines Agency (2010) *Committee for orphan medicinal products: overview*, available at: http://www.emea.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000123.jsp&mid=WC0b01ac0580028e32.

⁷⁵¹ FDA (2010) *Humanitarian device exemption*, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm>.

⁷⁵² Fins JJ, Mayberg HS, Nuttin B *et al.* (2011) Misuse of the FDA Humanitarian Device Exemption in deep brain stimulation for obsessive-compulsive disorder *Health Affairs* **30(2)**: 302-11, at page 305.

⁷⁵³ *Ibid.*, at page 306.

⁷⁵⁴ NIHR (2008) *Healthcare technology co-operatives*, available at: <http://www.nihr.ac.uk/infrastructure/Pages/HTCs.aspx>.

- 7.78 The hospital exemption was included in the ATMP Regulation in recognition of the fact that some non-routine development, preparation and use of ATMPs occur as a continuation of, or as part of, treatment at hospital level in accordance with a medical prescription for an individual patient. The exemption also aims to incentivise development of treatments for ‘orphan’ conditions: those for which the potential patient population is too small for the operation of the market alone to deliver the necessary treatment. The exemption applies to manufacturers and their supply of medicinal products to clinicians, and it frees non-routine products from the central European authorisation procedure. However, the *manufacture* of ATMPs under this exemption is still subject to authorisation by the MHRA. ATMPs manufactured under the hospital exemption must comply with the principles of Good Manufacturing Practice (GMP).⁷⁵⁵ When a licence is being sought by the manufacturer from the MHRA, the MHRA will consider whether a plan to mitigate risks is necessary.
- 7.79 Various conditions apply under the hospital exemption,⁷⁵⁶ particularly that the ATMP must be prepared and used in the same Member State and cannot be used to circumvent core features of regulation and enter a wider market. Other conditions are that:
- the ATMP must be commissioned by a medical practitioner;
 - the ATMP must be custom-made to meet an individual prescription;
 - the ATMP must have been prepared on a ‘non-routine basis’;⁷⁵⁷ and
 - the ATMP must be used in a hospital.
- 7.80 Guidance from the MHRA on the application of the hospital exemption stipulates that standards for traceability, quality, and pharmacovigilance must be equivalent to those for a centralised market authorisation. With regards to reporting, manufacturers operating under the hospital exemption are required to record any adverse reactions and notify ‘serious adverse reactions’ to the MHRA. The manufacturer is also required to provide an annual report to the MHRA concerning activities carried out under the hospital exemption.⁷⁵⁸ However, it is unclear how rigorously the guidance on incident reporting is enforced.
- 7.81 In addition to hospital exemptions, Member States may set up their own arrangements to allow individual patients access to non-licensed medicinal products on a named-patient basis. This process is called ‘Specials’ in the UK and it is currently embodied in the 2012 Regulations.⁷⁵⁹ This is to be contrasted with off-label prescribing which involves products that *do* have a licence but the use is *not* one for which this was originally granted. It has been deployed to allow cell and gene therapy in individual circumstances.⁷⁶⁰
- 7.82 It is not clear to what extent the hospital exemption or the Specials arrangements have been used in the UK to govern the manufacture of products to be used in neural stem cell therapies.

Ethical issues raised by exceptional and non-routine provision

- 7.83 The regulatory measures permitting access to novel neurotechnologies under the regulatory routes outlined above are sound in their motivation as they provide routes for unmet therapeutic

⁷⁵⁵ MHRA (2010) *Guidance on the UK’s arrangements under the hospital exemption scheme*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>, pp. 4-5.

⁷⁵⁶ *Ibid.*, at page 2.

⁷⁵⁷ ‘Non-routine’ means that the product is not being produced for a mass market. The MHRA takes the position that it is not possible to provide a simple numerical formula to distinguish routine from non-routine, instead this is determined by the scale and frequency of the production of the product.

⁷⁵⁸ MHRA (2010) *Guidance on the UK’s arrangements under the hospital exemption scheme*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>, pp. 5-6.

⁷⁵⁹ MHRA (2012) *Medicines that do not need a licence (exemptions from licensing)*, available at: <http://www.mhra.gov.uk/Howweregulate/Medicines/Doesmyproductneedallicence/Medicinesthatdonotneedallicence/index.htm>

⁷⁶⁰ See, for example, King’s College London (2012) *Rayne cell therapy suite*, available at: <http://www.kcl.ac.uk/medicine/research/divisions/cancer/research/sections/haematooncology/celltherapysuite.aspx>.

needs to be addressed even when the market has not delivered the necessary product. Regulators are alert to protecting these targeted arrangements from abuse by manufacturers or researchers seeking a more rapid route to the wider market – which has been raised as a concern with respect to the US HDE. For example, sanctions and penalties are applicable if the individual or organisation places an ATMP manufactured for non-routine use on the market without market authorisation.⁷⁶¹

- 7.84 There is, however, a dearth of evidence about the operation of the hospital exemption and Specials arrangements, and how far these assist in the development of therapies for rare conditions. The European industry group, the Alliance of Advanced Therapies, has welcomed the aims of the hospital exemption to encourage innovation to address the needs of small patient groups, but expressed the view that it is implemented inconsistently in Member States and may, in fact, “impede the development of new safe and effective treatments”.⁷⁶²
- 7.85 Questions may also be raised about whether provision of therapies via these routes is sufficiently well grounded in the regulatory or professional systems that support them. The regulatory oversight of the MHRA extends to the *manufacture* of ATMPs for non-routine use, but not to their uses in treatment. Anecdotal reports from practitioners working in the field of neurostimulation also reflect concerns that there is very little regulatory oversight with regards to patient-by-patient development of interventions.⁷⁶³ This raises important questions about gaps in the oversight and control of the use (in what might be seen as experimental contexts) of products approved in this way. These gaps are, of course, not unique to neurodevices or neural stem cell therapies, but are brought into sharp focus by the observations we have made in our ethical framework about the special status of the brain and continued uncertainty about the benefits and unintended effects of some novel neurotechnologies. In the absence of regulatory prescription, there is a greater onus upon those responsible for care in clinical settings to protect the safety and well-being of patients. This confronts the kinds of ethical challenges we considered in Chapter 5, including the difficulties of obtaining informed consent under conditions of uncertainty and constrained choices, and of assessing whether a treatment genuinely offers a patient their only ‘current best hope’.
- 7.86 It may be questioned whether there is currently sufficient guidance for actors to navigate relevant ethical matters in the context of more experimental uses of neurotechnologies with single patients. For example, the MHRA guidance states that, with regards to ethical issues presented by non-routine uses of ATMPs in clinical practice, there is no need to seek a favourable opinion from a REC if the ATMP is administered as part of treatment (provided it does not involve xenotransplantation and is not administered in the context of research).⁷⁶⁴ The guidance holds that these ethical matters would be covered by NHS trusts’ clinical governance arrangements. This implies that a clear line can be drawn between treatment, experimentation, and research. As we have noted at several points in this report, this does not reflect the reality. The risk is that this leaves a gap whereby experimental interventions are classified as treatment and, perhaps, inappropriately governed. We recall here our recommendation in Chapter 5 (at paragraph 5.60) for the provision of guidance to clinicians pursuing experimental treatment using novel neurotechnologies.
- 7.87 Regulatory provisions that permit small numbers of patients to access otherwise unavailable therapies are welcome insofar as they foster inventiveness to meet the needs of patients in rare and difficult circumstances. However, we suggest there is some doubt whether they sufficiently embody the virtue of responsibility by providing effective and proportionate protection of the safety and well-being of patients. The irony is that *precisely* because these regulatory routes will

⁷⁶¹ MHRA (2010) *Guidance on the UK's arrangements under the hospital exemption scheme*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>, at page 6.

⁷⁶² AFAT (2013) Focus hospital exemption on developing innovative and safe treatments for patients *Regenerative Medicine* **8(2)**: 121-3, at page 121.

⁷⁶³ Factfinding meeting with clinicians, 16 February 2012.

⁷⁶⁴ MHRA (2010) *Guidance on the UK's arrangements under the hospital exemption scheme*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>, at paragraph 23.

be used in exceptional circumstances, these patients are likely to be amongst the most vulnerable, due to the inevitable lack of evidence and practical clinical or research experience to inform professionals as to how to proceed in unusual or highly individual circumstances. These uncertainties coexist with the possibility that single-patient interventions are used chiefly with the most desperate, for whom all other therapeutic options are not available or have failed. Humility demands that their care and safety must be a principal consideration when the territory is so uncharted; it emphasises further the need for caution and for sharing of clinical experiences.

7.88 The requirement for responsible innovation in this field to proceed upon, generate, and disseminate robust evidence is, therefore, particularly pertinent in this context. However, the problem of the collection and dissemination of valuable evidence of the safety and efficacy of interventions (that we have noted at a number of points in this chapter) is particularly marked in respect of the permitted uses of non-licensed medical devices and ATMPs for non-routine or individual treatment. This is due, in part, to the inherent lack of transparency in the regulatory regimes that precludes the development of a realistic picture of how widely and for what kinds of conditions these regulatory routes are used. The regulatory mechanisms for capturing the outcomes of treatments delivered via these exceptional routes also lack teeth. Although the MHRA requires manufacturers operating under the hospital exemption to report any adverse events, it is unclear how well the guidance on incident reporting is enforced. There is no legal requirement for post-market surveillance or reporting to the MHRA for adverse events arising from the use of bespoke or in-house manufactured devices. These factors join the more general challenge of an absence of mechanisms to capture and share clinical (including patient reported) outcomes of these kinds of single-patient interventions that we have noted in earlier chapters.

7.89 We suggest, therefore, that (in addition to the broad recommendation we made in Chapter 5 for the establishment of registers for evidence of clinical experience), there is a need to capture and make accessible information on *all* instances for which regulatory approval is given for the use of medical devices and ATMPs under regulatory routes. This includes the supply of products for single patients or on exceptional or non-routine bases. **We recommend that the MHRA should record anonymised data on when, and for what purpose(s), approval has been given for the supply of neurodevices under exceptional use or custom made arrangements⁷⁶⁵ and for non-routine supply of ATMPs under the hospital exemption or Specials arrangements. In addition, we recommend that the MHRA establishes mandatory schemes by which manufacturers and clinicians report data on patient outcomes, and adverse events of resultant interventions.** The aim of this will be to enhance understanding the extent to which use is made of these routes, will help to assess the value of these regulatory mechanisms, and support dissemination of valuable evidence of efficacy and risks to promote further learning. Even though regulatory responsibilities for oversight of these exceptional and non-routine supply routes are devolved the Competent Authorities in Member States, it would nonetheless be valuable if data regarding when they are utilised and patient outcomes were also coordinated at a European level: by the EMA (for ATMPs) and through Eudamed (for medical devices). These data should be accessible by both health care providers and the public.

Concluding remarks

7.90 Novel neurotechnologies do not raise truly exceptional regulatory concerns. Nevertheless, we have identified several priority areas for attention. The regulatory regimes that apply to neurodevices are quite distinct from those that apply to neural stem cell therapies. For this reason, and for the most part, the concerns we have identified in this chapter differ, depending on the category of novel neurotechnology.

⁷⁶⁵ This should include in-house usage if EC proposals to bring these within the scope of regulatory compliance requirements are adopted.

- 7.91 In the case of neurodevices, the three most significant features are the fact that medical devices may be marketed without manufacturers being required to provide evidence of efficacy; secondly, the regulatory routes by which devices reach patients militate (albeit unintentionally) against the generation and dissemination of a robust body of evidence about their effects more generally; and thirdly, that the opaque system of Notified Bodies compounds questions about the adequacy of the evidence on which devices are licensed for sale. These factors are of particular concern in light of the ethical imperative, underscored by the virtue of humility, that we should *not* intervene in the brain unnecessarily – even if the known risks of doing so are low.
- 7.92 While the regulation of neurodevices chiefly raises questions about whether there may be gaps in regulatory oversight, the framework that applies to stem cell technologies raises the opposite concern: that in some circumstances, the layers of regulatory oversight may have (until recent changes) been disproportionately burdensome. In the context of effective and proportionate regulation, the virtue of responsibility requires achieving proportionate position that not only protects patients from harm, but also seeks to avoid impeding the development of much-needed therapeutic interventions without good cause. This is a particular threat where innovation in this sector is pursued to such a large degree by SMEs with limited resources. The regulatory landscape that applies to neural stem cells is currently undergoing significant changes and it is too soon for us to comment on the proportionality of any new approaches.
- 7.93 Our recommendations for addressing the evidence requirements in the field of neurodevices are equally constructed with acute awareness of avoiding detrimental regulatory burdens. Blanket requirements to conduct large-scale pre-market RCTs of devices would be disproportionate. Instead, we have recommended that, on as many fronts as possible (including, but not limited to, those mechanisms within the control of regulators) it is essential that data on how well these devices do or do not function are collected – both before and after devices enter the market – and widely shared. These concerns regarding transparency and dissemination of information are not limited to the medical device sector. Where either devices or cell-based therapies are developed to treat single patients, or on exceptional or non-routine bases, we have noted that there is a risk of valuable information about the risks and benefits of novel neurotechnologies being lost in the absence of formal tracing and collection mechanisms.
- 7.94 The value of this information goes beyond helping to underpin decision-making by regulators. The regulatory system is in a position to play an important role in addressing the persistent uncertainty that defines the ethical landscape in the field of novel neurotechnologies. Access to more, and better, evidence will equip professionals to make the most appropriate decisions regarding patients' and participants' care, and to support truly informed decision-making by those undergoing these interventions. However, improved transparency of evidence available to regulators can only fill this gap to a partial extent. Complementary collaborative efforts to improve information governance and data linkage by manufacturers, practitioners and other stakeholders such as NICE are also needed.
- 7.95 This chapter concludes our three part discussion of the governance and oversight of therapeutic neurotechnologies (see also chapters 5 and 6). We turn now to consider the ethical, social and regulatory challenges posed by their application for *non-therapeutic* purposes. As we note in Chapter 8, the actors and rules governing these uses are in many respects quite different from those we have discussed hitherto, although it is instructive to carry with us the understanding of the promises, risks and uncertainties of these technologies that we have developed over the previous chapters.

Chapter 8

Non-therapeutic
applications

Chapter 8 – Non-therapeutic applications

Chapter 8 – overview

We discuss three areas in which novel neurotechnologies might be used for non-therapeutic purposes: neural enhancement, gaming and military uses.

- **Enhancement:** A number of small studies using non-invasive neurostimulation report improvements in participants' performance in laboratory tasks, for example involving memory or language skills, or in their mood that could be construed as 'enhancements'. However, there is need for great care in extrapolating from small studies conducted under laboratory conditions to lasting real-world effects; the potential use of neurostimulation for neural enhancement is still far from proven.
- **Gaming:** There are already games on the market claiming to use non-invasive electroencephalography (EEG) based brain-computer interface (BCI) technology, although whether they all actually utilise brain signals is questionable. Nevertheless, there is considerable research activity to develop commercially viable games that are genuinely BCI-controlled. These recreational neurotechnologies overlap with EEG-based neurofeedback 'games' that are already being marketed for use as treatments for attention deficit / hyperactivity disorder or that purport to improve capacities such as concentration.

Uses of non-invasive neurostimulation or BCIs either for putative 'enhancement' purposes or gaming are unlikely to pose serious health risks. Nevertheless, the large number of people targeted by these applications and the lack of any clear associated health benefits mean that it is important to attend to several ethical concerns. In particular, to minimise the pursuit of unnecessary brain interventions, there is a need to ensure the originality and rigour of research investigating non-therapeutic uses in humans (paragraph 8.39) and also to disseminate existing evidence through publically accessible registers (paragraph 8.41).

Non-therapeutic applications of neurodevices (such as BCI games and those that purport to offer enhancements) are likely to be used privately and without medical supervision. This places greater onus on the effective regulation of the devices themselves. We recommend that the European Commission considers designating neurostimulation devices as products that should be regulated under the medical devices regime irrespective of the purpose for which they are marketed (paragraph 8.52).

Those marketing neurodevices and services with unsubstantiated or misleading claims about their putative benefits may be exploiting consumers and undermining wider public trust in neurotechnologies. We recommend that there is a need for responsible self-governance by businesses operating in this sector, establishing best practice standards both for the provision of honest and accurate information and for delivering services using neurodevices within parameters of safe use (paragraph 8.59).

Given the lack of evidence of the efficacy of these neurotechnologies for enhancement, we do not examine in detail the ethics of human enhancement *per se*. However, two concerns familiar from wider bioethical debates about human enhancement may arise. The first is that pursuit of non-therapeutic innovation might represent an opportunity cost at the expense of investigating applications of greater social value. The second is that, provided some believe that enhancements using neurodevices are realisable, pressure might be exerted on individuals to use these. This latter is a particular concern in children, in whom the effects of neurostimulation or BCIs on the developing brain are not well understood. We recommend that observational research with children who are already using neurotechnologies is needed to address this (paragraph 8.40) and also that advice is issued to teachers and parents about the current evidence of the efficacy of neurofeedback as an educational enhancement tool (paragraph 8.62).

- **Military:** Novel neurotechnologies have potentially valuable applications in treating physical and psychiatric injuries caused by combat. However, in this chapter our concern is with their non-therapeutic uses, and there are indications from the US that there is considerable investment in non-therapeutic military applications. These include the use of BCIs in enhancing fighters' effectiveness by augmenting their perceptual or cognitive capacities, or by permitting neural control of remote weaponry. It is also plausible that BCIs or neurostimulation could be used for interrogation purposes. The existing international conventions outlawing the use of biological and chemical agents in war do not cover the use of neurodevices.

We recommend that advice is issued to armed forces highlighting that the use of neurodevices in interrogation would be coercive and illegal under the Geneva Conventions (paragraph 8.84). Military applications of novel neurotechnologies raise particular challenges for research ethics. We suggest that military clinicians can play an important role in protecting the wellbeing of personnel within their own forces who may be subject to professional coercion to participate in experimental uses of neurotechnologies (paragraph 8.87). We further recommend that the education of neuroscientists should include ethical training that draws attention to the dual-use applications of neurotechnologies for military as well as civilian ends (paragraph 8.89).

Introduction

- 8.1 In this chapter, we turn from our focus upon therapeutic applications of novel neurotechnologies to consider their possible applications for non-therapeutic ends and by healthy users. Compared to the applications of novel neurotechnologies we have considered thus far – which offer respite from debilitating symptoms of illness or injury, or the opportunity to restore lost capacity to interact with the world – applications designed for enhancement or recreational purposes may seem trivial. However, the number of potential users in these fields is inevitably much greater than that for specialised medical interventions, so any ethical or social concerns that do arise warrant attention.
- 8.2 This chapter is divided into two parts, looking first at the use of novel neurotechnologies for the purposes of **neural enhancement** and **recreation**, before turning to consider **military** applications. We consider these topics separately from our discussion of therapeutic applications because several of the ethical and social issues they raise differ, in either kind or degree, from those that apply to interventions intended for use to treat brain disease or injury. This means that the ethical framework we developed in Chapter 4 may not always be applicable in non-therapeutic contexts. Though some ethical concerns may be shared between the two contexts, for example regarding uncertainties about unintended long-term effects of repeated brain stimulation.
- 8.3 A key respect in which non-therapeutic and therapeutic applications differ is in the range of actors involved in their development, regulation, and use. The size and nature of the market raises the prospect of direct to consumer (DTC) marketing of devices and services and private use of neurotechnologies unmediated by healthcare professionals. Where devices do not fall under the definition of medical devices, their regulation will not fall under the remit of the Medicines and Healthcare products Regulatory Agency (MHRA). These factors mean that oversight of the safe use of these applications may be fragmented and inadequate.
- 8.4 However, therapeutic and non-therapeutic uses may not always be easily distinguishable from each other where the line between treatment and enhancement is blurred. Nor can their development trajectories be easily separated: studies investigating therapeutic applications may deliver findings that help to inform non-therapeutic innovation trajectories (and vice versa); and unsubstantiated claims made for enhancement or recreational benefits carry the risks of undermining understanding and trust in novel neurotechnologies which may help to address profound impairment in those living with brain illness and injury.
- 8.5 Exploration of the non-therapeutic uses of novel neurotechnologies is still in its infancy, with few applications currently in use outside research settings. Yet in the areas of neural enhancement and brain-computer interface (BCI) gaming, the economic incentives of large potential markets create powerful motives to translate research findings into commercial applications. Military research concerning novel neurotechnologies is subject to quite different drivers, and receives significant funding from both military and security budgets. Examination of the ethical and social impacts raised in all three of these fast growing fields of development is therefore timely.
- 8.6 In undertaking our assessment of the ethical issues in this chapter, we seek to strike a particular balance. If there is indeed a ready market for non-therapeutic applications of neurotechnologies, we cannot afford to be overly sanguine in respect of any ethical concerns simply because real-world applications may still be some way off. Equally, we wish to avoid engaging in ethical speculation unsubstantiated by robust evidence or driven by hype. We suggest that it is incumbent upon those involved in ethical and policy scoping not to exacerbate the detrimental effects of hype by overselling speculative ethical concerns.

Neural enhancement

- 8.7 Cognitive enhancement may be understood as the use of interventions to improve cognitive functioning and performance, where these are not impaired in clinically significant ways (see Box 8.1 below). This encompasses improvements in capacities such as attention, understanding, reasoning, learning, and memory.⁷⁶⁶ Induced loss of painful memories might equally be viewed as a functional improvement.⁷⁶⁷ More widely, *neural* enhancement may be understood to include improvements in wakefulness, perception, mood, and social or moral cognition.⁷⁶⁸
- 8.8 While conventional educational tools or nutrition can be regarded as means of cognitive enhancement, bioethical discussions of the methods of boosting the brain's capacities focus chiefly on pharmaceuticals and other newer neurotechnological methods. In recent years, considerable attention has been paid to the possibilities of advances in drugs, particularly the off-label use of stimulants commonly prescribed for attention- or sleep-disorders.⁷⁶⁹ While pharmacological enhancement provides a useful comparator, detailed discussion lies outside the remit of this report.⁷⁷⁰
- 8.9 At present, it is not thought plausible that invasive neurotechnologies involving surgical implantation of electrodes or stem cells into the brain itself would be used to improve the capacities of healthy individuals, as the risks of brain surgery are disproportionate to non-therapeutic goals. However, perhaps given evidence of the possible psychiatric applications of deep brain stimulation (DBS), its future exploration as a means of mood enhancement cannot be ruled out. Prospects for the use of neural stem cell therapies to improve cognitive capacities such as memory beyond 'normal' function, however, remain even more speculative. Here, we focus on the prospects of non-invasive transcranial brain stimulation (TBS) (using transcranial magnetic stimulation (TMS), repetitive TMS (rTMS), and transcranial direct current stimulation (TDCS)) as means of neural enhancement.

Box 8.1: Human enhancement: definitions and debate

Both the definition of enhancement and its ethical significance are fiercely contested. The following provides an overview of some of the central issues only.

Defining enhancement

Human enhancement has been defined as "the directed use of biotechnical power to alter, by direct intervention, not disease processes but the "normal" workings of the human body and psyche, to augment or improve their native capacities and performances", and in that sense is taken to be "beyond therapy".⁷⁷¹ Cognitive enhancement, the sub-category that is of particular interest in this report, has been defined as "the amplification of extension of core capacities of the mind through improvement or augmentation of internal or external information processing systems."⁷⁷²

⁷⁶⁶ Bostrom N and Sandberg A (2009) Cognitive enhancement: methods, ethics, regulatory challenges *Science and Engineering Ethics* **15**(3): 311-41, at page 312.

⁷⁶⁷ Farah MJ, Illes J, Cook-Deegan R *et al.* (2004) Neurocognitive enhancement: what can we do and what should we do? *Nature Reviews Neuroscience* **5**(5): 421-5, at page 422. Although, this might more properly be framed as treatment if it is designed to alleviate the effects of a recognised health impairments such as post-traumatic stress disorder.

⁷⁶⁸ Hamilton R, Messing S and Chatterjee A (2011) Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation *Neurology* **76**(2): 187-93.

⁷⁶⁹ Farah MJ, Illes J, Cook-Deegan R *et al.* (2004) Neurocognitive enhancement: what can we do and what should we do? *Nature Reviews Neuroscience* **5**(5): 421-5; Greely H, Sahakian B, Harris J *et al.* (2008) Towards responsible use of cognitive-enhancing drugs by the healthy *Nature* **456**(7223): 702-5, at page 702; Smith ME and Farah MJ (2011) Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals *Psychological Bulletin* **137**(5): 717-41; Ragan CI, Bard I and Singh I (2012) What should we do about student use of cognitive enhancers?: An analysis of current evidence *Neuropharmacology* **64**(1): 588-95.

⁷⁷⁰ Low-tech or no-tech methods such as conventional educational tools or nutrition may also be regarded as means of cognitive enhancement.

⁷⁷¹ President's Council on Bioethics (2003) *Beyond therapy: biotechnology and the pursuit of happiness* (Washington DC: President's Council on Bioethics), at page 13.

⁷⁷² Bostrom N and Sandberg A (2009) Cognitive enhancement: methods, ethics, regulatory challenges *Science and Engineering Ethics* **15**(3): 311-41, at page 311.

Contested distinctions

The most fundamental debate is whether it is even possible to draw a meaningful distinction between treatment and enhancement.⁷⁷³ Some have framed this distinction in terms of a question about the legitimate scope of health care.⁷⁷⁴ However, health care is often concerned with more than treating illness.⁷⁷⁵ Others have objected that the concept of enhancement is premised on problematic and discriminatory presumptions about what constitutes 'normal' functioning. It has been suggested that a less problematic distinction between treatment and enhancement takes into account the level of contextual impairment to physical or mental functions. If these are not impaired at clinically significant levels in a given context, the motivation for interventions can be considered enhancement. It is certainly not possible to draw a hard line between treatment and enhancement as there are interventions that occupy a grey area between these two categories. What is considered 'normal' (and therefore 'enhanced' by comparison) is socially, contextually, and technologically fluid, and has changed within the lifetime of those who read this report. For example, one may ask whether contact lenses or a walking stick count as treatments or enhancements. In separating our discussions of the therapeutic applications of novel neurotechnologies from the non-therapeutic in this report, our intention is not to deny that some uses of novel neurotechnologies will inevitably occupy an ambiguous space between that which is therapeutic and that which is not – for example, BCI-assisted neurofeedback to improve concentration in children. Moreover, the enhancement / treatment dichotomy is not exhaustive of all possible categorisations; some applications – for example BCI games – may be enjoyed for purely recreational reasons.

Ethical implications

Even if a line can be drawn between treatment and enhancement, this still leaves open the question of whether this demarcates any meaningful *ethical* distinction with which to guide responses to biotechnological enhancement.⁷⁷⁶ Some commentators have suggested that enhancement is, by definition, 'good';⁷⁷⁷ or at least that biotechnological enhancements do not differ in ethically significant ways from conventional and well-accepted methods of self-improvement, such as education.⁷⁷⁸ Other commentators have taken a contrasting view that many, if not all, biotechnological enhancements are, in themselves, ethically problematic because they threaten to undermine aspects of human existence, such as dignity, achievement through effort, authenticity, humility, or solidarity, that give our lives meaning.⁷⁷⁹ Between these polar positions are those that hold that the ethical status of enhancement cannot be decided *a priori*. Accordingly, it is argued that even if it were possible to differentiate treatment from enhancement this, in itself, does not determine the relevant ethical distinction – the risks and benefits of each particular means of enhancement must be assessed on the basis of empirical evidence where possible.⁷⁸⁰ This broadly reflects the position we adopt in this report.

Research evidence of the 'enhancement' effects of neurostimulation

8.10 It is common for studies using TMS (including rTMS) or TDCS to report changes in the performance of healthy adult participants in standardised laboratory tasks (or variations on these) that might be construed as evidence of improvement or 'enhancement'. Studies with the explicit aim of inducing such effects represent only a small fraction of research using non-invasive brain stimulation in healthy participants. Nevertheless, many examples may be found in

⁷⁷³ Parens E (1998) Is better always good? The enhancement project *Hastings Center Report* **28(1)**: s1-s17, at page s1.

⁷⁷⁴ See, for example, Norman Daniels' position discussed in Parens E (1998) Is better always good? The enhancement project *Hastings Center Report* **28(1)**: s1-s17, at page s2.

⁷⁷⁵ Parens E (1998) Is better always good? The enhancement project *Hastings Center Report* **28(1)**: s1-s17; World Health Organization (1946) *Definition of health: preamble to the constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, at page 100) and entered into force on 7 April 1948.*

⁷⁷⁶ Bostrom N and Sandberg A (2009) Cognitive enhancement: methods, ethics, regulatory challenges *Science and Engineering Ethics* **15(3)**: 311-41, at page 324.

⁷⁷⁷ Harris J (2007) *Enhancing evolution: the ethical case for making people better* (Princeton: Princeton University Press); Chan S and Harris J (2008) In support of human enhancement *Studies in Ethics, Law, and Technology* **1(1)**: 1-3.

⁷⁷⁸ Greely H, Sahakian B, Harris J *et al.* (2008) Towards responsible use of cognitive-enhancing drugs by the healthy *Nature* **456(7223)**: 702-5, at page 703; Bostrom N and Sandberg A (2009) Cognitive enhancement: methods, ethics, regulatory challenges *Science and Engineering Ethics* **15(3)**: 311-41.

⁷⁷⁹ Parens E (1998) Is better always good? The enhancement project *Hastings Center Report* **28(1)**: s1-s17; Sandel MJ (2011) The case against perfection: what's wrong with designer children, in *Atlantic Monthly*, Jecker N (Editor) (Mississauga, ON: Jones & Bartlett Learning).

⁷⁸⁰ Smith ME and Farah MJ (2011) Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals *Psychological Bulletin* **137(5)**: 717-41.

the scientific literature reporting effects upon, *inter alia*, memory,⁷⁸¹ language skills,⁷⁸² vision,⁷⁸³ mathematical ability,⁷⁸⁴ reasoning,⁷⁸⁵ emotional processing,⁷⁸⁶ what is termed ‘social cognition’ (that is, the interpretation of others’ behaviour),⁷⁸⁷ and mood.⁷⁸⁸

- 8.11 The methodologies of these studies vary, but generally participants receive neurostimulation to particular brain regions. ‘Enhancement’ is then measured in terms of improved performance. Some of these findings are interesting and worth further pursuit, but in the majority of cases, the effects have been obtained after a single session of brain stimulation and performance effects are small, and probably not behaviourally (even if statistically) significant. Concerns have been raised about the absence of adequate control conditions in some studies. In particular, the absence of stimulation at a control site negates any claims that can be made about the specificity of any effects.⁷⁸⁹

Future prospects: limitations and opportunities

Real world limitations

- 8.12 While scientifically interesting, the leap from a small effect in a single session to claims of utility in cognitive, perceptual, social, or emotional enhancement are unwarranted without further evidence. The putatively ‘enhancing’ effects of non-invasive TBS have not been demonstrated to be practically achievable or meaningful outside research laboratories. This is in marked contrast to the maturity of the science and the volume of empirical data accrued about the effectiveness of TBS in therapeutic fields – for example relating to its use in the treatment of drug-resistant depression.
- 8.13 There are several grounds for scepticism about the possibilities of extrapolating from effects observed under experimental conditions to expectations of practical applications. The cognitive improvements observed in these research studies pertain to performance in specific, and often quite artificial, experimental tasks.⁷⁹⁰ That such tasks transfer to real world challenges is sometimes assumed, but rarely tested. Neural enhancement applications of practical utility must be able to contend with distractions, confounding factors and tasks that demand more multifaceted and complex cognitive (emotional or perceptual) capacities than those tested by narrow, artificial standardised laboratory exercises. Furthermore, even if changes in performance under research conditions are statistically significant, if these improvements are not observed to be large in scale, they are unlikely to be useful for most practical purposes. Effects are also often short-lived, lasting only the duration of the stimulation,⁷⁹¹ although some

⁷⁸¹ Marshall L, Mölle M, Hallschmid M and Born J (2004) Transcranial direct current stimulation during sleep improves declarative memory *The Journal of Neuroscience* **24(44)**: 9985-92.

⁷⁸² Flöel A, Rössler N, Michka O, Knecht S and Breitenstein C (2008) Noninvasive brain stimulation improves language learning *Journal of Cognitive Neuroscience* **20(8)**: 1415-22.

⁷⁸³ Walsh V, Ellison A, Battelli L and Cowey A (1998) Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5 *The Royal Society* **265(1395)**: 537-43.

⁷⁸⁴ Cohen Kadosh R, Soskic S, Luculano T, Kanai R and Walsh V (2010) Modulating Neuronal activity produces specific and long-lasting changes in numerical competence *Current Biology* **20(22)**: 2016-20.

⁷⁸⁵ Dockery CA, Hueckel-Weng R, Birbaumer N and Plewnia C (2009) Enhancement of planning ability by transcranial direct current stimulation *The Journal of Neuroscience* **29(22)**: 7271-7.

⁷⁸⁶ Harmer C, Thilo K, Rothwell J and Goodwin G (2001) Transcranial magnetic stimulation of medial-frontal cortex impairs the processing of angry facial expressions *Nature Neuroscience* **4(1)**: 17-8.

⁷⁸⁷ Knoch D, Pascual-Leone A, Meyer K, Treyer V and Fehr E (2006) Diminishing reciprocal fairness by disrupting the right prefrontal cortex *Science* **314(5800)**: 829-32; Young L, Camprodon JA, Hauser M, Pascual-Leone A and Saxe R (2010) Disruption of the right temporoparietal junction with transcranial magnetic stimulation reduces the role of beliefs in moral judgments *Proceedings of the National Academy of Sciences of the United States of America* **107(15)**: 6753-8.

⁷⁸⁸ Schaller G, Lenz B, Friedrich K *et al.* (2011) Repetitive transcranial magnetic stimulation influences mood in healthy male volunteers *Journal of Psychiatric Research* **45(9)**: 1178-83.

⁷⁸⁹ Walsh V, Pascual-Leone A and Kosslyn SM (2003) *Transcranial magnetic stimulation: a neurochronometrics of mind*. MIT press Cambridge, MA).

⁷⁹⁰ For example, being asked to recall randomly presented sequences of consonants with which they had been earlier presented: Kirschen MP, Davis-Ratner MS, Jerde TE, Schraedley-Desmond P and Desmond JE (2006) Enhancement of phonological memory following transcranial magnetic stimulation (TMS) *Behavioural Neurology* **17(3)**: 187-94.

⁷⁹¹ Thut G and Pascual-Leone A (2010) A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience *Brain Topography* **22(4)**: 219-32.

studies have reported improved competence in the task learned under stimulation conditions for up to six months.⁷⁹²

- 8.14 There is no doubt that brain stimulation can have positive therapeutic effects (see paragraphs 2.29 to 2.31). However, when considering non-therapeutic uses, it must be borne in mind that the standards for what constitutes an enhancement have not been formalised. In this emerging field of research there are likely to be methodological shortcomings that would not be acceptable in delivering a therapeutic intervention, and instances where effects are overstated. It is well established, however, that TBS can change the brain and behaviour. The challenge for those working in the field is to find the route from small laboratory changes to real world effects that merit the use of the term ‘enhancement’.

Opportunities

- 8.15 Nevertheless, it is plausible that, were indications from early research to be translatable into practical applications, there would be a large and enthusiastic market for applications of novel neurotechnologies from a wide range of users.⁷⁹³ One reason for this assumption is the evidence, largely from college populations in the US, of the prevalence (estimated to be 5-15%) of use of prescription drugs such as Ritalin apparently for enhancement purposes.⁷⁹⁴ A 2009 report conducted on behalf of the European Parliament observed that of all possible fields of technological human enhancement, those directed at improvements in human cognition are most likely to have public appeal and gain widespread use.⁷⁹⁵ The report attributes this to a number of factors including the reversibility of interventions,⁷⁹⁶ and fertile cultural climates in which the ‘knowledge society’ and round-the-clock working increase demands on our cognitive capacities.⁷⁹⁷ Cognitive enhancements, perhaps unlike physical enhancements, may also be seen as offering universally useful benefits rather than being limited to positional advantages in particular competitive environments such as sport.
- 8.16 Given these kinds of considerations, it is plausible that school teachers and educationalists might show interest in the potential application of neuroscience and neurotechnologies in the classroom. However, whilst neuroscientific findings about the development of the brain and cognition may indeed help formulate educational strategies tailored to particular age groups or children with specific learning disabilities,⁷⁹⁸ the weak evidence for the enhancing effects of neurostimulation outside the laboratory recommends caution. The Royal Society has warned against the propagation of what they describe as educational ‘neuromyths’.⁷⁹⁹ It should also be noted that the kinds of cognitive improvements (for example, in memory) supposedly achieved through neurostimulation are likely to be more effectively accomplished through conventional educational means. While education, at its best, seeks to inculcate transferable skills required for global improvements in learning, findings from these kinds of studies referred to above tend

⁷⁹² Cohen Kadosh R, Soskic S, Luculano T, Kanai R and Walsh V (2010) Modulating Neuronal Activity Produces Specific and Long-Lasting Changes in Numerical Competence *Current Biology* **20(22)**: 2016-20, pp. 2017-8.

⁷⁹³ Hamilton R, Messing S and Chatterjee A (2011) Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation *Neurology* **76(2)**: 187-93, at page 191.

⁷⁹⁴ Smith ME and Farah MJ (2011) Are prescription stimulants “smart pills”? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals *Psychological Bulletin* **137(5)**: 717-41; Ragan CI, Bard I and Singh I (2012) What should we do about student use of cognitive enhancers? An analysis of current evidence *Neuropharmacology* **64(1)**: 588-95.

⁷⁹⁵ European Parliament: Science and Technology Options Assessment (2009) *Human enhancement study*, available at: [http://www.europarl.europa.eu/RegData/etudes/etudes/JOIN/2009/417483/IPOL-JOIN_ET\(2009\)417483_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/etudes/JOIN/2009/417483/IPOL-JOIN_ET(2009)417483_EN.pdf), at page 26.

⁷⁹⁶ This observation was made specifically with reference to pharmaceutical enhancement, but holds equally of the majority of neurotechnological interventions discussed below.

⁷⁹⁷ European Parliament: Science and Technology Options Assessment (2009) *Human enhancement study*, available at: [http://www.europarl.europa.eu/RegData/etudes/etudes/JOIN/2009/417483/IPOL-JOIN_ET\(2009\)417483_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/etudes/JOIN/2009/417483/IPOL-JOIN_ET(2009)417483_EN.pdf), at page 26.

⁷⁹⁸ Blakemore S-J and Frith U (2005) *The learning brain: lessons for education* (Bodmin: Blackwell).

⁷⁹⁹ Royal Society (2011) *Brain waves 2: neuroscience: implications for education and lifelong learning*, available at: http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/publications/2011/4294975733.pdf, at page 18.

not to represent generalised or global improvements in abilities, only transient improvements in relation to specific tasks.

Uses of BCIs for gaming and neurofeedback

- 8.17 Research into practical applications of BCIs is a rapidly growing field.⁸⁰⁰ The 2011 report of the EC-funded *Future BNCI* project predicted that, as the costs of developing BCIs fall, gaming applications are likely to be the fastest growing sector, due in large part to the number of potential users.⁸⁰¹
- 8.18 As we observed in Chapter 2, the majority of BCI research involves non-invasive electroencephalography (EEG). BCI games also use EEG to record brain activity using electrodes that rest on the scalp or forehead. The brain activity thus recorded is converted into information that is used to control or bring about effects in computer-operated games, either on-screen or in three-dimensional toys (see Box 8.2 for examples). Although limited by the spatial resolution at which it can measure brain signals and its vulnerability to interference, EEG nevertheless has high temporal resolution, is relatively easy and cheap to use, and does not carry the surgical risks associated with implanted electrodes. There is some speculation that, in the future, some serious enthusiasts might be prepared to have implanted electrodes to enhance their gaming experience, but this is not yet a reality.⁸⁰²
- 8.19 Currently available commercial gaming applications of BCIs utilise brain signals in ways that fall broadly under one or more of the following three categories:
- **Passive:** the BCI automatically records brain signals associated with the affective state of the user and converts these into instructions that bring about changes in the game environment.⁸⁰³ These signals may also be used to monitor the player's experience so that the game may adjust accordingly to sustain a desired state of absorption.⁸⁰⁴
 - **Active:** users can control activity in the game either by imagining movement – in which case the BCI records associated signals from their motor cortex,⁸⁰⁵ or by trying to change their affective state, for example by shifting from feeling frustrated to calm. On this latter principle, the University of Twente in the Netherlands conducts research using a game in which changes in players' brain's alpha activity recorded over a particular brain region will transform their avatar from a bear to an elf.⁸⁰⁶
 - **Reactive:** the BCI makes use of brain signals associated with event-related potential (ERP) responses elicited through the user's reaction stimuli such as the recognition of significant information.⁸⁰⁷
- 8.20 The kinds of games included in Box 8.2 tend not to be based upon peer-reviewed scientific research. There is some scepticism that all commercially available EEG headsets sold for

⁸⁰⁰ Vlek RJ, Steines D, Szibbo D *et al.* (2012) Ethical issues in brain–computer interface research, development, and dissemination *Journal of Neurologic Physical Therapy* **36**(2): 94-9.

⁸⁰¹ Future-BNCI (2012) *Future BNCI: a roadmap for future directions in brain / neuronal computer interaction research*, available at: http://future-bnci.org/images/stories/Future_BNCI_Roadmap.pdf, at page 95.

⁸⁰² Nijholt A, Plass-Oude Bos D and Reuderink B (2009) Turning shortcomings into challenges: brain-computer interfaces for games *Entertainment Computing* **1**(2): 85-94, at page 86.

⁸⁰³ Plass-Oude Bos D, Reuderink B, van der Laar B *et al.* (2010) Brain-computer interfacing and games, in *Human-computer Interaction Series*, Tan DS, and Nijholt A (Editors) (London: Springer-Verlag), at page 161.

⁸⁰⁴ Nijholt A, Plass-Oude Bos D and Reuderink B (2009) Turning shortcomings into challenges: brain-computer interfaces for games *Entertainment Computing* **1**(2): 85-94, at page 90.

⁸⁰⁵ *Ibid.*, at page 90.

⁸⁰⁶ Plass-Oude Bos D, Reuderink B, van der Laar B *et al.* (2010) Brain-computer interfacing and games, in *Human-computer Interaction series*, Tan DS, and Nijholt A (Editors) (London: Springer-Verlag), pp. 162-3. Alpha waves are the kind of brain activity associated with being awake and in a relaxed state.

⁸⁰⁷ Nijholt A, Plass-Oude Bos D and Reuderink B (2009) Turning shortcomings into challenges: brain-computer interfaces for games *Entertainment Computing* **1**(2): 85-94, at page 86.

recreational purposes are *genuinely* recording brain signals; the suggestion is that they might instead be responding to facial muscle movement.⁸⁰⁸ If this is the case, misleading marketing could indeed have a detrimental impact on public understanding of the capabilities and limitations of non-invasive BCIs. It has been suggested that it would be to the benefit of games developers to be open about the likelihood of signal interference and make a virtue of the fact that they are not ‘pure BCI’.⁸⁰⁹

Box 8.2: Commercially available BCI-based games

Current commercially available gaming applications are relatively limited. These include:

- A range of on-screen games based around simple challenges, such as rebuilding Stonehenge from fallen blocks, that can be downloaded onto a personal computer or mobile device for use with an EEG headset;⁸¹⁰
- an EEG headset incorporating furry ‘cat ears’ that adopt upright, lowered or wiggling positions purportedly depending on whether the user is in a state of mind described as ‘focused’, ‘relaxed’, or ‘in the zone’;⁸¹¹ and;
- three-dimensional games in which players can try to make a ball hover suspended in vertical tube⁸¹² or to move across a board using a signal recorded from an EEG headband. In the latter, the ball’s movement apparently depends on the players maintaining a calm or relaxed state of mind.⁸¹³

Other related applications

Neurofeedback

8.21 Bridging the categories of novel neurotechnologies designed for enhancement or recreational purposes are non-invasive EEG-based BCI devices marketed with the purported purpose of permitting users to improve their concentration, relaxation, cognitive capacities, or mood using ‘neurofeedback’.⁸¹⁴ Neurofeedback refers to the method by which a BCI-controlled device provides the user with information (usually visual) about the kind of brain signals they are producing in performing particular task, thus permitting them to adjust the way they go about this task and thereby, supposedly, ‘training’ their brain. These devices often comprise a gaming element. The ‘Mindball’ application described in Box 8.2, in which a ball is moved across a table using active BCI control, is marketed in both ‘game’ and ‘training device’ forms, with the latter apparently particularly aimed at use in children.⁸¹⁵

8.22 Attention deficit/hyperactivity disorder (ADHD) is a recognised mental health disorder in children. However, the potential for over-diagnosis of ADHD⁸¹⁶ and the diversion of pharmacological treatments such as Ritalin to be used for cognitive enhancement suggest that ADHD diagnoses can be used to exploit the ambiguous area between treatment of impairment

⁸⁰⁸ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* 4(3): 1-22, at page 12; Future-BNCI (2012) *Future BNCI: a roadmap for future directions in brain / neuronal computer interaction research*, available at: http://future-bnci.org/images/stories/Future_BNCI_Roadmap.pdf, at page 73.

⁸⁰⁹ Plass-Oude Bos D, Reuderink B, van der Laar B *et al.* (2010) Brain-computer interfacing and games, in *Human-computer Interaction Series*, Tan DS, and Nijholt A (Editors) (London: Springer-Verlag), at page 172.

⁸¹⁰ Emotive.com (2013) *Featured applications*, available at: <http://emotiv.com/consumers/>; NeuroSky (2013) *MindWave Mobile: MyndPlay Bundle*, available at: <http://store.neurosky.com/products/mindwave-mobile>.

⁸¹¹ Neurosky (2013) *Necomimi: brainwave cat ears*, available at: <http://www.neurosky.com/necomimi/>.

⁸¹² NeuroSky (2009) *Uncle milton star wars force trainer* available at: <http://company.neurosky.com/products/force-trainer/>;

Mindball (2012) *Interactive productline*, available at: <http://www.mindball.se/product.html>.

⁸¹³ Mindball (2012) *Products*, available at: <http://www.mindball.se/trainer.html>.

⁸¹⁴ Nijholt A, Plass-Oude Bos D and Reuderink B (2009) Turning shortcomings into challenges: brain-computer interfaces for games *Entertainment Computing* 1(2): 85-94. Neurofeedback is a kind of ‘biofeedback’ which refers to generally to the use of tools to gain information about the effective functioning of physiological systems so that intentional efforts can be made to improve performance of these systems.

⁸¹⁵ Mindball (2012) *Products*, available at: <http://www.mindball.se/trainer.html>.

⁸¹⁶ Scituito MJ and Eisenberg M (2007) Evaluating the evidence for and against the overdiagnosis of ADHD *Journal of Attention Disorders* 11(2): 106-13.

and improvement of function beyond the normal range. As such, new treatments targeted at ADHD may be a means of neuroenhancement for some users, as well as a treatment for others.

- 8.23 EEG-based neurofeedback is growing rapidly as a form of alternative treatment for attention deficit/hyperactivity disorder (ADHD). Neurofeedback software and equipment advertised as improving the symptoms of ADHD are being marketed in the form of toys and games, such as simple video games (for example, Pac-Man)⁸¹⁷ and systems that connect to commercially-available video games using Sony PlayStation or Nintendo Xbox.⁸¹⁸ Immersive virtual reality environments are also in development.⁸¹⁹ At present, the majority of reviews are cautious about recommending neurofeedback for treatment of ADHD.⁸²⁰ However, the practice of 'home neurofeedback' is likely to grow, given that the method combines gaming with an ostensible therapeutic function.

Research and training uses

- 8.24 BCI games are still predominantly used in research environments rather than in commercial applications. This research is not only aimed at developing commercial gaming products. Basic games are used to maintain users' interest and encourage performance improvement as part of the training phase of research into the potential assistive uses of BCI technologies.⁸²² Research using games is also conducted to better understand features of human-computer interaction that would improve the experiences of anyone using a computer for work, recreation, therapeutic, or assistive purposes.⁸²³

Box 8.3: Investigating the uses of invasive BCIs

Given the disproportionate balance of the risks of surgery to anticipated benefits, using BCIs implanted directly in the *brain* for non-therapeutic purposes still lies in the realm of science fiction. However, Professor Kevin Warwick of the University of Reading has experimented with a series of technological enhancements enabled by such an implant in his own peripheral nervous system (PNS) – in his arm – over a three-month period. This permitted him to extend his sensory range by experiencing ultrasonic sensory input to give an indication of distance. It took six weeks for his brain to learn to recognise the electrical pulses injected into his nervous system. Electrodes were also inserted into his wife's PNS, permitting electronic signals to be transmitted between their nervous systems via the internet. Every time his wife closed her hand, an electrical pulse was injected into Professor Warwick's nervous system which his brain was able to recognise and *vice versa*.⁸²¹

Creative applications

- 8.25 Studies have been conducted into applications permitting users to make music or to 'paint' using non-invasive BCIs. These not only offer novel means of self-expression for both able-

⁸¹⁷ Fuchs T, Birbaumer N, Lutzenberger W, Gruzelier JH and Kaiser J (2003) Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate *Applied Psychophysiology and Biofeedback* **28**(1): 1-12, at page 4.

⁸¹⁸ SmartBrain Technologies (2008) *Smartbrain technologies*, available at: <http://www.smartbraintech.com/>.

⁸¹⁹ OpenViBE (2012) *A BCI based virtual reality solution for ADHD treatment (prototype)*, available at: <http://openvibe.inria.fr/a-bci-based-virtual-reality-solution-for-adhd-treatment-prototype/>.

⁸²⁰ Bard I and Singh I (2013) ADHD: improving performance through BCI, in *Handbook of Neuroethics*, Clausen J, and Levy N (Editors) (London: Springer).

⁸²¹ Warwick K, Gasson M, Hutt B *et al.* (2004) Thought communication and control: a first step using radiotelegraphy *Communications, IIE Proceedings* **151**(3): 185-9, pp. 187-8.

⁸²² Marshall D, Coyle D, Wilson S and Callaghan M (2013) Games, gameplay and BCI: the state of the art *IEEE Transactions on Computational Intelligence and AI in Games* **5**(2).

⁸²³ Plass-Oude Bos D, Reuderink B, van der Laar B *et al.* (2010) Brain-computer interfacing and games, in *Human-computer Interaction Series*, Tan DS, and Nijholt A (Editors) (London: Springer-Verlag), at page 172.

bodied users, but also offer particular pleasure and even therapeutic benefits for disabled users.⁸²⁴

Future prospects: limitations and opportunities

8.26 The potential customer-base for recreational BCI applications is far greater than that for assistive BCIs, and the regulatory requirements for devices not intended for medical uses will be less stringent. Recreational BCIs are therefore likely to present an attractive investment opportunity.⁸²⁵ One company that sells a chip chiefly for use in gaming BCIs has estimated that five million devices incorporating this chip were sold in 2011.⁸²⁶ The literature in this field reflects optimism and inventive ambition amongst BCI researchers about what might be achieved through BCI gaming in the future.⁸²⁷ However, the real-world promise of BCI-controlled games and any corollary commercial viability remains under debate. One clear point of agreement is that these benefits will not be realised unless BCI offers improvements over traditional gaming interfaces, about which indications are mixed. On one hand, currently commercially available BCI games are primitive in what they permit players to do when compared with the sophistication of popular non-BCI games.⁸²⁸ On the other hand, games that are able to make direct use of brain signals offer novel and potentially more direct mode of interaction than games that are reliant on conventional controls (such as joysticks and keyboards) which may assist players' sense of immersion in a game. For example, game-play could respond directly to a player's affective state,⁸²⁹ or to brain signals that precede players' conscious awareness of which move they plan to make.⁸³⁰ One indication of the kind of enthusiasm that might greet these kinds of capabilities may be seen in the following response to the Working Party's consultation:

"I would use technology that intervenes in the brain for many non-medical uses, think of a simulation game where it tricks your brain into believing you are working out or using your muscles vigorously, therein building actual muscle mass. Or being in such immersive virtual reality that you can actually fly or live out your dreams in a completely safe and isolated environment."⁸³¹

⁸²⁴ Muenssinger JI, Halder S, Kleih SC *et al.* (2010) Brain painting: first evaluation of a new brain-computer interface application with ALS-patients and healthy volunteers *Frontiers in Neuroscience* **4(182)**; Future-BNCI (2012) *Future BNCI: a roadmap for future directions in brain / neuronal computer interaction research*, available at: http://future-bnci.org/images/stories/Future_BNCI_Roadmap.pdf, at page 75.

⁸²⁵ Nijboer F, Allison BZ, Dunne S *et al.* (2011) A preliminary survey on the perception of marketability of brain-computer interfaces (BCI) and initial development of a repository of BCI companies, in *Proceedings 5th International Brain-Computer Interface Conference* (Verlag der Technischen Universitaet Graz, Austria), pp. 344-7; Plass-Oude Bos D, Reuderink B, van der Laar B *et al.* (2010) Brain-computer interfacing and games, in *Human-computer Interaction Series*, Tan DS, and Nijholt A (Editors) (London: Springer-Verlag), at page 150.

⁸²⁶ Wired (2011) *Meet NeuroSky's mind controller headset*, available at: <http://www.wired.co.uk/magazine/archive/2011/07/start/mind-controller>.

⁸²⁷ Marshall D, Coyle D, Wilson S and Callaghan M (2013) Games, gameplay and BCI: the state of the art *IEEE Transactions on Computational Intelligence and AI in Games* **5(2)**.

⁸²⁸ Nijholt A, Plass-Oude Bos D and Reuderink B (2009) Turning shortcomings into challenges: brain-computer interfaces for games *Entertainment Computing* **1(2)**: 85-94, at page 88.

⁸²⁹ Plass-Oude Bos D, Reuderink B, van der Laar B *et al.* (2010) Brain-computer interfacing and games, in *Human-computer interaction series*, Tan DS, and Nijholt A (Editors) (London: Springer-Verlag), at page 172; Allison BZ, Dunne S, Leeb R, Millan JdR and Nijholt A (2013) Recent and upcoming BCI progress: overview, analysis, and recommendations, in *Towards practical brain-computer interfaces: bridging the gap from research to real-world applications*, Allison BZ, Dunne S, Leeb R, Millan JdR, and Nijholt A (Editors) (London: Springer), at page 2.

⁸³⁰ Although not yet commercially realised, it has been suggested that devices which record lateralised readiness potential (LRP - signals thought to be associated with preparation for motor activity) will allow 'preconscious' game play of this kind. See: Plass-Oude Bos D, Reuderink B, van der Laar B *et al.* (2010) Brain-computer interfacing and games, in *Human-Computer Interaction Series*, Tan DS, and Nijholt A (Editors) (London: Springer-Verlag), at page 153.

⁸³¹ An anonymous respondent, response to Working Party's Public Consultation.

Ethical and governance issues raised by enhancement and recreational applications

8.27 In many respects, non-invasive neurostimulation and EEG-based neurofeedback used for neural enhancement, and BCI gaming applications raise similar ethical issues. On the basis of current research evidence, a question mark hangs over whether these technologies can actually deliver *practical* applications. However, in each field, the promise of early research is subject to a degree of popular and commercial hype. We examine these shared issues below, alongside those raised more particularly by neural enhancement.

Need

8.28 As we noted at the start of this chapter, the ethical framework we developed in Chapter 4 is designed to assess the ethical issues raised by therapeutic applications and may not always be suitable for non-therapeutic contexts. Most obviously the question of ‘need’ clearly has less obvious applicability in respect of non-therapeutic applications. The absence of need nevertheless sets a challenge to demonstrating how innovation in these fields fulfils one of the criteria we endorse for Responsible Research and Innovation ((RRI), as described in Chapter 6): that there must be a clearly identified need for a technology that fulfils a valuable social benefit and does not threaten to undermine other social values.

8.29 In the absence of a clear demonstration of need, research and development of non-therapeutic interventions does not straightforwardly instantiate the virtue of inventiveness. One respect, however, in which it *may* be present, is where innovation in these fields could also help development of therapeutic or assistive technologies. For example, there are close similarities between BCI gaming devices and EEG-based devices used in therapeutic contexts.⁸³² It is tempting to infer from this that investment and innovation in the field of gaming could give rise to valuable corollary innovations for disabled users, for example in designing assistive neurotechnologies with more user-friendly interfaces and equipment.⁸³³ Caution is warranted in making this assumption, however, as devices offering genuine utility to disabled users will typically require a higher number of electrodes, to be more robust, and to have more specialised training and support available than with those used for gaming.⁸³⁴ Crucially, while performance and reliability do not pose serious problems in gaming, they present significant barriers to ethically and legally acceptable therapeutic uses.⁸³⁵ This notwithstanding, the benefits offered by BCI games – in terms of users’ enjoyment, relaxation and imaginative expression – should not be overlooked. This is particularly so for individuals with severe movement disorders, for whom BCI gaming offers a valuable avenue for entertainment and competition; for example, by providing a disabled parent with a new opportunity to play with their children.⁸³⁶

⁸³² Nijholt A, Plass-Oude Bos D and Reuderink B (2009) Turning shortcomings into challenges: brain-computer interfaces for games *Entertainment Computing* **1(2)**: 85-94, at page 88.

⁸³³ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4(3)**: 1-22, at page 11; Zander TO and Kothe C (2011) Towards passive brain-computer interfaces: applying brain-computer interface technology to human-machine systems in general *Journal of Neural Engineering* **8(2)**: 1-5.

⁸³⁴ Coyle D, Carroll A, Stow J *et al.* (2012) Enabling Control in the minimally conscious state in a single session with a three channel BCI (Paris: 1st international DECODER workshop); Future-BNCI (2012) *Future BNCI: a roadmap for future directions in brain / neuronal computer interaction research*, available at: http://future-bnci.org/images/stories/Future_BNCI_Roadmap.pdf, at pages 65 and 212.

⁸³⁵ Luna P (2011) Controlling machines with just the power of thought *Lancet Neurology* **10(9)**: 780-1, at page 781. Indeed, it has been suggested that unreliability may provide an enjoyable challenge for gamers: Nijholt A, Plass-Oude Bos D and Reuderink B (2009) Turning shortcomings into challenges: brain-computer interfaces for games *Entertainment Computing* **1(2)**: 85-94, at page 89.

⁸³⁶ Coyle D, Carroll A, Stow J *et al.* (2012) Enabling Control in the minimally conscious state in a single session with a three channel BCI (Paris: 1st international DECODER workshop)

Uncertainty

8.30 While the virtue of inventiveness might not be wholly absent from research and innovation in this field, the imperative to reconcile this with the virtues of responsibility and humility is even stronger than in innovation directed at therapeutic ends. Research into uses of novel neurotechnologies to improve human capacities, or for gaming, is in its infancy and the potential benefits, let alone risks, remain largely unknown. The problem of uncertainty is particularly acute outside of paradigmatic treatment contexts as it is not clear how benefits are to be assessed and what constitutes proportionate risk where an intervention is non-essential.

Uncertain benefits

8.31 Uncertainty about the benefits of neural enhancement applies not only to the specific question of whether neurodevices can actually deliver improvements in cognitive abilities or mood in real world settings, but also to the broader question of whether neural enhancements constitute unequivocal advantages at all. For example, some *prima facie* enhancements, such as improved memory, may, in practice, turn out to be detrimental if they prevent someone from discarding painful memories or disregarding distracting information.⁸³⁷ The individual benefits of neurostimulation for neural enhancement purposes remain unproven. Even if they *were* shown to be effective, the public (as opposed to individual) benefit that would be served by widespread enhancement is questionable when individual positional advantages enjoyed by those with improved capacities are, inevitably, enjoyed at the expense of others.⁸³⁸

Uncertain safety risks

8.32 Expectations of serious health risks in respect of the kinds of non-therapeutic applications we discuss here are low. However, as we have observed in earlier chapters, our still limited knowledge of how the brain works, coupled with its central role in many aspects of a meaningful existence, means that unintended effects of intervening come at a potentially high cost.

8.33 As we observe in Chapter 2, neither TMS nor TDCS raise serious safety issues if they are used according to the appropriate parameters for treatment or research involving humans.⁸³⁹ Nevertheless, the long-term unintended effects of *repeated* uses of non-invasive neurostimulation are not yet clear.⁸⁴⁰ The uncertainty here is of particular relevance where neurostimulation may be self-administered without appropriate medical supervision. While TDCS, compared with TMS, poses even fewer safety concerns, it is also a more portable, cheap, and easily self-administered technology. This raises the prospect that it may be more widely marketed directly to consumers, widening the field for any concerns we might have about its use.

8.34 Seeking to modify brain function through neural stimulation has been likened to “adjusting the weights on a complicated mobile”, in the sense that enhancement of abilities of one kind could be accompanied by deleterious effects to other abilities.⁸⁴¹ Humility therefore requires that all parties remain mindful of how little is known about the effects of intervening in the brain in this

⁸³⁷ Farah MJ and Wolpe PR (2004) Monitoring and manipulating brain function: new neuroscience technologies and their ethical implications *Hastings Center Report* **34(2)**: 35-45, at page 42.

⁸³⁸ Indeed, some have suggested that cognitive enhancement only increases the likelihood of the emergence of destructive malicious powers. See: Persson I and Savulescu J (2008) The perils of cognitive enhancement and the urgent imperative to enhance the moral character of humanity *Journal of Applied Philosophy* **25(3)**: 162-77.

⁸³⁹ Rossi S, Hallett M, Rossini PM and Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research *Clinical Neurophysiology* **120(12)**: 2008-39, at page 2022.

⁸⁴⁰ Illes J, Gallo M and Kirschen MP (2006) An ethics perspective on transcranial magnetic stimulation (TMS) and human neuromodulation *Behavioural Neurology* **17(3-4)**: 149-57, at page 151.

⁸⁴¹ Hamilton R, Messing S and Chatterjee A (2011) Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation *Neurology* **76(2)**: 187-93, at page 190.

way. It also recommends that, in conducting research and reporting findings, researchers attend equally to unintended or disappointing findings, rather than seeking only to publicise positive findings of enhanced performance.

- 8.35 The risks of non-invasive BCIs using EEG are thought to be minimal. However, there has been no systematic research into the long-term effects of their use for recreational purposes.⁸⁴² The most plausible long-term risks are those relating to the brain's inherent plasticity and the potential to change connectivity and the functions of particular regions due to repeated use of the same neuronal pathways, for example, while striving to generate the motor signals required to play a game.⁸⁴³ If we accept that non-invasive BCIs may, through exploitation of brain plasticity, be effective rehabilitation tools (for example, in assisting stroke patients to re-learn motor functions), then we cannot reasonably exclude the possibility of less desirable effects related to plasticity.⁸⁴⁴

Risks to children

- 8.36 Particular attention is warranted in respect of any unintended impacts on children's brains of devices that use neurostimulation, function by influencing brain plasticity, or encourage the repeated use of particular neural pathways, as the effects of these on the developing brain are still largely unknown. This concern is particularly acute given that children are likely to be a key target group both for cognitive enhancement for educational purposes, and for BCI gaming. Several of the games referred to in Box 8.2 above are explicitly targeted at younger age groups, using images of children in their marketing materials.⁸⁴⁵
- 8.37 The use of neurodevices (and chemical agents) by children and young people for purposes of enhancement has particular social and ethical implications that require focused scrutiny and analysis. It is especially important that these analyses do not simply translate normative judgments on adult enhancement practices or intentions to children. Because children are more vulnerable to many effects of neuro-enhancers than adults and rely on proxies for their care, the barriers to use of cognitive enhancers should be much higher than those for adults.⁸⁴⁶

Addressing uncertainty

- 8.38 These uncertainties appear to point to the need to gather more evidence about the efficacy of neural enhancements using novel neurotechnologies and the longer-term effects of BCI gaming. However, research into the non-therapeutic applications discussed here itself raises ethical concerns because it would involve non-essential interventions – albeit non-invasive – in the human brain. While it is still not possible to provide prospective research participants with clear information about the longer-term and unintended effects of interventions, questions arise about whether their consent to participate can yet be truly informed. Unlike therapeutic research, these concerns are not so readily offset by arguments that a small degree of risk might be proportionate and defensible in relation to the public good served by health-focused research.
- 8.39 The reasonably anticipated risks of neurostimulation and non-invasive BCI use are not so serious as to warrant prohibiting neurostimulation research directed at non-therapeutic ends in adults. Moreover, given the complex and non-linear innovation trajectories of many novel

⁸⁴² Vlek RJ, Steines D, Szibbo D *et al.* (2012) Ethical issues in brain–computer interface research, development, and dissemination *Journal of Neurologic Physical Therapy* **36(2)**: 94-9, at page 97.

⁸⁴³ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4(3)**: 1-22, at page 7.

⁸⁴⁴ Caria A, Weber C, Brötz D *et al.* (2011) Chronic stroke recovery after combined BCI training and physiotherapy: a case report *Psychophysiology* **48(4)**: 578-82; Vlek RJ, Steines D, Szibbo D *et al.* (2012) Ethical issues in brain–computer interface research, development, and dissemination *Journal of Neurologic Physical Therapy* **36(2)**: 94-9, at page 97.

⁸⁴⁵ See, for example, NeuroSky (2009) *Uncle Milton star wars force trainer* available at: <http://company.neurosky.com/products/force-trainer/>.

⁸⁴⁶ Singh I and Kelleher KJ (2010) Neuroenhancement in young people: proposal for research, policy, and clinical management *AJOB Neuroscience* **1(1)**: 3-16.

technologies, it may not always be possible wholly to disentangle the generation of new knowledge in this area from that which may benefit our understanding of brain structure and functioning in way that serves therapeutic or assistive ends. Nevertheless, because of the uncertain balance between public benefits and individual risks to participants, there is a need for ethical oversight to ensure the value and quality of studies using neurotechnologies directed at non-therapeutic research questions and to avoid unnecessary interventions in the brain. **We recommend that institutional ethics committees reviewing research proposals for studies using neurostimulation directed at non-therapeutic ends ensure that these meet high standards of originality and rigour. The aim should be to prevent the use of poorly defined protocols and the unnecessary repetition of similar studies, and to make sure participants are informed about the limited knowledge of long-term unintended health effects.**

- 8.40 Given that some children currently play BCI games, and it is possible that parents and educators may be interested in using non-invasive BCIs and neurostimulation to bring putative educational benefits for children, a responsible approach requires that further research is conducted to better understand the effects of these uses on the developing brain. However, precisely this uncertainty means that an unqualified call to explore these questions through *interventional* research involving children would be in tension with the virtues of responsibility and humility. **We therefore recommend that there is a need for observational studies of children, who are already using neurodevices for gaming, or to improve their capacities for attention or learning, to assess the benefits and risks of these interventions, including their effect on the developing brain.**
- 8.41 **Recalling our recommendation from Chapter 5 for clinical experiences of experimental treatment interventions and small studies to be recorded in registers, we would further recommend that the findings – including negative or inconclusive outcomes – from research investigating non-therapeutic effects of novel neurotechnologies should also be included in these registers.** This would not only mean that current evidence of benefits and unintended effects are brought together to reach the widest audience and achieve cross-fertilisation of valuable findings from therapeutic and non-therapeutic protocols, it would also help to prevent the unnecessary repetition of similar studies and to challenge and correct some of the problems of small sample sizes and research and reporting integrity noted earlier in this chapter.

Privacy and data protection

- 8.42 As we noted in Chapter 5, all neurodevices that use electrodes are vulnerable to interference and disruption (paragraph 5.52). Furthermore, where BCIs collect or transmit data about brain activity or brain states, this raises ethical and legal questions about how data collected by these devices can be used.⁸⁴⁷ These issues do not differ significantly in this context from those we have already discussed in Chapter 5 in relation to therapeutic applications. However, as gaming applications of BCIs become more prevalent and affordable, their sheer ubiquity raises the prospect of greater quantities of data relating to users' neural activity being transmitted or collected by devices. A distinct privacy issue arises in respect of the capacity for some BCI games to respond to directly to players' affective states. This provides one of their unique selling points, but might also expose emotional states in ways for which players used to conventional games might not be prepared.⁸⁴⁸ A further kind of privacy concern relating to the involuntary extraction of information has only been demonstrated through research and is not yet a realistic threat, but introduces a possible area for vigilance. One study has indicated that EEG computer-

⁸⁴⁷ Future-BNCI (2012) *Future BNCI: a roadmap for future directions in brain / neuronal computer interaction research*, available at: http://future-bnci.org/images/stories/Future_BNCI_Roadmap.pdf, at page 106.

⁸⁴⁸ Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* 4(3): 1-22, at page 13.

gaming headsets could be maliciously modified in ways intended to obtain private information. Hacked headsets might permit a third party to identify when a user is viewing something important (such as their bank PIN).⁸⁴⁹ These headsets would work by permitting an unauthorised party to know when the user's brain produces signals (those associated with the recognition of a stimulus of particular significance), combined with information about the stimulus that elicited this response.

- 8.43 These examples illustrate ways in which BCI-game players' expectations about who will have access to information about their brain activity or their states of mind might differ from the expectations of patients. While a person using neurodevices for therapeutic or assistive reasons might reasonably expect data collected by these devices to be shared within the team responsible for their clinical care, an online gamer might, in contrast, require more explicit advance notification if data about their neural activity were to be gathered, (for example, for consumer research purposes). As we discussed in Chapter 5, what counts as a 'reasonable expectation' of how such data will be used could make a difference to whether privacy and confidentiality concerns arise. The European Radio and Telecommunications Terminal Equipment Directive, under which computer gaming devices are regulated, empowers the European Commission to decide that certain classes of equipment must incorporate safeguards to protect privacy and personal data.⁸⁵⁰ As commercially available BCI-based games become more sophisticated, it may be necessary for the European Commission to consider enhanced regulation under this provision.

Particular ethical concerns raised by neural enhancement

- 8.44 Our analysis thus far has not yet addressed the much debated ethics of neural enhancement *per se* – that is, when might it be unacceptable, defensible, or even obligatory for people to use technologies to 'extend or amplify the core capacities of the mind' (using the definition introduced Box 8.1).⁸⁵¹ It is not obvious that the kinds of neural enhancement that might potentially be achieved using the categories of neurotechnologies we discuss in this report differ in ethically significant ways from those achieved through the use of pharmaceuticals. For example, *if* the pertinent concern is that neural enhancement could undermine the authenticity of one's actions by removing personal effort and endeavour, then it is not clear that the particular kind of technology by which the advantage is achieved is strongly relevant – although its cost and availability might be. The discussions of this report so far have been premised on the assumption that, just because novel neurotechnologies are tools external to and intervening in our brains, this does not mean that the mere fact of their use automatically undermines the autonomy or authenticity of the activities they enable (see paragraph 4.29). Moreover, in this report, we have sought to avoid speculation about the ethical implications of (as yet) unrealised technological capacities. The very early state of research and the limited evidence of the possibility of achieving meaningful neural enhancement using neurostimulation mean that detailed discussion of its harms or benefits *qua* enhancements (rather than *qua* intervention) is not yet warranted. For this reason, we limit our discussion here to ethical issues that might arise even if novel neurotechnologies were not effective in extending human capacities, but some people (either developers or users) were nevertheless sufficiently convinced that they *could* be.
- 8.45 Concerns that unequal access to the means and benefits of neural enhancement might give rise to injustice (and a consequent corrosion of solidarity between members of a community)

⁸⁴⁹ Martinovic I, Davies D, Frank M *et al.* (8-10 August 2012) On the feasibility of side-channel attacks with brain-computer interfaces *Presentation to the Usenix Security Symposium 2012*, (Bellevue, WA).

⁸⁵⁰ Article 3, paragraph 3(c) of Directive 1999/5/EC of the European Parliament and of the Council of 9 March 1999 on radio equipment and telecommunications terminal equipment and the mutual recognition of their conformity.

⁸⁵¹ Farah MJ, Illes J, Cook-Deegan R *et al.* (2004) Neurocognitive enhancement: what can we do and what should we do? *Nature Reviews Neuroscience* **5**(5): 421-5; BMA (2007) *Boosting your brainpower: ethical aspects of cognitive enhancement* (London: BMA); Greely H, Sahakian B, Harris J *et al.* (2008) Towards responsible use of cognitive-enhancing drugs by the healthy *Nature* **456**(7223): 702-5; Bostrom N and Sandberg A (2009) Cognitive enhancement: methods, ethics, regulatory challenges *Science and Engineering Ethics* **15**(3): 311-41; Hamilton R, Messing S and Chatterjee A (2011) Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation *Neurology* **76**(2): 187-93.

depends on there being a demonstrable benefit to healthy users at all – precisely what is yet to be demonstrated in the case of neurostimulation or neurofeedback. Nevertheless, injustice could arise even (or perhaps particularly) if the evidence of effective enhancement is doubtful, if finite resources and expertise are invested in pursuing non-essential innovations for the privileged few, or the ‘worried well’, at the expense of therapeutically-directed research. This could be seen as the hijacking of inventiveness for ends of questionable social value. However, even this might not represent an unalloyed harm, given the non-linear and intertwined nature of research and innovation trajectories of therapeutic and non-therapeutic novel neurotechnologies.

- 8.46 A further ethical concern that arises in respect of enhancement technologies is that people may be coerced into using them when they would not otherwise choose to; either by explicit pressure from employers, educators or parents,⁸⁵² or because the use of a (putative) enhancement becomes so widespread that individuals fear positional disadvantage if they do not join in. Each of these possibilities, but especially explicit pressure, may be seen as infringements of autonomy. Importantly, given our caveat above, this pressure could persist irrespective of actual efficacy, provided some of the parties involved believe neurotechnological interventions to be effective. Coercive pressure to improve oneself is, of course, not uncommon in educational or employment contexts. However, it is of particular concern in respect of neurotechnologies because it pertains to individuals’ choices about what is done to their brain (an organ that we have recognised has special status in people’s lives, in which the effects of intervening remain uncertain). It is not clear the extent to which coercive pressure to use neurotechnologies for enhancement purposes is yet a problem in civilian life, however it may be a particular ethical concern in military contexts, which we consider further in the second part of this chapter (see paragraph 8.86).

Effective and proportionate oversight of neurodevices for non-medical purposes

- 8.47 One commentary on the ethics of neural enhancement has observed that, despite persistent uncertainties about safety and longer term impacts of neural enhancement technologies, these do not raise serious ethical problems because all stakeholders will be equally motivated to protect against them.⁸⁵³ We suggest that this conclusion is too swift in the context of the technologies we are discussing here because it ignores two practical distinctions between the oversight of pharmaceuticals and neurodevices. The first of these relates to the nature of the regulatory frameworks that apply to marketing neurodevices, particularly when these are not classed as ‘medical devices’. The second relates to the likelihood that neurodevices will be used for non-therapeutic purposes outside health care settings.

Regulating the technologies

- 8.48 When a manufacturer wishes to place particular classes of product (including electronic and medical devices) on the market in Europe, it is necessary for that product to conform to the relevant European legislation governing its marketability.⁸⁵⁴ The ‘CE-mark’ is the indication that the manufacturer has taken the necessary steps to ensure their product’s conformity. Devices intended to be marketed for non-therapeutic neurostimulation, neurofeedback or recreational purposes are unlikely to be classed as ‘medical’ under the definition of the Medical Devices Directive.⁸⁵⁵ If a manufacturer seeks to market a non-invasive neurostimulation or BCI device

⁸⁵² The Academy of Medical Sciences, British Academy, Royal Academy of Engineering, The Royal Society (2012) *Human enhancement and the future of work*, available at: <http://www.acmedsci.ac.uk/p47prid102.html#downloads>, pp. 44-5.

⁸⁵³ Hamilton R, Messing S and Chatterjee A (2011) Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation *Neurology* **76(2)**: 187-93, at page 190.

⁸⁵⁴ Department for Business, Innovation and Skills (2012) *CE marking*, available at: <https://www.gov.uk/ce-marking>.

⁸⁵⁵ A “‘medical device’ means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human

for non-medical purposes, it is likely to be regulated under the regimes relating to generic electrical equipment or radio and communications devices.⁸⁵⁶ CE-marks have been granted for the sale of BCI games and EEG neurofeedback devices (see Box 8.2). However, as far as we are aware, neither TMS nor TDCS devices have received CE-marks for non-therapeutic purposes.

- 8.49 Under the regulatory regimes covering non-medical devices, the scrutiny and oversight of health impacts on users is likely to be light touch. Non-medical electronic products must meet basic safety requirements if they are to carry a CE mark, which will take into account, for example, risks from high temperatures, or electromagnetic fields.⁸⁵⁷ However, this is unlikely to encompass the kinds of obligations to provide data from clinical investigations, or from the relevant scientific literature, that fall upon manufacturers of devices seeking CE-marking for *medical* purposes.⁸⁵⁸ This raises concerns about the effectiveness and proportionality of regulation of devices for non-therapeutic purposes.
- 8.50 Our discussion in Chapter 7 acknowledges that the current framework for regulating medical devices in UK and the rest of Europe is not perfect. This includes, for example, the lack of transparency and oversight of the Notified Bodies responsible for determining conformity of devices with legislative requirements; the fact that devices can receive CE-marks on the basis of equivalence data rather than specifically conducted clinical investigations; and uneven oversight and reporting of post-market surveillance activities. However, we also welcome current proposals from the European Commission that signal improvements on all these fronts.⁸⁵⁹ Moreover, despite current shortcomings, the obligations upon manufacturers under the Medical Devices Directive require conformity with clinical safety and performance standards that are appropriate to devices that intervene in the human body and impact upon human health.⁸⁶⁰ Furthermore, medical devices are regulated by the MHRA with the attendant oversight informed by expertise and experience in matters of human health that this entails. The MHRA is not, however, responsible for regulating devices intended for non-medical purposes. A further lacuna relates to the transparency of information, and post-market surveillance data in particular, which will not be captured on the centralised European Databank on Medical Devices (Eudamed) if a neurodevice is not regulated as a medical device.
- 8.51 It might seem both inconsistent and disproportionate that a neurostimulation device marketed for a non-medical purpose, but which nevertheless has the same capacity to intervene in the brain and impact upon its functions, should not be subject to the same level and kind of regulatory oversight as it would if marketed for a medical purpose. We suggest that this is a considerable gap in the regulation of novel neurotechnologies, one that is of particular concern in respect of TMS and TBS devices, which are classified under the Medical Devices Directive as ‘medium risk’, because they are ‘active’ in administering or exchanging energy.⁸⁶¹

beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process; [or] control of conception.” See: Article 1, Paragraph 2(a) Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.

⁸⁵⁶ Non-invasive BCI devices that are sold for gaming purposes in Europe are likely to receive marketing approval under either: Directive 1999/5/EC of the European Parliament and of the Council of 9 March 1999 on radio equipment and telecommunications terminal equipment and the mutual recognition of their conformity or, if powered by a voltage not exceeding 24 volts, Directive 2009/48/EC of the European Parliament and of the Council of 18 June 2009 of the safety of toys (as amended). Electrical equipment with a voltage input or output of 50-1500 volts is regulated under: Directive 2006/95/EC of the European Parliament and of the Council of 12 December 2006 on the harmonisation of the laws of Member States relating to electrical equipment designed for use within certain voltage limits.

⁸⁵⁷ For example see Annex 1 of Directive 2006/95/EC of the European Parliament and of the Council of 12 December 2006 on the harmonisation of the laws of Member States relating to electrical equipment designed for use within certain voltage limits.

⁸⁵⁸ MHRA (2012) *Guidance for manufacturers on clinical investigations to be carried out in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf>.

⁸⁵⁹ Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁸⁶⁰ Annex 1 to Council Directive 93/42/EEC of 14 June 1993 concerning medical devices

⁸⁶¹ MHRA (2008) *Bulletin No. 4: conformity assessment procedures*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007492.pdf>.

8.52 As we note in Chapter 7, the EC published proposals for reform to the regulation of medical devices in Europe in 2012 (see Box 7.1). Amongst these is the proposal that some categories of devices – which will be specified in the legislation – “shall be considered medical devices, regardless of whether or not they are intended by the manufacturer to be used for a medical purpose”.⁸⁶² The categories of devices currently falling within the scope of this proposal include contact lenses, dermal fillers, and equipment for delivering intense pulsed light.⁸⁶³ We suggest that non-invasive neurostimulation devices represent interventions in the human brain that could be comparable both in terms of risks to safety, and in terms of the likelihood of being marketed or administered for non-therapeutic purposes, as the devices to be classed as ‘medical’ in the proposed regulation. **We recommend, therefore – in the interests of consistency and of providing effective and proportionate oversight of devices that intervene in the brain – that the European Commission consider including neurodevices that deliver TMS and TBS amongst the categories of devices that would (irrespective of their intended purpose) be regulated as medical devices and that their marketing in the UK is overseen by the MHRA.**

Marketing neurodevices and services

8.53 A CE-mark determines the purpose for which a device may be marketed, but it does not extend to restricting the kind of purpose for which it may then be used. A device may be lawfully used ‘off-label’ (that is, for purposes other than those for which it has received a CE-mark) provided it does not jeopardise customers’ safety or defraud them. The matter of ‘safe use’, however, is somewhat question-begging in this context, as there will not have been regulatory oversight of what constitutes ‘safe use’ for off-label purposes. A device may not, however, be marketed by the manufacturer for an off-label purpose.

8.54 As far as we can ascertain, neurodevices that are most likely to be sold ‘direct to consumers’ (DTC) for their private use at present are non-invasive BCIs designed for gaming or neurofeedback.⁸⁶⁴ In addition to the kinds of games referred to in Box 8.2, it is possible to purchase EEG headbands to monitor the quality of one’s own sleep.⁸⁶⁵ The value of the market for BCI-like personal monitoring devices is potentially considerable.⁸⁶⁶ The risks to user’s health posed by such devices are low. Nevertheless if, for example, BCI games are designed to be particularly immersive, this potentially increases any discomfort or effects on brain plasticity associated with overextended periods of use.

8.55 There is some evidence of online businesses based outside the UK selling TBS⁸⁶⁷ devices or ‘portable’ TMS devices online to consumers.⁸⁶⁸ Non-medically qualified providers also appear to offer non-therapeutic services using neurostimulation devices directly to consumers in the UK.⁸⁶⁹ Where non-invasive neurostimulation devices or services are marketed directly to consumers for non-therapeutic purposes, this means – almost invariably – that they are likely to be used without medically qualified supervision or advice. Even where interventions are not self-administered, there may still be risks associated with service providers who lack the necessary training or skills to determine safe parameters of use, or to recognise if a customer is otherwise

⁸⁶² Article 2(1)(1) to the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).
⁸⁶³ Annex XV of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).
⁸⁶⁴ Factfinding meeting on non-therapeutic applications, 7 September 2012.
⁸⁶⁵ Zeo (2012) *Zeo sleep manager*, available at: <http://myzeo.co.uk/pages/what-is-zeo/>. There is increasing interest in recording and monitoring one’s own health and daily routine inspired by movements such as the ‘Quantified Self’. See: Quantified Self (2012) *About the quantified self*, available at: <http://quantifiedself.com/about/>.
⁸⁶⁶ Mobihealthnews (4 May 2011) *NeuroVigil lands venture funding, impressive valuation*, available at: <http://mobihealthnews.com/10855/neurovigil-lands-venture-funding-impressive-valuation/>.
⁸⁶⁷ Mind Alive Inc. (2012) *Oasis pro*, available at: http://www.mindalive.com/Products_OASIS_Pro.htm.
⁸⁶⁸ Biophysica (2013) *Transcranial magnetic stimulator*, available at: <http://shop.biophysica.com/articles/526.php>.
⁸⁶⁹ Biofeedback & Neurofeedback in York (2012) *Transcranial direct current stimulation*, available at: <http://www.york-biofeedback.co.uk/neurofeedback/tcds.aspx>.

vulnerable or unwell in a way that would make neurostimulation unsafe or unsuitable for them. Furthermore, as discussed in Chapter 5, private businesses may not adequately protect customers' interests in other respects, such as in safeguarding their confidentiality or providing follow-up care (see paragraphs 5.28 to 5.29). There may also be inadequate recording or reporting of incidents in which result in adverse effects. These concerns are compounded by the fact that, outside health care settings, there is a lack of any professional bodies that might oversee services and offer guidance to practitioners or consumers.

- 8.56 The most immediate threat to consumers' interests from the direct marketing of neurodevices and services might relate not to users' physical health, but to their exploitation and the abuse of their trust from false or misleading claims about the benefits of devices or services. The uses and positive effects implied by some of the marketing materials associated with DTC marketing in this field may be seen to extrapolate beyond that which is supported by peer-reviewed evidence and contribute to hype about the capabilities of neurostimulation and neurofeedback, to provide benefits for otherwise healthy users. One business marketing TMS devices states that conditions such as "memory impairment [and] sleepiness" have been "successfully treated" using "Magnetic Deep Brain Stimulation [sic]" and that "savant like creative abilities" have been enhanced.⁸⁷⁰ Another business which markets TDCS devices suggests these might be used for "mood elevation" and "increased concentration".⁸⁷¹ Yet another refers to the use of EEG for "self-improvement" and "mental conditioning".⁸⁷² There is also evidence of UK businesses marketing neurostimulation services by implying that these can improve cognitive performance or mood.⁸⁷³ Those who market devices and services in this way arguably demonstrate a failure of responsibility as unsubstantiated claims of the kind illustrated here interfere with autonomous choice by preventing the informed weighing of risks and benefits by inflating or fabricating the latter.
- 8.57 The European Directives that regulate these technologies are unlikely to offer protection against misleading claims, except insofar as these pertain to the purpose for which the device has received CE-marking and basic product function. The compliance requirements for CE-marking are not concerned with questions of efficacy. So, for example, where a device makes claims for positive benefits in terms of improved concentration or mood, manufacturers would not be required to demonstrate this as a proven benefit in order to use the CE-mark.
- 8.58 This suggests that there are regulatory gaps around the provision of full and honest information to consumers about the limits of knowledge regarding the long-term effects of these devices and the benefits they actually confer. If the claimed benefits *are* sufficiently misleading, this could constitute fraud. Where there is a commercial relationship or contract with a UK business, the gap associated with misleading or fraudulent marketing claims may be partially filled by consumer protection laws including the Consumer Protection from Unfair Trading Regulations 2008, which make it an offence for businesses intentionally to make false claims about the goods or services they sell; and the Control of Misleading Advertising Regulations 1988. The Sale of Goods Act 1979 and the Supply of Goods and Services Act 1982 may also provide for a means for consumers to respond where the goods or services they receive do not conform to those they were led to expect. However, in this context, inefficacy will undoubtedly be challenging for consumers to prove, and it is preferable that users are alerted to any limitations of such technologies *before* undertaking interventions involving their brains.
- 8.59 The risks to consumers' health and well-being from non-invasive neurostimulation are unlikely to be sufficient to warrant restricting consumers' freedom to undertake interventions of questionable efficacy. Where neurodevices and services are marketed to consumers for non-

⁸⁷⁰ Biophysica (2012) *Transcranial magnetic stimulation*, available at: <http://biophysica.com/content/electromedical-devices-instruments/electromedical-devices/transcranial-magnetic-stimulator/tms/>.

⁸⁷¹ Mind Alive Inc. (2012) *Oasis pro*, available at: http://www.mindalive.com/Products_OASIS_Pro.htm.

⁸⁷² Brain Master Technologies, Inc. (2012) *About brainmaster*, available at: <http://www.brainmaster.com/page/about-brainmaster/>.

⁸⁷³ Biofeedback & Neurofeedback in York (2012) *Transcranial direct current stimulation*, available at: <http://www.york-biofeedback.co.uk/neurofeedback/tDCS.aspx>.

therapeutic purposes, we echo here the doubts we expressed in Chapter 5 that attempts to control this are unlikely to be effective or practical, particularly if vendors are based outside the UK. Nevertheless, given the special status of the brain and the potential for hype to distort public understanding of the capacities of neurotechnologies to offer improvements to individuals without brain disorders, businesses offering services using neurodevices for non-therapeutic purposes have a responsibility to adhere to responsible standards of practice that protect their customers' health, and equip potential consumers to make informed choices about the interventions they undertake. **We recommend therefore, that service providers should form a trade association to establish and uphold best practice standards in the sector of non-therapeutic neurostimulation and neurofeedback. These standards would encompass best practice for both the *delivery* of interventions, and the *kind* of information provided to customers.** This means ensuring that customers do not have health problems that would be contraindications were the device to be used in a health care setting; and only delivering interventions in accordance with the most up-to-date information available on safe parameters, including the maximum duration and frequency, of the devices' use. Responsibility and humility also require that service providers supply clear, accurate, and up-to-date information on the purposes for which the device has been approved to be marketed and information about current knowledge (or lack thereof) of its risks and effectiveness in relation to the services they are marketing.

Misrepresentation and trust

- 8.60 Responsibility to represent the capabilities of neurotechnologies extends beyond those who market products and services. As we observed in our brief review of the status of current scientific evidence of the enhancement capacities of neurostimulation and neurofeedback at the beginning of this chapter, some academic researchers may overstate or misrepresent the real-world applications of their findings. The BCI research community has itself recognised that hype regarding the technological capabilities of neurotechnologies is a problem in its own field.⁸⁷⁴ Innovations impacting upon the brain and promising improvements from which we all may benefit (not only when we are unwell) inevitably capture the public imagination and thus also media attention. Small neurostimulation studies, of the kind referred to earlier in this chapter, have been reported in the mainstream media in terms of devices that “unlock our inner potential” or of “morality being modified in the lab”.⁸⁷⁵
- 8.61 While there is undoubted potential in some research into the non-therapeutic utility of neurostimulation, premature claims can impede, rather than accelerate, scientific progress. Unsustainable claims about the enhancement or recreational promise of novel neurotechnologies deceive consumers and raise false expectations. This risks the kind of disenchantment that was evidenced by the backlash against neurofeedback methods in the late 1960s when the promises of (unsuitably designed) research studies were not fulfilled.⁸⁷⁶ Such a backlash could potentially harm research funding.⁸⁷⁷ More importantly, hype by researchers and the popular media undermines public understanding of the current state of scientific understanding of the benefits and risks of these technologies. Where unsubstantiated claims to benefits are made in a commercial context, these risk exploiting the vulnerable or credulous by marketing unproven interventions (at potentially great expense) and intervening in the brain without sound scientific reasons to do so. The ethical consequences of hype would perhaps be

⁸⁷⁴ Nijboer F, Clausen J, Allison BZ and Haselagerd P (2011) Researchers' opinions about ethically sound dissemination of BCI research to the public media *International Journal of Bioelectromagnetism* **13**(3): 108-9.

⁸⁷⁵ BBC News (30 Mar 2010) *Morality is modified in the lab*, available at: <http://news.bbc.co.uk/1/hi/8593748.stm>; Mail Online (8 February 2011) *How a zap to the brain could bring out the genius in you*, available at: <http://www.dailymail.co.uk/sciencetech/article-1353039/How-zap-brain-bring-genius-you.html>.

⁸⁷⁶ Allison BZ, Dunne S, Leeb R, Millan JdR and Nijholt A (2013) Recent and upcoming BCI progress: overview, analysis, and recommendations, in *Towards practical brain-computer interfaces: bridging the gap from research to real-world applications*, Allison BZ, Dunne S, Leeb R, Millan JdR, and Nijholt A (Editors) (London: Springer), at page 10.

⁸⁷⁷ *Ibid.*, at page 10.

at their most serious if disappointment relating to the capabilities of non-essential non-therapeutic applications undermines public understanding of, and trust in, related technologies that offer genuine and much needed therapeutic benefits.

- 8.62 The need to exercise humility and a responsible approach to communicating the non-therapeutic capacities of neurotechnologies, and the limits to these, extends to a wide range of actors. We return to discuss the problem of hype and the respective responsibilities of those involved in more detail in Chapter 9. In view of the priorities for ethical attention identified in this chapter, one particular area of concern that emerges is the coercive use of neurostimulation and neurofeedback interventions with children. As we have noted, the effects of these interventions on the developing brain are, as yet, unclear and children and young people may be less well equipped to resist pressures from educators or parents who wish them to use neurotechnologies to enhance their capacities for learning and educational performance. **We recommend that the departments for education in each of the governments in the UK and the Royal College of Paediatrics and Child Health should issue advice directed to both teachers and parents on the current best evidence, and the evidence gaps, of the efficacy and risks of neurofeedback and neurostimulation for cognitive enhancement in children.**

Military applications of novel neurotechnologies

Introduction

- 8.63 This second part of this chapter concerns the uses of novel neurotechnologies by states for either offensive or defensive military purposes in international and domestic conflicts. As with the other non-therapeutic applications discussed in this chapter, these uses are currently chiefly at a research or proof-of-concept stage. In addition, much of the research being conducted is classified. The examples we draw upon are primarily from development activities funded by the US *Defense Advanced Research Projects Agency* (DARPA), as public access to information on US defence activities is surprisingly open, meaning that it is possible to find out more about US military research than that of perhaps any other nation.⁸⁷⁸
- 8.64 As we noted in the introduction to this chapter, non-therapeutic applications raise a range of distinct ethical and social issues that do not always fit easily into our ethical framework, which was constructed with *therapeutic* neurotechnologies foremost in mind. This distinction is particularly marked when we come to consider military applications, where normative concepts such as 'need' or the duty to avoid harming others take on quite different meanings, as contrasted with those they have in medical contexts. It may, therefore, be appropriate to treat the remainder of this chapter as somewhat separate from our earlier discussions.
- 8.65 This notwithstanding, consideration of military-focused activities is pertinent to the central concerns of this report because investment in this field is considerable. War, medicine and science have long had a symbiotic relationship, and the military has a clear interest in fostering advances in science and technology to enhance the capacities of its own troops and to degrade those of the enemy. Military research and development comprises a significant part of the research and development budget of many high and middle income countries, notably the US, UK, Russia, France, and China.⁸⁷⁹ Since the fall of the USSR, the US military research and development budget has dwarfed that of any other state and has grown following the events of 11 September 2001 through a huge increase in funding for 'biodefense', allocated by the US Department of Homeland Security.⁸⁸⁰ There are no publicly-available statistics on the proportion

⁸⁷⁸ DARPA (2013) *Our work*, available at: http://www.darpa.mil/our_work/.

⁸⁷⁹ Guardian online (17 April 2012) *Military spending: how much does the military cost each country, listed*, available at: <http://www.guardian.co.uk/news/datablog/2012/apr/17/military-spending-countries-list#data>.

⁸⁸⁰ Franco C and Kirk Sell T (2011) Federal agency biodefense funding, FY2011-FY2012 *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* **9(2)**: 117-37; Moreno JD (2012) *Mind wars: brain science in the military in the 21st Century* (New York: Bellevue Literary Press). See also: National Research Council (2013) *Emerging cognitive neuroscience and related technologies* (Washington D.C: National Academies Press).

of this spend which is allocated to research on neurotechnologies, but it is likely to be only a small percentage of the total budget.⁸⁸¹

- 8.66 Psychology was also an early recruit into military science, with an emphasis on interrogation and ‘brainwashing’, and also for the treatment of military personnel suffering from what came to be called post traumatic stress disorder (PTSD). During the 1960s, psychotropic drugs with effects on perception and behaviour such as LSD were explored in a series of clandestine and unethical experiments by the CIA and other US agencies.⁸⁸² DARPA has also funded research into the early development of artificial intelligence and robotics which have played an important role in the development trajectories of today’s novel neurotechnologies.⁸⁸³ In the first decade of the 21st Century, other biological sciences, hitherto more allied to medicine than weaponry, including the neurosciences, have been added to the list of military research priorities.⁸⁸⁴ There has been a steady rise in US military funding of neurobiological research in recent years, along with military and civil research interest in neuroactive agents.⁸⁸⁵
- 8.67 Potential interest in the application of the biomedical sciences to conflict settings is no longer necessary limited to wars fought between states, but may also extend to today’s asymmetric conflicts where the armed forces of technologically advanced, weaponised states may be set against groups of ‘insurgents’. In such conflicts, methods of obtaining *information* (concerning both individuals and organisations) may be of great importance, as is preventative or pre-emptive action taken before any presumed or actual threat. This has led to a convergence of interest between the military, and civil security and policing concerns.⁸⁸⁶ The threat of terrorism has also raised concerns about the so called ‘dual use’ of the products of scientific research for hostile ends.⁸⁸⁷

Defence-funded research into novel neurotechnologies

- 8.68 In addition to considerable investment by government departments in the therapeutic uses of neurotechnologies for treating physical and psychological injuries sustained during conflict (again the evidence of this investment is most apparent in the US, see Box 8.4), there is also notable interest in the *non*-therapeutic military potential of novel neurotechnologies, as we will now discuss. These applications include methods for enhancing the performance of a country’s own troops (for example, through improving surveillance and intelligence-gathering capacities),⁸⁸⁸ but also using neurotechnologies to undermine the capacities of enemy forces, including through enhanced means of interrogation.⁸⁸⁹

⁸⁸¹ It is reported that, in 2011, DARPA invested \$240 million in the brain-machine interaction programme. See: Moreno JD (2012) *Mind wars: brain science and the military in the 21st century* (New York: Bellevue Literary Press), at page 53.

⁸⁸² *Ibid*, pp. 89-90.

⁸⁸³ Graubard SR (1988) *The artificial intelligence debate* (Boston: MIT Press).

⁸⁸⁴ Moreno JD (2011) Brain trust: neuroscience and national security in the 21st century, in *Oxford Handbook of Neuroethics*, Illes J, and Sahakian B (Editors) (USA: Oxford University); Rose H and Rose S (2013) *Genes, cells and brains: the promethean promises of the new biology* (Croydon: Verso).

⁸⁸⁵ Moreno JD (2012) *Mind wars: brain science and the military in the 21st century* (New York: Bellevue Literary Press), pp. 164-5.

⁸⁸⁶ Lutterbeck D (2005) Blurring the dividing line: the convergence of internal and external security in Western Europe *European Security* **14**(2): 231-53.

⁸⁸⁷ For further discussion of the issues of dual use, see: Dando M (2009) Biologists napping while work militarized *Nature* **461**(7258): 950-1; Marchant G and Gulley L (2010) National security neuroscience and the reverse dual-use dilemma *AJOB Neuroscience* **1**(2): 20-2.

⁸⁸⁸ The Greenwall Foundation (2013) *Enhanced warfighters: risk, ethics, and policy* (San Luis Obispo: The Greenwall Foundation).

⁸⁸⁹ Tennison MN and Moreno JD (2012) Neuroscience, ethics, and national security: the state of the art *PLoS Biology* **10**(3): e1001289.

Enhancing effectiveness

- 8.69 In the UK, the Defence Science & Technology Laboratory (DSTL) adopts the role of maximising “the impact of science and technology for the defence and security of the UK.” An indication of DSTL’s interest of the role of neuroscience for military applications may be found in their programme supporting doctoral research on the role of cognitive neuroscience in “understanding, managing and optimising human performance”.⁸⁹⁰ However, as we have already suggested, greater detail may be found in relation to US Government-funded research into enhanced military effectiveness.
- 8.70 With the increasing automation of the battlefield and the complexity of weaponry, there is continued pressure to enhance the speed and accuracy of analysis and decision-making both by combatants themselves and intelligence analysts.⁸⁹¹ For example, on the basis of proof-of-concept research, it has been hypothesised that a helmet-mounted non-invasive EEG worn by pilots could be used to detect neural indications of fatigue or cognitive overload, which would then be used by the BCI system to calibrate the kind of information and support supplied to the pilot.⁸⁹²
- 8.71 BrainGate, a company developing invasive BCIs for assistive technologies (as discussed in Chapter 2), received DARPA funding to enhance the speed, sensitivity and accuracy with which a combatant might analyse incoming information and respond appropriately to threats.⁸⁹³ Similarly, in 2010, DARPA awarded a \$2.4 million contract to a company called Neuromatters to develop a prototype of a novel BCI ‘image triage’ system, termed C3Vision, under its *Cognitive technology threat warning system* research programme.⁸⁹⁴ This programme includes investigation of the use of non-invasive BCIs to enhance the capacity of military personnel conducting intelligence analysis. It identifies potential signs of threat by recognising signals associated with event-related potential (ERP) responses that are triggered by recognition of significant stimuli (in ways similar to the ‘reactive’ games discussed in the first part of this chapter). These signals can be recorded in an operational environment as the analyst views photographic, binocular or video images, and are then processed in real time to select images that merit further review, thus speeding up decision making. In 2012, DARPA demonstrated a successful prototype.⁸⁹⁵
- 8.72 One further DARPA funded research programme is premised on the potential use of invasive BCIs in remote weaponry, controlled directly by operators’ brain signals.⁸⁹⁶ A US patent has been granted jointly to Duke University and DARPA for “apparatus for acquiring and transmitting neural signals” for purposes including, but not limited to, “weapons or weapons systems, robots or robot systems”.⁸⁹⁷
- 8.73 Attempts to enhance the cognition of military personnel have hitherto generally employed drugs. Notably, these drugs have included the stimulant Ritalin, which is used to improve performance in some attention-related activities, and Modafinil, which was originally developed to treat

⁸⁹⁰ Defence Science and Technology Laboratory (2013) *About us*, available at: <https://www.dstl.gov.uk/>.

⁸⁹¹ Kruse AA, Boyd KC and Schulman JJ (2006) Neurotechnology for intelligence analysts. In Defense and Security Symposium, (Florida, United States: International Society for Optics and Photonics).

⁸⁹² Schnell T, Melzerb JE and Robbins SJ (2009) The cognitive pilot helmet: enabling pilot-aware smart avionics *Proceedings of the SPIE* **7326**: 1-9.

⁸⁹³ Moreno JD (2012) *Mind wars: brain science and the military in the 21st century* (New York: Bellevue Literary Press), at page 144.

⁸⁹⁴ Neuromatters (2010) *Neuromatters awarded \$2.4M DARPA contract to develop C3Vision™ prototype* available at: <http://www.neuromatters.com/news-darpaniap3.html>.

⁸⁹⁵ Kasanoff B (2012) DARPA’s new “brain-computer interface” makes you a pattern recognition machine, on at: <http://www.digitaltrends.com/cool-tech/this-is-your-brain-on-silicon/>; DARPA (2012) *Tag team threat-recognition technology incorporates mind, machine*, available at: <http://www.darpa.mil/NewsEvents/Releases/2012/09/18.aspx>.

⁸⁹⁶ White SE (2008) Brave new world: neurowarfare and the limits of international humanitarian law *Cornell University Cornell International Law Journal* **41**: 177-210.

⁸⁹⁷ Wolf PD, Nicoletis M, Morizio J and Chaplin J (2007) *Apparatus for acquiring and transmitting neural signals and related methods*, available at: <http://www.google.com/patents/US20050090756>

narcolepsy, but supplied to pilots on long flight missions to ensure wakefulness.⁸⁹⁸ However, there has recently been increased military interest in the use of both TDCS and (r)TMS for purposes of enhancement. For example, DARPA programmes have focused on the use of such neurotechnologies to achieve accelerated learning and improved memory retention. Indeed, there are currently both in-helmet and in-vehicle TMS projects under trial.⁸⁹⁹ As discussed in the first part of this chapter, however, the efficacy of such methods outside the controlled conditions of a research environment remains in doubt (see paragraph 8.12 to 8.14).

8.74 Although the focus of this chapter is upon non-therapeutic applications of novel neurotechnologies, any discussion of the role of military research and development programmes involving these technologies would be incomplete without reference to the considerable investment in therapeutic or assistive technologies, the aim of which is to address the grave physical and psychiatric damage suffered by military personnel. Some examples of these research programmes are provided in Box 8.4.

Box 8.4: Military research into therapeutic applications of novel neurotechnologies

Advances in frontline medical intervention have dramatically reduced the deaths of US and NATO troops in recent conflicts, notably in Iraq and Afghanistan. Concomitant with the increased survival rate, however, has been a great increase in the number of service personnel who lose limbs. Although vehicle armour and protective helmets aid in survival from roadside explosives, there is increasing evidence of long-term brain damage resulting from the blast. In addition, large numbers of army veterans suffer mental health disturbance and are diagnosed with PTSD (32% of those who had been physically injured, 14% of those who had never been injured).⁹⁰⁰ This has provided a powerful spur to research on improving prosthetics and treating brain and psychiatric damage, including PTSD.

The hippocampus is a brain region essential for the encoding of new memories. The emotional salience of those memories engages another deep brain region, the amygdala. Animal research over the past decade has shown that if a memory is evoked, it becomes labile and can potentially be erased by pharmacological or neurophysiological intervention.⁹⁰¹ As PTSD is often associated with such painful memories, there have been suggestions that applying TMS directed towards such deep brain structures whilst evoking the memory might help erase it, or at least modulate its painful aspects.⁹⁰²

US military-funded research in these fields includes:

- **BrainGate** is a research programme that uses invasive BCIs to investigate the use of assistive devices by people with spinal cord injury, brainstem stroke, and motor neurone disease. People with these conditions are trained to control a computer cursor simply by thinking about the movement of their own paralysed hand. This research is funded, in part, by the US Department for Veterans Affairs.⁹⁰³
- DARPA '**Revolutionizing Prosthetics**' is a DARPA programme that has developed prosthetic arm systems including promising initial results with "brain control of an advanced arm system" in tetraplegic volunteers at the Johns Hopkins University Applied Physics Lab worked.⁹⁰⁴
- **REMIND (Restorative encoding memory integration neural device)** is a DARPA programme looking at memory loss and the inability to acquire new memories. They suggest that "A biomimetic model of the hippocampus could serve as a neural prosthesis for lost cognitive function and memory impairment."⁹⁰⁵
- **REPAIR (Reorganisation and Plasticity to Accelerate Injury Recovery)** is a DARPA programme that aims to better understand "neural computation and reorganisation to improve brain modelling and our ability to interface with

⁸⁹⁸ Moreno JD (2012) *Mind wars: brain science and the military in the 21st century* (New York: Bellevue Literary Press), at page 136-7.

⁸⁹⁹ National Research Council (2013) *Emerging cognitive neuroscience and related technologies* (Washington D.C: National Academies Press).

⁹⁰⁰ Kean S (2012) From soliders to veterans, good health to bad *Science* **336(6086)**: 1226-7.

⁹⁰¹ Sara SJ (2000) Retrieval and reconsolidation: toward a neurobiology of remembering *Learning & Memory* **7(2)**: 73-84.

⁹⁰² Osuch EA, Benson BE, Luckenbaugh DA *et al.* (2009) Repetitive TMS combined with exposure therapy for PTSD: a preliminary study *Journal of Anxiety Disorders* **23(1)**: 54-9.

⁹⁰³ Department of Veterans Affairs (2012) *BrainGate research*, available at: http://www.providence.va.gov/features/BrainGate_Research.asp; BrainGate (2012) *About Us*, available at: <http://www.braingate2.org/aboutUs.asp>.

⁹⁰⁴ DARPA (2012) *Revolutionizing prosthetics*, available at: http://www.darpa.mil/our_work/dso/programs/revolutionizing_prosthetics.aspx.

⁹⁰⁵ DARPA (2012) *Restorative encoding memory intergration neural device (REMIND)*, available at: [http://www.darpa.mil/Our_Work/DSO/Programs/Restorative_Encoding_Memory_Integration_Neural_Device_\(REMIND\).aspx](http://www.darpa.mil/Our_Work/DSO/Programs/Restorative_Encoding_Memory_Integration_Neural_Device_(REMIND).aspx)

it.” The Agency’s aim is that these approaches could lead to new classes of devices to help rehabilitation following brain injury, restore impaired sensory function, and manipulate external devices.⁹⁰⁶

- **Regenerative medicine:** DARPA also provides large amounts of funding to research in regenerative medicine, although not specifically neural regeneration.⁹⁰⁷

Degradation of enemy personnel

8.75 DARPA has funded studies on the possible long range uses of microwave radiation or magnetic fluxes to disorient enemy forces or insurgents at a distance,⁹⁰⁸ although no realistic weapons system has yet been developed.⁹⁰⁹ Similar mass-disruption applications using TMS (or other neurostimulation technologies) are currently beyond the bounds of practicability as these can only be administered at close proximity and on an individual level. More foreseeable applications of such technologies are in the interrogation of prisoners of war.

Interrogation

8.76 As we have seen in the first part of this chapter, there are early suggestions in research environments that neurostimulation could have an effect on some kinds of brain activity associated with cognitive processes. For example, one study has reported an association between non-invasive neurostimulation and the slowing of participants’ generation of deceptive, but not truthful, responses.⁹¹⁰ It is therefore *hypothetically* possible to envisage the future employment of neurostimulation as a coercive interrogation technique, either to disorient an individual under interrogation, or to acquire information. However, as we have noted, the nature of research studies in which such effects have been recorded means that speculation as to their practical real-world application should be treated with caution.

8.77 Similarly, BCIs that identify brain signals associated with particular affective states, or ERP signals associated with the user’s recognition of significant images or information – for example, those relating to a crime scene – could potentially be used for interrogation. There have been proposals to employ technologies that measure ERP using EEG-based BCIs in this way, either pre-emptively to identify criminal, psychopathic or terrorist intent, or retrospectively to determine guilt or innocence. Indeed, there are commercial companies claiming to be able to identify terrorists on this basis.⁹¹¹ It has been questioned whether such techniques would actually be effective or ethically defensible, particularly as they may be susceptible to false positive readings and to countermeasures adopted by those undergoing questioning.⁹¹² Nevertheless, the company NoLieMRI, which makes similar claims, though based on the use of functional magnetic resonance imaging (fMRI), estimates its own market as \$3.6 billion.⁹¹³

⁹⁰⁶ DARPA (2012) *Reorganization and plasticity to accelerate injury recovery (REPAIR)*, available at: http://www.darpa.mil/Our_Work/DSO/Programs/Reorganization_and_Plasticity_to_Accelerate_Injury_Recovery_%28REPAIR%29.aspx.

⁹⁰⁷ Mason C (2007) Regenerative medicine 2.0 *Regenerative Medicine* **2**(1): 11-8, at page 15.

⁹⁰⁸ Rose S (2005) *The 21st-century brain: explaining, mending and manipulating the mind* (Reading: Jonathan Cape), at page 292.

⁹⁰⁹ Weinberger SS (2012) Microwave weapons: wasted energy *Nature* **489**(7415): 198-200.

⁹¹⁰ Lo Y, Fook-Chong S and Tan E (2003) Increased cortical excitability in human deception *NeuroReport* **14**(7): 1021-4; Hamilton R, Messing S and Chatterjee A (2011) Rethinking the thinking cap: ethics of neural enhancement using noninvasive brain stimulation *Neurology* **76**(2): 187-93.

⁹¹¹ BBC Online (17 February 2004) *Brain fingerprints under scrutiny*, available at:

<http://news.bbc.co.uk/1/hi/sci/tech/3495433.stm>; Rosenfeld JP (2005) Brain fingerprinting: a critical analysis *Scientific Review of Mental Health Practice* **4**(1): 20-37.

⁹¹² Canli T, Brandon S, Casebeer W *et al.* (2007) Neuroethics and national security *The American Journal of Bioethics* **7**(5): 3-13, at page 6.

⁹¹³ No Lie MRI (2006) *Investors overview*, available at: <http://www.noliemri.com/investors/Overview.htm>.

Ethical and regulatory issues raised by military applications

8.78 In this report, we recognise that engagement in armed conflict, the conduct of armed forces in war and in the treatment of captured enemy combatants, raise vast and contested ethical questions. Some would argue that war is itself unethical, irrespective of how it is conducted.⁹¹⁴ Even if it is conceded that some wars may be fought for just causes, there remain unresolved debates about what constitutes defensible grounds for going to war or ethical conduct in war. Philosophical and theological debates about what constitutes a ‘just war’ date at least as far back as ancient Greece.⁹¹⁵ We do not enter into these wider debates here. That being said, it is clear that ethical and legal concerns and constraints *do* apply to military applications of novel neurotechnologies.

8.79 A network of rules of engagement, international treaties and conventions that attempt to govern military activities and the treatment of combatants, non-combatants and prisoners in ways broadly considered ethical have their origins in ‘just war’ debates and in international humanitarian law. For example, the treaties and additional protocols that make up the Geneva Conventions establish standards for the humane treatment of people during war.⁹¹⁶ The Hague Convention, meanwhile, concerns the use of weapons in war.⁹¹⁷ The specific threats of chemical and biological weapons, meanwhile, have led to international conventions forbidding the use of both of these categories of weapons, though not the research, development or even stockpiling of such agents. Subsequent revisions of the Biological Weapons Convention and the Chemical Weapons Convention banned these kinds of preparatory activities too. However, research into means of defending against the potential use of these kinds of weapons is, permitted.⁹¹⁸ This has arguably served several nations with a useful ‘get-out’ clause to continue studying potential agents under the rubric of developing defences. Although neuroactive chemicals or biological agents are covered by these conventions, it is notable that there are no instruments of international law which specifically address the fusion of physical sciences, informatics, and neuroscience that underpin the categories of neurotechnologies with which this report is concerned.

8.80 In the paragraphs below, we consider what we take to be the three main areas in which ethical questions arise in respect of the least speculative military applications of the neurotechnologies outlined above. These concern:

- the use of neurodevices in interrogation;
- the involvement of serving military personnel as participants in research; and
- the dual-use of neurotechnologies developed for therapeutic applications, but used for military purposes.

8.81 We have not included amongst these issues the possibility of using neurodevices for the direct injury or degradation of enemy combatants as we consider such applications still to be too speculative to warrant further attention. Some have suggested that special ethical issues are raised by the use of BCIs (as opposed to conventional controls) to operate weapons (for example, drones) from remote locations, on the grounds that neural responses may be too swift or non-conscious to be appropriately weighed or considered, thus raising doubts about moral

⁹¹⁴ See, for example, Russell B (1915) The ethics of war *International Journal of Ethics* **25(2)**: 127-42, at page 127.

⁹¹⁵ Orend B (2008) *War*. In, Zalta EN, ed. (The Stanford Encyclopedia of Philosophy).

⁹¹⁶ International Committee of the Red Cross (1949) *The Geneva conventions of 12 August 1949* (Geneva, Switzerland: ICRC).

⁹¹⁷ Carnegie Endowment for International Peace (1915) *The Hague conventions and declarations of 1899 and 1907* (New York: Press OU).

⁹¹⁸ Petro JB, Plasse TR and McNulty JA (2003) Biotechnology: impact on biological warfare and biodefense *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* **1(3)**: 161-8, at page 166.

and legal responsibility for any consequences.⁹¹⁹ However, in our view, the ethical issues associated with remote weaponry – which are very serious – relate not primarily to the use of neurotechnology in this context but to the context in which drones are employed in the first place.

Interrogation

8.82 There are no specific treaties or conventions relating to the use of these neurotechnologies on prisoners of war as either methods of interrogation or torture. However, the use of neurostimulation or BCIs as interrogation devices may be seen as coercive. Their use to interrogate or disorient prisoners is therefore of dubious legality under Article 17 of the third Geneva Convention, which states, *inter alia*, that:

“No physical or mental torture, nor any other form of coercion, may be inflicted on prisoners of war to secure from them information of any kind whatever. Prisoners of war who refuse to answer may not be threatened, insulted, or exposed to any unpleasant or disadvantageous treatment of any kind.”⁹²⁰

8.83 In recent conflicts arising from the ‘War on Terror’, both actual and suspected fighters who were captured were deemed to fall outside international humanitarian law by the Bush administration. As a result these fighters were subject to varying forms of interrogation under physical and psychological pressure⁹²¹ (the Obama administration has since changed this policy).⁹²² Even parties who are not strictly classed as prisoners of war (for example, those who have laid down arms or have been taken prisoner in internal armed conflicts or civil unrest) are still covered by Article 3 of the Geneva Conventions, the Additional Protocol II to these Conventions: the Convention against Torture, and by international human rights law, including Article 3 of the European Convention on Human Rights that prohibits torture and inhuman or degrading treatment.⁹²³

8.84 The involvement of doctors in cruel, inhuman or degrading treatment of detainees is also prohibited under the Declaration of Tokyo.⁹²⁴ However, as we have already noted in this report, non-invasive neurostimulation devices do not necessarily require operation by a medical professional. **We recommend that the armed forces and intelligence services consider issuing advice to their personnel that the use of neurodevices in interrogation is coercive and as such is prohibited under international humanitarian law.**

Research and development

8.85 While the military use of a novel neurotechnology demonstrated to be safe and effective (as a means, for example, of enhancing perception or attention) would not raise ethical issues distinct from those we have considered in respect of civilian populations, their experimental use in military contexts prior to their safety and efficacy having been established does raise some different concerns. As we have observed, the long-term unintended effects of enhancement uses of even non-invasive neurotechnologies on otherwise healthy individuals have not been systematically investigated and are still uncertain. These are still experimental technologies and, as such, their research uses are governed by the Declaration of Helsinki. This requires that in all

⁹¹⁹ White SE (2008) Brave new world: neurowarfare and the limits of international humanitarian law *Cornell University Cornell International Law Journal* 41: 177-210, at page 196.

⁹²⁰ International Committee of the Red Cross (ICRC) (1949) *Geneva convention relative to the treatment of prisoners of war (third Geneva convention)*, available at: <http://www.unhcr.org/refworld/docid/3ae6b36c8.html>.

⁹²¹ Cobain I (2012) *Cruel Britannia: a secret history of torture* (London: Portobello Books).

⁹²² The Washington Post (23 January 2009) *Obama reverses Bush policies on detention and interrogation*, available at: http://articles.washingtonpost.com/2009-01-23/news/36920354_1_executive-orders-detention-and-interrogation-task-force.

⁹²³ Article 3 of the European Court of Human Rights (1950) *Convention for the protection of human rights and fundamental freedoms*, available at: http://www.echr.coe.int/NR/ronlyres/D5CC24A7-DC13-4318-B457-5C9014916D7A/0/Convention_ENG.pdf.

⁹²⁴ World Medical Association (1975) *Declaration of Tokyo: guidelines for medical doctors concerning torture and other cruel, inhuman or degrading treatment or punishment in relation to detention and imprisonment* (Tokyo: WMA).

research with human participants, the well-being of the individual research subject must take precedence, that the research protocol must be reviewed by a research ethics committee. The Declaration also requires free and informed consent by the participant.⁹²⁵

- 8.86 Military personnel, however, are subject to a disciplined regime in which the concept of freely given consent becomes problematic. It is questionable what role, if any, informed consent has in some military contexts, because those serving in the armed forces have to obey reasonable orders from their commanding officers.⁹²⁶ This raises the question of what counts as a ‘reasonable order’ and whether this would include instructions to undertake unproven neurological interventions in the interest of improving – or increasing the understanding of how to improve – combat effectiveness. In the context of the administration of an unproven prophylactic drug during the first Gulf War, a US federal appeals court held that it was possible that “legitimate government interests” could counterbalance an individual soldier’s interest in only taking part experimental treatment if they have given their informed consent.⁹²⁷
- 8.87 Clinicians and researchers conducting clinical investigations, in which military personnel are participants, are bound by professional ethical codes of conduct. In the UK, studies involving human participants that are undertaken, funded, or sponsored by the MOD must undergo scrutiny by its Research Ethics Committees (MODREC) and meet internationally recognised ethical standards.⁹²⁸ However, in situations where the use of neurotechnologies constitutes experimental use rather than a formal research study, the position regarding ethical guidelines and informed consent may be more ambiguous. **We suggest that clinicians working with the armed forces may play a crucial role by exercising their duty of care to protect the welfare of personnel who may feel under pressure to participate in experimental military applications of novel neurotechnologies that carry uncertain risks and benefits.**
- 8.88 The question also arises as to whether military authorities would be legally liable for any harm experienced by military personnel required to make use of such devices in research contexts, or potentially, in the future, as part of their combat training. In the US the Feres doctrine – according to which members of the armed forces are barred from collecting damages from the US Government for injuries sustained while performing their duties – might seem to preempt such claims.⁹²⁹ However, in the UK, the MOD long contested veterans’ claims relating to their experiences of ‘Gulf War syndrome’, before conceding that veterans suffering long term illnesses could be provided with “appropriate support” and financial assistance.⁹³⁰

Dual use and opportunity costs

- 8.89 Concerns about ‘dual use’ technologies and products have been raised amongst those engaged in updating and revising conventions on chemical and biological warfare; that is, the use of these products for hostile as well as peaceful purposes without significant modifications being required.⁹³¹ The potential for the kinds of neurotechnologies we have discussed in this report to

⁹²⁵ World Medical Association (2008) *WMA declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/>.

⁹²⁶ Moreno JD (2012) *Mind wars: brain science and the military in the 21st century* (New York: Bellevue Literary Press), at page 156; The Greenwall Foundation (2013) *Enhanced warfighters: risk, ethics, and policy* (San Luis Obispo: The Greenwall Foundation), at page 72.

⁹²⁷ *John Doe et al. vs Louis W. Sullivan, Secretary of Health and Human Services et al.* 938 F.2d 1370 291 U.S. App.D.C. July 16 1991, discussed in Miles SH (2013) The new military medical ethics: legacies of the Gulf wars and the war on terror *Bioethics* **27(3)**: 117-23. The drug was pyridostigmine and was administered to soldiers with the aim of protecting them from the effects of exposure to some chemical or biological weapons.

⁹²⁸ Defence Science and Technology (2012) *Research ethics committees (MODREC)*, available at: <http://www.science.mod.uk/engagement/modrec/modrec.aspx>.

⁹²⁹ *Feres v. United States*, 340 U.S. 135 (1950).

⁹³⁰ Ministry of Defence (2012) *Gulf veterans' illnesses*, available at: <https://www.gov.uk/gulf-veterans-illnesses>.

⁹³¹ Miller S and Selgelid MJ (2007) Ethical and philosophical consideration of the dual-use dilemma in the biological sciences *Science and Engineering Ethics* **13(4)**: 523-80, pp. 527-9.

be put to dual use has been raised by some commentators.⁹³² It has been argued that special ethical responsibilities are associated with technologies amenable to dual use and that it is important that scientists working in fields of research associated with these technologies are aware of the hostile uses to which they might be put – even if it is not possible to be specific about particular dual-use applications. Here the concern is not specifically with scientists who are already work on defence or security programmes (and who would, therefore, be aware of the military applications of their work), but with education and awareness-raising amongst the wider disciplines from which these researchers are drawn. We have suggested that continuous reflexive evaluation of innovation pathways is an important element of responsible research and innovation in neurotechnologies. We therefore welcome initiatives such as the Wellcome Trust-funded collaborative project on dual-use bioethics, one strand of which has investigated the current provision of ethical training in undergraduate and postgraduate neuroscience curricula in the UK.⁹³³ This investigation reported that at the time it was conducted, only one neuroscience course had a dedicated ethics module and only a very small proportion of courses addressed the ethics of dual-use.⁹³⁴ **We recommend that, as part of their ethical training, those studying for a higher degree in neuroscience should be alerted to the possible dual-use implications of neurotechnologies.**⁹³⁵

- 8.90 Even when neuroscientists *are* adequately informed of the possible applications for which innovations in neurotechnology could be directed, concerns may still arise as to the opportunity costs and cooption of inventiveness for military (as opposed to therapeutic) ends. This may be seen as a particular ethical concern where research is resource-intensive, ties up limited facilities and expertise, or risks participation fatigue amongst a small population of eligible participants. One response to this is that, not infrequently, research conducted for military purposes – such as research in the fields of regenerative and rehabilitative medicine – could have significant ‘reverse dual-use’ applications for wider therapeutic applications in civilian populations. Nevertheless, it might be argued that rather than rely on the hope of spin-offs that are of benefit to civilian populations, it would be a more efficient use of research resources to channel these *directly* towards unmet therapeutic needs of the population in general.

⁹³² Tennison MN and Moreno JD (2012) Neuroscience, ethics, and national security: the state of the art *PLoS Biology* **10(3)**: e1001289.

⁹³³ University of Bradford (2012) *About the project on building a sustainable capacity in dual-use bioethics*, available at: <http://www.brad.ac.uk/bioethics/about/>.

⁹³⁴ University of Bradford: Bradford Disarmament Research Centre (2011) *Where is the ethics? ethical training in neuroscience curricula in UK universities*, available at: <http://www.brad.ac.uk/bioethics/monographs/>.

⁹³⁵ Dando M (2009) Biologists napping while work militarized *Nature* **461(7258)**: 950-1.

Chapter 9

Communication of
research and the media

Chapter 9 - Communication of research and the media

Chapter 9 - overview

The novel neurotechnologies discussed in this report attract considerable media attention. We consider issues raised by the reporting and representation of scientific research in the popular and non-specialist media. In particular we look at the representation of novel neurotechnologies and the possible impacts of these representations.

The ways in which science and technology are reported and framed in the media may help to shape public understanding and expectations and to influence social norms and the policy and investment landscapes. However, it should not be assumed that media representation determines public attitudes in straightforward or predictable ways.

Some of the ways in which science is reported in the media can be attributed to the pressures upon journalists in an increasingly competitive and accelerated media environment. The demands of this environment can, for example, lead to uncritical reproduction of press releases. Scientists themselves are increasingly engaged in the public communication of science. However, the political and economic pressures on academic researchers to demonstrate the practical and economic impacts of their work can encourage practices that lead to misleading reporting of research evidence through premature emphasis upon commercial applications, or publication bias towards positive or newsworthy findings. These combined factors can contribute to a cumulative spiral of hype.

Some of the hallmarks of poor science reporting practices in general are evident in communication about novel neurotechnologies. These include: headlines that misrepresent research, stories that emphasise the benefits of interventions without mentioning risks or longer-term uncertainties, speculation and extrapolation beyond the evidence and lack of contextual balance in the use of compelling images or personal stories.

Social media might be assumed to provide a more direct connection between scientific researchers and the public and an outlet for personal stories. Indications are, however, that content about novel neurotechnologies on social media platforms is significantly populated by commercial and academic organisations promoting therapeutic services and innovations.

Using the media to promote research into novel neurotechnologies may encourage investment and foster inventiveness, but hype can also be harmful. For example, it may offer false hope to patients and those close to them by failing to alert them to the limits or risks of current technological capabilities. This in turn may undermine their abilities to make informed, autonomous treatment choices. Wider risks include loss of public trust in these technologies and engendering misplaced conceptions that individuals are reducible to their brain functions. Communication practices, therefore, need to exhibit the virtues of humility and responsibility no less than clinical research and care practices do.

Responsible communication of the capabilities of novel neurotechnologies should not only include accurate, evidence-based reporting, but it should also take account of the possible personal and social impacts of the (mis)representations of the capabilities of these technologies. These impacts provide a particular ethical dimension of the ways in which novel neurotechnology research is framed by the media. We recommend that the behaviour of researchers, press officers and journalists involved in the communication of novel neurotechnologies should be informed by humility and responsibility, exercised through reflecting on how their representations of these technologies might contribute to cumulative hype. Points on which to reflect include: vigilance for institutional pressure to hype; the need to contextualise compelling, but potentially misleading, images; attention to use of language that might prematurely imply availability of effective treatments; and recognition that novel neurotechnologies may not be the preferred therapeutic route for every eligible patient (paragraph 9.72).

In addition to research institutions and journalists, we recommend that two further groups of actors should reflect on their role in practices that might drive hype: policy makers and higher education funding councils in framing the value of research in relation to the impact agenda (paragraph 9.73); and commercial enterprises in seeking to attract investment and promote their products (paragraph 9.74).

Introduction

- 9.1 Novel neurotechnologies attract a great deal of media attention. For example, deep brain stimulation (DBS) has generated claims of patients being “walking miracles”;⁹³⁶ transcranial magnetic stimulation (TMS) has been reported to awaken a “car crash victim from [a] coma”;⁹³⁷ and brain-computer interfaces (BCIs) are the subject of stories such as “BrainGate gives paralysed the power of mind control”.⁹³⁸ It is also reported that neural stem cell research “can rescue the memory from Alzheimer’s disease”.⁹³⁹ The majority of media coverage emphasises the potential *therapeutic* benefits of the novel neurotechnologies we consider in this report. However, as we observe in Chapter 8, there are also reports of potentially exciting or sinister applications in non-therapeutic settings, such as the portrayal of the brain as “the next hacking frontier”.⁹⁴⁰
- 9.2 The aim of this chapter is to explore the representation of novel neurotechnologies in the popular, non-specialist media and the possible impacts of this. We locate this discussion in the wider social contexts that influence the nature of these representations, in particular the communications and publications strategies of academic institutions. This chapter concentrates predominantly on traditional print and broadcast media; though we also briefly consider the emerging role of social media in conveying the role and promise of novel neurotechnologies.
- 9.3 Although we focus our discussion on novel neurotechnologies, the issues addressed can usefully be explored in relation to a wide range of applications of science and technology. Over recent years, many controversies have arisen about how science has been represented by the media in the UK – for example, in debates about ‘global warming’,⁹⁴¹ ‘mad cow disease’, GM crops, or the MMR vaccine.⁹⁴² The media profile of issues such as these has caused major furore, impacting on stakeholders from politicians to scientists, and supermarkets to consumers. Intellectual and economic productivity have also played a particular role in this debate, by focusing on innovation in science and technology as significant national assets. For example, when the BBC Trust commissioned a review of its own coverage of science, the backdrop to this review was characterised in terms of the UK producing a tenth of the world’s scientific research, and deriving a third of its GDP from science, technology, engineering, and mathematics.⁹⁴³
- 9.4 This chapter begins by mapping out why media representations matter at all, before discussing the role of scientists, press officers, and journalists in shaping the representations of science and technology. It then reviews some possible criticisms of the representation of emerging technologies in general, and neurotechnologies in particular. The chapter concludes

⁹³⁶ Mail Online (7 January 2012) *Standing tall: battery-operated boy who can walk again after doctors ‘rewired’ his brain to stop his body twisting*, available at: <http://www.dailymail.co.uk/news/article-2083523/Battery-operated-boy-walk-doctors-rewired-brain.html>.

⁹³⁷ The Telegraph Online (15 October 2008) *Magnet treatment awakens car crash victim from coma*, available at: <http://www.telegraph.co.uk/science/science-news/3353412/Magnet-treatment-awakens-car-crash-victim-from-coma.html>.

⁹³⁸ The Observer (17 April 2011) *BrainGate gives paralysed the power of mind control*, available at: <http://www.guardian.co.uk/science/2011/apr/17/brain-implant-paralysis-movement>.

⁹³⁹ The Telegraph Online (20 July 2009) *Stem cells can rescue the memory from Alzheimer’s disease, claim scientists*, available at: <http://www.telegraph.co.uk/science/science-news/5873215/Stem-cells-can-rescue-the-memory-from-Alzheimers-disease-claim-scientists.html>.

⁹⁴⁰ Wired (9 July 2009) *The next hacking frontier: your brain?*, available at: <http://www.wired.com/wiredscience/2009/07/neurosecurity/>.

⁹⁴¹ Boyce T (2009) *Climate change and the media, volume 5* (New York: Peter Lang Publishing Inc.); Holliman R (2011) *Advocacy in the tail: exploring the implications of ‘climategate’ for science journalism and public debate in the digital age* *Journalism: Theory, Practice and Criticism* **12(7)**: 832-46.

⁹⁴² Allan S (2002) *Media, risk and science*, volume 9 (Buckingham: Open University Press); Boyce T (2007) *Health, Risk and News, volume 9* (New York: Peter Lang Publishing Inc.).

⁹⁴³ BBC Trust (2011) *BBC trust review of impartiality and accuracy of the BBC’s coverage of science*, available at: http://www.bbc.co.uk/bbctrust/assets/files/pdf/our_work/science_impartiality/science_impartiality.pdf, at page 4.

by proposing recommendations for the responsible representation of novel neurotechnologies in the media.

Why representation matters: the mechanisms of media influence

9.5 The quantity, and indeed prominence, of representations in the mass media have been shown to have an ‘agenda setting’ function – that is, telling the audience what to think *about*, even if not actually telling us *what* to think. This means that issues given significant media attention often become the focus for public concern and policy interest. In addition, patterns in the way in which the media represents the world can also cultivate particular understandings – for example, conceptions of what is safe or dangerous, desirable or undesirable. Underlying assumptions reiterated across diverse media outlets, such as ‘economic growth is good’ can come to seem like incontestable common sense.⁹⁴⁴ Media influence also occurs through the so-called ‘framing’ of any representation, for example through tone, emphasis, narrative structure, language and images – often influenced by the key role played by scientists as news sources.⁹⁴⁵ This framing can subtly shape how people understand, and respond to, an issue. A number of other quite simple factors have also been shown to be at work. For example:

- a single powerful headline or image can leave the reader or viewer with a strong sense of a threat or hope;⁹⁴⁶
- an emerging issue, described by analogy and linked to previous issues from the past, can create a powerful ‘template’ framing how people understand an issue as it unfolds;⁹⁴⁷
- a dramatic personal account can be particularly powerful, inviting identification and making people remember these stories disproportionately to more prosaic facts and figures;⁹⁴⁸
- clear provision of key facts can help people understand and assess the technology. However, gaps in information leave readers with a limited tool-kit for developing an informed opinion on an issue;⁹⁴⁹ and
- where a narrow range of ethical debates are represented in the media, the ethical debates that fall outside the range are less likely to be discussed by the readers, listeners and viewers.⁹⁵⁰

9.6 As well as influencing understandings of the science itself, communication about a novel technology can also have a number of broader social implications. It may challenge or reinforce particular social norms, for example that a certain state of being is one that should be accepted or conversely, one we should seek to cure. Issues such as these have been brought into focus, for example, by debates about the existence of a ‘gay gene’⁹⁵¹ or in the rejection of cochlear implants by parents in the deaf, sign language-using community who objected to imposition of standards of normalcy.⁹⁵²

⁹⁴⁴ Lewis J (2013) *Beyond consumer capitalism: media and the limits to imagination* (London: Polity).

⁹⁴⁵ See: Allan S, Anderson A and Petersen A (2010) Framing risk: nanotechnologies in the news *Journal of Risk Research* **13**(1): 29-44.

⁹⁴⁶ Corner J, Richardson K and Fenton N (1990) *Nuclear reactions: form and response in "public issue" television* (Luton: University of Luton Press).

⁹⁴⁷ Kitzinger J (2000) Media templates: patterns of association and the (re) construction of meaning over time *Media, Culture & Society* **22**(1): 61-84.

⁹⁴⁸ Henderson L and Kitzinger J (2001) The human drama of genetics: ‘hard’ and ‘soft’ media representations of inherited breast cancer *Sociology of Health & Illness* **21**(5): 560-78.

⁹⁴⁹ Hargreaves I, Lewis J and Speers T (2003) *Towards a better map: science, the public and the media* (Swindon: Economic and Social Research Council).

⁹⁵⁰ Haran J (2007) *Human cloning in the media* (London: Routledge).

⁹⁵¹ Kitzinger J (2006) Constructing and deconstructing the “gay gene”: media reporting of genetics, sexual diversity, and “deviance”, in *The nature of difference: science, society and human biology*, Ellison G, and Goodman AH (Editors) (Boca Raton: FL: CRC Press Taylor and Francis Group).

⁹⁵² Tucker BP (1998) Deaf culture, cochlear implants, and elective disability *Hastings Center Report* **28**(4): 6-14; Lane H (2005) Ethnicity, ethics, and the deaf-world *Journal of Deaf Studies and Deaf Education* **10**(3): 291-310.

- 9.7 While recognising the depth and breadth of potential media influence, it is also crucial not to over-simplify this effect. Audiences do not uncritically accept everything they hear and see.⁹⁵³ The audience is also not a single, uniform entity. Whether it comprises those with general or personal interests, or more particular professional interests, such as policy-makers or investors, the ways in which these groups receive messages will be complex. Audiences will be influenced by their own values and experiences in how they take in and interpret messages. This has been demonstrated specifically with respect to the perception of emerging technologies. For example, in a recent study, a group of Muslim women were the only research participants to have predominantly negative images of nanotechnology. This was attributable to the links made by these participants between nanotechnology and spy-technology and the surveillance of Muslim communities following the events of 11 September 2001.⁹⁵⁴
- 9.8 Claims about how media representation will influence public attitudes or policy decisions should be treated with caution unless supported by thorough research. Moreover, references to media influence can themselves be used for instrumental ends, such as when media are blamed for creating a climate of opinion, or patterns of behaviour, that the accusers themselves find problematic or illogical. A simplistic accusation of media influence can assume an ignorant lay public who are easily duped (the implication being that the public would agree with the accuser if only they were better informed).⁹⁵⁵ It can also confine the cause of the perceived problem to a problem of media misrepresentation. For example, just because people often reference their concerns about emerging science and technology using examples from science fiction, this does not mean that science fiction *causes* public concern about such science and technology.⁹⁵⁶ Ascribing blame to media misrepresentation can distract from other influences or present an obstacle to addressing (or responding to) public concerns in other, potentially more effective ways.
- 9.9 Media representation can have significant impacts, but it is important to recognise that these are subject to complex influences and will not always operate in completely predictable ways. The amount of media attention given to a novel scientific or technological development and the way it is represented can, however, potentially undermine *or* support its development and uptake. Theorists point out that “the future of science and technology is actively created in the present through contested claims and counterclaims over its potential”.⁹⁵⁷ From this perspective, there is a need to explore “how the future is mobilized in real time to marshal resources, coordinate activities and manage uncertainties”.⁹⁵⁸ The media can play a crucial role in these processes. Sociological studies have highlighted ‘the medialisation of science’, which:

⁹⁵³ For examples related to science, see: Corner J, Richardson K and Fenton N (1990) *Nuclear reactions: form and response in “public issue” television* (Luton: University of Luton Press); Miller D, Kitzinger J, Williams K and Beharrell P (1998) *The circuit of mass communication: media strategies, representation and audience reception in the AIDS crisis* (London: Sage Publications Ltd).

⁹⁵⁴ Economic and Social Research Council (2008) *Media discourses and framing of risk*, available at: <http://www.cardiff.ac.uk/jomec/resources/KitzingerWkPaper27.pdf>, at page 22.

⁹⁵⁵ This is highlighted in a discussion of how policy-makers/scientists discussed ‘Frankenbunny’ headlines and images from a leading tabloid reporting of the creation of hybrid embryos. While this could be seen simply as ‘scaremongering’ about GM, it could also be read as deploying humour and could be read ironically by readers. See: Haran J, Kitzinger J, McNeil M and O’Riordan K (2007) *Human cloning in the media: from science fiction to science practice* (London: Routledge); Haran J (2007) Managing the boundaries between maverick cloners and mainstream scientists: the life cycle of a news event in a contested field *New Genetics and Society* **26(2)**: 203-19.

⁹⁵⁶ For a detailed discussion, see: Kitzinger J (2010) Questioning the sci-fi alibi: a critique of how ‘science fiction fears’ are used to explain away public concerns about risk *Journal of Risk Research* **13(1)**: 73-86.

⁹⁵⁷ Brown N, Rappert B and Webster A (2000) Introducing contested futures: from looking into the future to looking at the future, in *Contested futures: a sociology of prospective techno-science*, Brown N, Rappert B, and Webster A (Editors) (Aldershot Ashgate Press), at page 5.

⁹⁵⁸ Brown N and Michael M (2003) A sociology of expectations: retrospectively prospecting and prospectively retrospectively *Technology Analysis & Strategic Management* **15(1)**: 3-18, at page 4.

“[I]n so far as it guides the public communication strategies of scientific actors, increases the chances of scientific actors being noticed and taken seriously by the political-administrative system. Effects are seen in a contribution to the legitimization of science by reinforcing the perception of its social relevance and in improving the chances of scientific expertise becoming effective in policy-making”.⁹⁵⁹

Representation (or lack thereof) of a technology may help inform the timing and nature of regulation – for example whether it is perhaps premature or belated, permissive or restrictive. This is why, for example, scientists sometimes lobby via the media to try to ensure a supportive debate.⁹⁶⁰ It can also influence the level of support and cooperation from potential research participants, users or investors. As we observe in Chapter 3, the presentation of the incidence of neurological and mental health disorders in terms of unmet health needs and the opportunities and capacities for technological innovation to address these, can play promissory and performative roles, capturing the interest of potential funders and shaping the direction of research and investment. Efforts to influence media representations are not limited to those with commercial interests. Patient groups may also play a role in seeking to raise the profile of the prospects of particular health technologies in the media.⁹⁶¹ However, unfulfilled promises and hype might equally lead to disinvestment of the kind witnessed in the field of psychopharmaceuticals (see paragraphs 3.32 to 3.33).

9.10 In sum, while there are well-known mechanisms by which media outlets can influence and shape views, opinions and reactions, and even policy in some cases, this does not warrant automatic accusations of undue influence. A balance needs to be struck between awareness of the power of media to shape and frame opinions, and consideration of the many other factors that may add to, change, mitigate or reverse such influence. The NHS initiative *Behind the headlines*, part of the NHS Choices website, is one example of an initiative that seeks to have such a mitigating effect. This online resource provides elucidation and balance by setting representations of health-related research in the popular media in the context of the most robust current scientific evidence.⁹⁶²

9.11 In order to understand the constraints and drivers that shape the nature of existing approaches to communication and representation, it is important to examine the role of those producing media messages (including press officers, journalists and scientists) and the impact that their values and judgments, and the structures within which they work, on media representation. The next section of this chapter outlines the role of two sets of key players: the scientists and press officers in research institutions on one hand and the journalists on the other.

The role of researchers and press officers – and the context in which they operate

9.12 Studies of the activities of those who act as sources for journalists – research institutions, businesses and their press offices – suggest that some problems with the representation of science and technology in the media can be traced to these sources rather than journalists.⁹⁶³

⁹⁵⁹ Peters H, Heinrichs H, Jung A, Kalfass M and Petersen I (2008) Medialization of Science as a Prerequisite of Its Legitimization and Political Relevance, in *Communicating Science in Social Contexts*, Cheng D, Claessens M, Gascoigne T *et al.* (Editors) (Springer Netherlands).

⁹⁶⁰ Williams A and Gajevic S (2012) Selling science: source, struggles, public relations, and the newspaper coverage of hybrid embryos *Journalism Studies*: 1-16, at page 2.

⁹⁶¹ Herxheimer A (2003) Relationships between the pharmaceutical industry and patients' organisations *British Medical Journal* **326(7400)**: 1208-10.

⁹⁶² NHS Choices (2012) *Behind the headlines*, available at: <http://www.nhs.uk/news/Pages/NewsIndex.aspx>.

⁹⁶³ See: Anderson A, Petersen A, Wilkinson C and Allan S (2009) *Nanotechnology, risk and communication* (Basingstoke: Palgrave Macmillan); Allan S, Anderson A and Petersen A (2010) Framing risk: nanotechnologies in the news *Journal of Risk Research* **13(1)**: 29-44.

- 9.13 There is an increasing focus on ‘communicating science’ not only in the UK, but internationally. This focus is profoundly marked in the UK by past debacles such as those surrounding BSE (mad cow disease) and GM crops and food. The emphasis on good science communication has also been shaped by national and international health crises, as well as by financial concerns and fierce debates about the values underpinning research.⁹⁶⁴ In the late 20th and early 21st centuries, the ‘science community’ (including researchers, academic institutions, funding bodies, companies and policy makers) have adopted a more proactive approach to both public relations (PR) and public engagement around science issues. Recent examples may be found in the communications efforts associated with the mapping of the human genome and in the field of stem cell research.⁹⁶⁵ If the ratio of professional science communications and PR experts (working in universities, businesses, NGOs and for government) to specialist science journalists follows the patterns seen more generally in the communications sector it is likely that the former now outnumber the latter.⁹⁶⁶
- 9.14 Professional organisations have been established such as the Science Media Centre (SMC), which describes itself as “an independent press office helping to ensure that the public have access to the best scientific evidence and expertise through the news media when science hits the headlines”.⁹⁶⁷ Such bodies can be crucial allies for scientists and make strong connections with specialist journalist, providing them with briefings. Scientists are also increasingly being trained in media-communication skills (including use of on-line media) and a wide range of research organisations (including commercial businesses and higher education institutions) have invested in public engagement and PR.⁹⁶⁸
- 9.15 Such developments can be lauded as evidence of improved communication and an opening up of science to public scrutiny and debate. The expansion in the number of communication/PR specialists and the emphasis on publicising scientific research could be seen as having positive aims and impacts, such as:
- helping to encourage accurate science reporting;
 - encouraging scientific literacy;
 - providing accountability for publically funded science;
 - promoting trust;
 - recruiting scientists and technologists of the future; and
 - informing the public and hence opening up channels for consultation and upstream public engagement.
- 9.16 However, the increasing emphasis on science PR (or at least some branches of it) can be seen in a less benign light.⁹⁶⁹ It can, in particular, be viewed as evidence of efforts to influence public attitudes and the policy-making, regulation and funding environments by emphasising the (imminent) social and economic value of scientific advances.⁹⁷⁰ One study examined the

⁹⁶⁴ Allan S (2011) Introduction: science journalism in a digital age *Journalism: Theory, Practice and Criticism* **12(7)**: 771-7.

⁹⁶⁵ Smart A (2003) Reporting the dawn of the postgenomic era: who wants to live forever? *Sociology of Health & Illness* **25(1)**: 24-49; Haran J, Kitzinger J, McNeil M and O’Riordan K (2007) *Human cloning in the media: from science fiction to science practice* (London: Routledge); Henderson DL and Kitzinger J (2007) Orchestrating a science ‘event’: the case of the human genome project *New Genetics and Society* **26(1)**: 65-83; Williams A and Gajevic S (2012) Selling science: source, struggles, public relations, and the newspaper coverage of hybrid embryos *Journalism Studies*: 1-16.

⁹⁶⁶ In a study by researchers at Cardiff University, cited in Davies N (2009) *Flat earth news: an award-winning reporter exposes falsehood, distortion and propaganda in the global media* (London: Random House), at page 85, it was estimated that the number of people employed in PR in the UK was 47,800 compared with 45,000 journalists.

⁹⁶⁷ Science Media Centre (2013) *Science media centre*, available at: <http://www.sciencemediacentre.org/>.

⁹⁶⁸ Illes J, Moser MA, McCormick JB *et al.* (2010) Neurotalk: improving the communication of neuroscience research *Nature Reviews Neuroscience* **11(1)**: 61-9.

⁹⁶⁹ Peters HP, Brossard D, De Cheveigné S *et al.* (2008) Science-media interface: it’s time to reconsider *Science Communication* **30(2)**: 266-76.

⁹⁷⁰ Rödder S (2009) Reassessing the concept of a medialization of science: a story from the “book of life” *Public Understanding of Science* **18(4)**: 452-63, at page 453; Rödder S and Schäfer MS (2010) Repercussion and resistance. an empirical study on the interrelation between science and mass media *Communications* **35(3)**: 249-67; Schäfer MS (2011) Sources,

efforts of a particular research community to influence the regulation of their work by implementing a communications campaign to try to ensure a supportive policy environment for the creation of hybrid embryos for stem cell research. While the strategies were successful in recruiting positive coverage that promoted the value of hybrid embryos, the authors argue that there was a risk of distorting the actual potential of this form of stem cell research over other avenues – and losing sight of broader issues.⁹⁷¹ Some commentators warn of the risks of a shift away from a dialogic and public-centred model of science communication to a one-way, business-influenced, persuasion-oriented model which commentators have termed “PUS [public understanding of science] Inc.”⁹⁷²

- 9.17 The pressure on researchers and press officers working to translate their work into the public domain to underline the social usefulness and imminent practical applications of their work is perhaps only to be expected given the economic pressures for ‘spin-out’ enterprises originating in academic institutions to secure private investment to bridge the ‘valley of death’ that we noted in Chapter 3.
- 9.18 The orientation towards expected or hoped-for impact is also driven by the subordination of wider UK research policy to the priority of economic growth. The *Strategy for UK life sciences* places great emphasis on the potential of publicly funded research to contribute to economic growth by delivering innovative products and services.⁹⁷³ The requirement for universities to demonstrate an extensive record of research published in peer reviewed journals is a long-standing feature of higher education funding. However, the impact agenda is now also part of this landscape. Academic departments are now required to include evaluations of the impact of past research of their members in their submissions to the Research Excellence Framework (REF), which is used to determine future university funding.⁹⁷⁴ In addition, research councils require research proposals to show that researchers have considered routes by which their research may have social and economic impact. Reduced funding for higher education from central government also means that universities are increasingly encouraged to seek revenue streams from elsewhere, including the private and voluntary sectors. This increases pressure on those applying for research funding to make strong claims about the potential impact of their work.⁹⁷⁵
- 9.19 These combined economic, policy and reputational drivers can influence what types of studies are conducted, which are reported, and increase a bias in favour of positive results.⁹⁷⁶ The need for prospective demonstration of impact means claims about effective practical applications of novel technologies may be made without sufficient evidence. Results may be reported prematurely, for example prior to peer review. There can also be a failure to caveat uncertainties or the need for further investigations. Another problematic practice in science communication is that of excessive inference, that is, reporting conclusions that go beyond the available evidence and fail to acknowledge the limits of data in a study. The literature reporting

characteristics and effects of mass media communication on science: a review of the literature, current trends and areas for future research *Sociology Compass* **5(6)**: 399-412, at page 402.

⁹⁷¹ Williams A and Gajevic S (2012) Selling science: source, struggles, public relations, and the newspaper coverage of hybrid embryos *Journalism Studies*: 1-16, pp. 7-8.

⁹⁷² Bauer M and Gregory J (2007) From journalism to corporate communication in post-war Britain, in *Journalism, science and society: science communication between news and public relations*, Martin W. Bauer MB (Editor) (New York: Routledge), pp.33-52; Rödder S (2009) Reassessing the concept of a medialization of science: a story from the “book of life” *Public Understanding of Science* **18(4)**: 452-63; Rödder S and Schäfer MS (2010) Repercussion and resistance. an empirical study on the interrelation between science and mass media *Communications* **35(3)**: 249-67.

⁹⁷³ Department for Business Innovation & Skills (2011) *Strategy for UK life sciences*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf.

⁹⁷⁴ Research Excellence Framework (2014) *Assessment criteria and level definitions*, available at: <http://www.ref.ac.uk/panels/assessmentcriteriaandleveldefinitions/>.

⁹⁷⁵ This topic is explored in more detail in Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, pp104-6.

⁹⁷⁶ Fins JJ (2010) Deep brain stimulation, free markets and the scientific commons: is it time to revisit the Bayh-Dole Act of 1980? *Neuromodulation: Technology at the Neural Interface* **13(3)**: 153-9.

the putative enhancing effects of neural stimulation gleaned from small studies, as discussed in Chapter 8, provides some illustrations of some of these kinds of problems (see paragraphs 8.10 to 8.14). The compound outcome of these various factors is that the findings of research and innovation may be hyped. One scientist who responded to our public consultation stated that hype “is inevitable given the highly competitive nature of science funding and publications (which are linked) and the pressure put on scientists and clinicians (by their employers, grant givers etc.) to be seen to be doing high impact work.”⁹⁷⁷

- 9.20 The pressures upon researchers and their institutions to hype their work coincide with parallel pressures upon academic journals to publish the most ‘newsworthy’ studies and upon the non-specialist media to attract a greater proportion of an increasingly fragmented and thinly spread audience. It may be seen therefore that there are influences operating on all actors, at every stage of the journey of translating research into the public domain (from seeking funding, to presenting research findings, to publication in a journal, to press release, and to media report). Even if each set of actors only adds a small amount of emphasis on the significance or implications of the findings, this can lead to a spiral of hype spinning into gross exaggeration of, and a disproportionate focus upon, the significance and promises of one area of scientific enquiry.

The role of journalists, and the context in which they operate

- 9.21 Although the media are traditionally seen as ‘mediators’ of the promotional and PR activities of sources, or even as ‘watchdogs’, journalists work in increasingly difficult times and the media industries are under increasing financial pressures. For example, the increasing speed of journalism and the competitive environment in science and in the media, alongside the impact of online media, might mean that journalists are encouraged to sensationalise stories in order to compete for page space or airtime and attention, or that they simply might not have enough time to research stories properly. As a major study of the current situation concluded:

“news media, and newspapers in particular, are in crisis. With newspaper circulation declining sharply and advertising revenue migrating to online classified sites and search advertising, the newspaper industry is without a workable business model.”⁹⁷⁸

- 9.22 One study found that there has been an increase in the number of specialist science journalists in the UK national news media, and that there is a growing appetite for science news within newsrooms. However, the economic and institutional constraints under which science journalists now operate have led to workload increases and reduced time to seek out stories, check facts, and do basic research. This, in turn, increases reliance on PR material from a very limited pool of news sources, and a growing homogeneity in science coverage.⁹⁷⁹ Some researchers suggest that the original craft of journalism is being replaced by a sort of creative “cannibalisation”.⁹⁸⁰
- 9.23 A high proportion of journalistic texts about science are derived directly from press releases. For examples, one content analysis found that 84% of journal articles referred to in newspaper

⁹⁷⁷ Robin Lovell-Badge, responding to the Working Party’s consultation.

⁹⁷⁸ Goldsmiths: University of London (2013) *Goldsmiths Leverhulme media research centre*, available at: <http://www.gold.ac.uk/media-research-centre/project1/>.

⁹⁷⁹ Cardiff University School of Journalism, Media and Cultural Studies (2009) *Mapping the field: specialist science news journalism in the UK national media*, available at: http://cf.ac.uk/jomec/resources/Mapping_Science_Journalism_Final_Report_2003-11-09.pdf, at page 44.

⁹⁸⁰ Phillips A, Couldry N, Freedman D and Fenton N (2009) Old sources: new bottles, in *New media, old news: journalism and democracy in the digital age*, Fenton N (Editor) (London: Sage), at page 95.

stories were promoted by the press release.⁹⁸¹ Sophisticated PR strategies can sometimes lead to a high rate of journalists reproducing source material with little change and a low rate of stories generated by journalists themselves. Such practices have been referred to as ‘churnalism’.⁹⁸² In such cases, journalists enable the distribution of ‘newsworthy’ science results without playing any gate-keeping or quality controlling role. As former science and health journalist Nigel Hawkes commented:

“We are ‘churning’ stories today, not writing them. Almost everything is recycled from another source [...]. It wouldn’t be possible to write so many stories otherwise. [...]. Specialist writing is much easier because the work is done by agencies and/or writers of press releases. [...]. The work has been deskilled, as well as being greatly amplified in volume, if not in quality.”⁹⁸³

- 9.24 The acceleration of communication and shift in format to ever more brief and rapid commentary and response (for example the greater use of blogging), while bringing positive benefits, can also have detrimental effects. One freelance science writer, for example, in reflecting on the changes he has witnessed over the course of his career, comments on the pressure to shrink science reporting into ever faster and shorter snippets and argues that the competition for readers and the acceleration of the speed of reporting has led to “fast food” journalism – “only topics that can be presented in a tempting light and easily digested tend to survive, replacing food for thought with a more superficial mental diet.”⁹⁸⁴
- 9.25 For some commentators, one key safeguard lies in championing specialist science journalists and ensuring they get priority in reporting science, and are supported by science communicators and by their editors. Specialists can be assumed to understand the science, and have relevant experience which enables them to report it with accuracy and understand the context.⁹⁸⁵ Because of this, they can also engage critically with the developments they are reporting on. There are some outstanding examples of excellent science reporting in the UK and a recent report on BBC science reporting praised “the precision and clarity of most material”⁹⁸⁶. Science journalists are also working together to debate and improve good practice, for example through collaborative initiatives such as the UK Science, Technology, Engineering and Medicine (or Maths) Public Relations Association (STEMPRA) and the Association of British Science Writers (ABSW).⁹⁸⁷
- 9.26 However, in general, the state of science journalism is hotly contested. For example, at the 2009 World Conference of Science Journalism the UK’s Minister for Science and Innovation praised the UK’s science reporters as “among best in the world” at “speaking truth to society about science”. However, academic analysts commenting on the same conference have noted:

⁹⁸¹ A study of four quality papers which found that 60 per cent of their home news stories were wholly from wire agencies, mainly the Press Association, or PR material, 20 per cent partially so, eight per cent from unknown sources, and just 12 per cent generated by reporters: Davies N (2009) *Flat earth news: an award-winning reporter exposes falsehood, distortion and propaganda in the global media* (London: Random House), at page 95. de Semir V RCRG (1998) Press releases of science journal articles and subsequent newspaper stories on the same topic *JAMA* **280(3)**: 294-5

⁹⁸² The first use of the term ‘churnalism’ has been attributed to a journalist Waseem Zakir, see: Robbins M Science Churnalism, on *The Lay Scientist hosted by the Guardian* [internet blog] 25 April 2011, available at: <http://www.guardian.co.uk/science/the-lay-scientist/2011/apr/25/1> and has achieved prominence through its use in Davies N (2009) *Flat earth news: an award-winning reporter exposes falsehood, distortion and propaganda in the global media* (London: Random House).

⁹⁸³ Commissioned report for the Joseph Rowntree Charitable Trust (2006) *The quality and independence of British journalism*, available at: <http://www.cardiff.ac.uk/jomec/resources/QualityIndependenceofBritishJournalism.pdf>, at page 45.

⁹⁸⁴ Gross M (2008) Is science reporting turning into fast food? *Ethics in Science and Environmental Politics*, available at: <http://www.int-res.com/articles/esep2009/9/journalism/e009pp1.pdf>, at page 1.

⁹⁸⁵ Weigold MF (2001) Communicating science: a review of the literature *Science Communication* **23(2)**: 164-93.

⁹⁸⁶ BBC Trust (2011) *BBC Trust review of impartiality and accuracy of the BBC’s coverage of science*, available at: http://www.bbc.co.uk/bbctrust/assets/files/pdf/our_work/science_impartiality/science_impartiality.pdf, at page 15.

⁹⁸⁷ stempra (2013) *STEMPRA*, available at: <http://stempra.org.uk/>.

“[B]arely three hours later, and in the same room, *Guardian* columnist and doctor Ben Goldacre referred to a room full of these journalists as ‘murderers with blood on [their] hands’. His argument was that science journalism was now of such a poor standard that it was having a serious detrimental impact on public health at least in part because of the increasingly harsh economic and institutional constraints under which journalists now operate.”⁹⁸⁸

- 9.27 During the recent Leveson Inquiry, which examined the culture, practices and ethics of the press in the UK, evidence was heard relating to the quality of science reporting. Although this topic was not central to the remit of the inquiry, report of the inquiry noted that:

“Given the important public interest in science journalism, and the potential harm caused by overblown or sensational science reporting, greater care is needed by parts of the press prior to publishing sensational headlines of breakthroughs or scares.”⁹⁸⁹

The evidence submitted to the inquiry included the observation that inaccurate or misleading reporting of science issues are not covered by press complaint procedures.⁹⁹⁰ The SMC was invited to submit draft guidelines on how to report science and health stories responsibly (cited at paragraph 9.59 to 9.60), which the report of the inquiry suggested should be borne closely in mind by any new media regulator.⁹⁹¹

- 9.28 Some factors that threaten to undermine responsible reporting may result not from journalists’ poor representation of research findings, but rather the lack of transparency about the commercial interests reflected in the putatively robust sources on which they draw. For example, one commentator suggests that, in many ways, journalists often accurately present the evidence found in peer-reviewed journals, noting that:

“[A] more subtle problem, and one that may have more long term implications than simply bad reporting, is the faithful portrayal of commercially influenced research results”.⁹⁹²

Others have highlighted, at its most extreme, the problem of “cheque book science” including the direct involvement of companies in ghost writing articles in prestigious journals.⁹⁹³

- 9.29 It can also be problematic if specialist journalists are, or are regarded as being, too close to their sources, and as uncritical champions of science. In 1987, the sociologist of science Dorothy Nelkin argued that “[m]any journalists are in effect retailing science and technology more than investigating them, identifying with their sources more than challenging them.”⁹⁹⁴ This problem

⁹⁸⁸ Cardiff University School of Journalism, Media and Cultural Studies (2009) *Mapping the field: specialist science news journalism in the UK national media*, available at: http://cf.ac.uk/jomec/resources/Mapping_Science_Journalism_Final_Report_2003-11-09.pdf, at page 4.

⁹⁸⁹ The Right Honourable Lord Justice Leveson (2012) *The Leveson inquiry: an inquiry into the cultures, practices and ethics of the press: volume II*, available at: http://www.official-documents.gov.uk/document/hc1213/hc07/0780/0780_ii.pdf, at paragraph 9.74.

⁹⁹⁰ Evidence from Fiona Fox (Science Media Centre) to the Leveson inquiry, The Right Honourable Lord Justice Leveson (2012) *The Leveson inquiry: an inquiry into the cultures, practices and ethics of the press: volume I*, available at: <http://www.official-documents.gov.uk/document/hc1213/hc07/0780/0780.pdf>, at paragraph 2.6.

⁹⁹¹ The Right Honourable Lord Justice Leveson (2012) *The Leveson inquiry: an inquiry into the cultures, practices and ethics of the press: volume II*, available at: http://www.official-documents.gov.uk/document/hc1213/hc07/0780/0780_ii.pdf, at paragraph 9.75.

⁹⁹² Caulfield T (2004) The commercialisation of medical and scientific reporting *PLoS Medicine* **1(3)**: 178-9, at page 178.

⁹⁹³ Zuckerman D (2003) Hype in health reporting: “checkbox science” buys distortion of medical news *International journal of health services* **33(2)**: 383-9.

⁹⁹⁴ Dorothy Nelkin, quoted in Hotz RL (2002) The difficulty of finding impartial sources in science, on at: <http://www.nieman.harvard.edu/reports/article/101280/The-Difficulty-of-Finding-Impartial-Sources-in-Science.aspx>.

is increasingly discussed, for example one journalist working as science correspondent for the BBC World Service has observed that:

“My colleagues felt that we reported on published papers without significant analysis, depth or critical comment: we just translated what scientists said. You could say that this is not exactly a description of a journalist – more that of a priest, taking information from a source of authority and communicating it to the congregation. This perception is reinforced when you compare our role with that of other journalists. Political journalists, for example, take an active part in the political debate. They produce expert commentary on the subtleties of the political process, highlighting strengths, weaknesses and potential pitfalls of policy ideas. They interview politicians as equals, challenging them to explain their ideas and, crucially, picking them up on inconsistencies, contradictions and mistakes. These journalists are active participants in the process of knowledge creation [...]. Although science news reporting can influence science funding and research priorities, science journalists are not players in the scientific process. Again this is like a priest, who has little or no effect on the activities of the deity itself and who is not actually needed for the deity to continue.”⁹⁹⁵

9.30 Moreover, in view of the wider context of science in society, there could be an ongoing role for columnists, political and economic reporters to cover science and technology topics. Leaving all science reporting to specialist journalists could result in an altogether too narrow picture, and might, in itself, not increase or serve the public interest unless a wide remit is pursued.⁹⁹⁶

Concerns about media coverage of new technologies

9.31 There are two main types of research about the communication of science and technology. The first kind is that conducted by scientists, industry and professional science communicators and is chiefly concerned with whether the science has been represented ‘well’ and whether the reporting might have misled the public or undermined trust in science. The second is that conducted by social scientists and media studies academics who are also interested in this question, but, in addition, focus on critical analysis of underlying values – including analysing the claims of science and of science communicators themselves. Those conducting research under the first rubric tend to focus on producing recommendations for journalists, such as how they can be more faithful to the science. Those coming from the second sphere of concern are more likely to critically assess the sources and their strategies (including analysing press releases) and place these in the context of wider debates about the place of science in society. Although very different findings result from these two strands of enquiry, the concerns that between them they have raised include:

- **Inaccuracy, mistakes or lack of detail** in reporting (for example, of figures or statistics), and failing to provide details regarding the methodology of the study, or where it can be followed up.⁹⁹⁷
- **Misuse of ‘balance’ in reporting:** for example, citing a ‘maverick’ scientist to balance the views of the majority of mainstream scientist – giving a false impression of the balance of

⁹⁹⁵ Murcott T (2009) Science journalism: toppling the priesthood *Nature* **459(7250)**: 1054-5, at page 1054.

⁹⁹⁶ Hargreaves I, Lewis J and Speers T (2003) *Towards a better map: science, the public and the media* (Swindon: Economic and Social Research Council).

⁹⁹⁷ The Right Honourable Lord Justice Leveson (2012) *The Leveson inquiry: an inquiry into the cultures, practices and ethics of the press: volume II*, available at: http://www.official-documents.gov.uk/document/hc1213/hc07/0780/0780_ii.pdf, at paragraph 3.29 and 9.74.

opinion among scientists about an issue such as the safety of a vaccine or issues such as climate change.⁹⁹⁸

- **Over-reliance on a narrow range of sources**, for example over-dependency on the scientist who made the discovery or breakthrough.⁹⁹⁹
- **Disproportionate focus on some stories over others**. This includes undue attention to a single case study showing spectacular results and an unduly pronounced interest in studies that are newsworthy (regardless of conflicts of interest arising from their sources), and a bias in favour of positive results both in journal publication, and in subsequent media reporting.¹⁰⁰⁰
- **Reactive reporting and ‘pack journalism’**: journalists can be led by press releases rather than undertaking proactive enquiries of their own.¹⁰⁰¹ This can lead to over-dependence on particular sources, which may be academic or commercial organisations. It can also result in celebrity-led reporting (for example, news pieces that focus on the experiences of well-known figures with Parkinson’s disease or spinal cord injuries and their views on the potential offered by an emerging technology).¹⁰⁰²
- **Emotive language which emphasises positive outcomes**, for example referring to the ‘promise’ of the research (instead of ‘possibility’) and the strategic use of human interest stories such as those that emphasise ‘suffering’ or ‘need’ in such a way as to frame the scientific or technological research being promoting as the *only* answer.
- **Rhetorical techniques which privilege some positions over others**: for example, presenting some views as the voice of reason and others as emotional, or structuring reports around a narrow focus on some ethical issues which sideline other, important ethical aspects from the debate.¹⁰⁰³
- **Excessive deference for science**: for example, a lack of cautionary comments about scientific claims, perhaps *especially* from science correspondents. Indeed, it has been reported that such comments are least likely to feature in news items by science correspondents.¹⁰⁰⁴
- **Lack of information about economic drivers**, for example, failing to mention sources of funding for the research reported,¹⁰⁰⁵ or profiling an area of research as focused on therapeutic or assistive technologies when a bigger market might be games industry or military.
- **Over-stepping the expertise, or the ‘voice of science’**, for example when scientists assume the role of experts when commenting on the social implications of a technology they are working on, even though they have done no research in this area, and have little expertise in

⁹⁹⁸ BBC Trust (2011) *BBC Trust review of impartiality and accuracy of the BBC’s coverage of science*, available at: http://www.bbc.co.uk/bbctrust/assets/files/pdf/our_work/science_impartiality/science_impartiality.pdf, at page 5.

⁹⁹⁹ BBC Trust (2011) *BBC trust review of impartiality and accuracy of the BBC’s coverage of science*, available at: http://www.bbc.co.uk/bbctrust/assets/files/pdf/our_work/science_impartiality/science_impartiality.pdf, at page 5.

¹⁰⁰⁰ Harrabin R (2003) *Health in the news: risks, reporting and media* (London: King’s Fund); Schlaepfer TE and Fins JJ (2010) Deep brain stimulation and the neuroethics of responsible publishing *The Journal of the American Medical Association* **303(8)**: 775-6.

¹⁰⁰¹ BBC Trust (2011) *BBC Trust review of impartiality and accuracy of the BBC’s coverage of science*, available at: http://www.bbc.co.uk/bbctrust/assets/files/pdf/our_work/science_impartiality/science_impartiality.pdf, at pages 5 and 41.

¹⁰⁰² For example, see: BBC News (23 October 2004) *Reeve stem cell appeal airs in US*, available at: <http://news.bbc.co.uk/1/hi/entertainment/3947029.stm>.

¹⁰⁰³ Kitzinger J and Williams C (2005) Forecasting science futures: legitimising hope and calming fears in the embryo stem cell debate *Social Science & Medicine* **61(3)**: 731-40.

¹⁰⁰⁴ BBC Trust (2011) *BBC Trust review of impartiality and accuracy of the BBC’s coverage of science*, available at: http://www.bbc.co.uk/bbctrust/assets/files/pdf/our_work/science_impartiality/science_impartiality.pdf, at page 5.

¹⁰⁰⁵ Caulfield T (2004) The commercialisation of medical and scientific reporting *PLoS Medicine* **1(3)**: 178-9, at page 175.

understanding or interpreting the social consequences of science and technology. This can be reinforced when journalists fail to distinguish between ‘fact’, as established through scientific methods, and simple opinion or unsupported speculation by a scientist or clinician.

- **Excessive science or technological optimism**, for example, focusing only on benefits, or under-reporting – or indeed failing to report – risks.¹⁰⁰⁶
- **Hype about the *object of the research***, an example of which occurred when research on the human genome was presented in a very deterministic way as the ‘holy grail’ of research, or the “language in which God created life”.¹⁰⁰⁷
- **Hype about the significance of a research *finding***, for example overstating findings as breakthroughs to play to a ‘wow factor’; a tendency to leap to unwarranted conclusions (for example, the translation of research findings in rats to human application), over-simplified accounts which fail to address the incremental nature of scientific exploration, and the uncertainty of outcomes.¹⁰⁰⁸
- **Hype about the *practical applications of the research findings***: for example, accounts which suggest the imminent use of a technology which has only just been funded for research, or which ‘clinicalise’ fundamental discoveries in biology and anticipate medical benefits which may or may not occur.¹⁰⁰⁹ Accounts may also exaggerate how soon an application will be available, overstate the *number* of people who will benefit (for example, stating that *all* patients with a particular illness will be potential users, when only a proportion would benefit), or presenting a ‘breakthrough’ as a global solution without acknowledging that its delivery might be context- and resource-dependent.¹⁰¹⁰

Concerns about representations of novel neurotechnologies

9.32 As noted by one response to the Working Party’s consultation,

“[i]n the case of neurotechnologies this habit [of hype in biomedicine and biotechnologies] is likely to be exacerbated by their novelty, by the apparent authority of very sophisticated and complex science, and by the awe that direct intervention in the brain is likely to inspire.”¹⁰¹¹

This is borne out to a considerable extent by the available evidence.¹⁰¹² Many of the features listed paragraph 9.31 can be found in media representations of novel neurotechnologies specifically, and related concerns about this seem to be increasingly recognised within the neuroscience community. For example, following a recent workshop on the challenges of communicating about neuroscience, one expert stated that:

¹⁰⁰⁶See, for example, Petersen A (2001) Biofantasies: genetics and medicine in the print news media *Social Science & Medicine* **52(8)**: 1255-68.

¹⁰⁰⁷BBC News Online (26 June 2000) *Leaders’ genetic code warning*, available at: http://news.bbc.co.uk/1/hi/uk_politics/806819.stm.

¹⁰⁰⁸For example, see: The Telegraph Online (20 July 2009) *Stem cells can rescue the memory from Alzheimer’s disease, claim scientists*, available at: <http://www.telegraph.co.uk/science/science-news/5873215/Stem-cells-can-rescue-the-memory-from-Alzheimers-disease-claim-scientists.html>.

¹⁰⁰⁹BBC Trust (2011) *BBC trust review of impartiality and accuracy of the BBC’s coverage of science*, available at: http://www.bbc.co.uk/bbctrust/assets/files/pdf/our_work/science_impartiality/science_impartiality.pdf, at page 47.

¹⁰¹⁰Turner-Stokes L, Kitzinger J, Gill-Thwaites H *et al.* (2012) fMRI for vegetative and minimally conscious states *British Medical Journal (Clinical Research Edition)* **345:e8045**, at page 7.

¹⁰¹¹Jackie Leach Scully, Janice McLaughlin, Simon Woods and Michael Barr of the Policy, Ethics and Life Sciences Research Centre, Newcastle University, responding to the Working Party’s consultation.

¹⁰¹²A large portion of the literature looking at the media representation of novel neurotechnologies concerns coverage of neuroimaging technologies such as fMRI. Here we have attempted to limit our discussion to the representation of the kinds of technologies with which we are concerned in this report. These are increasingly gaining attention in analyses of media coverage.

“[media] communication outside the academic literature is a vital source of information flow, but its value is heavily yoked to timeliness and accuracy, and to the trade-off of hope and hype.”¹⁰¹³

One widely discussed study confirms this conclusion. A media analysis of major UK and US print news sources identified 1,256 articles featuring neurotechnology (published from 1995 to 2004).¹⁰¹⁴ The study found that certain techniques such as functional magnetic resonance imaging (fMRI) and neurostimulation gained significantly more coverage than other neurotechnologies over the time period examined and that “[o]verall, the tone of the media coverage was optimistic (featuring benefits or research and its applications) or neutral (no mention of benefits, risks or challenging issues)”.¹⁰¹⁵

- 9.33 An earlier analysis, which was conducted by some of the same authors, examined press coverage of neurostimulation techniques only and underscored concerns about hype in this field.¹⁰¹⁶ For example, 41 per cent (of a total of 235) of articles emphasised the promise of new treatments with headlines such as “Currents of hope: a revolutionary device. An electrical pacemaker implanted in the brain gives welcome relief to people afflicted by the shakiness of Parkinson’s disease.”¹⁰¹⁷ In addition, 19 per cent of headlines were classified as those which signalled new scientific breakthroughs with headlines such as “With tiny brain implants, just thinking may make it so.”¹⁰¹⁸ The ‘human interest’-effect was also evident in this study’s sample, as personal accounts were indicated by 29 per cent of articles.

“This included first person narratives of patients and sometimes of celebrities undergoing neurosurgery with DBS. Some statements resembled ‘miracle stories’ of patients cured of PD [Parkinson’s disease], dystonia, and Tourette’s syndrome.”¹⁰¹⁹

- 9.34 Overall, the research found an imbalance in the reporting of risks versus benefits. For example, 51 per cent of the articles about neurostimulation featured only the benefits of research on neurostimulation and its application, whilst 31 per cent of articles were “balanced”, featuring both benefits *and* risks or issues. However, the authors note that, in their sample, they “did not find any statements discussing the reliability of neurostimulation techniques, discrimination and stigma, or policy and public involvement.”¹⁰²⁰
- 9.35 One analysis – describing what it characterises as an “enthusiastic media shock wave” following the publication of a study associating DBS with improved memory function – has drawn parallels between contemporary media portrayals of DBS and the overly optimistic media representation of leucotomy and other forms of psychosurgery in the 1930s and 1940s.¹⁰²¹ The analysis criticises the fact that there was no mention in the media coverage of

¹⁰¹³David Kopf Instruments (2009) *Communicating ethics and neuroscience*, available at: <http://www.kopfstruments.com/Carrier/downloads/Carrier68.pdf>, at page 2.

¹⁰¹⁴Racine E, Waldman S, Rosenberg J and Illes J (2010) Contemporary neuroscience in the media *Social Science Medicine* **71(4)**: 725-33.

¹⁰¹⁵Ibid, at page 728.

¹⁰¹⁶Racine E, Waldman S, Palmour N, Risse D and Illes J (2007) “Currents of hope”: neurostimulation techniques in US and UK print media *Cambridge Quarterly of Healthcare Ethics* **16(3)**: 312-6.

¹⁰¹⁷The Buffalo News (11 May 2002) *Currents of hope: a revolutionary device. An electrical pacemaker implanted in the brain gives welcome relief to people afflicted by the shakiness of Parkinson’s disease*, available at: <http://www.buffalonews.com/apps/pbcs.dll/article?AID=/20020511/CITYANDREGION/305119971>.

¹⁰¹⁸New York Times (13 April 2004) *With tiny brain implants, just thinking may make it so*, available at: <http://www.nytimes.com/2004/04/13/health/with-tiny-brain-implants-just-thinking-may-make-it-so.html?pagewanted=all&src=pm>.

¹⁰¹⁹Racine E, Waldman S, Palmour N, Risse D and Illes J (2007) “Currents of hope”: neurostimulation techniques in US and UK print media *Cambridge Quarterly of Healthcare Ethics* **16(3)**: 312-6, at page 314.

¹⁰²⁰Ibid, at page 314.

¹⁰²¹Gilbert F and Ovadia D (2011) Deep brain stimulation in the media: over-optimistic portrayals call for a new strategy involving journalists and scientists in ethical debates *Frontiers in Integrative Neuroscience* **5(16)**: 1-6, at page 2.

DBS of any ethical issues potentially raised by its use in vulnerable populations, for example in patients with Alzheimer's disease.¹⁰²²

9.36 Other commentators draw attention to bias in use of compelling stories or images. For example, in relation to psychiatric uses of DBS it has been emphasised that:

“it is an ethical requirement to help patients, their relatives, and the public at large to separate solid data from hype. [...] Public events [...] about DBS sometimes risk conveying mainly treatment benefits by presenting patients with large motor and quality of life improvement who report about the treatment success and have not experienced any adverse event. In contrast, short-, medium- or long-term adverse events, e.g., hemorrhages, dysarthria, psychosocial misadjustments or insufficient treatment responses are hardly ever reported in such a demonstrative and intriguing way, e.g., by displaying computed tomography scans or by inviting patients who have experienced complications.”¹⁰²³

Box 9.1: Examples of hype in the UK media headlines

BCIs

*“Paralysed man’s mind is ‘read’”*¹⁰²⁴

The article reports that electrodes were implanted into the brain of a man who had developed ‘locked-in syndrome’ following a car crash. It explains that the experiment used the brain signals he creates to drive “speech software”, and further notes that there is a huge difference between the technique being described, which is able to pick up signals the subject wants to be picked up, and being able to “delve deep into the mind”. It is also conceded that reading people’s minds is still a far-off prospect, a sentiment that is not conveyed through the headline.

Neural Stem Cell Therapies

*“Stem cells can rescue the memory from Alzheimer’s disease, claim scientists”*¹⁰²⁵

The article goes on to explain that scientists at the University of California had shown that stem cells injected into the brain could rescue memory in mice. Professor LaFerla, director of the university’s Institute for Memory Impairments and Neurological Disorder, is also quoted as saying “this gives us a lot of hope that stem cells... will be a useful treatment for Alzheimer’s disease.” However, this message is not conveyed by the article’s headline.

TMS

*“Coma victim able to speak again after pioneering magnetic field therapy”*¹⁰²⁶

The article opens by stating “[a] man who suffered brain damage in a car crash can speak again after doctors waved a magnet against his head while he was in a coma. Doctors believe the electromagnetic field encouraged nerve cells to send a ‘wake-up’ signal to the brain.” The article later concedes that neuroscientists said that it was “too soon to say whether magnets made any difference.”

DBS

*“Alzheimer’s: deep brain stimulation ‘reverses’ disease”*¹⁰²⁷

The article reports that scientists in Canada “have raised a tantalising prospect – reversing Alzheimer’s disease.” The article explains that, in two patients, the hippocampus had *grown* rather than shrunk (shrinkage is normal in Alzheimer’s disease). However, only one of the two patients had experienced an improvement in their “symptoms”; it is unclear whether these included indications apart from memory.

¹⁰²² Gilbert F and Ovadia D (2011) Deep brain stimulation in the media: over-optimistic portrayals call for a new strategy involving journalists and scientists in ethical debates *Frontiers in Integrative Neuroscience* **5(16)**: 1-6, at page 2.

¹⁰²³ Schlaepfer TE, Lisanby S and Pallanti S (2010) Separating hope from hype: some ethical implications of the development of deep brain stimulation in psychiatric research and treatment *CNS Spectrums* **15(5)**: 285-7, at page 286.

¹⁰²⁴ BBC News Online (15 November 2007) *Paralysed man’s mind is ‘read’*, available at: <http://news.bbc.co.uk/1/hi/health/7094526.stm>.

¹⁰²⁵ The Telegraph Online (20 July 2009) *Stem cells can rescue the memory from Alzheimer’s disease, claim scientists*, available at: <http://www.telegraph.co.uk/science/science-news/5873215/Stem-cells-can-rescue-the-memory-from-Alzheimers-disease-claim-scientists.html>.

¹⁰²⁶ The Daily Mail Online (16 October 2008) *Coma victim able to speak again after pioneering magnetic field therapy*, available at: <http://www.dailymail.co.uk/health/article-1077947/Coma-victim-able-speak-pioneering-magnetic-field-therapy.html>.

¹⁰²⁷ BBC News Online (28 November 2011) *Alzheimer’s: deep brain stimulation ‘reverses’ disease*, available at: <http://www.bbc.co.uk/news/health-15890749>.

9.37 Closely related to the problem of hype is that of speculation. Commentators have pointed to the temptations and dangers of excessive speculation observing, for example, that the topic of mindreading is particularly likely to attract media attention.¹⁰²⁸ Referring to headlines such as “[p]aralysed man’s mind is ‘read’”, it has been suggested that such reports deal predominantly with *future* possibilities. They note that this is not objectionable in itself if it helps potentially problematic developments to be appropriately considered, acknowledging that “it is logical that future expectations do play a role in ethical analyses and in communication between scientists and journalists”.¹⁰²⁹ However, they also comment:

“The big question, of course, is what constitute reasonable expectations concerning which point (nearby, distant) in the future. It is precisely regarding these aspects that self restraint and clarity are called for. When talking to the press about BCI it, therefore, would be advisable to be extremely reluctant to engage in speculations concerning anything beyond the near future (3-5 years or so) or depending on breakthroughs that, at present, are not foreseeable.”¹⁰³⁰

9.38 A survey of 145 BCI researchers recorded their concern about inaccurate representations of BCI as meaning that science is now capable of “reading people’s thoughts and dreams”, though, as we have already discussed, the kinds of brain signals used by BCI devices do not permit anything of the sort (see paragraph 4.37).¹⁰³¹ The same survey noted that BCIs feature with increasingly prominence in popular culture, for example in popular television shows such as *House* and *Star Trek*.¹⁰³²

9.39 Examples of hype and of unjustified extrapolation have been highlighted in the discussion of neural enhancement in Chapter 8 of this report. For instance in the coverage of brain stimulation research in terms of discoveries that will allow users to “unlock their inner genius”.¹⁰³³ As we have observed, this way of framing research findings is unlikely to be warranted by the methods and observations of small exploratory studies (see paragraphs 8.12 to 8.14). However, it is instructive to note that the implication that neurostimulation might ‘unlock genius’ was not solely a gloss added by journalists; the academic publication referred to by this report itself describes neurostimulation as revealing “savant-like” capacities.¹⁰³⁴ The introduction of speculation and hype is therefore by no means the preserve of journalists alone. Nor are such unwarranted extrapolations from research findings solely a problem affecting small studies conducted in competitive academic or commercial domains. Similar hype may also be observed in references to “military modifications and the rise of the supersoldier”¹⁰³⁵ in the reporting of large publically-funded neurotechnology research programmes such as those supported by the US Defense Advanced Research Projects Agency (DARPA).

¹⁰²⁸BBC News Online (15 November 2007) *Paralysed man’s mind is ‘read’*, available at: <http://news.bbc.co.uk/1/hi/health/7094526.stm>; UCTelevision (2011) *Reading the mind: brain-computer interface*, available at: http://www.youtube.com/watch?v=Gweo_ipsYLg.

¹⁰²⁹Haselager P, Vlek R, Hill J and Nijboer F (2009) A note on ethical aspects of BCI *Neural Networks* **22(9)**: 1352-7, at page 1356.

¹⁰³⁰Ibid, at page 1356.

¹⁰³¹Nijboer F, Clausen J, Allison BZ and Haselager P (2011) The asilomar survey: stakeholders’ opinions on ethical issues related to brain-computer interfacing *Neuroethics*, at page 2.

¹⁰³²Ibid.

¹⁰³³The Daily Mail (30 Sept 2008) *The ‘thinking cap’ that could unlock your inner genius and boost creativity*, available at: <http://www.dailymail.co.uk/sciencetech/article-1064431/The-thinking-cap-unlock-inner-genius-boost-creativity.html>.

¹⁰³⁴Snyder A (2009) Explaining and inducing savant skills: privileged access to lower level, less-processed information *Philosophical Transactions of the Royal Society: Biological Sciences* **364(1522)**: 1399-405; Snyder A, Bahramali H, Hawker T and Mitchell DJ (2006) Savant-like numerosity skills revealed in normal people by magnetic pulses *Perception* **35(6)**: 837-45.

¹⁰³⁵Wired (6 September 2012) *Military modifications and the rise of the supersoldier*, available at: <http://www.wired.co.uk/news/archive/2012-09/06/supersoldiers>.

The role of social media¹⁰³⁶

- 9.40 Newspapers, radio and television are not the only sites of representation of novel neurotechnologies. The internet allows the possibility of mainstream media circulating via new forms – for example, ‘newsworthy’ stories may be amplified in historically unprecedented ways as they spread, or even ‘go viral’, via social media. It also allows journalists to be bypassed altogether as, for example, scientific researchers can publish blogs that reach their online followers directly. Indeed, early-career scientists and researchers are actively encouraged to adopt a social media profile.¹⁰³⁷ Individual members of the public can also gain a platform for their views, for example by maintaining blogs about their experiences of ill health or treatment (see paragraph 9.46 below). In addition, it is possible that by posting material about their products or services, companies can use social media as a promotional environment (for example see Box 9.2).
- 9.41 One advantage of the internet in general, and social media more specifically, is that both scientists and journalists can reach new audiences and engage them in dialogue. However, care has to be taken in assuming that this aspect of social media always plays a ‘democratising’ role. Recent research looking at the behaviour of journalists on Twitter concluded that, although using social media offers a good way to market oneself, they did not “advance accountability or transparency in any meaningful way”.¹⁰³⁸ They found that 43 per cent of Tweets contained “at least an element of opinion” and 16 per cent were *primarily* opinion.¹⁰³⁹ This shows a significant deviation from the traditional role of journalists as providers of non-partisan information. The use of the internet for the communication of scientific research may be seen as offering opportunities for increased public engagement, transparency and trust, but also threats in terms of the quality and integrity of the reporting taking place online.¹⁰⁴⁰
- 9.42 Social media are often seen as ‘empowering’ users because they are granted access to people and information around the world.¹⁰⁴¹ However, it is also argued that through these connections, social media can exploit users by connecting them to corporations; turning users into a source of valuable income. It is therefore important to consider the types of messages and content available on social media platforms, what types of connections are taking place, and whether users of social media are benefitting from these connections.
- 9.43 A snapshot study of the coverage of novel neurotechnologies on social media platforms, conducted to inform this report,¹⁰⁴² raised questions about the extent to which private individuals were generally responsible for posting content.¹⁰⁴³ For example, use of the search term “neural stem cell therapy” on social media video platform YouTube revealed that the US-based health care provider StemCellRegenMed had uploaded five of the first 20 videos returned by that particular search, the US Government-funded agency the California Institute of Regenerative Medicine (CIRM) had uploaded three of the videos, and the US research foundation the Neural Stem Cell Institute had uploaded two of the videos. Another search of

¹⁰³⁶Research informing paragraphs 9.40 to 9.46 was carried out as part of a study commissioned by the Working Party to provide a brief overview of the representation of novel neurotechnologies on social media platforms: Purcell-Davies, A (2013) *Novel neurotechnologies in social media: final report*, unpublished manuscript. More information about this study can be found at appendix 2.

¹⁰³⁷Minocha S and Petre M (2012) Handbook of social media for researchers and supervisors available at: http://www.vitae.ac.uk/CMS/files/upload/Vitae_Innovate_Open_University_Social_Media_Handbook_2012.pdf

¹⁰³⁸Lasorsa DL, Lewis SC and Holton AE (2012) Normalizing Twitter *Journalism Studies* **13**(1): 19-36, at page 27.

¹⁰³⁹Lasorsa DL, Lewis SC and Holton AE (2012) Normalizing twitter *Journalism Studies* **13**(1): 19-36, at page 30.

¹⁰⁴⁰See, for example, Allan S (2011) Introduction: science journalism in a digital age *Journalism: Theory, Practice and Criticism* **12**(7): 771-7.

¹⁰⁴¹van Dijck J (2012) Facebook and the engineering of connectivity: a multi-layered approach to social media platforms *Convergence: The International Journal of Research into New Media Technologies*: 1-15, at page 4.

¹⁰⁴²Purcell-Davies, A (2013) *Novel neurotechnologies in social media: final report*, unpublished manuscript. The methodology included categorising the first 20 results returned by entering the search terms “deep brain stimulation”, “brain computer interface” and “neural stem cell replacement therapy” into each of the social media platforms Delicious, Facebook, Twitter and YouTube. The generic search engine Google Blog Search was used to search for blogs.

¹⁰⁴³Purcell-Davies, A (2013) *Novel neurotechnologies in social media: final report*, unpublished manuscript.

YouTube using the term “deep brain stimulation” revealed that health care providers published 16 of first 20 videos returned by search results. This suggests that YouTube, as a social media platform, is being used to a great degree by health care providers or research institutes to promote their work or to market their services.

- 9.44 One video uploaded to YouTube illustrates the use of social media by research institutes seeking to communicate their work directly to the public, but also reflects some of the problematic aspects of hype that we have noted in relation to traditional media. A professionally produced video depicts three different types of BCI research taking place at the University of California, San Diego.¹⁰⁴⁴ However, the video is titled *Reading the mind: brain-computer interface* and the presenter introduces the research as a “world where computers read our thoughts and emotions”. There is little discussion of when BCI-based assistive technologies might be widely available, which could promote the idea that the results of the experiments can be replicated outside of the laboratory, and that such developments will soon be widespread. The author of the snapshot study of novel neurotechnologies in social media noted:

“Furthermore, there is no discussion of the ethics of such applications or the potential side effects of these technologies. It is assumed that the research being conducted is beneficial and that such neurotechnological products will become the norm. The posting shows scientists and researchers as active participants in the creation of products and procedures, in order to help those with neurodegenerative disease; but those with neurodegenerative disease are not given a voice within the video.”¹⁰⁴⁵

- 9.45 As we discuss further below, the risk is that hype about the therapeutic promise of novel neurotechnologies may exploit the desperation of patients who lack other options for treatment. This risk is especially acute if the media conveying this hype are also marketing unproven or unregulated treatment services. We have noted in our earlier discussions that limited availability of licensed therapies, including neural stem cell therapies, and the high costs of some therapeutic neurotechnologies risk encouraging people to travel for treatment in countries with potentially less well-regulated systems of protection (see Box 3.5). The direct marketing of these medical tourism services online compounds the problem of effective oversight and protection of patients, as both the services themselves and the online environments in which they are advertised are very likely to be located or hosted overseas and therefore lie outside the competence of UK regulators (see Box 9.2).

Box 9.2: 'China Medical Tourism': social media representations of stem cell therapy

A video posted on YouTube by a company called 'China Medical Tourism' depicts the experience of one patient, a young woman, at a clinic in Guangzhou. It is explained in the blurb below the video that the patient was in a car accident in 2003. She was initially in a coma and is reported in the video to have “progressed from a vegetative state to being minimally conscious”. The video commentary also says that the patient’s parents felt that they had exhausted all treatment options in the US and thus decided to travel to the clinic in Guangzhou.¹⁰⁴⁶ The audience is also told that the patient was given “four stem cells injections via lumbar puncture and a nutritious stem cell cocktail treatment”, and that she was admitted to the hospital for 60 days.

The video depicts the patient and her parents in the clinic. In the first shot, we see the patient’s father and a clinician from the Chinese clinic encouraging her to sit up, but with little success. In the second shot the patient’s father talks to the camera about her care and intensive physiotherapy routine at the hospital. We then see the patient’s mother feeding her and the person behind the camera asks if she thinks her daughter can understand her. She says yes, the patient can understand her but cannot respond. The third shot shows the patient and her father, and he is asked what the result of

¹⁰⁴⁴UCtelevision (2011) *Reading the mind: brain-computer interface*, available at: http://www.youtube.com/watch?v=Gweo_ipsYLg.

¹⁰⁴⁵Purcell-Davies, A (2013) *Novel neurotechnologies in social media: final report*, unpublished manuscript.

¹⁰⁴⁶China Medical Tourism (2012) *China medical tourism brain injury stem cell therapy three clip*, available at: <http://www.youtube.com/watch?v=Lpre3UoObKs>.

the treatment has been. He says that, two months after the treatment, the biggest difference is that the patient's eyes are considerably more alert and that her attentiveness seems to have improved. He also reports that the patient's neck and head control has improved, although he concedes that it might be hard to notice because she does not have full neck and head control. The patient's father suggests that she now tried to respond to requests such as "open your hand" but she is unable to complete these tasks. This video is apparently intended to promote the stem cell therapy services offered by the medical tourism company. However, the dubious and distressing representation of the patient's treatment outcomes means that it is not unambiguously promotional in its effect. What is apparent, however, is that it is neither an unmediated personal account given by the family who participated in video, and nor does it provide any journalistic 'framing' of the information presented which could provide a wider context or critical reflections on what has been filmed.

- 9.46 The snapshot social media study did, however, find evidence that the internet could provide a platform for voices which might not ordinarily be heard. For example, across the social media platforms examined by the study (YouTube, Facebook, Delicious, Twitter and Google Blog search), the search term 'deep brain stimulation' produced results of which 22 per cent were categorised as 'personal'.¹⁰⁴⁷ This was reported to be the result of social media platforms, blogs and social networking sites which record the personal experiences of those with Parkinson's disease and severe depression. These personal experiences were observed to be more complex than the representations of DBS surgery posted by health care providers. Detailed reports about the problems connected with DBS for an individual with Parkinson's disease are often absent from the mainstream media reporting of novel neurotechnologies and their exploration in, for example, blog posts by individuals who have themselves undergone this kind of treatment, may be useful for people facing similar choices. For example 'Karyn's journey with DBS' is a blog which charts the experiences of a woman being treated for Parkinson's disease using DBS. One of her blog posts, entitled '*One week to go! Lots of questions*' provides a list of questions she asked her surgeon before surgery, while another blog post with the heading, 'Honeymoon is over; I retract the last post' arguably provides a more nuanced insight into what DBS users might expect.¹⁰⁴⁸

Possible impacts of (mis)representation of novel neurotechnologies

- 9.47 Many scientists, clinicians and patient organisations express concern about the dangers of hype, premature claims, unbalanced coverage, and over-simplified reporting of novel neurotechnologies in the mainstream media, as well as what can be found on the internet.¹⁰⁴⁹ Communication in this field is an ethical matter because of the individual and social harm that may occur as a result of overstating the capabilities of these technologies or misrepresenting their risks. The protection of trust, at both an individual level and as a shared public interest, through responsible communication comprises one of the central elements of our ethical framework (see Chapter 4). In addition, realistic representations of the capacities and limitations of particular neurotechnologies to provide effective therapies for neurological and mental health disorders for which there are few other treatment options is crucial to supporting autonomous choice. This is particularly important in this complex area of technology and

¹⁰⁴⁷The highest level of result-type were 'news reports', with 26 per cent. 'Personal' sources were categorised as such if the origin of the source of the information came from an individual. This category is difficult to assess and should be treated as indicative rather than definitive. On the internet, individuals are not always truthful about their motives and/or status. However, sources placed into this category had either uploaded media as an individual or had a personal profile. Even though they were placed into this category, some of these individuals advertised the fact that they were recipients or potential recipients of medical procedures for neurodegenerative disease, carers of people with neurodegenerative disease or had worked in neuroscientific companies and/or university research departments.

¹⁰⁴⁸Karyn (24 August 2012) *Honeymoon is over; I retract the last post, on Young @Park [internet blog]*, available at: <http://karynsjourneywithdbs.blogspot.co.uk/2011/08/honeymoon-is-over-i-retract-last-post.html>.

¹⁰⁴⁹Racine E, Waldman S, Palmour N, Risse D and Illes J (2007) "Currents of hope": neurostimulation techniques in US and UK print media *Cambridge Quarterly of Healthcare Ethics* **16**(3): 312-6; Bell E, Maxwell B, Pat McAndrews M, Sadikot A and Racine E (2010) Hope and patients' expectations in deep brain stimulation: healthcare providers' perspectives and approaches *Journal of Clinical Ethics* **21**: 112; Racine E, Waldman S, Rosenberg J and Illes J (2010) Contemporary neuroscience in the media *Social Science Medicine* **71**(4): 725-33; Schlaepfer TE and Fins JJ (2010) Deep brain stimulation and the neuroethics of responsible publishing *The Journal of the American Medical Association* **303**(8): 775-6. Also see footnote 1049 below.

medicine because of the current paucity of evidence and, in some cases, the means by which these technologies achieve their effects, and about longer term and unintended effects. In previous chapters, we have outlined how this responsibility applies to the professional practices of clinicians and researchers – indeed the generation and dissemination of robust evidence is a key element of responsible research and innovation. In this chapter, we have considered what this means when applied to the practices of communications professionals. In order to understand the ethical significance of responsible communication in the context of media representations, it is important to understand the nature of the negative impacts that hype and misrepresentation may have. In the following paragraphs we explore the nature of these potential impacts.

Hope

9.48 It is hard to assess exactly what the impact of media representations may be on patients' behaviour and in particular their expectations and trust. It has been suggested that parallels may be drawn between the effects of representation of DBS in the media today and the relatively fast and widespread adoption of lobotomy in the early 20th Century, which may have, in part, been attributable to enthusiastic and optimistic media coverage of this new surgical procedure.¹⁰⁵⁰

9.49 One key concern is that hype could mislead and cause distress, for example by offering false hope while failing to alert patients to possible risks, and the extent to which these may still be unknown. This may prompt patient groups to mobilise inappropriately and to create demands for treatments that may not be effective or suitable. Concerns of this kind were reflected by representatives from patient organisations contacted during the preparation of this report. These representatives suggested that media portrayals could 'spur' desperate patients into action, noting that there had been cases in the past where, following a misleading media portrayal, patients approached organisations for support in accessing treatments that remained highly experimental or not yet sufficiently evidence-based to be recommended in regular clinical practice (particularly as an alternative to available and established treatment). For example, one of the representatives reported:

"[F]ollowing articles in the media about neurostimulation [for migraine], patients will call us and ask 'where do I get this, and how much does it cost?' And these treatments are not available in the UK, and we do not have any clinical guidelines for their use. But people would try absolutely anything they read about."¹⁰⁵¹

9.50 It cannot be assumed that everyone will react in the same way to therapeutic or assistive promises conveyed in the popular media. The effects may not always be detrimental. Hope can be an important sustaining force where individuals and those close to them are living with distressing or debilitating neurological or mental health conditions for which no other effective treatments are available. Raising awareness of new interventions might also alert individuals to the possibility of participating in clinical research, which might offer a sense of respect and purpose (see Box 5.2). Responsible communication recognises that information about emerging therapeutic applications of new technologies may therefore be valued by such individuals, but that it must be delivered in a realistic and honest way, making plain the limits of our knowledge and remaining sensitive to the potentially desperate circumstances of some who will receive these messages. This is essential to maintaining the trust in these new neurotechnologies that we identified as a key interest in our ethical framework.

¹⁰⁵⁰Bell E, Mathieu G and Racine E (2009) Preparing the ethical future of deep brain stimulation *Surgical Neurology* **72**(6): 577-86, at page 582; Diefenbach GJ, Diefenbach D, Baumeister A and West M (1999) Portrayal of lobotomy in the popular press: 1935-1960 *Journal of the History of the Neurosciences* **8**(1): 60-9.

¹⁰⁵¹Joanna Hamilton-Colclough, Director, Migraine Action, personal communication, 10 May 2012.

- 9.51 Hope may not only be valuable to individuals but can also help create a framework for innovation and engagement. Without hope, there is the danger of denying recuperative potential and adopting a position of therapeutic nihilism that abandons patients – such as those assumed to be in a permanent vegetative state (PVS) or ‘minimally conscious’ – to a situation where they are ‘warehoused’ and ignored.¹⁰⁵² However, hope can also be misleading, and even harmful. One UK study, for example, showed how families with a relative who is in a minimally conscious state or in a PVS may be influenced by the imperative ‘not to give up’ on their loved one, combined with the message that science and technology might offer future hope that is ‘just around the corner’. This can lead them to press for life-sustaining interventions, often against the advice of clinicians. In retrospect, families may come to view the ‘false hope’ as having contributed to their relative being left in limbo, sustained in what the family may now view as “a fate worse than death”.¹⁰⁵³ This research also highlighted the different perspectives regarding the investment in, or the rebuttal of, hope in different technologies. While the reporting of techniques such as DBS assume that trying to stimulate consciousness in a vegetative patient is a good thing, this was not a view shared by every family in this study. Some interviewees had come to view the return of some consciousness in a vegetative relative as a threat, rather than an aspiration. One family member, for example, commented: “to be honest I’d rather medical science didn’t come up with anything”, commenting that she had seen how patients who developed some minimal consciousness could become distressed. Another member of this family agreed, adding that if her daughter showed some signs of becoming aware of her situation, then she would be “scared”, indeed “terrified” on her behalf.¹⁰⁵⁴
- 9.52 A recent qualitative study examined how families of patients with severe brain injuries understood the potential of neurotechnologies such as fMRI and DBS to make a difference to these patients.¹⁰⁵⁵ This study found that some family members (especially those in the earlier stages of dealing with severe brain injury) responded with a strong sense of excitement and hope – echoing that expressed in the media – and for some families, any consciousness or possibility for communication is viewed with excitement and hope. However, other interviewees, especially those who had lived with the implications of severe brain injury for longer periods of time, reflected negatively on the effects of media representation, including complaining about disappointed hopes, misleading information and a narrow focus on technologies (see Box 9.3). This work also highlighted how the portrayal of families in media coverage (as happy and hopeful) left out the possibility of more varied and contextually complex reactions from families dealing with the realities of caring for a relative in such circumstances – families who raise questions about whether such technologies will really be deployed in a way which supports their relative.

¹⁰⁵²Fins J (2010) Minds apart: severe brain injury, citizenship, and civil rights *Law and Neuroscience: Current Legal Issues* **13(18)**: 367-84.

¹⁰⁵³Kitzinger J and Kitzinger C (2012) The ‘window of opportunity’ for death after severe brain injury: family experiences *Sociology of Health & Illness*: 1-18 doi: 10.1111/1467-9566.12020.

¹⁰⁵⁴Kitzinger, J and Kitzinger, C (2013) Neuroscience in the news, lecture at Cardiff School of Biosciences, 15 February 2013 available at: http://www.cardiff.ac.uk/jomec/resources/fMRI_KitzingerTalk.pdf.

¹⁰⁵⁵Samuel, G and Kitzinger, J (2013) Media publicity about fMRI and DBS for vegetative patients: reactions from families, *Working Paper*. Summary available at: <http://www.cardiff.ac.uk/jomec/contactsandpeople/profiles/kitzinger-jenny.html>.

Box 9.3: Example of quotes from families with experience of severe brain injury talking about media representation¹⁰⁵⁶

“They [the newspaper articles] are really misleading cos they give you hope and I suppose whilst all you cry for is a bit of hope I do understand why they [doctors] don’t give you it because when you get given it... you make your own conclusions don’t you? And you twist what’s been said... that’s what doctors don’t want you to do, they don’t want you to hear something different from what they’re saying and that’s what the media does. It changes everything and makes you think there’s answers out there that just aren’t...”

One interviewee picked up on a newspaper’s articles talk of ‘hope’ and said “I’m struggling with that word, not that I don’t believe in an afterlife but it [what the article is referring to] is hope for this life. [...] my question would be there’s hope for whom? For her to make any further recovery? Probably not. [...] ...so basically hope for what?...”

Another interviewee responded angrily to the representation of a comatose woman and what new neurotechnologies might be able to do for her: “but why isn’t there any discussion of whether she’s getting good quality care, whether people are visiting her, it’s totally divorced from humanity, she’s just a brain [...] This is just someone in a lab – who’s going to pay for scans for the vast majority of people [and] it’s the language of smoke and mirrors, this word ‘recovery’ – does it mean she can blink..? And there’s no mention of expense, community, loved one’s...as if the science determines it all, it should have been written by a philosopher or a psychologist. Scientists can’t analyse this out of context”

Another talked about the hopes raised by the fMRI coverage, and then her own decision not to pursue this as she didn’t want her partner to ‘fail’ the test: “People still now send me links about the fMRIs. This is amazing, maybe we can help [partner] through these amazing fMRIs. [...] ...I spent months really pressing for fMRIs, not really understanding what they were. I thought they were, you know, what everyone else thinks, I saw all the articles. And then I decided against them and I said, ‘I don’t want him to have one’. Because I don’t want him to be judged against an fMRI when he may not be conscious. Do you know, he’s got pockets of awakensess and sometimes he doesn’t have a pocket for two or three days. Do you know, and I’m not going to take that away from him.”

Autonomy and informed consent

- 9.53 One particularly problematic consequence of creating unrealistic expectations about how effective, well-established, or risk-free a novel therapeutic technology is, is that this may interfere with the capacity of individuals to make well-informed, autonomous choices – and therefore to give informed consent – to undertake interventions.¹⁰⁵⁷ A study of health care providers from five Canadian DBS centres, for example, identified extremely high expectations as a key challenge, which could undermine patients’ understanding of risks and benefits, due, “[i]n part, to overestimated media reports on ‘miracle cures’ through DBS.”¹⁰⁵⁸
- 9.54 Similar problems may be particularly acute in the field of research into assistive BCIs, which is still at a relatively early stage of investigation in humans. It has been noted that “the presentation of BCI research within the public media is an important factor in the creation of reasonable expectations about the possibilities and limits of BCI.”¹⁰⁵⁹ These authors emphasise that it is important to establish whether individuals understand the extent to which coverage of BCIs in the popular media has been ‘glossed’ or exaggerated, or whether they are “under the mistaken impression that BCI has already allowed communication by people who cannot otherwise communicate at all?”¹⁰⁶⁰ Problems for informed consent extend not only to decisions that individuals make about their own treatment or participation in research, but also to relatives or carers who are in a position of giving consent on behalf of individuals who lack capacity, and for whom hype only adds to the challenges of determining what is in the best interests of someone who cannot exercise their own choices.

¹⁰⁵⁶Samuel, G and Kitzinger, J (2013) Media publicity about fMRI and DBS for vegetative patients: reactions from families, *Working Paper*. Summary available at: <http://www.cardiff.ac.uk/jomec/contactsandpeople/profiles/kitzinger-jenny.html>.
¹⁰⁵⁷Bell E, Mathieu G and Racine E (2009) Preparing the ethical future of deep brain stimulation *Surgical Neurology* **72(6)**: 577-86, at page 582.
¹⁰⁵⁸Clausen J (2011) Conceptual and ethical issues with brain–hardware interfaces *Current Opinion in Psychiatry* **24(6)**: 495-501, at page 497.
¹⁰⁵⁹Haselager P, Vlek R, Hill J and Nijboer F (2009) A note on ethical aspects of BCI *Neural Networks* **22(9)**: 1352-7, at page 1352.
¹⁰⁶⁰Ibid, at page 1353.

Policy and investment

9.55 One potential positive consequence of raising the profile of novel neurotechnologies is that this could inspire and support innovation by attracting both public and private funding.¹⁰⁶¹ Conversely, however, raising the profile of these technologies could promote inaccurate or exaggerated representations which could impact negatively on future innovation trajectories, for example by channelling investment or policy support towards particular solutions such as hi-tech innovations, at the expense of alternative low-tech approaches. Here too, trust is important; as we note in Chapter 8, there is a concern that hyping the potential of a novel neurotechnology risks provoking a public backlash where promises are unfulfilled (see paragraph 8.61).

Perceptions of ourselves and others

9.56 A less concrete – but potentially no less influential – effect of representations of neuroscience in the mainstream media has been highlighted by some commentators. This is the potential problem of ‘neuroessentialism’, that is, the perception that the brain is the defining essence of a person.¹⁰⁶² Some have argued that essentialist conceptions of the brain could lead to evidence of our brain structures or neural functions being used to reach decisions about what kind of person someone is, or to explain our behaviour and experiences.¹⁰⁶³ These concerns have been raised with particular reference to brain imaging. However, they also could also apply to the technologies with which we are here concerned, for example in respect of the perception that accessing information about our neural signals is the same as accessing information about our memories or emotions, or that the most effective treatment for neurological or mental health conditions will be direct technological interventions in the brain, rather than other kinds of care. A recent study echoes and expands upon these speculations, arguing that while clinical applications of neurotechnologies retain an important profile, neuroscience was:

“more commonly represented as a domain of knowledge relevant to ‘ordinary’ thought and behaviour and immediate social concerns. Brain science has been incorporated into the ordinary conceptual repertoire of the media, influencing public understanding of a broad range of events and phenomena.”¹⁰⁶⁴

What constitutes good representation?

9.57 In the remaining paragraphs of this chapter, we consider the question of what constitutes ‘good’ representation in relation to novel neurotechnologies. Two key qualities are accuracy in conveying the findings of the research and clarity about the robustness of the research itself. These aspects have been long standing sources of concern. In 1999, the UK’s House of Commons Science and Technology Committee’s (responding to disputes in the UK) recommended that “media coverage of scientific matters should be governed by a Code of Practice which stipulates that scientific stories should be factually accurate.”¹⁰⁶⁵ Since then, there have been a series of efforts to improve science reporting, including the production of guidelines (for example, through the collaboration in 2001 between the Social Issues Research Centre, the Royal Society, and the Royal Institution of Great Britain),¹⁰⁶⁶ the establishment of the SMC (in 2002),¹⁰⁶⁷ and a great many research projects and reviews. These reviews have

¹⁰⁶¹ Bell E, Mathieu G and Racine E (2009) Preparing the ethical future of deep brain stimulation *Surgical Neurology* **72(6)**: 577-86, at page 582.

¹⁰⁶² Racine E, Bar-Ilan O and Illes J (2005) fMRI in the public eye *Nature Reviews Neuroscience* **6(2)**: 159-64, at page 160.

¹⁰⁶³ *Ibid.*

¹⁰⁶⁴ O’Connor C, Rees G and Joffe H (2012) Neuroscience in the public sphere *Neuron* **74(2)**: 220-6, at page 22.

¹⁰⁶⁵ Select Committee on Science and Technology (1999) *Scientific advisory system: genetically modified foods* available at: <http://www.publications.parliament.uk/pa/cm199899/cmselect/cmsctech/286/28604.htm>, at paragraph 7.28.

¹⁰⁶⁶ Social Issues Research Centre (2001) *Guidelines on science and health communication*, available at: http://www.sirc.org/publik/revised_guidelines.shtml#guide1.

¹⁰⁶⁷ Science Media Centre (2013) *Science media centre*, available at: <http://www.sciencemediacentre.org/>.

included a report on the state of science journalism in the UK, commissioned by the Science and Media Expert Group on behalf of the UK Department for Business Innovation and Skills (2009),¹⁰⁶⁸ and the BBC Trust's review of the BBC's impartiality and accuracy of the BBC's coverage of science (2011).¹⁰⁶⁹

9.58 Guidelines produced collaboratively by the Social Issues Research Centre, the Royal Society and the Royal Institution of Great Britain include recommendations that journalists should address issues such as:

- Source credibility, for example noting whether research been peer reviewed, and making it clear if it has not been;
- Research procedure and method, for example, how was the research was conducted;
- Relationships with other work, for example, that it should be clearly stated when findings are at variance with previous knowledge; and
- The significance of findings, with any limits clearly spelled out.¹⁰⁷⁰

9.59 Transparency and clarity about the significance of findings is also a key concern. The SMC underlines the need for journalists to:

- “state the source of the story [...] ideally with enough information for readers to look it up or [access] a web link”;
- “specify the size and nature of the study” and;
- “when reporting a link between two things, indicate whether or not there is evidence that one causes the other.”

9.60 The SMC also suggest that journalists should give some indication of the speed with which a treatment may, or may not, become available, and be aware of the dangers of overstatement. The SMC guidelines recommend that journalists:

- “Give a sense of the stage of the research – for example, cells in a laboratory or trials in humans – and a realistic timeframe for any new treatment or technology”;
- “Distinguish between findings and interpretation or extrapolation”;
- “Be wary of scientists and press releases over-claiming for studies”;
- “Headlines should not mislead the reader about a story’s contents and quotation marks should not be used to dress up overstatement”;
- “Remember patients; don’t call something a ‘cure’ that is not a ‘cure’.”¹⁰⁷¹

The SMC also provides a *‘Before the headlines’* service, which underpins these guidelines and supports adherence to robust reporting practices by providing independent statistical analyses of scientific papers.¹⁰⁷²

9.61 In recognition of the role of professionals in the responsible communication of science and technology, similar guidance has also been issued to researchers themselves. For example, the

¹⁰⁶⁸Cardiff University School of Journalism, Media and Cultural Studies (2009) *Mapping the field: specialist science news journalism in the UK national media*, available at: http://cf.ac.uk/jomec/resources/Mapping_Science_Journalism_Final_Report_2003-11-09.pdf.

¹⁰⁶⁹BBC Trust (2011) *BBC Trust review of impartiality and accuracy of the BBC’s coverage of science*, available at: http://www.bbc.co.uk/bbctrust/assets/files/pdf/our_work/science_impairality/science_impairality.pdf.

¹⁰⁷⁰Social Issues Research Centre (2001) *Guidelines on science and health communication*, available at: http://www.sirc.org/publik/revised_guidelines.shtml#guide1.

¹⁰⁷¹Science Media Centre (2012) *10 best practice guidelines for reporting science and health stories*, available at: <http://www.sciencemediacentre.org/wp-content/uploads/2012/09/10-best-practice-guidelines-for-science-and-health-reporting.pdf>. These are the guidelines that the SMC was invited to submit by the Leveson inquiry (see paragraph 9.27 above).

¹⁰⁷²Science and Media Centre (2013) *Before the headlines*, available at: <http://www.sciencemediacentre.org/working-with-us/for-journalists/headlines-for-journalists/>.

Committee on Freedom and Responsibility in the Conduct of Science recommends, among other things, that scientists should:

- “always be accurate and reflect the status of scientific evidence and uncertainty, and be realistic in estimating the importance and future implication of scientific results”;
- “despite pressures to the contrary, public communication of new scientific findings should normally follow acceptance by peer review” and;
- “be transparent in communicating the limits of their own personal expertise and make the distinction between those areas of science in which they might reasonably be considered by their peers to have expertise and other areas on which they may express views.”¹⁰⁷³

9.62 The guidelines produced by the Social Issues Research Centre, the Royal Society, and the Royal Institution of Great Britain highlight further the need for all of those involved in communicating science to consider the likely public reaction and approach their tasks with empathy, considering the following hypothetical question:

“Imagine you have a relative or close friend who is sensitive or vulnerable to information about a particular topic... If the only source of information available to that relative or close friend was the interview you are about to give, or the report you are about to publish, would you feel comfortable with the way you propose to characterise and interpret the story?”¹⁰⁷⁴

9.63 The various sets of guidelines produced over the last 15 years and cited in the preceding paragraphs are extremely useful. Nevertheless, concerns about representation continue. This may be partly due to the (perhaps increasing) pressures on researchers, PR professionals, and journalists to communicate in certain ways (for example, to hype findings). It is also clear that the way in which research is represented can be a source of concern without necessarily being inaccurate or lacking key criteria such as peer review, and different stakeholders have diverse views on what counts as ‘over-claiming’ or exceeding expertise, or indeed, what may be a useful message for an audience. While there is some consensus about some basic issues, the broader questions of what constitutes good reporting will often be the subject of debate. This is, in part, because representation of any emerging technology involves complex medical, scientific and social information, and various types of speculation and value judgments. These include speculation about the expected effects of a technology, value judgments about the nature of the problems the technology addresses and how these should be solved, assessment of potential risks, contested predictions of the time-scale and scope of availability of applications, and assessments of the effectiveness of the policy context for management or delivery.

9.64 Different individuals working in communication might make judgments about these issues and shape messages according to their own perspectives – hence debates about what good reporting, and good PR ‘look like’. For example, in a recent study, different science press-officers were interviewed. During the interview, they were shown press releases for key newsworthy studies on DBS and on fMRI. This study found that, while the press officers could agree on what constituted good technique for the press releases, they had different assessments of the values which imbued the information presented; for example, whether it was manipulative, over-optimistic or extrapolated too far beyond the available evidence.¹⁰⁷⁵ Similarly, it is not uncommon for there to be disputes between different clinicians and scientists

¹⁰⁷³International Council for Science (2010) *Advisory note “science communication”*, available at: <http://www.icsu.org/publications/cfrs-statements/science-communication/advisory-note-science-communication>.

¹⁰⁷⁴Social Issues Research Centre (2001) *Guidelines on science and health communication*, available at: http://www.sirc.org/publik/revised_guidelines.shtml#guide1.

¹⁰⁷⁵Samuel, G and Kitinger, J (2013) Media publicity about fMRI and DBS for vegetative patients: reactions from families, *Working Paper*. Summary available at: <http://www.cardiff.ac.uk/jomec/contactsandpeople/profiles/kitinger-jenny.html>.

about whether a particular press report or documentary has been accurate or misleading, helpful or damaging.¹⁰⁷⁶

- 9.65 It is possible to assess whether a research programme or clinical trial taken on its own terms delivers robust and consistent findings – but beyond these immediate assessments, it cannot tell us the ‘true’ nature of the wider impact of a technology. This is due to the incremental and non-linear nature of technological trajectories, which depend on wider social contexts beyond science and technology, including how the meanings and consequences of findings are presented. The questions of what ‘good’ communication and representation of novel technologies looks like, and by what principles these efforts should be guided, therefore require both insight into social and economic processes, and the consideration of ethical and social considerations that are judged to be most pressing.

Applying our ethical framework

- 9.66 Our ethical framework offers the means to negotiate the kinds of debates that may arise in determining what ‘good communication’ means in the context of novel neurotechnologies. It may not always provide easy or definitive answers and it will still be necessary to engage with the details of any particular situation. Our ethical framework does, however, provide the tools with which to characterise the various interests at stake and the virtues associated with responsible communication and representation practices. The framework invites all parties involved in communication about novel neurotechnologies to consider the kinds of challenges outlined in paragraphs below.
- 9.67 In recognition of the need for caution in the creation of expectations and hope, and thus in the protection of autonomous decision-making and trust, there is a need to attend to what constitutes a proportionate balance between communicating enthusiasm about the possible therapeutic applications of a novel neurotechnology, while also drawing attention to any limits in our knowledge of its efficacy, or of how it achieves its therapeutic effects. For example, the virtues of responsibility and humility each point to the importance of considering the extent to which celebrating the benefits of DBS for *some* people with Parkinson’s disease might occlude clear messages about unintended effects of treatment, or the possibility that only a sub-group of patients might be eligible for, or able to access, DBS treatment. Hype, speculation, and misinformation expose vulnerable patients, prospective research participants (and indeed consumers) and those close to them to false hope. This could undermine their capacities to make the best decisions regarding treatment and care. Realistic and accurate communication is also essential to maintaining wider trust and understanding of therapeutic interventions in the brain.
- 9.68 Awareness of the demands of equity and justice (and the harm of raising unjustified hope) leads to the question of whether, in the contexts of economic austerity and global inequalities, it is fair or realistic to talk of particular treatments or assistive neurotechnologies as if they could soon be universally available to patients worldwide. Concerns about injustice also signal questions about whether portrayals of users of novel neurotechnologies might serve to reduce the stigmatisation of individuals living with particular neurological or mental health disorders. However, the corresponding risks of objectifying these individuals, or suggesting that technological solutions are the *only* appropriate response to their conditions, must also be considered.
- 9.69 We recognise that those communicating the capacities of emerging neurotechnologies may make a valuable contribution to promoting inventiveness and shaping a policy and funding

¹⁰⁷⁶See, for example, Turner-Stokes L, Kitzinger J, Gill-Thwaites H *et al.* (2012) fMRI for vegetative and minimally conscious states *British Medical Journal (Clinical Research Edition)* **345**:e8045, and the subsequent rapid response from the science journalist, clinician, and scientist involved in the programme criticised, available at: <http://www.bmj.com/content/345/bmj.e8045?tab=responses>.

climate in which valuable therapeutic interventions can be developed. In the spirit of contributing to the inventiveness of others, it may be judged that positive representations of the therapeutic and commercial promises of novel neurotechnologies may play a necessary role in encouraging discussion, public acceptance, and incentives for investment which will each support the realisation of the potential of these technologies. However, there are also responsible reasons to avoid overly optimistic predictions and representations that suggest that particular neurotechnologies will deliver effective therapies within defined short-term timeframes such as ‘within five to ten years’.

- 9.70 Responsibility also recommends considering what kinds of images or analogies would illustrate the role and effects of these technologies in realistic ways that promote trust and understanding. In the case of novel neurotechnologies, this might, for example, include reflecting on whether focusing on dramatic images of DBS reducing tremor in people with Parkinson’s disease is responsible, when other less immediately visible effects such as those on mood, identity or personal relationships will not be captured by these images. Responsible communication also involves reflecting on social context and being aware of the history (as well as the future) of a technology in considering what are the most appropriate historical analogies. For example, this might involve asking whether highlighting the connection between novel interventions in the human brain and the (problematic) history of lobotomy and electroconvulsive therapy (ECT) – as we have in Chapter 1 of this report – would have the effect of evoking unjustified fears, or alternatively, whether it might operate as a strategy to distance the current explorations from past mistakes and abuses.

Responsible communication in the context of novel neurotechnologies: our recommendations

- 9.71 In view of the need to protect vulnerable individuals while promoting innovation and trust, we suggest that research scientists, press officers within research organisations, and journalists should each seek to exemplify the virtues of humility and responsibility by grounding their communication of the implications of research concerning novel neurotechnologies in the most robust evidence available. Furthermore, as we have emphasised in Chapter 6, generating and disseminating robust evidence is a central element of responsible research and innovation (RRI). In calling for responsible communication practices, we endorse the existing guidelines for the accurate and responsible reporting of science in general (cited at paragraphs 9.57 to 9.62) and re-emphasise the importance of adhering to these in light of the potential professional duress and incentives to exaggerate the capacities of novel neurotechnologies and the risks of hype in this field. Moreover, the importance of protecting the interests of trust and autonomous decision-making in relation to technologies that intervene in the brain means that responsible communication must also take into account the *impact* that the framing and style, as well as the content, of communications can have on people’s lives, hopes and self-conceptions. Given the heightened public interest in neuroscience and the workings of the human brain, and the widespread lack of understanding of many of the complexities of these, it is important to avoid vague statements that could attract misleading interpretations. This is especially important given the particular pressures on patients and carers facing devastating brain injuries or degenerative conditions who could be damaged by representations which generate distorted expectations.
- 9.72 For these reasons, **we recommend that all actors working in professions involved in communicating the findings of research involving novel neurotechnologies have a responsibility to reflect upon how their representation of the current and future applications of novel neurotechnologies might impact on others and to remain circumspect about the promises of these applications (however exciting they may be to them professionally or personally).** In recommending this, we have deliberately not produced a simple checklist, but instead a set of considerations that are intended to not only guide the reflections of individual actors, but also to be taken into account by institutions and professional bodies involved in the entire circuit of neurotechnology communications in drawing up professional guidance on good practice in this field. **Specifically, we recommend that these professionals and organisations should attend to the following elements of responsible communication practices:**

- to reflect on the pressures that may be imposed by institutional and structural forces to add a ‘pinch of hype’ and to consider the *successive and cumulative* effect of this upon on the way in which a story may enter the public domain;
- to resist pressure to publish only positive or PR-attractive findings;
- to be clear about any features of a research study’s aims, scope or methodology that might preclude generalising its findings to wider populations or to practical real-world applications, and to resist the temptation to over-claim or engage in unjustified extrapolation beyond that which is supported by research evidence. It can be as important to say what the research does *not* imply, as what it does. Existing guidelines (from organisations including the SMC) have highlighted a similar imperative in relation to science reporting in general; we re-emphasise it here in the context of novel neurotechnologies where investigations are often pursued through single patient interventions or small studies;
- to be transparent about the source of funding of the research reported, especially if it has been conducted on behalf of, or supported by, an organisation with a commercial interest in the findings;
- while the use of vivid language, metaphors and images are intrinsic to professional communication practices, it is nevertheless important to refrain from misusing powerful visual devices or engaging personal stories in ways that might mislead. For example, where treatment outcomes are not unequivocally positive, accounts of patients with dramatically reduced symptoms should be accompanied by the stories of those who have different experiences. It may also be important to consider how using language such as ‘promise’ or ‘therapeutic’ to describe research outcomes might undermine efforts to communicate the uncertainties or limits of this research by eliding aspirations for a technology with its current capabilities;
- where an explicit connection is made between a neurotechnology and a particular therapeutic application, to be clear not only about the kinds of conditions the intervention would address and the balance of risks to benefits for patients, but also any continuing uncertainties, including those relating to longer term outcomes. Given the likely high cost of many novel neurotechnologies and the long development trajectories of stem cell-based therapies, it is also important to reflect accurately the realistic prospects for wide availability to patients;
- to acknowledge diversity in the perspectives of patients with neurological and mental health disorders and those close to them, by recognising that novel neurotechnologies may not be the only or indisputable means of addressing their needs and that, for some, a focus on restoring lost function or ‘normalisation’ might not represent their priorities or best interests; and
- to be aware of the broader social, legal, and political implications of research in the sensitive area of the human brain, including the ways in which the research might be applied to other domains.

9.73 Our recommendations regarding the practices and virtues that would be exemplified by responsible reporting of novel neurotechnologies by researchers, press officers, and journalists are a significant part of ensuring responsible communications. However, insofar as these recommendations are made with a particular emphasis on preventing hype, they risk futility if the other components of the engine that drives hype remain unchecked. It is neither reasonable nor desirable to excise all the reasons researchers have to be excited about and share the fruits of their inventiveness and inquiry – indeed, throughout this report, we have emphasised the need for greater dissemination of research and experimental findings. Nevertheless, in light of

the problems of hype in this field we recommend that the UK governments, higher education funding councils and universities reflect on the effects that the 'impact agenda' might be having on the ways in which the promises and limitations of novel neurotechnologies are communicated by academic institutions and their researchers.

- 9.74 **Businesses and universities developing and promoting commercial products from neurotechnological research should also reflect on their own responsibilities when seeking to publicise this research, attract funding for development, and market their products.**

Chapter 10

Conclusions and
recommendations

Chapter 10 - Conclusions and recommendations

- 10.1 This report draws together a number of different neurotechnologies that differ in several ethically relevant respects. Three of the categories of interventions that we discuss utilise devices, while the fourth involves transplantation of cells. Some of these are physically invasive, others are not. Some achieve their effects by stimulating the brain; others do so by recording brain signals. These technologies occupy different points along their respective development trajectories, ranging from those still only explored in laboratory settings, to those that are already established treatments. They also span a variety of applications: not only divided by the therapeutic/non-therapeutic distinction; even within the category of therapeutic applications, technologies that treat physical and psychiatric symptoms may be distinguished from those that assist movement or communication.
- 10.2 This diversity not only entails a wide variety of actors, the development and use of these technologies also engages a complex and sometimes overlapping network of professional ethical norms, governance frameworks and statutory regulations. This multifaceted picture presents a challenge to drawing together the common threads that define the social and ethical issues raised by these novel neurotechnologies considered collectively. However, despite this diversity, one central feature which unites this wide-range of applications remains: these technologies intervene in the human brain. Without falling prey to reductive conceptions of the role of the brain in human existence, we may still acknowledge its special status: the healthy functioning of the brain plays central role in our capacities for leading fulfilling lives and for sustaining both our senses of ourselves and our close personal relationships.
- 10.3 This captures one side of the dynamic that lies at the foundation of our ethical analyses in this report: the tension between *need* and *uncertainty*. The significance of the healthy functioning of the brain in human existence gives us a powerful reason to intervene when illness or injury damages its functions. However, it similarly gives us reason to pause before intervening without good evidence that it will be safe and beneficial to do so. In part due to the newness of these technologies and in part because we still understand remarkably little about how the brain functions, there remain gaps in our understanding of the efficacy of some of these technologies, the biological mechanisms by which desired outcomes are achieved, and of their longer-term and unintended effects.
- 10.4 The discussions and recommendations of this report attempt to negotiate this tension. We suggest that a cluster of interests – safety, autonomy, privacy, equity, and trust – are engaged by the development and use of novel neurotechnologies, and that these warrant particular attention. In recognition of the challenges of protecting and promoting these interests across a wide variety of applications and contexts, we appeal to a particular set of virtues – inventiveness, humility, and responsibility. We suggest that these virtues provide a flexible and dynamic framework within which to characterise the values and outlooks that should be exemplified by a diverse range of actors, professions and organisations in striking a balance between responding to need while exercising caution.
- 10.5 We do not argue that the ethical issues raised by novel neurotechnologies (considered collectively) are unique or exceptional. Nevertheless, several cross-cutting priorities for ethical attention do arise: some owe their significance to the fact that these technologies intervene in an organ with a special status in human life; some relate to the vulnerability of prospective users; and others are attributable also to the sheer novelty of the products and techniques involved.

Cross-cutting themes

Supporting innovation while protecting patients

- 10.6 The virtue of inventiveness is crucial to research and innovation, yet manufacturers, particularly those operating as smaller enterprises, face significant economic obstacles to developing novel neurotechnologies from the laboratory into marketable products. Developers are competing for scarce investment in long, costly, and often precarious innovation trajectories. Some enterprises may fail before their products reach the stage of commercialisation. New funding partnerships may be needed to mitigate this risk and to ensure that scarce resources are directed at responsible research and innovation that targets the spheres in which therapeutic needs is most clearly identified. Inventive funding models could also be of benefit in supporting the development of neurotechnologies that are more affordable and easier to use, and thus more widely and equitably available. Effective and proportionate regulatory frameworks also serve these ends by encouraging innovation and clearly signposting the pathways to market.
- 10.7 To a great extent, the interests of patients who lack other treatment options, and the economic interests of those developing therapeutic applications of novel neurotechnologies, coincide in wanting a smooth passage for these technologies to clinical use as swiftly as possible. However, these respective sets of interests diverge if therapies reach the market without adequate and impartial scrutiny of their safety or efficacy, or if they are rendered too expensive by manufacturers' efforts to recoup high development costs. Oversight that is both effective and proportionate must protect prospective patients' interests in accessing much needed therapeutic neurotechnologies on two fronts: primarily by ensuring these technologies do not enter the clinical use until they have been demonstrated to do good rather than harm, but also by ensuring that the regulatory hurdles to reaching market are not so burdensome that they drain resources or deter investment. We have suggested that neither the regulatory framework applying to neurodevices, nor that governing neural stem cell therapies, currently achieves an optimal balance between these aims.

Providing access to novel therapies while safeguarding vulnerable individuals

- 10.8 Whenever therapeutic interventions involve invasions of patients' bodily integrity and impact significantly upon the functions of their physiology or mind it is essential to protect them as far as possible from potential harms and to ensure that any unavoidable risks are proportionate to the benefits that these patients might expect. However, many candidates for neurological interventions will, in a number of respects, be especially vulnerable. The majority of the neurotechnologies we have considered in this report represent new therapeutic or assistive approaches to conditions where patients have few or no other options available to them. Desperation potentially constrains the freedom with which patients and those close to them make decisions to undertake potentially risky or ineffective interventions. Moreover, due to the very nature of the kinds of conditions for which therapeutic applications of novel neurotechnologies are indicated, many prospective candidates for treatment lack capacity themselves to consent to interventions. They must rely on others to determine what is in their best interests. Each of these factors means that there is a particular imperative to protect the safety of, and support autonomous decision-making by, patients, research participants, and those close to them. This includes ensuring that they understand what is known, and just as importantly what is currently *unknown*, about the efficacy and risks of these technologies. It also means taking care not to characterise an intervention as someone's 'last best hope' without strong justification.
- 10.9 The number of people living with some of the most severe and treatment-resistant types of brain injury and illness, and who are the most likely candidates for neurotechnological interventions, is small. This may preclude the pursuit of large scale clinical trials to determine safety and efficacy. Due to the need to develop effective treatments, we recognise the necessity of

investigating these technologies through the experimental treatment of small numbers or even individual patients. However, in light of the vulnerability of many of these patients, a responsible approach to doing so will require supplementing the professional practices and ethical norms associated with treatment relationships with relevant practices from the clinical research paradigm.

- 10.10 Many therapeutic applications of novel neurotechnologies are likely to remain expensive, as much due to the highly skilled care required, as because of the costs of the technologies themselves. Equitable access to their potential benefits on a global scale is not yet foreseeable. This underscores the need to protect vulnerable individuals from exploitation by services offered outside well-regulated health care systems. This entails ensuring that patients do not seek treatment from private providers at home or overseas without appropriate referral routes and assurances as to the qualifications of these providers. Vulnerability takes on a somewhat different meaning in the context of the marketing of non-therapeutic services using neurodevices, where the devices are non-invasive and unlikely to pose serious health risks. Nevertheless, ineffective interventions in the brain on the basis of misleading claims abuse the trust of individual users and may undermine wider public understanding of the therapeutic applications of these technologies. Greater awareness-raising of the capacities and limitations of novel neurotechnologies is an important part of protecting trust and autonomy.

Maintaining trust and being honest about the limits of current knowledge

- 10.11 The vulnerability of some users underscores the responsibility of professionals to engage in clear and thorough information provision and counselling in their relationships with patients and research participants, and to reflect on individual circumstances and evolving understanding of these technologies. An essential element of this is humility with respect to making clear what is not known. Moreover, these efforts will only be as successful as the information available to professionals, and the wider popular conceptions of novel neurotechnologies, allow. Therefore important responsibilities accrue both to researchers (working in commercial enterprises and academia) and to journalists working in the non-specialist media to communicate realistic representations of these technologies and their capacities. We have observed there is evidence of hype (of overstating the capabilities of these technologies) in media representations that may be driven, at least in part, by a bias in academic publications towards publishing positive findings, and to public relations efforts on behalf of those working in product development. At an individual level, hype risks raising false hopes in those already dealing with the challenges of neurological or mental health disorders. At the level of innovation and commerce, it may initially help to attract investment, but overheated early expectations might not be capable of sustaining investor commitment throughout long and complex development trajectories.

- 10.12 In assessing the ethical and social impacts of novel neurotechnologies in this report, we are aware of the responsibilities of bioethics itself not to contribute to the cumulative engine of hype; for example, by engaging in speculation about the impacts of technological capabilities that are not yet realised. Non-therapeutic applications of neurotechnologies, including those enhancing human and military capacities, attract considerable interest from commentators. We have sought here to negotiate a balance between refraining from speculative ethical deliberations unsubstantiated by robust evidence of real-world applications of research in these emerging fields, whilst also avoiding being overly sanguine about ethical concerns arising from them, given the potentially wide demand for these applications if the ambitions of early research were to be realised.

Collecting evidence while preserving scientific integrity

- 10.13 Hype is by no means the only barrier to a full and robust understanding of the capabilities and limits of novel neurotechnologies. A significant factor is also the dispersed and undocumented nature of the evidence of clinical experiences of using these technologies. We have observed in this report a number of factors contributing to this: not least that many investigational uses of these technologies are taking place as experimental treatments, and that the framework under which medical devices are regulated does not itself enhance the public availability of pre- or

post-market evidence of safety (much less efficacy) of devices. The fragmented nature of manufacturers' and clinicians' professional experience and understanding of these technologies not only perpetuates the uncertainty that characterises this field, with associated detrimental impacts on clinical decision-making and informed consent. It also means that too little is known about therapeutic avenues that have already been explored, meaning that – contrary to the demands of responsible care – risky or fruitless interventions might be repeated unnecessarily.

- 10.14 Responsible research and innovation practices must not only be based in and reflect upon sound scientific evidence, they should also seek to generate and disseminate robust findings. We have recommended a number of areas in which the collection and transparency of this evidence could be improved by encouraging approaches that look beyond the standard model of conducting clinical trials. This includes support for collaborative registers to capture experiences of clinical uses of neurodevices and regulatory mechanisms for improved reporting and transparency of post-market incident data. These data will often record information about (sometimes deeply personal aspects of) individuals' lives. This has two implications for what is collected. First that we must attend to privacy and data protection sensitivities in sharing information about patients' care. Second, humility also reminds us of the value of documenting the kinds of outcomes that matter most to *patients*, which may not always be the same as those that are the chief focus for manufacturers or clinicians.

Treating brain disorders while monitoring impacts on the whole person

- 10.15 One reason why is important for registers, through which information on clinical experiences are disseminated, also to record patient-reported outcome measures is that the impacts of neurotechnologies often extend beyond their effects on physical or psychiatric health. The complex, potentially unintended, effects of DBS on patients' cognition, behaviour and mood are a striking example of this. Another is the particular detriment to well-being and autonomy that might be suffered by those who have come to rely on assistive neurotechnologies as participants in research studies, only to lose access to these at the conclusion of the study. Similarly, we recognise that when someone other than the patient takes non-consensual control of an implanted neurodevice, or intercepts and uses sensitive information collected by this device, these might be experienced as significant breaches of personal privacy or autonomy.
- 10.16 Therapies using novel neurotechnologies are not unique in their potential to alter how patients see themselves, are viewed by those close to them, or in impacting upon their relationships with and dependence upon others; many other serious health conditions will be similarly disruptive. Nevertheless, these kinds of effects warrant careful attention in the context of neurotechnologies because we are concerned with interventions in the brain, an organ that plays a particularly central role in the functioning of patients' bodies, minds, personal and professional lives. Any attempts to govern the uses of novel neurotechnologies must look beyond objectively-defined clinical outcomes and remain flexible enough to respond to individuals' personal and idiosyncratic reactions to the roles that these technologies might play in their lives.

Recommendations

Responsible research governance

- 10.17 The concept of 'responsible research and innovation' (RRI) is gaining increasing currency amongst policy makers as means to articulating the considerations necessary to secure ethically sound and scientifically robust research objectives, conduct and governance. We have suggested that RRI in the context of novel neurotechnologies comprises six key elements. These are:

- Clearly identified need;
- Securing safety and efficacy;
- Generating robust evidence;
- Continuous reflexive evaluation;
- Coordinated interdisciplinary action; and
- Effective and proportionate oversight.

These principles, alongside our ethical framework, inform the recommendations we have made in respect of the governance – understood both in terms of professional behaviours and regulatory controls – of research practices in the field of novel technologies

10.18 We have observed that there is a substantial unmet need for therapies for many kinds of brain disease or damage for which existing treatments have proved ineffective. Many of the novel neurotechnologies we consider in this report, however, have not yet reached the stage of being available as commercial applications, but are still only being used in research contexts. The ethical care of research participants is therefore a particular priority – not only with regard to their safety and autonomy, but also to avoid building false hopes where investigational interventions offer uncertain outcomes.

Guidance on sham controlled neurosurgical trials

10.19 In many circumstances, the best model for deriving the most robust evidence from clinical investigations is the randomised double-blinded controlled trial. However, one circumstance in which blinded controls may not always be appropriate is when this involves ‘sham neurosurgery’, involving surgical intervention upon a participant’s skull without the insertion of the active biological product under investigation. We suggest that ethical guidance on the use of sham neurosurgery is needed in time to inform the progression of UK clinical trials of neural stem cell therapies to Phase II in which efficacy is assessed. **We recommend that – to support decision-making by clinical investigators, sponsors and Research Ethics Committees – the Health Research Authority should develop guidance on the kinds of circumstances in which sham neurosurgery may, or may not, be an appropriate part of clinical investigations, and what post-trial obligations should hold in respect of participants assigned to the sham arm of trials.** (Paragraph 5.41)

Non-abandonment of research participants

10.20 There may be practical reasons why it might not be possible to continue to provide investigational therapeutic or assistive neurotechnologies to participants beyond the conclusion of a research study. The withdrawal of these technologies may nonetheless impact significantly on participants’ quality of life. We therefore reiterate here our recommendation from the Nuffield Council on Bioethics 2002 report *The ethics of research related to healthcare in developing countries*, that “researchers should endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee.” **In view of this we recommend that researchers should provide, as part of their submissions to Research Ethics Committees, exit strategies for circumstances in which they are unlikely to be in a position to provide patients with continued use of neurodevices beyond the conclusion of the study.** These strategies should be proportionate to the harm (or loss of benefit) to participants from withdrawal of the device. At minimum, these submissions should include what participants will be told as part of consent procedures about access to treatment beyond the study’s duration, and details of arrangements to offer appropriate counselling and support at the study’s conclusion. **We further recommend that the Health Research Authority guidance on care after research includes explicit recognition of the issues raised by the withdrawal of access to assistive technologies.** (Paragraph 5.45)

Guidance on conducting experimental treatment

10.21 The line between research and treatment is not always a clear one, particularly in an emerging field such as this where many novel neurotechnologies are investigated in experimental treatment contexts. However, treatment and research are governed under two distinct paradigms, neither of which is ideally suited to oversight of these kinds of experimental uses. **We recommend that the General Medical Council, the Health Research Authority and the Medical Research Council work together to produce guidance for clinicians pursuing experimental therapies. This would address lacunae between the regulation of research and treatment, with the aim of ensuring that experimental interventions are pursued in a responsible way that protects patients' interests, while supporting inventiveness thorough the generation of new knowledge in the public interest.** (Paragraph 5.60) The recommended guidance would adopt the best features of each of the treatment and research governance paradigms, while seeking to eliminate the worst. For example, the primacy of patient interests would be imported from the treatment paradigm, whilst the clinical research paradigm would recommend adopting clear investigatory protocols, including means of assessing efficacy and risk, independent ethical oversight, and robust methods of recording and sharing findings. We suggest that this guidance might usefully build on MRC's *Experimental medicine toolkit*.

Research into non-therapeutic applications

10.22 Uncertainties about the benefits and risks of novel neurotechnologies extend to non-therapeutic uses of non-invasive neurostimulation for non-therapeutic purposes. Though these technologies used in clinical settings do not present serious risks to health, their use for non-therapeutic purposes do not bring clear social benefits either. There is a need to understand better what the long-term effects of frequent private use of these devices might be, without research itself contributing to unnecessary interventions in the brain. **We recommend that institutional ethics committees reviewing research proposals for studies using neurostimulation directed at non-therapeutic ends ensure that these meet high standards of originality and rigour. The aim should be to prevent the use of poorly defined protocols and the unnecessary repetition of similar studies, and to make sure participants are informed about the limited knowledge of long-term unintended health effects.** (Paragraph 8.39)

10.23 Military personnel are subject to a disciplined regime in which the concept of freely given consent may be problematic where this applies to participation in the experimental use of new technologies. Studies involving human participants conducted on behalf of the Ministry of Defence in the UK must undergo scrutiny by the MOD Research Ethics Committees.¹⁰⁷⁷ However, in situations where the use of neurotechnologies does not constitute a formal research study, the position regarding ethical guidelines and informed consent may be more ambiguous. **We suggest that clinicians working with the armed forces may play a crucial role by exercising their duty of care to protect the welfare of personnel who may feel under pressure to participate in experimental military applications of novel neurotechnologies that carry uncertain risks and benefits.** (Paragraphs 8.87)

Understanding impacts on the developing brain

10.24 Some children already use BCI games, and it is possible that parents and educators may be interested in using non-invasive BCIs or neurostimulation for the purposes of achieving cognitive or educational benefits for children in their care. There is therefore a need to better understand the effects of these neurotechnologies on brain development during childhood. However, precisely this uncertainty means that an unqualified call to explore these questions

¹⁰⁷⁷ Defence Science and Technology (2012) *Research Ethics Committees (MODREC)*, available at: <http://www.science.mod.uk/engagement/modrec/modrec.aspx>

through interventional research involving children would be in tension with the virtues of responsibility and humility. **We therefore recommend that there is a need for observational studies of children, who are already using neurodevices for gaming, or to improve their capacities for attention or learning, to assess the benefits and risks of these interventions, including their effect on the developing brain.** (Paragraph 8.40)

Ethical education on dual-use applications

10.25 The development trajectories of many novel neurotechnologies are likely to be complex and non-linear. This means it may not always be possible to anticipate their dual-use applications (those that have both peaceful and hostile applications). The potential for the kinds of neurotechnologies we have discussed in this report to be put to dual use has been raised by some commentators. We have suggested that continuous reflexive evaluation of innovation pathways is an important element of responsible research and innovation in this field. We therefore welcome initiatives such as the Wellcome Trust funded collaborative ‘dual-use bioethics’ project, one strand of which has investigated the current provision of ethical training in undergraduate and postgraduate neuroscience curricula in the UK. **We recommend that, as part of their ethical training, those studying for a higher degree in neuroscience should be alerted to the possible dual-use implications of neurotechnologies.** (Paragraph 8.89)

Effective and proportionate oversight

10.26 The broad requirement that the regulation of any new technology should be both proportionate and effective takes on particular salience in view of the tension between need and uncertainty which potentially arises in the case of novel neurotechnologies.

Oversight of Notified Bodies

10.27 We have observed that there is insufficient oversight and scrutiny of the activities of Notified Bodies: the organisations responsible for confirming medium and high risk medical devices conform to statutory safety and performance requirements. **We welcome the European Commission’s proposals for tighter controls on Notified Bodies, but suggest that in the interests of transparency there is still a pressing need for the evidential bases on which Notified Bodies reach compliance decisions to be a matter of public record.** (Paragraph 7.27)

Reliance on equivalence data

10.28 European legislation currently permits medical device manufacturers to demonstrate the safety and performance of their device (for which marketing approval is being sought) on the basis of data pertaining to an ‘equivalent’ device that has already received marketing approval, rather than conducting their own clinical investigations. While recognising this may be a proportionate approach for some kinds of devices, it might not always be so for those that intervene in the brain. We therefore welcome the European Commission’s legislative proposals to introduce more specific criteria for the demonstration of equivalence, including the presumption that, for implantable and high risk devices, demonstration of equivalence with existing devices will “generally not be considered as sufficient justification” for relying on existing clinical data alone. **In recognition of the special status of the brain and continued uncertainty regarding the consequences of intervening in it, we recommend to the Medicines and Healthcare products Regulatory Agency that, where equivalence data are relied upon to demonstrate the regulatory conformity of a neurodevice, the condition of equivalence must be satisfied in relation to its effect, not only its purpose, performance and safety. Furthermore, clear justification for approving neurodevices on the basis of equivalence data alone must always be provided and open to public scrutiny.** (Paragraphs 7.33 and 7.47)

Post-market surveillance

- 10.29 The regulatory system that applies to medical devices in Europe places considerable emphasis on post-market surveillance as a means of ensuring the safety and performance of devices on the market. While reporting of adverse incidents by manufacturers is mandatory, health care professionals are encouraged, but not obliged, to report these. **We endorse the House of Commons Science and Technology Committee’s recommendation that a *Black Triangle Scheme*, similar to that used in the pharmaceutical sector, be introduced (especially when devices have received marketing approval on the basis of equivalence data) to signal to patients and professionals when an invasive medical devices is newly approved and to encourage incident reporting. We further recommend to the Medicines and Healthcare products Regulatory Agency that the reporting of adverse incidents involving all neurodevices by professionals should be mandatory. Information regarding adverse incidents and incident trend reports should be made publically available.** (Paragraph 7.55)
- 10.30 Risks to physical health are not the only kinds of potential harm posed to users of neurodevices. It is possible that accidental, unauthorised or malicious interference with the functioning of a device might lead to malfunctions that could impair health, patients’ confidence in their devices, or lead to the interception of sensitive personal data about health or neural activity. **We recommend that the Medicines and Healthcare products Regulatory Agency monitors the vulnerability of neurodevices to accidental, unauthorised or malicious interference, especially where these could impair health, undermine patients’ confidence in their devices, or lead to the interception of sensitive personal data about health or neural activity. Appropriately anonymised records of any such incidents should be made publically accessible.** (Paragraph 5.54)

Regulating neurostimulation devices under a medical regime

- 10.31 The preceding sets of recommendations relate to the regulation of devices that have received approval to be marketed for medical purposes. If a manufacturer seeks to market a neurodevice for *non*-medical purposes (such as improving concentration or mood in healthy users) then it will not fall within the scope of the European directives that apply to medical devices or be regulated by the Medicines and Healthcare Products Regulatory Agency. This means that these products will not necessarily be subject to the kinds of oversight appropriate to devices that intervene in the functions of the human body. However, the European Commission has proposed legislative reforms that would mean that some categories of active or invasive devices (such as equipment for delivering intense pulsed light) would be regulated as medical devices, *irrespective* of whether they are intended by the manufacturer to be used for a medical purpose. **We recommend, therefore, that in the interests of consistency and of providing effective and proportionate oversight of devices that intervene in the brain, that the European Commission consider including neurodevices that deliver TMS and TBS amongst the categories of devices that would (irrespective of their intended purpose) be regulated as medical devices and that their marketing in the UK is overseen by the Medicines and Healthcare products Regulatory Agency.** (Paragraph 8.52)

Proportionate oversight of the development of neural stem cell therapies

- 10.32 The regulatory system applying to regenerative medicine and advanced therapeutic medicine products (ATMPs - the category of products to which neural stem cell therapies belong) is very different from that for medical devices. In keeping with the invasive nature of these therapies, and the potentially higher risks of biological manipulation, there are strict requirements for pre-market clinical trials, involving ethical oversight and the involvement of a number of regulatory agencies. It has been suggested that, historically, the regulation of regenerative medicine has been subject to delays and regulatory overlap. **We welcome the recent and ongoing changes to achieve effective collaboration between the regulators responsible for overseeing regenerative medicine in the UK. We would encourage continued dialogue between**

regulators and researchers, genuine sharing of experiences, and reflexive systems of oversight in order to foster innovation while protecting patient safety. (Paragraph 7.72)

High standards of care for patients

10.33 The potential vulnerability of individuals with neurological or mental health disorders, many of whom will have no treatment options other than those offered by novel neurotechnologies, the special status of the brain in human existence and uncertainty about the unintended effects of intervening in it, together provide a particular imperative for robust ethical oversight of the treatment and care of patients.

Counselling prior to treatment

10.34 Given these combined factors, prospective patients and those close to them are likely to benefit from counselling to complement information provision by clinicians. **We recommend that those responsible for commissioning specialised services for the NHS in each of the UK countries make it a requirement that, where treatments involving invasive neurostimulation (and, in the future, neural stem cell therapies) are provided, patients must be offered the opportunity to receive independent counselling from suitably qualified professionals about the implications of these treatments.** (Paragraph 5.9)

Features of this counselling should include:

- That it is offered as part of the referral pathway before consent is given; this would be in addition to, rather than a replacement for, the provision of clinical information supporting informed consent;
- It should also be distinguished from any parallel provision of therapeutic counselling for patients with mental health disorders; and
- The counselling services recommended here would be analogous in delivery and aims to NHS genetic counselling services in that they should: be delivered by a member of an interdisciplinary health care team; be non-directive; provide information suitable to patients' individual circumstances and treatment options; and provide support to family members and others close to and caring for the patient.

NICE Interventional Procedures Guidance

10.35 The National Institute for Health and Care Excellence (NICE) plays a valuable role and fills an important gap in the regulatory structures governing the marketing of medical devices. It provides evidence-based guidance on the use of particular interventional procedures, which clearly sets out the ethical and practical responsibilities of practitioners and makes recommendations for appropriate oversight measures. However, while decisions about the practical application of NICE *Interventional procedures guidance* is determined at a local level by decision-makers such as commissioners and clinicians, they can only go so far in supporting good patient outcomes. **It is essential that the National Institute for Health and Care Excellence (NICE) continue to work with stakeholders, including patients, to maximise usefulness of its *Interventional procedures guidance* (IPG) and its application in real life settings. At present, compliance with NICE IPG is voluntary. We recommend that compliance with NICE IPG should be made compulsory within the NHS and that the Care Quality Commission is assigned the role of inspecting NHS trusts (and boards) to ensure compliance.** (Paragraph 5.24)

Patients using private services

10.36 Not all interventions using novel neurotechnologies will necessarily take place in the NHS. Private businesses already offer non-invasive neurostimulation services for conditions such as depression. We judge that the greatest risk to patients' health and well-being from the provision of services by private providers arises where practitioners do not have medical qualifications

and operate outside the governance structures of the health service and the norms of professional medical ethics. **We recommend that the relevant professional bodies, including the Association of British Neurologists and the Royal College of Psychiatrists, should work together to issue a set of guidelines to establish a benchmark for responsible professional standards in the delivery of non-invasive neurostimulation treatments. These guidelines should state those categories of neurostimulation treatment that should only be provided by a suitably qualified professional, following clinical evaluation of a patient by a doctor. The aim is to ensure that neurostimulation treatments are provided only where there are appropriate clinical indications and where individual risk factors have been assessed.** (Paragraph 5.31)

Making existing evidence transparent and accessible

10.37 Many investigations of novel neurotechnologies take place in small studies or interventions with individual patients. This presents a challenge to gathering a consolidated body of accessible and assessable evidence. We suggest that a number of measures might help to achieve this goal. This would be particularly valuable in the medical devices sector, where regulatory requirements for pre-market clinical investigations are light-touch.

Registers of clinical experience

10.38 **We recommend that professional bodies, such as the Association of British Neurologists, the Society of British Neurological Surgeons and the Royal College of Psychiatrists, work with each other and with relevant patient groups and charities to establish registers (where these do not already exist), or to improve the quality, accessibility and profile of those which already exist. These registers would gather data on clinical experiences of treatments using novel neurotechnologies, record the outcomes of these interventions, and make these publically available.** (Paragraph 5.63) As these registers would encompass a potentially wide range of different technologies and clinical uses, it is not possible to be prescriptive about their exact form or scope. However, we suggest that essential features would include:

- independent oversight to ensure the impartiality of registered data;
- robust mechanisms for protecting patient confidentiality;
- academic involvement to ensure the quality of data;
- dedicated curatorship, to ensure that the data collected is of a kind that is useful and informative to the intended users of the register, and collected and presented in ways that facilitate comparisons and meta-analyses of aggregate data;
- recording negative or inconclusive findings, as well as positive treatment outcomes; and
- capturing patient-reported outcomes as part of building a comprehensive picture of benefits and risks that includes subjective experiences.

Registers of this kind might initially cover data collected in the UK, but an aspiration to create connections with international data repositories as well would be valuable.

10.39 **We would further recommend that the findings – including negative or inconclusive outcomes – from research investigating non-therapeutic effects of novel neurotechnologies should also be included in these registers.** (Paragraph 8.41) This would mean that current evidence of benefits and unintended effects are brought together to reach the widest audience and achieve cross-fertilisation of valuable findings from therapeutic and non-therapeutic protocols. It would also help to prevent the unnecessary repetition of similar studies and to challenge and correct some of the problems associated with small sample sizes and research and reporting integrity that have been observed in some studies reporting enhancement effects of neurostimulation techniques.

Transparency of regulatory information

10.40 The lack of transparency in the European system for the regulation of medical devices can be seen as perpetuating the scarcity of evidence upon which patients, health professionals, and health care providers can take decisions about treatment using neurodevices. However, the European Commission has announced a number of changes that may improve the current situation. These include the recent establishment of a voluntary European Health Technology Assessment network (which aims to enable sharing of knowledge among Member States and facilitate assessment of which devices might contribute to efficiency gains and improved services), and the proposals to make key aspects of a new European Databank on Medical Devices (Eudamed) publically accessible and enhance the range of data it contains, including those on clinical investigations and post-market surveillance. **We welcome these proposed changes and the extent to which they would enhance the transparency of the European system. However, we suggest to the European Commission that Eudamed should aspire to a similar degree of transparency as that which operates in the US Food and Drug Administration (US FDA), the body charged with regulating medical devices in the US.** (Paragraph 7.28)

Evidence from regulation of exceptional or non-routine uses

10.41 Regulatory routes that oversee the provision of treatments (which are not approved for wider market distribution) to individuals or to small groups of patients are a welcome means of addressing unmet need. Nevertheless, there appear to be inadequate procedures for capturing and making accessible information on when and for what purpose regulatory approval has been given for the supply of medical devices and ATMPs under the regulatory routes encompassing exceptional or non-routine uses of products. This lack of information hampers understanding of the extent to which these regulatory mechanisms are used and of their value in providing patients with access to safe and effective treatments. Improved reporting mechanisms would support dissemination of valuable evidence of efficacy and risks to promote further learning. **We recommend that the Medicines and Healthcare products Regulatory Agency (MHRA) should record anonymised data on when, and for what purpose(s), approval has been given for the supply of neurodevices under exceptional use or custom made arrangements and for non-routine supply of ATMPs under the hospital exemption or Specials arrangements. In addition, we recommend that the MHRA establishes mandatory schemes by which manufacturers and clinicians report data on patient outcomes, and adverse events of resultant interventions.** (Paragraph 7.89) Even though regulatory responsibilities for overseeing the supply of these exceptional and non-routine uses of ATMPs and devices are devolved to the competent authorities in Member States, we suggest that it would nonetheless be valuable if data regarding their use and patient outcomes were also coordinated at a European level: by the European Medicine Agency (for ATMPs) and through Eudamed (for medical devices). These data should be accessible by health care providers and the public.

Protecting the interests of users in non-therapeutic contexts

10.42 Not all interventions using novel neurotechnologies are directed at therapeutic ends. Some may be offered for putative 'enhancement' purposes, for example to improve cognitive capacities or mood. The technologies used to deliver these services might not differ significantly from those used in therapeutic settings, thus the same ethical issues regarding their safe use, uncertainty about unintended long-term effects, and consent apply here too.

Industry standards for non-therapeutic services

10.43 The possible risks to customers' health from non-invasive neurostimulation for non-therapeutic ends (such as putative enhancement effects) are unlikely to be sufficient to warrant restricting consumers' freedom to undertake them. Nevertheless, the special status of the brain and the potential for hype to distort public understanding of the capacities of neurotechnologies to benefit individuals without brain disorders or damage, places a responsibility on businesses

offering services using neurodevices for non-therapeutic purposes to adhere to safe and honest practices that protect their customers' health and equip them to make informed choices about undergoing these kinds of interventions. **We recommend therefore, that service providers should form a trade association to establish and uphold best practice standards in the sector of non-therapeutic neurostimulation and neurofeedback. These standards would encompass best practice for both the delivery of interventions, and the kind of information provided to customers.** (Paragraph 8.59)

Cognitive enhancement uses in children

10.44 Where neurodevices are used for the putative purposes of cognitive enhancement, one particular area of concern is the coercive use of neurostimulation and neurofeedback in children. The effects of these interventions on the developing brain are, as yet, unclear, and children and young people may be less well equipped to resist pressures from educators or parents who wish them to use neurotechnologies to enhance their capacities for learning and educational performance. **We recommend that the departments for education in each of the governments in the UK and the Royal College of Paediatrics and Child Health should issue advice directed to both teachers and parents on the current best evidence, and the evidence gaps, of the efficacy and risks of neurofeedback and neurostimulation for cognitive enhancement in children.** (Paragraph 8.62)

Coercive interrogation uses

10.45 There is some evidence that non-invasive BCI devices have been marketed for purposes analogous to lie detection, or to ascertain whether individuals under suspicion recognise particular images or information. It has also been speculated that neurostimulation could be used in interrogation contexts. Coercive interrogation is prohibited under the Geneva Conventions and the involvement of doctors in cruel, inhuman or degrading treatment of detainees is prohibited under the Declaration of Tokyo. However, non-invasive neurostimulation devices or non-invasive BCIs do not necessarily require operation by a medical professional. **We recommend that the armed forces and intelligence services consider issuing advice to their personnel that the use of neurodevices in interrogation is coercive and as such is prohibited under international humanitarian law.** (Paragraph 8.84)

Responsible communication

10.46 Exaggerating the capacities of novel neurotechnologies and extrapolation beyond that which is supported by the available evidence risks exposing vulnerable patients, customers, prospective research participants, and those close to them to false hope and misinformation. This could interfere with their capacities to make the best decisions regarding treatment or use, and it could also undermine wider trust and understanding of therapeutic interventions in the brain.

Responsibilities of professional communicators

10.47 We endorse existing guidelines (from multiple sources)¹⁰⁷⁸ for the accurate and responsible reporting of science in general and re-emphasise their importance in communicating the capacities of novel neurotechnologies. In addition to adhering to these guidelines, **we**

¹⁰⁷⁸ For example, see: Social Issues Research Centre (2001) *Guidelines on science and health communication*, available at: http://www.sirc.org/publik/revised_guidelines.shtml#guide1; International Council for Science (2010) *Advisory note "science communication"* available at: <http://www.icsu.org/publications/cfrs-statements/science-communication/advisory-note-science-communication>; BBC Trust (2011) *BBC trust review of impartiality and accuracy of the BBC's coverage of science*, available at: http://www.bbc.co.uk/bbctrust/assets/files/pdf/our_work/science_impartiality/science_impartiality.pdf; Science Media Centre (2012) *10 best practice guidelines for reporting science and health stories*, available at: <http://www.sciencemediacentre.org/wp-content/uploads/2012/09/10-best-practice-guidelines-for-science-and-health-reporting.pdf>.

recommend that all actors working in professions involved in communicating the findings of research involving novel neurotechnologies have a responsibility to reflect upon how their representation of the current and future applications of novel neurotechnologies might impact on others and to remain circumspect about the promises of these applications (however exciting they may be to them professionally or personally). In recommending this, we have deliberately not produced a simple checklist, but instead a set of considerations that are intended to not only guide the reflections of individual actors, but also to be taken into account by institutions and professional bodies involved in the entire circuit of neurotechnology communications in drawing up professional guidance on good practice in this field. **Specifically, we recommend that these professionals and organisations should attend to the following elements of responsible communication practices:**

- to reflect on the pressures that may be imposed by institutional and structural forces to add a ‘pinch of hype’ and to consider the successive and cumulative effect of this upon on the way in which a story may enter the public domain;
- to resist pressure to publish only positive or PR-attractive findings;
- to be clear about any features of a research study’s aims, scope or methodology that might preclude generalising its findings to wider populations or to practical real-world applications, and to resist the temptation to over-claim or engage in unjustified extrapolation beyond that which is supported by research evidence. It can be as important to say what the research does not imply, as what it does. Existing guidelines (from organisations including the SMC) have highlighted a similar imperative in relation to science reporting in general; we re-emphasise it here in the context of novel neurotechnologies where investigations are often pursued through single patient interventions or small studies;
- to be transparent about the source of funding of the research reported, especially if it has been conducted on behalf of, or supported by, an organisation with a commercial interest in the findings;
- while the use of vivid language, metaphors and images are intrinsic to professional communication practices, it is nevertheless important to refrain from misusing powerful visual devices or engaging personal stories in ways that might mislead. For example, where treatment outcomes are not unequivocally positive, accounts of patients with dramatically reduced symptoms should be accompanied by the stories of those who have different experiences. It may also be important to consider how using language such as ‘promise’ or ‘therapeutic’ to describe research outcomes might undermine efforts to communicate the uncertainties or limits of this research by eliding aspirations for a technology with its current capabilities;
- where an explicit connection is made between a neurotechnology and a particular therapeutic application, to be clear not only about the kinds of conditions the intervention would address and the balance of risks to benefits for patients, but also any continuing uncertainties, including those relating to longer term outcomes. Given the likely high cost of many novel neurotechnologies and the long development trajectories of stem cell-based therapies, it is also important to reflect accurately the realistic prospects for wide availability to patients;
- to acknowledge diversity in the perspectives of patients with neurological and mental health disorders and those close to them, by recognising that novel neurotechnologies may not be the only or indisputable means of addressing their needs and that, for some, a focus on restoring lost function or ‘normalisation’ might not represent their priorities or best interests; and

- **to be aware of the broader social, legal, and political implications of research in the sensitive area of the human brain, including the ways in which the research might be applied to other domains.** (Paragraph 9.72)

10.48 Our recommendations regarding the practices and virtues that would be exemplified by responsible reporting of novel neurotechnologies by researchers, press officers, and journalists are a significant part of ensuring responsible communications. However, insofar as these recommendations are made with a particular emphasis on preventing hype, they risk futility if the other components of the engine that drives hype remain unchecked. It is neither reasonable nor desirable to excise all the reasons researchers have to be excited about and share the fruits of their inventiveness and inquiry – indeed, throughout this report, we have emphasised the need for greater dissemination of research and experimental findings. Nevertheless, in light of the problems of hype in this field **we recommend that the UK governments, higher education funding councils and universities reflect on the effects that the ‘impact agenda’ might be having on the ways in which the promises and limitations of novel neurotechnologies are communicated by academic institutions and their researchers.** (Paragraph 9.73)

10.49 **Businesses and universities developing and promoting commercial products from neurotechnological research should also reflect on their own responsibilities when seeking to publicise this research, attract funding for development, and market their products.** (Paragraph 9.74)

Concluding remarks

10.50 In this report, we have examined the diverse therapeutic and non-therapeutic purposes to which novel neurotechnologies might be applied. Where these technologies offer therapeutic benefits, they frequently represent one of the few, or only, treatment options currently available to individuals living with serious neurological or mental health disorders. There is, therefore, considerable value in inventive and reflective research and innovation practices in this field. However, this is also an area marked by uncertainty, vulnerability and hype. The virtues of responsibility and humility require that decisions – taken by professionals and patients – about undertaking interventions using novel neurotechnologies should be based on the best available evidence of their benefits and risks. This evidence is still being accumulated and we have recommended a number of ways to capitalise more effectively on existing knowledge. We have also indicated where further investigations must be governed by ethical standards appropriate to interventions in the brain. The global need for effective treatments for serious neurological conditions is substantial. Where interventions using novel neurotechnologies have been demonstrated to be safe and effective, and provided they are subject to appropriate regulatory oversight, we would hope that the exercise of inventiveness would mean that they also become cheaper, easier to use, and more widely and equitably available.

Appendices

Appendix 1: Method of working

Background

The Nuffield Council on Bioethics established the Working Party on *Novel neurotechnologies: intervening in the brain* in October 2011, and the Working Party subsequently met 10 times between November 2011 and April 2013. In order to inform its deliberations, the Working Party launched a consultation in February 2012 and held a series of “factfinding” meetings with clinicians, investors, regulators, patients, academics and those working in the industry. It also commissioned a report looking at novel neurotechnologies and social media.

The Working Party would like to thank all those who gave their time and expertise for the invaluable contribution they made to the report.

Consultation

The Working Party launched a consultation in February 2012 which ran until April 2012. 60 responses were received in total of which 20 were submitted by organisations and 40 were submitted by individuals. Those responding to the consultation included academic researchers, clinicians, patients and faith groups. A full list of respondents is set out in appendix 2. A summary of the responses will be made available on the council’s website. Individual responses will also be made available where permission has been granted.

Factfinding meetings

A series of factfinding meetings were held to help the Working Party benefit from the personal and professional expertise of others. A total of 15 meetings were held, the details of which can be found below.

Clinicians: 16 February 2012:

- Dirk de Ridder, neurosurgeon, University Hospital Antwerp, Belgium
- Declan McLaughlin, research professor of Psychiatry Trinity College Dublin Ireland
- Ludvic Zrinzo, consultant neurosurgeon and senior clinical researcher, UCL institute of Neurology

Conversation with Dr Hilary Walklett: 15 May 2012

Industry: 16 August 2012

- Nicholas Hatsopoulos, previously of Cyberkinetics
- Zack Lynch, Neurotechnology Industry Organization
- John Sinden, ReNeuron
- Andrew Thomas, Rogue Resolutions

Non-therapeutic applications: 7 September 2012

- Roi Cohen Kadosh, Wellcome research career development fellow, Department of Experimental Psychology, University of Oxford
- Femke Nijboer, researcher in the 3TU Centre for Ethics and Technology and Postdoctoral Researcher in the Human Media Interaction group at the University of Twente

Military applications of novel neurotechnologies: Thursday 16th August 2012

- Malcolm Dando, International Security, University of Bradford
- James Revill, research fellow, Harvard Sussex Program, SPRU, University of Sussex

Regulating the technologies: 20 September 2012

- Elaine Godfrey, Clinical Trials Unit, MHRA
- Neil Ebenezer, New and Emerging Technologies, MHRA
- Jane O'Brien, Head of Standards and Ethics, General Medical Council
- Lucia D'Apote, Committee for Advanced Therapies Scientific Secretariat (*by teleconference*)
- Andrew George, chairman of GTAC and chair of the NRES Research Ethics Advisors' Panel

Investment: 21 September 2012

- Cathy Prescott, director, Biolatris Ltd, chair of the UK National Stem Cell Network Advisory Committee, director of the East of England Stem Cell Network

Neuroethics: 5 November 2012

- Paul Root Wolpe, professor of bioethics at Emory University

Meeting with deep brain stimulation patient: 20 November 2012

- Richard Smith

Meetings with those involved in brain-computer interface research: 7 December 2012

Participants:

- Mai Ryan
- Gary Mulligan
- Eoin, Eddie and Karen O'Mahony

Clinicians:

- Áine Carroll, national director of Clinical Strategy Programmes and immediate past chair of the Medical Board of the National Rehabilitation Hospital
- Jacqueline Stow, specialist registrar in rehabilitation medicine, National Rehabilitation Hospital

Researcher

- Damien Coyle, University of Ulster

Meeting with the Royal Academy of Engineers: 11 March 2013

- Philippa Shelton and Katherine MacGregor

NICE: 4 April 2013

- Mirella Marlow, programme director, Devices and Diagnostic Systems

Social media study

As part of factfinding for this report's discussion of the role of the media in communicating about novel neurotechnologies, the Working Party commissioned a study looking specifically at the representation of these technologies in the social media. The purpose of this study was to provide a brief review of the literature relating to the representation of science and technology by social media, a 'snapshot' of content on social media platforms in which novel neurotechnologies are mentioned, and an analysis of the sources responsible for creating or uploading this content. The methodology included categorising and analysing the first 20 results returned by entering the following terms into the search functions of each of the social media platforms Delicious, Facebook, Twitter and YouTube: "deep brain stimulation", "brain computer interface" and "neural stem cell replacement therapy". The generic search engine Google Blog Search was used also to search for blogs. The study necessarily provides only a 'snapshot' of the representations of novel neurotechnologies on social media due to time limitations and the fact that the results returned by any particular search will depend on variables and contingencies such as the precise search terms used, the date on which the search was carried out and the online profile of the researcher. The findings of this study are drawn upon in chapter 9.

This study was conducted by Allyson Purcell-Davis, a lecturer at the School of Communication, Culture & Creative Arts at St Mary's University College Twickenham and a PhD candidate at Cardiff School of Journalism, Media and Cultural Studies.

External review

A draft version of this report was reviewed by 12 external reviewers listed below:

- Professor Stuart Allan
- Professor Richard Ashcroft
- Dr Damien Coyle
- Dr Dirk De Ridder
- Dr Neil Ebenezer
- Professor Charles French-Constant
- Dr Joseph Fins
- Dr Elaine Godfrey
- Professor Emily Jackson
- Professor Peter Littlejohns
- Professor Paul Martin
- Professor Chris Mason
- Dr Jonathan Moreno
- Dr Cathy Prescott
- Professor John Stein
- Professor Gregor Thut

The Working Party would like to express their gratitude to these individuals for their insightful and detailed comments, which played an important role in the final production of the report.

Appendix 2: Wider consultation for the report

The aim of the consultation was to obtain views from as wide a range of individuals and organisations interested in the area as possible. The consultation document was published on line in February 2012 and remained open until April 2012. The consultation set out the terms of reference for the report, provided some background information and asked a series of questions, reproduced in the box below.

The document was split into three substantive sections:

- Brain-computer interfaces
- Neurostimulation
- Neural stem cell therapy

Consultation questions

- Have you ever used a technology that intervenes in the brain, and with what consequences? Please describe your experience.
- If you have not used a technology that intervenes in the brain before, would you do so if you were ill? Why / why not?
- Would you use a technology that intervenes in the brain for non-medical purposes, such as gaming or improving your cognitive skills? Why / why not?
- What are the most important ethical challenges raised by novel neurotechnologies that intervene in the brain?
- In what ways, if at all, should the development and use of these technologies be promoted, restricted and/or regulated? Please explain your reasons.
- Have you used a BCI, and if so, with what consequences? Please describe your experience
- If you have not used a BCI before, under what circumstances would you do so?
- What are your expectations and concerns for BCIs?
- Are there any particular ethical or social issues associated with BCIs?
- What would robust and effective regulation of research in this area look like? Is more or less regulation needed? Please justify your response
- Have you used neurostimulation and if so, with what consequences? Please describe your experience.
- If you have not used neurostimulation before, under what circumstances would you do so?
- Under what circumstances do you think it might be acceptable to use neurostimulation in non-medical context (that is to say, not for the treatment of a disease or disability)?
- Are there any particular ethical or social issues associated with neurostimulation?
- What would robust and effective regulation of research in this area look like? Is more or less regulation needed? Please justify your response.
- Under what circumstances would you use neural stem cell therapy?
- What do you think of the risks and benefits of neural stem cell therapy?
- Are there any particular ethical social issues associated with neural stem cell therapy?
- How do you feel about neural stem cell therapy being used for non-medical purposes one day, for example for enhancement?
- What would robust and effective regulation of research in this area look like? Is more or less regulation needed? Please justify your response.

In total the Working Party received 60 responses to the consultation, 20 of which were submitted by organisations and 40 of which were submitted by individuals. Those responding to the consultation

included academic researchers, clinicians, patients and faith groups. These responses, along with the factfinding meetings set out in Appendix 1, played an important role in shaping the report and the Working Party would like to express their thanks to all the respondents.

List of respondents to the call for evidence

Anonymous

- Four respondents wished to remain unlisted.

Individuals

- Tipu Aziz and Alex Green
- Ryan Carlow
- Markus Christen, Institute of Biomedical Ethics, University of Zurich
- David Coe
- Fofi Constantinidou, PhD, Professor of Psychology and Director, Center for Applied Neuroscience, University of Cyprus
- Damien Coyle
- Raymond De Vries, University of Michigan, Center for Bioethics and Social Sciences in Medicine
- Dr Patrick Degenaar, Newcastle University
- Cristina Fernandez-Garcia
- Professor James Giordano, PhD
- Dr Judy Illes, Professor of Neurology and Canada Research Chair in Neuroethics, University of British Columbia Illes, Professor of Neurology and Canada Research Chair in Neuroethics, University of British Columbia
- Sara Joaquim
- Thomas R Kerkhoff, PhD, ABPP/RP Clinical Professor, University of Florida, Department of Clinical and Health Psychology
- Patricia Limousin
- Alma Linkeviciute
- Professor Dr Fernando Lolas, Interdisciplinary Center for Studies on Bioethics, University of Chile
- Robin Lovell-Badge
- Michael Madary
- Dr Andrea L Malizia, Psychiatrist and Clinical Psychopharmacologist
- Dr Paul McCullagh
- Femke Nijboer
- Chijioke G Ogbuka, Albert Gnaegi Center for Health Care Ethics Organisations
- Dr Martyn Pickersgill, University of Edinburgh
- Vincenzo Romei
- Jane Rowlands
- Gerwin Schalk
- Mim Schwartz
- Jackie Leach Scully, Janice McLaughlin, Simon Woods and Michael Barr at Policy, Ethics and Life Sciences Research Centre, Newcastle University
- Annette Smith
- Professor David Stanley, School of Health, Community and Education Studies, Northumberland University
- Gilbert Tan, Gilbert Tan TS AKA Oogle
- Gregor Thut
- Dr J H Waters
- Bob Whitcombe
- Professor Lewis Wolpert
- Deng Zhuo

Organisations

- Academy of Medical Sciences
- Addiction Neuroethics, UQCCR, The University of Queensland

- Animal Procedures Committee
- Association of British Neurologists
- British Medical Association
- British Neuroscience Association
- CARE (Christian Action Research and Education)
- CESAGEN – the ESRC Centre for Economic and Social Aspects of Genomics
- Christians Against Mental Slavery
- Christian Medical Fellowship
- Dementia Services Development Centre, University of Stirling
- European Brain Council
- European Medicines Agency (EMA)
- Foresight, Government Office of Science
- Mission and Public Affairs Council, Church of England
- National Bioethics Committee of Jamaica
- Royal College of General Practitioners
- Royal Society for the Prevention of Cruelty to Animals
- The Royal College of Physicians
- The Wellcome Trust

Appendix 3: The Working Party

Professor Thomas Baldwin (Chair)

Tom Baldwin is Professor of Philosophy at University of York. He works across a broad range of issues in contemporary philosophy, including bioethics, and is currently editor of the philosophy journal *Mind*. He has been a member of the Human Genetics Commission (HGC), the Human Fertilisation and Embryology Authority (HFEA), and the Department of Health's expert advisory committee on obesity. He is a co-opted member of the Nuffield Council on Bioethics for the duration of the Working Party on novel neurotechnologies, and has previously contributed to the Council's reports on stem cells, patenting DNA, genetics and behaviour and public health.

Professor Jonathan Cole

Jonathan Cole Consultant in Clinical Neurophysiology at Poole Hospital; Honorary Senior Lecturer in Clinical Neurosciences, University of Southampton; and Professor at the Centre for Postgraduate Medical Research and Education and at the School of Design, Engineering and Computing, University of Bournemouth. His academic research has focused on the effects of sensory deafferentation and motor control. He leads a group at the University of Bournemouth investigating the use of virtual reality therapeutically in neurological impairment, and is part of the Economic and Social Research Council (ESRC) network on brain-computer interfaces (BCIs).

Professor Maria Fitzgerald

Maria Fitzgerald is Professor of Developmental Neurobiology at University College London. She is also a Fellow of the Academy of Medical Sciences, a current member of the Council of the British Pain Society and the Biological Sciences panel of the UK Research Assessment Exercise (REF), and a past member of the MRC Neuroscience and Mental Health Board and of French and Norwegian national research agencies. Her research focuses on neural mechanisms of pain in infants and children.

Professor Jenny Kitzinger

Jenny Kitzinger is Professor of Communications Research at Cardiff School of Journalism, Media and Cultural Studies, Cardiff University. She comes from a background in social and political sciences, anthropology and communications studies. Her work focuses on examining social and ethical debates around science and medicine. Her previous research has examined issues such as human genetics, stem cell research, and serious brain injury. Recent appointments include serving on the Royal College of Physicians Working Party on the management of disorders of consciousness. She is a Member of Cesagen (The ESRC Centre for Economic and Social Aspects of Genomics).

Professor Graeme Laurie

Graeme Laurie is Professor of Medical Jurisprudence and Director of Research at School of Law, University of Edinburgh and Founding Director of the JK Mason Institute for Law, Medicine and Life Sciences at the University of Edinburgh. His research interests are in medical law and intellectual property law. He has previously served as Chair of the UK Biobank Ethics and Governance Council and is current Chair of the Privacy Advisory Committee in Scotland. He is member of the BMA Medical Ethics Committee and sits on a Working Party of the Royal Society examining Science as an Open Enterprise. He is a member of the Nuffield Council on Bioethics, and has previously contributed to the Council's report on the forensic use of bioinformation.

Professor Jack Price

Jack Price is Professor of Developmental Neurobiology and Director at the Centre for the Cellular Basis of Behaviour, King's College London. He is a neuroscientist with a specific interest in stem cells. His research is pursuing stem cells both as therapeutics for neurodegenerative diseases, and as cellular models of neurodevelopmental disorders. He also acts as consultant to ReNeuron Ltd, a UK Biotech company developing stem cells for therapeutic and drug discovery applications.

Professor Nikolas Rose

Nikolas Rose is Professor of Sociology and Head of Department of Social Science, Health and Medicine at King's College London. He initially trained as a biologist and psychologist. His current research is on the social and political implications of the new sciences of the brain. He was a member of the Nuffield Council on Bioethics until 2013, and has previously contributed to the Council's reports on personalised healthcare and pharmacogenetics.

Professor Steven Rose

Steven Rose is Emeritus Professor of Neurobiology, Department of Life, Health and Chemical Sciences at Open University and Emeritus Professor, Genetics and Society, Gresham College, London. He is a neuroscientist whose research has focussed on the molecular and cellular mechanisms of learning and memory. His books include *The 21st Century Brain*, *Lifelines and The Making of Memory*, and, with Hilary Rose, *Genes, Cells and Brains: the promethean promises of the biosciences*. He has received several awards, including the Edinburgh Medal and the silver medal of the Scottish Royal Society of Arts. He has had a long term engagement with the ethical, legal and social aspects of the neurosciences, and was for several years a regular panellist on the BBC's Moral Maze.

Professor Iliana Singh

Iliana Singh is Professor of Science, Ethics and Society, Department of Social Science, Health and Medicine at King's College London. Iliana has a doctorate in Human Development and Psychology from Harvard University, and spent four years as an affiliated lecturer in Social and Political Sciences at the University of Cambridge before moving to the LSE in 2004 and Kings College London in 2012. Her work explores the psycho-social and ethical implications of advances in bioscience and biomedicine for young people and families. Her current projects focus on psychotropic drugs, neuroimaging, cognitive and other forms of enhancement, and biomarkers associated with the development of criminality, psychopathy and psychiatric disorder.

Professor Vincent Walsh

Vincent Walsh is Professor of Human Brain Research, Institute of Cognitive Neuroscience at University College London. He is interested in all aspects of visual cognition including: visual search; awareness; motion and colour perception; eye movements; and visual memory. He also studies the perception of time; numerical representation; synaesthesia; plasticity in visual and motor systems; and all aspects of human brain stimulation, including DBS and TMS. He is on the Editorial Board for the journal *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*.

Professor Kevin Warwick

Kevin Warwick is Professor of Cybernetics at University of Reading. His studies have focused on direct interfaces between computer systems and the human nervous system, as well as artificial intelligence, control systems and robotics. He presently heads a research project supported by the Engineering and Physical Sciences Research Council which investigates the use of machine learning and artificial intelligence techniques in order to suitably stimulate and translate patterns of electrical

activity from living cultured neural networks in order to utilise the networks for the control of mobile robots. He heads the University of Reading team in a number of European Community projects such as FIDIS looking at issues concerned with the future of identity and ETHICBOTS which is considering the ethical aspects of robots and cyborgs.

Glossary

Ablative brain surgery/brain lesioning: The surgical removal of sections of brain tissue by various surgical methods to treat neurological or psychological disorders.

Astrocytes: A star-shaped form of glial cell.

Autonomic nervous system: The part of the peripheral nervous system that controls bodily functions, such as digestion and heart rate, that operates chiefly below the level of consciousness.

Axon: Also known as a nerve fibre, it is the long projection of a nerve cell that typically conducts electrical impulses away from the neuron's cell body, transmitting a neural signal.

Batten disease: Also known as Spielmeyer-Vogt-Sjögren-Batten disease, it is a rare and fatal neurodegenerative disorder that begins in childhood.

Biofeedback: Refers to the use of devices to gain information about the functioning of physiological systems so that intentional efforts can be made to change or improve the way in which these systems function (see also neurofeedback).

Brain-computer interfaces (BCIs): These technologies use electrodes (either implanted in the brain, or resting on the scalp) to record users brain signals that are then translated into commands to operate computer-controlled devices. By actively producing the required type of brain signal users can control these devices.

Basal ganglia: A group of nuclei of varied origin in brain. They are situated at the base of the forebrain and strongly connected with the cerebral cortex, thalamus and other brain areas. They are associated with a variety of functions, including voluntary motor control, procedural learning relating to routine behaviours, eye movements, cognitive and emotional functions.

CE mark: A mandatory conformity marking for products sold in the European Economic Area. It acts as the manufacturer's declaration that the product meets the requirements of the relevant EC directives.

Cluster headache: Is the term used to describe a condition that involves an immense degree of pain that is almost always on only one side of the head. The cause is unknown.

Clinical trial: a way of testing the efficacy of a treatment or a hypothesis related to the cause of a disease. 'Phase I' trials evaluate safety and dose of a prospective treatment in human participants. 'Phase II' trials evaluate effectiveness. 'Phase III' trials confirm effectiveness and safety in preparation for wide-scale use.

Common law: Law developed by judges through court decisions, as contrasted with Civil Law which is adopted through legislative processes or regulations.

Cerebrum: The cerebrum is the largest and most developed part of the brain. It accounts for about two-thirds of the brain mass and lies over and around most of the structures of the brain.

Cerebral cortex: The surface layer of gray matter of the brain.

Deep brain stimulation: A neurosurgical treatment that involves implanting electrodes in the brain through small holes in the skull. A power source, usually also implanted in the body, supplies repeated pulses of current to stimulate the brain via the electrodes.

Dendrite: The branched projections of a neuron that act to conduct the signal received from other neural cells to the cell body.

Disorders of consciousness: See 'persistent / permanent vegetative state' and 'minimally conscious state'.

Dopaminergic neurons: Neurons whose primary transmitter is dopamine.

Dual use: The tangible and intangible features of a technology that enable it to be applied to both hostile and peaceful ends with no, or only minor, modifications.

Dystonia: Is a neurological movement disorder which causes uncontrollable and sometimes painful muscle spasms.

Electroencephalography (EEG): The non-invasive recording of brain activity via electrodes on the scalp.

Event-related potential (ERP): The brain signal produced in response to a stimulus, that may be recorded using EEG.

Glial cell / glia: Brain cells that are distinct from neurons, that maintain homeostasis, form myelin, and provide support and protection for neurons.

Hippocampus: Is a major component of the human brain. Humans and other mammals have two hippocampi, one in each side of the brain. It is thought to be the centre of emotion, memory, and the autonomic nervous system.

Homeostasis: The tendency of an organism or a cell to regulate its internal conditions, usually by a system of feedback controls, so as to stabilise health and functioning, regardless of the outside changing conditions.

Intracortical: Something situated or occurring within the cerebral cortex.

Locked-in syndrome: a disorder in which damage to the brain leads to individuals being awake and aware, but unable to move or communicate due to total or almost-total paralysis.

Mesenchymal (stem cells): Multipotent stromal cells that can differentiate into other cell types.

Motor cortex: The region of the cerebral cortex involved in planning, control, and execution of voluntary movements.

Minimally conscious state: A disorder of consciousness in which individuals experience partial or intermittent conscious awareness.

Movement disorders: These include a range of disorders that give rise to involuntary bodily movements, including but not limited to, tremor (such as that associated with Parkinson's disease), ticks, slow movement (bradykinesia), or sustained contortion or twisting of the body (for example, see 'Dystonia')

Neural stem cells: Stem cells found in the nervous system that can self-renew and are 'multipotent', that is they can differentiate to form different kinds of nerve and brain cells.

Neural stem cell therapy: This involves the injection of stem cells into the brain in order to repair damage caused by acute events such as stroke or neurodegenerative conditions.

Neurofeedback: A type of biofeedback that provides sensory information (for example visual displays) about brain activity, often recorded using electroencephalography, to the user to enable them to self-regulate this activity.

Neuron: Nerve cells, including brain cells, which transmit information using electrical and chemical signals.

Neuroprotection: Treatment options which aim to prevent or slow disease progression and secondary injuries by halting or slowing the loss of neurons.

Neurogenesis: The development of new nervous tissue.

Neuromodulator: A substance that alters nerve impulse transmission.

Neuroprosthetics: A discipline concerned with developing devices that can substitute motor, sensory or cognitive functions that may have been damaged due to illness or injury.

Notified Body: An organisation in the European Union that has been accredited by a Member State to assess whether a product, for example a medical device, meets regulatory standards.

Off-label: The expression 'off-label' is most commonly used in relation to prescription drugs where it refers to the practice of clinicians prescribing drugs for conditions, in categories of patients, or at doses other than those for which it has been licensed. It is used in this report to refer to the analogous practices in respect of CE-marked medical devices.

Oligodendrocytes: A type of brain cell whose main functions is to provide support and to insulate the axons.

Orphan drug: a pharmaceutical developed and produced for a patient population that too small to be considered economically feasible to provide for under standard pharmaceutical industry business models.

Orthosis: Orthopedic appliance or apparatus used to support, align, prevent, or correct deformities or to improve function of movable parts of the body.

Persistent / permanent vegetative state: Refers to disorders of consciousness, caused by severe brain damage, in which individuals are wakeful but unconscious.

Phase I clinical trials: (see 'clinical trial').

Randomised control trial (RCT): A type of scientific experiment in which research participants are randomly assigned to either the group receiving the active treatment under research, or to the 'control' group. It is a method used to reduce opportunity for allocation bias and to help determine factors such as placebo effect. Blinded or double-blinded RCTs involve the patient or the patient and research clinicians not knowing which participants have been assigned to each group.

Regenerative medicine: interventions (often involving the use of stem cells) that aim to repair or replace organs, tissues or cells damaged by disease or injury.

Stereotactic surgery: A technique used to locate precise targets for surgery using a coordinate system.

Tetraplegia and Quadraplegia: Paralysis caused by illness or injury which results in partial or total loss of use of limbs and torso.

Transcranial alternating current stimulation: A form of transcranial brain stimulation that delivers small alternating electrical currents to the head via electrodes attached to the scalp.

Transcranial brain stimulation (TBS): A group of non-invasive neurotechnologies, which stimulate the brain either by inducing an electrical field using a magnetic coil placed adjacent to the head, or by applying weak electrical currents via electrodes on the scalp.

Transcranial magnetic stimulation: A form of transcranial brain stimulation that involves a current being passed through a coil placed adjacent to the head to produce an electromagnetic field, which induced an electrical field in the brain.

Transcranial direct current stimulation: A form of transcranial brain stimulation (TBS) that delivers small electrical currents to the head via electrodes attached to the scalp to either increase or decrease neuronal excitability in the area of the brain thus stimulated.

Trepanning: The removal of parts of the skull to expose the brain, for example to relieve pressure. There is archaeological evidence of its prehistoric use.

Thalamus: Situated between the cerebral cortex and midbrain, its function includes relaying sensory and motor signals to the cerebral cortex, regulation of consciousness, sleep, and alertness.

Venture capital: A kind of private equity that involves the investment of financial capital in start-up companies, conferring ownership of equity and control over company decisions to the investors. Venture capital investments are associated with new technology sectors and are typically characterised as being high risk, in expectation of relatively short-term and potentially high returns.

List of abbreviations

AIMD	Active implantable medical device
AIMDD	Active Implantable Medical Device Directive
ATMP	Advanced therapeutic medicinal product
ADR	Adverse drug reaction
AMRC	Association of Medical Research Charities
ADHD	Attention deficit/hyperactivity disorder
BCI	Brain-computer interface
ABC	Definition
CQC	Care Quality Commission
CNS	Central nervous system
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products in Human Use
DPA	Data Protection Act
DBS	Deep brain stimulation
DSTL	Defence Science & Technology Laboratory
DARPA	Defense Advanced Research Projects Agency
DTC	Direct to consumer
ECT	Electroconvulsive therapy
EEG	Electroencephalography
EBC	European Brain Council
EUDAMED	European Databank on Medical Devices
EEA	European Economic Area
EMA	European Medicines Agency
EAG	Expert Advisory Group
fMRI	Functional magnetic resonance imaging
FDA	US Food and Drug Administration

GTAC	Gene Therapy Advisory Committee
GMC	General Medical Council
GHIF	Global Harmonization Task Force on Medical Devices
GMP	Good manufacturing practice
HSE	Health and Safety Executive
HRA	Health Research Authority
HTA	Health Technology Assessment
HTC	Health Technology Co-operatives
hESC	Human embryonic stem cell
HFEA	Human Fertilisation and Embryology Authority
HTA	Human Tissue Authority
HDE	Humanitarian Device Exemption
IOM	US Institute of Medicine
IPG	Implantable pulse generator
IPG	Interventional procedures guidance
IPP	Interventional procedures programme
LRP	Lateralised readiness potential
LTD	Long term depression
LSD	Lysergic acid diethylamide
MEPS	Medical Expenditure Panel Survey
MDD	Medical Devices Directive
MRC	Medical Research Council
MTEP	Medical Technologies Evaluation Programme
MHRA	Medicines and Healthcare products Regulatory Agency
MCAo	Middle cerebral artery occlusion
MS	Multiple sclerosis
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIH	National Institutes of Health

NRES	National Research Ethics Service
OCD	Obsessive-compulsive disorder
NRT	Neuron replacement therapy
PD	Parkinson's disease
PNS	Peripheral nervous system
PTSD	Post traumatic stress disorder
PMA	Premarket approval
PR	Public relations
RCT	Randomised controlled trial(s)
rTMS	Repetitive transcranial magnetic stimulation
REC	Research ethics committee
REF	Research Excellence Framework
RRI	Responsible research and innovation
SMC	Science Media Centre
SCG	Specialised Commissioning Group
SCS	Spinal cord stimulation
STEMPRA	UK Science, Technology, Engineering and Medicine (or Maths) Public Relations Association
TBI	Traumatic brain injury
TSB	Technology Strategy Board
TBS	Transcranial brain stimulation
TDCS	Transcranial direct current stimulation
TMS	Transcranial Magnetic Stimulation
VBP	Value-based pricing
VC	Venture capital
VNS	Vagal nerve stimulation
WHO	World Health Organization

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