REPORT ON NEUROSCIENCE RESEARCH

A REPORT BY
THE BIOETHICS ADVISORY COMMITTEE
SINGAPORE

2021

NEUROSCIENCE
RESEARCH

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The Bioethics Advisory Committee, Singapore is an independent advisory committee that was established by the Government in December 2000 to address the ethical, legal and social issues arising from human biomedical research and its applications. The Bioethics Advisory Committee, Singapore studies emerging areas in human biomedical research and develops and recommends policies to the government as appropriate, with the aim of protecting the rights and welfare of individuals, while allowing the biomedical sciences to develop and realise its full potential for the benefit of mankind.

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FOREWORD

With an increase in the global burden of neurological and psychiatric disorders, neuroscience research has become a priority in many countries. The search for effective therapies for these disorders has become one of the greatest challenges of the twenty-first century, with many developed countries embarking on research endeavors in this area. We observe similar trends in Singapore given our aging population, where the prevalence of aging-associated diseases is expected to increase.

In response to this global challenge, Singapore established its largest research institution specialising in neuroscience research, the National Neuroscience Research Institute Singapore (NNRIS) in 2014. A joint venture between the National Neuroscience Institute (NNI) and Duke-NUS Graduate Medical School, the NNRIS aims to further biomedical research on brain and nervous system disorders such as Alzheimer's Disease, Parkinson's Disease, dementia and stroke, leading to the development of effective treatments for these disorders and improving patient outcomes.

However, ethics must not lag behind scientific developments. As the brain is the seat of one's mind and underlies our thoughts, emotions, and behaviours, research on the brain could be seen as different from research on other organs or tissues. With new and more powerful neurotechnologies to study and modify the brain, questions have been raised about the potential impact of neuroscience research on individual research subjects and patients in the future.

Therefore, the Bioethics Advisory Committee (BAC) embarked on this project to study the potential ethical, legal and social issues arising from neuroscience research. Through this review, the BAC recognised that many of the ethical challenges could already be addressed by BAC's existing ethics recommendations and research governance frameworks including the Human Biomedical Research Act 2015 and its subsidiary legislation.

This review has been an important exercise to re-assure all Singaporeans that neuroscience research will be conducted in accordance with high ethical standards. I thank the members of the Review Group, the BAC and our International Panel of Experts for their dedication in completing this difficult albeit vital review to ensure the conduct of good and ethical science in Singapore.

Chief District Judge (Ret.) Richard Magnus
Chair
Bioethics Advisory Committee
2021

EXECUTIVE SUMMARY

I. Introduction

1. Neuroscience is the study of the nervous system. This includes the central nervous system that consists of the brain and spinal cord, and the peripheral nervous system that consists of all the nerves distributed throughout the body. Much of neuroscience research is aimed at understanding, preventing or treating disorders of the nervous system. Although much progress has been made in recent years to understand the anatomy, cell biology and physiology of the brain, many aspects of this complex organ have yet to be uncovered.

2. In recent years, there have been notable developments in the use of neurotechnologies in the biomedical field. With emerging technologies, new discoveries of how the brain functions in healthy, ageing and diseased states can be expected. As major scientific findings and technological advances are made with what seems to be increasing frequency, novel therapeutic solutions and applications which will allow us to better understand and modify the brain function. These scientific and technological advances have made it possible to examine and modify the human brain to greater extents.

3. While such interventions to the human brain have the potential to treat or cause the development of motor or behavioural symptoms, they also have the potential to alter cognition, emotion and even personality. This raises potential ethical, legal, social and philosophical issues. Some of these issues are not novel and have been discussed in other fields of inquiry in bioethics such as genetic research. However, as the human brain has the capacity to influence all our physiological processes of thought, emotion and behaviour, research on the human brain has implications beyond that of other organs or tissues. Therefore, extra care should be taken in any research involving the brain, as well as any technological applications stemming from such research.

4. In light of this, the BAC formed a Review Group in 2011 to examine the potential ethical, legal, and social issues arising from recent developments in neuroscience research, and the use of neurotechnologies, focusing particularly on human biomedical research involving physical and chemical interventions on the brain. In developing this report, the BAC considered international practices and guidelines on neuroscience research, together with expert views on the subject. It has also carefully considered the feedback received from extensive public consultation with research, governmental and healthcare institutions, professional and religious organisations, and the general public.

5. The BAC recognises that the brain has an exceptional status because it is the seat of human consciousness and sentience, and is crucial to human functioning. While existing research ethics frameworks provide adequate safeguards for most neuroscience research, the BAC is of the view that extra caution is warranted in some exceptional cases. As such, BAC recommends that existing research ethics frameworks be enhanced to reflect this.

II. Types of Neurotechnologies

6. Neurotechnologies can broadly refer to any technological innovations that interact with the workings of the brain. This can include tools that help scientists observe the brain and study its functions, as well as innovations that help clinicians investigate and potentially treat

neurological disorders. During its review, the BAC examined some of the recent scientific developments in neurotechnologies such as neuroimaging, brain stimulation, brain-computer interfaces, stem cell therapy, neuropharmaceuticals, and human cerebral organoids.

7. Neuoroimaging, or brain scanning, encompasses a variety of techniques to visualise the brain, and is used in diagnosing disease, examining brain functions and understanding how activities may affect the brain. Some of these imaging techniques include Computed Axial Tomography (CT), Magnetic Resonance Imaging (MRI), Functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET). While CT and MRI scans are established diagnostic methods to detect structural abnormalities in the brain, the use of functional neuroimaging as a diagnostic tool for neuropsychiatric disorders is still at an early stage, and further work is required before it can transition from research into the clinical setting. Although the physical risk associated with neuroimaging technologies is relatively low as it does not involve surgical procedures, appropriate precautions still need to be observed to ensure the individual's safety from risks such as exposure to ionising radiation.

8. Brain stimulation is the application of an electric or magnetic stimulus to the brain to modify or improve its function. The most common brain stimulation techniques are Deep Brain Stimulation (DBS) and Transcranial Magnetic Stimulation (TMS). DBS involves the surgical implantation of an electrode(s) into specific regions of the brain, to deliver electrical impulses to modulate neural activity at the targeted site(s). As brain surgery is required for DBS, there are associated risks such as infection, anaesthesia-related complications, damage to healthy brain tissue and bleeding in the brain. On the other hand, TMS is a lower-risk procedure as it is a non-invasive method of stimulating the brain using focused, pulsed magnetic fields. Studies are still underway to explore the use of DBS and TMS to treat a wide variety of medical conditions, such as depression, obsessive-compulsive disorder (OCD), Alzheimer's disease and Parkinson's disease. DBS has also been accepted as a treatment modality in certain jurisdictions. However, the long-term risks and effects of both technologies require further study.

9. Brain-computer interfaces (BCIs) are systems that allow its users to interact with their surroundings by controlling external devices such as computers, automated wheelchairs and artificial limbs solely with brain activity. BCI applications are typically targeted at people with spinal cord injuries or neuromuscular disorders resulting in limited or no neuromuscular control, and are also being explored as tools to aid neurorehabilitation for patients suffering from lost motor functions. BCIs involve the application of electrodes onto the patient and can exist in varying levels of invasiveness depending on whether these electrodes are placed on the patient's scalp, surgically placed on the surface of the brain, or surgically implanted into the brain. The risks involved in the use of BCIs depend largely on method of electrode placement, with the risk of adverse outcomes increasing for more invasive methods that require brain surgery.

10. Stem cell therapy refers to the use of neural stem cells derived from specific areas of the brain or developed from progenitor cells from various sources such as embryonic stem cells (ESCs), bone marrow stem cells, human umbilical cord blood stem cells and mesenchymal stem cells. These neural stem cells could be injected directly into an affected area of the brain, where they could transform into cells that were lost or had become dysfunctional. This may be an effective treatment for neurological disorders such as stroke, Parkinson's disease and Alzheimer's disease, which are typically caused by a loss or altered function of certain brain cells. Such therapies are still in the research stage, and involve significant risks such as the possibility of tumour formation arising from the inherent self-renewing

and pluripotent properties of stem cells, or other adverse side effects such as inappropriate stem cell migration, immune rejection of transplanted stem cells, and infection from viruses within transplanted cells.

11. Neuropharmaceuticals are drugs used to treat neurological and psychiatric disorders. These drugs affect cognition and behaviour through alteration of brain chemistry and function. They are developed to manage symptoms that negatively affect quality of life, such as poor concentration, severe pain, diminishing memory, impulsive behaviour, negative emotions and mood disturbances. As with other types of drugs, there are side effects associated with the consumption of neuropharmaceuticals. The side effects may be mild and transient such as dry mouth and headache, or more severe such as irregular heart rhythms, personality change, addiction or psychosis.

12. Human cerebral organoids are three-dimensional tissue structures derived from pluripotent stem cells which mimic the architecture and function of mature organs, serving as models for the study of fundamental biology of brain development, function and disorders. Such models are also expected to be used for the development of personalised medicine for brain disorders. Recent developments in the growth of such organoids have led to sensationalised media reports terming them as "mini brains". However, all induced pluripotent stem cells derived organoids generated to date have only reached the peak maturity and complexity of a prenatal state, and there are still technological hurdles to overcome before it is possible to develop functionally mature organs. Although brain organoid technology is still in its nascent stages, there may be a need to also ascertain the relevant ethical considerations for conducting such research in the long run.

III. ETHICAL, LEGAL AND SOCIAL CONSIDERATIONS

13. In its deliberations on this topic, the BAC has been guided by the following five ethical principles: respect for persons, solidarity, justice, proportionality and sustainability. With these five principles as basis, the BAC examined the potential ethical, legal and social issues arising from recent developments in neuroscience, with the aim to identify the additional safeguards required ensure the protection of research participants of neuroscience research.

14. Over the course of its review, the BAC came to the conclusion that many of the ethical, legal and social issues faced in neuroscience research are not exceptional and do not differ fundamentally from those found in most biomedical research. In most instances of neuroscience research, especially for research involving the medical use of neurotechnologies, these concerns are sufficiently addressed by applying existing research ethics frameworks on issues such as obtaining of informed consent, withdrawal of consent, recruitment of participants lacking mental capacity, and recruitment of research participants who are minors. As such, many of the recommendations made within this report affirms the application of BAC's previous guidelines and recommendations.

15. However, there are a few exceptional cases in neuroscience research which may require additional safeguards to ensure the safety and welfare of research participants. Such cases include the conduct of high-risk neuroscience research involving healthy participants in sham brain surgeries, or research that may have an impact on the personal identity and autonomy of participants. There are also the non-medical uses of neurotechnologies which may fall outside the remit of existing frameworks for biomedical research, such as consumer neuroscience research, neuroenhancements, and research involving human cerebral organoids. The BAC also highlights and addresses exceptional cases within its recommendations.

16. To ensure the safe and ethical conduct of neuroscience research in Singapore, the BAC makes the following 13 recommendations:

Recommendation 1

17. Prospective participants should be informed during the consent-taking process that while they are free to withdraw their consent to participate in research at any time without any explanation and without penalty or prejudice to any treatment they may be receiving, there could be unavoidable implications in some circumstances. They should be provided with information on the procedures for withdrawal, and any possible implications or risks involved in withdrawing from the proposed research.

Recommendation 2

18. Researchers should ensure that there is a protocol for follow-up to monitor participants for an appropriate period of time after they have discontinued their participation in a study. Researchers and their institutions are responsible for providing medical care to participants who suffer from any proximate and direct harm arising from their participation in, as well as withdrawal from, the research.

Recommendation 3

19. Prior to the commencement of the research, research participants should be given the choice of whether or not they would like to be informed about clinically significant incidental findings. Researchers should ensure that research participants, who so choose, are informed and advised to seek medical attention and confirmation of the incidental finding in a clinical laboratory – this should be documented. Communication of such findings may be done directly by the researcher, or through a healthcare provider or other authorised party, who is appropriately qualified and in a position to advise and discuss the implications of such findings.

Recommendation 4

20. If a research participant's wishes or preferences with regard to the return of incidental findings are unknown, researchers must consider whether the potential harm of returning the incidental finding would outweigh the expected benefits. The onus is on researchers to seek expert advice if necessary for the thorough assessment of this consideration.

Recommendation 5

21. Researchers should submit any screening protocols that will be used for the recruitment of research participants for their Institutional Review Board's (IRB) approval. IRBs and researchers should ensure that sufficient safeguards are in place to avoid unintentional harm and handle clinically significant findings.

Recommendation 6

22. Where prospective participants are noted to have cognitive impairment/disturbance (whether it is permanent or temporary), researchers should conduct assessments to determine their capacity for decision-making. When necessary (e.g. in high risk cases), an independent party

should be involved in this assessment. In the event participants are assessed to be mentally incapacitated, a surrogate decision maker (as described in the Human Biomedical Research Act 2015) should be consulted and any decision taken should be in the best interest of the participant.

Recommendation 7

23. In the event that participants are anticipated to gradually decline into a state of non-mental capacity, researchers should proactively ascertain such participants' wishes in respect of continued study participation in the future should they be deemed to have lost mental capacity. IRBs need to take extra care in approving such protocols, and only permit them when researchers are able to demonstrate the necessity of such research, and show that participants would be exposed to no greater than minimal risk.

Recommendation 8

24. In research involving minors as participants, the primary consent is provided by the parents or guardian of the participant. Additionally, researchers should justify to their IRBs why their research cannot be conducted in an older population. Where possible, research should be conducted on older children capable of providing informed consent before involving younger children. In cases concerning high-risk research, an independent third party should be brought in to conduct the assessment of the child's capacity.

Recommendation 9

25. Except under very exceptional circumstances, such as where a more suitable control arm cannot be designed to test the safety and efficacy of an invasive intervention, sham brain surgery should not be allowed. Research involving sham brain surgery should be subject to a second stage of ethics review, conducted by an appropriate authority independent of the research institution.

Recommendation 10

26. During the consent taking process, prospective participants must be properly informed that they may be assigned to the control arm, provided with details about the procedure(s) involved, and understand the possible risks.

Recommendation 11

27. When obtaining participants' informed consent, researchers should inform participants of the possibility of an intervention affecting a participant's personal identity or autonomy. Should any personality changes be detected in the participant, researchers should re-seek consent to continue with the intervention, and put in place appropriate safeguards necessary for the protection of the interest and welfare of their participants.

Recommendation 12

28. For research involving neuroenhancement, researchers should conduct risk-benefit assessments based on the principle of proportionality with special considerations given to the degree of invasiveness, the possibility of adverse effects, age group of research participants and the impact on self-identity or autonomy to the research participants. These risk-benefit assessments should be submitted to the relevant IRB.

Recommendation 13

29. Research involving human cerebral organoids should be regarded the same as human biomedical research involving the use of human brain tissue and subjected to the same guidelines and requisites.

ETHICAL, LEGAL, AND SOCIAL ISSUES ARISING FROM NEUROSCIENCE RESEARCH

I. Introduction

1.1 Neuroscience is the study of the nervous system. This includes the central nervous system, which consists of the brain and spinal cord, and the peripheral nervous system that consists of all the nerves distributed throughout the body. It is an interdisciplinary science, involving collaborations between fields such as medicine, biomedical sciences, engineering, computer science, linguistics, and psychology. Research in neuroscience includes studying the cellular, molecular, developmental, structural, functional and medical aspects of the nervous system. Much of neuroscience research is aimed at understanding, preventing or treating disorders of the nervous system. Other studies have been conducted to understand the basic functions of the nervous system, its evolution, and understand processes such as cognition, emotions, social interactions, and behaviour.

1.2 Although much progress has been made in recent years in the understanding of the anatomy, cell biology, and physiology of the brain, many aspects of this complex organ have yet to be uncovered. For instance, understanding the processes in the development of neural circuits during youth; their modification by experience throughout the lifespan; details of neural pathways that underlie brain functions, especially in the generation of thoughts, feelings, memory and complex behaviour. With new and powerful emerging technologies, and more research aimed at neural mapping, valuable discoveries on how the brain functions in healthy, ageing and diseased states are anticipated.

1.3 Major scientific and technological advances have made it possible to examine and modify the human brain to greater extents. Interventions to the brain have the potential to treat or cause the development of motor or behavioural symptoms, as well as alter cognition, emotion and even personality. This has given rise to a new discipline, referred to as "Neuroethics". Neuroethics examines the ethical, legal, social and philosophical issues raised by advances in neuroscience.[i] Some of the ethical and legal issues overlap with the broad purview of bioethics. These are exemplified in challenges such as obtaining informed consent for research participation from individuals with cognitive impairment or mental illness, as well as the need to protect the privacy of research participants. However, other issues go well beyond traditional bioethics such as the neural substrates of personality, personal identity, moral agency and their alteration by disease, therapeutic interventions or enhancement technologies.

1.4 Some of these issues are not novel, and have been discussed in other fields of inquiry such as genetic research. However, as the human brain has the capacity to influence all our physiological processes of thought, emotion, and behaviour, research on the human brain has implications beyond that of other organs or tissues. The human brain holds a special status because it is essential to our proper functioning as human beings. At the most basic level, brain function, or lack thereof, is used as an indicator of legal death in many jurisdictions. More importantly, the brain shapes how we perceive the world, how the world perceives us, how we think, what we believe, and how we act. Thus, extra care should be taken in any research involving the brain, as well as any technological applications stemming from such research.

1.5 In recent years, there have been notable developments in the use of neurotechnologies in the biomedical field. These include the use of neuroimaging as a diagnostic tool, brain stimulation

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[i] Neuroethics may also refer to studying of "the biological basis of ethical thought and behaviour, and the ways in which this could influence and inform our ethical thinking", but this is outside the scope of this report.

technologies for the treatment of neurological disorders, and the use of brain-computer interfaces (BCIs) to aid neurorehabilitation. In addition to such research, the Bioethics Advisory Committee (BAC) is also aware that neurotechnologies are being explored for non-medical purposes. For example, some interventions developed to treat neuropsychiatric disorders may be used to enhance cognition in healthy individuals. Others may be used to alter memory. Enhancement of cognitive abilities and how one perceives the world may have an impact on one's sense of identity, and raises societal issues such as distributive justice and the risk of implicit coercion ("arms races") at school or work.

1.6 This Report examines the ethical, legal and social issues in neuroscience research and the use of neurotechnologies, focusing particularly on human biomedical research involving physical and chemical interventions on the brain. The BAC recognises that the brain has an exceptional status because it is the seat of human consciousness and sentience, and is crucial to human functioning. While existing research ethics frameworks provide adequate safeguards for most neuroscience research, the BAC is of the view that extra caution is warranted in some exceptional cases. As such, BAC recommends that existing research ethics frameworks be enhanced to reflect this. This Report will highlight the additional safeguards to put in place for the research ethics framework to offer better protection for participants of neuroscience research, and also address the potential ethical issues arising from some non-medical uses of neurotechnologies.

1.7 Before arriving at these recommendations, the BAC held a public consultation from 9 January 2013 to 31 March 2013. A Consultation Paper titled "Ethical, Legal and Social Issues in Neuroscience Research", which is provided in Annexe A, was sent to research, governmental and healthcare institutions, as well as professional and religious organisations for comment. The distribution list is given in Annexe B. The Consultation Paper was also made publicly accessible on the BAC's website. Two dialogue sessions were held: one with the Institutional Review Board (IRB) members and researchers, another with religious leaders and the general public. Three separate lectures were also conducted with the scientific community, the legal community, and the general public.

1.8 In the consultation sessions, opinions were sought on the following questions:

(a) Should persons who lack mental capacity be included in research besides clinical trials? If so, under what conditions?

(b) Do researchers have a duty to return incidental findings? If so, under what circumstances?

(c) Should sham surgery (placebo surgery) be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or Deep Brain Stimulation (DBS)? If so, under what conditions?

(d) What factors should be considered when assessing research with neurotechnologies, in particular research where one's sense of identity may be affected?

(e) Should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement? If so, under what conditions?

(f) Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

(g) Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

1.9 All written responses received are set out in Annexe C. This Report was finalised following careful consideration of public feedback received. The recommendations also take into account the advice, comments, and suggestions from local experts and members of the BAC's International Panel of Experts.

II. Types of Neurotechnologies

2.1 Neurotechnologies can broadly refer to any technological innovations that interact with the workings of the brain. This can include tools that help scientists observe the brain and study its functions, as well as innovations that help clinicians investigate and potentially treat neurological disorders. This section aims to provide a brief and non-exhaustive overview of some of the recent advancements in neurotechnologies (which can be used in both medical and non-medical research) which will be referred to in later parts of the report.

Neuroimaging

2.2 Neuroimaging or brain scanning, encompasses a variety of techniques to visualise the brain, and is used in diagnosing disease, examining brain functions and understanding how activities may affect the brain. For example, brain scans can be used to assess structural brain differences, study biochemistry, or detect activity in particular brain areas through measuring blood flow or metabolic activity. Some of these imaging techniques are Computed Axial Tomography (CT), Magnetic Resonance Imaging (MRI), Functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET). Details of the techniques are listed in the Glossary.

2.3 While CT and MRI scans are established diagnostic methods to detect structural abnormalities in the brain, the use of functional neuroimaging as a diagnostic tool for neuropsychiatric disorders is still at an early stage.[1] Functional neuroimaging techniques such as fMRI and PET have significantly increased the understanding of the human brain in normal and diseased states. This allows the examination of differences that may not be reflected structurally, and may lead to the development of tools to evaluate and even predict human behaviour. In the clinical context, there is potential for more accurate neurological mapping, better monitoring of drug development and new approaches to disease screening, diagnosis, and management. However, for functional neuroimaging to transition from research into the clinical setting, further work is required to establish that the sensitivity and specificity of the respective tests are of clinical value.

2.4 Advances in the analysis of neuroimaging data have provided researchers some ability to detect particular perceptions, thoughts, or intentions to perform an action under certain conditions. Studies have shown that researchers were able to predict, using neuroimaging data, whether participants would add or subtract two numbers presented to them,[2] as well as demonstrate the possibility of real-time neuroimaging and cognitive monitoring.[3] There is also an increasing interest in admitting neuroimaging data and analysis as evidence in legal proceedings, but this has generally either not been successful or accorded little weight in many countries.[ii]

2.5 The physical risk associated with neuroimaging is relatively low compared to neurotechnologies that involve surgical procedures. In CT and PET scans, subjects are exposed to low levels of ionising radiation, a risk also present in other forms of radiological imaging techniques, and are mainly of concern in children and pregnant women. A major consideration in using MRI is the effect of the strong magnetic field on implants, which may result in serious injury or death. While most ferromagnetic implants confer physical risk, and persons with such implants should not undergo MRI imaging, the use of such implants is decreasing, and is being replaced by MRI-safe implants. In clinical and research settings,

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[ii] A significant issue with such technologies is that their experimental results require highly compliant research subjects to identify putative differences between truth and lies. Indeed, in much research on detection of deception, investigators typically ask subjects to lie, which is a cognitively and emotionally very different task from real world attempts to deceive authorities and avoid detection.

appropriate precautions are widely observed to ensure the individual's safety. Although the use of intravenous contrast agents is of relatively low risk, there is still a risk of potentially serious complications in patients with kidney problems.

Brain Stimulation

2.6 Brain stimulation is the application of an electric or magnetic stimulus to the brain to modify or improve its function. The most common brain stimulation techniques are Deep Brain Stimulation (DBS) and Transcranial Magnetic Stimulation (TMS).

Deep Brain Stimulation

2.7 DBS involves the surgical implantation of an electrode(s) into specific regions of the brain, to deliver electrical impulses to modulate neural activity at the targeted site(s). The electrode(s) is connected via an insulated wire that runs down the neck under the skin to a battery-operated stimulator, which is implanted in the upper chest or abdomen. The stimulator can be switched on and off, or adjusted to provide an appropriate level of stimulation, through a control device used by a doctor. This is known as open-loop or conventional DBS. Another form of DBS that is still in its early stages is closed-loop or adaptive DBS.[4] Unlike open-loop DBS, closed-loop DBS employs a sensor for feedback signal recording to enable the automatic adjustment of stimulation levels in real-time without the need for an external controller.[5]

2.8 DBS has been approved by the U.S. Food and Drug Administration (FDA) for the non-first line treatment of several medical conditions, such as epilepsy,[6,7] essential tremors, dystonia, and the debilitating symptoms of Parkinson's disease. In respect of psychiatric conditions, DBS is now an accepted treatment modality for refractive obsessive-compulsive disorder (OCD) in most countries. There have also been studies conducted on the use of DBS for treatment-resistant depression.[8,9] While the precise mechanism of DBS is still unclear, its effects replicate those of neurosurgical lesioning, and is considered a preferred alternative to traditional ablative surgery due to its reversibility and the ability to adjust the magnitude of the electrical impulse.

2.9 As brain surgery is required for DBS, there are associated risks such as infection, anaesthesia-related complications, damage to healthy brain tissue and bleeding in the brain. These may lead to severely negative outcomes, such as paralysis, speech impairment, or seizures. Other potential negative outcomes include numbness of the face or limbs, facial weakness, dizziness or mood swings.

2.10 Although DBS is relatively well accepted for the treatment of motor symptoms, its long-term cognitive, psychiatric and behavioural effects are not well established. While some studies have mentioned memory enhancement after DBS for conditions such as obesity and epilepsy,[10,11] documentation of negative outcomes associated with DBS have featured more prominently in the literature, possibly due to concerns related to patient safety. Studies have reported patients developing cognitive dysfunction after DBS, such as speech disturbance and deficits related to attention and learning.[12,13] There have also been reports of negative psychological outcomes associated with DBS, such as apathy, hallucinations, depression and suicidal tendencies.[14,15] Some patients also reported experiencing personality changes and developing behaviours such as compulsive gambling and hypersexuality.

Transcranial Magnetic Stimulation

2.11 TMS is a non-invasive method of stimulating the brain using focused, pulsed magnetic fields. An electric current is passed through an electromagnetic coil, which is placed against the patient's scalp over the area to be stimulated, generating a magnetic field. The magnetic field passes through the scalp and skull, inducing an electric current within the underlying brain region.

2.12 TMS can be delivered in single, paired, or repetitive pulses. Repetitive TMS treatment has been reported to be effective in patients with major depression who have failed to respond satisfactorily to, or who are unable to tolerate, antidepressant medication. TMS is currently being studied as a treatment option for disorders such as tinnitus, OCD, schizophrenia, autism, attention deficit hyperactivity disorder (ADHD), migraine, post-traumatic stress disorder, Alzheimer's disease and Parkinson's disease. Other possible therapeutic applications of TMS include stroke rehabilitation and drug addiction management. As TMS has been shown to improve some aspects of cognition, there is ongoing research to develop TMS for the purpose of enhancement, such as memory improvement, problem-solving ability and creative thinking.

2.13 Since it is non-invasive, TMS is generally a low risk procedure. Seizures are the most serious acute risk associated with TMS. However, it has been shown that the incidence rate of seizures for TMS delivered within published guidelines to individuals without risk factors (e.g. no pre-existing conditions such as brain lesions or family history of epilepsy) is lower than 1 per 60,000 sessions.[16] Other risks include fainting and minor pain such as headache or local scalp discomfort. Minor cognitive changes have also been observed and there is a low risk of mania in depressed patients. Though the reported occurrence and severity of the side effects from TMS are low, its long-term risks remain unknown.

Brain-Computer Interfaces

2.14 A brain-computer interface (BCI) is a system that allows its users to interact with their surroundings by controlling external devices such as computers, automated wheelchairs and artificial limbs solely with brain activity, without the normal intermediaries of peripheral nerves and muscles. BCIs measure brain activity associated with the user's intent and translates the recorded activity into specific commands, such as clicking a computer cursor.

2.15 There are non-invasive, partially invasive and invasive BCIs. Non-invasive electroencephalography (EEG)-based BCIs consist of electrodes placed on the scalp that detect brain signals from different brain areas. It is the most widespread recording modality due to the low risk involved, but the quality of the signals detected is reduced by the scalp and skull, as well as background noise. Partially invasive electrocorticography (ECoG)-based BCIs consist of electrodes surgically placed on the surface of the brain. As these electrodes are closer to the brain, the signal detection is improved as the signals do not need to pass through the skull. Invasive intracortical-based BCIs consist of micro-electrodes surgically implanted into the brain. These are the most effective at signal detection.

2.16 BCI applications are typically targeted at people with spinal cord injuries or neuromuscular disorders such as amyotrophic lateral sclerosis, cerebral palsy or stroke. People with these conditions tend to have limited or no neuromuscular control, and studies have shown the possibility of using BCI to help patients in a locked-in state to communicate.[17] BCIs may restore basic capabilities and sense of agency for these people, potentially improving their quality of life.

2.17 BCIs are also being explored as tools aiding neurorehabilitation after a stroke to recover one's lost motor functions. Clinical uses of BCI aim at providing a technological alternative to a lost function, or as a training tool for promoting adaptive neuroplasticity. In such applications, a robotic aid or functional electrical stimulation of the muscles is used to execute an intended movement of the user's limb, facilitating functional recovery through neural feedback. A trial has shown that two people with long-term tetraplegia were able to reach for and grasp objects in a three-dimensional space using a robotic arm that they had controlled directly with brain activity through a neural interface system.[18]

2.18 Most notable BCI research findings remained largely confined to controlled research settings, with data that were obtained from studies involving animals or healthy human participants using non-invasive BCIs. Clinical trials involving people with disabilities who might potentially benefit from the use of BCIs (e.g. people with spinal cord injuries) are currently ongoing under close supervision.[19,20]

2.19 The risks involved in the use of BCIs depend largely on electrode placement and how invasive that might be. When a non-invasive BCI is used, there is a possibility of skin infection after application of electrodes. The risk of adverse outcomes is greater in more invasive methods that require brain surgery. Implants and/or the associated surgery can damage brain tissue or lead to infection. Moreover, infection may present a long-term risk for invasive BCI users, since cables extend outside the body and provide an entry point for organisms. Although wireless BCIs may circumvent this complication,[21] it may be associated with the security risk of unsolicited access and control of the BCI.

Stem Cell Therapy

2.20 Stem cells are cells that are able to self-renew and have the capability to differentiate into diverse specialised cell types, offering significant potential for replacement of damaged cells and restoration of brain function. Stem cell therapy may be an effective treatment for neurological disorders such as stroke, Parkinson's disease and Alzheimer's disease, which are typically caused by a loss or altered function of certain brain cells. At present, there are no curative treatments for these disorders.

2.21 Neural stem cells may be derived from specific areas of the brain or developed from progenitor cells from various sources such as embryonic stem cells (ESCs), bone marrow stem cells, human umbilical cord blood stem cells and mesenchymal stem cells. Induced pluripotent stem cells (iPSCs), which are reprogrammed from differentiated somatic cells, have capabilities similar to ESCs. As autologous iPSCs could be produced, i.e. originating from the patient, they would be less likely to cause an immune response when transplanted back to the patient.

2.22 Neural stem cells could be injected directly into an affected area of the brain, where they could transform into cells that were lost or had become dysfunctional. As neural stem cells could be attracted to specific brain sites (where there was a loss or malfunction of cells) via certain chemical signals, they could also be injected into the blood stream to exert the desired effect at the affected sites. Pharmacological interventions could be used to enhance the migration of the injected stem cells to the brain, and modulate their proliferation, differentiation and efficacy at the site of pathology. Survival and engraftment of the transplanted neural stem cells are obstacles that have to be overcome before therapy can be effective. Researchers are using tissue engineering approaches, such as the use of biomaterials to provide physical protection and improve the survival of transplanted neural stem cells. Finding the ideal material and innovative technologies to efficiently deliver neural stem cells across the blood-brain barrier is of great value in neural stem cell therapy and research.

2.23 Stem cell therapy for specific neurological disorders is still in the research stage. The world's first clinical trial involving the injection of neural stem cells into the brains of disabled stroke patients started in November 2010 in Scotland, and is currently undergoing phase II trials in the US.[22] The study aims to assess the effectiveness of the treatment to change the patient's level of dependency and disability, and measure several safety parameters. Another clinical research project, the Transeuro Transplant project, involved grafting dopamine-producing foetal tissue into the brains of patients with Parkinson's disease.[23] Yet another clinical trial (phase III) for the treatment of amyotrophic lateral sclerosis is evaluating the safety and efficacy of autologous stem cells transplanted intrathecally.[24]

2.24 Since neural stem cell therapy is invasive, there are significant risks involved, especially if the cells are to be injected directly into the brain.[25] A serious concern is tumour formation arising from the inherent self-renewing and pluripotent properties of stem cells. Other possible adverse side effects include inappropriate stem cell migration, immune rejection of transplanted stem cells, and infection from viruses within transplanted cells. As with all invasive procedures, there are also anaesthetic and surgical related risks.

Neuropharmaceuticals

2.25 Neuropharmaceuticals are drugs used to treat neurological and psychiatric disorders. These drugs affect cognition and behaviour through alteration of brain chemistry and function. They are developed to manage symptoms that negatively affect quality of life, such as poor concentration, severe pain, diminishing memory, impulsive behaviour, negative emotions and mood disturbances. Some examples of neuropharmaceuticals are modafinil (Provigil®) or armodafinil (Nuvigil®), which are used to treat narcolepsy and prescribed in some countries to shift workers to improve wakefulness; methylphenidate (Ritalin®) and dextroamphetamine (Adderall®), which are used to treat attention deficit hyperactivity disorder (ADHD); and donepezil (Aricept®) for the treatment of Alzheimer's disease.

2.26 As with other types of drugs, there are side effects associated with neuropharmaceuticals consumption. The side effects may be mild and transient such as dry mouth and headache, or more severe such as irregular heart rhythms, personality change, addiction or psychosis. To understand the mechanisms of neuropharmaceuticals, researchers have studied the link between molecular actions of drugs and specific behavioural or physiological effects in humans via brain imaging.

2.27 The Human Genome Project has revealed that genetic variance between persons may lead to differing responses to drug treatment.[26] Knowledge of how these genetic differences may affect an individual's response to a specific drug could be used to assess the risk of adverse effects associated with taking the drug and predict the therapeutic efficacy of the drug.

Human Cerebral Organoids

2.28 Organoids are three-dimensional tissue structures derived from pluripotent stem cells which mimic the architecture and function of mature organs, serving as models for the study of developmental biology and embryogenesis.[27] They offer an advantage over single-cell cultures or two-dimensional tissue models which are unable to capture the complexity and interdependent development of varied cell types. Clinical relevance of organoid research lies in disease modelling, drug testing in precision medicine, and regenerative medicine. Common tissue types grown include gastrointestinal, eye and brain (cerebral organoids).

2.29 In 2016, a team from Duke-NUS Medical School and A*STAR grew human cerebral midbrain-like organoids comprising distinct cell layers with functional dopamine producing neurons.[28] These findings show promise in developing a disease model to develop treatments for chronic brain diseases such as Parkinson's disease. More recently, another team transplanted a human brain organoid grown in vitro, into mouse brain in vivo. They found that the organoid continued to differentiate and integrate into the host tissue,[29] as vascular and neuronal networks developed between the human PSC-derived organoid and mouse brain. This was a significant achievement because the establishment of a functional circulatory system facilitates the delivery of nutrients and oxygen into deep tissue, which has been an obstacle in the development of organoid growth.

2.30 Sensationalised media reports of "mini brains" might raise both expectations and fears of the general public. However, all iPSC-derived organoids generated to date have only reached the peak maturity and complexity of a prenatal state.[30] Furthermore, even though pluripotent stem cells have the ability to differentiate into all cell types, their ability to self-organise into a specific temporal and spatial configuration is limited,[31] and technological hurdles to develop functionally mature organs remain. Nevertheless, brain organoids are expected to become invaluable models for better understanding of the fundamental biology of brain development, function and disorders, as well as the development of personalised medicine for brain disorders. This is because brain organoids derived from individuals maintain the major characteristics of the developing brain with identical genetic information. Although brain organoid technology is still in its nascent stages, there may be a need to also ascertain the relevant ethical considerations for conducting such research in the long run.[32]

III. Ethical, Legal and Social Considerations

3.1 Over the course of its review, the BAC has come to the conclusion that many of the ethical, legal and social issues faced in neuroscience research are not exceptional and do not differ fundamentally from those found in most biomedical research. In most instances of neuroscience research, especially for research involving the medical use of neurotechnologies, these concerns are sufficiently addressed by applying existing research ethics frameworks. As such, many of the recommendations made within this report affirms the application of BAC's previous guidelines and recommendations on issues in the field of neuroscience research such as informed consent and the recruitment of participants lacking mental capacity.

3.2 However, there are a few exceptional cases in neuroscience research which may require additional safeguards to ensure the safety and welfare of research participants. Such cases include the conduct of high-risk neuroscience research involving healthy participants in sham brain surgeries, or research that may have an impact on the personal identity and autonomy of participants. There are also the non-medical uses of neurotechnologies which may fall outside the remit of existing frameworks for biomedical research, such as consumer neuroscience research, neuroenhancements, and research involving cerebral organoids. These exceptional cases will be explored further and addressed in the BAC's recommendations below.

General Ethical Principles

3.3 In its deliberations, the BAC is guided by the following five principles:

(a) *Respect for persons*: Individuals are to be respected as human beings and treated accordingly. This includes respecting their rights to make their decisions without being coerced, misled, or kept in ignorance. Individuals' welfare and interests are to be protected, especially when their autonomy is impaired. This principle underlies the importance of informed consent for participation in research, respect for privacy, safeguarding confidentiality, and minimising harm to research participants. It also requires a proper regard for religious and cultural diversity;

(b) *Solidarity*: The BAC believes that some measure of mutual obligation exists between the individual and society such that a common interest may be invoked as reason for subordination of individual interest in specified circumstances. In the context of biomedical research, acceptance of agreed social benefits—considered as a public good—implies an in-principle willingness to consider participation in research of the kind yielding the accepted benefits. This means that there is a balance to be struck between the interests of the public and the rights of individual participants, and that incompatible and irreconcilable ethical perspectives should be resolved with some regard to public interest. Solidarity reflects the importance of general altruism as a basis for participation in biomedical research;

(c) *Justice*: The principle of justice encompasses the concepts of fairness and equality, which imply that access to the benefits of research and the burden of supporting it, should be equitably shared in society. In the event that research yields an immediate benefit that could apply to participants in the research, justice would dictate that the benefits be offered to them. Justice further implies that researchers and their institutions incur some responsibility for the welfare of its participants, and their compensation and treatment in the event of an adverse outcome that results directly from their participation;

(d) *Proportionality*: The regulation of research should be proportional to the degree of possible threats to autonomy, individual welfare, or the public good. As such, interference with individuals' decisions and/or actions should not exceed what is needed to achieve necessary regulation. The risk in any acceptable programme of research, and the stringency of its regulation, should not be disproportionate to any anticipated benefits; and

(e) *Sustainability*: Research processes and outcomes should not jeopardise or prejudice the welfare of future generations. The principle can also be understood broadly, to support arguments for the conservation of nature and the minimisation of resource depletion for the good of the planet as a whole.

Research Involving Medical Use of Neurotechnologies

Informed Consent

3.4 The principle of respect for persons dictates that informed consent should be obtained from prospective individuals prior to the start of any research. The BAC has provided detailed guidance on the general consent-taking requirements for the conduct of ethical biomedical research, in its *Ethics Guidelines for Human Biomedical Research ("Guidelines")*,[33] which was published in June 2015, and in its earlier reports. Those guidelines remain applicable in the context of neuroscience research. IRBs should review the consent-taking process whenever it considers a research proposal, to ensure that there is adequate protection for research participants, especially for vulnerable persons e.g. cognitively impaired individuals, incarcerated individuals, elderly persons and children.

3.5 To ensure that a prospective participant is fully informed before making a decision to participate in neuroscience research, the consent-taking process should include the following information where applicable:

(a) The nature and purpose of the research;

(b) The anticipated risks and benefits of the research, and how risks will be managed and minimised;

(c) The alternative procedures or treatments available, and the potential risks and benefits of such alternatives;

(d) An explanation of any intervention that is not part of standard care, and an emphasis of its experimental nature to minimise any misconception about the potential for therapeutic efficacy;

(e) The right to withdraw from research at any time, the procedure to do so, and any possible implications or risks pursuant to such withdrawal;

(f) Compensation and/or treatment that will be provided in the event of any proximate and direct harm arising directly from research participation or withdrawal from research;

(g) Anticipated costs that the research participant might likely incur as a result of participating in the research;

(h) Reimbursement for participation in research, if any;

(i) Safeguards for protecting the participant's privacy and confidentiality of his or her personal information;

(j) Possible uses of individually-identifiable information collected for future research;

(k) Whether biological materials removed from the participant will be destroyed, discarded or stored for future research;

(l) The circumstances in which the participant will be contacted for further consent (e.g. changes in the research procedures);

(m) The possibility of an incidental finding occurring, and how such findings will be returned, should the participant indicate a wish to know; and

(n) The person(s) to contact for further research information.

3.6 The language, timing and means of explanation and the degree of details relayed to prospective participants should help the individual make an informed decision. Also, the level of maturity and comprehension, especially in respect of legal minors and those lacking mental capacity, should be considered. The communication of information for research participation should be dependent on the prospective participant's level of understanding and mental development.

Withdrawal of Consent

3.7 As research participation is voluntary, research participants should be free to withdraw their consent to participate in research at any time, without explanation, and without penalty or prejudice to any treatment they may be receiving. However, withdrawal from some types of neuroscience research, such as those involving neurotechnologies that are surgically implanted into the brain, may present difficulties or carry accompanying risks. For instance, in the case of DBS, surgery would be required to remove the electrodes which were implanted deep in the brain, and the risks include intracranial haemorrhage, infection, as well as the risks associated with the administration of general anaesthesia.

3.8 Hence, for research involving neural implants, prospective participants should be advised at the point of taking consent that withdrawal from such research may be associated with irreversible effects on the brain at the point of taking consent. For example, the removal of implants may cause haemorrhagic stroke or alterations to brain structures and neural pathways. Prospective participants should be informed of the procedures for withdrawal, and any possible implications or risks involved—such as irreversible effects, or how future treatment options available to the participant may be affected.

3.9 For research that involves the use of identifiable personal information or data such as brain images, or human biological material donated for research, prospective participants should be informed that they may withdraw consent as long as the data or tissue has not yet been used. If the data or tissue has already been used and the participant withdraws consent, data or tissue obtained up to the point of withdrawal may be retained and used for the research, depending on the nature of the research.

Recommendation 1

Prospective participants should be informed during the consent-taking process that while they are free to withdraw their consent to participate in research at any time without any explanation and without penalty or prejudice to any treatment they may be receiving, there could be unavoidable implications in some circumstances. They should be provided with information on the procedures for withdrawal, and any possible implications or risks involved in withdrawing from the proposed research.

3.10 IRBs should ensure that researchers have put in place a protocol of follow-up to monitor participants for an appropriate period of time after they have discontinued their participation in a study. As research participation is voluntary, participants should be provided with medical care should they suffer any proximate and direct harm arising from their participation in, as well as withdrawal from, the research. This responsibility, which rests with the researchers and their institution, also entails ensuring that provisions are made to compensate these participants appropriately for the medical costs incurred from such adverse events. It is reasonable for researchers to refer monitoring to the participants' physicians, who should ideally be from the same institution, at the point of withdrawal or after the study ends, provided they possess the required expertise and have received sufficient guidance on the post-trial management of such participants.

Recommendation 2

Researchers should ensure that there is a protocol for follow-up to monitor participants for an appropriate period of time after they have discontinued their participation in a study. Researchers and their institutions are responsible for providing medical care to participants who suffer from any proximate and direct harm arising from their participation in, as well as withdrawal from, the research.

Incidental Findings

3.11 Incidental findings are discoveries made unintentionally during the course of research that were carried out for other purposes. These findings may be clinically significant, in that they have clear implications for the health of the research participant to whom they relate, and they may be clinically actionable or non-actionable. Clinically actionable findings are those for which medical intervention(s) may be available to improve patient outcome in terms of mortality or the avoidance of significant morbidity, for instance, the discovery of a tumour. Clinically non-actionable findings are those for which there may be no available treatment or cure, such as Huntington's disease.

3.12 The improved capability of neurotechnology modalities, especially in imaging technology, has led to an increase in the likelihood of incidental findings. As we move towards the era of big data, where more thorough data collection may elicit more findings, researchers may increasingly find themselves faced with the ethical predicament of what to do with incidental findings.

3.13 Several reasons have been advanced for not returning incidental findings discovered during the course of research. Firstly, as research participation is altruistic, it has been argued that there should be no expectation to return individual incidental findings to research participants. This is also to avoid the problem of therapeutic misconception, whereby research participants mistakenly expect to derive direct medical benefits from taking part in research. Secondly, research procedures are often not carried out at the same standard as for diagnosis—for example, research brain scans may not be of clinical grade nor optimised for diagnosis—hence incidental findings may be non-conclusive, or may even be misleading. Therefore, there is a concern that unnecessary psychological harm could be inflicted on research participants by the disclosure of false positive incidental findings discovered during research. Furthermore, researchers may not be suitably qualified to verify and communicate clinically relevant findings.

3.14 The BAC is of the view that researchers have a duty to return *clinically significant* incidental findings, whether actionable or not,[iii] to research participants who have indicated a wish to know. This qualified duty on researchers arises from the principles of respect for persons, as well as justice. As mentioned above, the interests and welfare of individuals participating in research are to be protected, and researchers and their institutions incur that responsibility. Given the view that harm to research participants should be minimised, and any immediate benefits that could apply to research participants be offered to them, clinically significant incidental findings should be disclosed to participants who have indicated a desire to be informed, so that they could choose to seek further medical confirmation and action. Further, as solidarity imposes an obligation on individuals towards other members of their society, researchers should be willing to act in the interests, and support the welfare, of their research participants.

3.15 As such, during the consent taking process, potential research participants should be:

(a) Informed of the possibility of incidental finding(s) arising in the course of the research study;

(b) Informed of the plan for the management and disclosure of any clinically significant incidental findings that may arise; and

(c) Given adequate time to decide whether or not they wish to be informed of such findings.

3.16 Researchers therefore have the responsibility to consider the likelihood of incidental findings arising during the course of their research, and develop a management plan for the handling of clinically significant incidental findings. Further, as stated in the BAC's 2015 *Guidelines*, "researchers should ensure that research participants, who so choose, are informed and advised to seek medical attention and confirmation of the research results in a clinical laboratory".[iv,33] Communication of such findings may be done directly by the researcher, or through a healthcare provider or other authorised party who is appropriately qualified and in a position to advise and discuss the implications of such findings.

3.17 The BAC is aware that for many ongoing research projects, participants' preferences with regard to the return of incidental findings had not been sought during the consent-taking process. The BAC is of the view that moving forward, this should no longer be the case. For ongoing research where the preference of the research participants for receiving incidental

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[iii] Incidental findings that are not clinically actionable or even curable are still considered to be clinically significant as participants could make lifestyle decisions they might otherwise not have.

[iv] *Guidelines,* Paragraph 3.32 and 3.33

findings is unknown, researchers should refer to their IRBs for advice on the handling of such findings. In advising researchers, IRBs should consider the likelihood that the returning of such incidental finding would cause harm to the research participant. In doing so, researchers should provide IRBs with an assessment concerning the accuracy of the incidental finding and whether the disclosure of such findings may cause any stigmatisation or other negative outcomes for the individual involved. In the absence of any indication of the research participant's preference, and should an IRB be of the view that the potential harm of returning an incidental finding would outweigh the expected benefits, it may be reasonable for the IRB to advise researchers against the disclosure of the incidental finding to the research participant.

3.18 Incidental findings should be disclosed to parents who have indicated the wish to be informed of findings relating to their child's health that were discovered during the course of research. Once the participant reaches the age of 21 years and if the research is still ongoing, the participant should be asked whether they want to be informed of such incidental findings. The participant's decision of not wanting to know the findings should be respected.

Recommendation 3

Prior to the commencement of the research, research participants should be given the choice of whether or not they would like to be informed about clinically significant incidental findings. Researchers should ensure that research participants, who so choose, are informed and advised to seek medical attention and confirmation of the incidental finding in a clinical laboratory – this should be documented. Communication of such findings may be done directly by the researcher, or through a healthcare provider or other authorised party, who is appropriately qualified and in a position to advise and discuss the implications of such findings.

Recommendation 4

If a research participant's wishes or preferences with regard to the return of incidental findings are unknown, researchers must consider whether the potential harm of returning the incidental finding would outweigh the expected benefits. The onus is on researchers to seek expert advice if necessary for the thorough assessment of this consideration.

Recruitment of Research Participants

3.19 As part of its ethics review of research protocols, IRBs should also review the screening protocols, if any, that will be used for the recruitment of participants. Researchers should ensure that proper management plans are put in place to avoid causing harm unintentionally (e.g. recruitment or non-recruitment could imply the presence of neurological or behavioural issues leading to stigmatisation) and to deal with clinically significant findings (e.g. if screening protocols may reveal early signs of neurological decline).

Recommendation 5

Researchers should submit any screening protocols that will be used for the recruitment of research participants for their IRB's approval. IRBs and researchers should ensure that sufficient safeguards are in place to avoid unintentional harm and handle clinically significant findings.

3.20 According to the Mental Capacity Act (MCA) 2008,[34] all persons who are 21 years of age and above are presumed to have capacity to make their own decisions—including whether or not to participate in a research project—unless it can be established otherwise.[v] A person may only be considered as lacking capacity to make a decision, if he or she is unable to make that decision by him or herself because of an impairment of, or a disturbance in the functioning of, the mind or brain, which could be permanent or temporary.[vi] However, it should be noted that the presence of neurological impairment or disturbance does not necessarily render a person unable to make a decision about research participation, as the mental impairment may not be so severe, or degree of impairment may fluctuate over time. Mental capacity is therefore the ability of a person to make a specific decision at a particular time.[35]

3.21 Assessment of capacity may be made on a formal or informal basis, by reference to a number of cognitive and communicative abilities that underpin the act of decision-making.[vii] A person is considered unable to make a decision for him or herself, if he or she is unable to: (1) understand the information relevant to the decision; (2) retain that information; (3) use or weigh that information as part of the process of making the decision; or (4) communicate the decision.[viii] Furthermore, a person should not be deemed unable to decide on a matter unless all practicable steps to help him or her to make that decision have been taken and failed.[ix] As best practice when conducting research with vulnerable groups, for instance, the elderly or patients with mental health issues, it is recommended that independent third parties such as accredited general practitioners or mental health specialists be involved to determine if prospective participants have the capacity to consent to research participation.

3.22 Under the MCA 2008, adults (a "donor") may make a Lasting Power of Attorney (LPA), while they still have the capacity to execute it, to appoint one or more persons (a "donee") to make decisions on his or her behalf should he or she lose the capacity to do so.[x] Donees authorised to make decisions about the donor's personal welfare may also give or refuse consent for participation in clinical trials, if and only if, they are also given explicit authorisation to do so.[xi] In the absence of an LPA, an application may be made to the court for a deputy to be appointed.[xii]

3.23 The MCA 2008 sets out a legal framework for decision-making on behalf of an adult assessed to be lacking capacity to make that decision. Any act done or decision made on behalf of a person who lacks capacity must be in that person's best interests.[xiii] The person making the determination of a donor's best interests must take into consideration their past and present wishes and feelings, beliefs and values, or any other factors that would be likely to influence his or her decision if he or she had capacity.[xiv] In its 2015 *Guidelines*, the BAC had pointed out that biomedical research other than clinical trials was not expressly provided for or mentioned under the MCA 2008.[xv] The BAC articulated a view that it may

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[v] MCA 2008, Section 3(2)

[vi] MCA 2008, Section 4(1) and (2)

[vii] Formal assessments are usually conducted by registered medical professionals and specialists in mental health such as psychiatrists for important decisions (for example, assets management) while informal assessments may be performed by someone who is not trained to conduct mental capacity assessments such as caregivers on most day-to-day decisions.

[viii] MCA 2008, Section 5(1)

[ix] MCA 2008, Section 3(3)

[x] MCA 2008, Section 11 and 12

[xi] MCA 2008, Section 13(6) and (7)

[xii] MCA 2008, Section 20(2)(b)

[xiii] MCA 2008, Section 3(5)

[xiv] MCA 2008, Section 6(7)

[xv] *Guidelines,* Paragraph 3.16

be ethical for a court deputy or donee to enrol an adult lacking capacity in minimal risk research, where this is consistent with that adult's beliefs and values and not contrary to the adult's present wishes and feelings.

3.24 International documents such as the UNESCO Universal Declaration of Bioethics and Human Rights (UDBHR) and Council for International Organisations of Medical Sciences' (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects provide clear ethical justifications for the inclusion of those lacking mental capacity in research.[36,37] For example, Article 7 of the UDBHR states that those lacking mental capacity may be included in research as long as: (i) the authorised representative consenting on behalf of those lacking mental capacity decides based on the best interest of the person concerned; (ii) the research is carried out for his or her direct benefit; and (iii) there is no research alternative of comparable effectiveness with research involving mentally competent participants. An exception may be made for research without prospect of direct health benefit if it is of minimal risk and minimal burden, and may benefit people of the same category. These justifications are similarly found in the CIOMS Guidelines.

3.25 Shortly after the BAC's *Guidelines* was issued, the Human Biomedical Research Bill was passed by Parliament in July 2015.[38] The Human Biomedical Research Act (HBRA) 2015 provides guidance on research other than clinical trials involving those lacking mental capacity. Research involving those lacking mental capacity is permissible provided consent is obtained from donee or deputy, and there are reasonable justifications that research of comparable effectiveness is not possible without the participation of this group of people. However, in cases where there is no donee or deputy, consent should be obtained from: (i) the spouse; (ii) adult children; (iii) parent or guardian; (iv) adult sibling; or (v) any adult named by the individual as someone to be consulted. It should be in this order of priority, when persons in prior classes are unavailable, and in the absence of actual notice of contrary indications by the adult, or actual notice of opposition of a member of the same class or a prior class.[xvi]

3.26 The BAC agrees with and welcomes, the legal provisions introduced by the HBRA 2015 that would facilitate the inclusion of persons lacking mental capacity in biomedical research other than clinical trials. The BAC regards ethically conducted research to be a public good, because even if direct medical benefits do not result, research may generate knowledge contributing to the development of future therapy. On the basis of justice, the benefits that could be reaped from research, as well as the burdens of supporting research, should be equitably distributed in society. Hence, vulnerable populations should not be categorically excluded from participating in research on the basis of their vulnerability alone, so that such populations may be able to benefit from research if their interests may be adequately protected in the process.

3.27 Similarly, in research where potential participants have neurological conditions likely to diminish cognitive capacity over time, researchers should, as part of the consent process, proactively ascertain such participants' wishes in respect of continued study participation at such time in the future they are deemed to have lost mental capacity. This would allow participants to give researchers consent to proceed with research in the event that participants' condition progresses to the point where they lack capacity, and ostensibly no longer consent to continued participation. IRBs toned to take extra care in approving such protocols, and only permit them when researchers are able to demonstrate the necessity for such research on such populations. Additionally, IRBs should be of the view that such participants would be exposed to no greater than minimal risk.

[xvi] HBRA 2015, Section 7(1)

Recommendation 6

Where prospective participants are noted to have cognitive impairment/disturbance (whether it is permanent or temporary), researchers should conduct assessments to determine their capacity for decision-making. When necessary (e.g. in high risk cases), an independent party should be involved in this assessment. In the event participants are assessed to be mentally incapacitated, a surrogate decision maker (as described in the Human Biomedical Research Act 2015) should be consulted and any decision taken should be in the best interest of the participant.

Recommendation 7

In the event that participants are anticipated to gradually decline into a state of non-mental capacity, researchers should proactively ascertain such participants' wishes in respect of continued study participation in the future should they be deemed to have lost mental capacity. IRBs need to take extra care in approving such protocols, and only permit them when researchers are able to demonstrate the necessity of such research, and show that participants would be exposed to no greater than minimal risk.

Neuroscience Research Involving Children

3.28 ADHD, Tourette syndrome (TS) and Autism Spectrum Disorder (ASD) are neurological disorders frequently diagnosed in children and adolescents. Even though there is currently no cure for these disorders, medication and/or additional treatment options are used to reduce the symptoms or improve cognitive abilities. For instance, clinical studies have been conducted to explore the clinical effects of repetitive TMS in combination with atomoxetine for the treatment of ADHD;[39] DBS for the treatment of TS;[40] and EEG-based BCIs for the treatments of ASD.[41] In order to establish efficacy and to translate these treatments into the clinical routine, such research involving children are increasingly being conducted. As subjects of such research are not only minors but may also lack mental capacity due to their neurological disorders, it is imperative to ensure that there are additional safeguards to justify the conduct of such research in children.

3.29 In general, as clinical trials may not offer direct benefit and have the potential to expose child participants to risk, only a limited number of clinical trials have been conducted with children. As a result, there is little information on dosage requirements, efficacy and safety of medications for children. In cases where conditions affect both adults and children, the dosage for children's medications are usually extrapolated from studies involving adults. However, this may not be possible for conditions only affecting children. To tackle this problem, the US Best Pharmaceuticals for Children Act (BPCA and Pediatric Research Equity Act (PREA) were instituted in 2002 and 2003 respectively.[42,43] The PREA requires studies to assess the safety and effectiveness of drugs in relevant paediatric populations unless it can be shown that extrapolation from adult data is sufficient or the studies are impracticable. The BPCA gives an additional six months of market exclusivity for studies done on children, which is similar to the EC Regulations.[44]

3.30 As part of the principle of justice, it is important to ensure that children are not categorically excluded from research so that they may be able to benefit from research activity. Given their status as a vulnerable class, additional appropriate safeguards should be put in place to protect their interests. Generally, research involving children should only be carried out when the following conditions are met:

(a) The research cannot feasibly be conducted in an adult population (e.g. in conditions that only occur in children);
(b) The research is likely to yield generalisable knowledge about the participants' condition which is of vital importance for the understanding or amelioration of the condition, or the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children;
(c) The potential risks to participants should not exceed minimal risk for research that does not offer potential direct benefit, or the potential risks to participants is justified in view of the anticipated benefits to participants; and
(d) Parental or guardian consent is obtained in addition to the minor's consent (in instances where the minor is capable of understanding and giving consent), wherever applicable.

3.31 Research may offer potential direct benefit to children,[xvii] or it may be conducted for generalisable knowledge. Both types of research may pose different levels of risk—minimal risk, slightly above minimal risk or greater than minimal risk. It is recognised that children may participate in research that incur some degree of risk even without being expected to be beneficiaries themselves. The BAC is of the view that the participation of children in research that does not offer potential direct benefit to them should be limited to research that poses no more than minimal risk. However, in cases where research offers potential direct benefit to the child, higher risks may be acceptable if the anticipated benefit (excluding monetary benefits or in-kind and adjunctive medical services) outweighs the potential risks. In all these cases, parental/guardian consent, in addition to the consent of the child who is of sufficient understanding, is required prior to research participation. A child's refusal to participate in research should be respected.

3.32 In the case of a child who lacks sufficient understanding, a parent or guardian may consent to the child's participation if the research cannot be carried out in an adult population. This position is codified in Section 8 of the HBRA 2015 and Section 16(7) of the Medical (Clinical Trial) Regulations 2016.[45]

3.33 As children have developing cognition, the BAC recommends that a "progressive age de-escalation" approach should be taken for neuroscience research involving children.[46] This safeguard was proposed by the US Presidential Commission for the Study of Bioethical Issues in its 2013 report on medical countermeasure research involving children. Where possible, research should be conducted on an older age group of children before the younger ones, so that data from research on the older children can inform and guide subsequent research, "to provide additional protection to the youngest and most vulnerable children".

3.34 The BAC notes that in the HBRA 2015, when the prospective research subject is a minor assessed to possess sufficient understanding and intelligence to understand what is proposed in the biomedical research, appropriate consent must be obtained from the minor, in addition to their parent or guardian. In order to ensure that the autonomy of children is also respected, research should be conducted on older children capable of providing informed consent where possible, before considering the recruitment of younger children. Additionally, in cases concerning high-risk research, an unbiased third party (such as an independent clinical psychologist) should conduct the assessment of the child's capacity.

[xvii] Direct benefit refers to benefits of scientifically necessary procedures, and which allows the potential benefits of one scientifically necessary procedure to justify the risks of other scientifically necessary procedures (Friedman et al. 2012).[58] For clinical trials, direct benefit is predicated on appropriate animal and other pre-clinical studies having been conducted, and the information derived from those studies and related evidence must support the potential for the proposed use of the test material to provide a direct benefit to the research participant.

Recommendation 8

In research involving minors as participants, the primary consent is provided by the parents or guardian of the participant. Additionally, researchers should justify to their IRBs why their research cannot be conducted in an older population. Where possible, research should be conducted on older children capable of providing informed consent before involving younger children. In cases concerning high-risk research, an independent third party should be brought in to conduct the assessment of the child's capacity.

Sham Brain Surgery (Placebo Surgery)

3.35 Similar to other types of research, the inclusion of healthy individuals in neuroscience research may be necessary, such as in the determining of the boundary between normal and pathological states. Healthy individuals may also serve as a control group in testing the safety of interventions, such as in the case of phase I clinical trials. The assessments of risks and benefits pertaining to research involving healthy participants are markedly different from patient participants, as they will not benefit from the research directly. Thus, the risks involved in a proposed research study recruiting healthy individuals should be carefully considered before justifying their inclusion, especially in high-risk research.

3.36 Subjecting a research participant to sham surgery (placebo surgery) may be proposed as part of the control arm protocol in randomised clinical trials to evaluate the efficacy of new surgical or pharmaceutical interventions. In the context of neuroscience research, sham surgery may involve the drilling of holes in the outer layer of the skull, and the injection of a placebo (e.g. saline solution) instead of the substance under evaluation.[47] As the research participants (and the researchers, in the case of double-blinded randomised clinical trials) are not aware if they had received the intervention or control substance, it is therefore possible to discount the probability of an observed benefit being due to the placebo effect.

3.37 Sham brain surgery could hence "be the most robust method of ascertaining efficacy of invasive interventions for serious conditions…[as] alternative control methods…may fail to distinguish which effects are due to surgery rather than the active treatment".[48] It is however, a highly invasive procedure, which carries significant risk but no immediate benefit for the participant. Some measure of deception is also required for the procedure to be properly blinded.

3.38 The BAC is of the view that the application of inefficacious procedures that carry high risks, such as those involving surgical intervention with the brain, is generally ethically unacceptable. As such, sham brain surgery may only be justifiable under exceptional situations, where a more suitable control arm to ascertain the safety and efficacy of an invasive intervention cannot be designed. There should also be reason to believe that the proposed treatment is susceptible to a placebo effect, and measures should be in place to minimise the potential harm caused to participants.

3.39 By virtue of the degree of risk involved in sham brain surgeries described above, additional safeguards should be in place. One option may be to examine the inclusion of research to the list of "Restricted Research" under the HBRA 2015.[xviii]

[xviii] HBRA 2015, Section 31

3.40 Only patients who have tried and are unresponsive to standard treatment, or for whom there are no other existing treatments, should be recruited for research involving sham surgery. Such patients should also have a poor prognosis in respect of the neurological condition which is the subject of the proposed research study. Prospective participants should be properly informed that there is a sham brain surgery arm of the research study, to which they may be assigned. Details of the surgical procedure, the placebo that will be applied, and all relevant risks should be disclosed to the prospective participant. The prospective participant should be given ample time to decide whether to participate.

Recommendation 9

Except under very exceptional circumstances, such as where a more suitable control arm cannot be designed to test the safety and efficacy of an invasive intervention, sham brain surgery should not be allowed. Research involving sham brain surgery should be subject to a second stage of ethics review, conducted by an appropriate authority independent of the research institution.

Recommendation 10

During the consent taking process, prospective participants must be properly informed that they may be assigned to the control arm, provided with details about the procedure(s) involved, and understand the possible risks.

Personal Identity and Autonomy

3.41 As the brain is the seat of human consciousness and cognition, any intervention on the brain may have an impact on one's personal identity or autonomy. For instance, it has been observed that DBS may elicit changes in personality, causing some patients to act and make decisions impulsively.[49] It is worth noting that despite the side effects that DBS may have on patients' decision-making, patients have expressed their desire to continue undergoing DBS, as the therapeutic benefit was perceived to outweigh the negative impact on their behaviour and personality.

3.42 Where there is evidence that an intervention on the brain may produce a side effect on participants' personal identity or autonomy, researchers should devise a management plan that would include obtaining re-consent to continue in the research, and appropriate safeguards, if necessary, for the protection of the interests and welfare of their participants. This should be disclosed to prospective research participants as part of the consent process. Researchers should also ascertain which interests participants deem important to them, and inform prospective participants of the need to seek their re-consent should any changes in their decision-making be observed. Participants should be informed that they may withdraw from participation in the research at any point, without any prejudice or penalty to the treatment that they may receive subsequently.

3.43 Should an unforeseen personality change be observed in research participants, researchers should report such observations to their IRBs. Researchers also have the duty to assess participants' mental capacity and seek re-consent to continue with the research protocol, and consider ways to protect the interest and welfare of the participants. If necessary, surrogate decision-makers can be consulted as per provisions in the HBRA 2015 and MCA 2008.

Recommendation 11

When obtaining participants' informed consent, researchers should inform participants of the possibility of an intervention affecting a participant's personal identity or autonomy. Should any personality changes be detected in the participant, researchers should re-seek consent to continue with the intervention, and put in place appropriate safeguards necessary for the protection of the interest and welfare of their participants.

Research Involving Non-Medical Uses of Neurotechnologies

3.44 In addition to the use of neurotechnologies in human biomedical research for medical purposes (i.e. research for medical interventions), the BAC is cognisant that there is research being performed for non-medical uses of neurotechnologies. These include research conducted on healthy participants for non-medical purposes, such as consumer neuroscience research and research involving "neuroenhancements". There is also an emerging field of research involving the use of cerebral organoids. While such research may not bear lower risks as compared to neuroscience research involving medical interventions, ethical concerns have been raised over whether such research should be permitted.

Consumer Neuroscience Research

3.45 Consumer neuroscience and neuromarketing is a rising field that has contentious definitions among the academic community. However, it is generally referred to as the use of neuroscientific methods, particularly neuroimaging methods such as MRI scans and EEG coupled with the increasing ability to gather and process such data, to study consumer behaviour and the decision-making processes during purchasing. This is done to better understand psychological phenomena and emotions in purchase decisions by analysing the underlying neurobiological basis. There have been calls to distinguish between consumer neuroscience as an academic field of study and neuromarketing where the sector-specific applications are used.[50]

3.46 Neuromarketing as a field has been the subject of some controversy, raising questions regarding whether it should be permissible for academic institutions (commonly seen as existing to serve the public good) to partner for-profit companies to conduct research with a profit motive. One such example was the collaboration between Bright House and Emory University in 2002 to use fMRI for marketing research. Another such study examined the effects of visual perception of sports cars on the dopaminergic reward circuitry in male subjects compared to limousines and small cars.[51] A country that has addressed this issue is France whom, in its 2011 revision of its law on bioethics, stated that "[c]erebral imaging techniques can only be used for medical or scientific research purposes, or in the context of forensic expertise",[52] effectively banning commercial uses of neuroimaging.

3.47 The BAC is of the view that consumer neuroscience research may fall within its definition of human biomedical research, and regards it as no different from other forms of neuroscience research that have been discussed. Accordingly, consumer neuroscience research should be subject to the same guidelines and requisites as any other kinds of neuroscience research.

Research Involving Neuroenhancement

3.48 The concept of enhancement, and its distinction from therapy, has been the subject of much discussion, with little consensus. For the purpose of this discussion, the BAC considers "enhancement" and "therapy" as describing the purpose for which the techniques or interventions in question are applied, and not a description of the techniques or interventions themselves. Additionally, the condition of the subject to whom these interventions are applied are relevant to determining the purpose of their application. For example, certain medication may be used for either purpose: the BAC considers the use of methylphenidate (Ritalin®) in the treatment of a person with ADHD to be therapeutic, and the use of the same drug in someone without a similar condition for the purpose of concentration improvement to be enhancement.

3.49 This approach that takes reference from the intended purpose and subject in question is echoed in a report by the US President's Council on Bioethics. It has described enhancement 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, in order to augment or improve their native capacities and performances".[53] The BAC acknowledges that some conceptual hurdles remain in this approach, such as delineating the boundary between pathological and normal states.

3.50 Neuroenhancement raises a few key ethical issues. Research in neuroenhancement may expose individuals to unnecessary risks and unintended effects on other brain functions, which may result in mood or sense of personal identity. As neuroenhancement seeks to improve the baseline function of healthy individuals, these safety risks are more pronounced given that participants in such research are likely to be healthy.

3.51 The use of interventions (most commonly neuropharmaceutical cognitive enhancers) for the purpose of neuroenhancement in healthy children, raises additional ethical considerations. In two position papers on neuroenhancement, the US Academy of Neurology has taken the position that off-label adult neuropharmaceutical use, after consultation with a physician, is permissible, while paediatric use is unjustifiable.[54,55] They cited lack of decision-making capability, protection of best interests, and neurodevelopmental uncertainty in the paediatric population as key factors in arriving at the position articulated. Other organisations have also viewed paediatric neuroenhancement as ethically contentious due to its potential effects on personality development.[56,57]

3.52 The BAC acknowledges that neuroenhancement research, while generally involving healthy persons, may generate data or insights subsequently applicable to therapeutic applications. As neuroenhancement research involves the participation of healthy volunteers, the BAC recommends that IRBs conduct risk-benefit assessments based on the principle of proportionality with special considerations given to the invasive nature of the proposed intervention, possibility of adverse effects, age group of research participants and the impact on the self-identity or autonomy of the research participants. Additionally, IRBs should take into consideration the principle of equipoise in the above assessment.

Recommendation 12

For research involving neuroenhancement, researchers should conduct risk-benefit assessments based on the principle of proportionality with special considerations given to the degree of invasiveness, the possibility of adverse effects, age group of research participants and the impact on self-identity or autonomy to the research participants. These risk-benefit assessments should be submitted to the relevant IRB.

Cerebral Organoids

3.53 The BAC is of the view that research involving human cerebral organoids does not require any additional safeguards at this time. Despite recent scientific developments in this area, the current state of cerebral organoid development does not pose any additional ethical, legal or social issues in human biomedical research. At this time, any in vitro research conducted in Singapore involving the use of human cerebral organoids is permissible, subject to the laws and regulations governing the use of stem cells in human biomedical research, and any in vivo use of such organoids would fall under the "Restricted Research" category of the HBRA 2015.[xix]

Recommendation 13

Research involving human cerebral organoids should be regarded the same as human biomedical research involving the use of human brain tissue and subjected to the same guidelines and requisites.

[xix] HBRA 2015, Section 31

IV. Conclusion

4.1 In developing this report, the BAC has considered international practices and guidelines on neuroscience research, together with expert views on the subject. It has also carefully considered the feedback received from the public and written responses from various organisations.

4.2 Many of the issues applicable to neuroscience research discussed in this report are not fundamentally different from those encountered in human biomedical research generally, and can be addressed by existing ethical principles and guidelines. Such issues include: the principles surrounding informed consent to participate in research (other than clinical trials) for persons lacking capacity, the circumstances in which a researcher has a duty (and the extent of that duty) to return incidental findings, the issues surrounding the ethics of sham surgery, and the concerns articulated surrounding recruitment of healthy participants in research studies.

4.3 Instead, what might make neuroscience research stand apart from other areas of human biomedical research are the qualities unique to the human brain: it is the organ from which our consciousness, thoughts, emotions and personalities emanate; it controls how we interact with the world, and how we perceive the world interacts with us.

4.4 As a result, research activities that may affect the brain require researchers and IRBs to bear in mind considerations applicable to research in general. Where research in general is primarily concerned with the prevention of physical insults to participants, neuroscience research is made more complex in that an objectively small physical, biochemical or physiological insult can have a disproportionately large impact on a participant. It may render them significantly physically or cognitively impaired, or even alter the subjective experience of who they are and their understanding of what has happened to them.

4.5 Applying the above to the consent process, there is the possibility that the mental calculus applied by a consenting participant may not be the same after suffering an adverse event causing personality change, such that they would not have consented to participate in the research project if the choice were to be posed to their post-event personality, independent of hindsight.

4.6 This raises profound ethical issues and reinforces the importance of a thorough assessment by researchers and IRBs of the ethical issues relating to the use of neurotechnologies on healthy people for non-medical purposes, such as cognitive enhancement. The possibility of irreversible changes to the brain, the implications that follow, and whether such risk is proportionate in relation to the potential benefit to participants and society in general, should be considered before such research proceeds.

4.7 The BAC trusts that the recommendations made in these reports will adequately address these abovementioned concerns and provide the additional safeguards necessary to ensure the safe and ethical conduct of neuroscience research in Singapore.

GLOSSARY

Adult stem cells	Unspecialised cells present in a tissue or organ that can replicate themselves and develop into specialised cell types of that tissue or organ, or into some other cell types.
Alzheimer's disease	A degenerative brain disorder, common in the elderly, characterised by progressive deterioration of mental functions leading to impaired cognition and increased reliance on others for daily activities.
Amyotrophic lateral sclerosis	A disease that affects the nerve cells in the brain and spinal cord that control voluntary muscles and is characterised by progressive muscular weakness leading to physical disabilities.
Apathy	A lack of interest in life activities or interactions with others. Apathy can be a symptom of several neurological and psychiatric disorder or syndrome, which can become more serious if a person has a chronic condition and does not treat it.
Attention-Deficit/ Hyperactivity Disorder (ADHD)	A brain disorder marked by ongoing pattern of inattention and/ or hyperactivity that interferes with functioning or development.
Autism/Autism Spectrum Disorder (ASD)	A developmental disorder of variable severity that is characterised by difficulty in social interaction and communication and by restricted or repetitive patterns of thoughts and behaviour.
Blood-brain barrier	Selective membrane barrier that separates the circulating blood from the brain extracellular fluid.
Brain Computer Interface (BCI)	Systems that allow communication between the brain and various machines, from collecting of brain signals to interpreting them and outputting commands to a connected machine according to the brain signal received.
Central Nervous System	Part of the nervous system consisting of the brain and spinal cord.
Cerebral Organoids	Cerebral organoids are three-dimensional tissue structures derived from pluripotent stem cells which mimic the architecture and function of the brain. Human cerebral organoids have the potential to be used as models to study human brain development and disorders.
Cerebral Palsy	A group of neurological disorders that affects body movements and muscle coordination due to a brain abnormality or damage occurring at, before, or shortly after birth.
Computer Axial Tomography (CT)	A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside of the body, used to help diagnose diseases, plan treatment, or find out how well a treatment is working. The pictures are taken from different angles and are used to create three-dimensional views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly.

Deep Brain Stimulation (DBS)	The electrical stimulation of the brain by a surgically implanted medical device.
Dystonia	A neurological disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures.
Electrocorticography (ECoG)	A test that detects electrical activity in the brain by placing electrodes directly on the exposed surface of the brain.
Electroencephalography (EEG)	A test that detects electrical activity in the brain by placing electrodes on the scalp.
Embryonic stem cells	An unspecialised cell derived from an embryo that can replicate itself indefinitely and develop into all types of cells.
Essential Tremors	A neurological disorder that causes involuntary, rhythmic movements of one or more parts of the body.
Ferromagnetic implants	Implants that exhibit magnetic behaviour when a magnetic field is applied.
Functional Magnetic Resonance Imaging (fMRI)	A technique for measuring brain activity by detecting the changes in blood oxygenation and flow that occur in response to neural activity. When a brain area is more active, it consumes more oxygen and to meet this increased demand, blood flow increases to the active area. fMRI can be used to produce activation maps showing which parts of the brain are involved in particular mental processes.
General Anaesthesia	Medically induced state of unconsciousness resulting from the administration of one or more general anaesthetic agents.
Hallucination	A profound distortion in a person's perception of reality, typically accompanied by a powerful sense of reality. A hallucination may be a sensory experience in which a person can see, hear, smell, taste, or feel something that is not there. Hallucinations may occur as a result of, taking illegal drugs or alcohol, a mental illness, such as schizophrenia or due to a progressive neurological condition, such as Alzheimer's disease or Parkinson's disease.
Huntington's disease	A fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain. It deteriorates a person's physical and mental abilities and has no cure. Most people with Huntington's disease develop signs and symptoms in their 30s or 40s, but the disease may emerge earlier or later in life.
Hypersexuality	An excessive, compulsive preoccupation with sexual fantasies, urges or behaviours that is disruptive, causes social or occupational dysfunction, and may relate directly to emotional status or stress.
Induced pluripotent stem cells	An adult somatic cell, such as a human skin cell, that has been reprogrammed (or induced) into an embryonic pluripotent state.

Institutional Review Board (IRB)	IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated. An IRB is ascribed with the responsibility of reviewing, prior to its initiation, all research (whether funded or not) involving human participants and is concerned with protecting the welfare, rights, and privacy of human subjects.
Intracranial Haemorrhage	Bleeding that occurs inside the skull (cranium).
Intravenous contrast agent	A substance/dye injected to enhance the visualisation of organs or blood vessels within the body during medical imaging.
Lasting Power of Attorney (LPA)	A LPA is a legal document that allows a person who is 21 years of age or older to plan the management of his affairs in the event of a loss of mental capacity. In the LPA, the person making the LPA (known as the donor) appoints one or more persons (known as the Donee) to act and make decisions on his behalf. A Donee should be someone you trust who is reliable and competent to act on your behalf. The use of an LPA is especially important if one is a sole breadwinner for the family or is frequently beset with health problems.
Magnetic Resonance Imaging (MRI)	A medical imaging technique that uses a magnetic field and computer-generated radio waves to create detailed images of the organs and tissues in a human body.
Mania	Mental illness characterised by periods of great excitement or euphoria, delusions, and over activity.
Mental Capacity	One’s ability to make their own decisions, of which may be lowered if there is an impairment of one’s cognitive abilities.
Mesenchymal stem cells	A type of stem cell that differentiate into bone, cartilage, muscle and fat cells.
Migraine	A neurological condition that can cause multiple symptoms. It’s frequently characterised by intense, debilitating headaches. Symptoms may include nausea, vomiting, difficulty speaking, numbness or tingling, and sensitivity to light and sound. Migraines often run in families and affect all ages.
Narcolepsy	A neurological disorder that affects one’s abilities characterised by an extreme tendency to wake and sleep. People with narcolepsy have excessive, uncontrollable daytime sleepiness and may suddenly fall asleep at any time, during any type of activity.
Neural	Relating to a nerve or the nervous system.
Neuroenhancement	The use of prescription drugs or other psychoactive substances by healthy individuals who try to improve their cognitive function or mood. People may use potentially enhancing substances to either boost attention, motivation, concentration, memory, vigilance, decision-making, mood or stress perception.

Neuroimaging	Imaging of the structure or function of the nervous system.
Neuroplasticity	Ability of the brain to reorganise itself by forming new neural connections.
Neuropsychiatric	Branch of medicine that deals with mental disorders attributable to diseases of the nervous system.
Neurorehabilitation	A doctor-supervised program designed for people with diseases, injury, or disorders of the nervous system. Neurological rehabilitation can often improve function, reduce symptoms, and improve the well-being of the patient.
Obsessive-Compulsive Disorder (OCD)	A mental disorder in which a person has uncontrollable, recurring thoughts (obsessions) and/or behaviours (compulsions) that he or she feels the urge to repeat over and over.
Optogenetic tools	Genetically-encoded light-activated ion channels and pumps used to map neural circuitry.
Parkinson's disease	A neurodegenerative disease of the nervous system that mainly affects the motor system.
Peripheral Nervous System	Part of the nervous system that exists outside of the brain and spinal cord.
Positron Emission Tomography (PET)	A nuclear imaging technique using radioactive tracers that helps reveal how a person's tissues and organs are functioning. PET scans are an effective way to examine and identify various types of conditions, cancers, heart disease and brain disorder.
Post-Traumatic Stress Disorder (PTSD)	A major psychological disorder that affects many people who survive major traumatic experiences. Symptoms may include flashbacks, nightmares and severe anxiety, as well as uncontrollable thoughts about the event.
Progenitor cells	Early descendants of stem cells that can differentiate to form one or more kinds of cells but cannot divide and reproduce indefinitely.
Psychosis	Severe mental disorder in which thought, emotions are so impaired that contact is lost with external reality.
Schizophrenia	A chronic and severe mental disorder that affects how a person thinks, feels, and behaves.
Seizures	A sudden, uncontrolled electrical disturbance in the brain that can cause changes in one's behaviour, movements or feelings, and in levels of consciousness. Seizure types vary by where and how they begin in the brain.
Sham Surgery (Placebo Surgery)	A faked surgical intervention that excludes the step(s) hypothesised to be therapeutically necessary. In clinical trials, it serves as an important control in assessing surgical interventions.

Somatic cell	Any mature (or differentiated) cell in the body that is not a sperm or an egg.
Surrogate Decision Maker	A health care proxy/agent for incompetent patients (i.e. lacking mental capacity) to make personal health care decisions on their behalf.
Tetraplegia	Paralysis caused by illness or injury that results in the partial or total loss of use of all four limbs and torso.
Tinnitus	A condition of experiencing noises (e.g. ringing, clicking) in the ears or head when no external physical noise is present. The sound may seem to come from one ear or both, from inside the head, or from a distance. It may be constant or intermittent, steady or pulsating.
Tourette Syndrome (TS)	A neurodevelopmental disorder that is characterised by multiple movement (motor) tics and at least one vocal (phonic) tic. Common tics are blinking, coughing, throat clearing, sniffing and facial movements.
Transcranial Magnetic Stimulation (TMS)	The application of a magnetic field to stimulate the brain.

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ANNEXE A

CONSULTATION PAPER: ETHICAL, LEGAL AND SOCIAL ISSUES IN NEUROSCIENCE RESEARCH

Annexe A

ETHICAL, LEGAL AND SOCIAL ISSUES IN NEUROSCIENCE RESEARCH

A CONSULTATION PAPER

BIOETHICS ADVISORY COMMITTEE

SINGAPORE

9 January 2013

Annexe A

ETHICAL, LEGAL AND SOCIAL ISSUES IN NEUROSCIENCE RESEARCH

CONSULTATION PAPER

Introduction

1. Neuroscience is the study of the nervous system, which includes the brain and spinal cord, making up the central nervous system; and the peripheral nervous system, consisting of all the nerves distributed throughout the body. It is an interdisciplinary science, involving collaborations among fields such as medicine, biomedical sciences, engineering, computer science, linguistics, and psychology. Different approaches are used to better understand how the nervous system works and to find treatments for neurological disorders or injuries. Research in neuroscience includes studying the cellular, molecular, developmental, structural, functional and medical aspects of the nervous system. Most neuroscience research is aimed at understanding, preventing or treating disorders of the nervous system. Others are conducted to understand the evolution of the nervous system, or to understand how biological systems affect social processes and behaviour.

2. Neuroscience has a long history, and developments in this field have been remarkable in the past few decades. In 1878, the scientific journal “Brain” was started, as one of the first journals devoted to reporting investigations into the brain. Today, there are over a hundred journals in different disciplines devoted to various aspects of neuroscience. Together with novel neurotechnologies and advances in the fields of genomics, optics and brain imaging, neuroscience research has resulted in significant benefits for society, such as improved diagnostic methods and management of psychiatric and neurological disorders. Examples of such disorders are: stroke, Parkinson’s disease, dementia, and attention deficit hyperactivity disorder.

3. In its report on public health challenges on neurological disorders, the World Health Organisation (WHO) reported that these disorders and their sequelae were estimated to affect as many as a billion people worldwide.[i] This staggering figure, coupled with the rising cost of healthcare services, add to the severity of the burden of neuropsychiatric disorders. Although much progress has been made in recent years in the understanding of the anatomy, cell biology, and physiology of the brain, many aspects of this complex organ have yet to be uncovered, such as understanding the processes in the development of neural circuits, particularly in the young; details of neural pathways that underlie brain functions, especially in the generation of thoughts, feelings, memory and complex behaviour; and how brain functions decline with age. With new and powerful tools, valuable discoveries on how the brain functions in healthy, aging and diseased states can be expected.

4. As the brain is the seat of one’s mind, intelligence, consciousness, thoughts and emotions, research on the human brain could be seen as different from research on any other organs or tissues. The brain holds the key to unique human characteristics, and any intervention in the brain has the potential of causing physical disability or altering cognition, emotion and even personality. Major scientific and technological advances have made it possible not only to explore the human brain in greater detail, but also to modify it. As a result, ethical, legal and social concerns have been raised, giving rise to a new discipline, “Neuroethics”, to address these challenges. Simply defined, neuroethics is an interdisciplinary field examining

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[i] WHO. *Neurological Disorders: Public Health Challenges.* 2006. Page 177.

the ethical, legal and social issues arising from neuroscience, and is concerned with the implications that neuroscience research has on the individual and on society in general.

5. Some of the concerns in neuroethics relate to research in general, such as obtaining informed consent of individuals with cognitive impairment to participate in research, the safety of proposed interventions, and the privacy and other interests of research participants. However, because the brain underlies thought, emotion, and behaviour, neurotechnologies also present unique issues. For example, some interventions developed to treat neuropsychiatric disorders can enhance cognition in healthy individuals. Others might be used to alter the content of memory and thus influence our sense of identity. Some technologies are being developed outside the purview of medicine. These include the possibility of detecting deception or even "mind reading" – the ability to tell one's thoughts and feelings; and the ability to externally control behaviour.

6. The Bioethics Advisory Committee (BAC) was established by the Singapore Government in 2000 to examine ethical, legal and social issues arising from human biomedical research and its applications; and to develop and recommend policies on such issues. With increasing global and local interest in neuroscience research, the BAC formed a Neuroethics Working Group in 2011 to:

   (a) Examine the recent developments in neuroscience research and the use of neurotechnologies, with a focus on research directly involving or affecting the brain;

   (b) Identify and consider the ethical, legal and social issues arising from such developments, and their applications;

   (c) Seek public views on the developments in neuroscience and their applications; and

   (d) Make policy recommendations, where appropriate, for neuroscience research.

7. This Consultation Paper provides an overview of neuroscience research internationally and in Singapore. It briefly describes various types of neurotechnologies that influence or modify brain functions, either directly or indirectly; and highlights the main ethical, legal and social issues related to such research. The BAC will focus its attention on research that involves any intervention on the brain, or which affects the brain or mind significantly. Before making any recommendations on neuroscience research, the BAC would like to invite the public to comment on the subject. At the end of the Paper are some questions relating to the ethical, legal and social issues in neuroscience research. Interested parties are welcome to respond to these questions, or provide their comments on any other issues relating to neuroscience research.

8. The following areas will be covered:

   (a) Neuroimaging;

   (b) Brain stimulation;

   (c) Brain-computer interfaces;

   (d) Stem cell therapy; and

(e) Neuropharmaceuticals.

9. The Consultation Paper excludes areas where the ethical issues and principles for conducting such research are similar to those previously considered by the BAC, and thus can be applied accordingly, for example, brain banks and research involving brain tissue.[ii]

Neuroscience Research Internationally

10. Given the immense economic and social burden caused by the chronic and debilitating nature of many psychiatric and neurological disorders, neuroscience research has become a priority research area in many countries. Both national and international bodies recognise this importance, and various initiatives have been set up to support and promote such research, the bulk of which involves research on the brain. In addition to conducting basic and applied neuroscience research, many of the initiatives also serve to increase public knowledge and awareness of psychiatric and neurological conditions and neuroscience research. Below is a summary of neuroscience research in the US, UK and Canada.

11. In 2004, the US National Institutes of Health (NIH) united 15 of its institutes, centres and offices to accelerate neuroscience research. The NIH Blueprint for Neuroscience Research is a collaborative framework that aims to develop research tools, create research resources to be shared by the entire neuroscience community, train a new generation of cross-disciplinary neuroscientists, and to develop a cooperative framework for the institutes and centres to plan and implement their neuroscience research effort.[iii] The Blueprint Grand Challenges, which comprise the Human Connectome Project to map the connections within the healthy brain, the Grand Challenge on Pain to gain better understanding of the cellular process in pain, and the Blueprint Neurotherapeutics Network to help small labs develop new drugs for neurological disorders, were launched in 2009. Current projects include discovering novel drugs for neurological disorders, studies on neuropathic pain and neural plasticity, and tools for brain and behavioural research.

12. The UK Medical Research Council (MRC) also provides strong support for brain research. Its Neurosciences and Mental Health Board is responsible for programmes and funding in these areas, and also for a number of strategic initiatives, which include mental health, neurodegeneration, neuroimaging, brain banking, and addictions and substance misuse. In 2010, the MRC boosted its funding for cognitive neuroscience research,[iv] and committed extra funding to the UK Brain Banks Network, which it established in 2009 to provide high quality brain tissue for the conduct of cutting edge neuroscience research.[v] The Network connects UK's 10 major brain banks, and supports key initiatives on research into neurological disorders, including dementia. In addition, the MRC will fund an imaging study involving 100,000 participants of the UK Biobank, which is the world's largest study to identify the environmental and genetic factors that affect aging, including the risks of developing dementia. The study will include brain images and the feasibility phase is scheduled to begin in mid-2013.[vi]

13. Acknowledging that brain disorders pose the greatest health challenge of the twenty-first century, with one in three Canadians likely to be affected by a neurological disorder, the

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[ii] The BAC had considered the ethical, legal and social issues on research involving human tissue (which includes brain tissue) and tissue banking, in its report on Human Tissue Research (2002).

[iii] Baughman RW et al. The National Institutes of Health Blueprint for Neuroscience Research. *Journal of Neuroscience*. 26, no. 41 (2006): 10329-10331.

[iv] Medical Research Council, UK. *25 Million Funding Boost for Cognitive Neuroscience Research. News*, 10 February 2010.

[v] Medical Research Council, UK. *MRC to Fund Retrieval, Transport and Diagnosis of Donated Brains*. News, 26 March 2012.

[vi] UK Biobank. *UK Biobank Welcomes Imaging Funding*. News, 8 November 2012.

Canadian Government recently announced the creation of the Canada Brain Research Fund, providing up to $100 million for research on brain disorders.[vii] The Brain Canada Foundation will be responsible for administering the funds and finding donors and partners to match this amount. Brain Canada was established in 1999, and is the only national non-profit organisation devoted to supporting all neuroscience research. The Canadian Institutes of Health Research also supports neuroscience research through the Institute of Neurosciences, Mental Health and Addiction.

Neuroscience Research in Singapore

14. In 2007, the International Advisory Council of the Biomedical Sciences Initiative in Singapore identified neuroscience as one of five areas of research priority. This led the Agency for Science, Technology and Research (A*STAR) and Duke-NUS (National University of Singapore) Graduate Medical School to form a Neuroscience Research Partnership,[viii] which established an integrated, multi-disciplinary programme in neuroscience with a focus on translational research. The resulting Neuroscience & Behavioural Disorders Programme, one of five Signature Research Programmes at Duke-NUS Graduate Medical School, includes molecular, developmental, systems and cognitive neuroscience research.

15. Neuroscience research is actively being pursued in the universities, pharmaceutical companies, and research and healthcare institutions in Singapore. For example, the NUS Life Sciences Institute has a neurobiology/ageing programme that focuses on age-related neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease, and stroke. Also, Nanyang Technological University (Singapore) and Warwick University (UK) have set up a collaborative programme of neuroscience research,[ix] based in Singapore’s custom-built biomedical research and development hub, Biopolis. Their research includes studying how specific areas of the brain affect mood and memory, the manner in which connections between neurons are made, and examining brain function using optogenetic tools.[x] Healthcare institutions, such as the National Neuroscience Institute and the Institute of Mental Health, conduct clinical research on neurological and psychiatric disorders.

16. A major neuroscience research project is the Singapore Translational and Clinical Research in Psychosis, a $25 million five-year programme funded by the National Research Foundation.[xi] It is led by the Institute of Mental Health, in collaboration with the Genome Institute of Singapore, Singapore Clinical Research Institute, NUS, University of Melbourne, and Duke University. The main aims are to identify key genetic, biological, cognitive and social risk factors for psychotic disorders; and to establish the efficacy of a new neurocognitive enhancer in patients with schizophrenia.

17. A recent initiative is the establishment of SINAPSE (Singapore Institute for Neurotechnology: Advancing through Partnership of Scientists and Engineers), which aims to greatly advance fundamental neuroscience/neurotechnology research, promote collaborations among various institutions and fields, and encourage cutting edge technology development, medical applications and entrepreneurship. It is funded by NUS, A*STAR and the Ministry of Defence.

[vii] Health Canada. *Harper Government Announces Funding to Support Brain Research*. Press Release, 3 May 2012.

[viii] A*STAR, Singapore. *Neuroscience Research Partnership Forged Between A*STAR and Duke-NUS GMS*. Press Release, 19 October 2007.

[ix] Nanyang Technological University, Singapore. *NTU and University of Warwick Boost Brainpower in Global Neuroscience Research*. Press Release, 13 September 2012.

[x] Optogenetic tools are genetically-encoded light-activated ion channels and pumps used to map neural circuitry.

[xi] Ministry of Health and A*STAR. *S$50 Million Research Funding Awarded for Research on Eye Disease and Severe Psychotic Disorders*. Media Release, 13 May 2008.

Annexe A

Types of Neurotechnologies

A. Neuroimaging

18. Neuroimaging (or brain scanning) encompasses a variety of techniques that visualise the brain and is used for diagnosing disease, assessing brain health, examining brain functions, and understanding how activities may impact the brain. For example, brain scans can be used to assess structural brain differences; or study the biochemistry of the brain or detect activity in particular brain areas, through measuring blood flow or metabolism.

19. The following are some imaging techniques:

    (a) *Computed Axial Tomography, also known as Computed Tomography (CT)* uses low level x-rays to build a three-dimensional image of the brain. It is useful for identifying tumours and other structural abnormalities;

    (b) *Magnetic Resonance Imaging (MRI)* is a non-invasive technique for examining structures within the body through the use of a powerful magnetic field and radio waves, without the use of x-rays. Detailed images of the brain can be produced to detect tumours or structural abnormalities;

    (c) *Functional magnetic resonance imaging (fMRI)* also uses a magnetic field and radio waves, but it measures localised brain activity based on blood flow changes in the brain associated with a particular mental process. It is an increasingly popular method for studying the functional anatomy of the brain; and

    (d) *Positron Emission Tomography (PET)* is a form of molecular imaging, whereby a metabolically active radiotracer is injected into the bloodstream in order to map functional processes in the brain. The compound accumulates in the brain and its radioactive emissions, which indicates the degree of brain activity, can be detected through the production of images based on the distribution of the compound in the brain. PET can also be used to label specific molecules, such as neurotransmitter receptors in the brain, and are thus useful in studying the metabolic and neurochemical mechanisms associated with cognitive, affective and behavioural processing.

20. While CT and MRI scans are established diagnostic methods to detect structural abnormalities in the brain, the use of functional neuroimaging as a diagnostic tool for neuropsychiatric disorders is still preliminary. Functional neuroimaging techniques such as fMRI and PET have significantly transformed the study of the human brain and mind, increased our understanding of normal and diseased brains, and provided the possibility of evaluating and predicting complex human behaviour. In the clinical context, there is potential for more accurate neurological mapping, better monitoring of drug development and new approaches to disease screening, diagnosis and management; but better specificity and sensitivity of results have to be developed before functional neuroimaging can be applied meaningfully in the clinics.

21. Recent advances in the analysis of neuroimaging data have given rise to a preliminary form of "mind reading" or detection of particular perceptions, thoughts, or intentions to perform an action. A study has shown that researchers were able to determine with a significant degree of accuracy whether the participants would add or subtract the two numbers that were

presented to them, using neuroimaging data.[xii] Although real-time data analysis is presently not possible, it may become possible in future. More recently, interest in the application of neuroimaging in legal proceedings has increased. However, neuroimaging data are currently not considered as sufficiently reliable or specific to be used in the courts as evidence in criminal cases in many countries.

22. The physical risk associated with neuroimaging is relatively low compared to neurotechnologies that require a surgical procedure. For CT and PET scans, subjects are exposed to very low levels of radiation - a risk also present in other forms of radioimaging techniques, and of concern mainly for pregnant women and children. A major problem with using MRI is the effect of the strong magnetic field on implants, which could result in injury or even death. While mostly ferromagnetic implants are dangerous and persons with such implants should not undergo MRI scans, appropriate precautions can be taken with other implants to ensure safety. Complications may also arise from the use of intravenous contrast agents, which is nevertheless still low risk, except in patients with kidney problems.

B. Brain Stimulation

23. Brain stimulation is the application of an electric or magnetic stimulus to the brain to modify or improve its function. There are various techniques, the most common of which are Deep Brain Stimulation (DBS) and Transcranial Magnetic Stimulation (TMS).

Deep Brain Stimulation

24. DBS involves surgical implantation of an electrode(s) into specific regions of the brain, in order to deliver electrical impulses to modulate neural activity at the targeted site(s). The electrode(s) is connected via an insulated wire that runs down the neck under the skin, to a battery operated stimulator, which is implanted in the upper chest or abdomen. The stimulator can be switched on and off, and adjusted to the appropriate level of stimulation required.

25. DBS is approved by the US Food and Drug Administration (FDA) for the treatment of essential tremors,[xiii] dystonia,[xiv] and to relieve the debilitating symptoms of tremors, rigidity, slowed movement and walking problem in Parkinson's disease, when medication is no longer effective. DBS is currently being investigated for treatment-resistant neurological and psychiatric disorders, such as obsessive-compulsive disorder, major depression, Tourette syndrome,[xv] and chronic pain. The exact mechanism of action of DBS is still unclear, but its effects replicate that of neurosurgical lesioning. It is considered to be a better alternative compared to traditional ablative surgery, as it is in a way reversible (as electric pulses could be switched off), and less destructive.

26. As brain surgery is required for DBS, there are associated risks such as infection, anaesthesia complications, damage to healthy brain tissue and bleeding in the brain; which could be severe, leading to paralysis, speech impairment, or seizures. Other possible complications include numbness of the face or limbs, facial weakness, dizziness or change of mood.

27. Although DBS is relatively well accepted for the treatment of motor symptoms, its long-term cognitive, psychiatric and behavioural effects are not well established, as studies thus

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[xii] Haynes JD et al. Reading Hidden Intentions in the Human Brain. *Current Biology*. 17 (2007): 323-328.

[xiii] Essential tremor is a neurological disorder that causes involuntary, rhythmic movements of one or more parts of the body.

[xiv] Dystonia is a neurological disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures.

[xv] Tourette Syndrome is a neurological disorder, which usually starts in childhood, and is characterised by repetitive physical and vocal tics.

far have resulted in inconsistent conclusions. Cognitive dysfunctions have been reported in some patients who underwent DBS and were found to develop speech disturbances, and problems with attention and learning.[xvi] The use of DBS has also been implicated in causing psychiatric side effects, for example, patients have been documented to be suffering from apathy, hallucinations, and depression following treatment with DBS. Suicidal tendency is recognised as a potential risk in patients undergoing DBS. Some patients also experienced personality changes, and developed compulsive behaviour like gambling and hypersexuality. While these side effects were observed in some studies, they were not reported in others. On the other hand, there have also been reports of memory enhancements after DBS for conditions such as obesity[xvii] and epilepsy.[xviii]

Transcranial Magnetic Stimulation

28. TMS is a non-invasive method of stimulating the brain using focused, pulsed magnetic fields. An electric current is passed through an electromagnetic coil, which is placed against the patient's scalp over the area to be stimulated, to generate a magnetic field. The magnetic field passes through the scalp and skull and induces an electric current within the underlying brain.

29. TMS can be delivered as a single pulse, paired pulses or repetitive pulses. Repetitive TMS treatment has been reported to be effective in patients with major depression who have failed to respond satisfactorily to or cannot tolerate antidepressant medication. TMS is currently being studied for the treatment of other disorders such as tinnitus, obsessive compulsive disorder, schizophrenia, autism, attention deficit hyperactivity disorder, migraine, post-traumatic stress disorder, Alzheimer's disease, and Parkinson's disease. Other possible therapeutic applications of TMS include stroke rehabilitation and drug addiction. As TMS has been shown to improve some aspects of cognition, there is ongoing research to develop TMS for enhancement purposes, for example to boost memory, problem-solving capabilities and creative thinking.

30. Since it is non-invasive, TMS is generally regarded as safe. The most serious acute risk of TMS is the rare occurrence of induced seizures (0.1 to 0.6%),[xix] which has been attributed in many cases to predisposing factors such as brain lesions and past or family history of epilepsy. Other risks include fainting, and minor pains such as headache or local scalp discomfort. Minor cognitive changes have also been observed, and in depressed patients, there is a low risk of mania. Though the reported occurrence and severity of the side effects from TMS seem very low, the long-term risks are unknown.

C. Brain-Computer Interfaces

31. A brain-computer interface (BCI) is a system that allows its users to interact with their surroundings by controlling external devices such as computers, automated wheelchairs and artificial limbs solely with brain activity, without the normal intermediaries of peripheral nerves and muscles. BCIs measure brain activity associated with the user's intent and translates the recorded activity into specific commands, for example, clicking a cursor.

[xvi] Clausen J. Ethical Brain Stimulation – Neuroethics of Deep Brain Stimulation in Research and Clinical Practice. *European Journal of Neuroscience*. 32, no. 7 (2010): 1152-1162.

[xvii] Hamani C et al. Memory Enhancement Induced by Hypothalamic/Fornix Deep Brain. *Annals of Neurology*. 63 (2008): 119-123.

[xviii] Suthana N et al. Memory Enhancement and Deep-brain Stimulation of the Entorhinal Area. *New England Journal of Medicine*. 366, no. 6 (2012): 502-510.

[xix] Croarkin et al. Applications of Transcranial Magnetic Stimulation (TMS) in Child and Adolescent Psychiatry. *International Review of Psychiatry*. 23, no. 5 (2011): 445-453.

32. There are non-invasive, partially-invasive and invasive BCIs. Non-invasive electroencephalography (EEG) based BCIs consist of electrodes placed on the scalp that detect brain signals from different brain areas. It is the most widespread recording modality due to the low risk involved, but the quality of the signals detected is reduced by the scalp and skull, as well as background noise. Partially invasive electrocorticography (ECoG)-based BCIs consist of electrodes surgically placed on the surface of the brain. As these electrodes are closer to the brain, the signal detection is improved as the signals do not need to pass through the skull. Invasive intracortical-based BCIs consist of micro-electrodes surgically implanted into the brain. These are the most effective as the micro-electrodes can detect signals easily.

33. In medicine, BCI applications are typically targeted at people disabled by neuromuscular disorders such as amyotrophic lateral sclerosis,[xx] cerebral palsy[xxi] or stroke. These people have no or limited neuromuscular control, for example weak eye or limb movements. BCIs may restore basic capabilities for these people, potentially improving their quality of life drastically.

34. Clinical uses of BCI aim at providing a technological alternative to a lost function, or as a training tool for promoting adaptive neuroplasticity so as to facilitate the recovery of a lost function in a process known as neurorehabilitation. A recent trial has shown that two people with long-term tetraplegia were able to reach for and grasp objects in three-dimensional space using robotic arms that they controlled directly with brain activity through a neural interface system.[xxii] BCIs are also being explored as tools aiding neurorehabilitation after stroke, to recover lost motor functions. In such applications, a robotic aid or functional electrical stimulation of the muscles is used to execute an intended movement of the user's limb. Movement of the limb creates a feedback in the user's brain, stimulating neural plasticity and hence facilitating functional recovery of the limb.

35. Most of the outstanding achievements of BCI research remains largely confined in the laboratories, with data obtained from studies using animals or healthy human participants. Clinical trials involving people with disabilities who might potentially benefit from the use of BCIs have commenced under close supervision.

36. The risk involved in the use of BCIs depends largely on the degree of invasiveness. When an EEG-based (non-invasive) BCI is used, there is a possibility of skin infections after applying the electrodes. The risk is clearly higher with invasive methods that require brain surgery to implant the electrodes. Implants can cause brain tissue damage and the surgery itself can cause injury or lead to infections. Moreover, infections may be a long-term risk for invasive BCI users, since cables extend outside the body, and provide a potential open entry point for infection.

D. Stem Cell Therapy

37. Stem cells are cells that are able to self-renew and have the capability to differentiate into diverse specialised cell types, offering significant potential for replacement of damaged cells and restoration of brain function. It is thought that stem cells may be effective treatments for neurological disorders such as stroke, Parkinson's disease and Alzheimer's disease, which

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[xx] Amyotrophic lateral sclerosis is a disease of the nerve cells of the brain and spinal cord that control voluntary muscles, and is characterised by progressive muscular weakness leading to physical disabilities.

[xxi] Cerebral palsy refers to a group of neurological disorders that affect body movements and muscle coordination, and is due to a brain abnormality or damage occurring at, before, or shortly after birth.

[xxii] Hochberg LR et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature*. 485 (2012): 372-375.

are caused by a loss or altered function of certain brain cells, and are currently without any effective treatment.

38. The brain consists of neurons, which are highly specialised cells responsible for the processing and transmission of cellular signals; as well as other cells that maintain and support the functions of the neurons. Neural stem cells may be derived from specific areas of the brain or developed from progenitor cells from various sources such as embryonic stem cells (ESCs), bone marrow stem cells, human umbilical cord blood stem cells, and mesenchymal stem cells. Induced pluripotent stem cells (iPS cells), which are reprogrammed from differentiated somatic cells,[xxiii] have capabilities similar to ESCs. As iPS cells could be tailored to be patient-specific, i.e. originating from the specific patient, it is less likely to cause an immune reaction when transplanted back to the patient.

39. Neural stem cells could be injected directly into an affected area of the brain, where they may transform into cells that were lost or have become dysfunctional. As neural stem cells may be attracted to specific brain sites (where there is a loss or malfunction of cells) via certain chemical signals, they could also be injected into the blood stream to exert the desired effect at the site. Pharmacological interventions could be used to enhance the migration of the injected stem cells to the brain, and modulate their proliferation, differentiation, and efficacy at the site of pathology. Survival and engraftment of the transplanted neural stem cells are obstacles that have to be overcome before therapy can be effective. Researchers are trying to use tissue engineering approaches, e.g. through the use of biomaterials to provide physical protection, to improve survival. The ideal material is yet to be found and innovative technologies to efficiently deliver neural stem cells across the blood-brain barrier will also be of great value in neural stem cell therapy. Stem cells could also be engineered to correct a genetic defect before transplantation into the patient.

40. Stem cell therapy for neurological disorders is currently in the research stage and not available as a medical treatment. Many of the current stem cell clinical trials involve adult stem cells.[xxiv] The world's first clinical trial of a neural stem cell therapy for disabled stroke patients started in November 2010 in Scotland, and is still ongoing. It involves injection of neural stem cells derived from foetal stem cells into a healthy region of the brain close to the area damaged by the stroke, in hope that the injected cells will stimulate growth of new brain cells and blood vessels, as well as heal scar tissue and reduce inflammation. This trial aims to evaluate the safety of the implantation technique and to establish the side effects associated with the implantation. Based on the progress of the first phase of the trial, plans are on the way for the second phase to begin in mid-2013. This phase is expected to take up to 18 months to complete.[xxv]

41. Since neural stem cell therapy is invasive, there are significant risks involved, especially if the cells are to be injected directly into the brain. A serious concern is tumour formation arising from the inherent self-renewing and pluripotent properties of stem cells. Other possible adverse side effects include inappropriate stem cell migration, immune rejection of transplanted stem cells, and infection from viruses within transplanted cells. As with all invasive procedures, there are anaesthesia and surgical risks.

[xxiii] A somatic cell is any mature (or differentiated) cell in the body that is not a sperm or an egg.

[xxiv] Adult stem cells are unspecialised cells present in a tissue or organ, that are able to replicate themselves and develop into specialised cell types of that tissue or organ, or into some other cell types.

[xxv] ReNeuron, UK. ReNeuron Announces Further Progress with Stroke Clinical Trial. All Three Patients in Penultimate Dose Cohort Successfully Treated. Press Release, 17 October 2012.

E. Neuropharmaceuticals

42. Neuropharmaceuticals are drugs used to treat neurological and psychiatric disorders. These drugs affect the brain chemistry, impacting cognition and behaviour. They are developed to manage distressing symptoms such as poor concentration, negative emotions and mood, severe pain, diminishing memory, and impulsive behaviour, which greatly reduce the quality of life in affected individuals. Some examples of neuropharmaceuticals are modafinil (Provigil® or Nuvigil®), which is used to treat narcolepsy, methylphenidate (Ritalin®) and dextroamphetamine (Adderall®), which are used to treat attention deficit hyperactive disorder and donepezil (Aricept®) for the treatment of Alzheimer's disease.

43. Recent developments in brain imaging techniques have enabled researchers to study the link between molecular actions of drugs to specific behavioural or physiological effects in humans. In addition, the human genome project has revealed that genetic polymorphisms - gene variants that define individual variation in genetic make-up - may lead to differences not only in cognition and behaviour, but also in drug effects. Knowledge of how genetic differences may affect an individual's response to a specific drug could be used to assess the risk of adverse effects associated with taking the drug and for predicting the therapeutic efficacy of the drug, the concept behind personalised medicine.

44. Neuropharmaceuticals have side effects, which could be mild and temporary, such as dry mouth and headache; or more severe, such as vomiting, joint pain and even irregular heart rhythms or psychosis. These drugs could also be addictive, and some users experience physical or psychological symptoms when the drugs are withdrawn.

Ethical, Legal and Social Considerations in Neuroscience Research

45. Neuroscience research, like all research, involves risks. It may involve the testing of an unproven diagnostic or evaluation method, or therapy, with or without any surgical intervention. It may also involve the use of brain tissue, brain scans or personal information derived therefrom. The ethical concerns raised by the various neuroscience research and the applications of neurotechnologies, are influenced by factors such as the degree of invasiveness, the severity of and uncertainties about expected side effects, the targeted research participant population, and the nature and interpretation of research results.

46. The BAC has identified some ethical issues relating to neuroscience research, and would like to invite comments on these issues.

A. Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

47. Based on the principle of respect for persons, informed consent from participants is a fundamental requirement in human biomedical research. However, obtaining informed consent could be a major challenge in neuroscience research, because research participants may be patients with neurological or psychiatric disorders, some of whom are particularly vulnerable, and protecting them requires special consideration. If the patients are either cognitively or emotionally impaired, they may not fully understand what they are consenting to, or they may be particularly susceptible to inducement or coercion.

48. Currently, according to the Mental Capacity Act (Cap.177A, revised 2010), only a donee who has been expressly given authority under a Lasting Power of Attorney (LPA) to give or refuse consent to the carrying out or continuation of medical treatment by a health care provider, or a deputy appointed by the court under the Act, may decide on the person's participation in clinical trials. In making such decisions on personal welfare, the deputy or the donee must follow the statutory principles under the Act, viz., act in the person (donor)'s best interests,[xxvi] have regard to the guidance in the Code of Practice of the Act, carry out the donor's instructions and make decisions within the scope of authority specified in the LPA. To give consent for the person lacking capacity to participate in clinical trials, the deputy or the donee must be satisfied that:

    (a) The individual has previously indicated a willingness to participate; or

    (b) Consent would, in the judgement of the deputy or donee, have been given had the individual (not being a child), been able to make an informed choice.

49. Biomedical research other than clinical trials is not covered under the Act. A deputy or donee is obligated under the Act to put the best interests of the person whom he is responsible for first, but participation in research, particularly non-clinical studies, does not usually benefit the participant directly. Consequently, consenting to participation in research on behalf of a non-competent person cannot be defended as in the person's best interest if no clinical trial is involved, since there is no reasonable expectation of direct benefit for the person.

50. But on the other hand, there is also much valuable research, outside the category of clinical trials, that would benefit persons lacking capacity as a class, and may subsequently lead to developments that are beneficial on an individual basis. For instance, genomic research may identify genetic variants that might reveal one's predisposition to developing neurological disorders, or how one's uptake or metabolism of neuropharmaceuticals may vary. Such research may be impeded if persons lacking mental capacity are not permitted to participate. Moreover, these research may pose less risk to the participants than clinical trials, which are usually of higher risk to participants because of possible adverse effects of the tested intervention. Arguing from the principle of proportionality, if persons lacking capacity can participate in clinical trials, their involvement in research that carries less risk should also be acceptable. Therefore, should provisions be made to allow for proxy consent for these persons to participate in research that is not a clinical trial? Can potential benefits for a class of persons be a criterion for permitting research that would be of no direct benefit to the participants? If so, who may give consent on behalf of persons lacking capacity, and what safeguards should be in place to ensure the protection of these participants?

51. Moreover, since not all persons lacking mental capacity would have an LPA, should proxy consent also be allowable for participation in clinical trials that pose low risk, such as clinical trials on locally registered drugs or their congeners (i.e. variant drugs which are structurally similar to an approved drug), in the absence of an LPA?

[xxvi] With regard to best interests, the Mental Capacity Act, section 6 (7) states: "He [the deputy or donee] must consider, so far as is reasonably ascertainable –

(a) the person's past and present wishes and feelings (and, in particular, any relevant written statement made by him when he had capacity);
(b) the beliefs and values that would be likely to influence his decision if he had capacity; and
(c) the other factors that he would be likely to consider if he were able to do so."

B. Do researchers have a duty to return incidental findings? If so, under what conditions?

52. In the course of research, findings which are not related to the research aim may be detected unexpectedly. Such findings are known as incidental findings, and they may be clinically significant, i.e. have implications for the health of the research participant. Incidental findings discovered in the course of research may not be clinically reliable – for example, the resolution of research imaging may be too low for clinical validation, or researchers may not have the appropriate competency to interpret scans for clinical purposes. Disclosing incidental findings which are not clinically validated could cause unnecessary fear and anxiety to research participants. Some have also argued that individual research findings, whether clinically significant or not, should not be returned to participants because participation in research ought to be altruistic, and participants should not expect to benefit from taking part. However, the principle of respect for persons (including their autonomy, well-being and welfare) suggests that research participants should be informed when clinically significant incidental findings are discovered. But psychological harm may result if the finding turns out to be a false positive, or treatment options for such findings are limited. Therefore, respect should also be accorded to participants' "right-not-to-know". Should incidental findings found in the course of research be returned to participants? If so, under what conditions?

53. As incidental findings are fairly common in brain imaging, special consideration should be given to the handling of such findings. The prevalence increases with age and detection is more likely when high resolution methods are used. Although structural abnormalities may be apparent in brain scans, not all researchers are suitably qualified to identify, or/and confirm such findings. Therefore, should all brain scans taken for research purposes be reviewed by a suitably qualified expert?

C. Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so, under what conditons?

54. Clinical trials are needed to establish the safety and efficacy of invasive neurotechnologies as a therapeutic modality. An issue of great concern with neurotechnologies involving brain surgery (for example stem cell transplantation into the brain) is the choice of appropriate controls for clinical research. Sham surgery controls have been used in double-blinded trials to test for the efficacy of stem cells in treating Parkinson's disease.[xxvii] These studies were highly controversial, as the control group underwent the same surgical procedure as the experimental group, but no stem cells were injected into the brain. Although the inclusion of a placebo surgery arm is essential to answering some research questions, patients undergoing surgery face substantial risks, particularly in brain surgery. Sham surgery has no direct benefit for the patient and violates the principle of minimising harm to the patient. However, it has also been argued that sham surgery controls are necessary for rigorous scientific testing of novel interventions, to avoid false positive trial results. Sham surgery controlled studies could therefore be considered as acceptable, because of the potential benefit to society, so long as informed consent is obtained from participants and the research observes certain restrictions.

55. Should sham surgery controls be used in research involving invasive neurotechnologies or are there alternative experimental designs that are adequate to address the placebo effect?

[xxvii] Freed CR et al. Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease. *New England Journal of Medicine*. 344, no. 10 (2001): 710-719; and Olanow CW et al. A Double-Blind Controlled Trial of Bilateral Fetal Nigral Transplantation in Parkinson's Disease. *Annals of Neurology*. 54, no. 3 (2003): 403-414.

Are the risks and burdens to research participants in randomised clinical trials with sham surgery controls reasonable in relation to the potential benefit to society (and possibly the participant)? Is informed consent from the participant, indicating willingness to undertake the risks involved if randomly assigned to the sham surgery control arm, sufficient? If sham surgery controls are acceptable in research involving transplantation of stem cells into the brain, under what conditions are they allowable, and subject to what restrictions?

D. What factors should be considered when assessing research with neurotechnologies, in particular research where one's sense of identity may be affected?

56. As most neurotechnologies are used with the intention to modify the functioning of the brain (in order to lessen disease symptoms, manage behavioural issues, or restore lost function), there may be resulting changes to one's notion of "personal identity" - the concept of how one defines one's "self". Changes to cognition and/or personality could have consequent implications on decision making and the patient's autonomy, such that one could be thought of as no longer being one's usual self. For example, neuropsychiatric side effects have been reported in users of DBS. As the changes could be perceived differently by different patients (as either welcomed or undesirable), the relevant ethical point seems to be whether the patient considers the changes in personality, mood, behaviour or cognition brought about by the neurotechnology as disruptive.[xxviii] Given the subjectivity of the impact neurotechnologies may have on one's personal identity, how do we assess the benefits versus risks involved in research with neurotechnologies?

57. Also pertinent is whether these changes are reversible. In the case of DBS, the personality and mood changes were often temporary, or were reduced, when electrodes were repositioned. On the other hand, stem cell therapy could possibly cause irreversible personality changes in recipients. Due to difficulties in limiting or directing the precise nature or extent of their reorganisation, transplanted stem cells could possibly migrate to unintended sites of the brain, which might lead to irreversible changes in mood, behaviour and abilities. What factors should be considered when reviewing research with neurotechnologies? Under what conditions would research with neurotechnologies that may result in irreversible personality changes be ethically permissible? Should healthy individuals be recruited in such research, or should these neurotechnologies be offered only to carefully selected patients? If healthy individuals are to be included, what safeguards should be in place?

E. Should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement? If so under what conditions?

58. Enhancement is a complex concept, but it is generally understood as making one "better than well", and this could be achieved through natural or artificial means. Natural enhancement is generally acceptable, such as rigorous training to achieve sports excellence; but enhancement through artificial means, for example the use of sports performance-enhancing drugs or genetic engineering, is ethically controversial. Some neurotechnologies have the potential to improve cognitive abilities, and there is great interest in developing these technologies for the purpose of human enhancement. Is the use of neurotechnologies for the purpose of enhancement ethically permissible? Should such research be allowed, and under what conditions? Is cognitive enhancement different from other forms of enhancement, for

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[xxviii] Schermer M. Changes in the Self: the Need for Conceptual Research Next to Empirical Research. *American Journal of Bioethics,* 9, no. 5 (2009): 45-47; and Synofzik M and Schlaepfer TE. Stimulating Personality: Ethical Criteria for Deep Brain Stimulation in Psychiatric Patients for Enhancement Purposes. *Biotechnology Journal.* 3, no. 12 (2008): 1511-1520.

instance, aesthetic enhancement through cosmetic surgery?

59. In recent years, prescription neuropharmaceuticals developed for patients with psychiatric and neurological conditions have been reportedly used by healthy persons as well, for the purpose of enhancement. Healthy individuals, including students, shift workers and soldiers, use neuropharmaceuticals to improve their mood, memory, alertness and attention span. It has also been reported that academics have used modafinil to overcome jetlag, or to increase their alertness and productivity during times when they face great intellectual demands.[xxix] However, such off-label use by healthy people is a controversial issue.

60. Besides safety issues, there are also concerns about the impact of neuropharmaceuticals (and in fact, all other neurotechnologies) on personal identity. As these drugs affect brain chemistry, they may cause mood and behavioural changes such as increased impulsiveness. The long-term effects of these drugs are poorly understood, especially on children, whose brains are still developing. It is also unclear whether the changes will be reversible. When taken for prolonged periods, the dependence on drugs in order to perform or to feel good about oneself, may affect one's sense of personal identity. With widespread use of neuroenhancers, there is the concern that the standard for what would be considered as normal would be altered, calling into question whether neuroenhancers should be allowed since it may contravene the principle of sustainability. Given the unknown long-term side effects, and uncertain consequences on personal identity, should healthy individuals be involved in research on the use of neuropharmaceuticals for non-medical purposes, particularly cognitive enhancement?

61. Non-pharmacological methods of neuroenhancement are also being pursued, such as through the use of TMS. Even though it is non-invasive, given the uncertainties about the risks of using TMS, it has also been questioned if it is ethical to conduct research using TMS on healthy participants when it may pose more than "minimal risk"[xxx] to them, and the long-term impact on the brain is unknown. Should research into cognitive enhancement using neurotechnologies and involving healthy persons be allowed?

62. Recognising the potential impact that various technologies in human enhancement will have on society, the UK Academy of Medical Sciences, British Academy, Royal Academy of Engineering and the Royal Society jointly hosted a workshop in March 2012, to consider issues on human enhancement and the future of work. Some key messages in the workshop report are that over the next decade, enhancement technologies could change how people work, the implications will be complex and associated with political and social tensions that needs to be addressed, and wider public discussion should be encouraged.[xxxi]

63. The prevalent use of technologies to enhance one's ability to learn or perform tasks could lead to employers expecting their employees to improve performance, for example through taking neuroenhancing drugs. How should one react to such an expectation? How should society as a whole respond to progress in neurotechnologies? How different is this from taking strong coffee to keep alert when working continuously for long hours?

F. Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

[xxix] Sahakian BJ and Morein-Zamir S. Professor's Little Helper. *Nature*. 450 (2007): 1157-1159.

[xxx] Minimal risk refers to "an anticipated level of harm and discomfort that is no greater than that ordinarily encountered in daily life, or during the performance of routine educational, physical or psychological tasks" (BAC. *Ethics Guidelines for Human Biomedical Research: For Comments*. June 2012).

[xxxi] Academy of Medical Sciences, British Academy, Royal Academy of Engineering and Royal Society, UK. *Human Enhancement and the Future of Work*. November 2012.

64. Children are recognised as a vulnerable population, deserving special consideration to ensure that their welfare and well-being are adequately protected when participating in research, as in many other aspects of life as well. Issues of consent, and acceptable levels of risk (in relation to the expected benefits, both for the individual and society) are some matters raised by research involving children. The long-term effect that neurotechnologies may have on their developing brains is a serious concern. Should children, particularly healthy ones, be involved in research with neurotechnologies? What are the factors for consideration? On the other hand, if such experiments are not conducted at some stage, how will it ever be known whether such interventions are safe for them?

65. Should non-invasive neurotechnologies be used for non-medical purposes by children? There is a concern over the increasing use of neurohancing pills or "smart drugs" by students,[xxxii] with the hope of improving their examination scores. Given the lack of rigorous scientific testing, it is questionable if these drugs really do make one "smarter", and if so, what is their mechanism of action. As these drugs have uncertain side effects and unknown long-term impact on the brain, should its use in children be restricted? Do taking these pills amount to "cheating", and should these pills be banned for students taking examinations like some drugs in competitive sports? It has also been questioned if there is any difference between using neuroenhancers and other methods of improving alertness or cognitive skills, such as drinking coffee or having tuition. There are further concerns that weaker students may be "coerced" into taking these "smart" pills as a result of peer pressure, or even by their parents due to societal pressures. As indicated above, these drugs are not without side-effects. Whose responsibility is it to educate the public on these matters; what is the government's role? Should the non-medical use of neuroenhancers be regulated? If so, how? Similar questions can be asked for cognitive enhancement through non-pharmacological methods such as TMS.

G. Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

66. The BAC noted that most of the issues raised by neuroscience research are not very different from other types of biomedical research, or could be addressed by existing principles and guidelines on the ethical conduct of human biomedical research. For instance, informed consent for persons lacking capacity to participate in research other than clinical trials is applicable generally. The question of the extent of a researcher's duty to return incidental findings is also relevant in genomic or genetic research, where there is also a high likelihood of such findings. Stem cell therapy is being explored for other disorders besides neurological ones, and the same question about the ethical acceptability of sham surgery exists. Similarly, concern about controls involving healthy participants arises for all high risk interventions.

67. Perhaps more unusual are the ethical issues relating to the use of neurotechnologies for non-medical purposes, particularly for cognitive enhancement; though the human enhancement debate is hardly exceptional to neurotechnologies, having also been discussed in the context of genetic, stem cell and reproductive technologies. What distinguishes neurotechnologies from other types of technologies is that they may affect the *brain*, generally regarded as an exceptional human organ because it is the seat of one's mind, intelligence, consciousness, thoughts and emotions. The potential to elicit irreversible changes to personality and personal

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[xxxii] Babcock Q and Byrne T. Student Perceptions of Methylphenidate Abuse at a Public Liberal Arts College. *Journal of American College Health.* 49, no. 3 (2000): 143-145; and McCabe SE et al. Non-medical Use of Prescription Stimulants Among US College Students: Prevalence and Correlates from a National Survey. *Addiction.* 99 (2005): 96-106.

identity suggests that the use of neurotechnologies when not absolutely crucial, such as for non-therapeutic purposes of enhancement, should be subject to careful consideration and appropriate safeguards.

68. The use of neurotechnologies for “mind reading” may be an exceptional ethical issue arising from neuroscience research. With increasing sophistication of neuroimaging techniques, the human brain and mind are increasingly at risk of becoming more “transparent”. Although current methods are unable to do so, neuroimaging studies could at some point reveal one’s innermost thoughts and unconscious attitudes, and information obtained from such research could therefore be sensitive and may threaten one’s sense of privacy. Moreover, if it is possible to “read” one’s mind, the technique could be exploited for purposes such as screening of job applicants.

69. The concept of selfhood may also be challenged, when computers are integrated into thought processes. Protection of an individual’s privacy is crucial, as BCIs may reveal psychological states, traits, and mental health vulnerabilities, and it may not be in the individual’s best interest to have such personal information available to others. There are also concerns that “mind reading” may become possible through machines that can tap into the user’s private brain processes. BCIs may also pose a threat to personal autonomy, as the brain can be conditioned or disrupted with implanted technologies. Will human dignity be compromised by the detection and interpretation of subconscious brain signals? What about thought implantation – is it ethically permissible? How do we ensure that cognitive liberty and freedom of thought are not compromised during research using BCIs?

Annexe A

Invitation to Comment

Before making any recommendations on neuroscience research and its implications, the BAC would like to seek public feedback on the subject. The BAC values views from both individuals and organisations. Interested parties may specifically address the following questions, or give their comments on any of the issues presented in this Consultation Paper or relating to neuroscience research.

A. Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

B. Do researchers have a duty to return incidental findings? If so, under what conditions?

C. Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so, under what conditions?

D. What factors should be considered when assessing research with neurotechnologies, in particular research where one's sense of identity may be affected?

E. Under what conditions should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement?

F. Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

G. Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

Please send your response, together with a completed respondent's form (which can be found on the next page) to the BAC Secretariat at:
contactus@bioethics-singapore.org; or
11, Biopolis Way, #10-12, Singapore 138667.

The closing date for responses is **31 March 2013**.

Respondent's Form to the Bioethics Advisory Committee's Consultation Paper on "Ethical, Legal and Social Issues in Neuroscience Research"

Please complete and send this form, together with your response, to the BAC Secretariat at contactus@bioethics-singapore.org or 11 Biopolis Way, #10-12, Singapore 138667 by 31 March 2013.

Name : ______

Email Address : ______

Are you responding in your personal capacity or on behalf of your organisation?

☐ Personal ☐ Organisation: _____

May we include your / your organisation's response in the final report?

☐ Yes, publish my / my organisation's response

☐ Yes, but anonymously

☐ No

Would you like to receive a copy of the final report when it is published?

☐ Yes, send a digital copy to:

- ☐ the email address indicated above
- ☐ the following email address(es) : _____

☐ Yes, send a printed copy to the following mailing address(es):

_____

☐ No

Please let us know how you got to know about the consultation:

☐ Received notification by email

☐ BAC's website

☐ Newspaper: _____

☐ Others: _____

Thank you for taking the time to respond to our consultation.

Annexe A

List of Useful Documents

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ANNEXE B

CONSULTATION PAPER DISTRIBUTION LIST

Annexe B

Annexe B – Distribution List for Consultation Paper on "Ethical, Legal and Social Issues in Neuroscience Research" (Public Consultation Period: 9 January 2013 to 31 March 2013)

Research Institutions
Alexandra Hospital
Bioinformatics Institute
Biomedical Research Council
Bioprocessing Technology Institute
Changi General Hospital
Defence Medical & Environmental Research Institute @ DSO National Laboratories
Duke-NUS Graduate Medical School
Experimental Therapeutics Centre
Gleneagles CRC Pte Ltd
Genome Institute of Singapore
Institute of Bioengineering and Nanotechnology
Institute of Medical Biology
Institute of Mental Health
Institute of Molecular and Cell Biology
Johns Hopkins Singapore International Medical Centre
Khoo Teck Puat Hospital
KK Women's and Children's Hospital
Nanyang Polytechnic
Nanyang Technological University
National Cancer Centre
National Institute of Education
National Medical Research Council
National Neuroscience Institute
National University of Singapore
Ngee Ann Polytechnic
NUHS Research Office
NUHS Tissue Repository
Parkway Hospitals Singapore Pte Ltd
Raffles Hospital
Republic Polytechnic
Singapore Bioimaging Consortium
Singapore Clinical Research Institute
Singapore Eye Research Institute
Singapore General Hospital
Singapore Health Services Pte Ltd
Singapore Immunology Network
Singapore Institute for Clinical Sciences
Singapore Management University
Singapore Polytechnic
Singapore Stem Cell Consortium
SingHealth Investigational Medicine Unit
SingHealth Polyclinics
SingHealth Tissue Repository
Tan Tock Seng Hospital
Temasek Polytechnic
Thomson Medical Centre

Institutional Review Boards
Nanyang Technological University
National Healthcare Group
National University of Singapore
Parkway Independent Ethics Committee
Raffles Hospital
Singapore Health Services Pte Ltd
Singapore Management University

Other Tertiary Institutions, Clubs and Societies
Academy of Medicine
Agency for Integrated Care
Alice Lee Centre for Nursing Studies
Alzheimer’s Disease Association
Association of Women for Action and Research
Autism Association (Singapore)
Biomedical Engineering Society
Bristol-Myers Squibb (S) Pte Ltd
Clinical Neuroscience Society of Singapore
College of Family Physicians Singapore
Drew & Napier LLC
Eisai (Singapore) Pte Ltd
Eli Lilly Singapore
Epilepsy Care Group
GlaxoSmithKline Pte Ltd
Health Promotion Board
Health Sciences Authority
Healthy Aging Association
iNova Pharmaceuticals (Singapore) Pte Ltd
Lilly-NUS Centre for Clinical Pharmacology
Moleac Pte Ltd
MSD International
Muscular Dystrophy Association Singapore
National Council of Social Service
Neurovision
Novartis (Singapore) Pte Ltd
NUS Medical Society
Parkinson’s Disease Society of Singapore
Pfizer Pte Ltd
Pharmaceutical Society of Singapore
Public Guardian Board
Roche Singapore Pte Ltd
Singapore Academy of Law, Law Reform Committee
Singapore Association For Mental Health
Singapore Cancer Society
Singapore Chapter of the Society for Neuroscience
Singapore Children’s Society
Singapore Epilepsy Foundation
Singapore Hospice Council
Singapore Medical Association
Singapore Medical Council
Singapore National Academy of Sciences

Annexe B

Singapore National Stroke Association
Singapore Neuroscience Association
Singapore Nurses Association
Singapore Nursing Board
Singapore Psychiatric Association
Singapore Psychological Society
Singapore Sleep Society
Singapore Sports Council
The Caregivers' Association of the Mentally Ill
The Law Society of Singapore

Religious Organisations
Association of Muslim Professionals
Buddhist Fellowship
Graduates' Christian Fellowship (Singapore)
Hindu Advisory Board
Inter-Religious Organisation Singapore
Islamic Religious Council of Singapore (MUIS)
Jewish Welfare Board
National Council of Churches of Singapore
Sikh Advisory Board
Singapore Buddhist Federation
Singapore Chinese Buddhist Association
Singapore Humanist Society
Singapore Taoist Federation
Taoist Mission (Singapore)
The Catholic Medical Guild of Singapore
The Parsi Zoroastrian Association of Singapore
The Spiritual Assembly of the Bahá'ís of Singapore

ANNEXE C

WRITTEN RESPONSES RECEIVED DURING THE PUBLIC CONSULTATION

Annexe C

Annexe C – Written Responses to Consultation Paper On "Ethical, Legal and Social Issues in Neuroscience Research"

Organisations and Institutions

1. Association of Women for Action and Research (AWARE)

2. Catholic Medical Guild Singapore

3. Chapter of Psychiatrists, Academy of Medicine, Singapore

4. Humanist Society

5. Law Society of Singapore

6. Moleac Singapore Pte Ltd

7. Nanyang Technological University Institutional Review Board

8. National Council of Churches of Singapore

9. Representatives from the Local Cognitive Neuroscience Community

Individual Responders

10. A/Prof John Elliott M

11. Dr Gabriel Oon Chong Jin

12. Member of the public

13. Mr Muhammad Shamir Bin Abdul Rahim

1. Association of Women for Action and Research (AWARE)

ETHICAL, LEGAL AND SOCIAL ISSUES IN NEUROSCIENCE RESEARCH
A CONSULTATION PAPER

BIOETHICS ADVISORY COMMITTEE
SINGAPORE

Please refer below to answers in Blue.

Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

47. Based on the principle of respect for persons, informed consent from participants is a fundamental requirement in human biomedical research. However, obtaining informed consent could be a major challenge in neuroscience research, because research participants may be patients with neurological or psychiatric disorders, some of whom are particularly vulnerable, and protecting them requires special consideration. If the patients are either cognitively or emotionally impaired, they may not fully understand what they are consenting to, or they may be particularly susceptible to inducement or coercion.

48. Currently, according to the Mental Capacity Act (Cap.177A, revised 2010), only a donee who has been expressly given authority under a Lasting Power of Attorney (LPA) to give or refuse consent to the carrying out or continuation of medical treatment by a health care provider, or a deputy appointed by the court under the Act, may decide on the person's participation in clinical trials. In making such decisions on personal welfare, the deputy or the donee must follow the statutory principles under the Act, viz., act in the person (donor)'s best interests, have regard to the guidance in the Code of Practice of the Act, carry out the donor's instructions and make decisions within the scope of authority specified in the LPA. To give consent for the person lacking capacity to participate in clinical trials, the deputy or the donee must be satisfied that:
    (a) The individual has previously indicated a willingness to participate; or
    (b) Consent would, in the judgement of the deputy or donee, have been given had the individual (not being a child), been able to make an informed choice.

49. Biomedical research other than clinical trials is not covered under the Act. A deputy or donee is obligated under the Act to put the best interests of the person whom he is responsible for first, but participation in research, particularly nonclinical studies, does not usually benefit the participant directly. Consequently, consenting to participation in research on behalf of a non-competent person cannot be defended as in the person's best interest if no clinical trial is involved, since there is no reasonable expectation of direct benefit for the person.

50. But on the other hand, there is also much valuable research, outside the category of clinical trials, that would benefit persons lacking capacity as a class, and may subsequently lead to developments that are beneficial on an individual basis. For instance, genomic research may identify genetic variants that might reveal one's predisposition to developing neurological

disorders, or how one's uptake or metabolism of neuropharmaceuticals may vary. Such research may be impeded if persons lacking mental capacity are not permitted to participate. Moreover, these research may pose less risk to the participants than clinical trials, which are usually of higher risk to participants because of possible adverse effects of the tested intervention. Arguing from the principle of proportionality, if persons lacking capacity can participate in clinical trials, their involvement in research that carries less risk should also be acceptable. Therefore, should provisions be made to allow for proxy consent for these persons to participate in research that is not a clinical trial? Can potential benefits for a class of persons be a criterion for permitting research that would be of no direct benefit to the participants? If so, who may give consent on behalf of persons lacking capacity, and what safeguards should be in place to ensure the protection of these participants?

51. Moreover, since not all persons lacking mental capacity would have an LPA, should proxy consent also be allowable for participation in clinical trials that pose low risk, such as clinical trials on locally registered drugs or their congeners (i.e. variant drugs which are structurally similar to an approved drug), in the absence of an LPA?

Response from AWARE

A person with lacking mental capacity could participate in research if:

- Consent is obtained via processes established in the Mental Capacity Act. Steps must also be taken to ensure that the individual, or the donee or deputy representing the individual is made fully aware of the purpose of the research, the procedures and all side effects, if any.
- The research must have some basis or motive that will benefit persons lacking capacity as a class
- The individual's dignity remains intact and the individual is not to be placed at risk. There must also be a guarantee that someone other than the investigator will assess the risks of the proposed research.
- Safeguards are in place for foreseen and/or unforeseen negative implications that the individual may encounter as a result of participating in the research. These safeguards can be in the form of compensation or coverage of medical expenses. The individual should be covered both during the period of the research and after the completion of the research.
- The individual is free to opt out of the study at any time

Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

64. Children are recognised as a vulnerable population, deserving special consideration to ensure that their welfare and well-being are adequately protected when participating in research, as in many other aspects of life as well. Issues of consent, and acceptable levels of risk (in relation to the expected benefits, both for the individual and society) are some matters raised by research involving children. The long-term effect that neurotechnologies may have on their developing brains is a serious concern. Should children, particularly healthy ones, be involved in research with neurotechnologies? What are the factors for consideration? On the other hand, if such experiments are not conducted at some stage, how will it ever be known whether such interventions are safe for them?

65. Should non-invasive neurotechnologies be used for non-medical purposes by children? There is a concern over the increasing use of neurohancing pills or "smart drugs" by students, with the hope of improving their examination scores. Given the lack of rigorous scientific

testing, it is questionable if these drugs really do make one "smarter", and if so, what is their mechanism of action. As these drugs have uncertain side effects and unknown long-term impact on the brain, should its use in children be restricted? Do taking these pills amount to "cheating", and should these pills be banned for students taking examinations like some drugs in competitive sports? It has also been questioned if there is any difference between using neuroenhancers and other methods of improving alertness or cognitive skills, such as drinking coffee or having tuition. There are further concerns that weaker students may be "coerced" into taking these "smart" pills as a result of peer pressure, or even by their parents due to societal pressures. As indicated above, these drugs are not without side effects. Whose responsibility is it to educate the public on these matters; what is the government's role? Should the non-medical use of neuroenhancers be regulated? If so, how? Similar questions can be asked for cognitive enhancement through non-pharmacological methods such as TMS.

Response from AWARE

The same criteria must be considered for children as stated above, with additional precautions including:

- Consent for participation should be given by the child itself and both parents and/or legal guardians and not only one parent as currently stated in the MCA
- The age of child should be defined according to the United Nations Convention on the Rights of the Child.
- Neurohancing pills could be listed and regulated under the same laws for drugs/medication and therefore should not be allowed for children unless otherwise advised by a medical professional.
- If the effectiveness of the drugs/"smart" pills has not been proven to be affective how is it possible to consider it as cheating?
- Students, children and parents must be made aware of the implication of using "smart" pills. Campaigns by authorities like the Ministry of Health could coincide in the same line as anti-drug education.
- TMS for cognitive enhancement as stated in this paper is still ongoing research. Therefore TMS availability to the public and effectiveness is questionable.

Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

66. The BAC noted that most of the issues raised by neuroscience research are not very different from other types of biomedical research, or could be addressed by existing principles and guidelines on the ethical conduct of human biomedical research. For instance, informed consent for persons lacking capacity to participate in research other than clinical trials is applicable generally. The question of the extent of a researcher's duty to return incidental findings is also relevant in genomic or genetic research, where there is also a high likelihood of such findings. Stem cell therapy is being explored for other disorders besides neurological ones, and the same question about the ethical acceptability of sham surgery exists. Similarly, concern about controls involving healthy participants arises for all high risk interventions.

67. Perhaps more unusual are the ethical issues relating to the use of neurotechnologies for non-medical purposes, particularly for cognitive enhancement; though the human enhancement debate is hardly exceptional to neurotechnologies, having also been discussed in the context

of genetic, stem cell and reproductive technologies. What distinguishes neurotechnologies from other types of technologies is that they may affect the brain, generally regarded as an exceptional human organ because it is the seat of one's mind, intelligence, consciousness, thoughts and emotions. The potential to elicit irreversible changes to personality and personal identity suggests that the use of neurotechnologies when not absolutely crucial, such as for non-therapeutic purposes of enhancement, should be subject to careful consideration and appropriate safeguards.

68. The use of neurotechnologies for "mind reading" may be an exceptional ethical issue arising from neuroscience research. With increasing sophistication of neuroimaging techniques, the human brain and mind are increasingly at risk of becoming more "transparent". Although current methods are unable to do so, neuroimaging studies could at some point reveal one's innermost thoughts and unconscious attitudes, and information obtained from such research could therefore be sensitive and may threaten one's sense of privacy. Moreover, if it is possible to "read" one's mind, the technique could be exploited for purposes such as screening of job applicants.

69. The concept of selfhood may also be challenged, when computers are integrated into thought processes. Protection of an individual's privacy is crucial, as BCIs may reveal psychological states, traits, and mental health vulnerabilities, and it may not be in the individual's best interest to have such personal information available to others. There are also concerns that "mind reading" may become possible through machines that can tap into the user's private brain processes. BCIs may also pose a threat to personal autonomy, as the brain can be conditioned or disrupted with implanted technologies. Will human dignity be compromised by the detection and interpretation of subconscious brain signals? What about thought implantation – is it ethically permissible? How do we ensure that cognitive liberty and freedom of thought are not compromised during research using BCIs?

Response from AWARE

To ensure protection of an individual privacy:

- Confidentiality agreement, the individual identity and researched findings must remain confidential and only be used for the purpose of the reached.
- The effects from the research programme, if any, should not put the individual participator at harm or lead the participator to inflict harm on others.

2. Catholic Medical Guild Singapore

26th March 2013

Response to the Bioethics Advisory Committee's Ethical Guidelines for Human Biomedical Research by the Catholic Medical Guild of Singapore

Dear Members of the BAC,

Thank you for inviting comments on your consultation paper on the ethical, legal and social issues in neuroscience research released on 9 January 2013. We would like to respond to the questions posed.

A. Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

As you have rightly mentioned, informed consent from participants is a "fundamental requirement" in biomedical research. The law has also allowed under the Mental Capacity Act, legal power of attorney for a deputy to decide in the place of a person lacking mental capacity whether or not to give or refuse consent based on the donor's best interests. However, this does not mean that the process is not without its problems. Based on the Mental Capacity Act, the deputy has to satisfy that 1) the individual has previously indicated a willingness to participate, and 2) that consent would have been given had the individual been able to make an individual choice. Even if the deputy can satisfy point 1 and show that the donor had indeed indicated a willingness to participate, he or she still faces two problems. The first is that the donor may have changed his or her mind in the time that has passed since professing his or her initial intent. In such a case, by following the initial expressed wish, the deputy would have made an erroneous judgment on behalf of the donor. Secondly, true informed consent entails the freely given consent by the patient, with the patient having understood the nature, risks, benefits, alternatives and limitations of the proposed treatment. In this sense, proxy consent can never be considered informed consent in the full sense of the term since it is almost always never the case that the donor has shown full understanding of the nature, risks, benefits, alternatives and limitations of the proposed treatment or research. Given that there is no true informed consent, there must be sufficiently grave reasons to allow for proxy consent. Most often, proxy consent is made for therapeutic treatments that are necessary for the good, namely the health, of the patient. In such cases, since there is no informed consent in the full sense of the term, the proxy is not really giving informed consent on behalf of the patient. Rather, the proxy is actually giving personal consent as one who is morally responsible for the care of the mentally incompetent person.

It is debatable then whether or not a proxy can give consent on behalf of an incompetent person for non-therapeutic purposes or purposes that have no direct benefit to the patient concerned as it does not fulfil the informed consent necessary for the principle of respect for persons to be upheld.

In the Declaration of Helsinki, which was enacted in response to the many atrocities committed to handicapped and vulnerable people in the name of science and research, it is stated that "medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research".

Annexe C

It is our view that proxy consent for incompetent persons for non-therapeutic purposes should not be allowed except in cases in which there is reasonable likelihood that the disadvantaged or vulnerable population involved stands to benefit from the result of a properly conducted clinical trial.

B. Do researchers have a duty to return incidental findings? If so, under what conditions?

It is our view that prudential clinical judgment needs to be exercised here. As the BAC report mentioned, the principle of respect for persons and their welfare demands that significant findings should be informed. We agree with that. However, there was also the concern about the participant's "right-not-to-know" and about psychological harm if the findings are false positive.

We suggest that in order to avoid these dilemmas, the participants and/or their proxies should be informed of the possibility of such incidental findings in writing before their participation in the research and be told that findings which have clinical significance will be made known to them and would be handled in the same way that incidental findings in medical practice are treated.

There are some intricacies regarding research that involves medical practitioners and those that do not in cases whereby the patient wishes to exercise his or her right not to know clinically significant incidental findings. Some might say that if the researcher is a medical practitioner, then he or she would still be ethical and professionally bound to investigate such findings, whereas if he or she is not one, then he or she would not have professional or ethical duty to report it. However, the Declaration of Helsinki is clear when it states in statements 2 and 3, " although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles"; and "it is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty". Based on this, it would seem that the distinction between medical practitioners and non-medical practitioners is an unnecessary one and that all research should handle the health of the participants with utmost care. As such, participants who want to exercise their right not to know clinically significant findings should be counselled and be informed that their participation in such research ethically warrants the mandatory informing and investigation of clinical significant findings.

Following from the above discussion, the next question, "Should all brain scans taken for research purposes be reviewed by a suitably qualified expert", can be answered with a clear affirmative. In Section 16, of the Declaration of Helsinki, it is stated that, "medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional".

C. Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so, under what conditions?

As the BAC report rightly states, "sham surgery has no direct benefit to the patient and violates the principle of minimizing harm to the patient". We could add that sham surgery not only does not have direct benefit to the patient, it can cause harm to the patient. This clearly violates the principle of beneficence and non-maleficence and further risks serious complications of the procedure such as infection, bleeding and anaesthetic risks to the patient.

Here, the risks surely outweigh the benefits of such a procedure. Furthermore, there are other methods of scientific research that can be used that are clearly within ethical boundaries. Furthermore, even if a subject indicates willingness to undertake such risks, prudential judgment would incline the researcher to send this person for psychological testing before allowing him or her to proceed. It is no wonder that no ethics committee would ever allow sham surgery in research in any part of the body, let alone on the brain. As such, we recommend that under no circumstances should sham surgery be allowed in research.

D. What factors should be considered when assessing research with neurotechnologies, in particular research where one's sense of identity may be affected?

Rene Descartes once said, "I think, therefore I am". While we do not necessarily agree with everything that Descartes had said, this statement of his reflects a truth about the importance and centrality of one's mind to one's being. The BAC paper also states something similar in no. 67, where it says that the brain is generally regarded as an "exceptional human organ" because it is "the seat of one's mind, intelligence, consciousness, thoughts and emotions". The fact that neurotechnological research may affect one's sense of identity should certainly make one question if the research is worth doing given the potential to affect something so personal and important to one's sense of meaning and purpose. Occasionally, neurotechnology such as deep brain stimulation has been used as a last resort therapy for debilitating diseases such as Parkinson's disease when all other conventional treatments have failed. In these cases, the principle of proportionality holds whereby the risks of the side-effects of personality or identity changes are weighed against a severe debilitating disease which has failed to respond positively to all other known treatments. However, the same cannot be said for neurotechnological interventions for purposes of research, which has no therapeutic benefit for the patient. Based on the principles of proportionality and non-maleficence, under no circumstances should non-therapeutic research with neurotechnologies that may result in irreversible personality changes be permitted.

E. Should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement? If so, under what conditions?

First of all, if enhancement refers to the action of making human beings radically different by enabling them to go significantly beyond the range of the developmental patterns, traits, and abilities that is currently observed and experienced presently in human beings such as through the use of technology to eliminate the human aging process and thereby to extend human lives indefinitely, then such research should be considered unethical from the Christian point of view since it goes beyond what human beings are responsible for in participating in God's creative activity.

If however, it qualifies more towards non-preventive optimization, which refers to the pursuit of some excellence within the range of possible human variations in development, traits, and abilities, then, it is only ethical if it does not (1) adversely affect the overall well-being or development of individuals by harming them physically, psychologically, or socially; or (2) undermine the principle of equal intrinsic dignity of all human beings, which entails enabling all human beings to share in the common good, that is, the good of the community considered as a whole, especially taking care of vulnerable people and others who have been excluded or are at risk of being excluded from participating in society.

In this light, the BAC paper has rightly pointed out that pharmacological and non-pharmacological neuro-enhancement methods often risk the mood, behaviour, personality and changes in identity to the person. Furthermore, the long-term ramifications of such treatment are often not well described. Given these risks, the principles of proportionality and non-maleficence would hold and such research should not be carried out on healthy individuals.

F. Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

As the BAC rightly pointed out, not only are children recognized as a vulnerable population and as such deserving of special consideration and protection, they also have developing brains which would make neuro-technological research a particularly serious concern in them. As such, neuro-technological research done for non-therapeutic purposes should especially not be permitted in this group given the risks involved. Furthermore, the issues surrounding informed consent for mentally incompetent persons also hold true for children.

Neuro-enhancing drugs should be prohibited from being used in healthy children for the same reasons as stated above and in section E due to the possible risks. Further, the non-medical use of such products should be regulated by the health authorities in view of potential public health concerns.

G. Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

As mentioned already in Section D, the human brain in which resides the human mind is the exceptional human organ that confers one's intelligence, consciousness, thoughts and emotions. As such, it is only prudent to have additional safeguards for neuro-technological research in addition to the safeguards already in place for other types of human biomedical research. This applies particularly in research involving vulnerable populations such as children and mentally incompetent persons.

Yours Sincerely,

Dr Colin Ong,
Deputy Master of the Catholic Medical Guild of Singapore
On behalf of the Council of the Catholic Medical Guild of Singapore

3. Chapter of Psychiatrists, Academy of Medicine, Singapore

Dr Daniel Fung
Chapter of Psychiatrists

A. Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?
   - Yes they should as there is a need to study the conditions that affect mental capacity. For example understanding the development of stroke as the disease progresses may require recruitment of these individuals into research. Research should be evaluated by an IRB

B. Do researchers have a duty to return incidental findings? If so, under what conditions?
   - I think researchers should inform participants of incidental findings under all conditions. How that is explained should be carefully considered and if possible articulated in the protocol. For example, a child participant in a trial may have cognitive testing that suggest language deficits, which may not be immediately obvious but will impact on academic performance over time without intervention. Parents and child should be told but how this is done is important as well and not create excessive panic and fear.

C. Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so, under what conditions?
   - Sham treatments should be allowed as long as there are adequate safeguards enforced by the IRB. After all, unless the treatment is already demonstrated to be the main mode of treatment in which a sham treatment arm is unnecessary?

D. What factors should be considered when assessing research with neurotechnologies, in particular research where one's sense of identity may be affected?
   - The most important factor should be that the sense of identity is affected negatively. However, it is hard to define what is negative but if such research is embarked, the participants must be fully informed of the effects that are expected.

E. Under what conditions should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement?
   - Again explaining this to participants is important and cognitive enhancement is desirable but the risks should be well documented.

F. Should children be included in research involving the use of neurotechnologies? If so, under what conditions?
   - Children should be included in such research with the same caveats as any other research in children. There is a clear lack of research in children and therefore an important need to have more. Performing the research ethically is the aim, not preventing the research.

G. Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?
   - I don't think it is exceptional in that the brain is an organ of the body and it is foolhardy to think that it is a higher organ. The body works as a whole and the brain cannot function alone. Therefore the research ethics should apply to all.

4. Humanist Society

The Humanist Society (Singapore) response to the "Ethical, Legal and Social Issues in Neuroscience Research"

A. Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

The definitions of "mental capacity" or the lack of it are broad, complex and often disputed even among psychologists. How a person is deemed to be "mentally incapacitated" or functional in a society is influenced by the social environment, which in return affects the requirements, evaluation and prognosis of the condition. Mental capacity should be assessed in context with the objectives, processes and possible outcomes of the research.

Persons lacking in mental capacity should be included in research because of the potential benefits to the class of those similarly disabled. It is possible for a "mentally incapacitated" person to retain communicative ability and his/her opinion sought be consulted as much as possible, even if it requires a simplified explanation of the research to be done.

Current medico-legal practice dictates that severely incapacitated persons are represented by their next-of-kin or an appointed trustee. This arrangement might not be adequate for consent to participation in research as the representative might not have sufficient medical knowledge or competence to make a weighty decision. The interests of severely incapacitated in mental capacity might be better served by a panel of medical professionals as well as individuals from other disciplines with demonstrated intellectual and ethical standing (psychologists, ethicists, social workers etc.). The final decision for giving consent would still lie on the next-of-kin or appointed trustee, as the burden of any consequent disability of incapacitation would fall on them.

B. Do researchers have a duty to return incidental findings? If so, under what conditions?

The definition of "researchers" needs to be better defined. The investigators in clinical study, whether publicly or privately funded, owe a basic duty of care to the study participants and should inform the participants of the discovery of any co-morbidities of unexpected idiosyncratic reaction to the intervention. The participants of the clinical study could then make an informed decision whether to continue participation in the trial and/or seek treatment for the newly-diagnosed condition. Investigators involved in basic research would be bound by obligations to their employer.

C. Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so, under what conditions?

The feasibility of sham surgery in neuroscience research is doubtful as it would be difficult, if not impossible to recruit participants in a randomised controlled trial for such an invasive technique. Furthermore, it is questionable if sham surgery on humans would add to the body of knowledge on the technique-that should have been demonstrated in animal models. In situations where randomised controlled trials pose serious ethical issues (due to the risk of invasive techniques), the preoperative condition of the participants would serve as the control outcome.

D. What factors should be considered when assessing research with neurotechnologies, in particular research where one’s sense of identity may be affected?

It is paramount to accept that research into neurotechnologies not be influenced, or held back by simply by a desire to keep the brain in ‘its natural state’ in an attempt to preserve an ideal of a person - for the sole purpose of preserving the sanctity of what some may be referred to as his/her soul. Such thinking serves no purpose but to hinder scientific progress, and thus needs to be removed as a factor for consideration early.

The day-to-day state of the brain is already always in flux, and that what constitutes a person’s sense of identity, his/her personality, mood, behaviour and cognition are already subject to daily variance offered by life. As long as adequate consideration and attention is placed on achieving informed consent prior to research, there need not be extraordinary reservations in the doing of research in where one’s sense of identity may be affected.

E. Under what conditions should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement?

Firstly, it is important to understand and accept that humanity has already accepted that the sanctity of the human body is not something that should hold back research for non-medical purposes. For examples, Humanity has accepted the invention of contact lenses, tooth polishing, plastic surgery, and Lasik eye surgery, all which can be seen as non-essential enhancement of the human body’s natural state.

Generally, the road to cognitive enhancement will need to consider these 2 factors:

1.) Accessibility: Cost, and availability to all socio-economic status classes to access an equal level of cognitive enhancement is needed. We risk creating a dystopian society of “haves” and “have-nots” if access to these technologies are not avaliable to all.

2.) Reversibility: The long-term impact of neuro-enhancement is not yet known. We caution that any research done should always be performed with an eye on reversing these enhancements if necessary.

F. Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

Certain neurological conditions can only be studied in children. For instance, children with heriditary congenital diseases may not have live long enough to become independent adults. In other instances, unfortunate accidents may result in children with permanant physical or mental disability. In these cases, standard treatments may as yet still offer a poor prognosis for afflicted individuals.

Hence, it is important that research with the potential to benefit and improve the treatment of these cases be carried out on these children. However, it should be required that the parents or guardians of these children should be thoroughly briefed and educated on the scope, potential risks and outcomes of these treatments. Consent should be sought from the parents or guardians, and regular updates on the course of treatment should be provided.

G. Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

Neuroscience research is exceptional because unlike other types of research, such as behavioral studies, the methods are much more invasive and the outcome permanent and long-term. One of the ethical concerns that we have would be that if we develop technologies or drugs that can enhance cognitive capacity, how accessible would it be to the masses? Or would this just favor an elite group of people who can afford it? One can argue that we already know from rat studies that living in a stimulatory-poor environments results in a poorer degree of neuronal synapse formation compared to rats that live in stimulation-enriched environments. However, creating drugs/technologies might exacerbate these already present differences in environment.Again, we think that neuroscience ethics governing councils should carefully examine such research in case it results in increasing the rich-poor divide in today’s society.

5. Law Society of Singapore

THE LAW SOCIETY OF SINGAPORE

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Your Ref: To be advised

12 March 2013

Bioethics Advisory Committee Secretariat
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Helios
Singapore 138667

BY EMAIL & POST
Email address:
contactus@bioethicssingapore.org

Dear Sir

CONSULTATION PAPER ON ETHICAL, LEGAL AND SOCIAL ISSUES IN NEUROSCIENCE RESEARCH

1. We refer to your email dated 15 January 2013 inviting the Law Society to provide feedback on the Consultation on Ethical, Legal and Social Issues in Neuroscience Research ("BAC Neuroscience Paper").

2. The consultation was referred to an ad-hoc Committee appointed by the Law Society (the "Committee"). Their views are enclosed in Annex A.

3. The Council of the Law Society has considered the Committee's feedback and shares their views in this regard.

4. Thank you for giving the Law Society the opportunity to present our views on this matter. We would be grateful for an update after the Bioethics Advisory Committee ("BAC") has considered the feedback provided.

Yours faithfully

Michelle Woodworth Cordeiro
Director, Representation and Law Reform Department

Encl.

Cc: 1. Council
2. Committee

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ANNEX A

VIEWS OF THE AD-HOC COMMITTEE APPOINTED BY THE LAW SOCIETY

BAC Consultation Paper on Ethical, Legal and Social Issues in Neuroscience Research dated 9 January 2013

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1. The BAC Neuroscience Paper has raised some very important and pertinent questions in relation to Neuroscience Research. The members of this ad hoc committee are involved in advising and representing individuals and organizations within the healthcare industry, as part of their legal practice. Some of the members also sit as members of Institutional Review Boards (IRBs) that review clinical research proposals. The questions discussed in the BAC Neuroscience Paper are issues that members of this Ad Hoc Committee would face from time to time.

2. We intend to deal with the questions raised and provide the Ad Hoc Committee's views on the issues raised.

3. We set out below our comments on the following specific issues highlighted in the BAC Neuroscience Paper:-

Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

4. Paragraphs 47 to 51 the BAC Neuroscience Paper deals with the concerns relating to persons lacking mental capacity. Most of the members take the position that such persons belonging to a vulnerable class of individuals should only be included in clinical trials only if their interest and welfare are not compromised. The BAC Neuroscience Paper has made specific reference to the Mental Capacity Act and the fact that donees who are expressly authorized to give or refuse consent to the carrying out or continuation of medical treatment by a healthcare providers, or a deputy appointed by the Court under the Act and given the same authority, may make decisions regarding participation in clinical trials. However no reference has been made to Regulation 11(3) of the Medicines (Clinical Trials) Regulations ("Regulation"). In reality, we believe that many investigators in clinical trials continue to follow Regulation 11(3) and seek consent from parents, spouses or guardians (as the case may be) where the subjects themselves lack capacity to give consent, and the Regulation legitimizes this practice so long as there is reasonable prospect that the clinical trial will directly benefit the subject in question. If the subject has previously given authority under a Lasting Power of Attorney to consent to the carrying out or continuation of medical treatment, then the Attorney's consent should be sought but again this should be done only if the Principal Investigator ("PI") and the subject's attending physician certify that there is reasonable prospect the clinical trial will directly benefit the subject and risk of injury is at an acceptable level.

5. We are of the view that the BAC should take this opportunity to address the fact that in the vast majority of cases where the research subjects lack capacity to consent, the research is more likely to proceed on the basis of consent obtained as provided for by Regulation 11(3) rather than on any authority given to a donee or deputy under the Mental Capacity Act. Deputies acting under the Mental Capacity Act remain accountable to the Court that appoints them. If donees or deputies fail to carry out their duties and responsibilities with full regard to the subjects' best interests they have to answer to the Court and the Office of the Public Guardian may also be notified and can investigate into cases of abuse of authority. However, where consent

is obtained as provided for in Regulation 11(3), there is arguably less oversight and hence less protection for the subjects.

6. Hence we would like the BAC to consider evaluating the consistency in the approaches adopted by the Medicines (Clinical Trial) Regulations and the Mental Capacity Act and in particular, whether there is a need for Regulation 11(3) to be reviewed with a view to providing additional safeguards to protect the interests of this vulnerable group.

7. In the case of invasive neurotechnologies, we are of the view that a requirement that the PI and the attending physician certify that either there is no available proven alternative treatment or such alternative treatment is unproven or unsatisfactory for the subject in question, would be prudent.

Should researchers have a duty to return incidental findings? If so, under what conditions?

8. In paragraph 52 and 53, the question is raised as to whether there is a real need to insist that all brain scans taken for research purposes be reviewed by a suitably qualified expert. Two sub-issues arise in this question. First, the subject's "right-not-to-know" having regard to the possible psychological harm that may result if the finding turns out to be a false positive. Secondly, whether suitably qualified experts should be appointed to review these findings particularly for brain imaging which requires special expertise to interpret.

9. We are of the view that ideally subjects should be notified of clinically significant findings (incidental or otherwise) that would impact on the subjects' health or well-being. This is because such findings may have a concomitant impact and consequence for the subjects. Alternatively, the subjects may be asked if they wish to be apprised of such incidental findings and this option should be included in the Patient Informed Consent. It can be provided in the Patient Informed Consent that unless the subject informs the PI in writing that they do not wish to be notified of clinically significant incidental findings, the PI will notify the subject of such findings. In other words, all subjects will be told of clinically significant incidental findings unless they inform the PI in writing that they do not wish to receive such information on such findings.

10. The Committee is of the view that where there is a possibility for the incidental findings to be provided to the subjects, it would be necessary for a suitably qualified expert to review the brain scans. We do not think this would necessarily add to the cost of the research given the nature of the research in question involving brain imaging, the research team is likely to have a suitably qualified expert in brain imaging already on the research team.

Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so, under what conditions?

11. Most of the members of the Committee take the position that invasive sham surgeries should be avoided as it impinges on the principle of non-maleficence. It is accepted that sham surgeries offer no direct benefit to the subject. Given the significant risks of neurosurgery, it will be difficult to draw the line as to when such invasive procedures are justified when considered against the possible benefits to society (and possibly the subjects)

12. One member takes the view that this should only be allowed under very exceptional circumstances where:-

    (a) There is no other less invasive and dangerous alternative experimental design which can adequately cover the control arm;
    (b) Risks of the sham surgery are set out in detail in the Patient Informed Consent and accepted by the subject;
    (c) Risks of the sham surgery are verbally articulated to the subject in the presence of the PI and his team, his attending physician and an independent neurologist familiar with the procedure.

What factors should be considered when assessing research with neurotechnologies, in particular research where one's sense of identity may be affected?

13. The Committee is of the view that healthy individuals should not be recruited for research using neurotechnology. This is because such technology when used on subjects can lead to change in personality and physical injury. There is no good reason to subject healthy individuals to such invasive and risky procedures.

14. As for subjects that may benefit from such research, this should still be allowed only in cases where there is strong justification that the subjects are likely to benefit from the procedure and sufficient and satisfactory safeguards are put in place such as:-

    (a) The subject and family have been thoroughly advised by the research team in the presence of an independent neurologist and the subject's attending physician of the risks of such procedures including risk of personality changes, and consent is given;
    (b) The subject and family have been thoroughly advised by the research team in the presence of an independent neurologist and the subject's attending physician of the potential benefit(s) of such a procedure. If there is a possibility that there may be no benefit to the subject, the subject and family should be informed.
    (c) Satisfactory data and records have been obtained confirming that such personality changes and other associated risks may be controlled; and
    (d) Close monitoring will be carried out by the PI and his team.

Should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement? If so, under what conditions?

15. The Committee is of the view that healthy individuals should not be involved in research using neurotechnologies for non-medical purposes. Such technologies should be focused on helping those who have medical needs. As stated in paragraph 46 of the BAC Neuroscience Paper, there are serious concerns regarding how neurotechnology may have long term effects on the development of the brain.

16. The Committee is not prepared to suggest conditions under which such research may be carried out on healthy individuals.

Should children be included in research involving the use of neurotechnologies? If so, under what circumstances?

17. Unless there are exceptional circumstances, the Committee takes the view that children should not be included in research involving use of neurotechnologies. In such cases consent is likely to be given not by the subjects themselves, but by parents or legal guardians, but it will be the children who will suffer any adverse effects of the research.

18. Some members are of the view that unless the following conditions are strictly complied with, children should not be included in such research unless all of the following conditions are satisfied:-

    (a) The child's parents or legal guardian have consented in writing to the child's participation in the research and the Patient Informed Consent has fully dealt with the issue of risks of the procedure etc;
    (b) Additionally, such consent is only sought in cases where the child is in a life threatening situation because there are no other viable treatment options available to the child;
    (c) There is a reasonable prospect that clinical trial using neurotechnology will directly benefit the child; and

    (d) An independent physician has certified (b) and (c) above.

Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in additional to what is already in place for other types of human biomedical research?

19. Given the increased risks associated with neurotechnologies, greater emphasis and focus must be paid to the prospect of benefit to the subjects. The Committee takes the view that it is not enough merely to say that the subjects may or may not benefit from the procedure. The expectation is for the research team to satisfy itself that there is a reasonable prospect for the subjects to gain direct benefit. The research team must be prepared to defend its assessment that there is a reasonable prospect of direct benefit. If there is a possibility that the subject may not benefit from the procedure, the subject should be informed.

20. Secondly, such research involving invasive neurotechnology would necessarily mean increased medical costs and extended hospital stay for the subjects. There must be a separate set of more definite criteria put in place as to how such costs are to be borne as well as costs of any complications or side effects

21. Thirdly, there may be a need to put in place a requirement that before any subject is recruited for research involving neurotechnology, an independent neurologist with adequate experience in treating patients using neurotechnology should be asked to review the subject's case notes to provide a second opinion as to the subject's suitability to participate in the research as well as to evaluate if the subject does in fact have a reasonable prospect of obtaining direct benefit from participating in the research.

6. Moleac Singapore Pte Ltd

Comments from: Moleac Singapore Pte Ltd
Re: Ethical, Legal and Social Issues in Neuroscience Research

We highly commend the Bioethics Advisory Committee of Singapore for tackling this particularly difficult topic of balancing the protection of the welfare of the individual neurological patients with the need to further scientific knowledge needed to develop more effective treatments. It is a fact that discoveries of new effective treatments for neurological diseases lag behind those in other fields, particularly because of the special situations outlined in the paper.

We agree that persons who lack mental capacity should be given the opportunity to be included in research, either in clinical trials or other types of research. Certainly the protection of their rights and welfare is foremost. The current state, however, is that persons without the mental capacity to decide is assumed to be unwilling to be included in research unless they or a legal representative explicitly express their wish to participate. This, however, is untenable precisely because of the person's mental incapacity.

Considerations may have to be taken into account in certain situations. The urgency and the risk of participation in the clinical trial versus the risk of no treatment may have to be evaluated in certain specially designed clinical trials. A precedence is the ProTECT III trial (Progesterone for the Treatment of Traumatic Brain Injury) in which patients who are enrolled in the study may be provided the progesterone hormone even without consent of family members or next-of-kin, in large part because success of the drug is highly dependent on being administered to the patient as quickly as possible after sustaining a brain injury. If that person is unconscious, such as in a traumatic brain injury (TBI), they will be unable to consent for themselves.

The US FDA has created special rules for "exception from informed consent" which applies if: (a) The person is in a life-threatening situation, (b) Current treatments are unproven or unsatisfactory, (c) The study might provide direct benefit to the person, and (d) It is not possible to obtain informed consent from:

1) the person because of his or her medical condition or 2) the person's guardian because there is a very short amount of time required to treat the medical condition. A similar approach may be considered for specific clinical trials in Singapore.

Short of clinical trials, knowledge on treatments may often be obtained from non-interventional studies, such as registries, observational studies, surveys, post-authorization safety studies, and retrospective studies. When such studies/research are of very low or no risk, does not interfere with medical decision-making as regards treatment, and does not involve additional diagnostic or treatment procedure beyond what was prescribed by the treating physician, it may be reasonable to include persons lacking mental capacity without the need for full written informed consent, especially when participation in such studies are voluntary. In certain situations, consent may be implied upon their active participation, e.g. answering survey forms, agreeing to see the interviewer staff, etc. The knowledge gained from such research other than clinical trials may become crucial, especially when conventionally designed clinical trials are not suitable for mentally incapable subjects.

Thank you very much for this opportunity to comment on the paper.

Annexe C

7. Nanyang Technological University Institutional Review Board

Feedback on Bioethics Advisory Committee (BAC) Consultation Paper on Neuroscience Research

A. Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

Persons (adults and children) with diminished ability in making judgments have routinely been included in non-invasive neurocognitive and neuroimaging studies. This includes individuals with mental illness, intellectual disabilities and developmental disorders. As long as the PI has made all efforts to justify the inclusion of such populations based on the principles spelt out in the Belmont report and Helsinki declarations (particularly the risk-benefit criteria), these persons could participate with assent and consent from their legal guardian/parents. Many of the non-invasive neurocognitive and neuroimaging studies are not clinical trials and do not have direct benefits to the participants. However, results from these studies have valuable contribution to research working towards treatment solutions. It would be difficult to implement the need of a legal power of attorney in all cases to provide consent. In any event, clear information about the study and risk-benefits considerations has to be presented to the legal guardian/parents providing consent.

B. Do researchers have a duty to return incidental findings? If so, under what conditions?

There are a range of options currently in practice for handling incidental findings at different research settings depending on the nature of the research and the professional resources available. There is currently no consensus on the "best" method. Please see table 1 below (Illes et al., 2008[i]):

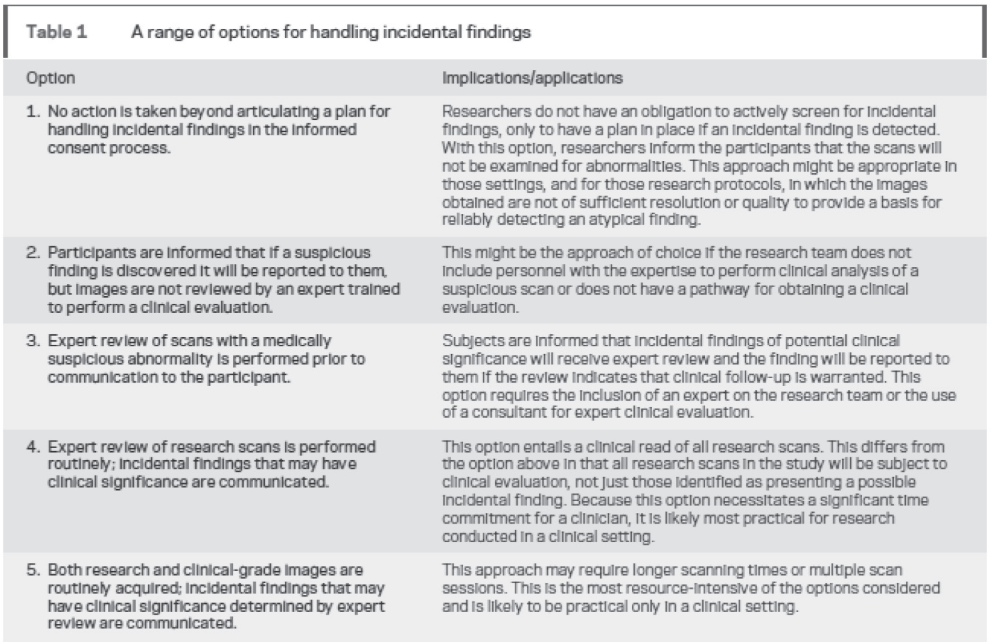

Table 1 A range of options for handling incidental findings

Option	Implications/applications
1. No action is taken beyond articulating a plan for handling incidental findings in the informed consent process.	Researchers do not have an obligation to actively screen for incidental findings, only to have a plan in place if an incidental finding is detected. With this option, researchers inform the participants that the scans will not be examined for abnormalities. This approach might be appropriate in those settings, and for those research protocols, in which the images obtained are not of sufficient resolution or quality to provide a basis for reliably detecting an atypical finding.
2. Participants are informed that if a suspicious finding is discovered it will be reported to them, but images are not reviewed by an expert trained to perform a clinical evaluation.	This might be the approach of choice if the research team does not include personnel with the expertise to perform clinical analysis of a suspicious scan or does not have a pathway for obtaining a clinical evaluation.
3. Expert review of scans with a medically suspicious abnormality is performed prior to communication to the participant.	Subjects are informed that incidental findings of potential clinical significance will receive expert review and the finding will be reported to them if the review indicates that clinical follow-up is warranted. This option requires the inclusion of an expert on the research team or the use of a consultant for expert clinical evaluation.
4. Expert review of research scans is performed routinely; incidental findings that may have clinical significance are communicated.	This option entails a clinical read of all research scans. This differs from the option above in that all research scans in the study will be subject to clinical evaluation, not just those identified as presenting a possible incidental finding. Because this option necessitates a significant time commitment for a clinician, it is likely most practical for research conducted in a clinical setting.
5. Both research and clinical-grade images are routinely acquired; incidental findings that may have clinical significance determined by expert review are communicated.	This approach may require longer scanning times or multiple scan sessions. This is the most resource-intensive of the options considered and is likely to be practical only in a clinical setting.

Currently in Singapore, several practices are in place as well:

1. Participants are informed that the neuroimaging procedures are not intended for diagnosis of medical conditions. The PI is not obligated to detect or inform participant of any abnormal findings.

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[i] Illes J, Kirchen MP, Edwards E et al. (2008) Practical approaches to incidental findings in brain imaging research, Neurology, 70; 384-390

2. Participants are asked to indicate on the consent form whether they would like to be informed about incidental findings. In the event of an incidental finding, persons who wish to be informed will be informed (either with or without electronic brain images) and suggested to consult a clinical professional or specialist. Courtesy referrals may be made upon request.

3. Some centres with adequate funding have neuroradiologists to view all images as part of the protocol. However, this puts the burden on the researcher/organization regarding actions to be taken in view of an anomaly which may not be appropriate. This may also add cost to studies without significant benefit.

The above practices are all acceptable under the various settings. Nevertheless, some recommendations to the Institutional Review Boards evaluating such research protocols will be important in terms of the key points to be made explicit in the consent form. The way incidental findings are addressed by the researcher should be based on the principles of protecting the participants' welfare and privacy and ensuring scientific integrity.

Most non-clinical neuroimaging protocols used for research with healthy participants are not comprehensive and not targeted to detect clinical conditions. Therefore, it is very important to for the investigators explicitly state that the procedure is of no diagnostic value to the participant if this is the case. The PI needs to bring up the possibility of incidental finding and make clear whether incidental findings of clinical significance or any incidental findings will be reported to the participant in the consent form (written and verbal).

Usually, research studies do not provide subsequent care for such findings (only clinical referrals as a courtesy at the most) and this also needs to be made very clear during consent. Benign cysts are not uncommon in healthy participants, however sometimes reporting this to the participant may cause unnecessary alarm where clinical attention is not needed. Therefore, the PI needs to weigh this carefully for the individual if such disclosure is decided, and safeguard procedures need to be in place for possible negative reactions. All major neuroimaging facilities conducting research studies do (or should) have a standard protocol for incidental findings however, whether to return incidental findings that are noted to have no clinical significance to the participant would depend on the PI's discretion.

C. Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so, under what conditions?

Sham intervention is an important scientific control. In these invasive studies, it is important to rule out placebo effects and possible confounds with subjective judgments of benefit from invasive neurotechnologies. However, these sham procedures should risks and discomforts to the participants. The nature of the research, alternatives and potential risks should be made clear to the participants and/or their guardians.

D. What factors should be considered when assessing research with neurotechnologies, in particular research where one's sense of identity may be affected?

The main issue here is the weight of the risks-benefits of the procedure for the participant. The definition of "one's sense of identity" can be quite broad. On one end it could be slight change in self-esteem, body image to physical and cognitive abilities and personality changes. The goal of neurotechnologies is to improve quality of life, some justifications and thought should be provided to what is considered a positive change for individuals or sample under study. The IRB involved may have to evaluate this on a case by case basis and ascertain that the information regarding the risks and benefits, alternative and possible changes are made clear to the participants and/or guardians.

E. Under what conditions should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement?

Yes. It is in fact very important to evaluate neurotechnologies that claim to have cognitive enhancement abilities in a vigorous scientific manner to rule out placebo effects and prevent false claims. The issue of whether we want to include usage of cognitive enhancers in our daily living is an ethical debate that can only be resolved at the society level and may depends on the maturity of the society to want to approach this debate.

F. Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

Children are considered a vulnerable population. Therefore, additional safeguards are taken into consideration when including them in research with the above 5 principles as minimal standards. The most crucial principle to consider carefully would be whether the benefits outweigh the costs. Proper assent from the child and consent from parents/guardian is mandatory. Most neuroscience methods applied to children are non-invasive, as they mainly measure signal changes in the brain. The invasiveness of the methodology though important may not be the ultimate factor. For example, single-pulse TMS has been considered non-invasive by the FDA, and repetitive TMS (rTMS), which has the potential to invoke epileptic seizures, when applied following the current safety guidelines have been uneventful. When evaluating the studies involving such protocols, we need to appreciate the various levels of invasiveness/risks within the cost-benefit analysis and not dismiss the consideration of using such protocols altogether. In any event, the potential risks of the procedures and the relevant safeguards in place need to be made clear to the participants during consent. The IRB evaluating such protocols should have some informed guidelines and ascertain that clear language, risks, benefits, and possible alternatives are fully communicated to the parents/guardians and participants in the consent procedure.

G. Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

The use of neurotechnologies and the nature of neuroscience research involve an intimate organ, our brain. It is judicious to want to proceed cautiously and provide safeguards to prevent possible abuse or possible compromise of the participants' rights. However, in considering the aims of neuroscience research to monitor, improve and minimize loss of function in comparison to other medical technologies, it is not much different. Therefore, the principles currently applied to human biomedical research are considered adequate.

8. National Council of Churches of Singapore

RESPONSE TO THE BIOETHICS ADVSIORY COMMITTEE'S CONSULTATION PAPER ENTITLED 'ETHICAL, LEGAL AND SOCIAL ISSUES IN NEUROSCIENCE RESEARCH' BY THE NATIONAL COUNCIL OF CHURCHES.

The National Council of Churches would like to thank the Bioethics Advisory Committee for preparing this consultation paper on neuroscience and its applications and for the invitation to respond to it. There can be no doubt that some of the most innovative and exciting work in contemporary medicine is in the area of neuroscience and its impact on psychiatry, neurology and neurosurgery. But the significant advances in the study of the human brain and the various technologies they have spawned do not only have their application in medicine. Neuroimaging in the form of computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and functional magnetic resonance imaging (fMRI) that can reveal several pathologies have also been used to ascertain the ability of an offender to control behaviour. These technologies and techniques, therefore, have profound implications to how society should respond to offenders with a diminished sense of responsibility due to compromised brain functions (for example, lesions in the orbitofrontal cortex of the brain that may result in antisocial behaviour).

In addition, accompanying the advances in neuroscience are the changing ways in which scientists and philosophers understand the relationship between the brain and the mind. This has in turn led to radical changes to the way in which we understand personhood as well as concepts like free will and responsibility. As the BAC has rightly observed, brain research must be distinguished in some significant sense from research on other tissues. This is because 'the brain is the seat of one's mind, intelligence, consciousness, thoughts and emotions'. Brain research and some of the resulting therapeutic applications are ethically controversial because, as the BAC again has perceptively pointed out, 'the brain holds the key to unique characteristics, and any intervention in the brain has the potential of causing physical disability or altering cognition, emotion and even personality' (para 4). This in itself should give us pause to reflect on the accelerating speed in which brain research is presently being conducted and the claims that neuroscience is making.

The BAC paper provides an excellent sketch of the history of neuroscience and the way in which brain research is being conducted internationally, with special reference to the US and the UK, the undisputed trailblazers for such research. The paper provides a helpful account of some of the work that is being done in the field in Singapore. It discusses the various key neurotechnologies including neuroimaging, brain stimulation and neuropharmaceuticals and presents a set of ethical questions, many of which are not exclusively associated with neurotechnologies. Totally absent from the paper, however, is a philosophical analysis and appraisal of neuroscience itself and the way in which it has urged some scientists and philosophers to conceptualise the relationship between the physical brain and the mind. Furthermore, the BAC's discussion on the various neurotechnologies is too brief to do justice to the many complex philosophical and ethical issues they raise. Because of these omissions, the BAC consultation paper in some ways fails to help readers to have a more adequate grasp of the numerous issues associated with neuroscience and its applications that have direct or indirect bearing on their ethical, social and legal implications.

In view of this, the Council's response will begin with a robust critique of neuroscience (its presuppositions and metaphysical claims) and discuss briefly the profound weaknesses of a physicalist or materialist view of the relationship between the brain and the mind. The Council will then discuss the different neurotechnologies, examining the particular ethical and metaphysical issues associated with each of them in some detail. The Council will also turn its attention to the specific ethical issues highlighted by the BAC paper, many of which are not unique to neuroscience and technology. The Council hopes that the reflections it offers in this paper would make some contribution to the wider discussion on this important topic. It also hopes that the points it raises would in some ways help the BAC to formulate its final report and recommendations.

NEUROSCIENCE: PHILOSOPHICAL ISSUES

Progress in neuroscience research has no doubt enabled us to better understand neural correlates of the mind. Researchers are beginning to identify the relationship between certain brain processes that may be said to have an influence on or are related to certain experiences which we have conceptualised as free will, moral agency and self. There are numerous studies that attempt to investigate how brain activity influences or shapes experiences like bodily self-awareness,[i] self-reflection,[ii] empathy[iii] and selfconsciousness or extraversion.[iv] While these studies have provided us with important insights on the importance of the brain in relation to the human person, it has also led to some radical changes in the way in which we understand personhood and the self. For example, there are scientists and philosophers who suggest that the self is only an epiphenomenon of brain states and the relevant structures in the brain. Thus, concepts like the ‘synaptic self’ or the ‘self-model’ theory of subjectivity see the self as merely the product of the electrochemical and computational processes in the brain and nothing more. Any ethical evaluation of the advances in neuroscience must therefore take into consideration their profound metaphysical or philosophical implications, some of which are already presented as dogma by some neuroscientists and philosophers. As we shall see, a philosophical critique of neuroscience and the materialist anthropology that is often associated with it has profound bearing on the ethical evaluation of the specific neurotechnologies. However we may wish to ignore or avoid these abstruse philosophical issues, the fact remains that our sciences and technologies are profoundly undergirded by metaphysical assumptions. This means that clarity in ethical evaluation of neurotechnology would be seriously compromised if these philosophical issues were simply brushed aside as unimportant or irrelevant.

Ontological and Methodological Reductionism

As already alluded to in the preceding paragraph, a number of neuroscientists implicitly (if not explicitly) hold a reductionist view of the relationship between the brain and the mind. Some maintain that the mind is only the epiphenomenon of the brain. Perhaps the most articulate and energetic presentation of this view comes from the pen of Francis Crick, the British molecular biologist and co-discoverer of the structure of the DNA molecule. In his now famous book, The Astonishing Hypothesis Crick famously argues that ‘“You”, your joys and your sorrows, your memories and your ambitions, your sense of personal identity and free will, are in fact no more than the behaviour of a vast assembly of nerve cells and their associated molecules’.[v] What Crick and many others are proposing in their particular view of the brain-mind relationship may be termed as ontological reductionism. Explaining this form of reductionism, Greg Peterson writes: ‘To study the brain is to study ourselves, but in a way that makes us both subject and object. It is as if we were trying to look in and out of the window at the same time’.[vi] It is also interesting to note that the European Brain Council has pledged to make 2014 the Year of the Brain. What is interesting in the context of this discussion, however, is not the fact that 2014 is chosen but the fact that it is called the Year of the Brain and not the Mind. The same is true of the designation for 1990-1999 as the Decade of the Brain by the then U.S. President George W. Bush. This perhaps

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[i] G. Berlucchi and S. Aglioti, ‘The Body in the Brain: Neural Bases of Corporeal Awareness’, *Trends Neuroscience* 1997, 20:560-564.

[ii] S.C. Johnson, L.C. Baxter, L.C. Wilder, *et el*, ‘Neural Correlates of Self-Reflection’, *Brain* 2002, 125:1808-1814.

[iii] J. Decety, P.L. Jackson, ‘The Functional Architecture of Human Empathy’, *Berhavioural Cognitive Neuroscience Review* 2004, 3:71-100.

[iv] N.I. Eisenberger, M.D. Lieberman, A.B. Satpute, ‘Personality from a Controlled Processing Perspective: an fMRI Study of Neuroticism, Extraversion, and Self-Consciousness’, *Cognitive Affective Behaivoural Neuroscience* 2005, 5:169-181.

[v] F. Crick, *The Astonishing Hypothesis* (London: Touchstone, 1995), 3.

[vi] Greg Peterson, ‘God and the Brain: The Neurobiology of Faith’, *Christian Century*, January 27, 1999.

betrays the pervasiveness of the ontological reductionism both in the scientific community as well as in the general public. As Jeffrey M. Schwartz and Sharon Begley have observed:

> It is telling that the Decade of the Brain … had that name rather than the Decade of the Mind. For it was in the brain rather than the mind that scientists and laypeople alike sought answers, probing the folds and crevasses of our gray matter for the roots of personality and temperament, mental illness and mood, sexual identity and even a predilection for fine food.[vii]

Alongside the ontological reductionism that reduces human ambitions and aspirations to neurological activities is explanatory reductionism. Again Crick has provided us with the most succinct description: 'The scientific belief is that our minds – the behaviour of our brains – can be explained by the interactions of nerve cells (and other cells) and the molecules associated with them'.[viii]

The ontological and explanatory reductionisms that we find in Crick and others have profound implications not only in the way in which we understand human beings and human behaviour. They also profoundly change the way in which we understand disease, especially mental illness. According to Thomas Fuchs, the mind-brain relation that neuroscience suggests may result in the medicalisation of some (anti)social behaviour.[ix] Because abnormal behaviour has been reduced to brain processes, Fuchs argues, it will be regarded as a medical problem and nothing more: 'Low cognitive performance becomes ADHD, shyness becomes social anxiety disorder, dissocial or criminal behaviour turns into mental illness and so on'. And with the proliferation of more efficacious psychotropic drugs with fewer side effects, the domain of illness will inevitably be enlarged. But reductionist approaches, as Fuchs has correctly pointed out, may lead to serious practical problems such as inaccurate diagnosis, because their myopic vision of what is human has prevented them from achieving a more sophisticated and holistic appreciation of the condition in question. This 'localising fallacy' as Fuchs calls it (where, for example, mental disorder is attributed only to the increased metabolic activity in certain regions of the cortex) prevents us from appreciating the fact that increased metabolic activity can be the result of disorders with different aetiologies. He also points to the fact that the relationship between the patients and their environment is seldom addressed when diagnosis is localised in the way he describes. The final difficulty is reification, where 'imaging and other methods of neuroscience tend to turn lived experience and dynamic processes into thing-like objects'.[x] As a result simplistic explanations are offered (like depression is caused by chemical imbalance) that fail either to recognise or acknowledge the causal complexity of mental disorders.

Concept of Moral Responsibility

One of the most important consequences of the reductionism in neuroscience's account of personhood or self has to do with the concept of free will. A man kills another man in a fit of rage and was arrested and charged with second-degree murder. In his defence, his lawyer points out that his client acted in this way because of a violent impulse that he simply could not control. The accused undergoes a PET scan that showed that the metabolic activity and blood flow in the frontal cortex is abnormally low. The scan also detected an abnormally high metabolic activity in and blood flow to the amygdala. Neuroscientists believe that the combination of these two factors has been closely related to uncontrollable impulses. The lawyer therefore argues that because of these abnormalities in his client's brain he should not be held responsible for his actions. He lacked free

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[vii] Jeffrey M. Schwartz and Sharon Begley, *The Mind and the Brain: The Neoplasticity and the Power of Mental Force* (New York: Harper Collins, Regan Books, 2003), 365.

[viii] Crick, *The Astonishing Hypothesis*, 11.

[ix] Thomas Fuchs, 'Ethical Issues in Neuroscience', *Current Opinion in Psychiatry* 2006, 19:604.

[x] Fuchs, 'Ethical Issues in Neuroscience', 605.

will to control his behaviour and therefore should be exonerated of his offense. The ontological and explanatory reductionisms associated with neuroscience can therefore inspire a deterministic view of human actions, emptying the concept of free will of its traditionally received meaning. Analogies of this type of argument and conclusion can be found in the narrative inspired by a certain interpretation of genetic science. Stephen Gay Gould, who is not a genetic determinist, offers a succinct account of the logic of determinism based on an ontological reductionism: 'if we are programmed to be what we are [by our genes] the [our traits are ineluctable. We may, at best, channel them, but we cannot change them either by will, education or culture'.[xi]

The liberterian concept of free will was challenged in a spectacular fashion by the famous but heavily criticised experiments counted in the 1980s by Benjamin Libet.[xii] Using a technique called event-related potentials (ERPs), Libet measured the brain activity of his subjects during voluntary hand movements. He found that between 500 and 1,000 milliseconds before his subjects moved their hands, a wave of brain activity (termed, the readiness potential) could already be detected. This means that brain activity can be detected even before his subjects consciously move their hands. This experiment therefore seems to suggest that free will, a concept that we have cherished for so long, is in fact an illusion. From his experiments Libet theorises that the time from the onset of the readiness potential to the actual hand movement is 500 ms. He argues further that it takes about 50 ms for the neural signals to travel from the brain and cause the actual hand movement. He maintains that there are only about 100 ms for the conscious self to either follow the unconscious decision or to veto it. If there is free will at all, Libet concludes, then it must be understood only as the power to veto. This has led behavioural neurologist Vilayanur Ramachandran to propose a slightly modified version of John Locke's theory of free will, namely, that 'our conscious minds may not have free will but rather "free won't"'.[xiii]

If Libet is right, the implications of his conclusions concerning mental causality to our understanding of free will are staggering. But Libet's approach and conclusions have been rightly criticised by neuroscientists and philosophers. This is not the place to offer a detail analysis and critique of Libet's work and conclusions. In what follows, we will merely highlight (in broad brush strokes) the methodological flaws of his experiments and the erroneous conclusions that they inevitably urge. From the methodological standpoint, Libet's experiments seem to be premised on a certain understanding of the timing of mental and brain events. He assumes that each type of event takes place in a discretely identifiable moment. Libet also seem to assume that human actions always begin with unconscious brain events that bring about conscious mental events. This abstract theory of causality is however challenged by the studies of the aetiology of depression, anxiety and mental illness that seem to suggest that the pathway can go in two directions.[xiv]

Libet's approach from the very start presupposes a dualistic framework that postulates that physical motor action must be preceded by a mental state that somehow acts on the body. Whether Libet is aware of it or not, the metaphysics that undergirds his paradigm of 'mental causation' is reminiscent of Cartesian dualism.[xv] But the dualistic paradigm implicit in Libet's experiments surely misses the point. That which acts is not a certain abstract mental state but the embodied subject. In other words a physical act is the act of the entire person. This means that free will can never be associated

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[xi] Stephen Gay Gould, *Ever Since Darwin* (New York: W.W. Norton, 1997), 35.

[xii] B. Libet, 'Conscious vs Neural Time', *Nature* 352 1991, 6330: 27-28; 'Do We Have Free Will?' *Journal of Consciousness Studies* 8 (1999): 8-9, 45.

[xiii] V. Ramachandran, Quoted in 'The Zombie Within', *New Scientist*, September 1998.

[xiv] Glannon, *Bioethics*, 56.

[xv] The philosopher Charles Siewart perceptively draws a parallel between Cartesian dualism and eliminative materialism when he argues that 'Descartes granted a certain privileged epistemic status to our judgements about what is "in our minds" relative to judgements about what is "outside of them", in the realm of matter. And the eliminativist recognizes a similar asymmetrical epistemic relation between the "mental" and "physical" – only the assignments of privilege and subordinate status are reversed. Our right to claims made in a mind-including ideiom is made to depend entirely on their providing the best theory of what is conceived of in a mind-excluding one, while our right to apply this latter conception does not in turn depend on what our warrant for claims about attitudes and experience'. Charles P. Siewert, *The Significance of Consciousness* (Princeton: Princeton University Press, 1998), 53.

with neurons, muscles and limbs. Rather it must be associated with rational and self-transcending beings whose actions are meaningful and purposeful. Free will, therefore, can never be attributed to mental states but to the whole person. The reductionism in Libet's approach is seen in the way in which the results of a simple experiment conducted within its narrow scope become the bases for addressing profound concepts like free will and moral responsibility. The decision to pick up a glass of water to quench a thirst is not distinguished from the decisions that we make concerning our education, our career, our politics and our health. More provocatively, can Libet's theory of 'mental causation' be used to explain the great enterprises and achievements of human civilisation and culture – art, music, architecture, philosophy, politics, and science (neuroscience)? Is it not simply too incredulous to suggest that Libetian causation is responsible for Beethoven's Fifth Symphony, the Mona Lisa and La Sagrada Familia?

The denial of free will that some materialist philosophies seem to urge not only contradicts our experience but also the very assumptions upon which we organise ourselves as a society. Take our judiciary systems. The basic and indispensable assumption of the judiciary system is that human beings possess free will and are therefore responsible for their actions. Although the concept of free will has been subjected to complex analyses in the history of philosophy, it is not unreasonable to surmise that philosophers of almost every stripe would broadly agree that free actions must have the following characteristics: (1) they can be explained by their motivations, (2) the authors of these actions must have the experience of performing them, and (3) the possibility of taking a different course of action under the same external circumstances. To say that our actions are causally determined purely by brain functions is to reject the reality of free will and turn it into an illusion. It is impossible to see how the judiciary system is necessary or meaningful if this is indeed true. In many mental disorders, first-person experience is restricted in various degrees. The aim of psychiatry and other forms of therapy in such cases is to restore autonomy and agency in the patients. One of the aims of psychotherapy is the restoration of the patient's self-determination, of at least to enable the patient to achieve greater autonomy. If free will does not exist and is only an illusion, the goal of such therapy would merely be the restitution of a 'healthy illusion', and nothing more. Ontological reductionism (and the accompanying explanatory reductionism) has led to determinism, which in turn results in fatalism.

The Mystery of Personhood

While neuroscience has undoubtedly made possible a better understanding of the relationship between the brain and the mind, concepts of personhood and the self, constructed solely on neuroscience will surely suffer from serious reductionistic distortions. According to the Christian faith, the human being cannot simply be reduced to his physical body (including his brain) without remainder. The narrative in Genesis 2 brings out the complex nature of the human being who is a psychosomatic unity: 'the Lord God formed the man from the dust of the ground and breathed into his nostrils the breath of life, and the man became a living being' (Gen 2:7). That the human being is formed from the dust of the ground shows that he is a physical and material being, whose bodily reality should never be ignored or marginalised. But the fact that God breathed into the lump of clay turning it into 'a living being' emphasise that the human being must never be understood purely in physicalist or materialistic terms. Although Christian theologians have proposed many ways of understanding the human soul, many (if not all) of them would reject a purely physicalist definition of the human being. This is not only the view of Christian theologians. It is also that of many philosophers of mind who are dissatisfied with the materialist account. Although the materialist philosophy of mind is gaining ascendency and greater acceptance in the modern discussion, the theories that reject this view – substance dualism, nonreductive physicalism, and hylomorphism (to name just a few) – are still attracting interest and rigorously debated.

Annexe C

What does it mean to reject the materialist understanding of the human being? It is to assert that just because everything is made up of matter does not mean that the human being can be ontologically reduced to his nervous system. It is to hold that although human beings are made up of different parts that are composed of certain chemical elements, these parts are not identical to the human being. In relation to neuroscience, it is to insist that even the most complex and privileged of our organs – the brain – cannot be said to be constitutive of or identical with the human being. It is to maintain that the characteristics and attributes we possess are not the characteristics and attributes of our brains. It is to maintain that to say that the human being is nothing more than just an assembly of nerve cells is as ludicrous as saying that a painting is just a collection of pigments or brush strokes.[xvi] To reject the materialist view is to reject the theory that the self is simply an epiphenomenon of brain states. It is to say that the human self is complex and dynamic, transcending itself and interacting freely and creatively with other selves and with the environment, shaped in many ways by its past and open to the future. To reduce human agency and behaviour to no more than the activities of the bundle of cells and molecules or a mass of neurons is to commit what Bennett and Hacker call the 'mereological fallacy'.

As we have seen above, the physicalist understanding of the brain-mind problem is unable to provide a satisfactory account of human free will and moral responsibility. Neither is it able to convincingly explain concepts like consciousness and self. Michael Lemonick provides a succinct summary of the way in which materialists like Francis Crick and Christoph Koch attempt to explain consciousness: 'Consciousness is somehow a by-product of the simultaneous, high-frequency firing of neurons in different parts of the brain. It's the meshing of these frequencies that generates consciousness … just as the tones from individual instruments produce the rich, complex and seamless sound of a symphony orchestra'.[xvii] This eloquent account of how consciousness may possibly arise is, by Crick's own admission, highly speculative and neuroscience, at least in its current state of development, cannot demonstrate to be the case. The fact remains that human self-consciousness cannot be directly observed.[xviii] It is impossible to locate consciousness in any part of the brain (Crick and Koch recognise this), and ipso facto it is impossible to locate it in the activity of certain neurons or in the chemistry in the neurons. In other words, there is no specific brain activity that is active when we are conscious and idle when we are not. As philosopher of mind, B. Alan Wallace, has observed:

> Despite centuries of modern philosophical and scientific research into the nature of the mind, at present there is no technology that can detect the presence or absence of any kind of consciousness, for scientists do not even know what exactly is to be measured. Strictly speaking, at present there is no scientific evidence even for the existence of consciousness! All the direct evidence we have consists of non-scientific, first-person accounts of being conscious.[xix]

The puzzle of consciousness is so insurmountable for materialists like Crick that the only way out is to assert that we are insufficiently evolved (or that evolution does not require us) to explain it:

> Our highly developed brains, after all, were not evolved under pressure of discovering scientific truths but only to enable us to be clever enough to survive and leave descendents.[xx]

[xvi] M.R. Bennett and P.M.S. Hacker, *Philosophical Foundations of Neuroscience* (London: Blackwell, 2003), 359.

[xvii] Michael D. Lemonick, 'Glimpses of the Mind', *Time*, July 17. 1995.

[xviii] Related to the problem of consciousness is that of qualia, that is, how things (the colour 'red' for instance) appear to us individually. Crick admits that science is unable to explain this phenomenon: 'It is certainly possible that there may be aspects of consciousness, such as qualia, that science will not be able to explain. We have learned to live with such limitations in the past (e.g., limitations of quantum mechanics) and we may have to live with them again', Crick, *Astonishing Hypothesis*, 258.

[xix] B. Alan Wallace, *The Taboo of Subjectivity: Religion as a Natural Phenomenon* (New York: Viking 2006), 3.

[xx] Crick, *Astonishing Hypothesis*, 262.

This is not the place to develop an alternative account (inspired by a Christian theological anthropology) of important concepts like personhood, consciousness, moral responsibility and self. The purpose of this discussion, which we must now draw to a close, is to show that neuroscience can sometimes lead to reductionist accounts of the human being (and consequently, of human mental pathology) that would have serious implications not only to the practice of medicine and the law, but also to the ways in which we understand ourselves and society. It is not unusual for protocols on neuroscience and its applications to focus on the more 'practical' concerns related to ethics, the law and best practices, while totally bracketing away philosophical discussions on the presuppositions of the science and its portrait of the human being. It is the view of the Council that this philosophically uncritical approach would willy-nilly be drawn into the naïve reductionisms (ontological and explanatory) that sometimes dictate both the science and its conclusions. A truism for all human disciplines is surely especially poignant in this case: neuroscience (and neuroethics) is too important to be left only to the neuroscientists!

NEUROTECHNOLOGIES: ETHICAL ISSUES

Neuroimaging

In its discussion on diagnostic neuroimaging through the use of CT, PET, SPECT, MRI and fMRI the BAC rightly noted that these methods used to 'detect structural abnormalities in the brain' and neuropsychiatric disorders' are still 'preliminary' (para 20). The paper also pointed out that neuroimaging has also been used in recent years as the preliminary method of 'mind reading' and the 'detection of particular perceptions, thoughts, or intentions to perform an action'. It however notes that 'neuroimaging data are currently not considered as sufficiently reliable or specific to be used in the courts as evidence in criminal cases in many countries' (para 21). The BAC paper does not discuss in any great detail the ethical issues related to neuroimaging that is used either for diagnosing psychiatric disorders or recognise violent offenders. The Council maintains that such discussions are important for a consultation paper on neuroethics because it would help participants, especially those who are unfamiliar with the field, to understand the plethora of issues surrounding the use of this technology. To address this lack, the Council would like to point briefly to four main areas related to neuroimaging that require more robust analysis and reflection.

Reliability and Validity

The first issue has to do with the reliability and even the validity of brain imaging. Brain imaging techniques, such as fMRI has been used not only to map salient cortical areas before surgery, the technology is also employed to aid the diagnosis of Alzheimer's disease (AD), mental illness in adults, and pediatric pathology such as attention deficit hyperactivity disorder (ADHD). The use of fMRI has expanded to include studies of lying and deception, competition and cooperation, and brain differences in violent people. Some scientists have even used a combination of fMRI, EEG and PET to investigate the neural bases of religious experience. Others anticipate the effective use of such technologies in the legal arena. Henk Greely has summarised what many see to be the promise of neuroscience when he wrote: 'Neuroscience may provide answers to some of the oldest philosophical questions, shedding light, for example, on existence limits, and meaning of freewill. It may also provide new ways to distinguishing truth from lies or real memories from false ones. This ability to predict behaviour with the help of neuroscience could have important consequences for the judicial system as well as for society as a whole'.[xxi]

Scanning the brain to understand or even predict a particular social behaviour in the subject, however, has been criticised to be a severely problematic at various levels. At one level, the assumptions of such approaches may be shown to be just too simplistic. It may be fallacious to

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[xxi] H. T. Greely, 'Neuroethics?' *Health Law News*, July 2002, 5.

think that complex subjective experiences can be understood by simply observing electromagnetic signals derived from brain activity. For example, how far can the complex phenomenon of social attitude or behaviour be really understood by employing simple scenarios of neuroscience experiments like using video games or faces on a screen instead of real social interactions? Furthermore, as some philosophers and scientists have pointed out, the design of the study and the interpretation of its results are influenced by cultural and anthropological frameworks of those conducting the studies. As Judy Illes has put it, 'We must ask, for example, whether all studies of normative neurobehavioural phenomena are ethically acceptable. How might social or racial biases affect applications of the technology, the conditions under which imaging is performed, or the interpretations are made?'[xxii]

According to Walter Glannon, although brain imaging has increased our understanding of the neural bases of many psychological traits, it is still limited in five aspects. Firstly, we do not have a reference data of brain imaging from the general population that is large enough to confirm a diagnosis. To achieve this database, large numbers of the population must be scanned over a period of time. Secondly, a mental state may be due to activation in some brain area and inhibition in others. 'While a substantial degree of metabolic under- or overactivation of an area of the brain may correlate with a psychopathology, it is unclear whether metabolic activity slightly less or greater than normal for the general population would have any clinical significance'. Thirdly, since cognitive and affective capacities relate to numerous circuits distributed throughout the brain, an image in one region may be inconclusive. Fourthly, although brain imaging can show the relationship between normal and abnormal brain states and mental states, it cannot provide the 'causal explanation of the etiology and pathogenesis of neurological and psychiatric diseases'. And finally, brain imaging cannot capture the interaction between the subject and the environment.[xxiii]

Interpretation and Prediction

In a recent study, brain scans of adolescents judged to have a high risk for developing schizophrenia revealed structural and functional abnormalities in their brains.[xxiv] These subjects have diminished gray matter, especially in the frontal and temporal lopes, and in the cingulated gyrus of their brains. Diminished gray matter is these regions of the brain are often associated with a sign of schizophrenia. But what is of note is that the brain abnormalities in these subjects indicate the mental disease before they exhibit full-blown symptoms. Some neuroscientists have regarded diagnostic or predictive neuroimaging as an important development especially in treating mental disorders because it enables early detection of disease. But the problem with using brain images to either diagnose a mental disorder or predict its onset has to do with the often-unexamined assumptions of the procedure as well as the interpretation of the results.

One of the problems with the whole approach is that brain imaging tends to oversimplify complex genetic and brain data. This has often led to the ontological and explanatory reductionisms discussed in the previous section. Long-standing studies of developmental brain plasticity, however, have shown that reductionist accounts cannot do justice to the complex phenotype in consideration. These studies have also shown that organisms – in this case the human being – cannot be understood without taking into consideration environmental, social and other factors. In addition, it must be pointed out that the interpretation of brain imaging studies is not only bound by the scientific framework, but is also influenced by cultural sensibilities and philosophical commitments. This is the case especially when brain scans are used to interpret psychological states and emotions, which are always (and mostly unconsciously) value-laden concepts. Another important concern, which should not be brushed aside lightly, is the tendency for scientists and others (like the court of law)

[xxii] Judy Illes, 'Neuroethics in a New Era of Neuroimaging', *American Journal of Neuroradiology* 2003, 24:1739-1740.

[xxiii] Walter Glannon, *Bioethics and the Brain* (Oxford: OUP, 2007), 47.

[xxiv] C. Pantelis *et el.*, 'Neuroanatomical Abnormalities Before and After Onset of Psychoses: A Cross-Sectional and Longitudinal MRI Comparison', *Lancet* 2003, 361:281-88.

to have an exaggerated estimate of what brain imaging can do. In this regard, it may be prudent to heed the caution of analysts like Winslade and Rockwell, who maintain that 'Humans are forever prone to make premature and presumptuous claims of new knowledge … One may think that brain imagery will reveal mysteries of the human mind. But it may only help us gradually comprehend organic life, chemical and physiological features of the brain rather than provide the keys to unlock the secrets of human behaviour and motivation'.[xxv]

It must be stressed that brain imaging is always bound to momentary states. This means that inferences on personality and propensities for violence made on the basis of the results of brain scans highly problematic. For example, brain imaging may indicate that people with the propensity to commit violent crimes have significant abnormalities in the prefrontal cortex of their brains. But not every person with the same brain abnormalities is violent, making generalisations and predictions of behaviour highly problematic. Some neuroscientists have rightly pointed out that the complexity and plasticity of the brain would significantly limit the reliability of such prognoses. Focusing only on the prefrontal cortex, for example, may prove to be an oversimplified approach to ascertaining the link between brain and behaviour. Abnormality in this region, as some studies have shown, does not necessarily result in the disruption of the disruption cognition and emotion or the loss of the ability to reason. It is therefore important that the limits of the current technology is clearly presented and understood. If left unchecked, the wide-spread myth that brain scan can enable us to understand psychological states and even character traits would lead courts, immigration services and insurance companies to use these technologies prematurely.[xxvi]

Perhaps one of the most important problems in relating brain scans to social behaviour is the move from empirical claims about the brain and normative claims about proper and acceptable behaviour. When free will and responsibility are not understood primarily as normative notions informed by social conventions and expectations and see only as empirical realities, another form of reductionism is at work. While the study of brain activity can in some sense enable us to understand free will and responsibility, these normative claims cannot be reduced to empirical notions without skewing our perception of them. To make matters even more complicated, brain imaging alone cannot be used to ascertain psychological traits. As has already been pointed out, the design of brain imaging experiments and the interpretation of its results is not free from bias. Furthermore, these experiments are conducted under conditions that are far removed from the chaos of real-world situations. For all these reasons, caution must be exercised in claiming that these are diagnostic in that they help us to understand the link between the brain and social behaviour. And as Walter Glannon has pointed out: 'Even if functional neuroimaging is perfected, it will not necessarily translate into simple answers to normative questions such as when and to what degree people are responsible. These will always be influenced by social norms'.[xxvii] In light of this, brain imaging should supplement and not supplant existing criteria for responsibility in the criminal justice system.

Disclosure and Treatment

The question concerning what to do with findings also raises some important ethical concerns. The question of whether brain abnormalities would invariably result in cognitive and behavioural abnormalities, and whether the correlation between the two is the same as the causal relation between them is an important one in deciding on treatment. It is not necessarily the case that the individual with less gray matter in his brain will become psychotic later in life. Treating a person with brain abnormalities early to prevent the onset of schizophrenia, for example, raises some ethical concerns because of the possible adverse side effects. Antipsychotic drugs can

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[xxv] W.J. Winslade and J. W. Rockwell, 'Bioethics', *Health Law News* (Health Law and Policy Institute, University of Houston Law Centre, 2002), 1.

[xxvi] See M.J. Farah and P.R. Wolpe, 'Monitoring and Manipulating Brain Function: New Neuroscience Technologies and their Ethical Implications', *Hastings Centre Report* 2004, 34:35-45.

[xxvii] Walter Glannon, 'Neuroethics', *Bioethics* 2006, 20(1): 41-2.

result in a movement disorder called tardive dyskinesia. And even though newer psychotropic medications boast of fewer side effects, their long-term use would still result in adverse side effects. Glannon clearly states the ethical concern thus: 'Administering these drugs on predictive rather than definitive diagnostic grounds might mean that an iatrogenic disorder would result from treatment for a possible disorder that never would have developed. The risk of using these drugs must be weighed against the risk of not using them for those who are at high risk of developing schizophrenia'.[xxviii]

Even if neuroimaging techniques are perfected and the interpretation of the results are less problematic, ethical concerns still remain. One of the most controversial has to do with of whether we should intervene in the neuro circuitry of biochemistry of people who have brain abnormalities related to violent behaviour in the first place. Such interventions tantamount to forced behaviour control, a procedure that can be seen as a form of eugenics, and is therefore ethically problematic. There are basically two forms of intervention, each with their own peculiar ethical concerns. The first, more controversial, approach is the surgical manipulation of the brain, which permanently alters brain and possibly the identity of the person (although 'identity' is a philosophically complex concept). Because of the modifications to the brain is permanent, many find this approach ethically more controversial. The second is behaviour control through pharmacological intervention. This approach would be less controversial because it is not invasive and the modification to the brain is not permanent. The problem with treatment is especially acute when it has to do with children with severe prefrontal cortex abnormalities and (in some cases) with no moral sensibility. These children are destined to a life of crime and violence. Would intervention be the ethically responsible action even if consent cannot be obtained? The philosopher Patricia Smith Churchland presents the moral conundrum in this way:

> Certainly, some kinds of direct intervention are morally objectionable. So much is easy. But all kinds? Even pharmacological? Is it possible that some forms of nervous-system intervention might be more humane than life-long incarceration or death? I do not wish to propose specific guidelines to allow or disallow any form of direct intervention. Nevertheless, given what we now understand about the role of emotion in reason, perhaps the time has come to give such guidelines a calm and thorough reconsideration.[xxix]

Privacy and Discrimination

One of the concerns of brain imaging is the protection of the privacy of individual subjects. Because brain imaging claims to be able to reveal the neural correlates of our thoughts and attitudes – conscious or unconscious – the invasion of the privacy of subjects has become an important consideration. This is the case even if the claims of what brain imaging can do are often exaggerated. In fact, this poses a dual problem: not only is there a possibility that the privacy of individuals may be violated, conclusions regarding their mental states and behavioural traits may be skewed and inaccurate because of the method used, the interpretation of the results, and the inadequacies of current technology. There must therefore be sufficient measures in place to safeguard the privacy and confidentiality of data subjects such as replacing names and other identifiers with codes, and storing paper and electronic research material and records in a secure manner. In situations where researchers wish to use identifiable data without the consent of the data subjects, an IRB must review not only the project in question but also the legitimate use of data. Furthermore, the potential identifiability of anonymous files and data continues to pose a serious problem. The problem of privacy is in some ways related to that of stigmatisation and discrimination. There is a growing recognition of the fact that health information is not entirely private. This has naturally fanned the fear that such information may be used in justifying denial

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[xxviii] Glannon, 'Neuroethics, 44.

[xxix] Patricia Smith Churchland, *Brain-Wise: Studies in Neurophilosophy* (Cambridge, MA: MIT Press, 2002), 235-6.

of assess to health insurance, education, employment and even bank loans. Neuroimaging will eventually lead to widespread neuroprofiling, and this in turn may result in an ever-widening scope for abuses, especially in relation to stigmatisation and discrimination against certain individuals as well as certain groups.

Brain Enhancement

Another important if controversial aspect of the application of neuroscience and technology is cognitive enhancement. Although the common method of brain enhancement is achieved by neurophramaceuticals designed to improve alertness, memory, or mood, non-pharmacological approaches such as Transcranial Magnetic Stimulation can also be employed for this purpose. As the BAC has rightly noted, 'enhancement is a complex concept'. It can be broadly defined as improving a person's abilities and wellbeing either through natural and artificial means. Human beings have always been involved in the quest for self-improvement. For example, athletes strive to run faster or jump further through rigorous exercise, strict diet and with the help of better equipment, like running shoes. But as the BAC has again rightly noted, to achieve enhanced abilities through the use of 'performance enhancing drugs or genetic engineering' is ethically controversial (para 58). Neurotechnologies and neuropharmaceuticals have the potential to improve human performance in ways that cannot be matched by rigorous training or even psychotherapy. What are some ethical problems associated with cognitive enhancement?

Safety

The most obvious concern is of course safety. The BAC raises this issue and is rightly concerned with the use of prescription neuropharmaceuticals for psychiatric patients by healthy individuals (para 59). But the discussion on the dangers of these drugs when used for the purpose of enhancement in the consultation paper is very sketchy and rather vague. Because the use of neuropharmaceuticals for neurocognitive enhancement involves intervention in a highly complex system, the consequences and long-term side effects are often difficult to anticipate. Even when the drugs are use for the manipulation of a certain part of the brain, it is difficult to predict how this may affect other parts and indeed the whole brain. Enhancing one function of the brain could produce both desired and undesired outcomes at the same time.

- For example, fortifying one's memory could lead to 'over-enhancement – and being plagued by unwanted and traumatic memories that cause us distress and possibly psychological harm'.[xxx]
- Another example is the enhancement of reasoning ability may result in the impairment of freewheeling thinking, imagination or aesthetic sensibilities. In addition, enhancements may make the individual overly dependent on the technology or drug. If supply is for some reason interrupted or cut off, users may suffer serious withdrawal symptoms or impairment.
- Drugs like modafinil are used to promote alertness in people with regular sleep-wake cycles. Although researches believe that modafinil does not produce the hyperactive or addictive effects of other stimulants, sleep plays an important role in the plasticity of the brain. Lack of sleep would therefore reduce the brain's ability to adjust to the environment. 'Chronic uses of these drugs', writes Glannon, 'could remodel synapses, alter neural circuits, and result in permanent changes in the brain'.[xxxi]

[xxx] BMA, 'Boosting Your Brainpower: Ethical Aspects of Cognitive Enhancements. A Discussion paper from the British Medical Association', http://www.bma.org.uk/images/Boosting_brainpower_tcm41- 147266. Pdf.

[xxxi] Glannon, 'Neuroethics', 49.

Even proponents of cognitive enhancement have indicated the need for more research on smart drugs.[xxxii] Some have argued that all drugs have side effects and pose a risk to the health of the patient, and that the presence of risks in itself may not be sufficient reason to prohibit their use. Although it is true that all drugs have side effects and risks, our tolerance for risk must be smallest when treatment is elective. With cognitive enhancement, the issue is complexified by the fact that the individuals who wish to derive some benefit from the drugs or the technology are healthy. In other words, the issue becomes more salient because the drugs are used for non-therapeutic purposes, and they neither reduce nor prevent morbidity in the user.

Altering the Human Condition

The BAC is also rightly concerned that the use of neuropharmaceuticals may have an adverse impact on 'personal identity' (para 60). The use of such drugs may result in mood swings and behavioural changes, and the long-term consequences of such side effects are hard to predict with any accuracy. Some of course would argue, rather naively, that enhancement with cognitive drugs and new technologies pose no new ethical problems at all because this is what we have been doing throughout human history. Transhumanists would argue that the science and technology that evolution has made possible should in turn be used to hasten human evolution. Accompanying this development is the constructionist views of reality that is often associated with neuroscience and which the current postmodern ethos supports. Once again, we are reminded of the importance of a rigorous appraisal of the philosophical assumptions that undergird the science. Thomas Fuchs has summarised the constructionist argument well: 'if every brain creates its own world, then why should not we intervene in this construction to select a better version?'[xxxiii] But at the very fundamental level, we must ask the question whether we want to allow the use of drugs for nontherapeutic purposes that have the possibility of changing what some neuroscientists are even calling 'the human condition' when we are not able to even chart the possible ramifications of this to the health of individuals and the welfare of society.

Competition and Inequality

Some writers have argued that enhancements would create a more equitable society. However, even the most cursory survey of the distribution of existing technologies and their benefits would show that this view is obviously mistaken. It is more likely that cognitive enhancement drugs and technology, like most biotechnology, will not be fairly or evenly distributed. For example, in the US Ritalin is used by healthy college students who mostly belong to the middle-class, a privileged segment of the population. The cost barrier to legal cognitive enhancement drugs will compound the education and employment problems of the already disadvantaged people who belong to the low socioeconomic strata of society. Of course the question of inequality in bioethics is always a complex one and is therefore irreducible to the availability of a particular pharmaceutical or technology. But, as Nick Bostrom and Anders Sandberg have perceptively noted: 'There might … be a degree of complexity that is often overlooked in the ethical literature on inequality'.

> One should also have to consider under what conditions society might have an obligation to ensure universal access to interventions that improve cognitive performance. An analogy might be drawn to public libraries and basic education. Other relevant factors include the speed of technology diffusion, the need for training to achieve full utilization of an enhancement, whether and to what extent/what type of regulation is appropriate, and accompanying public policies. Public policy and regulations can either contribute to inequality by driving up prices, limiting access, and creating

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[xxxii] See I. Singh and K. Kelleher, 'Neuroenhancement in Young People: Proposal for Research, Policy, and Clinical Management', *AJOB Neuroscience*, 2010, 1:13-16.

[xxxiii] Fuchs, 'Ethical Issues in Neuroscience', 603.

> black markets; or reduce inequality by supporting broad development, competition, public understanding, and perhaps subsidized access for disadvantaged groups.[xxxiv]

Another possible problem associated with enhancement is that it will raise our standards of normalcy once the practice becomes widespread. This would mean that individuals who either choose not to enhance or who are unable to (because of cost) will be put at a disadvantage. This situation would result in coercion. Thus, even individuals who do not wish to be enhanced are 'forced' to do so since remaining in a job or in a school is dependent on it. But coercion works both ways with the dawn of accessible enhancement drugs and technology. Martha Farah, Judy Illes et el explain:

The straightforward legislative approach of outlawing or restricting the use of neurocognitive enhancement in the workplace or in school is itself also coercive. It denies people the freedom to practice a safe means of self-improvement, just to eliminate any negative consequences of the (freely taken) choice not to enhance.[xxxv]

The widespread use of enhancement will increase social competition as students try to secure places in the best schools, get the best grades, and, after graduation, secure the best jobs. Competition would in turn increase the frequency of 'brain doping', exposing large segments of the population – especially children and young adults – to the adverse side effects and unknown long-term consequences of the overuse of neurocognitive enhancements drugs.

<u>Other Issues</u>

Although there is only anecdotal evidence for this, some have argued that enhancement may impede the maturity of the individual because it would enable him to achieve success without putting in too much effort. Those who raise this issue often use of the analogy of wealthy parents who make their children work during summer holidays to earn their spending money because they wish their children to learn the value of the experience. People generally are of the view that there is value in earning one's success, happiness, etc., and that this experience is important for individual growth and maturity. By creating shortcuts to success, enhancement drugs and technology, some have argued, have interfered with this important and necessary process. Some have also argued that the use of enhancement drugs to deal with social ills and bad behaviour has become a convenient way of refusing to acknowledge the failings of our institutions. The use of Ritalin is a case in point. Addressing the situation in some schools in America, Bostrom and Sandberg write:

> These medications can function as cognitive enhancers in healthy subjects, but their widespread use in the school-aged population in the U.S. has sparked fierce debates, with some arguing that these medications are often used to paper over the failings of the education system by making rowdy boys calmer instead of developing teaching methods that can accommodate a wider range of individual learning styles and needs.[xxxvi]

Another problem with enhancement is that it may result in the commodification of human abilities. Many ethicists maintain that human beings are an end in themselves and should never be treated as commodities that can be bought and sold. Put differently, persons have a special value that distinguishes them from other material things. One of the most fundamental qualities of the human being is his ability to live a meaningful life. An aspect of what constitute a meaningful life is the

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[xxxiv] Nick Bostrom and Anders Sandberg, 'Cognitive Enhancement: Methods, Ethics, Regulatory Challenges', Sci Eng Ethics, 2009, 15:329.

[xxxv] Martha j. Farah, Judy Illes, Robert Cook-Deegan et el, 'Neurocognitive Enhancement: What Can We Do and What Should We Do?' *Nature Reviews Neuroscience* 2004, 6:243.

[xxxvi] Bostrom and Sandberg, 'Cognitive Enhancement Methods', 324.

achievements and accomplishments of one's life that came about as the result of work and effort one has invested. Cognitive enhancements would infringe on some of these important aspects of our personhood in a way that raises a number of important concerns. As Martha Farah and Paul Wolfe has put it, 'Maximising the performance capabilities of already healthy, functional person can be viewed as commodifying human abilities'. This would in turn result in the devaluation of human achievements, and in the final analysis, the devaluation of the human person.

Neurostimulation

Another neurotechnology discussed in the BAC paper is brain stimulation which it defines as 'the application of an electric or magnetic stimulus to the brain to modify or improve its function' (para 23). Some doctors see brain stimulation as a promising alternative to standard neurosurgery for the treatment of neuropsychiatric disorders. There are basically two types of neurostimulation. The first type is sometimes described as deep-brain stimulation (DBS) where electrodes connected to batteries in a pacemaker are implanted in a region in the brain. Patients can control stimulation to the brain by switching on and off the device. This technique can help patients whose physical functions were either impaired or lost due to neurodegenerative disorders to regain them to some extent. The technique is especially used on patients with advanced Parkinson's disease to restore coordinated movement and regain some motor control. Many patients with Parkinson's have opted for neurostimulation after Angen, the maker of glial-cell-line deprived neurotrophic factor, took the drug off the market in 2004.

The second type of neurostimulation technique is Transcranial Magnetic Stimulation (TMS). This non-invasive technique is reported 'to be effective in patients with major depression who have failed to respond satisfactorily to or cannot tolerate antidepressant medication' (para 29). TMS is also found to be effective in the treatment of a whole range of disorders (para 29). Other alternatives to DBS, not discussed in the BAC paper include electroconulsive therapy (ECT), vagus nerve stimulation (VNS) and echo-planar magnetic resonance spectroscopic imaging (EPMRSI). Although neurostimulation has arguably enjoyed modest success in treating certain neuropsychiatric disorders, there are a number of serious concerns associated with the technique that may have important ethical and social implications.

Problems with the Technique

In the case of DBS, great precision is needed in the implantation and stimulation of electrodes in the brain. Scientists have noted that implanting and stimulating the region even as narrow as one millimetre off the intended target could induce unforeseen adverse neuorological sequelae. Patients could as a result either suffer seizures, become emotionally passive or flat or even become suicidal. Even when the targeted area is stimulated as planned, the fact that one circuit of the brain is activated to the isolation of other circuits may lead to problematic outcomes, some of which are severe, such as the impairment of the patient's motor control. Such an outcome would of course defeat the very purpose of the treatment. Here, safety issues, which will be discussed below, are linked to the fact that the technique itself is imperfect or inadequate. Thus, careful selection of patients[xxxvii] and the strict guidelines for the application of these techniques on patients with psychiatric illness[xxxviii] are of paramount importance.

The fundamental problem with neurostimulation techniques, according to some neuroethicists, is that medical researchers working in this field do not know exactly how brain stimulation work.[xxxix] Some of these techniques are effective only up to a point because they can only

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[xxxvii] Sabine Müller and Markus Christen, 'Deep-Brain Stimulation in Parkinsonian Patients – Ethics Evaluation of Cognitive, Affective, and Behavioural Sequelae', *AJOB Neuroscience* 2011, 2 (1): 8.

[xxxviii] B. Nuttin et al, 'Ethical Guidelines for Deep-Brain Stimulation', *Neurosurgery* 2002, 51:519.

[xxxix] Glannon, *Bioethics and the Brain*, 140.

penetrate only so far into the brain. For example, TMS could only activate the cortex because the strength of the magnetic field falls sharply as the distance increases, even by only a few centimetres. Additionally, the effect of TMS on the targeted areas is only short term and therefore the improvement it brings is transient. This means that many patients would require repeated treatment, even though the risk of seizure increases in repeated TMS (rTMS). The problem of the isolated activation of one circuit in the brain has already been noted above. A somewhat related issue has to do with the fact that our brains are wired differently. This means that 'the location of the neural source or sources of a mental disorder may not be the same for two different people with the same disorder'.[xl] Furthermore, two people with the same disorder and exhibiting the same symptoms may not respond to brain stimulation in the same way. These considerations have ethical implications that should not be overlooked. They must determine how and to what extent the technology is used, and they must shape the guidelines and protocols governing the therapeutic application of these techniques.

<u>Question of Safety</u>

The main safety issue pertaining to neurostimulation is that the procedure may produce a seizure. The likelihood of this happening especially for TSM and rTSM is small, although the risks are higher with DBS. There are also relative and absolute contraindications to TMS. These include the presence of metal in the head, cardiac pacemakers, intracranial or intracardiac electrodes, a history of seizures and epilepsy and patients taking medicine that might increase the risk of seizures.[xli] Doctors and neurologists working with patients with Parkinson's have noticed that some have developed mania and other abnormal behaviour after receiving DBS treatment. Cases of patients developing edema and infection at the sites of the stimulation also been reported. Furthermore, there is to date insufficient studies to ascertain the long-term effects of such treatments. As we have seen, neural stimulation can either excite of inhabit neurons. In some cases, the techniques are used to achieve both, but it is difficult to balance and control the effects of the stimulation. The effects are dependent to some extent also on the frequency that is used and the areas of the brain that are targeted. And, as we have pointed out earlier, because our brains are wired differently, it is difficult to anticipate the risks without the benefit of long-term studies using placebo-controlled trials. As Steven and Pascual-Leone have pointed out, '… TSM has only been studied for approximately 20 years and the data on potential longterm effects in humans remain insufficient. Although animal studies using TSM have not indicated any risks of brain damage or long-term injury, caution remains imperative'.[xlii] Furthermore, it is not always clear whether neuorstimulation would be more effective in some cases of psychiatric disorders and some patients than drug therapy. These uncertainties and potential risks, however, does not mean that such techniques should be prohibited.

> Rather, more long-term studies are needed to adequately assess their benefits and risks. Given the uncertainty about the effects of these techniques, the same strict experimental conditions should be applied to all forms of neurostimulation, regardless of degree of invasiveness. In addition, informed consent from patients or subjects, or from surrogates, must be obtained. This requires that the researcher explain the potential benefits and risks of these techniques and risks. Finally, the medical uncertainty of these experiments indicates that they are ethically justifiable only when the neuropsychiatric conditions they are designed to treat are refractory to pharmacological or other proven treatments.[xliii]

[xl] Glannon, *Bioethics and the Brain*, 141.

[xli] Megan S. Steven and Alvaro Pascual-Leone, 'Transcranial Magnetic Stimulation and the Human Brain: An Ethical Evaluation', in Judyl Illes (Ed.), *Neuroethics: Defining the Issues in Theory, Practice and Policy* (Oxford: University of Oxford Press, 2006), 206.

[xlii] Steven and Pascual-Leone, 'Transcranial Magnetic Stimulation', 206.

[xliii] Glannon, 'Neuroethics', 49.

Annexe C

Brain-Computer Interfaces

One of the most fascinating of the new neurotechnologies is brain-computer interfaces (BCIs) or neural prosthetics. This technology enables people suffering from paralysis to control patterns of neural activity through their thoughts to indirectly perform movements and tasks. The BAC defines BCI as ‘a system that allows its users to interact with their surroundings by controlling devices such as computers, automated wheelchairs and artificial limbs solely with brain activity, without the normal intermediaries of peripheral nerves and muscles’ (para 31). As the BAC points out, there are non-invasive, partially-invasive and invasive BCIs, and therefore users of this technology face different degrees of risk. The BAC provides a list of possible risks such as injury to the brain and infections. These risks are especially associated with invasive forms of BCI. There are, however, several important philosophical and ethical issues associated with BCIs that the BAC paper does not address.

Intentions and Decisions

An important philosophical question surrounding the use of BCIs has to do with the distinction, if there indeed is one, between intentions and decisions. Intention is notoriously difficult to define, but it may be described as involving a complex combination of desires, beliefs and reasons. Philosophically (and logically), we must make the distinction between having and intention, making a plan and executing that plan in the form of concrete actions. Furthermore, it is possible for a person to have an intention and to draw up a plan of action, but failed in the end to execute it because he suddenly changed his mind. It is also possible for a person to have an intention and not act on it at all. This raises the question of whether the BCI system is sophisticated enough to make the distinction between intending to perform a particular act and deciding to execute the act. It raises the question of whether we are sufficiently confident that we know exactly which regions of the brain are involved in these different mental acts. Additionally, there is also the question of how much control a person can have of his brain signals and how these signals activate the neural prosthetics to perform a certain act. If neuro- scientists and technicians are unable to answer these questions with sufficient certainty, BCI systems could make people perform certain actions involuntarily, and this might have serious safety and ethical implications.

Agency and Responsibility

One of the most pressing ethical problems associated with this problem has to do with agency and responsibility. It is of course the responsibility of scientists and technicians to develop BCI systems with its devices and computational algorithms in such a way that they have maximum reliability. But regardless of how sophisticated our systems may be, they can never be 100% error-free. Should there be an involuntary act on the part of the user of BCIs due to an erroneous interpretation of intention and decision on the part of the system, should the user be held responsible for the resulting act? Should he bear the consequences? One possible way of achieving slightly more clarity in thinking about this is to determine the relationship between the neural prosthetics and the patient, that is, how integrated is the former to the latter. For example, when the prosthetics is external to the patient, that is, if it is not in some sense integrated to him, responsibility for the error of interpretation and execution can be attributed to the scientists, technicians and industrial agencies associated with the development and production of the device. But if the prosthetics in question is integrated to the self-concept of the patient, for example, an implanted chip, then the patient himself must bear some responsibility, even though the action is the result of an erroneous interpretation. The patient may be said to be responsible for a disaster caused by a mistake analogous to accidentally knocking over and smashing a vase. In any case, as Jens Claussen has wisely pointed out:

> Since possible malfunctions are not specific to neural motor prostheses but in principle inevitable whenever technical devices are used, established procedures may be adapted to the medical applications of BMIs. Possible risks due to technical failures are typically addressed by insurances. Insurances are obligatory for technical devices which put third persons at severe risks if one is to protect innocent people from damages and to be able to award compensations where necessary. Whether an obligatory insurance is appropriate for BMI-based prostheses depends on prostheses-related risks and their estimate severity. Additionally, as a precaution the execution of some actions (such a flying a passenger plane) with the help of BMIs may be prohibited.[xliv]

Other Issues

There are a number of other social and ethical issues that must be briefly mentioned at this point. BCIs and similar technologies can be used not only for the restoration of functions lost because of accident or injury but also to enhance the abilities of normal and healthy people. The use of neurotechnologies for such ends pose additional social and ethical problems, some of which are already discussed in a previous section of this paper. Although not associated only with neurotechnologies, implanted microchips can also be used to track humans, raising the problems of privacy.[xlv] Expanding on an issue already raised above, because the brain is the biological basis of human personhood or personality, the technological manipulation of the brain could result in radical changes whose long-term effects are still not properly studied and understood. Therefore, as Clausen has observed, ‘questions of mental changes, shifting personality and personal identity come up when interventions into the human brain in general and technological implants specifically are discussed’.[xlvi] Finally, even if these technologies were perfected so that the risks are significantly reduced, they would still be expensive. This means that certain segments of the population (perhaps the people who need these technologies the most) are not able to take advantage of them.

Stem Cell Therapy

The introduction of human stem cells to the brain to repair or restore certain functions is a promising strategy especially for patients with Alzheimer’s or Parkinson’s disease. Although the transplantation of cells and tissues into the brain is still at an experimental stage, exciting research is being conducted to ascertain its therapeutic applications. The Council broadly encourages such research because of its possible contribution to regenerative medicine that seeks to regenerate cells, tissues and organs that have either failed or are failing due to disease. However, the Council maintains that the use of human embryonic stem cells for such research should be prohibited. This is because the Council maintains that human life begins at conception and that the human embryo is a human being worthy of respect and protection. The Council supports the use of progenitor cells procured from bone marrow, adult humans, and human umbilical cord blood. The Council also encourages more research in the area of induced pluripotent stem cells (iPS cells) because of their malleability and because their use does not raise serious ethical issues.

Due to the fact that stem cell therapy to the brain is still at the experimental stage, it is imperative that we remain very cautious and alert to the risks associated with the therapy. The BAC has very briefly listed some of these risks (para 41). Perhaps a more detailed discussion is required to enable readers to better appreciate their seriousness.

[xliv] Jens Clausen, ‘Moving Minds: Ethical Aspects of Neural Motot Prosthese’, Biotechnol. J. 2008, 3:1498.

[xlv] Kenneth Foster, ‘Engineering the Brain’, Judy Illes (Ed.), *Neuroethics* (Oxford: Oxford University Press, 2006), 196.

[xlvi] Clausen, ‘Moving Minds’, 1496.

Annexe C

Risk of Tumours

According to reports of experimental Parkinson models, the risk of patients developing tumours as the result of stem cell therapy is a real one. One report cited a 20% risk of new onset tumours in experiments where undifferentiated stem cells are used. The use of viral vectors and the attempts to guide the differentiation and effectiveness of dopaminergic neurons (in the case of Parkinson's) has the risk not only of losing control of the viral transmission and missing the target but also that of mutagenesis (developing a mutation).

Inadequate Migration

As a more accurate and refined method of target migration is still a challenge for scientists, the risk of migration defects resulting in heterotopias (displacement of clumps of grey matter in the brain) is still great. This in turn could result in complications such as a form of epilepsy that is difficult to control (refractory) and other serious neuropathological conditions.

Transplant Rejection and Infections

There will always be immune rejection conditions in neural adult stem cell transplants. 'Theoretically, since cells are more differentiated in adult tissues and more antigenic they might require greater use of immunosuppressive drugs with the inherent additional risks such as liver and renal toxicity, hypertension and immunodeficiency'. In addition, the risk of infections resulting from the introduction of stem cells should also be taken seriously. 'This is a constant risk in every cell transplant process in which pathogens may be transmitted from the donor to the recipient, such as hepatitis B or C, lymphotropic virus, HIV/Aids, cytomegalovirus, and herpes simplex virus. In addition, there is also the risk of infection in the culture media and in handling the samples, either from bacteria (Staphylococcus, Streptococci, E. coli), yeasts, spores, and prion diseases'.[xlvii] In light of the above risks, we not only have the responsibility to expand research in this area, we also have the responsibility not to harm any individual. As Glannon has put it,

> We … have a responsibility to ensure that neural stem-cell transplantation is safe and effective so that people could benefit from it and not be harmed. This is especially important for the protection of vulnerable individuals such as children, who may not understand the risks of procedures designed to treat chronic neurological disabilities.[xlviii]

NEUROSCIENCE RESEARCH

In the final section of its consultation paper (paras 45-69), the BAC raises a number of important questions on research involving human subjects. Many of these questions and issues are pertinent to different types of research involving human subjects and are therefore not exclusive or unique to neuroscience. In fact, the BAC has already addressed a number of the issues raised in this section in previous consultation papers and reports. The recommendations and guidelines found in these earlier documents are therefore applicable to the cases and questions raised in this consultation paper that is focussed on research in neuroscience. For example, in its paper 'Ethics Guidelines for Human Biomedical Research' which was issued on 20 June 2012, the BAC has presented comprehensive guidelines on the issue of informed consent involving vulnerable persons (3.15). These guidelines should apply to neuroscientific research on persons with diminished mental capacity (A. para 47-51). That research involving such persons is important because it may yield results that would be of significant benefit to them and others is not in doubt. What is important

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[xlvii] Rodrigo Ramos-Zúñiga, Oscar González-Pérez et el, 'Ethical Implications in the Use of Embryonic and Adult Neural Stem Cells', *Stem Cells International* 2012, Article ID 470949, 4.

[xlviii] Glannon, *Bioethics and the Brain*, 129.

is that such persons must be protected from abuse and exploitation. The same applies to research involving children. In paras 3.22 to 3.26 of the 2012 paper, the BAC has also presented some guidelines on research involving children. Although terms like 'minimal risk' should be further clarified, the guidelines are generally sound and relevant to neuro-scientific research on children. The question of neuro-enhancement has been addressed in a previous section of this paper. The question of clinically significant incidental findings has also been addressed in the 2012 paper (para 3.29-3.33). The guidelines are sufficiently comprehensive to include research in neuroscience. However, there is one particular issue that deserves further discussion and closer attention.

Sham Surgery

As the BAC has rightly noted, the use of sham surgery in clinical trials especially for patients with Parkinson's disease is highly controversial (paras 54-55). Sham surgery is used to address the placebo effect in clinical trials and chiefly to ensure that the experimental design is adequate. Part of the difficulties associated with surgical studies has to do with determining to what extent is the effect due to the surgery itself and to what extent is it due to the placebo effect. Sham surgery is used in surgical trials to equalise the placebo effect of surgery. This procedure would enable researchers to more accurately assess the direct effect of the surgical procedure. Thus, the problem sham surgery poses has to do with the tension between the highest standard of research design and the highest standard of ethics. The question is when these two standards are on conflict, which should be allowed to prevail, and how can a balance be struck if researchers are unable to meet both simultaneously.

As with any surgical procedure, sham surgery presents risks to the research subject. For example, in a recent trial of the treatment of pain in cancer patients, researchers inserted capsules into a space at the base of the spine by lumbar puncture. In some subjects the capsules contain an analgesic that could relief pain, while in other subjects the capsules contain an inert substance. According to one report 10 percent of the patients experienced headaches that lasted a couple of days after the procedure. Furthermore, there is also a risk of permanent nerve injury or even paralysis. The risks of such surgeries cannot be described as minimal. The assessment of risks associated with sham surgery is of course subjective. For example, a group of researchers in Yale University decided against conducting sham surgery because of unjustifiable risks to research,[xlix] while another researcher likened the risk involved to that of going to the dentist.[l] Part of the problem in assessing the benefits and risks of a certain procedure is that the objectivity required for more precisely judgement is often elusive. The National Commision for the Protection of Human Subjects of Biomedical and Behavioural Research (in the US) recognises this in its report:

> It is commonly said that benefits and risks must be 'balanced' and shown to be 'in a favourable ratio'. The metaphorical character of these terms draws attention to the difficulty of making precise judgements. Only on rare occasions will qualitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible.[li]

Be that as it may, the Council believes that performing a surgery for non-therapeutic purposes is ethically problematic even if it is meant to ensure the integrity of the research in question. Thus, the Council would privilege ethical standards over research design. The Council believes that this basic approach is supported not just by the Christian moral tradition but also by the collective wisdom of society, especially in the wake of the atrocities of the Second World War. Thus, the

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[xlix] L. Johannes, 'Sham Surgery is Used to Test Effectiveness of Novel Operations', Wall Street Journal, December 11, 1998: A1, A8.

[l] S.G. Stolberg, 'Decisive Moment on Parkinson's Fetal-Cell Transplants', New York Times, April 20, 1999:F2.

[li] National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Washington, D.C.: Government Printing Office, 1978), 85.

Nuremberg Code of 1947 explicitly states that all research should avoid inflicting unnecessary physical or mental suffering. The Code also insists that the risks involved in any research involving human beings should not exceed the humanitarian significance of the problem it aims to solve. In similar vein, the Declaration of Helsinki of 1964 echoes the principles enshrined in the Nuremberg Code when it emphatically maintains that 'concern for the interests of the subject must always prevail over the interests of society and science'. In its 2012 consultation paper entitled, 'Ethics Guidelines for Human Biomedical Research', the BAC delineates the ethical principles that inspire and shape its recommendations. Two of these principles, namely respect for persons and beneficence, relate directly to the issue of sham surgery. The flipside of beneficence is nonmaleficence, which urges researchers and physicians to 'do no harm', that is to refrain from providing ineffective treatments. This principle should serve as the basis for prohibiting the use of sham surgery.

The Council maintains that performing a surgical procedure that has no other benefit except to produce the placebo effect violates the principle that risks of harm should be minimised in the conduct of research. Sham surgery must be distinguished from inert substance used as placebo in a drug trial for obvious reasons: the inert substance has no adverse effects on the research subjects. In a recent study to evaluate the intracranial implantation of fetal neural cells for Parkinson's disease, some study patients underwent randomised sham surgeries that simulated all aspects of the surgery, including the drilling of burr holes on the skull under anaesthesia. The Council maintains that such surgery should not conducted on study patients in order to achieve a certain standard of research design because it puts the research subjects at considerable risks. The Council therefore fully concur with Ruth Macklin of the Albert Einstein College of Medicine that:

> Sham surgery is ethically unacceptable as a placebo control in trials of fetal-cell transplantation in patients with Parkinson's disease. Sham surgery, with accompanying anaesthesia, poses risks of any surgical intervention that would not be used alone for therapeutic purposes. In trials that use antibiotics to protect subjects against inflection, there are the added risks associated with antibiotic treatment. In trials that forgo the use of antibiotics in the sham-surgery group, there are the added risks of infection … The placebo-controlled trial may well be the gold standard of research, but unlike pure gold, it can be tarnished by unethical applications.[lii]

[lii] Ruth Macklin, 'The Ethical Problems with Sham Surgery in Clinical Research', *The New England Journal of Medicine*, September 1999, 341: 996.

9. Representatives from the Local Cognitive Neuroscience Community

I'm pleased to enclose some comments from the local Cognitive Neuroscience community with representatives from different universities in Singapore. I circulated the BAC comments to colleagues who did not receive the document and a few of us contributed to this reply.

Annett Schirmer – NUS
Annabel Chen – NTU
George Christopolous – NTU
Joshua Gooley – Duke-NUS
Michael Chee – Duke-NUS

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Annexe C

Feedback on Bioethics Advisory Committee (BAC) Consultation Paper on Neuroscience Research

A. Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

Autism

Persistent vegetative state

Generally yes. It depends on what the definition of a "person lacking mental capacity" is. If it is a broad definition which includes patients with psychiatric disorders (for instance schizophrenia) then the international practice allows for their inclusion in research (in fact it is very common). Moreover, the research paradigms are rarely intrusive and rarely produce discomfort that is higher as compared to casual every-day discomfort.

I agree that the definition of "lacking mental capacity" needs to be clarified. Persons (adults and children) with diminished ability in making judgments have routinely been included in non-invasive neurocognitive and neuroimaging studies. As long as the PI has made all efforts to justify the inclusion of such populations based on the above principles, these persons could participate with assent and consent from their legal guardian/parents [AC].

Research in the intellectually disabled often focuses on improving social and mental health care for these individuals. As highlighted in a recent commentary (Wei et al., Singapore Med J, 2012), Singapore faces challenges in meeting the mental health needs of people with intellectual disabilities. Provided that the research is non-invasive, has minimum risk, and is meant to improve the well-being of those involved, it is appropriate to enroll participants with diminished mental capacity with consent from a legal guardian (JG).

B. Do researchers have a duty to return incidental findings? If so, under what conditions?

In present practice, participants in non-clinical studies are:

1. Informed that brain imaging is not intended for diagnosis of medical conditions. The imaging team is not obliged to detect or inform regarding any finding.

2. Asked to indicate on the consent form whether they would like to be informed about incidental findings.

In the event that an incidental finding is detected, persons who wish to be informed will be provided an electronic copy of the images and asked to consider consulting a specialist doctor.
No assessment on the clinical significance of the finding will be provided as part of standard operating procedure. Further information *might be* provided but only at the discretion of the investigator.

Having a medical specialist review images in non-clinical studies will:

1. Put an unsolicited burden on the researcher as well as the organization for making appropriate judgments regarding the presence of an anomaly as well as how to handle it.

2. Add cost to studies without significant benefit. Added testing to evaluate for incidental findings rarely results in clinical action[i]

There is another *very critical* reason to explicitly state *that we will not report any findings.* Participants very often come to the study believing that it will be a “free” medical diagnosis. Therefore, they might walk away believing that they are healthy, they might generalize the fact that no incidental findings were found and thus they will postpone more appropriate or specialized medical test. Thus, in fact and for the benefit of public health, neuroscience studies should * explicitly * state that the procedure is of no diagnostic value. [GC]

Most non-clinical neuroimaging protocols used for research with healthy participants are not comprehensive and not targeted to detect clinical conditions. Therefore, it is very important to make clear the point mentioned above by [GC] to the participant. The PI needs to make clear whether incidental findings of clinical significance or any incidental findings will be reported to the participant during consent. Usually, research studies do not provide subsequent care for such findings (only clinical referrals as a courtesy at the most) and this also needs to be made very clear during consent. Benign cysts are not uncommon in healthy participants, however sometimes reporting this to the participant may cause unnecessary alarm where clinical attention is not needed. Therefore, the PI needs to weigh this carefully for the individual if such disclosure is decided, and safeguard procedures need to be in place for possible negative reactions. All major neuroimaging facilities conducting research studies do (or should) have a standard protocol for incidental findings however, whether to return incidental findings that are noted to have no clinical significance to the participant would depend on the PI’s discretion.[AC]

C. Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so, under what conditions?

This is an important scientific control. Sham intervention is necessary to exclude the possibility that some other aspect of the procedure other than the designed intent can produce beneficial effects. The placebo effect is an important considering in neuro-psychiatric disorders – perhaps more so than other physical conditions because of the nature of subjective judgments of benefit.

I agree that sham condition is absolutely necessary for preventing false claims, even for invasive procedure. Participants and/or their guardians should be fully aware of alternatives and potential risks. The sham procedure should also be designed to minimize risks and discomforts for participants.

D. What factors should be considered when assessing research with neurotechnologies, in particular research where one’s sense of identity may be affected?

This is not a new issue. As with all interventions, there are cost-benefit trade offs.

The administration of dopamine agonists to treat Parkinson’s Disease can turn ‘normal’ persons into ‘compulsive gamblers’. This has not deterred their use because in many instances, the benefits outweigh the risks.

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[i] The Cognitive Neuroscience Lab Duke-NUS Graduate Medical School & co-users have collected well over 5000hrs of scan data over a period of 16 years. Of the last 1300 participants (some repeated), there have been 55 incidental findings (around 4%); this number could be higher if one counts white matter hyperintensities and medium sized Virchow Robin spaces. Only 1 has undergone (non-emergency) surgery for hydrocephalus. The most common incidental findings are arachnoid cysts (by far), cavum septum pellucidum (large ones), cavernous angioma*, meningioma* large white matter hyperintensities and incidental infarcts. (*referred to neurosurgeon on good faith basis).

As a counterpoint, aesthetic surgery doesn't directly affect the brain it is intended to change in the patient's sense of self-worth. If so, it can be argued that aesthetic surgery be subject to regulation by ethics committees.

Some objective measures should be made to weight the benefits against the risks and conveyed clearly to participants and/or guardians.

E. Under what conditions should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement?

Studies with the direct objective of improving human cognition under physical or emotional challenge (e.g. sleep deprivation, emotional stress) improve our understanding of how normal persons deal with such stresses and contrastingly, could inform about what is deficient in those less able to tolerate such stresses.

Studies that seek to improve cognition in healthy older adults could have significant positive impact on society by contributing to lowered dependency.

Studies that evaluate nutrition related products that claim to benefit mental state and well-being are already sponsored by companies (see footnotes for some examples)

Studies that evaluate educational methods or novel instruments to improve cognitive performance are an important application of 'neurotechnologies'.

Properly conducted, scientifically sound studies in this category sponsored by parties without commercial interests are important to protect the public good as there are already commercial establishments paid to facilitate product marketing using such techniques. (see footnotes for some examples)[ii]

Conversely, companies that use these technologies irresponsibly should be taken to task as they put consumers at risk in addition to discrediting credible researchers in the public eye.

In fact, the Government should seriously consider regulating these products.

It is in fact very important to evaluate neurotechnologies that claim to have cognitive enhancement abilities in a vigorous scientific manner to rule out placebo effects and prevent false claims. The issue of whether we want to include usage of cognitive enhancers in our daily living is an ethical debate that can only be resolved at the society level and may depends on the maturity of the society to want to approach this debate. [AC]

F. Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

Understanding the evolution of processing capacity and strategies engaged in the developing brain is an important endeavor that has neuroscience and education practice implications.

[ii] Brand's Essence of Chicken marketing: http://summerash.wordpress.com/2012/03/19/the-science-behind-brands-essence-of-chicken/
http://www.raindeocampo.com/2012/05/31/wellness-stop-brain-ageing-with-brands-essence-of-chicken/
http://www.linoralow.com/2012/ads-2/the-science-behind-brands-essence-of-chicken
Natural frequency technology for watches:
http://www.philipstein.com/frequencytech.aspx
oxytocin nasal sprays to enhance trusting.
http://www.huffingtonpost.com/2012/11/14/oxytocin-fidelity-committment_n_2130436.html

Understanding the effects of treatments or interventions (e.g. childhood anaesthesia) is likewise a useful application.

Conditions and safeguards described by US and international Ethic Research guidelines (for instance The Belmont Report, the Declaration of Helsinki or the Office of Human Research Protection) offer superb protection to children's rights and psychological well-being as research participants. Most neuroscience methods are non-intrusive (i.e. they only record signals) and therefore not dangerous. Potentially, special care should be taken for research that involves neuromodulation such as TMS. [GC]

Children are considered a vulnerable population. Therefore, additional safeguards are taken into consideration when including them in research with the above 5 principles as minimal standards. The most crucial principle to consider carefully would be whether the benefits outweigh the costs. Proper assent from the child and consent from parents/guardian is mandatory. The invasiveness of the methodology though important may not be the ultimate factor. For example, single-pulse TMS has been considered non-invasive by the FDA, and repetitive TMS (rTMS), which has the potential to invoke epileptic seizures, when applied following the current safety guidelines have been uneventful. When evaluating the studies involving such protocols, we need to appreciate the various levels of invasiveness/risks within the cost-benefit analysis and not dismiss the consideration of using such protocols altogether. In any event, the potential risks of the procedures and the relevant safeguards in place need to be made clear to the participants during consent. [AC]

Children are vulnerable yet often neglected in clinical research. Of course, the use of neurotechnologies in children would need to be considered on a case by case basis with appropriate safeguards in place. One of the biggest success stories in neurotechnology is the development of the cochlear implant. Although Singapore initially lagged behind other countries in their implementation, cochlear implants are now commonly implanted in children in Singapore. This has had a remarkable impact on the lives of many children, who would otherwise be deaf (unnecessarily). Clearly, children should be included in research on some neurotechnologies, especially if it is well established that the benefits far outweigh the risks in adults. (JG)

G. Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

The consensus is that neuroscience research isn't exceptional with respect to the principles that govern human research. Here are some comments made by the community:

The notions of brain, identity, independence, right to freedom of expression appear to be more strongly felt in Western societies. So this may be overkill. [MC]

There is a sense that East Asians are more vulnerable to misleading claims when these apply to education. However, the problem lies in the design and interpretation of these studies and their results and not on the technology used. In this sense, proper research should be encouraged. [MC]
Changing hormonal levels in the body by removing, for example an individual's thyroid, can have equal effects on changing an individual's personality. Hence, the justification of treating neuroscience differently from endocrinology, for example is void. [AS]

Again, the international practice and experience has demonstrated that adopting the ethical standards that are employed for socio-psychological research offers a very strong protection from misuse or abuse of neuroscience research. Psychology, economics and social sciences measure human responses using various methods (experiments, questionnaires, reaction time etc); neuroimaging just adds up a more diverse array of measurements (physiological response) that in many cases are more exact and specific thus offering more reliable results. Therefore, in a sense, neuroscience is not different from other socio-psychological research as it only differs with respect to the tools employed. [GC]

Following the above framework for evaluating research involving humans, neuroscience research should not be regarded differently. However, we would like to think so, as it involves an intimate organ, the brain. The main safeguard to be emphasized is the integrity of the researcher to be clearly educated on these principles and adhere to them [AC].

In principle, neurotechnology does not differ from other disciplines in its primary aims. Most medical technologies are developed 1) to monitor physiologic or behavioral changes that are clinically relevant, 2) to improve or replace a dysfunctional part of the body and its function, or 3) to minimize loss of function associated with injury or disease. Neurotechnologies assess these aims, but in the specific context of the brain, spinal cord, and peripheral nerves. Generally speaking, the safeguards should be similar to other medical technologies. (JG)

10. A/Prof John Elliott M

A. Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

Progress likely cannot be made in the eradication or treatment of the very conditions that affect mental capacity without, at some point, some participation by members of the affected population. My answer to the first question is 'yes'.

I would make the following specific points:

1. It is difficult to find any ethical basis for excluding such persons, given that they personally or through their responsible proxies (donees, deputies, family members) would normally welcome an available proven treatment if it became available. A desire for and expectation of treatment developed from the participation of others past cannot sit ethically with a refusal to even consider participation in research for the future benefit of others. If the law precludes participation through too exclusive an emphasis on the immediate personal interests of individual non-competent persons, than I would hope that the law can be changed to allow greater discretion to responsible proxies, with safeguards.

2. Clinical trials research build on a great deal of prior research that is not clinical, and may be quite basic, and it is artificial and could even be misleading, to imply that all the necessary research could be done without any participation by legally non-competent persons up the point where clinical trials commence.

3. If "persons lacking mental capacity" is taken to include children, as lacking fully mature judgement, or infants, who lack any judgement, then it should be self-evident that research into the nature of childhood diseases and their development (including psychological or psychiatric conditions) cannot be understood without a general knowledge of and research into the child development, of both mind and body. Such research has occurred in the past and continues today. I see no reason to assume that persons who at other stages of their lives are for other reasons unable to exercise sufficient autonomous mental capacity, should be in a different category when it comes to their participation in research.

4. It is exclusionary to assume that persons who are incapacitated would not wish to make a contribution to society through research participation. In some cases, it might be the only kind of participation they could make. Moreover, there is ample precedent for the public interest to take some priority over individual interest in other domains. Specifically, we are willing to expose healthy young adult males to the risks of life in the armed forces, without their consent, through compulsory national service in the perceived national interest.

As regards the second question, under what conditions should such persons participate in research, a considered view needs an extensive review, but the following would be some of the principles that need to be heeded:

1. The default, in law and in ethics, should be a presumed willingness to participate in *bona fide* research of a kind likely to lead to the amelioration of suffering or the treatment of

disease. For example, under the Mental Capacity Act, there is a requirement that; "He [the deputy or donee] must consider, so far as is reasonably ascertainable –

(a) the person's past and present wishes and feelings (and, in particular, any relevant written statement made by him when he had capacity);

(b) the beliefs and values that would be likely to influence his decision if he had capacity; and

(c) the other factors that he would be likely to consider if he were able to do so."

In my view this should be interpreted as favoring participation in research except where (a) to (c) clearly indicate otherwise, for example, by the person's having indicated an objection, or being known to have values that would lead them to repudiate participation.

2. The interest of the individual should not be interpreted – in the Act – in such a way as to preclude a concern with the interests of future others in the same condition.

3. The distinction between clinical research and non-clinical research should be deemed of relevance only insofar as it relates to issues of consent for treatment. Of more importance is the significance and importance of the research. Non-competent persons should not be asked to participate in research lightly, and research that is exploratory or unlikely to yield medically important findings should not normally involve non-competent participants.

4. The responsibilities of researchers, IRBs and others towards non-competent research participants should be no less than would be the case for competent participants.

B. Do researchers have a duty to return incidental findings? If so, under what conditions?

It is my view that researchers have such a duty in proportion to the likelihood that their research will uncover clinically important conditions. It cannot be the case that all research should be treated as if it was providing an incidental medical check, but conversely, research in patients where the procedure is highly likely to reveal clinically important findings should not be treated as if the possibility was of no concern to researchers.

I also feel that where a procedure is normally used for clinical purposes, and especially if (a) expensive and (b) carried out in a health-care setting, there is a greater obligation for the researcher to anticipate and make provision for likely incidental findings. Thus, it would be disquieting if research entailing the taking of a chest X-ray made no provision for advice to be offered to participants showing signs of, say, lung cancer; or ignored such a possibility. fMRI scans should, wherever possible, also be scanned by a competent clinician even when the research is not clinical in purpose; the more so as the procedure is expensive to repeat and likely to be carried out in a clinical setting.

Nothing written here is intended to conflict with the BACs previous positions on this issue as set out in the Genetics Report in particular.

C. Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so, under what conditions?

I do not feel the possibility of placebo surgery should be ruled out. New drugs are already tested in healthy participants on a 'first in man' basis, and rarely but occasionally and unforeseeably, accidents or even fatalities do occur. Placebo or sham surgery is in somewhat the same case. However, it should only be considered where there really is no prospect of developing important approaches to treatment without it. A very careful and thorough discussion of the risks among all parties including the participants should be required before informed consent can be taken.

D. What factors should be considered when assessing research with neurotechnologies, in particular research where one's sense of identity may be affected?

On the whole, my view is that assessment of neuroscience research is well covered by the five existing principles to which the BAC subscribes, viz., Respect for persons; Reciprocity (or Solidarity, in some formulations); Proportionality; Justice; and Sustainability. By and large I do not see neuroscience as somehow different. We affect our identity irreversibly in many ways through societally accepted or expected interventions – such as education – without finding such interventions ethically challenging (except insofar as they can lead to injustice, if unfair in practice).

I do however, recognise that the brain might be a special case. I have considered the issue of Neuroscience exceptionalism in research in a recent article (copy attached), and my conclusion was that;

> "Perhaps, therefore, an added [sixth] principle is needed, along the lines of Respect for the Brain, such that brains, being organs of self-awareness and the root of feelings, cognition and the control of bodies, should be respected with regard to their growth, structure and function, such that the importance of therapeutic primacy over experimental alteration is always observed in research and treatment. To this extent, perhaps some element of neuroscience exceptionalism is, after all, justified."
> (Elliott, J (2012). On not reinventing the wheel: Need we see the governance of research in neuroscience as somehow special? *Asian Bioethics Review, 4*(4), 330-343) (p342).

E. Under what conditions should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement?

I believe this is a matter where neuroscience exceptionalism does not apply, and that consenting healthy individuals should be included in such research in the same way, and with the same safeguards, as for any other research with human participants.

F. Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

This also I believe is a matter where neuroscience exceptionalism does not apply. It is entirely proper to take stringent safeguards in any research involving children. My experience with IRBs in Singapore is that they already do so. I do not see that neuroscience research per se adds anything extra to the situation.

G. Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

As indicated above, it is my view that perhaps we do need to consider a criterion which could be called "respecting the brain", which in practice would probably amount to adopting a precautionary approach in matters that could result in irreversible changes. However, in general I feel the requirements imposed on researchers in the interests of the protection of participants are already onerous, and if taken seriously, will already effectively protect participants in most neuroscience research.

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31 March 2013

11. Dr Gabriel Oon Chong Jin

Invitation to Comment

Before making any recommendations on neuroscience research and its implications, the BAC would like to seek public feedback on the subject. The BAC values views from both individuals and organisations. Interested parties may specifically address the following questions or give their comments on any of the issues presented in this Consultation Paper or relating to neuroscience research.

A. Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

Answer: The most important criteria are full proper informed consent so that the patient (where possible), and the next of kins know the liabilities that may happen in the conduct of such an experiment on themselves or loved one.

In the case of neuropsychiatric orphan experiments, 'the frontier of knowledge beyond what is known and unknown can be safety, and no disaster…to a huge crevasse and fatal disasters, for the victim, the investigator(s), the institution and the approving Ethic Committee...

(i) The full informed consent has to be obtained under strict independent observations by at least three qualified medical practitioners, one of whom must be trained in neurology, a second in psychiatry, and a third, a specialist in one of the specialties in Medicine. All must not be involved in any way in the research, be a colleague with shared interest, or have any pecuniary interest in the research. The opinions of all three specialists must concur. If anyone should detract or disagree, then the consent is not valid.

The opinion of these specialists is:

(ii) Is the patient able to understand clearly, without any coercion, the benefits and the serious harms to himself/herself? If the patient cannot clearly understand, then there is no consent, and the valid consent must come from the next of kin (see below)

(iii) If the patient is incapable of understanding, then a valid next of kin's permission has to be sought. Where there is more than one member in the family, one member from the family must be nominated by the family, as the spokesperson, and the decision would be that of the family and not of that one person.

(iv) The full scope of the research has to be explained.

(a) What this research is meant to discover and what is involved.
(b) How is this research to benefit the patient?
(c) What harm is expected whether these be mild to serious, expected or non-expected.
(d) What compensation and costs are to be incurred by the patient in the process, both during the experimentation and later for any complications that may arise, such as mild or serious disabilities, even any that may lead to death.
(e) Who bears all the cost for the experiment and complications of treatment or the procedure?
(f) The patient must bear no cost in any way to the experiments.

B. Do researchers have a duty to return incidental findings? If so, under what conditions?

Answer: Yes. Absolutely. There must be no concealment of the outcome of the research. The patient or the next of kin, must be beneficiary in knowledge of the research findings, (whether good or bad) to all information on the outcome of the experiment.

In the search for more grants, prestige and status, some investigators cheat, bluff, conceal and exaggerate their claims of discovery and effectiveness of their research and experiments, especially where there is secrecy of patents of inventions…scientific integrity and honesty is of the paramount importance.

They are only discovered either because their invention does not fit an International regulatory specification, or the workbook does not show that they have done the experiment, or there is a whistle blower.

False and adulterated results can cause serious harm and guide scientific research in a wrong pathway.

So, there has to be academic publication of research findings, but the detailed technical knowhow may need to be secret until the invention has been patented.

C. Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so, under what conditions?

Answer: Sham or deceitful experiments MUST be prohibited. These are scientific dishonesty and betrays trust in the truth of what the research is searching for, and destroys confidence in the researcher, the institution where it is done, and the Ethics Committee that has approve it.

Stem Cell transplants must not involve human embryos, fetus, or babies' tissues, from induced abortions, as this had been achieved by the killing of a human innocent.

Only autologous stem cells can be used.

D. What factors should be considered when assessing research with neurotechnologies, in particular research where one's sense of identity may be affected?

Answer: All these changes which may affect the identity of the patient MUST not be done. These would involve legal issues, if any which may come up due to the change of identity, such as identity on the National Identity Card, Passports, wills, Central Provident Fund, and any other legal documents. All these MUST be explained to the next of kins clearly.

E. Under what conditions should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement?

Answer: The criteria must be

(a) "Do no harm". The ability for the normal volunteer to undergo these neurotechnologies for non-medical purposes must be full and independently assessed by four experts.
    (i) a psychiatrist,
    (ii) a specialist in one of specialties of medicine,
    (iii) a neurologist,

(iv) a laity who is of high moral standing in the profession and trade. All must have no pecuniary interest in the experiment.

(b) Full informed consent witnessed by the above specialists and laity should be obtained before the start of the experiment.

F. Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

Answer: Yes, for sick children, where no cure has been found, and the child's condition is deteriorating. Full informed consent must be obtained.

Drugs, implants, or any form of psychotherapy which may change the behaviour, memory or intellect or any mental function, whether short lasting or permanent must not be conducted on healthy children. Young children are like an open slate, where any information can be programmed upon them.

G. Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

Answer: Neuroscience research is no different from any clinical experimental research for testing out orphan drugs. The results must be opened, and raw data opened for independent inspection by experts, and results published in peer reviewed journals.

(i) Orphan drugs are new products, never tested in humans yet, where information is only available in animal experiments or cell culture work. However, the animal results can never be extrapolated to humans, since there may be wide species difference in response to the product, from insignificant to disastrous. So, these orphan drugs are first tested in a few human healthy volunteers.
(ii) If there are no immediate toxicities, and there is a good result, next larger numbers are recruited, and these form the Phase I studies, whose aim is to see the response, both good and bad in a larger number.
(iii) The Phase II studies then would involve even larger numbers and in selected population to test the efficacy and the safety of the product. The safety concerns would-be short-term observation of any side effects and serious complications or product failure.
(iv) Phase III trials. These would involve many thousands all over the world to test for efficacy, safety, and product efficiency.
(v) Eventually, a product would be accessed for long term unknown complications for delayed unknown adversed effects.

Example: I was the Principal Investigator for the Singapore Government and the International Agency for Research in Cancer /World Health Organization Hepatitis B vaccine to prevent liver cancer, which was given to all new-borns (since 1985) and all young adults under 20 years old and population.

Technologies have changed from the 1980s human plasma derived HB Vaccine, to gene expressed HB vaccines. We have not encountered over 25 years, and long-lasting adverse side effects, such as was feared (mad cow disease, autoimmune disease, cancers) but protection from liver cancer and hepatitis B liver diseases.)

Annexe C

Transparency of this observation was the publication of the results opened to the public to read and given to all research institutions, National Library and the National Archives. It is called “A Cancer Vaccine that transformed Singapore and the World, (Published Singapore Straits Times Press (Ltd) 2010) with the official statistics given by the Minister of Health and a special message from the Director of the International Agency for Research in Cancer/W.H.O.

12. Member of the public

I have several comments about the paper.

1. Well written, scholarly, balanced, objective

2. Point 66. If the ethical questions are covered by current rules/policy/practice, then the paper should lay out what are considered the current standards. Is neuroscience research pushing the boundaries or should neuroscience practice follow different guidelines? I don't think so. Neuroscience and biomedical research are intrinsically linked and should follow the same rules. If neuroscience raises unique issues not covered by current ethical practice of biomedical research, then the paper is unclear on this point.

3. The paper lacked a certain big picture perspective. It read as a series of bullet points. The emphasis of the paper is on the current and anticipated near-term technologies as applied or might applied to human health and behavior. Most of the technology is devoted to describing the structure of the brain and tracing its circuitry. This should be considered not only doable, but the follow-on question is what will knowing brain and neuronal circuity enable? Point 68, mind reading may or may not be ethical but certainly achievable with some certainty. Don't forget, "mind reading" follows "eavesdropping". We are currently at the "eavesdropping" monitoring brain activity stage in neuroscience. The problem is that the language-words, logic, and grammar is not well understood. We have not reached the Rosetta Stone moment.

4. Contemporary neuroscience is relatively crude and unsophisticated with the state of art trying to reverse engineer the brain, for example the various brain mapping projects at all resolution scales. Reverse engineering reflects a relatively early stage in technology development and application. What follows reverse engineering is improved engineering, this is the part of the paper that describes the promise of stem cell repair and tissue engineering. But an end point is design and construction, where the structure, circuitry, sensing, and most importantly computing and control is understood. Once the brain is understood at the circuits and systems levels, then design, manufacture, manipulation and control are inevitable end points. But not in my lifetime.

5. These considerations may not govern current decision of ethical norms but should be kept in mind as a broad perspective on the direction and path that technology will develop and enable unimaginable or unspeakable applications in the future. Ethicists point out that what is ethical is governed by social, economic, religious, cultural, and scientific norms of the period. The ethics of the 15th century, 18th century, and 21st centuries were significantly different, especially in different regions of the globe. The ethics of the 22nd and subsequent centuries will not remain at the 21st century standard.

Annexe C

13. Mr Muhammad Shamir Bin Abdul Rahim

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A. Should persons lacking mental capacity be included in research other than clinical trials? If so, under what conditions?

The argument for the auto-exclusion of mentally-incapacitated research participants is their inability to comprehend and therefore give meaningful ‘informed consent’. Obtaining ‘informed consent’ is indeed an absolute requirement since the Nuremberg Code (and earlier) and that which is reinforced in contemporary research guidelines on sound ethical grounds.

The existing ethical framework for clinical trials is a thorough one that as correctly mentioned, has been developed to account for such mentally-incapacitated patients, via legal proxies etc. As such, all research involving such subjects, including presumably lower-risk genomic research, should ideally be conducted under a clinical trial framework.

The additional administrative and filing costs should not outweigh the ethical issues that would be pre-empted. Furthermore, patients’ medical information that will be obtained via genomic research must be protected under clinical trial provisions for patient confidentiality and privacy rights. Also, as highlighted, the state via A*STAR has budgeted $50M for neuroresearch (and eye disease), so there should be no lack of resources in ensuring proper documentation and diligence in obtaining informed consent.

B. Do researchers have a duty to return incidental findings? If so, under what conditions?

For the specific case of brain imaging, where it was mentioned that incidental findings are common, it would make sense for a suitably qualified expert to review and counsel the patient accordingly. In this instance, researchers should report incidental findings but with proper medical consultation and a qualified counselling process.

Brain scans are expensive and can add up to millions when conducted in a typical research study. The additional cost of consulting a medical expert where required is likely to be incremental and would ensure prudent use of the state’s resources. Furthermore, if that incremental cost of reporting can prevent a more expensive therapeutic procedure in future, the researchers then owe a duty to the state to report such findings.

C. Should sham surgery be allowed to test for the efficacy of invasive neurotechnologies, such as stem cell transplantation into the brain or DBS? If so,under what conditions?

While the concept of ‘randomized, double-blind, placebo-controlled trials’ has been upheld in pharmaceutical research as the gold standard, it is difficult to justify such an approach in research involving invasive surgical procedures. Deep brain surgery (DBS) is typically conducted over 1.5 days and places the patient under considerable risks as well as physical immobility. Such a suspension of a human’s rights to health and physical liberty can hardly be justified by the pursuit of scientific knowledge, regardless any monetary compensation involved.

However, in cases where the investigated surgical technique is done opportunistically vis a vis a life-saving procedure, for example in investigating the efficacy of different Cox Maize patterns in cardiac ablation post-open heart surgery (CABG), sham surgery may be justified. Similarly, such alternative designs could be explored in designing clinical trials, for example by only enrolling patients undergoing non-optional deep brain surgery anyway. In these cases, the investigative technique can 'ride on' the riskier but compulsory procedure, randomized as a sham or not.

D. What factors should be considered when assessing research with neurotechnologies, in particular research where one's sense of identity may be affected?

For any medical research involving stem cells, clearly the risk of uncontrolled cell lineage differentiation and migration, not to mention spontaneous neoplasm formation, must be assessed first. These present real biological risks that are more pressing and immediate than any hypothetical changes to higher neurological states.

In the quoted example of patients who underwent DBS, it appears that at least some neuropsychiatric effects observed were unintended and therefore not anticipated. The question then would be can those DBS results be consistently reproduced? If not, it might well be a moot question to be reserved until both these procedures are developed even further.

E. Under what conditions should healthy individuals be included in research involving the use of neurotechnologies for non-medical purposes, particularly cognitive enhancement?

Healthy individuals are regularly included in research as a matter of course in Phase I clinical trials, where the safety profile of investigational new drugs are assessed in healthy subjects. Increasingly, the 'efficacy' of nutraceuticals or pharmaceutical-grade health supplements is studied in such a manner too. Thus far, these similar precedents have not raised unique ethical problems not already encountered with all clinical trials.

On the flip side, even in research where only non-healthy individuals are studied, drug abuse for personal 'enhancement' occurs anyway. For example zolpidem (Stilnox®/Ambien®) is a controlled drug prescribed for the treatment of clinical insomnia. However there have been high-profile cases where zolpidem is consumed with alcohol to enhance sexual enjoyment. This then clearly constitutes drug abuse and there are existing laws that prevent or regulate this.

The freedom to knowingly choose the substances one ingests, harmful or not, is a basic human right. To prevent such a choice would be to adopt a paternalistic approach, which is ethically problematic.

It then seems sensible that in research involving healthy individuals, the same conditions should apply for neurotechnologies as that applied for other medical technologies.

F. Should children be included in research involving the use of neurotechnologies? If so, under what conditions?

The write-up is correct in highlighting the existing use of neurologically-active drugs. A prime example is the use of piracetam (Nootropil®), especially in enhancing children's memory to improve academic results. Indeed this drug is clinically indicated for the treatment of dementia, Alzheimer's and similar conditions of neurological deterioration only. However it is not uncommon to see boxes of Nootropil® stocked in shelves of GP clinics even in suburban neighbourhoods.

This might constitute a unique case whereby children should be included to research the safety profile of such drugs. For obvious reasons, children are a population typically excluded in clinical trial programs required by the FDA, CE and HSA, thus this research would yield new information that might be relevant in assessing the potential harm of this class of drugs in our society.

Annexe C

For starters, a retrospective trial or registry study could be conducted as a pilot research. This will forestall the ethical problems of conducting a prospective trial, at least until further information is collected.

Regardless, it should be made clear that this should not count as a precedent for future research because as correctly highlighted; children must be reserved special rights as a vulnerable population.

G. Is neuroscience research exceptional? What particular safeguards should there be in the ethics governance of such research, in addition to what is already in place for other types of human biomedical research?

While the human brain is sometimes seen to occupy a dramatic place in general perceptions of self and identity, from a clinical anatomy perspective it is just an organ like any other. The ‘seat’ of human nature and accompanying ideas of self, sentience, conscience and consciousness, might rest not so much in one particular organ, but the entirety of its parts. This is a question science still cannot satisfactorily answer and is outside the scope of this discussion.

It might thus be more practical to break down ‘neuroscience research’ into components and risk stratifications of ‘potential harm’ to humans. Classifications of non-invasive vs invasive techniques come to mind. This is because the definition of what constitutes a neurologically-active and therefore ‘neuroscientific’ drug can be hard to define. Certain compounds pass through the blood-brain barrier more easily than others yet have no significant effects on neural status other than inducing headaches and alertness, for example 1,3,7-trimethlyxanthine (caffeine).

Of course, what we wish to prevent is a recurrence of the notorious ‘bilateral prefrontal lobotomy’, a radically invasive neurosurgical procedure purported as a cure for psychosis but ultimately responsible for producing vegetative states in tens of thousands of women & children worldwide. Common sense should prevail.

As for brain computer interfaces (BCI), there are already commercially available products in the market, such as the Neural Impulse Actuator, a gaming-controller by OCZ Technology [discontinued] (http://www.ocztechnology.com/nia-game-controller.html). Even in local science exhibits, simple BCI devices that simulate ‘mind control’ have been displayed some years ago. While novel, these are far from being able to ‘read’ minds and it is only recently that systems have been developed to assist paraplegics in typing and keying in basic computer commands.

Responses by: Muhammad Shamir Bin Abdul Rahim
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