This response was submitted to the consultation held by the Nuffield Council on Bioethics on *Novel neurotechnologies: intervening in the brain* between 1 March 2012 and 23 April 2012. The views expressed are solely those of the respondent(s) and not those of the Council.

The **A P C**
Animal Procedures Committee

Nuffield Council on Bioethics consultation on Novel neurotechnologies: intervening in the brain

Response from the Animal Procedures Committee

1 Introduction

The Animal Procedures Committee (APC) is an independent, non-departmental public body that advises the Secretary of State on matters concerned with the Animals (Scientific Procedures) Act 1986 (ASPA). The ASPA regulates the use of 'protected' animals[1] in experimental or scientific procedures that may have the effect of causing pain, suffering, distress or lasting harm. It requires that the APC has '*regard both to the legitimate requirements of science and industry and to the protection of animals against avoidable suffering and unnecessary use in scientific procedures*'.

The APC has produced this response on the basis that a great deal of animal experimentation has gone into developing neurotechnologies, and their continuing development will inevitably generate further regulated procedures. This includes primate use and invasive neurostudies on a range of species, both of which are major concerns for the public. However, the consultation document makes no mention of the animal use that has been, and will be, integral to the development and application of neurotechnologies. The APC believes that these harms to animals must be considered and given due weighting alongside the potential societal benefits.

The discussion below relates to general questions (4) and (5); i.e.

> 4. What are the most important ethical challenges raised by novel neurotechnologies that intervene in the brain?
>
> 5. In what ways, if at all, should the development and use of these technologies be promoted, restricted and/or regulated? Please explain your reasons.

2 Animal experimentation in the development of novel neurotechnologies

All of the neurotechnologies mentioned in the consultation document have relied heavily upon the results of animal studies – in fact, it is probably true to say that none could have been developed without animal use. There are many publications describing invasive animal experiments conducted for the purpose of developing neurotechnologies such as brain

[1] Currently vertebrates and *Octopus vulgaris*; from 1 January 2013 a revised ASPA will be implemented which will regulate the use of vertebrates and all cephalopods (octopuses, cuttlefish and squid).

computer interfaces (BCI), transcranial magnetic stimulation (TMS), deep brain stimulation (DBS) and neural stem cell therapy [e.g.2,3] and we will not review the literature here.

In our view the report arising from this consultation should recognise that, in order to progress some of these technologies for the purposes outlined in the consultation document, there will inevitably be some assessment and development in animal models, for either scientific or regulatory reasons. It should also acknowledge the inherent ethical dilemma associated with creating and using these animal models, as is recognised within the ASPA, and emphasise that the harms to animals should be fully recognised and considered against the societal benefits of neurotechnologies.

There is already an ethical framework this within the licensing process for animal procedures under the current ASPA, which requires that for each proposed project the likely adverse effects on animals shall be 'weighed' against the benefits likely to accrue as a result. The recently revised European Directive 2010/63/EU, which will be implemented in the UK from 1 January 2013, also requires that the purposes of a proposed project should justify the use of animals, and that the project authorisation process includes '*a harm-benefit analysis of the project, to assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals or the environment*'. The interpretation of what may constitute an acceptable 'benefit' is discussed further below.

We also note that the application of some of these technologies has the potential to replace some animal experiments with studies on human subjects, provided that these could be safely and ethically conducted. For example, TMS on humans can be used to replace some studies that would previously have been conducted by creating brain lesions in non-human primates. However, this will likely be vastly exceeded by the animal use that will be created by the desire to develop and implement neurotechnologies, so it is absolutely essential that the potential benefits of neurotechnologies are realistically predicted and critically scrutinised – otherwise animals could suffer needlessly and their lives could be wasted.

3 Benefits of novel neurotechnologies

From the APC's perspective, there are three issues that are relevant to the potential benefits of neurotechnologies; (i) whether they should be applied to humans at all, (ii) the level of animal suffering that may be necessary to deliver these benefits, and (iii) whether each technology is likely to deliver what has been predicted of it.

3.1 Whether and how neurotechnologies should be applied

Whether each particular technology should be applied to humans at all, and if so to whom and under what circumstances, is the main topic under consideration in the consultation. This would clearly have to be considered on a case by case basis, and this decision-making process falls outside the remit of the APC as an advisory body on animal research and testing.

[2] Nuyujukian et al. (2011) Monkey models for brain-machine interfaces: the need for maintaining diversity. *Conf Proc IEEE Eng Med Biol Sci* 2011: 1301-5

[3] Tan SKh et al. (2010) Experimental deep brain stimulation in animal models. *Neurosurgery* 67: 1073-9

Nevertheless, we understand that it can be argued that there is a moral difference between applying neurotechnologies for therapeutic purposes (e.g. enabling people with 'locked in syndrome' to communicate and do some things for themselves) and for the purposes of enhancing normal human function. The majority personal view among APC members is that it is unacceptable to cause animal suffering in the development of neurotechnologies that will be used to improve gaming, or to enhance abilities in humans who do not have any disability or impairment[4]. However, there could be justification for animal studies with the purpose of developing neurotechnologies for applied medical purposes, although this of course has to be balanced against the possible risks to the patients. In these cases, the question of 'should it be done' (there seems no doubt that it can be done and therefore it will, somewhere[5]) is encompassed in the principle of 'do no harm' which should be applied in the clinical application of these technologies.

Where progress in neurotechnologies is dependent upon animal use, the public's view on whether the end result is acceptable should be factored into the harm-benefit assessment. For example, if the consultation finds that the public consensus is that it is wrong to use neurotechnology to enhance normal human function, then by definition there would be no demand for, or benefit from, an animal experiment that aims to further progress towards this, and it should not be licensed.

3.2 Levels of animal suffering

The present consultation will no doubt find that respondents consider it to be appropriate in principle to apply particular neurotechnologies to humans. It may also be the case that, in order to develop those technologies to the point where they could be routinely used in humans, animal procedures would be necessary that would cause unacceptable levels of suffering. This could be either because the predicted level of suffering would not justify the projected benefits of the study, or because the absolute level of pain or distress would be above that defined to be permissible in law (see box).

> Under the current ASPA, the Secretary of State will not license any procedure likely to cause severe pain or distress that cannot be alleviated. A similar limit is set within Directive 2010/63/EU, in which Member States are required to ensure that procedures are not performed if they involve severe pain, suffering or distress that is likely to be long-lasting and cannot be ameliorated, although there is an option to apply for permission to the European Commission in exceptional circumstances.

This consideration is especially relevant in relation to highly invasive procedures that involve interfering with the function of the brain, and to the use of non-human primates in the development of neurotechnologies. Primate use is of considerable concern to the public for a number of reasons, in particular the potential for suffering due to the complex behavioural and social requirements and cognitive capacities of these animals – hence the recent review of research using non-human primates by Bateson et al., which recommended *inter alia* that

[4] There have been analogous debates about the ethics of pharmaceutical cognitive enhancement and its acceptability for people without any cognitive dysfunction, in which some people feel very strongly against cognitive enhancement for those who are ostensibly healthy and not suffering from any neurodegenerative diseases, while others do not feel that this is an ethical problem at all.

[5] Arguments are sometimes made against increasing the regulation of controversial activities in the UK, on the grounds that it is better to conduct the work in the UK than overseas. However, this is not a valid argument if the work is deemed to be unethical. The ethical issues need to be addressed before the question of 'keeping up in the race' is even considered.

projects involving primates should only be funded where there is a '*very high likelihood of producing scientific, social or medical benefit*'[6].

Also in response to concerns about primate suffering in specific research areas, the APC and Home Office Animals (Scientific Procedures) Inspectorate are currently jointly conducting a review of the assessment of cumulative severity in non-human primates used in neuroscience research. The objective is to facilitate the assessment of the impact of multiple procedures administered over a period of time, so as to estimate the cumulative severity experienced by the animals in such procedures. The report of the project should be completed by the end of 2012.

The APC believes that it is vitally important that the public understands how requirements for developments in neurotechnologies can directly create demands for invasive animal use, including primate studies. If these studies would cause levels of suffering that cannot justify the outcome, the animal use should not be licensed and the neurotechnology should not be developed until it is possible to avoid, replace or refine the animal procedures involved.

NB the APC currently advises the Secretary of State on project applications that raise novel or contentious issues, or give rise to serious societal concerns, and projects that could cause severe suffering, with the purpose of developing neurotechnologies, would presumably come into those categories. It is not yet known whether the forthcoming National Committee for the Protection of Animals used for Scientific Purposes (NCPASP) under the new ASPA will also advise on novel/contentious projects, but the APC has recommended to the Home Office Animals in Science Regulation Unit that it should.

3.3 Whether promises can be fulfilled

The introduction to the consultation document rightly highlights how great hopes of medical and societal breakthroughs in brain science have led over the course of time both to serious disappointment and, through the pathologisation of socially unacceptable behaviour, to some grotesque and damaging interventions. There is no reason to suppose *a priori* that revived hopes in neuroscience today should be excluded from this problematic history.

Where there is a threat lurking in the background concerning a pathologisation of socially 'abnormal' subjects we must be very cautious. However, there are also difficulties involved in cases where the promise of neurotechnologies seems more clearly benign. Such is the case with certain hopes concerning the use of Brain Computer Interfaces (BCIs) in Medicine.

In this case, as the report suggests, the appeal of new neurotechnologies is understandably high. 'Potential benefits of BCIs could be very substantial in some patient groups. Being able to communicate again would be a major breakthrough for locked-in and other severely paralyzed patients'.

Since existing in a locked-in condition is so awful to contemplate it would seem totally heartless to stand in the way of those who are striving to alleviate it. However, there are some concerns about the cogency of the claims that are made by neuroscience in this area, and as the report notes, 'BCIs also carry some significant risks'. For this reason it is necessary to take great care – and avoid some false hopes – when holding out the possibility of 'substantial benefits' in this area. Conclusions drawn about the cognitive powers of people

[6] Bateson P et al. (2011) *Review of Research using Non-human Primates*.

with serious brain and nervous system disorders from empirical data concerning the brain functioning of normal people is far from trouble-free, and may be seriously questionable.[7]

To illustrate this, consider the case of comparing normal subjects with subjects displaying complete bodily unresponsiveness (CBU) of the type that is compatible with (although, of course, on its own no evidence whatsoever for) what is called 'locked-in syndrome'.

It is tempting to think that correlations between behaviour and brain activity in normal subjects may allow us to make inferences by induction to CBU subjects. Consider the exercise of two different kinds of mental powers – e.g. arithmetical calculation and verbal recall. The exercise of these different kinds of powers may be paralleled by differences in neural activity that are both stable within a normal subject and reproducible across normal subjects. Such a correlation permits inductive inferences from the brain activity of a normal subject to which kind of mental power is more likely to be being exercised in this case. The inferences can be tested by asking the subject what they were, in fact, doing.

It is then thought only a short step to suppose that if such brain activity is found in a CBU subject under comparable circumstances, then that subject too may, at least in theory, be engaging in mental activity in more or less the same way as a normal subject.

For example, a correlation might be found in normal subjects between the mental activity "imagining playing tennis" and certain brain activity, and between the mental activity "imagining exploring a house" and certain (different) brain activity. In this way we could predict which mental activity was being performed simply by identifying the cortical activity. The predictions can be tested and the cortical hypotheses revised if necessary. Should the predictions prove successful the hypotheses could then be extended to CBU subjects: if we find a CBU subject's brain is activated in the way a normal subject's brain is when that subject is asked to imagine playing tennis (or exploring her house) we should infer that the CBU subject is likely to have been imagining playing tennis (or exploring her house) in much the same way as the normal subjects were.

The first question is whether, in a normal subject, the characteristic neural activity can occur without the specific mental activity with which it is (demonstrably) correlated. In fact, it is well known that essentially identical patterns of neural signalling may be evoked by mental activities that are disparate. For example, activation of the supplementary motor area is observed not only when a normal subject imagines playing tennis but when she imagines performing any kind of action. If a subject were to respond to the command to imagine playing tennis by imagining playing chess we would certainly not think of him as having obeyed it – but the neural activity we can observe with current technologies would not distinguish between them. On the other hand, with a CBU subject we would never have the assurance that she is obeying (or trying to obey) the command or indeed any command, since the only thing that we can know is going on is certain neural activity – and we already know that this has been decoupled from behaviour.

So induction from the presence of certain brain activity is perhaps not reliable here.

An alternative would be to say that rather than inferring by induction one could reason to the best explanation. Suppose we found the grass outside to be wet and wanted to give a

[7] The central argument of this note is based on 'Covert cognition in the persistent vegetative state', P. Nachev and P.M.S. Hacker, *Progress in Neurobiology*, 91 (2010) 68–76.

causal explanation for this state of affairs. There are endless possibilities: rain, dew, garden sprinklers, emptied paddling pools, and so on. Add, however, that not only is the grass wet but the paving stones are too, and one might start to give rain the most weight. The best (but certainly not only) explanation is: rain. Similarly, we might say that the best explanation of certain neural activity in the CBU subject, when that activity is similar to activity in a normal subject, is that it is relevantly related to what is, in the CBU subject, otherwise unknowable: namely, the kind of mental activity correlated with such neural activity in normal subjects. The problem here is that 'best explanations' are arrived at by weighting the likelihoods of different candidate explanations. In the case of the wet grass, we have n potential explanations, but when paving stones are wet too rain is given the most weight as we know a good deal about the sorts of events that usually cause both wet grass and wet paving stones. The problem in the case of a CBU subject is that (ex hypothesi) we know nothing about the usual relation between their neural activity and their psychological attributes (if any). But doesn't our knowledge of this relation in normal subjects help here? Only if we can assume that there is a correlation between brain/psychology correlations in normal subjects and brain/psychology correlations in CBU subjects - but the cogency of that assumption depends on the very explanation we are aiming to identify as 'best'.

So, without more ado, reasoning to the best explanation may not be open to us either.

In short, the tempting assumption that mental activity in normal subjects can always shed light on cases where the normal range of behaviours that manifest our cognitive powers are not found is less compelling than contemporary neuroscience is likely to suppose. Hence caution is also necessary with regard to making overly optimistic claims about the likelihood of neurotechnological breakthroughs in this area either.

All of this has relevance to the consultation in that putative benefits should be subject to close scrutiny to ensure that they are realistic and likely to be achievable, otherwise it is not possible to conduct an effective harm/benefit assessment.

4 Concluding points

To return to the questions in the consultation document;

4. What are the most important ethical challenges raised by novel neurotechnologies that intervene in the brain?

The APC believes that the fact that animal experiments are currently an intrinsic part of the research and development process for novel neurotechnologies presents a serious ethical dilemma that should be fully recognised. The direct and indirect impacts on experimental animals should be an intrinsic part of any decision making processes relating to the development or application of novel neurotechnologies that intervene in the brain.

5. In what ways, if at all, should the development and use of these technologies be promoted, restricted and/or regulated? Please explain your reasons.

For reasons that we discuss above, the APC recommends the following in relation to the development of neurotechnologies, where this involves regulated procedures on experimental animals:

- If the Nuffield consultation finds that the public has ethical concerns regarding the application of particular neurotechnologies to humans, this will have significant

implications with respect to licensing projects involving regulated procedures on animals with the purpose of developing these technologies. Further consultation will be necessary to ensure that the harm-benefit assessment is properly applied in these cases.

- Regardless of whether there is a demand for the development of a neurotechnology, if this would require animal experiments that would cause levels of suffering that could not be justified, then those projects should not be licensed.
- The public should be made aware that the development of neurotechnologies can directly create demands for invasive animal use, including studies on non-human primates.
- The APC should review project licence applications that aim to develop neurotechnologies and involve procedures that may cause substantial (severe) suffering in any species. The NCPASP should take over this role when it comes into existence on 1 January 2013.
- Projected benefits of neurotechnologies should be critically scrutinised to ensure that they are realistic, not only to avoid animal wastage and unnecessary suffering but also to manage the expectations of patient groups.

Animal Procedures Committee
26 April 2012