Request for Information (RFI)
Guidance for Opportunities in Neuroethics
(NIH BRAIN Initiative)

Submission on behalf of the

International Neuroethics Society (INS)

INS Response Action Task Force*, Mark S. Frankel, PhD., Task Force Chair
Judy Illes, PhD, INS President and Chairman of the Board

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The International Neuroethics Society (INS) is pleased to offer comments in response to the above-referenced Request for Information (RFI). INS is an interdisciplinary group of scholars, scientists, clinicians and other professionals who share an interest in the social, legal, ethical and policy implications of advances in neuroscience. Our mission is to promote the development and responsible application of neuroscience through interdisciplinary and international research, education, outreach and public engagement for the benefit of people of all nations, ethnicities, and cultures. One of the Society's core values is to "provide guidance for our members and the general public through educational programs, information, analysis, and discussion of ethical policy issues involved in neuroscience." In the comments below, we offer views from the Society related to neuroscience research and its applications. The comments are not a comprehensive response to all the questions raised in the RFI, but reflect those we believe are among the most pressing.

More information about INS can be found at
http://www.neuroethicssociety.org/about.

EXECUTIVE SUMMARY

In neurotechnology research and development, several trends are currently converging that warrant particular ethical scrutiny and policy guidance, in particular the development of novel invasive devices for recording neural data and for direct cortical brain stimulation, novel computing methods for analyzing big data, and intelligent device programming for medical use based on machine learning (e.g., deep learning, neural networks). Technologies such as brain stimulation and neural stem cell therapies offer the potential to treat intractable forms of common neurological conditions as well as psychiatric disorders, such as addiction, depression, and obsessive compulsive disorders. These neurotechnologies also raise the possibility of predicting and monitoring brain patterns and to extending or enhancing human capacities. These possibilities present a range of complex social

and clinical challenges, in addition to the scientific imperative to demonstrate their safety and efficacy when used to treat persons with disorders. A summary of the key social and policy considerations from this submission is presented below:

Areas for policy guidance that might be useful for Principal Investigators and Institutional Review Boards regarding emerging neuroethics issues associated with neurotechnology research and development. We welcome responses that point to specific strengths or weaknesses in current policies and suggestions for how we can expand and/or improve these policies.

- Emerging neurotechnologies can have subtle but significant impacts (both positive and negative) on a person's health and well-being. These impacts may emerge despite effective treatment of the target symptoms. Clinical trials of emerging neurotechnological interventions must anticipate and examine potential side effects of neurotechnological interventions, including the impact on overall well-being and quality of life. Current assessment of neurotechnological interventions on patients' overall health and well-being often fail to provide the full picture needed to assess the benefits of the interventions. ***As such, a more comprehensive and uniform set of metrics should be developed to assess patient's quality of life and wellbeing before and after interventions.***

- Novel intracranial devices pose specific medical risks such as central nervous system infection or epileptic seizures. ***Therefore, current safety guidelines and regulations of invasive medicinal products should be reviewed with respect to whether they are adequate for risk assessment of these devices.***

- Assessment of the positive and negative consequences of novel neurotechnologies will also need to consider their impact on families and care-givers. ***As such, measurement of improvement, when applicable, should consider a broader definition of outcomes, one that includes these networks of care.***

- Initial trials of emerging invasive or risky neurotechnologies (e.g., deep brain stimulation (DBS)) involve case reports or case series of treated individuals. The trials of these technologies are particularly vulnerable to publication bias, both from non-publication of results and the small sample sizes reported in published work. Current repositories of research (such as clinicaltrials.gov) have some initial information on clinical trials but often no follow-up with updates or results is provided by the researchers. This ***lack of up-to-date information on clinical trials is worrying, as it distorts the evidence base supporting the use of these technologies, and should be addressed by researchers and policy makers.***

- The increasing capabilities of intelligent software in solving complex problems (e.g., the AlphaGo software of Google DeepMind or self-driving cars) makes these programs attractive for medical neuroscience, particularly for automated

image processing and for brain-computer interfacing. With the increasing complexity of the software, however, particular decisions of the programs may be impossible to predict or infer retrospectively. This may open an *accountability gap* in cases in which an intelligent systems fails and a user (e.g., a severely paralyzed patient with a brain-computer interface (BCI) or a third-party is harmed as a result. ***There is a need to review current regulatory oversight regarding intelligent, (semi)autonomous systems, and, where appropriate, to consider closing any policy gaps found to exist.***

- Pairing medical devices for brain-computer interfacing (or DBS) with intelligent software may also adversely affect a person's sense of self, personal identity and autonomy. Very few studies have investigated this area and further research employing various quantitative and qualitative methods is urgently needed. ***Researchers should consider, for example, whether trials with medical devices that interfere with or make use of neural activity should mandatorily include the collection of data on a person's mental well-being and effects of the device on personal identity and autonomy.***

- ***It is important to consider proactively the ethical implications of novel technologies before they are widely used. In doing so, researchers and others must be mindful of the impact that speculative concerns about possible misuses of a technology may have on public and patient views of the technologies***. Such speculation may unwittingly raise expectations about the effectiveness of experimental technologies, in ways that impair patients' ability to consider fully and accurately the risks of participating in trials of these technologies. The way in which health care is provided and the effectiveness with which it is delivered can be affected by diverse opinions towards the condition being treated. In such cases, risky or invasive neurotechnologies should not be used to compensate for a failure to provide good access to current treatments optimally provided.

- ***Neuroscientists also need to consider potential adverse social side effects of research on novel neurotechnologies***. One such effect is overemphasising the neurobiological causes of a disease and narrowly focussing on high-risk neurobiological solutions at the cost of providing good psychosocial care and support. Concentrating only on the neurobiological characteristics for many common mental disorders can lead to a focus on the severe forms of illnesses at the expense of ignoring the needs of the majority of individuals with less severe forms. Likewise one should not lose track of preventive strategies. As more is learned about the impact that environmental, epigenetic and the microbiome changes have for brain and mental health, initiatives to address and mitigate the negative influences of these factors to brain and mental health should be considered.

- It is often assumed that neurobiological explanations of mental illness, often captured in the phrase "a disease like any other" or in describing mental illnesses as "brain diseases," will increase acceptance of mental illness as real conditions and reduce the stigma and discrimination many face. This claim needs to be

rigorously evaluated. While it appears that this may have been the case with disorders such as depression, there is growing evidence that neurogenetic explanations of disorders such as schizophrenia and drug addiction may increase stigma and discrimination by making these individuals' behavior seem less under their control and therefore dangerous. ***Research needs to be conducted to examine the impact of neurobiological explanations on affected individual's belief in their ability to overcome their condition (e.g., self-efficacy) and their willingness to seek treatment.***

- ***It is important to assess how neurobiological explanations of mental illness impact the legal system, both in terms of responsibility as well as in cases when neurointerventions are offered as forms of rehabilitation***.

The evolving breadth of neural data and associated issues such as:

- Who should own the data (the research participant, the investigator, the institution, the public)?
- Storage of data (in the cloud, via federated databases?) and security concerns
- Who should have access to these data (by whom, how quickly, for how long, types of data)?
- Privacy concerns and protection from discrimination for those whose neural data are shared
- Unintended uses of data

- Progress in medical neuroscience is tightly linked to novel, evolving and intersecting fields of computer science such as data science, neuroinformatics, and machine learning. Because of the increasing computational capability for inferring mental states (mind-reading), ***identifying neurophysiological traits from neural data (neuro-typing), and de-identification, the question of data privacy (ownership) and security (access) is pertinent and largely unresolved.***

- There is a pressing need for the following steps to address the uncertainty attached to the growing mountain of neural data:

  (1) ***Review existing guidelines for study protocols, clinical trial guidelines and other relevant documents to determine whether data privacy and security norms, policies and procedures are up-to-date with respect to emerging computing capabilities;***
  (2) Survey of experts in the fields of neuroengineering and computational neuroscience (in both the public and private sectors) on the capabilities and current state of methods for neurotyping, mind-reading and other methods that pose threats for exposing personal information of subjects;
  (3) Support efforts to deliberate potential threats for neural data privacy and security with the help of experts in the field of computing science and data security, end-users and other relevant stakeholders (including

commercial interests involved in the manufacturing and selling of data devices).
(4) Solicit opinions of legal scholars in the field of data privacy and security on whether neural data constitute a special type of data that warrant other levels of data security as compared to conventional medical or personal data (which can also be used for de-identification, stigmatization or other misuses); and
(5) Encourage greater crosstalk between governmental agencies (e.g., NIH, FDA, Office of Civil Rights (OCR)) to align regulatory directives regarding device/information security in this sphere.

- There has been a wide discussion of the ethical, policy, legal and social implications of genetic information and biobank data. The Brain Initiative should examine work done in this area in order to: ***(1) assess if and how neural data is any different from other sources of biological data, and (2) draw insights from previous big initiatives regarding other types of biological data.***

Special considerations associated with novel neuromodulation and neuroimaging technologies:
- Activation and monitoring of devices (who does it, when is it done)
- Responsibility for the long-term maintenance of such devices
- Security regarding the telemetry of data to remote storage devices
- Potential culpability concerns regarding predictions from neural data

- Activation and monitoring of the device will depend on the technology being employed and the condition being treated. It is therefore unlikely that a fixed protocol can be developed for such studies. The protocol must be transparent, clearly communicated to the participant, and must be guided largely by what is in the participant's best interest. ***Developing more robust measures for determining the best interests of participants should be a priority***.

- More research is needed regarding the possibility of patients self-managing their own devices. On the one hand, this might provide them with greater ownership over something that essentially will become part of their body. On the other hand, this also might make easier for third parties to hack or interfere with the devices. Likewise more research is needed in the type of parameters that patients should be able to change and the level of freedom they should have over their devices. This ***research should also address concerns regarding the addictive potential of electronic "self-stimulation," the induction of severe personality changes (e.g., impulsivity or mania) or errors made in self-adjusting***.

- Trials of emerging neurotechnologies, such as the surgical implantation of recording or stimulating electrode devices, must take into consideration the long-term maintenance of the devices as well as continuity of care for the research participants, particularly in cases where adverse occur in the trial. Such responsibility needs to be factored into the initial design and budgeting of the

trials. ***Considering the vulnerability of research subjects undergoing these experimental procedures, contingencies should be established to manage the follow up of participants in cases where trials are discontinued***.

- It is researchers' responsibility to ensure the security of participants' personal information. It is critical that any potential risks to their privacy are articulated to the participant in a manner that is clearly comprehensible. For example, the risks created by the communication of information using modern wireless devices that record sophisticated personal information can be difficult for many research participants to understand. Therefore, ***research is needed to assess the means to responsibility for communicating the risk in a way that is understandable to the participant, possibly using visual aids*** (see Informed Consent below).

- Incidental findings and predictive quality of neuroimaging and related data. This point has been connected in the past to ways in which anatomical data are interpreted; interpretation of incidental findings of functional data is key for the future. For example, many authors have raised the issue that the current state of brain imaging one should be careful to use it for prediction***. Is there a point when neuroimaging data should be used for prediction? Should it be used only for predicting clinical outcomes, or other issues such as its use in neuromarketing and for predicting the likelihood that someone might commit a crime?***

- Another concern is the ***process of quality control of software tools that analyze neural data***. Often these programs are custom-made, in-house developments coming out of universities or other research facilities and are maintained by a dedicated group of (often just a few) individuals. The quality control of the program code and independent assessment of a program's validity are often lacking or incomplete. This is highlighted by a recent study that revealed a 15-year-old bug in a commonly used neuroimaging software and showed that statistical inference on brain activation at the cluster-level in functional magnetic resonance imaging (fMRI) is often invalid, calling up to 43.000 fMRI studies of recent years into question (Eklund *et al.*, 2016).

How to best integrate neuroethics, as appropriate, in workshops and training opportunities and when communicating neuroscience research findings to:

- Press
- Lay public
- Political leaders
- Scientific Community

- Neuroscience training and workshops need to routinely include training and education about the ethical, social and policy implications of neuroscience research. Scientists cannot turn a blind eye when their research leaves the lab and enters the public domain. This requires an appreciation of the ethical, political and social factors that can impact upon the way that the results of

scientific research (whether technological or theoretical) are perceived and used by various stakeholders within the community. ***Educational initiatives should encourage critical reflection on the practical consequences neuroscience and neurotechnology have for individuals and society.***

- Training in ***scientific outreach about neuroethical issues*** should be incorporated into academic training, particularly at the PhD level.
- People who are potential users of these technologies may be experiencing severe mental illnesses or cognitive disturbances that drastically impact on their quality of life. These individuals are often desperate for a panacea for their condition. Taking into account these patients' expectations is a significant challenge. ***More research is needed to better understand patient expectations and mitigate the adverse consequences of unrealistic expectations***.

- Other potential users of neurotechnologies are overall healthy people with a desire to improve certain cognitive areas or sustain well-being. In these cases, it is also important to ***engage with these other users, who might more easily get access to certain neuromodifiers (such as transcranial brain stimulation devices or drugs).***

- Neuroethics can play an important intermediary role in communicating neuroscience and moderating discussions between stakeholders. The neuroethics community consists of scholars and professionals from a variety of academic backgrounds such as clinical medicine, clinical neuroscience, basic neuroscience, philosophy, law, computer science, and neuroengineering. Many neuroethicists have expertise in multiple areas and in both the private and public sectors. Neuroethicists are therefore well placed to ***provide a moderating and mediating role between stakeholders with differing opinions and objectives.***

- Engagement with policy makers and politicians related to the development of policies/position statements or guidance must involve those directly affected (and their caregivers) by disorders of the brain or receiving brain interventions. ***Participatory models of political decision-making such as the concepts of deliberative democracy and citizen juries (Habermas, 1994) should be explored as useful frameworks for soliciting the knowledge and attitudes held by all stakeholders regarding novel neurotechnological devices.***

Informed consent issues, specifically pertaining to studies using novel neurotechnologies:

- Establishing greater uniformity in the informed consent process
- The participant perspective on the consent process
- How consent permits/hinders what is possible with technological advances
- Issues for special populations such as pregnant women, children, and those with physical and/or intellectual disabilities or cognitive impairment

- The complexity of research or clinical trials involving emerging neurotechnologies can be difficult to fully comprehend. Participants may also be experiencing neurocognitive adverse events that impair their ability to comprehend fully the implications of participating in research or trials. Participants may also be desperate for a cure for their condition or under some form of social coercion (e.g., from friends or family) to undergo treatment. The Informed consent process needs to be robust and aimed at sufficiently communicating to participants in ways they can understand and consider the issues pertinent to them and their wishes. ***The informed consent process requires adequate validation to determine that potential research participants heard, understood, and can recall what they were told***.

- ***The informed consent process needs to go beyond the single event of providing information exemplified by the legal process of signing an informed consent form***. For clinical trials in particular, obtaining consent should be an ongoing process that engages the patient and creates a strong and trusting researcher-patient relationship, one that validates the patient's experiences and aims to maximize autonomy.

- Patients with serious illnesses are often desperate and may have unrealistic expectations of the likely effectiveness and discount risks, particularly if the putative benefits of the technology have been hyped in media. Empirical research has, for example, highlighted this as a major challenge in studying DBS. ***Improved strategies are still needed to minimise the effects of media hype on patient populations.***

- All of the points above related to informed consent would benefit from more ***research to determine better approaches to obtaining informed consent in specific conditions, as are studies of attitudes and understanding of the issue of consent by physicians, caregivers and researchers***. Better training of research staff is desirable as a means to facilitate a better informed consent process.

Translation of new tools and technologies for neuroscience research to contexts beyond the clinic/bench: Ethics of commercialization, public-private partnerships, wider application of imaging technologies for commercial purposes, and conflicts of interest.

- Governments have invested heavily in neuroscience research, including several human brain mapping projects, in recent years. Establishing funding priorities is a critical issue in an era of finite resources. The civilian-military nexus is a good example. Just as civilians may benefit from assistive devices that come out of military research, soldiers may benefit from assistive devices developed for the civilian patient population with neurological injury. Research priorities in terms of the respective clinical target population may, however, be different between civilian and military research. ***How taxpayer funds should be allocated is a***

complex policy decision when one cannot predict what the next great advancement in neuroscience/technology will be. The need for public discussion on establishing national priorities is clearly needed.

- In analogy to ethical codes for the development of robotic systems–the concept of "responsible robotics"– we emphasize the need for such an ***ethical framework to include non-embodied software, "responsible algorithmics."***

- The commercialization of neurotechnological devices, particularly the increase in "do-it-yourself" brain stimulation devices like transcranial direct-current stimulation (tDCS) (Wexler, 2015; Wurzman *et al.*, 2016) and devices for EEG-based brain-computer interfacing raise concerns. Often these devices are marketed as enhancing human cognitive capabilities despite very little evidence for any positive and sustaining effect and risks of serious adverse effects such as skin burns (Horvath. *et al.*, 2015a, 2015b). The increasing use of emerging devices may require additional regulatory action. The current regulatory framework only covers the use of brain stimulation devices for medical purposes. The marketing of these products for enhancement or life-style devices is outside the scope of the FDA. ***More research into different strategies to educate the public and perhaps regulate these direct-to-consumer devices is needed***.

- Public-private partnerships (PPP) are very often at the frontier of developing novel neurotechnological devices. However, there is a thin line between political overregulation inhibiting innovative PPP research and lack of oversight that may put subjects in neurotechnological trials at risk. Many companies not historically considered biotech (e.g., data security firms) are entering this space and could benefit from greater ties to government agencies (e.g., FDA, NIH). Moreover, since companies developing neurotechnological devices often operate transnationally and may seek approval of medical devices in different countries, the international harmonization of guidelines, policies and regimes for regulatory oversight of neurotechnological devices is important. There is a need, therefore, to gather information, review and analyze:

  (1) the current landscape of neurotechnological research and development and the proportion of public, private and PPP research initiatives respectively;

  (2) the proportion of novel neurotechnological devices in the last couple of years that were successfully translated from "workbench-to-bedside," those that were exclusively developed commercially for consumer purposes and those with a "dual-use"; and,

  (3) journalistic reports and academic papers on misuse of neurotechnological devices.

  Depending on the outcome of this process, there could be a need to call for specific policy adjustments of PPP regulation and to publish trends of the use and misuse of neurotechnological devices.

- The increasing use of neuroimaging technology for commercial purposes like neuromarketing (e.g., inferring consumer preferences from brain activity

measured when subjects are presented with particular products) is a reason for concern (Ariely and Berns, 2010; Murphy *et al.*, 2008). With the possibility to infer hidden intentions from neural activity using novel methods of data analysis, the appeal of "neuromarketing" to consumer-oriented companies is obvious. Hence, ***there is a need to gather information, review, analyze and deliberate on***:

(1) the extent to which companies use these tools for marketing purposes;
(2) the existing guidelines on data privacy and security for gathering neural data for commercial purposes;
(3) the data safety and security protocols and practices of companies catering to consumers.

Depending on the outcome of these analyses, the effectiveness of existing consumer protections should be should be assessed in the context of the commercial use of neural data.

The use of ex vivo human brain tissue; including ownership and privacy issues.

- Some evidence in recent years points to a potential role of infectious agents (retroviruses, prion-like misfolded proteins) in the pathophysiology of neurodegenerative diseases like Alzheimer's dementia (Jaunmuktane *et al.*, 2015), fronto-temporal dementia (Diamond and Holmes, 2014) and amyotrophic lateral sclerosis (Li *et al.*, 2015). This raises potential concerns regarding the safety of medical professionals engaged in in-vivo (e.g., with invasive devices for deep brain stimulation or brain-computer interfacing) and ex-vivo (handling of neuropathological specimen) interaction with neural tissue as well as – potentially – for patients as well (sterilization of DBS equipment may not eliminate all pathogens). ***It is important to gather information on the role of novel pathogens in neurodegenerative diseases and their potential hazards for medical professionals and patients, and to review existing guidelines for sterilizing medical equipment that is in contact with neural tissue and, if necessary, make recommendations towards amending these guidelines***.

Specific neuroethics questions that could be addressed using a focused research approach.

In addition to the neuroethics questions raised above, we add that research is needed to understand ***the specific the impact of modern environmental change on biomedical and social understandings of brain and mental health, and how it aligns with ethical considerations, including those that relate to and integrate with emerging technologies*** (Cabrera et al. 2016).

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*** International Neuroethics Society, Response Action Task Force**

Chair
Mark S. Frankel, PhD (INS Board of Directors) AAAS, USA

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