The NIH BRAIN Initiative: Integrating Neuroethics and Neuroscience

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The NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is focused on developing new tools and neurotechnologies to transform our understanding of the brain, and neuroethics is an essential component of this research effort. Coordination with other brain projects around the world will help maximize success.

The Scientific Agenda of the NIH BRAIN Initiative

The U.S. Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is an ambitious neuroscience research program that aims to revolutionize our understanding of the human brain (Koroshetz et al., 2018). The National Institutes of Health (NIH) component of the Initiative is guided by *BRAIN 2025: A Scientific Vision*, a strategic plan developed with broad input from the scientific community (https://www.braininitiative.nih.gov/strategic-planning/brain-2025-report). The plan emphasizes accelerating technology development for neuroscience and applying these new tools and technologies to understand how dynamic patterns of activity in neural circuits are transformed into perception, emotion, cognition, and behavior in health and disease. Entering the fifth year of the Initiative, NIH has invested over $950 million to fund over 550 projects at institutions and research centers across the country through fiscal year 2018. This amount represents roughly 20% of the projected Initiative budget through 2026.

While earlier approaches in neuroscience have often focused on the functioning of specific cell types or brain regions in isolation, *BRAIN 2025* aims to foster innovation through investigating the dynamic interrelations of these varied components within circuits. *BRAIN 2025* focuses on neural circuitry not only because of its critical role in brain function, but also because circuit dysfunction is the basis of the symptoms and disability in many neurological, mental, and substance use disorders. In many such disorders (including substance use and chronic pain), there is no evident brain pathology or lesion that can explain the grave disability experienced by afflicted persons. Progress in treatment for these conditions is likely to require a fuller understanding of the function of brain circuits. Even in the case of conditions such as stroke where discrete pathologies are known, treatment is limited by our abilities to monitor and precisely modulate brain circuit function.

According to the 2016 Global Burden of Disease (GBD) study, the top 25 causes of disability-adjusted life years, a function of premature mortality and healthy years of life lost to disability, include cerebrovascular disease (stroke), low back and neck pain, depressive disorders, self-harm, Alzheimer's disease, and migraine (GBD 2015 Mortality and Causes of Death Collaborators, 2016). The early onset of most neuropsychiatric disorders, and their chronic or recurrent courses, makes this class of disorders the greatest contributor to disability and economic loss worldwide (Whiteford et al., 2013). There is a powerful imperative to develop an improved understanding of the circuits underlying these disorders, along with better diagnostics, and safer and more effective treatments.

The United States BRAIN Initiative is one of several international brain projects that are increasing investments in neuroscience research (Brose, 2016). Among these projects with complementary areas of emphasis, the NIH BRAIN Initiative uniquely focuses its mission on seven scientific priority areas (Figure 1). Together, these priorities support the overall goal of understanding how the nervous system processes massive amounts of information, in real time, to generate our experience of the world and our actions in it.

Neuroethics Efforts within the NIH BRAIN Initiative

Bioethics is a well-established discipline, focused on the ethics of biomedical research including the protection of human research participants, and grounded

NIH BRAIN Initiative Scientific Priority Areas
1. Discovering diversity: Identify and provide experimental access to the different brain cell types to determine their roles in health and disease.
2. Maps at multiple scales: Generate circuit diagrams that vary in resolution from synapses to the whole brain.
3. The brain in action: Produce a dynamic picture of the functioning brain by developing and applying improved methods for large-scale monitoring of neural activity.
4. Demonstrating causality: Link brain activity to behavior with precise interventional tools that change neural circuit dynamics underlying complex behavior.
5. Identifying fundamental principles: Produce conceptual foundations for understanding the biological basis of mental processes through development of new theoretical and data analysis tools.
6. Advancing human neuroscience: Develop innovative technologies to understand the human brain and treat its disorders; create and support integrated human brain research networks.
7. From BRAIN Initiative to the brain: Integrate new technological and conceptual approaches produced in Goals #1-6 to discover how dynamic patterns of neural activity are transformed into cognition, emotion, perception, and action in health and disease.

Neuroethics Guiding Principles
1. Make assessing safety paramount.
2. Anticipate special issues related to capacity, autonomy, and agency.
3. Protect the privacy and confidentiality of neural data.
4. Attend to possible malign uses of neuroscience tools and neurotechnologies.
5. Move neuroscience tools and neurotechnologies into medical or non-medical uses with caution.
6. Identify and address specific concerns of the public about the brain.
7. Encourage public education and dialogue.
8. Behave justly and share the benefits of neuroscience research and resulting technologies.

Figure 1. NIH BRAIN Initiative Scientific Priority Areas and Neuroethics Guiding Principles

in existing ethical principles such as those found in the Belmont Report: respect of persons, beneficence, and justice. Neuroethics is a newer field that rests on the belief that there are unique ethical considerations in studying the brain, and advances in our understanding of the brain and our ability to record and modulate brain function can challenge or transform our understanding of the human mind and human identity. Thus, neuroethics includes considerations beyond the scope of traditional bioethics such as cognitive or behavioral predictions based on neuroscience (e.g., that might be used to assign educational or vocational opportunities); drawing conclusions about past or future decision-making and behavior based on evidence from brain data; interventions in the brain that might influence personal identity, memory, impulsivity, or cognitive control; interpretation of decision-making capacity (e.g., in a psychotic or addicted person, or a person with closed-loop brain stimulation); and how the construction of better models of human brains, such as three-dimensional *in vitro* cell culture systems known as brain organoids, leads us to the question of when and to what degree a model becomes an object of concern for our existing ethical framework. Exploring these questions represents a unique opportunity for the NIH BRAIN Initiative to enrich the work of the broader neuroscience community.

The NIH, including through the NIH BRAIN Initiative, is committed to research that adheres to the highest ethical standards, and all research NIH supports is expected to follow existing policy and laws regarding the protection of human research participants. Since the inception of the BRAIN Initiative, the Initiative has endeavored to integrate neuroethics into its science. When the BRAIN Initiative began in 2013, the U.S. Presidential Commission for the Study of Bioethical Issues embarked on a two-year process of engaging with the scientific community, the public, and other stakeholders to proactively identify a set of core ethical standards both to guide neuroscience research and to address some of the ethical issues likely to be prompted by the application of neuroscience research findings. The Commission published a two-volume report entitled *Gray Matters*, which strongly endorses proactive integration of neuroethics into any neuroscience research endeavor (https://bioethicsarchive.georgetown.edu/pcsbi/node/3543.html). That notion of integration is at the heart of the NIH BRAIN Initiative's neuroethics strategy, which emphasizes proactive, ongoing assessment of the neuroethical implications of the development and application of BRAIN-funded tools and neurotechnologies (Bianchi et al., 2018).

The NIH BRAIN Initiative receives input from multiple sources, including an external Multi-Council Working Group (MCWG), a group of experts who provide ongoing perspective on the long-term scientific vision of the Initiative in the context of the evolving neuroscience landscape. Given the importance of neuroethics for the success of the Initiative, in addition to its importance across all NIH neuroscience efforts, the MCWG includes a dedicated Neuroethics Working Group (NEWG) comprising both neuroethicists and neuroscientists to provide expert input on neuroethics and help ensure that neuroethical considerations are fully integrated into the Initiative (https://www.braininitiative.nih.gov/about/neuroethics-working-group). The NEWG recently published a set of Neuroethics Guiding Principles, intended primarily for BRAIN Initiative researchers, to frame and help navigate the neuroethical questions that BRAIN-funded research may prompt (Greely et al., 2018; Figure 1). These Guiding Principles provide an overarching framework intended to inform a public dialog among a highly interdisciplinary group of stakeholders—investigators, clinicians, legal scholars,

philosophers, institutional review boards that oversee human research, funders, research participants, patients, and the public—regarding the design and conduct of research, the implications of the resulting advances on our understanding of human brain function, and the risks and benefits of interventions into the brain. The principles echo the neuroethics questions formulated at the 2017 Global Neuroethics Summit, for example urging researchers to work to share widely the benefits of neuroscience research and resulting technologies. Though the Guiding Principles are focused on the NIH BRAIN Initiative, they may prove useful to others engaged in cutting-edge technology development and research.

The NEWG organizes topical workshops that enable dialog regarding different areas of the NIH BRAIN Initiative's research portfolio, bringing together stakeholders representing neuroscience, neurosurgery, neuroethics, philosophy, law, and more. Recent workshops have focused on research with human neural tissue, and human neuroscience research utilizing novel invasive and non-invasive neural devices (discussed below). These workshops provide opportunities for discussion on how to advance cutting-edge neuroscience research in the most ethical manner. These neuroethics-focused activities form part of a growing international effort by groups engaged in neuroethics work that is focused on modern neuroscience advancements (for discussion, see Rommelfanger et al., 2018).

Internal to the NIH, a neuroethics project team comprising NIH scientific program staff ensures the integration of neuroethics as NIH leadership decide which applications to fund, informed by the peer review process, and throughout ongoing oversight of funded grants. The project team's efforts are informed by the Guiding Principles and the topical workshops organized by the NEWG. Additionally, the project team gathers neuroethics questions elicited by BRAIN-funded research and leverages the NEWG to explore and address these questions. The project team also considers these questions in their efforts to build a growing neuroethics research portfolio. Informed by a 2016 Request for Information that solicited public input on BRAIN-related neuroethics questions amenable to research, the NIH published a funding opportunity announcement (FOA) in 2017 to support research on the ethical implications of advancements in neurotechnology and brain science supported by the NIH BRAIN Initiative. The FOA was reissued in FY2018 and FY2019, with application due dates through FY2021 (https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-19-400.html). To date, nine R01 grants awarded under this FOA are addressing key neuroethical issues. The project team also promotes neuroethics training through BRAIN-supported training mechanisms, and administrative supplements to embed neuroethics in existing NIH BRAIN Initiative grants.

The authors of *BRAIN 2025* anticipated that rapid advances in neuroscience may merit revisiting the NIH BRAIN Initiative's strategic plan. To that end, a working group of the Advisory Committee to the NIH Director (ACD), the highest-level advisory committee at the NIH, is working to update *BRAIN 2025* in light of the cutting-edge tools and neurotechnologies developed through the Initiative, and the scientific possibilities they unlock. Neuroethics is integral to this effort, and NIH Director Dr. Francis Collins tasked a Neuroethics Subgroup of the ACD working group to develop a "Neuroethics Roadmap" that will characterize the potential neuroethical implications of the development and use of new neurotechnologies supported by the NIH BRAIN Initiative. A preliminary draft of this report is anticipated in spring of 2019 followed by an opportunity for public input, with the final report delivered to the ACD in June 2019. Once the updated strategic plan and Neuroethics Roadmap are approved, NIH staff will use them to shape the second half of the Initiative. The Neuroethics Roadmap will complement the Neuroethics Guiding Principles as an overarching framework for the Initiative, and the NEWG will continue to provide expert input on neuroethics questions that arise and help ensure that neuroethical considerations are integrated into the science.

Ethical Questions Related to NIH BRAIN Initiative Research

The NIH BRAIN Initiative, and other similar efforts focused on understanding the brain, will raise familiar bioethical issues pertaining to research conducted with human participants, such as questions about acceptable degrees of risk, necessary levels of antecedent evidence before conducting human trials, consent capacity, and the tension between data sharing and privacy. These issues can be more trenchant in the context of neuroscience research with novel neurotechnologies, as compared with other areas of biomedicine. For instance, concerns are heightened when considering acceptable degrees of risk for people receiving experimental deep brain stimulation to treat intractable mental illness, given that such interventions in the brain may affect the patient's mind. In other instances, ethical issues beyond the scope of traditional bioethics may arise because the brain is the organ of the mind and, for many, is believed to be the seat of the self. For example, emphasizing a mechanistic explanation of brain function may conflict with societal conceptions of personhood, individuality, and free will. In a sense, this is an example of the first question (Neuroethics Question [NeQN] 1) developed at the 2017 Global Neuroethics Summit: What is the potential impact of a neuroscientific account of *healthy* mental function on individuals, communities, and society? Further, novel neurotechnologies may enable not only measurement of brain activity underlying thoughts and moods but also precise modulation of that activity, which will raise ethical, legal, and societal questions, including questions regarding how such interventions might affect autonomy, and who bears responsibility for such effects. This is captured by NeQN 4.

Two specific examples serve to illustrate the nature of neuroethical questions elicited by NIH BRAIN Initiative research. The first pertains to research with human neural tissue, including *ex vivo* brain tissue and brain organoids. The NIH BRAIN Initiative's NEWG held a workshop on this topic in March 2018 to explore the state of the science and attendant ethical considerations (https://www.braininitiative.nih.gov/sites/default/files/pdfs/nihbrainneuroethicssummarymarch2018_508c.pdf). *Ex vivo* brain tissue, ranging from small cubes of tissue removed during surgical procedures to whole animal brains and potentially whole human brains, is particularly well suited for studying intact brain circuits, along

with visualization and reconstruction of detailed cell structure, and genetic analysis. This evolving approach allows researchers to investigate genetic and electrical properties of cell types and neural circuitry at unprecedented levels of resolution (Ting et al., 2018). Brain organoids are three-dimensional multicellular structures derived from pluripotent stem cells, grown in culture systems to resemble parts of the developing human brain. They represent a new avenue of research, one that is still being explored and refined by scientists, and which holds great potential for shedding light on human brain development and function in health and disease. Brain organoids may serve as useful predictive models of brain disorders specific to certain genetic mutations, including monogenic neurodevelopmental disorders such as Timothy syndrome. They may also help translate therapeutic approaches from animal models into clinical practice (Amin and Paşca, 2018), and could bridge the gap when there are no models for novel diseases, such as microcephaly associated with the Zika virus outbreak of 2016 (Qian et al., 2017).

Research with *ex vivo* brain tissue and brain organoids raises a number of neuroethical questions, including NeQN 3: What is the moral significance of neural systems that are under development in neuroscience research laboratories? And further, what functions or capacities would need to be present in a human brain model to lend it moral significance? Exploring these questions may inform a related one: What is appropriate stewardship for human brain organoids or *ex vivo* brain tissue? This reflects NeQN 2b: Should special regard be given to brain tissue and its donors due to the origin of the tissue and its past? In addition to the Initiative's NEWG deliberations on these questions, BRAIN-funded investigators working with these model systems are actively engaged in considering and addressing the unique ethical issues raised by these research approaches.

A second example of ethical questions elicited by BRAIN Initiative research pertains to basic neuroscience research made possible by direct access to brain recording and stimulation from invasive surgical procedures—i.e., conducting *in vivo* neuroscience research with patients undergoing neurosurgery for clinical indications, who elect to allow researchers access to their brains for research purposes during those surgeries. For example, some patients with epilepsy who have electrodes implanted to monitor their seizures may agree to permit researchers to implant additional electrode arrays to enable recording of brain activity via electrocorticography. These studies are reviewed and approved by institutional review boards and, like all NIH-funded research, are guided by ethical frameworks based on NIH policy and U.S. law. This cutting-edge work raises familiar bioethical questions about acceptable risk and informed consent, but because the brain is the organ of the mind, neuroethical implications include, for example, questions about how interventions may affect cognition, consent capacity, decision-making, and voluntary participation. The NIH BRAIN Initiative held a workshop in October 2017 and a meeting in August 2018 to explore these issues, with a publication planned that will offer relevant points to consider for investigators and institutional review boards. Additionally, the BRAIN-funded investigators working in this space are actively engaged in collaboration with ethicists to ensure ongoing deliberation on the unique ethical issues raised by human neuroscience research.

Future Directions

Large investments in neuroscience research around the world hold the potential to unlock unprecedented understanding of how the brain works and how to treat brain disorders. As national brain projects continue to develop around the world, there remains ongoing emphasis on global conversations about shared opportunities and challenges in neuroscience, and collaborative international efforts to overcome those challenges and maximize success. For example, the NIH has memoranda of understanding with Brain Canada, the Lundbeck Foundation of Denmark, and the Australian National Health and Medical Research Council to promote international collaboration on NIH BRAIN Initiative projects. More broadly, the emergence of the International Brain Initiative underscores the interest in coordination and synergy between the various brain projects around the world.

Embedding robust neuroethics efforts within these large neuroscience research programs is an important step to ensure the ethical conduct of research and the ethical application and use of resultant research findings. As is the case for neuroscience, coordination across brain projects around the world in the space of neuroethics has the potential to strengthen our collective efforts through sharing lessons learned and best practices. Multinational partnerships also invite new ideas and new approaches that may deepen our cross-cultural understanding of neuroscience advances and their ethical, legal, and social implications. This, in turn, maximizes the potential for international scientific collaboration and for reaping the benefits of neuroscience advances. Rommelfanger et al. (2018) discussed that the various brain projects will likely share human brain data, prompting questions around privacy. For example: Are brain data revealing or stigmatizing in ways that are unique compared to other biomedical data, or to data derived from psychological research? Exploring such questions while navigating cultural norms that differentially define and operationalize privacy will be complex, and proactive consideration of these ethical questions will maximize the ability to make use of, and learn from, human brain data.

Neuroethics is an essential partner to neuroscience, serving to anticipate and address ethical questions raised by neuroscience research, and to help guide the progress of the field. In our modern inter-connected world, international collaboration in neuroscience and neuroethics is essential to realize the transformative potential of understanding brain function, and to address the attendant implications for human self-understanding and society through a cross-cultural lens.

DECLARATION OF INTERESTS

Some of the paper authors serve in a variety of unpaid advisory positions. W.C., J.E., N.A.F., C.G., H.T.G., B.T.H., S.E.H., L.S.M.J., K.S.R., and E.E.S. are all members of the NIH BRAIN Initiative's Neuroethics Working Group. J.E. is a member of the NIH BRAIN Initiative's Multi-Council Working Group and co-chair of the Neuroethics Subgroup of the Advisory Committee to the NIH Director BRAIN Initiative Working Group 2.0. N.A.F. is a Board Member and President-Elect of the International Neuroethics Society, and a member of the National Advisory Neurological Disorders and Stroke Council. C.G. is a member of the Neuroethics Subgroup of the Advisory Committee to the NIH Director BRAIN Initiative Working Group

2.0. H.T.G. is a member of the NIH BRAIN Initiative's Multi-Council Working Group, Board Member and President of the International Neuroethics Society, and a member of the National Academy of Medicine's Forum on Neuroscience and Nervous System Disorders. B.T.H. is a member of the NIH BRAIN Initiative's Multi-Council Working Group. S.E.H. is a member of the Board of Directors of the Dana Foundation, and a Board Member of the International Neuroethics Society. K.S.R. is a member of the Neuroethics Subgroup of the Advisory Committee to the NIH Director BRAIN Initiative Working Group 2.0. E.E.S. is a member of the NIH BRAIN Initiative's Multi-Council Working Group, the Advisory Committee to the NIH Director Working Group on Diversity, and the Advisory Committee to the NIH Director Working Group on the Next Generation Researchers Initiative. Also, W.C. is the principal investigator on a neuroethics grant funded by the NIH, and K.S.R. has funding from The Kavli Foundation.

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