Response to Nuffield Council on Bioethics Consultation Paper
Novel neurotechnologies: intervening in the brain

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Preamble

The Addiction Neuroethics Unit is funded by a National Health and Medical Research Council (NHMRC) Australia Fellowship awarded to Professor Wayne Hall (2009-2013). The strategic focus of the unit is the analysis of public policy and ethical issues raised by genetic and neuroscience research on addiction, potential applications of this research to treat and prevent addiction, and its impact on public policies towards drug use and addiction.

The goals of the Addiction Neuroethics Unit are:

- To collaborate with neurobiologists, clinicians and public health professionals to explain cutting edge research on addiction to policy makers and the community.
- To identify new treatments that may arise from discoveries in genetics and neuroscience of addiction and assess their public health and ethical implications.
- To explore the views of addiction treatment practitioners, policy makers, drug users, people with addictions, family members, and those who care for addicted persons about neurobiological research on addiction and new treatments.
- To use epidemiological and economic modeling to assess the likely effectiveness and cost-effectiveness of potential applications of addiction neurobiology (such as pharmacogenetics and preventative vaccination).
- To give comprehensive and accessible briefings to policy makers and politicians on analyses of the public policy and ethical issues of genetic and neurobiological research on addiction.
- To identify the most promising translational opportunities for neurobiological research on addiction.

The Addiction Neuroethics Unit welcomes the opportunity to respond to the Nuffield Council on Bioethics consultation paper on novel neurotechnologies. This submission is based on work conducted by researchers working within the unit over the last five years or so. We do not attempt to address all novel neurotechnologies listed in the current consultation document. Instead we focus on three topics, deep brain stimulation and transcranial magnetic stimulation to treat addictive and other mental disorders, non-medical or enhancement uses of DBS and

TMS, and experimental trials of neural stem cell therapy because these have been topics of research and peer-reviewed publications by members of the Addiction Neuroethics Unit.

Executive Summary

Novel technologies such as deep brain stimulation and neural stem cell therapies offer the potential to treat intractable forms of common psychiatric disorders, such as addiction, depression, and obsessive compulsive disorders as well as neurological conditions. More speculatively, these technologies may also be used to extend or enhance human capacities. These technologies also present a range of complex social and clinical challenges, in addition to the scientific imperative to demonstrate their safety and efficacy, when used to treat persons with disorders. A summary of the key ethical considerations from this submission is presented below.

1. An important ethical challenge raised by novel neurotechologies is the potential for unsupported assertions to be made about the benefits of putative neurotechnologies in the academic literature and popular media. We have documented the occurred of such claims in the case of cognitive enhancing pharmaceuticals [1, 2] and DBS [3]. Scientists, ethicists and health care professionals must be careful not to unwittingly perpetuate such exaggeration and should anticipate likely misunderstandings by the public and the popular media and proactively attempt to minimise them.

2. Each technology should be assessed on its merits and regulated according to the risks that it poses and the feasibility of regulating or restricting its use [1]. Furthermore, the role of the medical device industry in promoting neurotechnology products should be carefully examined. Assessments of safety and efficacy should be rigorous for putative neuroenhancers, as we have recommended in the case of purportedly cognitive enhancing pharmaceuticals [1].

3. Emerging neurotechnologies are often expensive to research and develop. Ideally costs should not prevent the development of promising technologies, especially as costs may quickly come down with further research. A full consideration of the future utility of a novel technology should also consider the opportunity costs of first developing and then using the technology for its intended purposes. For example, DBS has been suggested as a future treatment of addiction when many addicted persons lack access to much less costly current treatments. The use of DBS in this area could worsen this situation and would put strain on the limited resources used to treat degenerative motor disorders in which there are no alternative treatments and in which DBS has been shown to be extremely effective [4].

4. It is important to attempt to proactively consider the ethical impacts of novel technologies before they are widely used. In doing so bioethicists must be mindful of the impact that speculative concerns about possible misuses of a technology may have on public and patient views of the technologies. Such speculation may unwittingly raise

expectations about the effectiveness of experimental technologies, in ways that impair patients' ability to fully consider the risks of participating in trials of these technologies, such as neural stem cell therapies, especially when the trials are unlikely to provide a direct benefit to such patients [5].

5. It may be challenging to obtain informed consent from patients to participate in trials of novel neurotechnologies. Patients with serious illnesses are often desperate, may have unrealistic expectations of likely effectiveness, and discount risks, particularly if the putative benefits of the technology have been hyped in media reports (sometimes by enthusiastic researchers and clinicians). Empirical research has highlighted this as a major challenge in studying DBS [4, 6]. Scientists and clinicians must be mindful of and work to minimise the risks of their research contributing to media hype that may adversely affect vulnerable patient populations. Patients participating in trials should be given a clear understanding of the likely effectiveness of the technology, the purpose of the research (to avoid a therapeutic misconception), and be made aware of and assisted to access conventional treatments for their condition. Patients, such as addicted individuals, are often in psychosocial situations that make access to health care difficult. Research participation should not become a de facto way to gain access to what should be standard care [4].

6. We also need to consider potential adverse side effects of research on novel neurotechnologies. One such effect is overemphasis upon the neurobiological causes of a disease and too narrow a focus on high-risk neurobiological solutions at the cost of providing good psychosocial care and support. Neuroessentialism can lead to a focus on the severe forms of illnesses at the expense of ignoring the needs of the majority of individuals with less severe forms of these disorders. This is a particular concern in the case of drug misuse and addictive disorders where much of the harm occurs in people with less severe disorders who can be helped by simpler approaches provided in primary care or over the web via self-help programs. It is also important to realise that research on novel neurotechnologies may obscure the social causes of mental illness and drug use and the beneficial impact of population level measures to reduce the harm caused by these disorders.

7. The way in which health care is provided and the effectiveness with which it is delivered can be adversely affected by common moral attitudes towards the condition being treated. Moral attitudes can restrict access to certain types of treatment (e.g. methadone maintenance treatment (MMT) for heroin dependence) or adversely affect the way in which it is provided (e.g. by imposing arbitrary time limits on treatment duration). Novel treatments (e.g. heroin prescription, implantable naltrexone, DBS) may be justified by the failure of existing treatments (e.g. MMT) when such treatments are either banned (e.g. as is the case in Russia) or are provided under such restrictive or punitive conditions that they are unlikely to work (e.g. methadone programs in some US states). Risky or invasive neurotechnologies should not be used to compensate for a failure to provide good access to current treatments optimally provided.

DBS and TMS to Treat Addictive and Other Mental Disorders

Deep Brain Stimulation (DBS) as a Treatment for Addiction

DBS is often described as a reversible alternative to neurosurgery, but is nonetheless an invasive intervention that carries significant risks [7]. Estimates of surgical complications vary markedly because of differences in the competence of the teams and hospitals performing the operation, and variations in the procedure but a recent meta-analysis estimated that approximately 11% of patients undergoing DBS experience adverse events [8]. Estimates of major adverse surgical outcomes, such as intra-cerebral haemorrhages and death range from 0 to 10% [7] with a consensus estimate of probably less than 2% in most centres [7]. The successful insertion of stimulating electrodes can also cause serious infections and produce cognitive, behavioural, emotional disturbances and irreversible psychosocial harm [8].

DBS is increasingly advocated for trial in the treatment of a range of intractable psychiatric disorders, including addiction. Given the risks associated with neurosurgery, there needs to be a careful assessment of the risks and benefits of the procedure before DBS use is trialled in these disorders. In the case of addiction, the case for trialling DBS is based on animal models, suggestive case study evidence and poorly controlled studies of stereotactic neurosurgery for opioid addiction. These proposals raise important ethical issues. We believe that there is insufficient evidence to warrant clinical studies of DBS in addiction at this stage. More basic preclinical work is needed to identify the optimal targets in the brain for treating addiction with DBS. We think that researchers should await the results of current trials of DBS in intractable depression and OCD.

The use of DBS in debilitating conditions such as Parkinson's disease is justified by the severity of the condition and its inexorably deteriorating course. Patients with Parkinson's disease who no longer respond to pharmacological treatment face a course of irreversible deterioration in motor function and increasing disability. In contrast, psychiatric conditions, like addiction, do not usually follow such an inexorable path to severe disability and death; addiction is generally more amenable to pharmacological and psychotherapeutic treatment, making drastic remedies less justifiable. Moreover, in the case of addiction, many treatment failures are due to inadequate access to well run and optimally provided forms of existing treatments [9]; a situation that could be exacerbated by an increased use of DBS to treat drug addiction. We think that the uncertain benefits of DBS in alleviating the symptoms of addiction in a minority of patients do not outweigh the risk of harms arising from the procedure, or the benefits or providing currently available addiction treatments to the highest standard [10].

There are other ethical and social issues that would need to be considered in evaluating the use of DBS for addiction. DBS is an extremely expensive procedure, costing about US$50,000 for the operation and US$10,000 for ongoing monitoring and maintenance over subsequent years. DBS would utilise scarce health resources to treat a very small number of addicted patients with the income to pay for it, while leaving untreated the majority. It may also reduce the provision of

DBS for Parkinson's disease, dyskinesia and essential tremor, given the scarcity of expert neurosurgeons. We have argued that the opportunity costs of trialling DBS for addiction, and the small number of patients who would benefit if it proved to be safe and effective, make such trials a low priority for public funding [4, 10].

Transcranial Magnetic Stimulation (TMS)

Other forms of electromagnetic stimulation, such as transcranial magnetic stimulation (TMS), may provide a non-invasive method alternative to neurosurgical addiction treatment [11]. By manipulating cortical activity, the hope is that TMS might prove to be a useful treatment for a range of psychiatric disorders, including addiction [12].

TMS raises fewer health and safety concerns than neurosurgery or DBS because it does not involve physical penetration of neural tissue [13]. However, it has been reported to cause psychotic and epileptic symptoms in a minority of patients [14, 15].

TMS is capable of producing significant behavioural changes. Studies have shown that a session of TMS can have a significant impact on the decisions individuals make [16]. A recent pilot study has shown that a session of high frequency repetitive stimulation of the right prefrontal cortex can reduce craving in cocaine addicted subjects [17].

There are, however, serious doubts about the clinical utility of these technologies [18, 19]. Firstly, double-blind studies using TMS are inherently difficult to conduct because TMS produces a contraction in the muscles of the scalp directly beneath the area of application. Current studies do not attempt to address this issue, and are in our view inadequate. Secondly, the effects in these experiments are very small, raising questions about their clinical usefulness. This technique requires more rigorous research to evaluate its clinical utility.

Given the very uncertain benefits of TMS for serious psychiatric conditions, it is important that TMS is not provided at the expense of proven current treatments (e.g. pharmacological or psychotherapeutic). A TMS device received FDA approval for the treatment of major depression despite significant doubts about its clinical utility [18]. Patients should be made aware of the limits of the technology, as well as the existence of alternative treatments, such as drug substitution treatments (e.g. methadone maintenance) for opioid dependence and electroconvulsive therapy (ECT) for refractory depression.

Non-medical or Enhancement uses of DBS and TMS

Non-medical use of neurostimulation technologies, for example to enhance cognitive performance in persons who were not impaired, would first need to be shown to be safe and effective in clinical trials in healthy individuals.

In the case of DBS, the effectiveness of the technology to ameliorate cognitive symptoms of psychiatric disease is uncertain. Balanced against the significant risks associated with the technology, the use and trialling of DBS for cognitive enhancement is not warranted. Further evidence of the ability of DBS to improve cognition in those trialling the technology for psychiatric conditions is necessary before it should be trialled in healthy individuals. Given the limited effectiveness of the technology in psychiatric conditions, and the serious risks associated with it, we doubt that a cost-benefit analysis would justify its use for enhancement purposes, assuming that there were any individuals interested in this use. We would urge extreme caution in any case.

It is possible to further examine the impact of DBS on cognition without trialling on healthy individuals, such as the neural stimulation of patients undergoing treatment for epilepsy or those trialling the technology for other conditions (e.g. OCD, depression). Both of these scenarios carry limitations in the extrapolation of the results to healthy individuals. However, given the current lack of evidence for benefit, and known risks, we believe that this is an appropriate first step. Should these studies be shown to shift the balance in favour of benefit over risk, this situation should be reassessed. We believe that such an outcome is unlikely.

The risks associated with TMS are far less than those for DBS (i.e. it is non-invasive; almost completely reversible; and very short acting in its effects). Consequently, the ethical arguments against the use of TMS in non-therapeutic situations are not as persuasive. TMS is a useful neuropsychological tool that is often used on healthy individuals, assuming certain protections commonly used in laboratory studies of TMS are in place – e.g. not using TMS in those prone to seizures and imposing limits on the length and strength of TMS stimulation. We therefore believe that trialling TMS for non-therapeutic purposes, especially scientific purposes, would be appropriate. We think that TMS promises to be a useful neuropsychological tool that will greatly assist neuroscientists in identifying the underlying mechanisms of cognition.

Our main concern with non-medical uses of TMS arises from possible exaggeration or misrepresentation of its potential to make lasting and meaningful improvements in cognition or behaviour. These concerns need to be adequately addressed by any medical regulatory bodies that evaluate and regulate the sale and use of medical devices such as those for TMS to the public or in non-medical settings such as the law courts. We discuss these below.

There is a common weakness in many analyses of the ethics of using neurotechnologies to enhance human cognitive performance: the assumption that these technologies have either in fact been shown to enhance human cognitive performance or could be straightforwardly shown to do so. It is relatively straightforward to show that TMS transiently improves memory performance on laboratory tasks in college student volunteers; it will be much more difficult to establish that it can be reliably used in a non-medical context such as enhancing the accuracy of eyewitness memories in criminal cases (e.g. [20]). We have argued that the courts cannot be expected to accept that effects observed in controlled laboratory studies of memories of little personal significance can be applied straightforwardly to the circumstances of criminal case where witnesses' answers may have serious consequences for the liberty or life of an accused person [21].

Regulation on the use and trialling of DBS and TMS

Deep Brain Stimulation

We have set out some minimum standards for the ethical conduct of future trials of DBS in addiction. These include: restricting trials to severely intractable cases of addiction (as documented by a failure to respond to optimally provided treatment); independent oversight of the consent process to ensure that patients have the capacity to provide free and uncoerced consent that is based on a realistic appreciation of the potential benefits and risks of DBS; and rigorous assessments of the effectiveness and safety of this treatment compared to the best available treatment that is currently provided [4].

The use of this technology should be restricted to medical research centres. This is appropriate given the invasive and largely experimental nature of this technology, particularly in the case of psychiatric disorders. There are a number of additional protections that should be employed to maximise the clinical and scientific utility of neurostimulation while minimising adverse consequences for the patient and unnecessary burdens upon limited health care and research resources.

- It is important that this technology be conducted by appropriately trained personnel in well-resourced clinical hospitals. As enthusiasm for experimental technologies such as DBS grows, there is a risk that it will be trialled by clinicians in hospitals without the requisite training and resources. This can lead to poor patient outcomes, undermine the apparent effectiveness of the treatment in leading hospitals, and increase costs as patients who have received inadequate treatment need to have complications of their treatment corrected in major medical centres [22]. Strict protocols for conducting DBS (e.g. target sites, use of technologies to locate electrodes) should be put in place to ensure the highest quality of care.
- There is an urgent need for the registration of all trials of DBS, particularly in psychiatric disorders where the effectiveness of the intervention is uncertain, in a comprehensive

public clinical trials registry, as is required for publication by member journals of the International Committee for Medical Journal Editors for other interventions likely to enter mainstream clinical practice [23]. Small case studies of individual trials can lead to publication bias through selective publication of positive results that may result in overestimation of the safety and efficacy of the technology.

- Informed consent procedures need to be strengthened to ensure that patients are able to fully and freely consent to a trial of the procedure. Typically, patients selected for the procedure have failed at all available treatments, and are therefore likely to be desperate for a solution to their condition. Overoptimistic beliefs may be fuelled by uncritical reporting of the efficacy of DBS and other neurostimulation technologies in the media [3]. Overcoming unrealistically high expectations among potential patients has been identified as one of the major hurdles facing clinicians trialling this technology [6].
- It is important that DBS is not used as a surrogate for the failure to provide currently available treatments to the highest standard or to control deviant or criminal behaviour. Psychiatric disorders for which DBS is currently being trialled, such as addiction, may be associated by some with deviant, criminal or disruptive behaviour. In some jurisdictions, valid treatments, such as methadone maintenance, are banned on moral grounds or are provided under such punitive conditions that they are ineffective. DBS should not be trialled in contexts where there is no access to current treatments provided to the highest standards, as a form of social control or extrajudicial punishment.
- The ability of individuals to consent to trialling DBS for the treatment of a psychiatric condition may also be impaired, either as a result of their condition or their social situation. DBS should not be trialled in patients who lack the capacity to provide free and informed consent either because of their illness or because of external pressure that may indirectly arise as a result of their illness, such as social or legal coercion to be treated for addiction. We believe it would be inappropriate, for example, to trial DBS on an addicted patient who is on parole and whose freedom is contingent on their abstaining from drug use. The threat of imprisonment is likely to impair their ability to consider the risks of trialling the technology.

Transcranial Magnetic Stimulation

The regulatory issues raised in the use of TMS for research purposes are not new, and so are adequately covered by the regulations and protections governing other forms of neuropsychological research (including the issues of subject selection and stimulation parameters mentioned above). Our major concerns with this technology are about its use in: clinical situations where patients are experiencing serious psychiatric disorders that are possibly life-threatening (e.g. patients with refractory depression); and its premature promotion to the public as an effective treatment that is provided at great expense to individuals. These concerns should be addressed by the regulatory bodies that approve the use of clinical technologies and monitor the promotion and sale of products directly to consumers.

Experimental trials of neural stem cell therapy

Bioethicists often see their role as anticipating potential adverse consequences of experimental medical technologies. In striving to anticipate all potentially adverse consequences of emerging technologies, bioethicists run the risk of highlighting implausible and unlikely adverse effects. This may be an understandable response to exaggerated benefits claimed by proponents of emerging technologies, such as neural stem cell therapies (nSCT). There is also a significant public investment in SCTs that advocates claim will provide safe and effective treatments for incurable and debilitating neurological disorders [24].

Participants in clinical trials of nSCTs should be informed of possible unintended consequences of these treatments when consenting to participate in clinical trials of their safety and efficacy. But the focus should be on plausible, potential harms. It has been suggested, for example, that nSCTs may produce undesirable cognitive, mood or behavioural changes by: 1) transferring the cell donor's traits; 2) modulating "a network of cells in a way that results in subtle changes in characteristics that the recipient regards as important to his or her sense of self"; 3) producing a "loss of function" in parts of the brain unrelated to the disorder (e.g. incorrect rewiring of neurons, the extinction of memory, or the loss of other abilities); and 4) modulating neural networks in ways that enhance cognition [25].

All of these putative risks presuppose that the progeny of transplanted stem cells are able to make functional connections with other neural cells or a network of cells in the adult brain in ways that will change brain function. We do not believe that this presumption is supported by evidence from animal studies. Analysis of such speculative risks may distract attention from the more plausible immediate risks of implanting foreign material into the human brain. These include: neurosurgical damage during implantation, immune rejection of the implant, the acquisition of genetic disorders or viral diseases (e.g. HIV), uncontrolled proliferation of the transplanted stem cells (e.g. tumorigenesis), and migration of cells from the site of implantation to produce seizures, neurogenic pain, and dyskinesias.

We believe that human trials of nSCTs are premature because we do not have good preclinical animal studies that establish proof of principle. More extensive pre-clinical research on animal models should be done before we begin to consider the ethical and clinical merits of human trials. There is, for example, very little preclinical, let alone human, research that grafted stem cells form functional neuronal connections that are likely to influence cognition for the better (or worse). Given this, the very speculative risks of cognitive harms identified above are much more remote and hypothetical than the more predictable harms of neurosurgical damage and tumorigenesis [26]. We believe that speculative cognitive risks of nSCT, while theoretically possible, do not give prospective participants a realistic appreciation of the risks of treatment and the low likelihood of benefits.

The current phase one trials of stem cell transplants for the treatment of neurological disorders, such as stroke [24] or spinal cord injury [27], are not expected to therapeutically benefit participants. They are designed primarily to assess safety and provide further scientific knowledge about stem cell technology. The participants in these trials will often have neurological diseases that cause severe pain, incapacity, disability, and premature death. Consequently, many may be desperate for a cure, and also have cognitive deficits that impair their capacity to consent. They are likely to be especially susceptible to the therapeutic misconception: the mistaken belief that their participation in a clinical trial is likely to be of therapeutic benefit to them [28]. Participants in such trials need to appreciate that they are undergoing an experimental procedure that carries significant risks for a very uncertain and improbable benefit.

There is a pressing need for further debate about the ethical and scientific validity of clinical trials in humans. We believe, however, these debates should first focus on whether there is enough pre-clinical evidence to indicate that these invasive treatments will provide any therapeutic benefit to patients. We do not think there is, and hence we have strong doubts about the ethicality of asking individuals with these serious disorders to participate in a risky procedure of doubtful therapeutic utility solely to increase scientific knowledge about the behaviour of transplanted stem cells in human subjects [29]. Ethical debates that focus on highly improbable adverse effects in clinical trials may distract us from asking whether there is sufficient evidence of benefit to justify *any* clinical trials.

Non-medical or enhancement uses of neural stem cell therapy

We believe, along with others [30] that there are no strong in principle objections to the use of neurotechnologies, such as nSCT, for the purposes of enhancement. However, as we noted above, we do not believe that there is significant evidence that SCT is likely to be effective in the treatment of serious neurological disorders. We are think that they are even less likely to have a place in non-therapeutic (i.e. enhancement) uses. The very unlikely prospect of benefit, and the very high risk of severe adverse consequences make the use of nSCT for human enhancement a very implausible proposition.

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