

**Brain Research through Advancing Innovative Neurotechnologies® (BRAIN)
Multi-Council Working Group (MCWG) – Neuroethics Workgroup Meeting**

Tuesday, February 9, 2016

Meeting summary

On February 9, 2016, the [Neuroethics Workgroup](#) of the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) [Multi-Council Working Group](#) (MCWG) held its first in-person meeting, in Rockville, Maryland. The primary goal for the day was to reach consensus on which neuroethics issues the workgroup would focus on, and how those issues might be addressed. In an effort to ground those deliberations in the science funded under the BRAIN Initiative, the meeting included presentations from five BRAIN-funded investigators, who discussed their research projects and their perspective on ethical issues associated with their work. The meeting also included participants from the additional four federal agencies participating in the BRAIN Initiative (Food and Drug Administration, Defense Advanced Research Projects Agency, Intelligence Advanced Research Projects Activity, and National Science Foundation).

Opening remarks

Dr. Walter Koroshetz, Director of the National Institute of Neurological Disorders and Stroke, opened the day by commenting on the historical trajectory of research involving recording from and stimulating the nervous system. He commented that though scientists have been conducting such work for decades, modern neurotechnologies and tools used by neuroscientists are enabling powerful, entirely new ways of studying and influencing nervous system function – which, in turn, raises critical ethical concerns. He reiterated the original charge to the Neuroethics Workgroup:

- Recommend overall approaches for how the BRAIN Initiative should handle issues and problems involving ethics.
- Consider proposed funding areas for BRAIN projects for questions of ethical risk.
- Inform the MCWG and NIH on research questions important for BRAIN that could be answered through focused Funding Opportunity Announcements.
- Examine selected projects or applications for ethical concerns and, when appropriate, provide an ethics consultation.
- Draft relevant guidance documents to address critical ethical issues associated with BRAIN research.

He also asked the group to focus on a few key points of discussion: What are the priority ethical issues of concern associated with BRAIN research? How might NIH work collaboratively with extramural investigators and partner agencies to promote a culture of ethics in neuroscience research? What are the high priority questions that require original neuroethics research?

Update on complementary efforts

Workgroup members Hank Greely, Dr. Karen Rommelfanger, and Dr. Rafael Yuste gave updates on various complementary efforts in neuroethics, in order to give context to the day's discussions.

Several organizations in North America consider neuroethics issues:

- The [Presidential Commission for the study of Bioethical Issues](#) has deliberated on neuroethics.

- The commission produced two reports, [Gray Matters Vol. 1](#) and [Gray Matters Vol. 2](#), in response to a request from President Obama to review the ethical issues associated with the conduct and implications of neuroscience research.
- The commission considers many areas of bioethical issues and cannot function as a day-in, day-out advisory group to the BRAIN Initiative.
- The [International Neuroethics Society](#) (INS) is a well-respected, but primarily scholarly, organization and is not in a position to advise the BRAIN Initiative on an ongoing basis.
- The [MacArthur Foundation](#) supports research at the intersection of neuroscience and the law, but it is thus narrowly focused and also not well-suited to provide ongoing consultation to the BRAIN Initiative regarding neuroethical issues.
- Many Canadian organizations promote the discussion of neuroethics, but none function in an advisory role.
- The [ELSI](#) (Ethical, Legal, and Social Implications) Research Program at the National Human Genome Research Institute funds and manages studies, and supports workshops, research consortia, and policy conferences.
- Various U.S. institutions have neuroethics centers, including the University of Pennsylvania, Stanford, Harvard, Duke, and Emory.
 - Some of these organizations do research ethics consultations—for example, [Stanford’s neuroethics advisory board](#) performs [benchside research consults](#)—which could serve as models for the MCWG neuroethics workgroup to emulate.

The [Human Brain Project](#) (HBP) has invested in ethics:

- HBP has an [Ethics and Society Programme](#).
- HBP utilizes an [ethics management team](#) and an external [ethics advisory board](#) to review HBP projects.
- HBP also funds a “Foresight Lab” that investigates the [potential impact of new technologies stemming from HBP](#).
- HBP through the Danish Board of Technology communicates directly with the public to raise awareness of the project’s research goals, as well as to solicit public opinion about ethics related to the project through an online tool.
- HBP has expressed interest in collaborating with the MCWG neuroethics workgroup, and has proposed an ambassadorship program between the two groups. Toward this end, Dr. Rommelfanger will meet with HBP ethics leaders in early March, 2016.

Additional suggestions for the MCWG Neuroethics Workgroup have come from members of the neuroethics community. These included:

- Summer ethics courses for neuroscience faculty;
- Writing a neuroethics handbook for neuroscience researchers;
- Brainstorming difficult, hypothetical ethical scenarios in neuroscience research, and how to identify, prevent, or mitigate them in the future;
- Funding research on neuroethics issues, as well as funding for graduate students and postdoctoral fellows;
- Holding workshops and meetings on neuroethics; and
- Developing best research practices for dissemination to BRAIN investigators.

BRAIN investigator talks

Several BRAIN-funded investigators (Drs. Leigh Hochberg, Gregory Worrell, Nikolas Schiff and co-investigator Joseph Fins, Edward Chang, and Michael Kahana) spoke about their human brain research projects utilizing next generation invasive devices. They articulated their perspectives on ethical issues associated with their work. Through their presentations and group discussion, various themes were highlighted as being important for consideration as this type of research progresses:

Data issues: Meeting participants discussed questions of ownership, both of neural data and of the implanted neural devices themselves. The clinical studies described often include relatively small numbers of patients, leading to concerns about whether data from such small-*n* trials can be fully de-identified. The investigators discussed that the neural data collected can contain various types of personal data, such as information about a patient's medication usage, intellectual capacity, or unknown future diagnoses; this can further complicate the already nuanced process of obtaining consent for these studies. Given the highly sensitive nature of neural data, combined with the push towards fully implanted (i.e. wireless) devices, the group noted the importance of considering data security and security of the devices themselves. They also broadly agreed on the importance of data sharing, though they discussed the complexity of deciding when and how to do so in the absence of standardized protocols, databases, etc. Relatedly, the group articulated the imperative of effectively utilizing human clinical data to improve health.

Obligations to patients: Workshop participants discussed questions around the long-term responsibility for the health and associated healthcare costs of study participants with implanted neural devices. How is this responsibility shared, and is there value in developing new models of indemnification for long-term financial support, e.g. if a patient is implanted with a device provided by a company that ceases to exist. There was also discussion around questions of culpability. For instance, if a patient's neurological disorder is managed by an implanted device, and that device fails in a way that results in harm to the patient or by the patient, who is responsible? The group discussed obligations to patients guided by the principle of beneficence. A specific cited example was the idea that any trial that is underpowered is unethical, since that trial cannot answer its basic clinical question. Finally, the question was raised of what level of antecedent evidence is necessary for studies on neuropsychiatric disorders.

Informed consent: The group discussed various issues associated with fairly and accurately informing patients during the consent process, such as: the vulnerability of neurosurgical patients; potential conflicts of interest; and the nuances of navigating the research vs treatment boundary. They underscored the lack of standardization for consent processes. Determination of consent capacity for individuals with neurological and/or psychiatric conditions is also a point of concern. Participants also discussed the value of understanding why patients consent to participate in research, and the investigators relayed their experience that often patients want to participate in clinical research because it may help other people.

Additional topics: These included the potential of providing guidance to institutional review boards (IRBs) for consideration of human brain research studies with invasive devices; issues surrounding the translation of animal research findings into effective diagnostic and treatment tools for human neuroscience/neurology; questions of altering personhood; concerns regarding unintended consequences of invasive neural devices (whether negative or positive); and societal considerations and equal access issues if/when implants can 'cure' particular conditions.

Background information; Prioritization of issues

In November 2015, the neuroethics workgroup of the BRAIN MCWG was asked to review the NIH BRAIN portfolio and consider three questions:

- 1) Which funding areas have ethical concerns?
- 2) What topics might be good for funding some neuroethics research?
- 3) Where might there be possibilities for guidance documents?

Prior to this meeting, the workgroup developed a list of priority areas for each of these three questions. During this portion of the meeting, the workgroup worked to refine and prioritize those lists.

Broad ethical concerns related to BRAIN research

In the course of discussing the various ethical concerns associated with BRAIN research (and with neuroscience research more broadly), the group agreed on the complexity of these issues and the need to address them thoughtfully, with involvement of appropriate content experts as necessary. There are many relevant ethical questions, but the following four topics emerged as highest priority (not listed in any particular order):

- Ethics of research with invasive technologies
 - Validity of informed consent and competency determinations
 - Obligations regarding long-term upkeep of implanted devices, and follow-up with research participants
 - Participants' physical and perceived non-physical harms, and how to manage such issues
- Altering, enhancing, and/or manipulating the self and agency
 - E.g. technologies that do or could involve brain stimulation; brain-computer interfaces; brain prosthetics; enhancers of memory, attention, reasoning; manipulation of memories, etc.
 - Perceived violations of autonomy; authenticity related to altering experiences, personal narratives, personal identity
- Privacy/discrimination concerns, and the need for privacy protections
 - Generation of information about individual traits/conditions that are of medical/social/legal relevance
 - Questions of cybersecurity
 - Neural signatures could be found that predict traits, personalities, cognitive abilities, etc.
 - Protecting the privacy of information when using wireless technologies in the brain
 - Lack of a neuroscientific analog of the Genetic Information Nondiscrimination Act
- Translation to contexts beyond the clinic/bench: Ethics of commercialization, public-private partnerships, and wider application of imaging technologies for commercial purposes
 - Standards for validity and safety of interventions
 - Privacy safeguards
 - Managing potential conflicts of interest

There are various other topics that the workgroup considers to be important, but likely won't be first points of consideration. These include: issues of enhancement for non-medical purposes; the use of *ex vivo* brain tissue from humans; potential humanization of animal models; understanding the science of science communication; and the need for neuroethics education and training, including being cautious of "neuro-hype."

Possibilities for NIH-funded neuroethics research

The group discussed various possible topics (listed in random order):

- Predictive/diagnosis research:

- Analyze participant and researcher perceptions of ‘risk’ in clinical research, particularly in studies with children and cognitively impaired adults.
- Develop best practices for managing false-positives and non-physical harms
- Explore policy implications of blurring the treatment/enhancement line (e.g. would health insurance cover interventions for a disease that is predicted but not confirmed, such as Alzheimer’s?)
- Ethics of research with invasive devices
 - Document participants’ long-term physical and perceived non-physical harm
 - Strategies to ensure a valid consent process
 - Investigate long-term investment/obligations for upkeep of implanted stimulators, including research on new models of cost-sharing for long-term medical upkeep of such devices and current hurdles for investigators
- Ethics of sham stimulation
 - Understanding placebo and nocebo effects for invasive and non-invasive technologies: how to capitalize on or minimize sham effects?
 - In research partnerships between the U.S. and international collaborators, examine how sham might be viewed/utilized differently
- Evaluation of methods for teaching neuroethics
 - Innovative models for educating researchers, healthcare professionals, and the public
- Cybersecurity/privacy:
 - Research on effective security and safeguards for human data and wireless transmissions to/from implanted neural devices
 - Research on gaps/provisions needed in existing regulatory models
- Public/researcher/participant attitudes and decision-making (using psychology and cognitive science) about altering/enhancing/manipulating brains. Such research could directly inform 1) guidance documents for scientists and 2) public outreach/education efforts.
- Participants’ interpretation of results

Guidance documents

The workgroup had previously identified these potential priority areas:

- Incidental findings
- Evaluating consent capacity and how interventions may alter it
- Essentialism and bias that could alter study design and interpretation of results, and reinforce stigma
- Guidelines for managing shared data, data privacy/legacy (with implications for insurance etc.), IRBs, consent
- Enhancement applications of interventions developed for therapeutic purposes
- Interfacing with policy makers and regulatory agencies; potential use of clinical data outside the clinic
- Points to consider for IRBs reviewing clinical studies with invasive devices

Throughout the course of this meeting, there was reaffirmed interest in the neuroethics workgroup developing guidance for researchers on data sharing, and for IRBs reviewing clinical studies with invasive devices. It was noted that the NIH BRAIN funding opportunities focused on research with invasive devices for recording and modulation in the human central nervous system have included a requirement for awardees to join a consortium, coordinated by NIH, to identify consensus standards of practice as

well as supplemental opportunities to collect and provide data for ancillary studies, and to aggregate and standardize data for dissemination among the wider scientific community.

Federal panel

During this portion of the meeting, NIH's partner federal agencies involved in the BRAIN Initiative were asked to comment on how each might contribute to the broader effort to advance neuroethics.

Justin Sanchez (DARPA):

Dr. Sanchez relayed that DARPA has an ELSI panel in place to inform its neuroscience research programs. The group provides a consultative service to DARPA program directors as they develop broad agency announcements, and once performers have been selected, the ethics panel members are invited to attend initial meetings with the performers. He affirmed DARPA's interest in being involved in ongoing trans-agency conversations about neuroethics and the BRAIN Initiative, as part of an effort to think proactively about ethical issues.

Howard Nusbaum (NSF)

Dr. Nusbaum noted that although NSF's mission is not health-related, there are several NSF programs relevant to neuroethics, including: [Science, Technology, and Society](#); [Research Infrastructure for Data Intensive Research](#); [Robust and Reliable Science](#); and [Secure and trustworthy cyberspace](#). In response to a question of how engineering programs are conceiving of problems in neuroethics, he noted that responsibility often is passed on to IRBs and institutional animal care and use committees. He indicated that NSF is interested in supporting future neuroethics workshops.

Alexis Jeannotte (IARPA):

Dr. Jeannotte explained that like NSF, IARPA does not have a health-focused mission. IARPA is not investing in invasive neurotechnologies; rather, the focus is on human neuroscience – specifically, optimization of human performance. She noted that IARPA staff have given thought to issues of research ethics, and various topics discussed throughout the day are central to IARPA's work, including questions of data sharing and underpowered studies. IARPA encourages its researchers to publish null results and each IARPA program has built-in measures for replication and cross-validation (data need to be amenable to meta-analysis, for example). Dr. Sanchez added that DARPA has made substantial investments in a data sharing infrastructure, and the agency hopes its data sets will be used for secondary analysis. Dr. Jeannotte relayed that IARPA is interested in others' perspectives on how to build neuroethics into IARPA projects, and how IARPA might measure the value-add of such efforts.

Carlos Peña (FDA):

Dr. Peña highlighted a November 2015 [Neurodiagnostics and Non-Invasive Brain Stimulation Medical Devices Workshop](#) hosted by the FDA. He offered that material from the workshop could be part of a broader FDA effort to inform the Neuroethics Workgroup, which could also include *ad hoc* presentations from FDA staff with expertise in ethics, cybersecurity, and the investigational device exemption process. He also suggested that a coordinated strategy for interacting with IRBs could be a significant step forward.

Neuroethics Workgroup next steps: goals and deliverables

The workgroup considered and discussed possible next steps. For example, the workgroup could:

1. Share ideas for neuroethics funding opportunities with the NIH joint BRAIN/Blueprint neuroethics project team;
2. Prioritize some of the topics highlighted during the day's meeting as areas of action;

3. Organize topical neuroethics workshops;
4. Create guidance for IRBs reviewing studies with invasive neurological devices in humans; and
5. Brainstorm and discuss difficult, near- and long-term ethical scenarios in neuroscience research.

Regarding the second item, specific suggestions included developing a whitepaper on ethical issues associated with data sharing, with a focus on issues unique to BRAIN Initiative research: small n trials, huge datasets, and meta-analysis questions; and developing a separate whitepaper on issues associated with long-term obligations to patients with implanted devices.

Regarding the third item, for the four priority ethical concerns related to BRAIN research identified earlier in the day, a similar process could be followed: release of a background document with a call for public comment; holding a topical workshop with experts invited to discuss the issues, with time allotted for public comment; and publication of each workshop's proceedings to identify the state of the field along with gaps that could be filled by targeted funding opportunities.

The group discussed additional suggestions:

- Empirical studies of public understanding of privacy, especially with respect to research with novel and invasive neurotechnologies, could be very valuable, and might reflect an important generational change from past attitudes and opinions. The NSF Science and Technology in Society program is open to proposals for this type of research.
- When thinking about how to address neuroethics issues across the portfolio of BRAIN Initiative research, it will be important to consider differing Federal agency missions and priorities.
- Going forward, the [workgroup webpage](#) could serve as a repository of recommended readings.
- Near the end of fiscal year 2016, NIH will award its next group of BRAIN grants under the funding opportunities focused on research with invasive devices for recording and modulation in the human central nervous system. In conjunction with the December 2016 BRAIN Investigators meeting, these grantees and their previously funded colleagues could gather to discuss developing guidelines for data sharing.