

Commentary

Neuroethics for the National Institutes of Health BRAIN Initiative

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Background on the National Institutes of Health BRAIN Initiative and neuroethics

The National Institutes of Health (NIH) works tirelessly to support the best science and ensure that its funded research adheres to the highest ethical standards. From its inception, the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, an ambitious effort focused on understanding the human brain, has made a concerted effort to integrate neuroethics into its science, motivated by the understanding that brain circuit activity is the foundation of individual human experiences and is uniquely entwined with our sense of personal identity. In the 5 years since the Initiative began, NIH has invested over \$950 million in BRAIN Initiative research throughout the United States and around the world to develop novel tools and neurotechnologies that will enable unprecedented detailed maps of neural circuits, measures of the fluctuating patterns of electrical and chemical activity flowing within those circuits, and understanding of how their interplay creates our cognitive and behavioral capabilities. Understanding neural circuit function is essential if we are to transform our ability to diagnose and treat neurological, mental health, and substance use disorders, which are the leading cause of disability in the United States. For this diverse group of disorders, the burden of illness results

from dysfunctional neural circuit activity. Despite decades of progress, our rudimentary understanding of brain function impedes our ability to compensate for atypical circuit activity in disorders such as depression, schizophrenia, bipolar disorder, chronic pain, addiction, autism, Alzheimer's disease, and dystonia. The NIH BRAIN Initiative aims to deliver the tools and neurotechnologies that will enable us to address this knowledge gap.

As has occurred throughout the history of medicine, the emergence of new technologies and capabilities may require the evolution of ethical standards to guide how they should be first introduced into human subjects research and later applied to the practice of medicine. NIH has several valuable ethical frameworks in place to guide the science, informed by policy and laws regarding the protection of human research participants and animal research subjects. NIH is committed to ensuring it considers and addresses the ethical implications of development and application of BRAIN-funded tools and neurotechnologies and the increased knowledge that they produce about the brain. In tandem with the BRAIN Initiative's launch in 2013, the Presidential Commission for the Study of Bioethical Issues embarked on a 2-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 dilemmas that may be raised by the application of neuroscience research findings. This process culminated in the publication of 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>). Another source of guid-

ance for the NIH BRAIN Initiative regarding neuroethics is its strategic plan, *BRAIN 2025: A Scientific Vision*, which was developed with broad input from the scientific community and has four specific goals for neuroethics: (1) establishing a shared vision for the ethical conduct of human neuroscience research; (2) collecting and disseminating best practices in the conduct of ethical scientific research, particularly clinical research; (3) supporting data-driven research to inform ethical issues arising from BRAIN Initiative research; and (4) developing outreach activities to engage diverse stakeholders in discussion of the social and ethical implications of neuroscience research (<https://www.braininitiative.nih.gov/strategic-planning//brain-2025-report>).

Neuroethics strategy for the NIH BRAIN Initiative

The neuroethics strategy for the NIH BRAIN Initiative operationalizes these *BRAIN 2025* goals, emphasizing proactive, ongoing assessment of the neuroethical implications of the development and application of BRAIN-funded tools and neurotechnologies. Early on, the Initiative established an external Neuroethics Working Group (NEWG) comprising both neuroethicists and neuroscientists to provide expert input on neuroethics (<https://www.braininitiative.nih.gov/about/neuroethics-working-group>). The NEWG is part of the Initiative's Multi-Council Working Group, a group of nongovernmental experts that provides scientific guidance for the Initiative. The synergistic efforts of these experts help to ensure that neuroethical considerations are fully integrated into the Initiative. The NEWG organizes topical workshops that explore neuroethical implications of BRAIN Initiative research. Topics to date have included human neuroscience research using invasive and non-invasive neural devices and research with hu-

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Table 1. 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. Use caution when moving neuroscience tools and neurotechnologies into medical or non-medical uses.
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.

man neural tissue. These workshops provide important venues for stakeholders with varying perspectives to discuss key neuroethical considerations associated with BRAIN research and to facilitate building agreement on how to advance research in the most ethical manner. In the spirit of transparency, meeting videocasts and summaries are available online. Concurrently, groups in the United States and around the world are engaged in neuroethics work focused on modern neuroscience advancements (Rose, 2014; Goering and Yuste, 2016; Greely et al., 2016; Farahany et al., 2018; Global Neuroethics Summit Delegates et al., 2018; <http://nationalacademies.org/HMD/Activities/Research/NeuroForum.aspx>).

Grounded in the scientific goals of the NIH BRAIN Initiative, the NEWG developed a set of *Neuroethics Guiding Principles* (Table 1) to frame and navigate the neuroethical questions that BRAIN-funded research will prompt. These Guiding Principles represent focused application of the ethical principles set forth in the Belmont Report (<https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>). They provide an overarching framework that can help inform dialogues among stakeholders, including investigators, clinicians, institutional review boards, funders, research participants, patients, and the public, both in the design and conduct of research as they grapple with ethical questions elicited by the Initiative that call for wider discussion and deeper understanding. For the NIH BRAIN Initiative, the purpose of applying the Guiding Principles and addressing these neuroethical considerations is to help NIH BRAIN Initiative stakeholders judiciously develop and deploy novel neurotechnologies for biomedical research. For example, in conducting human neuroscience research with novel neurotechnologies, the Guiding Principles emphasize the paramount importance of assessing safety for research participants given that unexpected consequences may

manifest as behavioral, cognitive, or emotional perturbations and may not be immediately apparent. Although the Guiding Principles were written for the NIH BRAIN Initiative, they may prove useful to other groups and organizations engaged in cutting-edge technology development and research.

To operationalize integration of neuroethics throughout the NIH BRAIN Initiative's research portfolio, an internal neuroethics project team composed of NIH program staff ensures that neuroethics are considered throughout the grant cycle, from developing funding plans for review and approval by NIH Institute and Center Directors and throughout the lifespan of managing funded projects. The internal project team's work is informed by the Guiding Principles and they interface with the external Neuroethics Working Group to share neuroethics questions elicited by BRAIN-funded research and receive expert input in return.

The project team is also responsible for a growing neuroethics research portfolio. In 2016, NIH issued a Request for Information (RFI) that solicited public input on BRAIN-related neuroethics questions amenable to research. Information from that RFI was used to develop a funding opportunity announcement (FOA) to support research on ethical implications of advancements in neurotechnology and brain science supported by the NIH BRAIN Initiative (<https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-17-260.html>). Through 2 years of this FOA, nine research project grants have been awarded (<https://brain-initiative.nih.gov/funding/fundedAwards.htm>). In addition to these projects, the neuroethics project team promotes neuroethics training through BRAIN-supported mechanisms (F32 and K99/R00), with two neuroethics postdoctoral fellowships awarded to date, and administrative supplements to embed neuroethics in existing NIH BRAIN Initiative grants. Our vision is that these neuroethics research efforts will add to the neuroethics knowledge base that we draw on to ensure that NIH BRAIN Initiative research holds to the highest ethical standards, for example, through development of new neuroethics frameworks or tools that can be used in human neuroscience research laboratories.

Lastly, the Guiding Principles are also considered during the grant review process. Applicants and reviewers are familiar with existing human subjects protections. Some NIH BRAIN Initiative FOAs, however, have gone beyond these, with approaches to integrate additional consideration of the neuroethical implications of

the proposed research. For example, a recent FOA supporting human neuroscience research using invasive neural recording and stimulating technologies required applicants to address neuroethical considerations, including obtaining the informed consent from research participants who can expect no direct therapeutic benefit from engaging in the proposed research (<https://grants.nih.gov/grants/guide/rfa-files/RFANS-18-010.html>). This neuroethics section was assessed as a nonscored, additional review consideration facilitated by expert neuroethicists on the review panel. Like all NIH-funded research with human participants, these studies were subject to review by institutional review boards, yet adding this additional review consideration underscores the sensitivity of studies involving monitoring and stimulating the human brain and supports ongoing oversight of the work. This approach will inform our efforts to establish a shared vision for the ethical conduct of human neuroscience research.

Looking ahead

As the NIH BRAIN Initiative continues to grow and increase our understanding of the human brain and how it functions, it should increasingly rely on a robust neuroethics infrastructure to identify and address neuroethical implications of the research it funds. We envision an ongoing, iterative process of neuroethics informing the trajectory of the neuroscience research and neuroscience research informing neuroethics. As part of this process, the Guiding Principles may evolve over time, perhaps as part of work to create a set of shared norms that extends beyond NIH.

BRAIN 2025 notes that the NIH BRAIN Initiative must adapt in response to the evolving scientific landscape and the Initiative is in the midst of an updated planning process. A working group of the Advisory Committee to the NIH Director (ACD), the highest-level advisory committee at the NIH, is working to revisit the priorities outlined in *BRAIN 2025* through the lens of progress achieved to date, rising scientific opportunities, and the new set of tools and neurotechnologies emerging from the NIH BRAIN Initiative (<https://acd.od.nih.gov/working-groups/brain2.0.html>). As part of this effort, NIH Director Dr. Francis Collins tasked a Neuroethics Subgroup of the ACD working group to develop a "Neuroethics Roadmap." The group will characterize the neuroethical implications that may accompany both the development and use of new neurotechnologies

supported by the NIH BRAIN Initiative. The Neuroethics Roadmap will enable NIH leadership and program staff and the greater scientific community to have a shared understanding of—and shared responsibility for—the areas needing neuroethics-focused consideration when proposing or supporting research agendas.

It is anticipated that the ACD working group will deliver its final report, including the Neuroethics Roadmap, to the full ACD in June 2019. The Neuroethics Working Group will then inform the NIH BRAIN Initiative's implementation of the Roadmap by providing ongoing input on the neuroethical implications of the Ini-

tiative's evolving research portfolio, continuing to host topical workshops on issues as they arise, and helping to shape the Initiative's neuroethics research portfolio. These efforts underscore the critical role that neuroethics will continue to have within the NIH BRAIN Initiative going forward and its utility for helping advance the tools and knowledge derived from the Initiative into clinical applications that reduce the burden of illness due to brain diseases and disorders.

References

- Farahany NA, Greely HT, Hyman S, Koch C, Grady C, Paşca SP, Sestan N, Arlotta P, Bernat JL, Ting J, Lunshof JE, Iyer EPR, Hyun I, Capestany BH, Church GM, Huang H, Song H (2018) The ethics of experimenting with human brain tissue. *Nature* 556:429–432. [CrossRef Medline](#)
- Global Neuroethics Summit Delegates, Rommelfanger KS, Jeong SJ, Ema A, Fukushi T, Kasai K, Ramos KM, Salles A, Singh I (2018) Neuroethics questions to guide ethical research in the international brain initiatives. *Neuron* 100:19–36. [CrossRef Medline](#)
- Goering S, Yuste R (2016) On the necessity of ethical guidelines for novel neurotechnologies. *Cell* 167:882–885. [CrossRef Medline](#)
- Greely HT, Ramos KM, Grady C (2016) Neuroethics in the age of brain projects. *Neuron* 92:637–641. [CrossRef Medline](#)
- Rose N (2014) The human brain project: social and ethical challenges. *Neuron* 82:1212–1215. [CrossRef Medline](#)