



Ethics assessment in different fields

Neurosciences and Neurotechnologies

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Ethical Assessment of Research and Innovation: A Comparative Analysis of Practices and Institutions in the EU and selected other countries *Deliverable 1.1*

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Contents

1	Abstract	3
2	Executive Summary	3
3	Introduction	6
4	Basic discription of the field	7
4.1	Neuroimaging.....	7
4.2	Novel neurotechnologies.....	7
4.3	Neuroenhancement.....	8
4.4	Ethical Issues in regard to Neurosciences.....	9
4.5	Neuroimaging.....	9
4.6	Novel neurotechnologies.....	11
4.7	Neuroenhancement.....	14
4.8	Overview – ehtical issues.....	17
5	Ethical Principles and Values.....	19
5.1	Ethical issues in relation to principles.....	21
5.1.1	Ethical issues in relation to the principle of autonomy	21
5.1.2	Ethical issues in relation to the principle of beneficence / non-maleficence	21
5.1.3	Ethical issues in relation to the principle of justice.....	22
5.1.4	Ethical issues in relation to the principle of privacy	22
5.1.5	Ethical issues in relation to the principle of trust	23
5.2	Organisations / Institutionalisation	23
5.3	International Frameworks and protocols.....	23
5.3.1	Declaration of Helsinki	24
5.3.2	Convention on Human Rights and Biomedicine.....	24
5.3.3	Universal Declaration on Bioethics and Human Rights	25
5.3.4	Clinical Trial Directive	25
5.3.5	Medical Devices Directive.....	26
5.3.6	Other issues	27
5.3.7	Responsible Research and Innovation	27
5.3.8	Conclusions.....	28
6	Journals / Sources used	29
7	Literature.....	29

1 Abstract

This contribution first offers a basic description of neurosciences. The chapter is divided into the description of neuroimaging, novel neurotechnologies, and neuroenhancement.

The following chapter analyses the ethics issue debate in international medical journals, medical ethics journals, ethics journals, and in reports of National Bioethics Commissions who have worked on the issues grouped according to the three fields identified in the previous chapter.

The ethics issues are grouped by principles and values suggested by the Nuffield Council in its report on ‘Novel Neurotechnologies: intervening in the brain’, which seems an appropriate framework for the discussion of neuroethics as a whole. This framework is based on principlism and is complemented by the principles of privacy and trust. The concept of Responsible Research and Innovation (RRI) as understood by the Nuffield Council, which interprets RRI as a complementing framework to ethical principles and values thus creating a third layer of evaluation of neurosciences, is also presented.

Finally the study offers a list of organisations which are leading the ethics debate in the field as well as a short description of the related institutional setting for reviewing research in the field of neurosciences, and a short description of the international legal framework governing therapeutic interventions in the neurosciences. A list of relevant journals and key publications rounds up the report.

2 Executive Summary

The question about the functioning of our brains and minds has led to rapid developments in the field of neuroscience. The developments are linked to neuroimaging, to novel neurotechnologies, and to neuroenhancement.

Neuroimaging is a means to learn more about the brain. Structural imaging deals with the structure of the brain and the diagnosis of intracranial diseases such as tumour or injury. Functional imaging is used to diagnose metabolic diseases, to conduct research in the field of neurology and cognitive psychology, and to build brain-computer interfaces. Neuroimaging techniques do not measure neuron activity directly. The pictures are therefore only an indirect reflection of neural activity.

Novel neurotechnologies are technologies which are intervening in the brain for therapeutic purposes, such as transcranial magnetic brain stimulation (TMS), deep brain stimulation (DBS), or brain-computer interfaces (BCI).

Biotechnologies which are applied to enhance people’s thinking or state of mind are generally described as neuroenhancers. Neuroenhancement can either be performed by medical / pharmacological interventions or by novel neurotechnologies, such as transcranial magnetic stimulation (TMS), which promise results in the enhancement of cognitive skills, and general mood.

The literature suggests several ethical issues which are presently discussed in expert circles. With regard to neuroimaging the issues relate to stigmatisation and discrimination arising from population-based data, the selection of research themes, the handling of incidental findings in healthy research subjects, the management of patient's expectations, the predictive value of today's brain images, and the protection of sensitive data.

In regard to novel neurotechnologies, the ethical issues which are presently discussed are the need for new therapeutic interventions in relation to uncertainty, access to novel neurotechnologies, the intrusion into an individual's private domain, the creation of hype by communicating exaggerated expectations in the technology, validity of informed consent in depressed and minimally conscious state patients, inclusion and exclusion criteria in research, the composition of the research team, possible alteration of personality and the question of identity, selective reporting, and the non-existence of a comprehensive case registry and quality outcome of reporting.

The definition of neuroenhancement remains difficult, as the line between therapy and treatment beyond therapy is difficult to draw with its impact on the perception of the "normal". This leads to an ethical discussion related to the loss of authenticity, the impact on self-perception, questions of implicit and explicit coercion to enhance one's mental capacity, new perception of competition and merit, societal implication, questions regarding reversibility of detrimental effects, inclusion of children in non-therapeutic enhancement research, questions of privacy in relation to data collected by enhancing devices, and creation of hype, as popular media undermines public understanding of the current state of scientific understanding.

The ethical issues which are discussed in the literature relate to the "classical set" of principles in biomedical ethics: Respect for autonomy, non-maleficence, beneficence, and justice. In addition to the values in accordance with principlism, issues of privacy in relation to novel neurotechnologies are being discussed, as brain implants obtain and can transmit digital data about the brain activity of their users. The discussion of privacy, although it goes beyond principlism can be considered as part of the standard debate in the field.

A totally new principle in comparison to principlism is introduced by discussing the issue of trust created by the communication of exaggerated research expectations. In addition to principles, one National Bioethics Committee suggests to include virtues into the ethical debate, which provide certain guidance in practical application, but are nevertheless abstract in comparison to ethical issues. The virtues mentioned are inventiveness, humility, and responsibility.

It can be noted that the Nuffield Council in its report on "Novel neurotechnologies: intervening in the brain", also discusses the concept of RRI. It identifies the following six issues as assessment framework: Clearly identified needs, securing safety and efficacy, generating robust evidence, continuous reflexive evaluation, coordinated interdisciplinary action, and efficacy and proportionate oversight.

In case we assume an interrelationship of these frameworks, the following levels of evaluation are relevant:

1. Evaluation of RRI framework on the societal level regarding needs, securing safety and efficacy, generating robust evidence, continuous reflexive evaluation, coordinated interdisciplinary action, and efficacy and proportionate oversight.
2. Evaluation of ethical principles within the scientific domain related to the respect for autonomy, non-maleficence, beneficence, justice, privacy, and trust guided by virtues in relation to scientific integrity.
3. Evaluation of ethical issues related to day-to-day work in research and treatment in combination with the virtues of inventiveness, humility, and responsibility.

Ethics assessment frameworks have already been codified to a certain extent. Codification has taken place either in soft law instruments, such as the Helsinki Declaration, the Universal Declaration on Bioethics and Human Rights; or in binding legal instruments such as the Convention on Human Rights and Biomedicine, which has a binding character for those Member States of the Council of Europe which have signed and ratified the Convention, the Clinical Trial Directive of the European Union, or the Medical Devices Directive of the European Union, which is binding for the Member States of the European Union.

As the development of scientific knowledge is a globalised phenomenon, the codification of the respective fields of knowledge has to be globalised as well. The existing regional instruments are a good start for further discussion.

3 Introduction

This document is one in a series of reports on the ethics assessment with regard to a certain scientific discipline in the framework of the European Commission funded SATORI project. The discipline which is studied here is the field of neurosciences.

Analysing existing ethics assessment frameworks in a given field first of all poses the challenge of scope. In order to limit scope it was decided to focus on those issues which can be considered a sub-discipline of medical ethics. Questions regarding military use and truth verification of imaging techniques have not been studied in this context. Neither will the report go into the debate of agency, as it is assumed that free-will is not questioned by the new findings. Although some scientists claim that actions are exclusively guided by the brain, this approach is not followed. For the purpose of this report it is assumed that human actions are at least partly guided by the mind, which exists separately from the brain.

A second difficulty in this report is the classification of debated issues in ethics issues and principles / values. There is a vivid discussion on particular ethical issues regarding neuroscience in the day-to-day work in research and treatment in neuroimaging, novel neurotechnologies, and neuroenhancement. The underlying “value-system” is however rarely discussed or presented, although it forms and guides the discussion of the issues. Only the Nuffield Council presents a conceptual framework in which the ethics issues can be debated based on “principlism”. As the issues debate very often also suggests that the “classical-set” of bioethical principles (autonomy, non-maleficence, beneficence, and justice) is used as reference framework, the report refrains from discussing other ethical theories (e.g. utilitarianism vs. Kantian ethics), but groups ethical issues along the lines of principlism. Those ethical issues which cannot be discussed under the umbrella of principlism are identified and are framed in a new context thus complementing the ethics assessment framework by introducing the principles of privacy and trust.

A further interesting conceptual question relates to the interrelationship of the studied ethics assessment framework (ethics issues in relation to principles / values) and the concept of RRI. Any given ethics assessment framework could be interpreted as the implementation of the concept of RRI. The Nuffield Council however offers an interpretation of RRI, which creates a new level of evaluation.

It has to be noted that the heterogeneity of the debate and the complexity in regard to the different levels of ethical evaluation poses a challenge to stringent analysis. The report tries to clarify matters, but has surely not succeeded in answering all the questions which are presently discussed.

- **Objectives**

The objective of this report is to analyse the ethics issues debate in the field of neuroscience in order to be able to identify principles and values which are used to conduct the ethics debate in the field.

- **Methodology**

Methodologically the report draws on a literature study. International medical journals, medical ethics journals, ethics journals and reports of the National Bioethics Commissions to firstly identify the neurotechnologies, which are worthwhile to study (neuroimaging, novel neurotechnologies, and neuroenhancement), second to identify the ethics issues debate according to the fields identified, and third to identify a reference framework for principles and values related to the ethics issues debated.

4 Basic discription of the field

The age-old question about the functioning of our brains and minds in combination with new technological developments has led to rapid developments in the field of neuroscience.¹ On the one hand, since the 1980s, we are increasingly being confronted with new neuroimaging techniques, which have enabled us to better understand the functioning of the brain and have thus led to new treatments and research findings in this field. On the other hand, we are experiencing the desire to enhance cognitive functioning of the brain in healthy human beings.

4.1 Neuroimaging

Neuroimaging is a means to learn more about the brain. Structural imaging deals with the structure of the brain and the diagnosis of intracranial diseases such as tumour or injury. Functional imaging is used to diagnose metabolic diseases, to conduct research in the field of neurological and cognitive psychology, and to build brain-computer interfaces.

Functional magnetic resonance imaging (fMRI) relies on the paramagnetic properties of oxygenated and deoxygenated haemoglobin to construct images of changing blood flow in the brain associated with neural activity, which enables scientists to retrieve both structural and functional data. This allows images to be generated that reflect which, and how, brain structures are activated during the performance of different tasks.²

It has to be mentioned that “fMRI techniques do not measure neuron activity directly, but rather a signal corresponding to the complex metabolic modifications associates with it and which involve the entire neuro-vascular unit.”³ The pictures are therefore only an indirect reflection of neural activity.

4.2 Novel neurotechnologies

Novel neurotechnologies are defined here as technologies which are intervening in the brain for therapeutic purposes, such as transcranial magnetic brain stimulation (TMS), deep brain stimulation (DBS), or brain-computer interfaces (BCI).

To stimulate the brain, a medical device is implanted into the brain or is fixed on the scalp in order to send electrical signals to the tissue. Depending on the area of the brain that is

¹ Illes, Judy, “Empowering brain science with neuroethics”, *LANCET* Vol. 376, 2010, pp.1294-1295.

² http://en.wikipedia.org/wiki/Neuroimaging#Brain_imaging_techniques.; see also: Leuthardt, Eric, Erwin Schalk, Jarod Roland, Adam Rouse, and Daniel Moran, “Evolution of brain-computer interfaces: going beyond classic motor physiology”, *Neurosurg Focus*, Vol 27, No. 1, 2009.

³ National Consultative Ethics Committee for Health and Life Sciences, *Ethical Issues arising out of Functional Neuroimaging*, Opinion Nr. 116, 2012, p.3.

targeted, the treatment is called "deep brain stimulation" or "transcranial stimulation". Brain stimulation is used to treat people who suffer from epilepsy, Parkinson's disease, or major depression.

Brain-computer interfaces are a direct communication pathway between the brain and an external device. BCIs are often aimed at assisting, augmenting or repairing human cognitive or sensory-motor functions. Research into BCIs began in the 1970s and has since focused primarily on neuroprosthetic applications that aim to restore impaired hearing (cochlear prostheses), sight and movement. Recently, brain-computer interface has been used to communicate with patients suffering from locked-in syndrome, who were unable to communicate through physical means such as nodding or eye-movements.⁴

The Nuffield Council also considers neural stem cell therapies as novel neurotechnologies. It is the first ethics body to consider neural stem cell therapies, which are still highly uncertain and are still performed only in a research setting and will not be treated in this report.⁵

4.3 Neuroenhancement

Biotechnological findings may also be applied to improve the functioning of the body, for example in sports and athletics. Biotechnologies which are applied to enhance people's thinking or state of mind are generally described as neuroenhancers. Neuroenhancement is rooted in clinical applications, which are used on healthy individuals to enhance their productivity, wakefulness, emotions and state of mind / the way they think and feel.^{6,7}

Examples of neuroenhancement in the field of psychopharmacology are modafinil and methylphenidate. Modafinil is normally used to treat narcolepsy. It helps to keep people awake and improves the short-term memory and planning ability of healthy individuals. Methylphenidate is used to treat children with attention disorders (ADHD) and is also used by students to improve their concentration during examinations. Fluoxetine and paroxetine, which are used in the treatment of depression, can also be used by healthy individuals to make them feel brighter and happier.⁸

Neuroenhancement can also be performed by novel neurotechnologies, such as transcranial magnetic stimulation (TMS), which promise results in the enhancement of cognitive skills, general mood, and social cognition.⁹

⁴ Singer, Emily, „Kommunikation mit Wachkomapatienten“, *Technology Review*, 8.2.2010.
<http://www.heise.de/tr/artikel/Kommunikation-mit-Wachkoma-Patienten-923926.html>

⁵ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013.

⁶ Illes, Judy, "Empowering brain science with neuroethics", *LANCET* Vol. 376, 2010, pp.1294-1295.

⁷ Larriviere, D., and M.A. Williams, "Neuroenhancement: wisdom of the masses or "false phronesis"?", *Clin Pharmacol Ther*, Vol. 88, No. 4, Oct. 2010, pp. 459-461.

⁸ The President's Council on Bioethics, "Beyond Therapy: Biotechnology and the Pursuit of Happiness", Washington, D.C., October 2003.
<https://bioethicsarchive.georgetown.edu/pcbe/reports/beyondtherapy/index.html>

⁹ Hamilton, Roy, Samuel Messing, and Anjan Chatterjee, "Rethinking the thinking cap – Ethics of neural enhancement using noninvasive brain stimulation", *Neurology*, Vol. 76, No. 2, 2011, pp. 187-193.

4.4 Ethical Issues in regard to Neurosciences

This chapter describes the ethical issues debate in National Bioethics Committees, international medical journals, medical ethics journals, and ethics journals in the framework of basic research and therapeutic interventions. Ethical issues are understood as an ethical problem or dilemma which arise in a practical situation and are less abstract than ethical principles or values. This distinction is however not always clear. We will therefore mention all issues debated in the relevant documents and will only then distinguish between “practical situations” and more abstract issues, which would classify an issue to be grouped among principles and values.

It has to be mentioned here again that questions regarding “dual use” aspects, such as military use¹⁰ and truth verification¹¹ will not be included in the analysis, as they do not fall under the remit of neuroscience as sub-discipline of medical ethics.¹² Mention also has to be made that the free-will debate, in case the brain is attributed a new role which questions the free-will, is excluded from this analysis, as we assume the separation of brain and mind.

4.5 Neuroimaging

The International Bioethics Committee (IBC) of UNESCO¹³ points to the problem of possible stigmatisation and discrimination in regard to the misinterpretation of data from neuroimaging. Images that suggest a non-standard or exceptional neuroanatomy could be interpreted as more informative as they really are, as respective predictivity is low. As regards predictivity the IBC refers to a similar discussion in the field of genetic data. IBC highlights particular problems arising from population-based data in the field, and to individual data which are part of the medical file in case confidentiality is not respected.

The French National Consultative Ethics Committee for Health and Life Sciences (CCNE) raises concerns regarding the selection of fMRI-based research themes. The CCNE argues¹⁴ that the question of priority and pertinence of research needs to be posed. Ethical behaviour regarding the selection of research themes is therefore of importance.

Furthermore the CCNE mentions the problem of incidental findings: “One very specific aspect of fMRI research (...) is the frequency with which various unexpected anomalies are discovered.”¹⁵ The CCNE identifies different questions on the ethical issues level in this regard, such as communication strategies, in case the fMRI scans are difficult to interpret even by specialists, or how to handle clinically relevant incidental findings in case the research subject does not want to be informed about result.

¹⁰ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, pp.182.

¹¹ See: <http://www.cephoscorp.com/lie-detection/index.php>.

¹² For the definition of scope, see internal paper “Matrix for WP1 and Workplan until May 1st, 2014” by Brey Philip, and Clare Shelley-Egan.

¹³ International Bioethics Committee, *Draft Report of the IBC on the Principle of Non-discrimination and Non-stigmatisation*, 29 August 2013. <http://unesdoc.unesco.org/images/0022/002211/221196e.pdf>

¹⁴ National Consultative Ethics Committee for Health and Life Sciences, *Ethical Issues arising out of Functional Neuroimaging*, Opinion Nr. 116, 2012, p.8.

¹⁵ National Consultative Ethics Committee for Health and Life Sciences, *Ethical Issues arising out of Functional Neuroimaging*, Opinion Nr. 116, 2012, p.8.

Due to the fact that imaging data must be computerised and are stored, privacy issues arise. In any of the three mentioned possible settings, neuroimaging data as part of the medical file, neuroimaging data as end result of biomedical research, or neuroimaging data relating to a particular group of people, put together by private and non-medical structures, the issue of “cyber protection of the confidentiality of private personal data, in particular those relation to mental faculties, is an imperative.”¹⁶

The German Ethics Council is presently working on a document on neuroimaging. They held several public hearings on the issue. The most recent hearing took place in November 2013.¹⁷ The German Ethics Council raises the question of the predictive value of brain images. It states clearly that today’s development in the field does not allow for diagnostic purposes of certain dispositions in the brain e.g. paedophile behaviour or the likelihood to get a certain disease. Expectations in the field need to be realistic in order not to create hype which might result in a loss of trust.

The German Ethics Council discusses the problem of incidental findings in research. Their approach in this regard would be to include human subjects in brain imaging research only if they renounce their right not-to-know. This is a clear breach of autonomy, but is supported by arguments in regard to the principle of beneficence.

Shoemaker et al.¹⁸ discuss different approaches for addressing incidental findings in neuroimaging. They argue that suggesting no review of research scans violates the principle of beneficence, restricted review violates the principle of justice and full clinical review for all research scans is simply too expensive. The authors suggest mandating radiology reviews for all patients, which reduces costs in comparison with full review, but respects the principle of justice. Whether the participants want to have a copy of their radiology report or not lies with the discretion of the participant thus respecting the principle of autonomy.

Rangel¹⁹ also addresses the issue of incidental findings in imaging research. She points to the necessity to disclose the potential of incidental findings and its possible consequences in the informed consent document. As regards incidental findings, which have not been addressed in informed consent documents, she highlights the responsibility of the researcher for ancillary care.

Zarzeczny et al.²⁰ describe various ethical challenges which relate to practical/financial restrictions to review all images, the access to relevant expertise and scan quality, the managing of patient’s expectations, the difficulty of ensuring properly informed consent, and

¹⁶ National Consultative Ethics Committee for Health and Life Sciences, *Ethical Issues arising out of Functional Neuroimaging*, Opinion Nr. 116, 2012, p.13.

¹⁷ Deutscher Ethikrat, „Informationen und Nachrichten aus dem Deutschen Ethikrat“, Infobrief, No. 14, Dezember 2013. <http://www.ethikrat.org/dateien/pdf/infobrief-02-13.pdf>

¹⁸ Shoemaker, J.M., M.T. Holdsworth, C. Aine, V.D. Calhoun, R. de La Garza, S.W. Feldstein Ewing, R. Hayek, A.R. Mayer, K.A. Kiehl, L.E. Petree, P. Sanjuan, A. Scott, and J. Stephen, J.P. Phillips, “A practical approach to incidental finding in neuroimaging research”, *Neurology*, Vol. 13, No. 24, pp.2123-2127.

¹⁹ Rangel, Erica K., “The management of incidental findings in neuro-imaging research: framework and recommendations”, *J Law Med Ethics*, Vol. 38, No. 1, 2010, pp. 117-126.

²⁰ Zarzeczny, Amy, and Timothy Caulfield, “Legal liability and research ethics bodies: the case of neuroimaging and incidental findings”, *Int J Law Psychiatry*, Vol. 35, No. 2, 2012, pp. 137-145.

the negative impact of false positives weighed against the potential consequences associated with failing to identify or communicate a possibly life-threatening condition.

Andrew Chow argues that research teams in the field of neurosciences should always include clinical medical personnel in order to help interpret incidental findings, and to ensure that research subjects are informed of incidental findings in an appropriate manner.²¹

4.6 Novel neurotechnologies

The Nuffield Council discusses novel neurotechnologies in an extensive report. Novel neurotechnologies are discussed in the realm of therapeutic interventions.²² The fact that novel neurotechnologies focus on therapeutic interventions creates a need for these technologies connected with a certain amount of uncertainty, as the technologies are new and their consequences unknown.

The Nuffield Council also discusses the access to novel neurotechnology treatment, which will not always be possible. Disproportional distribution will affect vulnerable groups due to age, socio-economic status, or geographical location (less developed regions).²³

The Nuffield Council points to the fact that brain implants obtain and can transmit digital data about the brain activity of their users, which can be seen as an intrusion into an individuals' private domain, especially in case the obtained data is stored for future use.

The Nuffield Council discusses the problem of hype by taking up the concern of Thomas Schlaepfer: "There are strong economic incentives for researchers and the neurotechnology industry to emphasise the translational value of their findings in order to secure public funding and private investment. Those seeking to market products to healthcare providers or directly to consumers have an incentive to expand the therapeutic applications of novel neurotechnologies. Indeed, novel neurotechnologies occupy a field characterised almost as much by what we do not know as that which we do. Hype is likely to result in a loss of trust and confidence if its promises are not sustained in practice."²⁴

As regards DBS in depressed patients Laura Dunn et al. describe the dilemma of valid informed consent in depressed patients.²⁵ Although the authors highlight that there is insufficient evidence to judge depressed patients, in general, as lacking capacity, they nevertheless point out unique aspects of DBS for severe psychiatric illnesses. On the one hand the arguments relate to the fact that invasive brain surgery goes well beyond regular clinical research studies involving depressed patients. On the other DBS research differs from other antidepressant research in its duration, and complexity, which leads to an impact on informed

²¹ Chow, Andrew, and Katherine Drummond, "Ethical considerations for normal control subjects in MRI research", *Journal of Clinical Neuroscience*, Vol. 17, 2010, pp. 1111-1113.

²² Beauchamp, Tom L., and James F. Childress, *Principles of Biomedical Ethics*, Oxford University Press, New York/Oxford, 2009.

²³ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, p. 83.

²⁴ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, p. 84.

²⁵ Dunn, B. Laura, Paul Holtzheimer, Jinger Hoop, Helen Mayberg, Laura Weiss Roberts, and Paul Appelbaum, "Ethical Issues in Deep Brain Stimulation Research for Treatment-Resistant Depression: Focus on Risk and Consent", *AJOB Neuroscience*, Vol. 2, No. 1, 2011, pp. 29-36.

consent, so that additional steps need to be taken to insure that subjects have understood the information necessary.²⁶

Anish Sen et al. discuss informed consent for the use of DBS for minimally conscious states. They argue that informed consent by surrogates should only be allowed for in a certain setting: “Given the abuses of psychosurgery in the previous century, the use of DBS in the minimal conscious should be supported by strong scientific evidence, stringent oversight, and the full interdisciplinary support of neurosurgeons, neuroscientists, psychiatrists, and physiatrists who can help to assess the patient’s suitability for DBS and provide continuous follow-up over time.”²⁷

Kathrine Bendtsen discusses informed consent of minimally conscious patients in end-of-life care.²⁸ She points out that although impressive progress has been made regarding communication with the minimally conscious through fMRI, we are still left with the problem that this communication is not a true two-way communication, where patients can ask questions, but is limited to a yes-no-communication. “Due to the current limitations of our communication methods with such patients, determining the meaning of their responses may not be possible. Further, patients suffering from MCS (Minimally Conscious State) may refuse or express treatment preferences through EEG or fMRI that conflict with previously expressed wishes.”²⁹ Joseph Fins describes this as follows: “So we need to appreciate the paradox that even as we give voice to some patients, we need to be careful not to undermine their prior articulations because of doubts that might be engendered by a non-response or a response that is incomplete or inconsistent. To do that would create the worrisome paradox that a prosthetic for communication could undermine the patient’s voice, potentially eroding the patient’s right to determine how to live and even die.”³⁰

Gilbert Frédéric discusses suicidal risks after DBS. Although evidence does not suggest that DBS is directly related to suicidal death, there is evidence that postoperative suicidality exists. He therefore poses the question whether patients with a pre-operative history of suicidal attempts should be excluded from treatment, as the possible suicidal harm is higher than the possible treatment benefit.³¹ Farah Focquaert argues that under the assumption that DBS treatment works, a general exclusion of these patients would do more harm than good, even though DBS for treatment resistant depression is at present still an experimental treatment.³²

²⁶ See also: Schlapfer, Thomas, Bettina Bewernick, Sarah Kayser, and Diane Lenz, “Modulating affect, cognition, and behaviour – prospects of deep brain stimulation for treatment-resistant psychiatric disorders”, *Frontiers in Integrative Neuroscience*, Vol. 5, June, Article 29, 2011, pp.1-6.

²⁷ Sen, Anish, Peter Campbell, Sanjay Yadla, Jack Jello, and Ashwini Sharan, “Deep brain stimulation in the management of disorders of consciousness: a review of physiology, previous reports, and ethical considerations”, *Neurosurg Focus*, Volume 29, No 2, 2010.

²⁸ Bendtsen, Kathrine, “Communication with the Minimally Conscious: Ethical Implications on End-of-Life Care”, *AJOB Neuroscience*, Vol.4. No.1, 2013, pp. 46-51.

²⁹ Bendtsen, Kathrine, “Communication with the Minimally Conscious: Ethical Implications on End-of-Life Care”, *AJOB Neuroscience*, Vol.4. No.1, 2013, p. 49.

³⁰ See also: Fins, Joseph J., “Neuroethics, neuroimaging, and disorders of consciousness: promise or peril?”, *Transactions of the American Clinical and Climatological Association*, Vol. 122. 2010, pp. 336-346.

³¹ Frédéric, Gilbert, “Deep Brain Stimulation and Postoperative Suicidality Among Treatment Resistant Depression Patients: Should Eligibility Protocols Exclude Patients with a History of Suicide Attempts and Anger/Impulsivity?”, *AJOB Neuroscience*, Vol. 4, No.1, 2013, pp. 28-35.

³² Focquaert, Farah, “Rethinking Vulnerability”, *AJOB Neuroscience*, Vol. 4, No. 1, 2013, pp. 44-45.

Samantha Copeland discusses the issue of patient selection for DBS treatment in treatment-resistant depression in general. She calls for greater consistency in the criteria for and documentation of patient selection. The importance of particular traits in determining the therapeutic effects of DBS can thus be made apparent. This will entail identifying which outcome is potentially more beneficial for which patient subgroups.³³ Also Schlaepfer et al. call for obligatory standards for inclusion and exclusion criteria until the DBS treatment method is scientifically validated.³⁴ In addition to the criteria mentioned above Nir Lipsman et al. call for multidisciplinary health care teams in psychiatric neurosurgery clinical trials, including psychiatry, neuropsychology, and social care and community care and access teams for pre- and postoperative psychiatric follow-up.³⁵

Hideki Oshima and Yoichi Katayama report on cases of addiction through DBS. As DBS can influence the reward system of a patient, the question remains of what is the normal range of reward oriented behaviour. The authors therefore pose the question on who has the right to control the mental condition and the stimulation. In case self-stimulation is prohibited, the patient's feelings are under someone else's control.³⁶

Emely Bell et al. discuss the influence of DBS on behaviour and personality in Parkinson's patients, where positive effects of the treatment have already been scientifically established. Changes in mood and anxiety are reported after DBS treatment. Consensus on whether these changes are substantial alterations in the personality of the patient has not yet been reached. A further issue the authors discuss are personal adaptation challenges faced by patients. Some patients report difficulty adapting to a new concept of themselves and the improvement of their illness.³⁷ Ron Berghmans discusses the question of identity and calls for additional philosophical analysis of what consequences the direct intervention of DBS in the brain has, as the brain is the organ which is most intimately connected to beliefs.³⁸

Ron Berghmans also discusses the question of safety and efficacy of DBS treatment in Parkinson's disease versus safety and efficacy of DBS treatment in other cases, especially treatment resistant depression. He indicates that since the first positive results of DBS in Parkinson's disease, expectations of DBS for other treatments are very high, which may endanger careful consideration of the initiation of trials in patients. He also argues that very little attention is given to psychological consequences of DBS: in particular, harm as a consequence of disappointment is largely disregarded.³⁹ He also mentions the question of

³³ Copeland, Samantha, "The Ethical Import of Patient Selection", *AJOB Neuroscience*, Vol. 4, No. 1, 2013, pp. 42-43.

³⁴ Schlaepfer, Thomas, Bettina Bewernick, Sarah Kayser, and Diane Lenz, "Modulating affect, cognition, and behaviour – prospects of deep brain stimulation for treatment-resistant psychiatric disorders", *Frontiers in Integrative Neuroscience*, Vol. 5, June, Article 29, 2011, pp.1-6.

³⁵ Lipman, Nir, Mark Bernstein, and Andres Lozano, "Criteria for the ethical conduct of psychiatric neurosurgery clinical trials", *Neurosurg Focus*, Vol. 29, No. 2, 2010, pp.1-3.

³⁶ Oshima, Hideki, and Yoichi Katayama, "Neuroethics of Deep Brain Stimulation for Mental Disorders: Brain Stimulation Reward in Humans", *Neurol Med Chir*, Vol.50, 2010, pp. 845-852.

³⁷ Bell, Emily, Bruce Maxwell, Mary Pat McAndrews, Abbas Sadikot, and Eric Racine, "A Review of Social and Relational Aspects of Deep Brain Stimulation in Parkinson's Disease Informed by Healthcare Provider Experiences", *Parkinson's Disease*, Vol. 2011, p. 8.

³⁸ Berghmans, Ron, "Time to Reconsider Deep Brain Stimulation", Vol. 4, No. 1, 2013, pp. 36-37.

³⁹ Berghmans, Ron, "Time to Reconsider Deep Brain Stimulation", Vol. 4, No. 1, 2013, pp. 36-37.

managing patient expectations and possible therapeutic misconceptions. “Having strong expectations about the benefits of a new ‘opportunity’ offered may lead to serious disappointment when the results are negative. (...) It is a well-known empirical fact that the therapeutic misconception in research is difficult to correct.”⁴⁰

Schlaepfer et al. discuss the problem of selective publication, which is a general scientific integrity problem, but in the field of novel neurotechnologies this is a particular problem, as there is excessive reliance on single-patient case reports.⁴¹ Schlaepfer and Fins also highlight that there is a tendency of selective reporting, which is highly problematic. This not only leads to an over-reporting of positive results, but can also be the basis for duplication of efforts. Research groups will reproduce studies not knowing that similar studies have already failed, which is highly problematic in the field of DBS due to the risks which go along with brain surgery. They therefore call for a comprehensive case registry and quality outcome reporting.⁴²

4.7 Neuroenhancement

The international ethical debate on enhancement among National Bioethics Committees was opened by the President’s Council on Bioethics of the US in 2002. The Council explored a variety of technologies related to enhancement, such as drugs and gene transfers enhancing athletic performance, genetic means of augmenting muscle strength and vigour, techniques for controlling the sex of our offspring, genetic and other means to retard senescence and increase the human lifespan, prospects for genetic enhancement through genetic diagnosis, and psychoactive drugs that can alter mood, memory, and behaviour. The President’s Council on Bioethics finally defined human enhancement as going “beyond therapy”. Instead of restoring an individual to a healthy normal state, enhancement enables a person to exceed this healthy or normal state.⁴³

The Danish Council of Ethics discusses medical/pharmaceutical enhancement “as a way of improving cognitive abilities”.⁴⁴ The term ‘medical enhancement’ refers to so called ‘off-label’ uses of medication, i.e. in situations where the medicine has not been prescribed by a doctor for the person taking the medicine. The Danish Council argues that medical enhancement is detrimental to fairness and justice, leads to a loss of authenticity, erodes valuable conditions for coexistence between people, and warns of side-effects, such as sleeplessness.⁴⁵

⁴⁰ Berghmans, Ron, “Time to Reconsider Deep Brain Stimulation”, Vol. 4, No. 1, 2013, pp. 36-37.

⁴¹ Schlaepfer, Thomas, Bettina Bewernick, Sarah Kayser, and Diane Lenz, “Modulating affect, cognition, and behaviour – prospects of deep brain stimulation for treatment-resistant psychiatric disorders”, *Frontiers in Integrative Neuroscience*, Vol. 5, June, Article 29, 2011, pp.1-6.

⁴² Schlaepfer, Thomas, and Joseph J. Fins, “Deep Brain Stimulation and the Neuroethics of Responsible Publishing”, *JAMA*, Vol. 303, No. 8, 2010, pp. 775-776.

⁴³ Kass, L.R., “Beyond Therapy: Biotechnology and the Pursuit of Human Improvement”, President’s Council on Bioethics, 2003. <http://bioethics.georgetown.edu/pcbe/background/kasspaper.html>

⁴⁴ The Danish Council of Ethics. *Medical enhancement*. 2011. English Summary. <http://www.etiskraad.dk/en/Udgivelser/BookPage.aspx?bookID=%7BCBE7B949-DD1F-4696-9829-90897B2C4B71%7D>

⁴⁵ The Danish Council of Ethics, *Medical enhancement*, 2011, p. 4.

In its opinion “Neuroscience and pharmacological cognitive enhancement: bioethical aspects” the Italian National Bioethics Commission - after a detailed discussion regarding possible risks and harms of pharmacological cognitive enhancement coming to the conclusion that it is still too early for a final and conclusive risk/benefit assessment due to the lack of data and associated research - identifies the following issues, which are of importance in assessing neuroenhancement:

1. coercion (direct and indirect) and freedom: discussion - in the hypothesis of legalisation - on the possibility that this practice could, even if it weren't compulsory, nevertheless become coercive for the population in general or for specific categories (both in the public and private sector) in terms of the penalisation-marginalisation of those refusing to use it;
2. equality: also cause for concern is the possibility that, leaving the regulation of distribution to the free market, only wealthy people could, however, afford access to PCE that is effective and likely to be very expensive, resulting in further accentuation of the already existing “natural” and social inequalities. This problem is the subject of animated discussion in the context of different models of *distributive justice* that have queried the criteria which is most suitable for a “fair” allocation of resources for enhancement;
3. fairness and merit: moreover the question arises as to how one could ensure fairness in competition and the principle of merit should the liberalisation of PCE be accepted;
4. self-perception and perception of the social bond: with regard to this it has been pointed out that there is the risk that the spread of the use of PCE may favour a view of one's actions directed more to one's immediate performance rather than to one's commitment to self formation and that this is likely to affect self-perception and the sense of one's “value” and, at the same time, accentuate the tendency to compete rather than to cooperate.”⁴⁶

The French National Consultative Ethics Committee for Health and Life Sciences (CCNE)⁴⁷ raises the question whether neuroenhancement has a detrimental influence on other functions of the brain which are not the target of enhancement. It could be the case that short term memory is being enhanced whereas intelligence might suffer. As this remains unclear in the absence of long-term studies, the question whether possible detrimental effects are reversible also has to be posed. The CCNE concludes that long-term risk/benefit scenarios are completely unknown.

As regards coercion the CCNE discusses the difference between explicit and implicit coercion in regard to neuroenhancement. In case a minor is being forced by his or her parents to take pills to perform better in school, this would be a case of explicit coercion, whereas implicit

⁴⁶ Comitato Nazionale per la Bioetica, “Neuroscience and pharmacological cognitive enhancement: bioethical aspects”, 2014, p.16.
http://www.palazzochigi.it/bioetica/eng/opinions/Neuroscience_and_pharmacological_cognitive_enhancement.pdf

⁴⁷ National Consultative Ethics Committee for Health and Life Sciences, « *Recours aux techniques biomédicales en vue de 'neuro-amélioration' chez la personne non malade: enjeux éthiques* », Opinion Nr. 122, 2013.

coercion relates to demands of the society in our competitive world (e.g. students taking pills to perform better). Both scenarios pose a serious risk to the autonomy of the individual.

The question of justice is discussed by the CCNE in regard to the possibility to afford neuroenhancing drugs under the assumption that they really work in the long term. As those drugs will not be paid for by social security, the CCNE draws a scenario of an “enhanced class” which can afford paying for those drugs which will enable them to perform better than those who cannot afford them.

Irina Singh and Kelly Kelleher highlight that “widespread neuroenhancement may also come to constrain concepts of “the normal” and lead to lower tolerance of cognitive and other notable differences and disabilities”.⁴⁸ Especially regarding young people this can lead to coercion, as children depend on their parents or teachers. Parents do also play a particular role regarding informed consent as surrogates. They therefore call for a standard “primary care management of neuroenhancement” for initiating such medication, monitoring outcomes and side effects, and for tracking abuses.

Although pharmaceutical/medical enhancement might be the more imminent problem, as pharmaceutical enhancers are widely available to the general public, the literature suggests that neuroenhancement can also relate to non-invasive brain stimulation techniques, which may enhance cognitive skills, mood, and social cognition.^{49,50}

The Nuffield Council takes up this issue and contests a need for enhancement, as it is defined as an intervention beyond therapy. The Council formulates a strong warning to include children in non-therapeutic enhancement research, whereas no concern is formulated when including adults under the precondition of informed consent and review of study protocols by an institutional review board. Mention is also made of privacy concerns in relation to data collected by those devices although they are still highly speculative. The Nuffield Council also mentions the possible infringement of autonomy through coercive pressure to improve oneself either by employers, educators or parents. The Nuffield Council points to the issue of trust: “Unsustainable claims about the enhancement or recreational promise of novel neurotechnologies deceive consumers and raise false expectations. (...) hype by researchers and the popular media undermines public understanding of the current state of scientific understanding of the benefits and risks of these technologies.”⁵¹

Roy Hamilton et al. discuss justice in relation to enhancement by novel neurotechnologies.⁵² They argue that noninvasive brain stimulation for self-enhancement may, just as pharmacological enhancers, not be covered by insurance companies. This could lead to injustice, as a certain minority of the population will be able to pay for the treatment out of

⁴⁸ Singh, Irina, and Kelly J. Kelleher, “Neuroenhancement in Young People: Proposal for Research, Policy, and Clinical Management”, *AJOB Neuroscience*, Vol. 1, No. 1, 2010, pp.3-16.

⁴⁹ Hamilton, Roy, Samuel Messing, and Anjan Chatterjee, “Rethinking the thinking cap – Ethics of neural enhancement using noninvasive brain stimulation”, *Neurology*, Vol. 76, No. 2, 2011, pp. 187-193.

⁵⁰ See also: National Consultative Ethics Committee for Health and Life Sciences, *Ethical issues arising out of functional Neuroimaging*, Opinion 116, 2012.

⁵¹ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, p.181.

⁵² Hamilton, Roy, Samuel Messing, and Anjan Chatterjee, “Rethinking the thinking cap – Ethics of neural enhancement using noninvasive brain stimulation”, *Neurology*, Vol.76, January 11, 2011.

their one pocket. Cognitive abilities will tend to become increasingly “medicalised” to a point where unenhanced cognition may be viewed as a pathologic state.

4.8 Overview – ethical issues

The following summarises the ethical issues in regard to neuroimaging, novel neurotechnologies, and enhancement, which are discussed by National Bioethics Committees, international medical journals, medical ethics journals, and ethics journals. It is intended to help keeping an overview of the different issues discussed.

As regards **neuroimaging** the ethical issues debated are the following:

- Stigmatisation and discrimination especially arising from population-based data of imaging research.
- The selection of research themes in accordance with the priority and pertinence in research needs.
- The handling of incidental findings especially in healthy research subjects.
- Practical/financial restriction to review all images for incidental findings, whereas no review violates the principle of beneficence; restricted review violates the principle of justice.
- Inclusion of incidental findings in the informed consent documents.
- Difficulty of ensuring properly informed consent.
- Management of patient’s expectations.
- Negative impact of false positives vs. potential consequences associated with failing to identify or communicate a possibly life-threatening condition.
- The renunciation of the right not-to-know as inclusion criteria for imaging research.
- The predictive value of today’s brain images, which tends to be overestimated, thus creating hype.
- The problem of protection of the confidentiality of private personal data, in particular those related to mental faculties.

As regards **novel neurotechnologies** the literature and the National Bioethics Committees suggest the following issues which are of ethical importance:

- The need for new therapeutic interventions in relation to uncertainty.
- The access to novel neurotechnologies, which will not be possible for all population groups due to age, socio-economic status, or geographical location.
- The intrusion into an individual’s private domain, as brain implants obtain and can transmit digital data about the brain activity.
- The creation of hype by communicating exaggerated expectations in the technology, which will result in a loss of trust and confidence in the general population and in disappointment of individual patients.
- The dilemma of valid informed consent for DBS treatment in depressed patients calling for additional steps to be taken to ensure that subjects have understood the information necessary for informed consent.
- The problem of surrogate consent for patients in minimally conscious state.
- The problem of communication with patients in a minimally conscious state and end-of-life decisions, as BCI-communication remains a one-way communication.

- Possible conflict of treatment preference expression by Minimally Conscious State patients through EEG or fMRI with previously expressed wishes.
- The problem of exclusion of patients with a pre-operative suicidal history in DBS treatment, as general exclusion might do more harm than good.
- Questions regarding the composition of the research team (inclusion of psychiatry, neuropsychiatry, and social care and community care).
- Problems in regard to self-stimulation in DBS and its possible limitation with impact on the control of a patient's feelings by someone else.
- Problems in regard to changes in mood and anxiety by DBS and the question whether this can be interpreted as a substantial alteration of personality.
- The problem of identity after DBS treatment.
- Safety and efficacy in one case (Parkinson's disease) vs. safety and efficacy in another case.
- The problem of selective reporting, which is a particular problem in the field of novel neurotechnologies due to an extensive reliance on single-patient case reports.
- The problem of the non-existence of a comprehensive case registry and quality outcome of reporting.

As regards **enhancement** the ethical issues debated are the following:

- The definition of enhancement remains difficult, as the line between therapy and treatment beyond therapy is difficult to draw with its impact on the perception of the 'normal'.
- Perception of the normal and its impact on the tolerance of cognitive and other notable differences and disabilities.
- Loss of authenticity.
- Erosion of valuable conditions for coexistence between people.
- Warning in regard to side-effects due to 'off-label' use.
- Coercion for the population in general to enhance themselves to avoid marginalisation or penalisation.
- Creation of an enhanced class, which is rich enough to buy enhancing drugs, as social security does not provide for it.
- New perception of competition and merit.
- The impact on self-perception, the perception of the social bond, and emotions.
- Question of reversibility of detrimental effects due to lack of long term risk/benefit scenarios.
- Problem of inclusion of children in non-therapeutic enhancement research.
- Question of privacy in relation to data collected by enhancing devices.
- Question of pertinence, as enhancement goes beyond therapy and is therefore not needed.
- Creation of a hype, as popular media undermines public understanding of the current state of scientific understanding.

5 Ethical Principles and Values

The discussion of ethical issues in the field of neuroscience in this report has been divided into three different applications in the field (neuroimaging, novel neurotechnologies, and enhancement), which was helpful for collecting the different issues debated in expert circles. The Nuffield Council in its report on novel neurotechnologies offers a chapter on principles and values, which is of interest also for a broader discussion of ethical principals in the field. For the purpose of the analysis of ethical principles, the ethics framework of the Nuffield Council will be presented.

The Nuffield Council starts from the discussion of the “classical set” of principles in biomedical ethics:⁵³ Respect for autonomy, non-maleficence, beneficence, and justice.

Due to the fact that the respective interventions take place in the brain, which on the one hand has a special status, and on the other hand distinguishes humankind from other species - including other primates⁵⁴ - the **principle of autonomy** is discussed, understood as the capacity to act for reasons that we ourselves identify with and endorse.⁵⁵

The Nuffield Council discusses the principle of caution. According to the report the principle of caution is rooted in the precautionary principle. However “in the face of clear suffering and unmet needs, the precautionary principle runs the risk of stifling the development of new neurotechnologies”⁵⁶. Thus the Nuffield Council proposes to introduce the principle of caution, which recognises that some risks and some uncertainty about risk may be tolerated where technologies can make a significant contribution to individual patients and the public good. The principle of caution, as used in the Nuffield Council’s definition seems to be identical with the **principle of beneficence** (one ought to prevent evil or harm, remove evil or harm, to do or promote good) in combination with the **principle of non-maleficence** (one ought to prevent evil or harm)⁵⁷, as it is less strict than the precautionary principle and acknowledges that a certain amount of risk is inherent to any new technology. For the purpose of this report we will stick with the terminology **beneficence / non-maleficence** to describe the dichotomy of need and uncertainty.

The **principle of justice** is discussed under the issue of equity or distributive justice, as access to novel neurotechnology treatment will not always be possible. Disproportional distribution will affect vulnerable groups due to age, socio-economic status, or geographical location (less developed regions).⁵⁸

In addition to the values in accordance with principlism, the Nuffield Council discusses the issue of privacy in relation to novel neurotechnologies, as brain implants obtain and can transmit digital data about the brain activity of their users, which can be seen as an intrusion

⁵³ Beauchamp, Tom L., and James F. Childress, *Principles of Biomedical Ethics*, Oxford University Press, New York/Oxford, 2009.

⁵⁴ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, p. 73.

⁵⁵ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, p. 79.

⁵⁶ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, p. 78.

⁵⁷ Beauchamp, Tom L., and James F. Childress, *Principles of Biomedical Ethics*, Oxford University Press, New York/Oxford, 2009, p.151.

⁵⁸ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, p. 83.

into an individual's private domain, especially in case the obtained data is stored for future use. The discussion of **privacy**, although it goes beyond principlism, can be considered as part of the standard debate in the field, as soon as data is recorded and goes beyond the privacy concept in principlism, which considers privacy mainly in relation to professional-patient relationships.

A totally new principle in relation to principlism is introduced by the Nuffield Council by discussing the issue of **trust** created by the communication of exaggerated research expectations.⁵⁹

In addition to principles, the Nuffield Council proposes **virtues**, which can possibly be best compared to values, which provide certain guidance in practical application, but are nevertheless abstract in comparison to ethical issues. The virtues mentioned are **inventiveness, humility, and responsibility**.⁶⁰ These virtues are supposed to guide practitioners to balance the needs and uncertainties of developing novel neurotechnologies.

Inventiveness describes the willingness of researchers and clinicians to move the standard of treatment forward. Inventiveness therefore helps to extend the benefits of technologies to those with profound therapeutic needs.

Humility refers to the acknowledgement of the limits of the scientists' understanding of the brain and the limited capacity to cure or remove all suffering. The virtue of humility goes beyond the principle of caution and suggests a need for permanent deliberation about the right action in a given situation.

Responsibility is the virtue that strives a balance between the principles of beneficence and caution. On the one hand it calls for ethical formation of researchers; on the other hand it also connects with the social responsibility of researchers regarding the translation of the researchers' work into the public sphere.

The principles, which are of importance for the discussion of neuroethics are:

- Autonomy
- Beneficence/non-maleficence
- Justice
- Trust
- Privacy

The virtues by which guidance is provided for the application of these principles are:

- Inventiveness
- Humility
- Responsibility

⁵⁹ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, p. 84.

⁶⁰ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, pp. 87.

5.1 Ethical issues in relation to principles

In order to demonstrate how principles and ethical issues are interlinked, the ethical issues identified in the respective section above will be grouped according to the ethical framework proposed regardless of the former division in order to be able to present one set of principles and values for neurosciences providing an idea of what they could mean in terms of ethics issues. The issues are only stated and not re-discussed, as a more detailed description is provided in the sections above.

5.1.1 Ethical issues in relation to the principle of autonomy

The following ethical issues relate to the principle of autonomy in neuroscience:

- Difficulty of ensuring properly informed consent.
- The renunciation of the right not-to-know as inclusion criteria for imaging research.
- Dilemma of valid informed consent for DBS treatment in depressed patients calling for additional steps to be taken to ensure that subjects have understood the information necessary for informed consent.
- The problem of surrogate consent for patients in Minimally Conscious State.
- The problem of communication with patients in a Minimally Conscious State and end-of-life decisions, as BCI-communication remains a one-way communication.
- Possible conflict of treatment preference expression by Minimally Conscious State patients through EEG or fMRI with previously expressed wishes.
- Problems in regard to self-stimulation in DBS and its possible limitation with impact on the control of a patient's feelings by someone else.
- Problems in regard to changes in mood and anxiety by DBS and the question whether this can be interpreted as a substantial alteration of personality.
- Problem of identity after DBS treatment.
- The definition of enhancement remains difficult, as the line between therapy and treatment beyond therapy is difficult to draw with its impact on the perception of the "normal".
- Loss of authenticity.
- The impact on self-perception, the perception of the social bond, and emotions.
- Problem of inclusion of children in non-therapeutic enhancement research.

5.1.2 Ethical issues in relation to the principle of beneficence / non-maleficence

The following ethical issues relate to the principles of beneficence/non-maleficence in neuroscience:

- The selection of research themes in accordance with the priority and pertinence in research needs.
- The handling of incidental findings especially in healthy research subjects.
- Practical / financial restriction to review all images for incidental findings, whereas no review violates the principle of beneficence; restricted review violates the principle of justice.
- Inclusion of incidental findings in the informed consent documents.
- Management of patient's expectations.

- Negative impact of false positives vs. potential consequences associated with failing to identify or communicate a possibly life-threatening condition.
- The need for new therapeutic interventions in relation to uncertainty.
- Problem of exclusion of patients with a pre-operative suicidal history in DBS treatment, as general exclusion might do more harm than good.
- Questions regarding the composition of the research team (inclusion of psychiatry, neuropsychiatry, and social care and community care).
- Safety and efficacy in one case (Parkinson's disease) vs. safety and efficacy in another case.
- The problem of selective reporting, which is a particular problem in the field of novel neurotechnologies due to an extensive reliance on single-patient case reports.
- Problem of the non-existence of a comprehensive case registry and quality outcome of reporting.
- Warning in regard to side-effects due to 'off-label' use.
- Question of reversibility of detrimental effects due to lack of long term risk/benefit scenarios.

5.1.3 Ethical issues in relation to the principle of justice

The following ethical issues relate to the principle of justice in neuroscience:

- Practical /financial restriction to review all images for incidental findings, whereas no review violates the principle of beneficence; restricted review violates the principle of justice.
- The access to novel neurotechnologies, which will not be possible for all population groups due to age, socio-economic status, or geographical location.
- Perception of the normal and its impact on the tolerance of cognitive and other notable differences and disabilities.
- Erosion of valuable conditions for coexistence between people.
- Coercion for the population in general to enhance themselves to avoid marginalisation or penalisation.
- Creation of an enhanced class, which is rich enough to buy enhancing drugs, as social security does not provide for it.
- New perception of competition and merit.
- The impact on self-perception, the perception of the social bond, and emotions.
- Question of pertinence, as enhancement goes beyond therapy and is therefore not needed.

5.1.4 Ethical issues in relation to the principle of privacy

The following ethical issues relate to the principle of privacy in neuroscience:

- Stigmatisation and discrimination especially arising from population-based data of imaging research.
- The problem of protection of the confidentiality of private personal data, in particular those related to mental faculties.
- The intrusion into an individual's private domain, as brain implants obtain and can transmit digital data about the brain activity.

- Question of privacy in relation to data collected by enhancing devices.

5.1.5 Ethical issues in relation to the principle of trust

The following ethical issues relate to the principle of trust in neuroscience:

- The predictive value of today's brain images, which tends to be overestimated, thus creating hype.
- The creation of hype by communicating exaggerated expectations in the technology, which will result in a loss of trust and confidence in the general population and in disappointment of individual patients.
- Creation of hype, as popular media undermines public understanding of the current state of scientific understanding.

5.2 Organisations / Institutionalisation

The policy debate of neuroscience as a sub-discipline of medical ethics is conducted mainly in the framework of National Bioethics Commissions. National Bioethics Committees are independent bodies commissioned to advise politics in the field of new developments in the life sciences. As they are commissioned to report on possible impact of new scientific developments in societal and legal issues, the analysis of their opinions in the field of neuroscience seems best fit to highlight values and principles in the field.

The following **National Bioethics Commissions** have the issue on the agenda or have already drafted respective opinions:

- German Ethics Council (http://www.ethikrat.org/welcome?set_language=en)
- Nuffield Council (<http://www.nuffieldbioethics.org/>)
- Comité Consultatif National d'Ethique (<http://www.ccne-ethique.fr/en>)
- Presidential Commission for the Study of Bioethical Issues (<http://www.bioethics.gov/>)
- Comitato Nazionale per la Bioetica (<http://www.governo.it/bioetica/eng/index.html>)
- The Danish Council of Ethics (<http://www.etiskraad.dk/Udgivelser.aspx>)

Scientific discussion on neuroethics is also taking place in **international scientific societies**. Some major organisations in the field are:

- World Federation of Neurology (<http://www.wfneurology.org/>)
- International Neuroethics Society (<http://www.neuroethicssociety.org/>)

Regarding individual research protocols, the debate takes place in **research ethics committees**:

- European Network of Research Ethics Committees (<http://www.eurecnet.org/index.html>)

5.3 International Frameworks and protocols

International frameworks and protocols which apply exclusively to neurosciences are rare. However several regulatory frameworks are applicable to neuroscience. These include the World Medical Association's Declaration of Helsinki in its latest version, the Universal Declaration on Bioethics and Human Rights of UNESCO, the Convention on Human Rights

and Biomedicine of the Council of Europe, and several Directives of the European Union, which are relevant for clinical trials in the field of neuroscience and for medical devices (BCIs, DBS, TMS, etc.). Principles and ethical issues which are treated in these legal instruments will shortly be described.

As regards medical / pharmaceutical enhancement there are no instruments which directly address neuroenhancement. Only rules of professional standards are applicable to medical / pharmaceutical neuroenhancement, because the problem - as described earlier - lies in the “off label” use of medication prescribed in another medical context. It is therefore very difficult to regulate the phenomenon as such.

Particular issues in the licensing procedure of non-invasive novel neurotechnologies for gaming purposes will not be discussed in this report in detail (they are only mentioned under “other issues”). The relevance may also be questioned, as limitations of the technology by ethical considerations cannot be justified by vulnerability and would thus be discriminatory.

5.3.1 Declaration of Helsinki

The World Medical Association (WMA) has adopted numerous policies that are recognised internationally as the global ethical standard for the topics they address. The most important guidance document in regard to professional standards is the Declaration of Helsinki which was first adopted in 1964 and has been amended periodically.⁶¹ The principles which are set out in the document are: risks, burdens, and benefits; vulnerable groups and individuals; scientific requirements and research protocols; research ethics committees; privacy and confidentiality; informed consent; use of placebo, post-trial provisions; research registration and publication and dissemination of results; unproven interventions in clinical practice.

The document does not address neurosciences as such, but gives general guidance on principles which should be respected in regard to biomedical research.

5.3.2 Convention on Human Rights and Biomedicine

The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine⁶² was signed on 4 April 1997. The convention is binding for those Member States of the Council of Europe who have signed and ratified it.⁶³ The document does however have guiding function for the whole bioethics discourse, as it spells out the major principles of autonomy, beneficence/non-maleficence, and justice.

The Convention stipulates that the interests and welfare of the human being shall prevail over the interest of society or science. The convention treats questions regarding consent, private life and right to information, human genome, scientific research, transplantation, prohibition of financial gains, and public debate. Although neurosciences are not treated as such, the Convention gives guidance on fundamental principles which are also valid in this field.

⁶¹ <http://www.wma.net/en/30publications/10policies/b3/>

⁶² <http://conventions.coe.int/Treaty/EN/Treaties/Html/164.htm>

⁶³ <http://conventions.coe.int/Treaty/Commun/ListeTraites.asp?CM=8&CL=ENG>

Further guidance in regard to scientific research is provided by the Additional Protocol on concerning Biomedical Research.⁶⁴

5.3.3 Universal Declaration on Bioethics and Human Rights

The Universal Declaration on Bioethics and Human Rights⁶⁵ was adopted in 2005. The Declaration is a soft law instrument and gives guidance in regard to ethical issues raised by medicine, life sciences and associated technologies as applied to human beings. Member States have committed themselves to respect and apply the fundamental principles of bioethics set forth within a single text.

The fundamental principles which are addressed in the Declaration are: human dignity and human rights; benefit and harm; autonomy and individual responsibility; consent; persons without the capacity to consent; respect for human vulnerability and personal integrity; privacy and confidentiality; equality, justice and equity, non-discrimination and non-stigmatisation; respect for cultural diversity and pluralism; solidarity and cooperation; social responsibility and health; sharing of benefits; protection for future generations; protection of the environment, the biosphere and biodiversity.

The Declaration also gives guidance on the application of the principles by formulating ideas on how bioethical issues shall be addressed in the Member States. It calls for the establishment of Ethics Committees, and professional risk assessment and management.

In regard to neurosciences the Declaration sets out the general framework in which research can take place, but does not have a particular focus on the issue. It has to be mentioned that the International Bioethics Committee of UNESCO (IBC) is presently working on a document which treats neuroscience in relation to the principle of non-discrimination and non-stigmatisation⁶⁶

5.3.4 Clinical Trial Directive

The Clinical Trial Directive on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use⁶⁷ stipulates that clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data.

Ethics Committees in the understanding of the Clinical Trial Directive are independent bodies in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety, and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other issues, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities,

⁶⁴http://www.coe.int/t/dg3/healthbioethic/activities/01_oviedo%20convention/195%20Protocole%20recherche%20biomedicale%20e43.pdf

⁶⁵ Universal Declaration on Bioethics and Human Rights

⁶⁶ <http://unesdoc.unesco.org/images/0022/002211/221196E.pdf>

⁶⁷ Directive 2001/20/EC

and on the methods and documents to be used to inform trial subjects and obtain their informed consent.

Ethical issues which have to be addressed according to the Directive:

- the relevance of the clinical trial and the trial design;
- whether the evaluation of the anticipated benefits and risks (...) is satisfactory and whether the conclusions are justified;
- the protocol;
- the suitability of the investigator and supporting staff;
- the investigator's brochure;
- the quality of the facilities;
- the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent;
- provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;
- any insurance or indemnity to cover the liability of the investigator and sponsor;
- the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the site;
- the arrangements for the recruitment of subjects.

The Directive does not address neurosciences specifically, but is relevant for clinical trials, which are performed in the field.

It also has to be mentioned that the Directive is subject for proposal to reform.

5.3.5 Medical Devices Directive

Technological devices in the field of novel neurotechnologies fall under the EU legislation of medical devices. The original directive was adopted in 1993⁶⁸ and has since been amended by several directives. The legislation stipulates that for devices - under which some of the devices in the field of novel neurotechnologies fall - Ethics Committees have to issue a favorable opinion. The directives stipulate several provisions in relation to safety, quality, and usefulness. The clinical evaluation which is an essential requirement for admission comes closest to the question of ethical preconditions.

⁶⁸ COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF>
Amendments:
Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998
Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000
Directive 2001/104/EC of the European Parliament and of the Council of 7 December 2001
Regulation (EC) No 1882/2003 of the European Parliament and of the Council of 29 September 2003
Directive 2007/47/EC

As regards methodology the directives stipulate that clinical investigations must be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims for the device; these investigations must include an adequate number of observations to guarantee the scientific validity of the conclusions. The procedures used to perform the investigations must be appropriate to the device under examination. Clinical investigations must be performed in circumstances similar to the normal conditions of use of the device. All the appropriate features, including those involving the safety and performances of the device, and its effects on patients must be examined.

As regards ethical considerations, the directive stipulates that clinical investigations must be carried out in accordance with the Helsinki Declaration adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, as last amended by the World Medical Association. It is mandatory that all measures relating to the protection of human subjects are carried out in the spirit of the Helsinki Declaration. This includes every step in the clinical investigation from first consideration of the need and justification of the study to publication of the results.

5.3.6 Other issues

Non-invasive novel neurotechnological devices (primarily BCIs) that are sold for gaming purposes may fall under several other directives:⁶⁹

- Directive 1999/5/EC of the European Parliament and of the Council of 9 March 1999 on radio equipment and telecommunications terminal equipment and the mutual recognition of their conformity or, if powered by a voltage not exceeding 24 volts,
- Directive 2009/48/EC of the European Parliament and of the Council of 18 June 2009 of the safety of toys (as amended).

Electrical equipment with a voltage input or output of 50-1500 volts is regulated under:

- Directive 2006/95/EC of the European Parliament and of the Council of 12 December 2006 on the harmonisation of the laws of Member States relating to electrical equipment designed for use within certain voltage limits.

5.3.7 Responsible Research and Innovation

It can be noted that the Nuffield Council in its report on “Novel neurotechnologies: intervening in the brain”, also discusses the concept of RRI. The following six priorities are suggested that apply specifically to RRI in the context of novel neurotechnologies:

- Clearly identified needs
- Securing safety and efficacy
- Generating robust evidence
- Continuous reflexive evaluation
- Coordinated interdisciplinary action
- Efficacy and proportionate oversight

⁶⁹ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, p. 178

The Nuffield Council interprets RRI as a complementing framework to the ethical principles and values and to the virtues established for guiding the practical application of principles and values. It therefore creates a third layer of evaluation of novel technologies. By stating that “the concept of ‘responsible research and innovation’ (RRI) has been adopted by policy-makers as a way of thinking systematically about the public benefits of science and technology-based research”⁷⁰, RRI is clearly situated in the developing chain of applied research, which needs to contribute to the direct benefit of society. It can therefore be concluded that RRI cannot be applied to basic or so called “blue sky” research, as public benefit is unclear in that stage of research.

5.3.8 Conclusions

The objective of the report was to answer the question of which ethics assessment framework exists in regard to neurosciences. The analysis showed that the classification of the debated issues in ethics issues and principles / values is difficult, as the underlying “value-system” is rarely discussed or presented in the literature, although it forms and guides the discussion of the issues.

It was shown that the ethical issues which are discussed in the literature relate to the “classical set” of principles in biomedical ethics: Respect for autonomy, non-maleficence, beneficence, and justice. In addition to the values in accordance with principlism, issues of privacy in relation to novel neurotechnologies are being discussed.

Trust forms a totally new principle in comparison to principlism and relates to possible hype created by the communication of exaggerated research expectations.

The principles which frame the ethics discussion on neurosciences are thus:

- Autonomy
- Beneficence/non-maleficence
- Justice
- Trust
- Privacy

A further interesting conceptual question relates to the interrelationship of the ethics assessment framework (ethics issues in relation to principles / values) and the concept of RRI.

The Nuffield Council in its report on “Novel neurotechnologies: intervening in the brain”, discusses the concept of RRI. It identifies the following six issues as assessment framework: Clearly identified needs, securing safety and efficacy, generating robust evidence, continuous reflexive evaluation, coordinated interdisciplinary action, and efficacy and proportionate oversight.

In case we assume an interrelationship of these frameworks, the following levels of evaluation would be of relevance:

⁷⁰ Nuffield Council on Bioethics, *Novel neurotechnologies: intervening in the brain*, May 2013, p. 118.

1. Evaluation of RRI framework on the societal level regarding needs, securing safety and efficacy, generating robust evidence, continuous reflexive evaluation, coordinated interdisciplinary action, and efficacy and proportionate oversight.
2. Evaluation of ethical principles within the scientific domain related to the respect for autonomy, non-maleficence, beneficence, justice, privacy, and trust guided by virtues in relation to scientific integrity.
3. Evaluation of ethical issues related to day-to-day work in research and treatment in combination with the virtues of inventiveness, humility, and responsibility.

Ethics assessment frameworks have been codified to certain extent. Codification has taken place either in soft law instruments, such as the Helsinki Declaration, the Universal Declaration on Bioethics and Human Rights; or in binding legal instruments such as the Convention on Human Rights and Biomedicine, which has a binding character for those Member States of the Council of Europe which have signed and ratified the Convention, the Clinical Trial Directive of the European Union, or the Medical Devices Directive of the European Union, which is binding for the Member States of the European Union.

As the development of scientific knowledge is a globalised phenomenon, the codification of the respective fields of knowledge has to be globalised as well. The existing regional instruments are a good start for further discussion.

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