ETHICAL, LEGAL AND SOCIAL ISSUES IN NEUROSCIENCE RESEARCH

A CONSULTATION PAPER

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SINGAPORE

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About the Bioethics Advisory Committee
The Bioethics Advisory Committee (BAC) was established by the Singapore Cabinet in December 2000 to examine the ethical, legal and social issues arising from research in the biomedical sciences and to develop and recommend policies on these issues. It aims to protect the rights and welfare of individuals, while allowing the biomedical sciences to develop and realise their full potential for the benefit of mankind.

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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.[1] 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

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

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 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.[2]

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.

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[2] 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).

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.[3] 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,[4] 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.[5] 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.[6]

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 Canadian Government recently announced the creation of the Canada Brain Research Fund, providing up to $100 million for research on brain disorders.[7] 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-

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

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

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

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

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

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,[8] 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,[9] 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.[10] 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.[11] 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.

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

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

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

[11] 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.

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.

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.[12] 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).

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

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,[13] dystonia,[14] 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,[15] 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 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.[16] 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

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

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

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

[16] 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.

other hand, there have also been reports of memory enhancements after DBS for conditions such as obesity[17] and epilepsy.[18]

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%),[19] 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.

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

[18] 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.

[19] 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,[20] cerebral palsy[21] 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.[22] 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

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[20] 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.

[21] 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.

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

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 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,[23] 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.

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

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.[24] 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.[25]

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.

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

[24] 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.

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

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,[26] 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

[26] 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."

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?

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.[27] 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? 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.[28] Given the subjectivity of the

[27] 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.

[28] 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

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 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.[29] However, such off-label use by healthy people is a controversial issue.

Schlaepfer TE. Stimulating Personality: Ethical Criteria for Deep Brain Stimulation in Psychiatric Patients for Enhancement Purposes. *Biotechnology Journal.* 3, no. 12 (2008): 1511-1520.

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

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"[30] 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.[31]

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?

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[30] 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).

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

F. 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,[32] 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

[32] 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.

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?

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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.

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