

# THE BRAIN INITIATIVE AND NEUROETHICS: ENABLING AND ENHANCING NEUROSCIENCE ADVANCES FOR SOCIETY

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*Note from Dr. Eberwine and Dr. Kahn*

This report represents the culmination of a months-long process, including multiple meetings of the BRAIN Neuroethics Subgroup, multiple personal interviews, a public workshop, feedback from the public on a draft report posted for public comment, and further refined in response to comments from members of the ACD at its meeting on June 14, 2019 as well as the BRAIN Initiative's Multi-Council Working Group. As co-chairs we want to acknowledge the hard work and commitment of our colleagues on the Subgroup in taking on the complex and sometimes controversial topics we were asked to address. Like other working group efforts for NIH, there was not a requirement for this report to be a consensus document and individual members may not agree with particular content, however, the analyses and recommendations in it faithfully represent the outcome of the work outlined above. We realize that it is impossible to predict the future, but in anticipation of continued and, indeed, accelerated progress of the BRAIN Initiative the group worked to make the analysis in this report forward-looking and to foretell areas in need of future discussions and attention. On behalf of the BRAIN Neuroethics Subgroup, we respectfully submit this report and its recommendations for consideration by the Advisory Council to the Director of the NIH.

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## EXECUTIVE SUMMARY

The Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative aims to revolutionize our understanding of the human brain. Begun in 2013, this unique and substantive 10-year investment prioritizes developing and using new tools and neurotechnologies to study, understand, and ultimately learn how to control nervous-system function at the level of circuits. The results of these scientific investigations may change our current understanding of the brain, how it works, and its relationship to concepts including consciousness, agency, and human nature. Moreover, while treating diseases is not a central goal for the BRAIN Initiative, given the anticipated progress of BRAIN Initiative-related work, the scientific and medical communities will be able to use the knowledge gained to develop ways to alleviate suffering from malfunctions of the brain that cause devastating consequences for millions of people. In 2019, midway through the BRAIN Initiative's initial 10-year funding period, BRAIN Initiative-funded research is progressing rapidly. These results invite tremendous excitement and also bring to the fore questions about how these findings will be understood and applied. Given the unique nature of BRAIN Initiative-funded research to provide insight into the workings of the brain and those deepest behaviors that, as humans we hold dear, the ongoing BRAIN Initiative work has considered neuroethics principles and approaches to help navigate these issues.

Neuroethics was designated an essential component of the BRAIN Initiative in the Presidential Commission for the Study of Bioethical Issues report *Gray Matters*, subsequently in [BRAIN 2025: A Strategic Vision](#), and its importance was exemplified in 2015 by formation of the [NIH BRAIN Neuroethics Working Group](#). More recently, in parallel with the interim scientific review of the progress of the BRAIN Initiative, the NIH Director re-emphasized the integral value of neuroethics in the BRAIN Initiative and established a neuroethics subcommittee (the BRAIN neuroethics subgroup, or BNS) of the Advisory Committee to the Director (ACD) conducting this mid-course review. The BNS was charged with reviewing the BRAIN 2025 priority areas in their current context, and in light of anticipated progress, and developing a Neuroethics Roadmap for the BRAIN Initiative (this document) as it moves forward, in particular with regard to potential neuroethics implications of new tools and neurotechnologies and their use. The primary goal of this Roadmap is to propose a feasible course for integrating neuroscience and neuroethics during the remaining years of the BRAIN Initiative, and beyond. The BNS was charged to create an independent document but also remained in regular communication with the ACD WG BRAIN 2.0 group and had overlapping membership. The major findings of the BNS, and projected implications, are detailed below (also, see text box) as suggested next steps for the BRAIN Initiative.

*1. The BRAIN Initiative should enhance integration of neuroscience and neuroethics.*

The vast breadth of BRAIN Initiative-funded research makes it difficult to create universal approaches or policies for the integration of neuroethics with neuroscience. While in some cases, such as those involving research with humans or with nonhuman primates (NHPs), neuroethics expertise and principles should be considered throughout the entire life cycle of a neuroscience research project –

from hypothesis generation to research design and conduct to dissemination of results and translation of knowledge. Other projects may not require the same type of neuroethics consideration at every stage, while still other projects may evolve to a future point in their funding period in which neuroethics expertise would be helpful or even necessary. Although the level of neuroethics involvement will vary significantly depending on the nature of the research question at hand, collaboration with neuroethicists facilitates not only ethical neuroscience, but also provides more opportunities to create high-impact work that considers broader societal implications. These diverse collaborations will undoubtedly add fresh perspectives to conceptualizing, conducting, and translating research for the broadest number of people.

This Neuroethics Roadmap (in particular, [Chapter 1. Neuroethics Past, Present, and Future](#) and [Chapter 6. Integrating Neuroethics and Neuroscience](#)) provides background, context, and specific approaches to achieve this level of interdependence. Dedicating additional resources will provide both a vehicle and the incentive for true collaboration between neuroethicists and neuroscience research teams and could be achieved via several steps. First, just as the establishment of the National Center for Human Genome Research required that “not less than” 5 percent of the NIH Human Genome Project budget be dedicated to research on ethical, legal, and social implications (ELSI), NIH

**About this Document**

In this Neuroethics Roadmap, the NIH ACD BRAIN Initiative Neuroethics Subgroup (BNS) presents its findings and analyses regarding neuroethics issues in current and potential research as part of the BRAIN Initiative. The BNS also offers some specific suggestions regarding NIH activities in the BRAIN Initiative. The BNS proposes that the Advisory Committee to the Director, NIH (ACD) recommend to the NIH Director that the NIH, specifically the NIH BRAIN Initiative, consider the findings, analysis, and suggestions in this report for integration, rather than as a parallel effort, into the BRAIN Initiative research program. The BNS recognizes that some of their findings and suggestions go beyond the mission of NIH or would require NIH to work with other federal agencies and non-federal entities and stakeholders. In those cases, the BNS proposes that the ACD recommend to the NIH Director that NIH look for opportunities to engage with broader stakeholder communities to address issues and achieve outcomes consistent with the spirit of the BNS Neuroethics Roadmap.

**Major Findings of the BRAIN Neuroethics Subgroup**

- Enhance integration of neuroscience and neuroethics
- Provide additional tools and resources for neuroscientists to recognize neuroethics issues and opportunities for neuroethics research
- Assess the development and use of innovative animal and neural-circuit model systems
- Establish guidelines for the neuroscience data ecosystem that address data capture, storage, sharing, and translation to humans and society
- Initiate conversations and collaborations to address neuroscience applications beyond biomedical and clinical contexts

should devote funding to ELSI (neuroethics) research and activities that should be increased over time, with the aim of approaching 5 percent of the overall BRAIN Initiative annual budget. Through this mechanism, NIH could provide enhanced support for BRAIN Initiative-funded neuroethics research and a commitment to developing the next generation of leaders conversant in both neuroscience and neuroethics. Building on existing BRAIN Initiative neuroethics initiatives (such as the NIH BRAIN Neuroethics Working Group), guidance efforts and establishing a broad neuroethics consultative network would enable a range of stakeholders (neuroscience researchers and trainees, institutional review boards, healthcare providers, and the non-scientific public) to consider neuroethics issues on an ongoing basis. This network could serve as a valuable resource enabling neuroethicists and scientists to work together to integrate experimental research with neuroethics considerations. Ideally, the constituency should include diverse and global perspectives given the international reach of neuroscience research and its beneficiaries.

*2. The BRAIN Initiative should provide additional tools and resources for neuroethics research and for neuroscientists and others developing neurotechnologies to better appreciate neuroethics issues.*

Neuroethics research is a vibrant field of inquiry that complements experimental neuroscience: The two broad methodological categories of work are empirical and conceptual (see [Types of Neuroethics Research](#), and for specific examples of potential research areas, see [Chapter 3. Neuroethics Implications of Neurotechnologies](#)). Empirical neuroethics research includes systematic data collection to ascertain views, values, or practices of researchers, patients, research participants, or the public. It often employs social-science methodologies such as quantitative surveys or qualitative interviews and may also include experimental designs to test the impact of interventions or other experimental manipulations. To date, the BRAIN Initiative has funded a number of such neuroethics empirical projects, and this investment should be expanded. Conceptual neuroethics research includes analyses of specific concepts such as privacy or personal identity – or philosophical research about defining social and cultural norms about behavior. Additional research could include building knowledge about poorly understood neural/behavioral concepts such as consciousness (see [Neuroethics Transformative Project](#)), and how that knowledge might affect research, diagnosis, treatment, as well as possible ill effects such as stigma. Such research could be complementary and conducted by interdisciplinary teams. A key issue that requires careful neuroethics consideration and planning by the BRAIN Initiative, for example, is protection and long-term care of individuals with implanted neural devices.

Neuroscientists and others developing neurotechnologies need the ability to identify ethical quandaries in the context of their work, and the BNS has observed through its analysis and interactions that neuroscientists usually welcome a resource to help them explore the ethical, social, and legal implications that may arise uniquely because their subject of study is the brain. The NIH BRAIN Neuroethics Working Group, in collaboration with the global neuroethics community, developed [Neuroethics Questions for Neuroscientists \(NeQNs\)](#) to aid scientists in identifying a neuroethics issue, developed by consensus at the 2018 Global Neuroethics

Summit. The NIH BRAIN Neuroethics Working group created a set of [Neuroethics Guiding Principles](#) to guide investigator behavior. The frontier nature of BRAIN Initiative neuroscience research will continue to present challenges related to unanticipated consequences deriving from its novelty. As time progresses, existing frameworks will evolve as well as be joined by new contributions from the collaborative interactions of neuroethicists and neuroscientists.

*3. The BRAIN Initiative should assess the development and use of animal and other biological models aimed to more closely approximate human brain function.*

Increasingly sophisticated approaches are being used to create animal and other biological models that approximate human neurological conditions, illnesses, and diseases. Various features of BRAIN Initiative-funded research involving animal models may raise ethical issues beyond those addressed by existing guidance for biomedical research involving animal models. Neuroethics research (both conceptual and empirical) is an important resource to help identify ethical issues for the use of these models. The BNS appreciates the extraordinary relevance of the use of animal models in neuroscience research and recognizes that existing guidance for responsible and compassionate use of such models is extensive. The BRAIN Initiative should encourage continued deliberation about the ethical issues arising in research involving animal models that more closely approximate the human experience, considering the experience of animals and possible human gain. These issues are particularly germane for research with NHPs, given their close genetic relationship to humans and the characteristics they offer as research models of human neuronal complexity. As research progresses, such as through development of genetically modified NHP models that more closely mimic human physiology, the neuroscience community should consider whether any additional neuroethics consideration is warranted. Further, encouraging data sharing for NHP work at predetermined designated times during research will increase transparency, likely reduce animal usage, and stimulate research progress.

*4. The BRAIN Initiative should establish guidelines for the neuroscience data ecosystem that address data capture, storage, sharing, and translation to humans and society.*

As with other aspects of potentially sensitive collections of large amounts of data like the Human Genome Project, neuroscience data management is a key focal area within the BRAIN Initiative. Responsible use of neuroscience data (acquisition, sharing, and translation) promotes equity, whereas exclusion of data may lead to hypotheses that reinforce previously held biases. It is critical that publicly funded research achieves maximum public benefit – paying particular attention to individuals and groups who are vulnerable and/or otherwise underserved. Emerging data-science applications, such as machine learning and its many derivatives, offer powerful and efficient investigational approaches to behavioral analyses and interpretation of massive imaging and recording datasets. Yet, while machine learning-based analyses of complex datasets promise to revolutionize our understanding of brain diseases, at the same time they may detect and possibly reveal unanticipated aspects of a research participant's brain health, thought processes and potentially stigmatizing information.

Analyses by the BNS suggest several actions related to use of neuroscience data to achieve a healthy balance between discovery and privacy. When neuroscience data are used to investigate human brain function, ethical use of the data should: i) note and acknowledge its source; ii) ensure that it was properly obtained according to ethical guidelines and relevant statutes; iii) use only the subset of data required to query the question of interest; and iv) ensure the appropriate consents are in place for the use of legacy data especially if it is repurposed. Equally or possibly more important, there are scenarios that may preclude universal data sharing. These special circumstances include, for example, when a research participant's identity and other personal information potentially inferable from brain data could be readily compromised from combining that individual's composite datasets, which was neither envisioned nor specified in the informed-consent process. Public engagement concerning awareness around the implications of data privacy and open data sharing should include stakeholders in developing/evaluating evolving policies of brain data use.

*5. The BRAIN Initiative should initiate conversations and collaborations to address neuroscience applications beyond biomedical and clinical contexts.*

There are a growing number of applications of neuroscience outside traditional biomedical and clinical contexts. For example, currently available direct-to-consumer applications include transcranial direct-current stimulation devices, brain-training games, consumer electroencephalography (EEG) devices, mental-health mobile apps, and many others. Investments in military neurotechnology aim to improve cognitive abilities of soldiers and reduce trauma from post-traumatic stress disorder. Lawyers are beginning to use neuroscience data as evidence. Marketing firms are gathering brain data with the goal of influencing consumer decision-making through targeted branding, selling practices, or product design and placement. In these and other domains, neuroscience is being regularly employed within societal arenas despite limited understanding of brain function and structure, with few scientific studies supporting the efficacy of such use. In each of these sectors outside the traditional boundaries of biomedicine, there is potential for unintentional outcomes or misuse: unjust legal outcomes based on bad brain science; invasions of brain privacy; inadequate protections for consumers; and concern about dual use. The view of the BNS is that the BRAIN Initiative could initiate and participate in addressing the many crucial questions surfacing at the interface of neuroscience and society. An expanded ethical framework that elicits, engages, and provides reasonable responses to these difficult issues is necessary and must involve experts beyond the BRAIN Initiative.

As foretold by the BRAIN 2025 report, the focused and carefully articulated vision for the BRAIN Initiative has already led to major advances in understanding of the human brain. As evidence, nascent discoveries await application from the multitude of technologies developed through this large, public investment in neuroscience research. As is to be expected in any biomedical research pursuit, BRAIN Initiative-funded endeavors have yielded unexpected findings and have yielded unanticipated new technologies with which to study the neurobiology of the brain. At this midway point in this journey for knowledge about the brain and its diverse functions, the scientific community has an opportunity to look ahead at what might come next. This



Neuroethics Roadmap aims to provide an anticipatory lens as well as offer an invitation for continued blending of expertise, knowledge, and participation from neuroscientists and neuroethicists working together. In so doing, it highlights what neuroethics can offer, promotes neuroethics research, and endorses integration of neuroethics with neuroscience at multiple levels.

# THE BRAIN INITIATIVE AND NEUROETHICS: ENABLING AND ENHANCING NEUROSCIENCE ADVANCES FOR SOCIETY

## CHAPTER 1. NEUROETHICS PAST, PRESENT, AND FUTURE

Brain diseases affect people across the lifespan and in every corner of the globe. Brain injury, combined with neurologic, psychiatric, and substance-use disorders, are leading causes of the global burden of disease, and their rates of incidence are expected to rise ([Whiteford et al., 2015](#)). These diseases and disorders exert considerable impacts on society, ultimately affecting public health and economic stability in ways yet to be fully comprehended. Thus, put quite simply, investing in neuroscience research not only represents a historic scientific era, but conveys an ethical imperative to drive advances in our understanding of brain function to improve human health.

Launched in 2013, the [Brain Research through Advancing Innovative Neurotechnologies® \(BRAIN\) Initiative](#) aims to revolutionize our understanding of the human brain with a priority of developing and using new tools and neurotechnologies for "... acquiring fundamental insight about how the nervous system functions through understanding circuit function from single cells to complex behaviors." The first 5 years of this unparalleled effort has yielded significant discoveries in all seven Priority Areas designated by the BRAIN Initiative's flagship strategic plan, [BRAIN 2025: A Scientific Vision](#) (see text box, BRAIN 2025: 7 Priority Areas), transforming our capacity to understand complex spatial and temporal circuits and systems. These advances span three-dimensional maps of cell types and activity-dependent gene expression, high-speed three-dimensional imaging of neural activity, novel methods of neuromodulation, a range of sensors and probes that continue to advance ongoing discovery, among others. Powerful new modes of computational analyses and data-science methods such as machine learning offer powerful and efficient investigational tools.

### The role of neuroethics in the BRAIN Initiative

From its beginning, the BRAIN Initiative highlighted the importance of neuroethics and acknowledge the potential for uniquely distinct ethical issues, as articulated in the BRAIN 2025 report:

#### BRAIN 2025: 7 Priority Areas

Priority Area 1. Identify and provide experimental access to different brain cell types to determine their roles in health and disease.

Priority Area 2. Generate circuit diagrams ranging from synapses to the whole brain.

Priority Area 3. Develop and apply improved methods to monitor neural activity.

Priority Area 4. Link brain activity to behavior through precise interventional tools that change neural-circuit dynamics.

Priority Area 5. Understand the biological basis of mental processes via new theoretical and data-analysis tools.

Priority Area 6. Develop innovative technologies to understand the human brain and treat its disorders.

Priority Area 7. Integrate new technological and conceptual approaches produced in goals 1-6 toward understanding cognition, emotion, perception, and action in health and disease.

“... mysteries unlocked through the BRAIN Initiative, and through neuroscience in general, are likely to change how we perceive ourselves as individuals and as members of society. Many of these discoveries will raise more questions than they answer. We may need to consider, as a society, how discoveries in the area of brain plasticity and cognitive development are used to maximize learning in the classroom, the validity of neuroscience measurements for judging intent or accountability in our legal system, the use of neuroscience insights to mount more persuasive advertising or public service campaigns, the issue of privacy of one’s own thoughts and mental processes in an age of increasingly sophisticated neural ‘decoding’ abilities, and many other questions. Questions of this complexity will require insight and analysis from multiple perspectives and should not be answered by neuroscientists alone.”

Deeper knowledge of the innermost workings of the brain has exciting but unknown potential to challenge the typical ways we think about life, death, each other, and ourselves, as the results are intended to inform what we know about how the brain produces complex functions and behaviors. This knowledge could reveal core mechanisms that underlie human thoughts, emotions, perceptions, actions, identity, and memories. Ethical questions, challenges, and opportunities are intertwined with this research, the results of which may change our understanding of what many people view as consciousness, agency (the capacity to act in a particular situation), and human nature. It is clear that as we learn more about the brain – along with the arrival of neurotechnologies to intervene with its many functions – neuroethics questions will likely emerge. Navigating these questions requires sensitive and systematic responses, as well as proactive development of concrete implementable goals to ensure that neuroscience research and neuroethics are tightly integrated.

The authors of the BRAIN 2025 report also noted, “Although brain research entails ethical issues that are common to other areas of biomedical science, it entails special ethical considerations as well. Because the brain gives rise to consciousness, our innermost thoughts and our most basic human needs, mechanistic studies of the brain have already resulted in new social and ethical questions.” Recognizing the centrality of ethics to the BRAIN Initiative and building on the recommendations in *Gray Matters*, NIH established the [NIH BRAIN Neuroethics Working Group](#) to anticipate and recommend overall approaches for how the BRAIN Initiative might navigate potential ethical issues. The NIH BRAIN Neuroethics Working Group has held several public meetings and published guiding principles and other papers in the neuroethics literature. The NIH BRAIN Neuroethics Working Group is part of the Initiative’s Multi-Council Working Group to help ensure neuroethics is embedded within the broader scientific initiative. Since 2017, the NIH BRAIN Initiative has also issued specific neuroethics funding announcements and has funded neuroethics research projects. In the recent, interim review of BRAIN 2025 (“BRAIN 2.0”), the NIH Director re-emphasized the integral value of neuroethics in the BRAIN Initiative and established this group – the NIH ACD BRAIN Initiative Neuroethics Subgroup (BNS) – to develop an accompanying Neuroethics Roadmap (this document) to highlight areas for neuroethics consideration and research that are engendered by anticipated progress of the BRAIN Initiative.

## What is neuroethics and why is neuroethics important?

Neuroethics, as defined by the International Neuroethics Society is “... a field that studies the implications of neuroscience for human self-understanding, ethics, and policy.” Neuroethics also considers brain-related dimensions of familiar and important bioethical issues. These include largely normative work (“what should we do?”) at the intersection of neuroscience and the responsible conduct of research, the ethics of research with humans and animal models, data privacy, risk mitigation, health-care access, and others. Given the unprecedented precision of new neurotechnologies and the brain's centrality to human identity, familiar bioethics topics take on new dimensions and complexities.

Because brain function is intimately connected to our understanding of identity, moral responsibility, liberty, privacy, authority, agency, personhood, and normality, there are neuroethics issues distinct from the broader scope of bioethics. Neuroethics also has an important role in exploring how neuroscience as a field evolves, addressing opportunities for development, application, and ramifications of the use of various neurotechnologies – defined as any technology that informs our understanding of the brain and its functions, including higher-order activities like consciousness and thought. Neurotechnologies are currently being developed as both research tools (to visualize or otherwise measure brain function) and as therapies, to repair brain dysfunction (see [Chapter 3. Neuroethics Implications of Neurotechnologies](#)).

At two extremes, neuroethics is misunderstood as esoteric or punitive. Importantly, neuroethics is not a set of rules or compliance mechanisms, and its role should not be seen as limited to implementing oversight of the responsible conduct of research. Rather, fully integrating neuroethics with neuroscience offers tremendous opportunity for new research insights, inviting new fields including the humanities into scientific discourse, bringing science and its discoveries to align with societal values and aspirations for science – in addition to its vital role of protecting research participants and guarding against potential malign intent by rogue actors. The intended reach of neuroethics goes beyond ethical conduct of neuroscience research, to the clinical and societal applications of this work, framing responsible acquisition and use of knowledge about the brain and the nervous system. It also facilitates planning for – and in some cases, adjusting for the implications of – how such knowledge is applied to human health, illness, and behavior.

Neuroethics may tackle a range of questions, for example: i) which brain circuits or function influence our ability to act rationally to be capable of voluntary, intentional actions; ii) what is authenticity, and is it jeopardized when our executive function is damaged or when an implanted central nervous system device alters our interests, evaluations, or responses; iii) when are people not responsible for their actions and behavior, and/or do certain neurological characteristics or neural devices reduce culpability for their actions; iv) what does privacy mean in the setting of neurotechnologies, and how does one protect against possible threats to people's innermost thoughts; and v) how should one apply considerations of justice related to neural development, plasticity, and access to possible technological improvements. Many more questions are easily conceivable and not necessarily unique solely to BRAIN, or to

neuroscience in general. However, given the importance of evaluating these issues prospectively alongside the BRAIN Initiative is key, we consider these topics throughout the chapters of this Neuroethics Roadmap, both in the context of current research and as they relate to future discoveries and technologies.

## **Integrating neuroethics and neuroscience**

The BRAIN Initiative has emphasized the value of integrating neuroscience and cognitive science with technology and engineering, as well as encouraging neuroscience to be a boldly multidisciplinary exercise. Similarly, to confront challenging and emerging ethical questions arising from studying the brain, neuroethics benefits from integration with neuroscience – intentionally including scholarship from philosophy, psychology, law, theology, sociology, and other areas. Integrating a neuroethics perspective into neuroscience research design and conduct can have a powerful, positive impact on research and the knowledge it generates. Neuroethicists can help to scan the horizon and assist in anticipating and navigating ethical concerns, and they can also help guide how neuroscience research is designed, conducted, interpreted, and applied. Neuroethics should be intentionally integrated into neuroscience projects when appropriate, but neuroethics research should also continue as independent scholarship that complements experimental neuroscience; neuroethics must be able to facilitate good neuroscience and also ask hard questions about when innovative neuroscience does not align with societal values and the people funding it. Opportunities are many and include: i) seeking the advice of a neuroethicist on experimental design and details of research protocols; ii) collaborating with a neuroethicist to explore a unique ethical concern related to the implementation of an experiment or possible implications of study findings; or iii) collaborating

### **Types of Neuroethics Research**

#### **Conceptual**

- Analysis of specific concepts such as privacy or personal identity
- Philosophical research about normative questions (i.e., What ought to constitute desirable or acceptable social behaviors?) or theoretical questions (i.e., What is consciousness and how can neuroscience inform how consciousness is conceptualized?)
- Examples: How should one define and treat people with various levels of consciousness? Does fluctuating capacity from disease, a brain injury, or a brain intervention indicate a need to rethink informed consent?

Conceptual and normative neuroethics research may draw from existing literature and theories, as well as practices from law, philosophy, theology, and neuroscience.

#### **Empirical**

- Systematic data collection to ascertain views, values, or practices of researchers, patients, research participants, or the public; testing the application of norms, principles, etc.
- Use of social-science methodologies such as quantitative surveys or qualitative interviews, experimental designs for testing the impact of interventions and/or other experimental manipulations.
- Examples: The BRAIN Initiative has funded a number of [neuroethics empirical projects](#).

with a neuroethicist to conduct parallel neuroethics research. Neuroethics research might be

conceptual, normative, empirical, policy-related, or some combination of these (see text box, Types of Neuroethics Research).

### **The need for neuroethics research**

Like the Human Genome Project, the BRAIN Initiative is a wide-ranging endeavor that can raise equally wide-ranging ethical, social, and legal issues. Tools and knowledge emanating from decoding the human genome transformed biomedicine dramatically. In the decades hence, individual laboratories across the globe – not to mention citizen scientists and children in school – have ready access to relatively easy-to-use methods to “read” DNA that bypass regulatory scrutiny ([Waltz, 2017](#)). Such access has opened many new doors of investigation, launching numerous new fields of ‘omics inquiry as well as numerous controversies. Newfound experimental access to our genome has even coined many phrases, such as the “language of life.”

Another important consequence of the Human Genome Project has been a tendency for people in many segments of society to embrace a form of genetic essentialism – some people equate “who we are” with our genes. It is important to consider the extent to which the BRAIN Initiative might have a similar reductionist effect on how we as humans view ourselves. Will we equate “who we are” with brain function at the expense of alternative, more relational conceptions of identity? Is society prepared? These are not just rhetorical questions, but a call for systematic neuroethics research to learn how neuroscience will have impacts beyond the bench and whether and how it will set new societal norms.

Moreover, the conduct of neuroscience research itself may raise important questions warranting further neuroethical study. For instance, some may consider brain tissue and associated data derived more sensitive given the connection between the brain and behavior. Robust ethical practices and federal regulations are in place for all research participants, regardless of species, but new technologies created by BRAIN may challenge this infrastructure. Thus, it is of utmost importance that existing biomedical research ethics guidelines are routinely assessed to ensure they keep pace with the way science is conducted and used.

### **Existing ethical guidance, role of neuroethics, and intersection with neuroscience**

Multiple sources of regulations, guidelines, and best practices currently inform research practices for all species, including the conduct of neuroscience research. Some of these are described briefly below. This summary does not constitute an exhaustive analysis but rather highlights recent useful approaches to thinking about and dealing with neuroethics issues. Using these and other guidelines and methods, however, also requires ongoing deliberation and dialogue, anticipating possible impacts on individuals, populations, and society (see [Chapter 6. Integrating Neuroethics](#)).

## Belmont Report

Often considered a seminal source of ethics guidance, the 1978 [Belmont Report](#), issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, is somewhat unique among ethical guidance in that it concisely analyzes three principles that underlie the ethics of research with humans (see text box, Belmont Principles). The report applies these principles – respect for persons, beneficence, and justice – to specific research-related activities. The Belmont principles are known for their simplicity, clarity, reach, and endurance – but they require context and balancing when applied to individual applications. They form the basis for U.S. federal regulations (both the [Common Rule](#) and Food and Drug Administration ([FDA regulations](#))) and other ethical-guidance documents that govern protection of human research participants. Importantly, however, the three Belmont principles are not unique to clinical research – they are familiar and applicable principles in other domains, such as health care. Over time, potential limitations of the Belmont principles have been raised in light of evolving research practices and the importance of other considerations such as transparency and the impact of research on groups ([Friesen et al., 2017](#)). This debate has led to rethinking possible additional principles for the ethical conduct of research ([Rhodes, 2005](#)). More recently, some have suggested the need for a set of Belmont principles specific to research with neurotechnologies and to neuroscience ([Goering and Yuste, 2016](#)).

<b>Belmont Principles</b> <b>National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978</b>		
<b>Principle</b>	<b>Explanation</b>	<b>Application to clinical research</b>
Respect for persons	To respect, and not interfere with, the self-determined choices and actions of autonomous individuals; and to provide additional protections for those with diminished autonomy	Informed consent for enrollment and ongoing participation
Beneficence	To not deliberately harm another, to maximize benefits and minimize risks, and to promote the welfare of others	Analysis of risks and benefits and determination that benefits justify the risks
Justice	To be fair in the distribution of social goods such as the benefits and burdens of research	Fair procedures and outcomes in the selection of subjects

*Presidential Commission for the Study of Bioethical Issues*

At the outset of the BRAIN Initiative in 2013, the Presidential Commission for the Study of Bioethical Issues was tasked to identify “... proactively 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.” The Commission sought the advice of many experts at multiple public hearings and published two volumes entitled [Gray Matters](#). The first recommends the integration of ethics early and explicitly throughout the processes of neuroscience research. Such integration could take several forms, such as education at all

**Gray Matters Vol. 2 Neuroethics Recommendations for Neuroscience**

1. Prioritize Existing Strategies to Maintain and Improve Neural Health
2. Prioritize Treatment of Neurological Disorders
3. Study Novel Neural Modifiers to Augment or Enhance Neural Function
4. Ensure Equitable Access to Novel Neural Modifiers to Augment or Enhance Neural Function
5. Create Guidance About the Use of Neural Modifiers
6. Responsibly Include Participants with Impaired Consent Capacity in Neuroscience Research
7. Support Research on Consent Capacity and Ethical Protections
8. Engage Stakeholders to Address Stigma Associated with Impaired Consent Capacity
9. Establish Clear Requirements for Identifying Legally Authorized Representatives for Research Participation
10. Expand and Promote Educational Tools to Aid Understanding and Use of Neuroscience within the Legal System
11. Fund Research on the Intersection of Neuroscience and the Legal System
12. Avoid Hype, Overstatement, and Unfounded Conclusions
13. Participate in Legal Decision-Making Processes and Policy Development
14. Establish and Fund Multidisciplinary Efforts to Support Neuroscience and Ethics Research and Education

levels; institutional infrastructure; research on the ethical, legal, and social implications of BRAIN Initiative research; consultation on research ethics; stakeholder engagement; and inclusion of an ethics perspective within the research team. The second volume recognized that while some ethical issues in neuroscience are not unique to neuroscience, many become even more pronounced. [Gray Matters, Volume 2](#) focused on three controversial and timely topics that illustrate ethical tensions and societal implications: cognitive enhancement, consent capacity, and neuroscience and the legal system, and issued 14 specific recommendations across these three areas (see text box, Gray Matters Vol 2 Neuroethics Recommendations for Neuroscience).

<b>Principles for Assessing Emerging Technologies Presidential Commission for the Study of Bioethical Issues 2010</b>	
Public Beneficence	Responsibility to maximize public benefits while minimizing public harms
Responsible Stewardship	Prudent vigilance- practical, sensible, cautious ways for assessing likely benefits, safety, and security risks both before and after projects are undertaken. Limiting scientific projects and



	exploration when necessary out of collective concern for current and future people and the environment
Intellectual Freedom and Responsibility	Intellectual freedom coupled with the responsibility of individuals and institutions to use their creative potential in morally responsible ways.
Democratic Deliberation	Collaborative decision making that embraces respectful debate of opposing views and active participation of citizens and the public
Justice and Fairness	Concern about fair distribution of the benefits and burdens across society

In addition to the *Gray Matters* reports, the Commission had previously published a set of principles useful for assessing emerging technologies, appearing in [New Directions: The Ethics of Synthetic Biology and Emerging Technologies](#). These principles are intended to illuminate and guide public policy choices to ensure that new technologies, including synthetic biology, are developed in an ethically responsible manner (see text box, Principles for Assessing Emerging Technologies). They complement other sources of ethical guidance and are relevant to development and application of new neurotechnologies and BRAIN Initiative research.

*Nuffield Council on Bioethics*

<b>Ethical Framework for Novel Neurotechnologies</b> <b>UK Nuffield Council 2013</b>
<b>Foundational Principles</b> <b>Beneficence-</b> developing interventions and technologies to address suffering from brain disorders, yet <b>Caution-</b> because of uncertainties and possible effects on our brains <b>Key Interests</b> Individual interests in <b>safety</b> , protection risks, impacts on <b>privacy</b> , and promotion of <b>autonomy</b> Public interests in <b>equity</b> of access and promoting <b>trust</b> in neurotechnologies <b>Virtues-</b> necessary in promoting and protecting the identified interests <b>Inventiveness, humility, and responsibility</b>

In [Neurotechnologies: Intervening in the Brain](#), the Nuffield Council on Bioethics – an independent body in the United Kingdom that examines and reports on ethical issues in biology and medicine – proposed two foundational ethical principles (beneficence and caution), as well as key interests and virtues that together form an ethical framework. Beneficence is required for developing and applying therapeutic neurotechnologies because of the “... suffering caused by brain disorders and an absence of other suitable treatments,” but caution is also needed because of uncertainty about the benefits and risks of these technologies, their novelty, and possible unexpected effects given our still-limited knowledge of brain function. In articulating implications of the two principles, the Council identified five interests warranting particular attention for individuals (for effects of treatment decisions on people’s lives) and to the public more generally. The five key interests are: i) protection of safety, taking into account risks and expected benefits; ii) promotion of autonomy, in the sense of supporting an individual’s capacity to make his or her own decisions ; iii) protection of individual privacy, bearing in mind that some devices may collect sensitive personal data; iv) promotion of equity both in terms of access to innovative products and for addressing social stigma and discrimination; and v) promoting public understanding of, and trust in, novel neurotechnologies. Finally, this Council proposed that in

seeking to protect and promote these identified interests, three virtues are especially relevant and should guide the activities of all involved parties across a wide range of settings and technologies. These are: inventiveness (such as technological innovation) and identifying ways to enhance access; humility in acknowledging the limits of our knowledge and capabilities; and responsibility, through robust research and clinical practices and avoiding exaggeration, hype, or premature claims.

### *Neurotechnology and Ethics Task Force*

Concerned that existing guidance was insufficient or not specific enough to address the complex issues presented by neurotechnologies, and especially focused on brain-computer interfaces and artificial intelligence, a multidisciplinary team convened meetings in 2016 and 2017. This group of neuroscientists, neurotechnologists, clinicians, ethicists, and machine-intelligence engineers identified four major distinct ethical issues related to neurotechnologies and artificial intelligence ([Yuste et al., 2017](#)): i) privacy and consent, ii) agency and identity, iii) augmentation, and iv) bias. They offered several recommendations to address these concerns globally, including adding "neuro-rights" to international treaties, regulating the use of neurotechnology for augmentation and military use, and regulating the use and sale of neural data.

### *Global Neuroethics Working Group of the International Brain Initiative*

Held annually in South Korea since 2017, the [Global Neuroethics Summit](#), a workshop hosted by the Neuroethics Workgroup of the [International Brain Initiative](#), links global neuroethics efforts around the globe. Leveraging momentum from an international consortium of seven large-scale nation-level brain-initiative efforts, the Summit recognized the critical influence of cultural values and perspectives related to both neuroethics and neuroscience – in particular, highlighting the need for culturally informed and culturally aware neuroethics inquiry. Summit delegates have developed a set of cross-cultural neuroethics questions meant to encourage neuroscientists across various brain projects to consider neuroethics questions ([NeQN](#), see text box, Neuroethics Questions for Neuroscientists). The questions are further discussed and applied throughout this Neuroethics Roadmap. The NeQNs are intended to be adaptable and informed by country-relevant cultural values and frameworks, with the goal of acknowledging possible diverse understandings and values related to specific concepts and interests. For example, the need to protect brain-research participant privacy is universally important but varies in scope. Summit delegates concluded that developing a culturally informed global framework for neuroethics requires attention to inclusivity, education, and communication. These questions were used by the International Brain Initiative projects in a special 2019 neuroethics-focused issue of *Neuron* ([Rommelfanger et al., 2019](#)).

<b>Neuroethics Questions for Neuroscientists (NeQN)</b>
1. What is the potential impact of a model or neuroscientific account of disease on individuals, communities, and society? 1a. Possible unintended consequences on social stigma and self-stigma

- 1b. Possible social or cultural biases in research design or interpretation of scientific results?
- 2. What are the ethical standards of biological material and data collection and how do local standards compare to those of global collaborators?
  - 2a. Protecting the privacy of human brain data (e.g. Images, neural recordings, etc.) and data, in immediate or legacy use beyond the experiment?
  - 2b. Special regard for brain tissue and its donors due to tissue origin and its past
- 3. What is the moral significance of neural systems that are under development in neuroscience research laboratories?
  - 3a. What requisite or minimum features of engineered neural circuitry generate concern about moral significance?
  - 3b. Are ethical standards for research adequate and appropriate for evolving methodologies and brain models?
- 4. How could brain interventions impact or reduce autonomy?
  - 4a. Identifying measures to ensure optimal autonomy and agency for participants/users
  - 4b. Responsibility for effects (where responsibility broadly encompasses legal, economic, and social contexts)
- 5. In which contexts might a neuroscientific technology/innovation be used or deployed?
  - 5a. Identifying applications that might be considered misuse or best uses beyond the laboratory?
  - 5b. Does this research raise different and unique equity concerns and, if so, have equitable access and stakeholder benefit been considered?

*NIH BRAIN Neuroethics Working Group Guiding Principles*

The NIH BRAIN Neuroethics Working Group proposed eight neuroethics guiding principles as points to consider for researchers, institutional review boards (IRBs), and others involved in the conduct of BRAIN Initiative-funded research (see text box, Neuroethics Guiding Principles). Two overarching principles frame the eight [Neuroethics Guiding Principles](#): i) pursuing neuroscience research is an ethical imperative because of the immense suffering and economic impact of brain disorders around the world; and ii) neuroethics is vital to and should be integrated with neuroscience research. The Neuroethics Guiding Principles are meant to guide neuroscientists, particularly BRAIN Initiative-supported researchers, to help them consider the ethical, legal, and societal implications of their work in dialogue with other key stakeholders.

<b>Neuroethics Guiding Principles NIH BRAIN Neuroethics Working Group</b>	
<b>Principle</b>	<b>Examples</b>
Make assessing safety paramount	Gene editing technologies such as CRISPR/Cas9 may offer hope for mitigating or eliminating brain disorders, yet we have insufficient understanding of risks and long-term effects. When researching innovative approaches, attend to preclinical data, monitor safety throughout, and inform participants about possible unexpected safety issues.
Anticipate special issues related to capacity, autonomy, and agency	Anticipate possible changes in preferences and agency, such as personality changes reported by some after deep brain stimulation for movement disorders; or deciding about control over stimulation parameters when brain stimulation paradigms target reward

	processing and motivation circuits. Seeking informed consent from participants, while simultaneously manipulating neural processes necessary for consent capacity and autonomous choice.
Protect the privacy and confidentiality of neural data	Protecting large, shared databases containing brain imaging data, as someday a brain MRI might be as identifying as a fingerprint. Determining who has access to personally identifiable information.
Attend to possible malign uses of neuroscience tools and neurotechnologies	Researchers have a responsibility to try to predict plausible misuses, prevent it when possible through design and security measures, and ensure that participants, IRBs, government officials, and others understand possible risks
Use caution when moving neuroscience tools and neurotechnologies into medical or non-medical uses	Discourage the premature widespread use or inappropriate adoption of new technologies such as neural markers of pain or deception, especially those offered directly to consumers or in non-health care settings, such as the legal system.
Identify and address specific concerns of the public about the brain	The public may worry that a beneficial improvement in ability to control a dysfunctional brain (e.g. from memory loss or seizures) has a flip-side, potentially threatening cognitive liberty. Or have justified concerns that research could "make a person someone else," or result in entities that have morally significant human-like features.
Encourage public education and dialogue	Balancing appropriate understanding of neurological advances while avoiding hyperbole and correcting overly optimistic interpretations.
Behave justly and share the benefits of neuroscience research and resulting technologies	Identifying strategies to ensure wide sharing of the benefits of novel technologies and interventions and avoid exacerbating existing health disparities or inequalities.

Many other important efforts not mentioned in this Neuroethics Roadmap include already-developed scientific and ethical guidance for particular neurotechnologies and contexts for their use. Examples include the [Human Performance Enhancement Report](#) from the American Academy of Arts and Sciences and the [Principles for Responsible Innovation in Neurotechnology](#), led by policy organizations such as the Organization for Economic Cooperation and Development. This latter group has had a [recent focus on neuroethics](#) and how neuroethics might be integrated into public-private-partner consortium led neuroscience research.

Ethical attention guided by frameworks such as those listed here, accompanied by careful reflection, will continue to be essential when decisions are made about how to obtain knowledge about the brain and how to interpret it; about who uses the knowledge generated; as well as the implications of such knowledge for clinical practice, public health, other social institutions, and society. The selected frameworks, principles, and recommendations highlighted in this chapter provide guidance at multiple levels, for those who conduct, fund, disseminate, implement, and use neuroscience research.

In addition to the frameworks and principles described herein, important legal and regulatory requirements apply to neuroscience – for example, those that regulate the protection of humans and animal models in research (see [Chapter 2. Understanding Ourselves: The Uniqueness of Neuroscience](#) and [Chapter 4: Neuroethics and Research with Animal Models](#), respectively). Scientists testing and developing emerging technologies should consider relevant general principles from the Belmont Report as well as the Presidential Commission’s principles for assessing emerging technologies. The BRAIN Initiative’s Neuroethics Guiding Principles, the Nuffield Council’s ethical framework, the NeQNs from the Global Neuroethics Summit, and others that address particular issues that arise in neuroscience and neurotechnology research offer useful guidance. These resources raise many considerations relevant to BRAIN Initiative research, including the possible effects of neurotechnologies on agency, identity, capacity, and public trust, and risks associated with augmentation, hype, bias, and possible misuse of technologies and data. As brain research develops, it is likely that new concerns will arise that require additional consideration and that may point to refining guidelines or developing new ones. Going forward, the BRAIN Initiative should be prepared to support these discussions.

In summary, neuroethics is integral to the BRAIN Initiative and cannot be separated from it. Neuroethics provides an opportunity for deliberation, analysis, and research that both catalyzes, improves, and enables neuroscience. This Neuroethics Roadmap proposes a way forward to maximize innovation and value from the BRAIN Initiative in a way that prioritizes benefits for humanity at large. To do so, it explains what neuroethics can offer, provides neuroethics principles and guidelines to help shape ethical neuroscience and its applications, promotes neuroethics research, and endorses integration of neuroethics with neuroscience at multiple levels.

## CHAPTER 2. STUDYING OURSELVES: THE UNIQUENESS OF NEUROSCIENCE

This chapter considers the moral significance of the brain, various approaches to neuroscience, and key assumptions underlying beliefs about the brain and modern neuroscience. The chapter concludes with a discussion of the ethical frameworks needed to guide the BRAIN Initiative as a scientific “moonshot.”

### The moral significance of the brain

#### *What do we know?*

Identity is intimately linked with the brain. This is true both for subjective views of identity (What makes me the kind of person that I am?) and for philosophical notions of personal identity (What is it that makes someone the same person over time?). A major goal of neuroscience is understanding how activity in our brains translates into thousands of behaviors on a minute-to-minute basis. With this aspiration come goals of better understanding “who we are” and fundamental behaviors that are believed to contribute to human attributes, such as forming personal narratives for identity, exercising free will, and defining socially acceptable actions.

The brain enables our experiences, memories, agency, creativity, and ideas. The emergence of these cognitive properties makes human life distinctive from other forms of animal life and distinctive from one person to another. Because the brain contributes so significantly to a sense of self, the prospect of a severe and irreversible brain injury casts doubts about whether post-injury the “same person” will emerge even as the body survives. Severe injuries to other organs, even those requiring whole-organ transplants, do not usually raise similar concerns about subjective identity.

Philosophical notions of personal identity invite many questions and assertions. For instance, in Western philosophical traditions, humans are classified as “persons” by virtue of their ability to make decisions independently and rationally (a concept known as rational agency). Personal autonomy – one contemporary variant of rational agency – is an individual’s ability to act thoughtfully on motivations, appetites, or desires they could endorse at a higher cognitive level of self-reflection ([Dworkin, 1970](#); [Frankfurt, 1971](#)). Put another way, an autonomous person acts deliberately according to his or her own values ([Hyun, 2001](#)). Both notions of personhood and autonomy require complex cognitive functions supported by the brain – functions which, in turn, give human existence its felt coherence. Seventeenth-century English philosopher and physician John Locke [wrote](#) in 1694 that a person is “a thinking intelligent being, that has reason and reflection, and can consider itself as itself, the same thinking thing, in different times and places.”

Second, in addition to providing the enabling conditions for personhood and autonomy, the brain plays a crucial role in theories of personal identity. What does it mean for someone to remain the same person over time? What does it mean for person A to be the same person as person B many decades later, or after a serious accident? One prevalent view of personal identity

defines it in terms of the continuity of memory between person A and person B; that is, person A is the same as person B only if B remembers experiences that A had. Even those philosophers who argue there is no single underlying self that remains the same across all our various stages of life nonetheless agree that people care most about the survival of their memories when faced with a catastrophic threat to the body, either sudden or gradually degenerative ([Parfit, 1984](#)). Because memory depends upon the physical integrity of the brain, personal identity too seems to be intimately tied to the physical continuity of the brain.

### *What could we learn? Neuroethics research opportunities*

One can appreciate how the effects of disease may change both subjective and personal identity. For example, it is relatively easy to understand that severe memory loss can affect perception of self and the ability to make rational decisions; but other disease processes may also influence the lens through which a person sees the world and how that person interacts with others. In addition to effects on an individual, disease can influence the dynamics of a group – family members or support systems – and thus potentially change the identity of that group and its interactions.

As described above, the moral significance of the human brain likely derives from its role in defining personhood, rational agency, personal identity, and personal interactions – all of which are crucial for grounding our everyday moral judgments of ourselves and others. In light of these considerations, it is important to consider several assumptions that accompany this modern view of the human brain. This area is ripe for conceptual and empirical neuroethics research by collaborative teams of ethicists, legal scholars, social scientists, philosophers, and others who explore these questions about research participants and users of new neurotechnologies and neuroscientific insights.

### **Assumptions about the brain and about neuroscience**

#### *What do we know?*

Ever since the 18<sup>th</sup> century Enlightenment period, superstitions and mystical beliefs have been progressively unseated by scientific, philosophical, and ethical rationalism. For many people, rationality is considered to be the most significant and valuable human characteristic. For proponents of rationalism, science provides the means by which everything in the world can be demystified and catalogued – understood – from the starry heavens above to humankind itself. If humans are rational beings by nature by virtue of the structure and functioning of their species-specific brains, then to study the human brain is thus to study “ourselves,” in essence.

While mechanistic views of the brain are evident in BRAIN 2025, a careful balance between mechanistic and humanistic approaches can provide a path forward, thus advancing science and gaining its benefits without creating the perception that individuals are simply a series of circuits and genes. Importantly, a single scientific approach cannot reconcile individual brain-cell function with combined, system-wide activity that drives behavior in an individual. Hence,

scientists must inevitably parcel study of these tasks and combine their outputs later to integrate the many dimensions of our lived experiences. Because one may never fully comprehend the entirety of the human brain and how it contributes to the identity of an individual, it will be useful to look in parallel at mechanisms as well as at influences due to cultures, societal structures, and other concepts related to the human experience (see [Neuroethics Transformative Project](#)).

### *What could we learn? Neuroethics research opportunities*

It is important to consider how social and cultural influences outside the body might affect brain structure and function in all its domains. Understanding behavioral or cognitive disorders may need to take into account cultural, genetic, and experiential influences. Many diverse factors can significantly influence research outcomes or applications at the levels of both individuals and populations. Given the extensive interconnectivity of neural networks that control motor, sensory, cognitive, and behavioral functions – even apparently simple motor functions may be influenced by cultural or experiential factors in ways that are not yet understood.

To what extent are psychological processes and neural activities universal or culture-specific ([Lin and Telzer, 2017](#))? The vast majority of functional magnetic resonance (fMRI) studies (about 90 percent) evaluating the effects of cultural background on brain activity during cognitive processing have been conducted in individuals from Western populations ([Chiao, 2009](#)) using Western participants, which constitute only 12 percent of the world’s people ([Arnett, 2008](#)). Given the potential for variations in neural processes between cultural groups and geographical regions, including a wide range of individuals and populations from across the globe in neuroscience research will undoubtedly enhance both rigor and applicability of the findings ([NeQN3](#)).

### *Ethical frameworks reconsidered*

Scientists can learn much about the brain through research studies involving human participants. But studies in humans must proceed with appropriate caution. Modern neuroscience may pose difficult ethical challenges for human studies, yet traditional research ethics alone may not be adequate, and prospective monitoring may be warranted to anticipate and deal with neuroethics issues. Some

consideration of the ethical frameworks used by the BRAIN Initiative may be necessary (see

#### **Considerations for performing neuroscience research involving human participants**

- As neuroscience research progresses, periodically re-examine neuroscience-specific ethical issues to ensure that the research and informed-consent processes remain ethically appropriate, and that IRBs are updated and well-informed.
- When conducting human studies with neuromodulators, including drugs, outline in detail potential end-of-trial and post-trial responsibilities.
- Develop and report plans for managing participants who may benefit from study participation.
- For non-clinical scientists working with human research participants, include a clinician on the research team.
- Specify in advance potential psychosocial risks to potential research participants. These include changes in self-identity, effects of personality changes on interpersonal relationships, and others.
- Consider using “real-world” samples in research whenever possible (such as including participants with co-existing conditions), to maximize research relevance and generalizability.



## [Chapter 1. Neuroethics Past, Present, and Future](#)

As with other emerging and rapidly advancing fields, a comprehensive understanding of the potential risks and benefits associated with novel neurotechnologies is unknown. First and foremost, this technology aims to improve human health. However, such effects on humans include those on physical and psychosocial parameters, as well as on family relations. Furthermore, the BRAIN Initiative ultimately strives to understand non-diseased brain function, but researchers are limited in what they learn from typical study populations – even when healthy individuals are included as control populations in research designs and data analyses. Researchers and regulators will inevitably see tensions as proposals seek to study healthy brains, and as risk/benefit ratios for healthy volunteers shift. These are difficult ethical challenges, but they may be solvable as many have been throughout the history of biomedical research. The key is to tackle these challenges through systematic analysis of emerging technologies paired with thoughtful and innovative rubrics for evaluating risk-benefit ratios in research.

### *Implementable goals:*

- Given the potential for characterizing core characteristics of human brains as well as variations in neural processes between cultural groups and geographical regions, neuroscientists should strive to include a wide range of individuals and populations from across the globe in neuroscience.
- Although not unique to neuroscience, nomenclature is ever important. Efforts should be made to clarify concepts such as consciousness, empathy, and free will, as these terms are not always used to impart the same meaning in neuroscience research. Even hypotheses that attempt to explore human difference based on socially constructed identities such as race and gender must be carefully examined to avoid replicating and even enhancing already damaging biases in society.
- Interdisciplinary research teams can help facilitate exploration of how assumed meanings and socially constructed identities influence study design and interpretation of results. As we gain deeper insights about early disease stages – for example, pre-symptomatic markers indicating atypical circuitry – we should prepare for and investigate the possible shifting distinction between “typical” and “atypical.” Such an integrated approach involving neuroethics and neuroscience is a significant opportunity for the BRAIN Initiative.
- Finally, the BRAIN Initiative may need to assess over time whether an additional ethical approach may be needed that goes beyond that of human-subject research ethics.

Consider the metaphor of the “moonshot” that sometimes frames discourse around the BRAIN Initiative. The original Moonshot – the United States Project Apollo mission that landed a human on the moon in 1969 – is widely heralded as a great triumph and is often cited as an example of what American science can achieve under the best circumstances of dedicated effort and

focused funding. But it is easy to forget that the Moonshot was a very controversial program in its day. It involved enormous financial expenditures and the diversion of resources from other pressing social needs. It even cost the lives of three astronauts who volunteered for the Apollo 1 mission. And it was never certain to succeed. The Moonshot, and all other metaphorical “moonshots” thereafter, heighten the need for an ethics framework that can operate at the level of large, government coordinated scientific initiatives. What would such an ethical framework look like?

An overarching ethical framework for the BRAIN Initiative should place the principles of social beneficence and distributive justice front and center. While the BRAIN Initiative aims to expand knowledge, its *moral worth* derives not from the intrinsic value of new knowledge, but from the ways in which that knowledge can be used to improve the human condition. Social beneficence is implicit in the moral justification for science. What would it mean therefore for the BRAIN Initiative to fulfill its social obligation of beneficence? There are open questions involving *what* counts as relevant social benefits, *who* bears the duty of providing and distributing these social benefits, *to whom* such benefits are owed, and *how far* this duty extends. The questions of “what,” “who,” “to whom,” and “how far” are crucial and have not been adequately addressed in the BRAIN Initiative. An ethical framework that elicits, engages, and provides reasonable answers to these difficult questions will be helpful.

## CHAPTER 3. NEUROETHICS IMPLICATIONS OF NEUROTECHNOLOGIES

The BRAIN Initiative is dedicated to revolutionizing the world’s understanding of the human brain through the development of tools, methods, and knowledge bases that will advance fundamental understanding of brain function – with a particular focus on circuit-level analyses. This work is expected to lay the groundwork for a dramatically enhanced understanding of ways in which the brain can be coopted by disease, as well as to provide new frameworks for effective interventions and therapies to treat brain disorders. However, as new neurotechnologies are developed, and new insights into the mechanisms of brain function and disease are discovered and refined, there is an obligation – and an opportunity – to continually consider, anticipate, and address potential neuroethics issues that may arise. In this way, neuroethics may be used not to impede, but rather to advance the ability of BRAIN research to have the greatest societal impact. The first 5 years of the BRAIN Initiative saw progress in each of its designated research Priority Areas, some resulting in exceptional and unexpectedly rapid knowledge growth. BRAIN 2.0 will likely see significant advances in integrative strategies cross-cutting these Priority Areas, building upon groundwork laid during BRAIN 1.0.

### Neuroethics Questions for Neuroscientists (NeQN)

1. What is the potential impact of a model or neuroscientific account of disease on individuals, communities, and society?
  - 1a. Possible unintended consequences on social stigma and self-stigma
  - 1b. Possible social or cultural biases in research design or interpretation of scientific results?
2. What are the ethical standards of biological material and data collection and how do local standards compare to those of global collaborators?
  - 2a. Protecting the privacy of human brain data (e.g. Images, neural recordings, etc.) and data, in immediate or legacy use beyond the experiment?
  - 2b. Special regard for brain tissue and its donors due to tissue origin and its past
3. What is the moral significance of neural systems that are under development in neuroscience research laboratories?
  - 3a. What requisite or minimum features of engineered neural circuitry generate concern about moral significance?
  - 3b. Are ethical standards for research adequate and appropriate for evolving methodologies and brain models?
4. How could brain interventions impact or reduce autonomy?
  - 4a. Identifying measures to ensure optimal autonomy and agency for participants/users
  - 4b. Responsibility for effects (where responsibility broadly encompasses legal, economic, and social contexts)
5. In which contexts might a neuroscientific technology/innovation be used or deployed?
  - 5a. Identifying applications that might be considered misuse or best uses beyond the laboratory?
  - 5b. Does this research raise different and unique equity concerns and, if so, have equitable access and stakeholder benefit been considered?

In this chapter of the Neuroethics Roadmap, we employ the structure of these scientific Priority Areas for BRAIN as a framework for identifying potential companion neuroethics issues and neuroethics research opportunities. For each Priority Area, efforts were made to discuss an array of ethical scenarios – some may be likely in the near term, some may reflect challenges

for broader neuroscience research enabled by BRAIN technologies, and some may appear to be science fiction that may only materialize in the distant future, if ever. These efforts – while probing and which in some instances may appear alarming – are deliberate and meant to make the point that efforts should be made to prospectively identify potential scenarios and work with stakeholders to avoid or mitigate the greatest risks.

In anticipation of such issues it is useful to align scientific progress of BRAIN with the previously derived [Neuroethics Questions for Neuroscientists](#) (NeQNs), developed by consensus at the Global Neuroethics Summit (see [Chapter 1. Neuroethics: Past, Present, and Future](#)) in collaboration with many large-scale brain research efforts including members of BRAIN. These NeQNs can help focus attention on potential neuroethics issues and research opportunities that can then be judiciously addressed. To illustrate this rubric for identifying neuroethics issues, the anticipated scientific advances highlighted in this section of the Roadmap will be cross-referenced with NeQNs that may be useful in eliciting any associated neuroethics concerns. As well, the frontier nature of neuroscience research also presents challenges related to unintended consequences deriving from their novelty. These include, for example, appropriate informed-consent procedures when it is impossible to quantify unintended consequences of controlling brain circuits. It is important to view neuroethics issues in context of the [Neuroethics Guiding Principles](#), which can also be informed by the NeQNs. The principles offer a framework for prioritizing values and for ethical guidance for the conduct of BRAIN research including new technology development.

#### **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.

### **Priority Area 1. Discovering Diversity**

#### *What do we know?*

This BRAIN 2025 goal aims to develop a systematic and detailed understanding of the genetic, morphological, and physiological characteristics of different cell types throughout the nervous system as well as their potential roles in brain processes. Achieving this goal will permit development and use of genetic and molecular tools to identify cells and ultimately, to modulate their behavior in specific brain areas and circuits. This aspect of BRAIN 1.0 has been very successful, greatly expanding our knowledge of the number and diversity of cell types in the

brain of different organisms, while also enabling us to quantify differences and likenesses between organisms.

### *What could we learn? Neuroethics research considerations*

The rapid growth of technologies for gene editing (e.g., CRISPR), creating better viral vectors, tissue processing, imaging, and in-situ analysis of cells suggest that researchers are on the cusp of identifying and selectively modifying specific cell types, genes, or proteins in living systems. As research using models of human neural circuitry becomes more sophisticated, questions will arise about the appropriate boundaries for cell-type based manipulations that involve animal models (see [Chapter 4. Neuroethics and Research with Animal Models](#)) as well as how increasingly sophisticated engineered neural circuitry and systems may challenge how we consider these circuits on a moral basis ([NeQN3](#)).

### *Research samples*

Aside from general issues noted above, specific questions may be posed concerning the nature of analyzed samples and privacy. Related to the former, initial work on discovering and characterizing cell types should not focus on a single species, or on one societal group or sex or race or age, ensuring that bias is mitigated, and that the benefits of neuroscience research can apply to individuals from numerous populations, including children and adolescents ([NeQN1b](#)). Related to privacy, consent from individuals who provide tissues, either while alive or after death, should address the long-term consequences of such a donation for themselves and their relatives. Issues related to information that may eventually be derivable from these tissues leading to consequences such as stigma or use in unanticipated applications should be addressed within the informed-consent process and on a continuing basis ([NeQN1b](#), [NeQN5b](#), [Guiding Principles 3, 8](#)). In an era of widespread data sharing, long-term use of data derived from a sample warrants consideration of privacy ([NeQN2a](#)). Further, as model systems using or replicating organized human brain tissue attain higher levels of circuit-level and systems complexity, they may warrant additional scientific and ethical review: At what point should *in vitro* or *ex vivo* human cells or samples be considered to warrant greater moral significance or revised research standards? These issues raise neuroethics questions about moral significance that should not only involve scientists and ethicists but also incorporate concerns from the general public ([NeQN3a,b](#), [Guiding Principle 6](#)).

### *Cell/tissue manipulation*

#### **Neuroethics Research Opportunity**

What are the requisite or minimum features of engineered neural circuitry required to generate a concern about moral significance? ([NeQN3a](#))

Collaborative research involving scientists, philosophers, and ethicists can define and create systematic approaches in conceptual and empirical work, as well as analyze testable measures of neurally derived features that would cause tension for donors, scientists, and members of the public. Importantly, exploring these ethical perspectives from a variety of stakeholders should incorporate multicultural research design and dissemination of information. The work should also explore the global relevance of these neuroethics considerations.

This cell-census component of the BRAIN Initiative raises familiar ethical, legal, and social implications that have already emerged from genomic research; for example, the ability to introduce whole genes into cells warrants forethought about the resulting effects on function (e.g., on circuits, both in the recipient individual but also in later generations) ([NeQN5a](#), [Guiding Principle 1](#)). However, there may be unique considerations with manipulations that alter brain function. Along with decisions on which cells should be targeted (healthy or diseased), a framework will be needed to revisit aspirations for these methodologies. Generally, our society will need to decide whether neurotechnologies should stop with restoring cognitive health or proceed toward enhancing cognitive function. The alteration of learning and memory is an example where a valuable therapeutic goal could be extended toward enhancement of learning capabilities or implantation of memories ([NeQN1a](#), [NeQN5](#), see also [Chapter 5: Beyond the Bench: Real-World Translation of Neuroscience Research](#)). Analysis of tissues can reveal important information about disease risk and potentially about more subtle individual traits. How might accessibility of this data bear on privacy for the individuals who participate in studies, and also for family members? ([NeQN2a](#), [Guiding Principle 3](#)).

## **Priority Area 2. Maps at Multiple Scales**

### *What do we know?*

This BRAIN 2025 research area is focused on developing detailed knowledge of the structural and functional properties of brains of different model organisms, including patterns of activity and interconnectivity, at scales ranging from individual synapses to large-scale connectivity of human brain regions. This project has supported the development of significantly enhanced methods for generating structural and functional maps from *ex vivo* and living brains in species ranging from worms and flies to humans. Although improvements to non-invasive human-brain imaging technologies during BRAIN 1.0 have been incremental, technologies such as fMRI are improving in speed and signal-to-noise ratio. Moreover, portable, near-infrared spectroscopy can already provide non-invasive readouts of brain activity in social settings (and portable PET and MRI systems are in development). These enhanced imaging methods, combined with studies across species, could soon reveal functional activity and connectivity patterns that may potentially be interpreted in terms of thought, mood states, behavior, and personality. As described in the BRAIN 2025 report, an eventual goal is to discover how the human brain produces cognition and behavior at the “speed of thought,” information that could inform an understanding of the neural basis of personality and self. The wider availability of such techniques for human use may prompt non-medical, commercial, consumer, or judicial use of such technologies, and care will be needed to determine in which contexts technology or innovation can be justly deployed ([NeQN5](#), [Guiding Principle 8](#); see [Chapter 5: Beyond the Bench: Real-World Translation of Neuroscience Research](#)).

### *What could we learn? Neuroethics research considerations*

Distinct in this Priority Area are neuroethics questions related to mapping studies. For example, currently, transcranial direct current stimulation is being used in non-medical, non-research settings toward improving neurological performance. Such issues are not directly within the scope of current BRAIN Initiative-funded research, but they are relevant to consider as federally funded research finds application in everyday life (see [Chapter 5: Beyond the Bench: Real-World Translation of Neuroscience Research](#), [NeQN5](#), [Guiding Principle 5](#)).

A pervasive challenge with all research involving humans is defining “normal” in the context of health and disease, but also in the context of human variation and individual identity and personality. Scientific studies in animal models and in humans using male-only samples have sometimes generated incorrect general assumptions resulting in adverse health consequences or reinforced negative biases already present in society about socially constructed groups ([Yoon et al., 2014](#)). Large-scale studies to understand the brain’s maps and networks should sample from (and can thus benefit) a fully representative cross-section of our society. Communication and use of the results of such studies should also be carefully managed to ensure that the design of experiments and interpretation cannot be subverted to fuel existing negative societal biases or prejudices ([NeQN1a,b](#), [Guiding Principle 7](#)).

#### **Neuroethics Research Opportunity**

How can human brain data (e.g., images, neural recordings, etc.), and the privacy of participants from whom data is acquired, be protected in case of immediate or legacy use beyond the experiment? ([NeQN2a](#))

There is an opportunity for collaborative study about the scientific capabilities of BRAIN Initiative research as well as consideration of legal definitions and historical and evolving public views about neuroprivacy. Part of the assessment of public views could involve exploring new types of informed-consent processes, in particular for research involving neural recordings. Other projects could explore and assess best practices for community engagement and communication strategies with neuroethics issues on stigma, bias, and privacy. Cultural views across and within cultures and geographic regions will provide greater insight into how such technologies might be received and used within a global landscape.

### **Priority Area 3. Brain in Action**

#### *What do we know?*

This BRAIN 2025 research area aims to identify and understand neural activity patterns that underlie cognitive processing and behavior. The BRAIN Initiative has supported many recent advances enabling recording and modulation technologies that are to be used in animal models. Studies are now deploying new technologies for large-scale recording of multiple variables (including neural activity and neurotransmitter concentrations) within animals engaged in complex tasks or more naturalistic behaviors compared to previous anesthetized or head-fixed activities. A parallel area of significant growth has been the application of machine vision and deep-learning approaches to large-scale automatic quantification of animal behavior allowing the continuous tracking of multiple body parts, such as limbs, facial features, and even individual whisker movements of a mouse, as well as the automatic classification of movements. This analysis can be combined with real-time brain imaging. While much of this work and preliminary insights are from animal models, it is anticipated that at some point these

techniques, with current recording methods or with novel non-invasive imaging technologies, could be extended to humans.

### *What could we learn? Neuroethics research considerations*

New combinations of brain activity and behavioral data are beginning to enable development of models and theories that more closely mimic and reproduce the brain’s computational codes that lead to complex behaviors. In this Priority Area, similar neuroethics considerations about potential for bias and stigma as well as neuroprivacy apply as detailed in Priority Area 2. Maps at Multiple Scales. Specific issues in this area concern developing non-invasive brain recording devices.

For instance, wearable human-brain imaging technologies are permitting brain-to-behavior correlative studies in humans. Knowledge emerging from these studies could allow us to assess mood states, behavior, and personality directly from physical observations of the brain, or even from analyses of externally measured aspects of physical behavior. Therefore, the same careful considerations will be needed concerning risks of reinforcing bias by dividing participants along socially constructed identities, as well as privacy ([NeQN1b](#) and [NeQN2a](#)). Wearable neurotechnology is not only an interest of biomedical researchers, but it is already an area of active exploration in the commercial sector as a wellness or cognitive enhancement tool. While not the intended context for BRAIN research, insights will likely extend beyond the BRAIN community and its mandate. Ethical stewardship of studies exploring “brain in action” maps of designated “normal” and “abnormal” brains, particularly as they relate to mental health as well as implications for enhancement will require considerations of privacy and best uses and possible restricted uses beyond the biomedical setting ([NeQN5](#) and [Guiding Principle 5](#)). Indeed, there is an important opportunity for research to provide more thorough delineation of concepts of privacy in the context of brain data. The weight and responsibility of these judgements are not work for neuroscientists alone: questions of uses “beyond the bench” are best explored as a multi-stakeholder research project (see text box). In addition, performing appropriate ethical practices also relies on mechanisms and infrastructure to support scientists’ ability to do so.

#### **Neuroethics Research Opportunity**

In which contexts might a neuroscientific technology/innovation be used or deployed? ([NeQN5](#))

Ethical stewardship of neuroscience and its products requires a scientist’s involvement in anticipating best uses and possible misuse. However, to identify frameworks for use and misuse, research should involve an anticipatory approach scanning the horizon for possible contexts for use in the near and intermediate future. This should include exploring the applicability of existing ethical and legal guidelines with a diverse set of stakeholders including end users, consumers, scientists, ethicists, clinicians, legal scholars, as well as members from the policy community. Such discussions should include assessment of dual-use potential. Importantly, the exploration of this anticipatory work should include a global community who may have differing values and priorities for the use of such research findings and developments that may be at odds with national views and policies.

### **Priority Area 4. Demonstrating Causality**



### *What do we know?*

This BRAIN 2025 research area aims to test our understanding of the brain through perturbations that lead to predictable outcomes (cause and effect). This research encompasses technological development and refinement of experimental methods such as optogenetics that permit specific cells within the brain to be turned on or turned off or chemogenetics that enables pharmacological manipulation of specific cells – enabling evaluation of the immediate and long-term effects of these perturbations on brain function or behavior. As techniques for performing manipulations of brain cell activity become more refined and selective, our understanding of how such manipulations affect brain function and behavior is also becoming more sophisticated. At the heart of this Priority Area is the development of interventional technologies to understand causal relationships and intervene in the case of aberrant neural circuit function. In order to ensure that such insights and abilities to intervene with the brain have the greatest impact for alleviating suffering, careful consideration should be made of how such interventions may intentionally or unintentionally impact or reduce autonomy, capacity, and agency ([NeQN4](#), [Guiding Principle 2](#)).

### *What could we learn? Neuroethics research considerations*

#### *Unknown consequences of manipulation*

Although physiological manipulation of cells and tissues is currently a valuable tool for neuroscientists seeking to understand brain circuits in animal models, and in some cases in humans, these techniques hold significant potential for therapeutic use. For example, they could also be used to intentionally augment, restore, and/or redirect brain function (see Priority Area 6, below). Current genetically targeted methods of brain cell manipulation such as optogenetics require genetic modification of an animal through breeding or viral transfection, as well as delivery of intense light to a location requiring activation. Other technologies such as chemogenetics also require genetic modification of specific cells and require systemic drug delivery for activation. While most researchers do not envision this technology being widely used in humans, genetic therapies are being explored in limited contexts (including optogenetics in the eye as a treatment for blindness). What is more likely in humans are invasive studies including deep-brain stimulation and multi-electrode arrays

#### **Neuroethics Research Opportunity**

Debate about cognitive enhancement has been active for many years. See, for example, [The President's Council on Bioethics. Beyond therapy: Biotechnology and the Pursuit of Happiness](#). Deeper exploration is warranted about the scientific possibilities and limits of today's and tomorrow's neuroscientific advances – and the conceptual separation between therapy and enhancement. Collaborative research in this space is needed involving scientists, ethicists, legal scholars, and practitioners exploring evolving societal definitions of disease and aspirations for wellness, as well as research involving ethical and legal standards on a global scale. These conceptual ethics approaches can also be complemented by public-engagement research exploring public awareness, opinions, and assumptions about neuroscience and enhancement. One significant question to explore with regard to neurotechnology development in this space is: Does neuroscience raise different and unique equity concerns and, if so, have equitable access and benefit of stakeholders been considered? ([NeQN5b](#))

recording and stimulating the surface of the brain, as well as noninvasive stimulation such as ultrasound and transcranial magnetic stimulation. With any of these technologies, the aim would be to manipulate or control the brain in a way that a patient or participant could not do on their own. This poses a potential challenge to the user's autonomy and agency. These qualities, along with those of identity and free will need to be more clearly defined and explored ([NeQN4, Guiding Principle 2](#)). A more complete understanding of these nuances should involve exploration of how user control of stimulation parameters can be offered in ways that would be not only beneficial and desired by participants, but also balanced with a scientific understanding of optimized parameters for use in treating particular aspects of disease. Further, considerations for safeguards from hacking or misuse, understanding who takes ultimate responsibility for ongoing support for the technology beyond the lifetime of a research project, and guidelines guarding against unintended consequences of device use will also ensure sound ethical standards for technologies developed under this Priority Area ([NeQN4b, Guiding Principle 4](#)). Additional neuroethics research considerations could also include how neurotechnologies might affect users' social experiences – such as their relationships with family members and how these changed relationships impact conceptualizations of self and quality of life.

### *Risk analysis*

Research is needed to understand the unique health and safety risks, as well as potential unanticipated consequences of an intervention, for a person's autonomy, capacity, and agency including those related to altering features of personality and memories ([NeQN4a, Guiding Principles 1,2](#)). A valuable part of this risk analysis might include comparisons of a newly developed BRAIN intervention with existing ones and even re-evaluation of older ones based on

#### **Neuroethics Research Opportunity**

Can neurotechnology be designed with technological safeguards that enhance an individual's autonomy, or that protect negative impacts on his or her agency? ([NeQN4](#))

Such research should involve a mixed team of scientists, ethicists, and future end users. Collaborative research evaluating current societal, ethical, legal meanings of responsibility when technologies function well (or when they do not) could help inform new best practices and guidelines for this type of research. Approaches would include conceptual work on understanding divergent and shared meanings for these terms for stakeholders as well as empirical work assessing understanding, values, and preferences in BRAIN-Initiative funded research.

new insights derived from research in BRAIN. A better understanding of how existing interventions, even psychostimulants, affect the brain (acutely and long-term) is sorely needed and should represent a backdrop for considering the advantages and disadvantages of new interventions. Focal interventions may be safer than pharmacological interventions in terms of side effects. Importantly, "risk" should encompass not only physical harms, but also social ones. Given the potential complexity of the effects of interventions on autonomy, agency, and capacity, neuroethics research combined with scientific efforts could help sort out what participants and scientists understand about these terms and how they evaluate their importance in the context of these interventions. Because participants may have difficulty understanding the unique risks that result from manipulating circuit function, informed-consent processes may warrant deeper review ([NeQN4,](#)

[Guiding Principle 2](#)). Further, as understanding of brain manipulation grows, careful thought should be applied to the extension of emerging treatments to children and adolescents. Given the vulnerability of this population and the unique clinical, ethical, policy, and social implications of making technologies available for them, research is needed to examine and address the neuroethics implications of using emerging neurotechnologies in pediatric settings.

## **Priority Area 5. Identifying Fundamental Principles**

The BRAIN 2025 report identified a central role for data analysis, theory, and modeling for the purpose of extracting information from data sets, and for developing conceptual and algorithmic frameworks for interpreting circuit dynamics underlying key brain processes like sensory processing, motor control, and decision-making. As noted above, such work will ultimately provide the conceptual backbone for interpretation of data and ultimately understanding of how the brain functions and malfunctions. Neuroethics issues and research in this Priority Area overlap with those described in the other Priority Areas, above, and are not repeated here. However, data sharing is a key element associated with this Priority Area, as elaborated further below. Sharing raises ethical concerns familiar to any field which collects large datasets, but also could raise a greater degree of tension due to the potential sensitivity of brain-based data.

### *Data sharing*

Large amounts of data are required to enable development and testing of theories and models. Data sharing – including analyses, algorithms, and shared access to infrastructure – is an essential component of open and equitable science ([Akil et al., 2011](#)) and a hallmark of rigorous and ethical research. Responsible data sharing promotes equity, whereas exclusion of data can lead to knowledge confined to a limited group of individuals. Purposeful exclusion of data may lead to hypotheses that reinforce incorrect assumptions or previously held biases ([NeQN1b](#)). However, the imperative for experimentalists to share data – and the need for others to mine and extract information from highly complex, multi-dimensional and multi-modal data – presents significant opportunities and challenges, and there are legitimate concerns that must be addressed.

Neurotechnologies continue to become more sensitive, more robust, more portable, and multimodal. The proliferation of neuroscience into society offers great promise for new insights and improved social policy. But with these dramatic and rapid shifts come difficult ethical questions about the collection, interpretation, application and access of scientific data. A key component to this Priority Area is the aggregation of data collected across large numbers of animals, humans, laboratories, and institutions. In particular for the BRAIN Initiative, invasive recordings from humans will necessarily be rare, and it is ethically imperative to make the most of this precious data resource. While many of the challenges related to data sharing are technical, just as significant are the social, cultural and ethical challenges; i.e., convincing a profession that relies on the currency and attribution of peer-reviewed publications to openly share data without the guarantee of “credit” raises tensions in any discipline.

NIH has several data-sharing policies, as [does the BRAIN Initiative itself](#). These policies have been implemented in multiple ways, including developing a central repository for data, standardized analysis procedures, and policies for data sharing. Responsible data sharing promotes equity, whereas exclusion of data can lead to knowledge confined to a limited group of individuals. Purposeful exclusion of data may lead to hypotheses that reinforce previously held biases ([NeQN1b](#)).

For human data, participant-privacy issues have always been paramount, primarily with regard to identity. We consider human brain data different because of its potential to gain insight into an individual's thoughts and other aspects of an individual. As the BRAIN Initiative moves ahead (and neuroscientists work across the globe outside of the BRAIN Initiative), increasing amounts of data will accumulate from diverse experimental approaches that will likely be more individually precise – and potentially more identifiable. We need to understand more about public awareness and concern about brain privacy (see [Chapter 5: Beyond the Bench: Real-World Translation of Neuroscience Research](#), [NeQN2a](#)) and to establish forward-looking standards that address these concerns.

*Should all brain data be shared?*

Brain data come in many formats, including measurements from genomic, protein, functional, imaging, and behavioral analyses. To facilitate sharing, efforts are afoot to create standard data formats for these diverse data types, including [Neurodata Without Borders](#). As the need for integration across data types and platforms evolves – a key goal for BRAIN 2.0 – it may be necessary to revise data-sharing policies to encompass the widening utility of the data.

Ethical principles guiding collection of data, including neuroscience data, support the use of practices including i) noting its source; ii) insuring that it was properly obtained according to ethical guidelines and university, company and/or local, national, or international policies and regulations; and iii) using only the subset of data required to query the question of interest. Circumstances may preclude universal data sharing, for example, when a research participant's identity could be compromised from combining that individual's composite datasets, which was neither envisioned nor specified in the informed-consent process. Advances in data-analysis methods as well as increased data access have transformed

#### **Neuroethics Research Opportunity**

What are the ethical standards of biological material and data collection and how do local standards compare to those of global collaborators? ([NeQN2](#))

The European Union-funded Human Brain Project (HBP) has produced a report on data sharing, privacy, and practices moving forward as informed by exploration of conceptual analyses of privacy, public opinions on privacy, as well as technical and legal analysis. Not only does this represent the type of interdisciplinary work that BRAIN's neuroethics research should strive to do, it offers a rich opportunity for collaboration. The HBP's current activities related to the ethics of data sharing align with similar goals of the BRAIN Initiative and could provide a fertile ground for research on best practices for neuroethics research, neuroscience data collection, and public engagement. International collaboration and active dialogue about these practices will also be critical as much of these data-sharing practices occur on a global backdrop and will require deeper reflection of the ethical standards of data collection nationally and how these compare to those of global collaborators ([NeQN2](#)).

possibilities related to the applications of data and what types of information can be derived. The purpose of big-data analytics is to create new knowledge – and in so doing, appreciating what information can be derived from data and anticipating risks is a significant challenge ([Metcalfe and Crawford, 2016](#)). One way to address this issue is to have routine review in collaboration with scientists, data analysts and ethicists to evaluate how new analyses might open new opportunities for risk, particularly of re-identification.

IRB approval is an important practice for conducting research with human participants and, in cases where collecting brain data is the goal of an experimental protocol, local IRBs should obtain neuroethics input to address any potential circumstances unique to neuroscience data. As the datasets become more complex and include multimodal data, more information about human participants will be decodable beyond the goals of the initial study (including from unanticipated data disclosure). Anticipating the impact of the availability of these data can be difficult and will likely pose new neuroethics concerns. Given this changing data and analysis landscape, it would be prudent for institutional and Office for Human Research Protections IRB guidance to be assessed and revisited on an ongoing basis to ensure that current guidance sufficiently protects participants, and if not, new guidance should be proffered to manage associated issues.

International collaboration and active dialogue about these practices will also be critical as data-sharing practices occur on a global scale and will require deeper reflection about the ethical practices of data collection nationally and how these compare to those of global collaborators ([NeQN2](#)).

#### **Neuroethics Research Opportunity**

What are the possible unintended consequences of neuroscience research on social stigma and self-stigma? Is it possible that social or cultural bias has been introduced in research design or in the interpretation of scientific results? ([NeQN1](#))

Develop practices to enhance inclusiveness and reduce bias. Studies should be designed to investigate the impact of many variables on brain function, including but not limited to, sex, race, and cultural experiences. Explicit attention should be given to questions about who will benefit from neuroscience research advances and how to promote equitability across these and other important domains. Neuroethics deliberation is necessary and requires thoughtful input beyond neuroethics alone – including, for example, experts in sex/gender differences, cultural and societal differences, disease advocacy, and other topics related to human variation.

### **Priority Area 6. Human Neuroscience**

This BRAIN 2025 research area aims to develop innovative technologies to understand the human brain, with the ultimate goal of treating its disorders. In this Priority Area, new technological and conceptual approaches are integrated and applied to discover how dynamic patterns of neural activity become cognition, emotion, perception, and action in both health and

disease. Such neurotechnologies can be used to monitor the brain to understand details of how it works in health and disease, as well as to treat brain dysfunction. Currently, there is nothing that replaces the human brain as a model for understanding high-level complex outputs of the brain such as cognition. While human studies are conducted judiciously, studies in humans are often considered the most ethically complex (see [Chapter 2. Studying Ourselves: The Uniqueness of Neuroscience](#))

*What could we learn? Neuroethics research considerations*

*Human samples and recordings*

Most human brain samples (and invasive recordings) come from diseased brains in which intervention has been warranted, or after the individual has died. Neuroethics research should inform processes by which scientists acquire tissues and measurements from healthy brain tissue to provide valuable and necessary control information ([NeQN1a](#)). Additional studies can explore how to coordinate efforts between researchers (including internationally) to ensure that large-scale census type work spans sufficiently diverse populations to ensure equitable benefit ([NeQN1b](#)). Other topics include potential guidance pertaining to the use of human cells in multicellular assemblies such as organoids and assembloids that, as complexity increases, may raise unique ethical issues ([NeQN3](#) as mentioned in Priority Area 1 and [Chapter 2: Studying Ourselves: The Uniqueness of Neuroscience](#)).

*Noninvasive human recording and imaging*

The ability to perform non-invasive neuroimaging presents a number of areas of potential neuroethics issues, including: i) unexpected access to incidental findings; ii) detection of clinical biomarkers of latent or impending disease; and iii) use of neuroimaging for national security, legal, or marketing activities. Imaging for clinical biomarkers is becoming more common, and it will likely be combined with self-reports and expert observations to better evaluate clinical states. Neuroethics research could explore the ethical consequences when neuroimaging results diverge from what an individual research participant or patient experiences as well as what his or her provider anticipates from the technology. Other questions surround decision-making related to data sharing and how that may differ among disease contexts (e.g., concussion vs. depression, [NeQN1a](#)). Another scenario to consider might be the prospect of identifying the potential to develop disease – such as Alzheimer’s – decades before symptoms appear or a treatment exists. This may have implications for employment and insurance coverage, for example ([NeQN1a](#)).

Both implanted electrodes and noninvasive approaches that generate behavioral and neural recordings may uncover decodable information that, may create privacy violations for an individual and at times family members as well. As discussed in Priority Area 3, these potential issues raise questions about appropriate use, sharing, and protections for data beyond its first use in an experiment. Importantly participants must have knowledge about and realistic expectations for de-identification and future use in order to consent to providing their data. This

is particularly important as technology and decoding algorithms as well as coupling with other experimental modalities may advance to the point that it may be possible to extract considerable information about a person from recorded brain states without the research participant's explicit permission ([NeQN2a](#) and discussed above in Priority Area 3). Importantly, algorithms – which may be assumed to be objective – should be explored and acknowledged for the possibility of carrying unrecognized biases of their creators ([NeQN1b](#)).

### *Invasive human recording and modulation*

Brain-computer interfaces are already in use; the work of the BRAIN Initiative will accelerate their development and the precision with which they can influence brain function with the aim of improving human health. Devices implanted into the brain entail a high level of risk, as by design they inevitably create an intimate connection between a device and an individual – along with risk of infection, rejection, and the need for long-term care of the recipient and maintenance of the device. This reality raises significant and immediate neuroethics questions.

One current example is use of deep-brain stimulation to shorten or block seizures, a relatively widespread neurological disorder that can cause severe disability. New technologies under development will likely have the capability to monitor neural or neurotransmitter activity over long periods of time and to provide detailed patterned stimulation in a closed-loop (operator-independent) manner. This means that device monitoring and adjustment occur in real time without burdening the individual wearing the device. The detail with which brain states can be monitored will likely improve as we obtain more robust/sensitive recording technology, such as flexible mesh electrodes that detect and potentially modulate electrical activity of many cells and can thus displace current limitations of available electrodes, such as static immobility and stiffness. The impact of these technologies is likely to increase dramatically with nanotechnologies that bring innovation related to materials science, optics, chemistry, and learning algorithms.

It is of note that the health and well-being of participants in invasive technology research presents heightened sensitivity, especially as this research is typically only conducted in patients seeking therapeutic options. The question of what happens at the end of a study is critical. For instance, what responsibilities exist for ongoing support or removal of an implanted device? If a device is therapeutically beneficial, should it remain implanted and functional? What happens if it is removed, if it is likely that the participant would return to his/her pre-therapeutic status? If the device remains, who is responsible for its maintenance, ensuring that it functions well and for monitoring the participants' health consequences long-term? These are important questions as a participant may be particularly vulnerable given his or her motivations for seeking the study at the time of informed consent. These issues raise long-term consequences for both the participant and for his/her immediate family.

Neuroethics research is a valuable tool for addressing these and other scenarios. Examples include the value and risks of implantation of an experimental device that alters brain activity in healthy individuals and informed-consent processes for neurosurgical patients for research

associated with (but not necessary for) medical care. Research and development partners need clarification on, and guidelines for, long-term responsibilities for participants; participating scientists; funding agencies; and device companies that implant devices in research participants. Also needed is elaboration of ownership and rights of participants to access data from an implanted device, along with creating standards for data security.

#### **Neuroethics Research Opportunity**

Collaborative research projects between neuroscientists and neuroethicists could explore how to define and operationalize in a laboratory setting terms and features of sentience. These studies could also work toward developing technologies to measure sentience and other features (see also [Neuroethics Transformative Project](#)).

#### *Conclusion*

The examples provided above illustrate neuroethics considerations framed by opportunities to integrate neuroscience research with what we expect to learn (as well as where it is difficult to anticipate what to expect) about the human brain and behavior. When considering the important issues of agency, self, emotions, decision making – and even more familiar issues of learning and memory and consciousness – it is important to recognize that the biological underpinnings of these aspects of our personhood remain obscure (see [Neuroethics Transformative Project](#)). Yet, there is a moral imperative to use the knowledge gained from the BRAIN Initiative to alleviate suffering from brain diseases and disorders. Intellectual freedom for scientists must be coupled with individual and institutional responsibility to assure responsible behavior. Further – practical and sensible strategies should be established to assess societal benefits, safety, and security risks both before and after research, as well as to limit scientific projects and exploration when necessary. The neuroethics impacts and implications of BRAIN Initiative-funded research should be assessed on an ongoing basis. Also essential are ongoing efforts contributed by the global neuroethics community to monitor the progressing landscape, inform appropriate limits, and participate in the development of concrete guidelines.



## CHAPTER 4. NEUROETHICS AND RESEARCH WITH ANIMAL MODELS

There is a long history of the use of animal models in biomedical research and a significant and longstanding set of best practices, regulations, and oversight for the care and use of those animals. These include the prospective ethical review of research by Institutional Animal Care and Use Committees (IACUCs) and ongoing institutional review of animal care. BRAIN-Initiative funded research involving animal models is conducted with these best practices in mind and is subject to the same oversight. Given the goals of the BRAIN Initiative, there is a clear rationale for research with animal models, and the insights sought through research with animal models are critical for fundamental understanding in neuroscience. Further, there is a rationale for research with higher-order species whose brains are more likely to reflect fundamental properties that underlie the organization and function of the human brain.

Neuroscience research with animal models is an active area of both scientific and ethical exploration as reported in [2012](#) and [2019](#) by the National Academies of Science, Engineering, and Medicine. As mentioned in some of these prior reports, particular features of neuroscience research involving animal models warrant specific ethical attention. Certain BRAIN Initiative-funded studies use animal models that mimic human neurological disease and symptoms, seeking to clarify neurobiological underpinnings of neural diseases. Various other animal models reflecting the contributions of human genes and cells in the nervous system ([Shi et al., 2019](#), [Leung and Jia, 2016](#), [Windrem et al., 2014](#), [Mansour et al., 2018](#)) are being used to better study human behavior and disease. These efforts are sometimes referred to as “humanized” animal models, although we have chosen not to use this term in this Roadmap to avoid potential misunderstandings of the results of such efforts.

To illustrate how neuroethics has been integrated into novel research with animal models, one recent high-profile example of a BRAIN Initiative-funded project involving animal models that raises ethics questions is the recent restoration of microcirculation and molecular and cellular activity in a large mammalian (pig) brain after a prolonged post-mortem interval ([Vrselja et al., 2019](#)). These researchers developed a novel and powerful tool for studying brain cells and circuits. At the same time, these experiments raise multiple ethical implications for future research in animal models and potentially in humans, as well as ethical questions about studying live disembodied brains. In this instance, neuroethics issues were discussed at earlier stages of the project’s development through the point of publications with the NIH BRAIN Neuroethics Working Group. Collaborations are ongoing and were successful in accurately representing the scientific findings, noting the potential ethical issues and how they had been already explored, as well as in minimizing misrepresentations of the findings in the public domain.

The prospect of ongoing and future work in these and other areas raises complex ethical questions that are also shared by other areas of biomedical research. These include:

- How to identify the most appropriate animal model for a given research proposal
- How to best minimize animal use while maximizing data output from animal models used in BRAIN Initiative-funded research

- How to apply appropriate justificatory criteria for research that involves developing and using animal models with inserted human genes or which mimic human diseases and disorders
- How to take into account research results that yield deeper understanding of animal consciousness, and its implications for the understanding of animal suffering

Addressing these and other questions will help to provide greater clarity and rationale in support of the evolving uses of animal models in BRAIN Initiative research – and in so doing help to make more explicit the importance of and justification for that research in support of human health. One particular challenge will be the likely increased value of research with NHPs in BRAIN-Initiative funded research. Many of the technological advances of BRAIN 1.0, initially made in other species, are becoming widely available for use with NHPs. The enhanced cognitive capacity of these animals, and their relative physiological and genetic proximity to humans, make them valuable subjects for research aiming to illuminate principles of human-relevant cognition and biology. NHPs have a particularly important role to play in establishing models of human disease, because research based on other species has often failed to transfer to humans. Thus, research with NHPs is likely to be necessary to translate knowledge gained with other species to applications in humans and also to pioneer new knowledge on specific aspects of brain function that NHPs uniquely share with humans, such as face recognition or other complex cognitive processes. The general public is divided in their views about research with animal models and the BNS is aware that this is a sensitive and multifaceted topic. Importantly, our queries and analyses are not intended to limit the use of animal models in research, but rather to help articulate and refine the criteria for when and why research with animal models is critically important to pursue – and by the same token, when it is not. Analysis of these types of ethical issues also has implications for the humane care and treatment of animals engaged in BRAIN Initiative-funded studies and other research.

Neuroethics questions related to animal research apply to all species of animals, from rodents to NHPs, with some suggestion that these questions deserve particular attention for research involving NHPs because of their greater neurological complexity and therefore greater parallels to states of consciousness and suffering experienced by humans. Research with NHPs is an important part of neuroscience research, and it has been essential for learning how to treat disease and alleviate human suffering. Because NHPs are more similar to humans than other animal models in their behavioral, anatomical, and physiological properties, they have been indispensable for studying drug and vaccine efficacies, psychiatric disorders, brain function, periodontal disease, and aging, among other conditions. In addition, neuroscience research, including BRAIN-Initiative funded research, seems poised to enter a period where the value of NHPs may increase as the ability to observe and manipulate brain circuitry becomes increasingly possible. The conceptual and ethical analysis of neuroethics research results will continue to provide greater understanding not only about animals and animal life, but in support of greater understanding of human neurobiology and human health.

#### *What do we know?*

There is longstanding evidence for the value of research with animal models in support of human health, and the animal-ethics literature (both conceptual and empirical) is important for

identifying ethical issues in research with animal models. This scholarship helps to identify ethical principles and ensure that they are applied consistently in various animal models – as well as affirms the relevance and appropriateness of specific animal models for specific neuroscience research studies. Discussions of the ethical issues of animal use and neuroethics research regarding the use of animal models should be ongoing to keep pace with rapid developments in research. These include development of genetically identical monkey clones for research ([Liu et al., 2018](#)); development of transgenic rhesus monkeys with a human version of a gene involved in brain development ([Shi et al., 2019](#)), and others. In addition, discussions among diverse stakeholder groups – neuroscientists, animal behaviorists, veterinarians, researchers who work with animal models, primatologists (when appropriate), ethicists, and others – will inform a deeper and more sophisticated understanding of ethical issues in neuroscience research involving animal models.

Engaging in research related to questions about consciousness, pain, and suffering may offer insights into human cognition and the neurological bases for personhood, as discussed in [Chapter 2. Understanding Ourselves: The Uniqueness of Neuroscience](#). In examining questions about pain and consciousness, neuroscience research may also lead to better understanding about animal behavior that may challenge our intuitions about both animals and humans. Greater understanding of animal models through research may affect balancing risk-benefit ratios as we better understand the experience of animals and as animal models more closely approximate the human experience. To make the point more succinctly, greater understanding of the various ways that animals experience the world is both a research advantage and an ethical challenge. This is particularly true of research with NHPs, given their close genetic relationship to humans and the characteristics they offer as research models of human complexity, but also may become true of other animal models that are engineered to model features of human brain function.

Increasingly sophisticated approaches are being used to create animal models that approximate human neurological conditions, illnesses, and diseases. The tools used for such research blend stem-cell advances and precise genome-editing techniques ([De Los Angeles et al., 2018](#)), which both facilitate progress in research and elicit unique ethical issues ([Neuhaus, 2018](#)). As noted in the report of a recent National Academies workshop on creating NHP models of neurological diseases, the value of such animal models must be carefully assessed in review and oversight processes in light of the information they might yield for human health. Moreover, there are many ethical questions when developing such models, including: “Does it matter what disease is being modeled?” “How are the symptoms associated with the disease managed?” and “Is creating human diseases or inserting human genes in animal models different in NHPs compared with other species?”

#### *What could we learn? Neuroethics research opportunities*

The BRAIN Initiative should support or participate in efforts to explore and characterize ethical aspects of different animal models in neuroscience and have a process for using the results of these explorations to inform policy and practice. As noted below, we suggest that the BRAIN Initiative develop a strategy to create guidance for researchers who develop and use animal models created to mimic human physiology. This will be particularly important and useful with

the emergence of NHP models of human neurological conditions, illnesses, and diseases, and as work with these models yields insight and information. Animal models such as *Aplysia* and mice have been used successfully to help understand higher-order brain behaviors such as the molecular biology of learning and memory.

Each model system brings addressable well-developed “species-shared” biologies to experimental paradigms. This is likely true for research with NHPs as experiments move toward understanding traits that are more human, such as particular aspects of consciousness that inform concepts, such as personhood. As biological aspects and their resulting characteristics are added to non-human species such as NHPs to make them more biologically similar to humans, might they become more morally similar, and in the process, raise unique animal welfare issues. As neuroscience research yields greater scientific insights into the structure and function of animal brains, insights will follow that could inform our understanding of sentience, consciousness, the experience of pain and suffering – and more generally, what we understand about the inner lives of animals. These conceptual aspects of animal experiences are closely connected to the ethical use and treatment of animals. They also deserve attention as fundamental research questions that require carefully constructed projects involving neuroscientists, ethics scholars, and other individuals engaged in animal care and use. The findings of such research will have important implications for training, education, funding priorities, policies, and practices related to the use of animal models in neuroscience research.

#### *Ethics and the use of research animal models in BRAIN Initiative research*

As noted above, biomedical research with animal models is governed by a longstanding set of policies, regulations, and practices: BRAIN Initiative-funded research included. However, as BRAIN Initiative-funded research makes technological breakthroughs, it may require continued attention to and explication of existing policies and practices so that they provide the most up-to-date guidance for evolving areas of research. The BNS identified four research areas that warrant attention and potential further study related to ethics and BRAIN Initiative-funded research with animals:

1. *Conduct ethical analysis and assess guidance for research involving the insertion of human genes or the mimicking of human brain diseases and disorders in animal models.* In 2018 alone, at least three separate national workshops convened to discuss various aspects of the use of NHPs in research included presentations and discussions on neuroscience research and on the creation and use of NHPs with human characteristics or disease symptoms. These models generally seek to take advantage of physiology or characteristics that primates have in common with humans or to mimic or parallel features of human neurophysiology and/or neurological disease, with the expectation that symptoms and therefore experience in the animals are similar to humans. This raises questions about both the quantity and quality of animal suffering, since it can be posited (and is an interesting and important neuroethics research question) that such modifications in animal models could concomitantly increase these animals’ experience of the symptoms created, or could result in more invasive or burdensome interventions than in animals not so modified. How should such alteration of animal physiology and symptomology be factored into ethical consideration of the use of animal models, and does the species matter?

2. *Evaluate existing frameworks and related criteria when using animal models and in novel neuroscience research models that approximate human brain function.* While current frameworks may suffice for reviewing current research, advances in neuroscience might require advances in evaluation tools and training in novel uses of animal and biological models that are used as proxies for human brains. Advances in neuroscience research may lead to an increasing value of conducting research with NHPs. Accountability and careful stewardship require clear standards for determining the ethical acceptability and best uses of this valuable and scarce resource.

3. *Enhanced data sharing among animal researchers, reflecting responsible stewardship.* This is also related to Priority Area 3. Brain in Action and highlighted in [Chapter 3: Neuroethics Implications of Neurotechnologies](#). To enhance data sharing and research transparency, the BRAIN Initiative could encourage investigators to share data at predetermined intervals rather than waiting for publication. In particular, this would be advantageous for NHP research for which limited numbers of research animals are available. Such data sharing might result in a decrease in the number of animals used in similar experiments, while promoting scientific discovery by ensuring these datasets are available for use by other scientists soon after the data is generated rather than waiting for extended periods of time to complete the formal study. As highlighted in the original BRAIN 2025 report, the BRAIN 2.0 report and the Neuroethics Roadmap, data sharing improves transparency and makes science better. As a concrete example, data sharing has been useful in the field of genomics, where data is shared on a pre-determined schedule, and this practice has hastened scientific discovery. Data sharing of animal research could be facilitated by a BRAIN Initiative-sponsored online portal facilitating deposition of data and experimental protocols pre-publication.

4. *Greater collaboration among researchers conducting NHP research in the United States and globally would increase transparency and reduce duplication.* Such collaboration could take advantage of the types and numbers of research animals used with the goal of learning as much as possible while reducing duplication and numbers of NHPs used in research studies. Such collaboration could begin among BRAIN Initiative-funded investigators, or among NIH-funded neuroscientists, and expand to include collaborations with other investigators internationally. NIH could encourage global cooperation with other international brain-research initiatives and take leadership to facilitate it, consistent with both efficient and responsible use and stewardship of NHPs wherever they are used and is an important role for NIH to play.

## CHAPTER 5. BEYOND THE BENCH: REAL-WORLD TRANSLATION OF NEUROSCIENCE RESEARCH

The implications of BRAIN Initiative research stretch beyond traditional clinical and research contexts. Many fields of study outside the natural sciences are now directly engaging with neuroscience as reflected by the emergence of interdisciplinary “neuro-and-” fields. These include neuroanthropology, neuroeconomics, neurosociology, educational neuroscience, neurolaw, neurohistory, neuroscience and literary criticism, and even neuropolitics. Paralleling this scholarly interest in neuroscience is increased private-sector investment in neurotechnology. In recent years, more than 10,000 neurotechnology patents have been filed. Firms now offer brain-based consulting for corporations and political campaigns, and companies are developing brain-based virtual-reality video games. Even professional sports teams are now using EEG headbands to monitor and improve athlete performance.

Given these novel uses of neuroscience in new sectors, a number of ethical questions arise. For instance, should a scientist-entrepreneur in a private-sector setting be held to the same standards as a scientist in an academic setting? Does a scientist who knows that her or his research may be used in a setting beyond research and medicine have an ethical obligation to engage with stakeholders in that setting? Should NIH-funded researchers consider potential unintended uses of their scientific discoveries and technological developments? Do some partnerships – for instance those that raise concerns about militarizing neuroscience – run counter to the NIH mission to promote human health?

These questions take on added importance when new technologies are used on vulnerable populations such as children, inmates, individuals experiencing mental illness, racial and ethnic minorities, and people with disorders of consciousness. For instance, the ethics of neuromarketing studies on adults may not be the same as the ethics of similar studies on youth. Similarly, the use of brain and genetic data to predict a criminal offender’s risk of future violence deserves special attention, distinct from more general ethics of using predictive analytics for the non-incarcerated population. The BRAIN Initiative can support neuroethics research specifically exploring the ethics of neurotechnology use in marginalized and vulnerable populations.

This chapter considers progress to date and the need for greater attention and increased interagency dialogue regarding unresolved questions of accountability and potential regulatory gaps beyond the bench.

### **Brain privacy**

*What do we know?*

Brain privacy is at the forefront of concerns about the growing application of neuroscience in society ([Ryberg, 2017](#); [Gray Matters, 2014](#)). A 2018 nationally representative survey of the American public found that “mental thoughts” and “image content in mind” were both ranked highly as sensitive content ([Farahany, 2019](#)). Concerns about brain privacy are justified because collection and analysis of brain data could theoretically allow for (either unintentionally

or intentionally) decoding thoughts that an individual may prefer not to share ([Haynes and Rees, 2006](#)).

But how to protect brain privacy optimally is challenging. Scientists and citizens do not yet agree on what constitutes “brain privacy” and how much protection is needed. Moreover, the threat to mental privacy is in part a function of the improving quality of the brain data measured. For instance, a low-resolution structural brain scan showing no gross anatomical abnormalities tells us little about an individual’s deepest thoughts. But greater spatial and temporal resolution from tools developed through the BRAIN Initiative, combined with ever-improving methods of data analysis, suggests the possibility that future neuroimaging techniques may paint a more intimate picture of our mental lives.

In 2025 – the horizon line for the BRAIN Initiative – neuroscience will likely remain limited in its ability to decode complex mental life. But even if science-fiction visions of mind-reading are not accurate in the short term, there are realistic scenarios that pose significant privacy concerns. For example, more diverse forms of data, including brain data, are being used alongside descriptive data from many sources such as traditional clinical interviews eliciting symptoms, signs, and behaviors related to mental disorders. The availability of biomarkers will lead to the recognition of pre-symptomatic and prodromal disease stages. The medical and research justifications for introducing biomarkers are logical: why wait until full-blown symptoms arise to start treating a disease if we could use brain (and other biological) indicators to intervene earlier?

Yet the privacy concerns introduced by the potential use of such biomarkers are profound. Take, for example, the biomarker-based definition of Alzheimer’s Disease proposed in 2018 that, if eventually adopted, would be based upon multiple biomarkers, including evidence of neurodegeneration ([Jack et al., 2018](#)). Under the revised definition, many individuals would find themselves cognitively healthy, but on the “Alzheimer’s spectrum,” based upon their biomarkers ([Silverberg et al., 2018](#)). It would be of paramount importance to keep such a diagnosis private because it could negatively affect an individual’s job outcomes, social relationships, psychological health, and insurance premiums ([Arias and Karlawish 2014](#)). Yet, existing legal protections are lacking ([Arias et al., 2018](#)).

#### *What could we learn? Neuroethics research opportunities*

Neuroethics research on brain privacy requires more data and less speculation. Interdisciplinary research, both theoretical and empirical, should be conducted to provide stakeholders with a realistic understanding of what will be possible, and what will not be possible, in brain decoding in the near future. Empirical research, both quantitative and qualitative, is needed to identify more precisely how brain data is actually being collected, stored, used, and shared outside the laboratory. These studies might, for instance, examine the adequacy of the informed-consent process, explore the ownership of brain data, and compare policies protecting human research participants in sectors outside traditional research paradigms.

**Table 1. Comparison of Contexts: When Neuroscience Leaves the Laboratory**

	<b>Context: Neuroimaging in Medical Research</b>	<b>Context: Neuroimaging in Clinical Treatment</b>	<b>Context: Neuroimaging in Criminal Prosecution</b>	<b>Context: Neuroimaging in Market Research to Increase Product Sales</b>	<b>Context: Direct to Consumer Sale of Neurotechnology</b>	<b>Context: DIY Neurostimulation</b>	<b>Context: Neuroimaging in Military Intelligence Interrogation</b>	<b>Context: Neurostimulation of Healthy Soldiers to Enhance Abilities/Reduce Sleep Dependency</b>
<i>Brain scan/ Brain stimulation of:</i>	Research participants	Patients	Criminal defendants	Paid focus group members	Consumers	Citizens	Enemy Combatants	Soldiers
<i>Purpose:</i>	Improve knowledge and health	Improve patient health	Criminal prosecution or criminal defense	Increase sales of products	Productivity; Entertainment; Enhancement	Enhancement; entertainment	Elicit actionable intelligence	Improve combat capabilities of soldiers
<i>NIH mission applicable?</i>	Yes	Yes	No	No	No	No	No	No
<i>Already happening?</i>	Yes	Yes	Yes: thousands of cases involving brain science	Yes: many companies now offering neuromarketing services	Yes: DTC neurotech market predicted to be \$3 billion in 2020	Yes: DIY neurostimulation is well established	Unknown: Military has not revealed extent of its interrogation methods	Yes: DARPA-funded research projects



### *Potential next steps: Implementable goals*

Multiple ethics guidelines currently informing neuroscience research (see [Chapter 1. Neuroethics: Past, Present, and Future](#)) address privacy concerns and the need to balance privacy with data-sharing imperatives. Building off these general frameworks, a next step is to identify sector-specific privacy concerns more precisely and then develop policy responses collaboratively. Concrete goals might include the development of model brain-privacy legislation, revised informed-consent procedure, and consensus statements from relevant professional bodies within a given sector.

To aid in the development of policy responses, as well as public-engagement activities, studies assessing stakeholder and public attitudes regarding brain privacy will be useful. For instance, in the context of research, the Human Brain Project, in collaboration with the Danish Board of Technology Foundation, has conducted public-engagement forums to inform integration of a data-protection action plan throughout the life of the Human Brain Project ([Aicardi et al., 2017](#)). Similar public-engagement forums can be informative as BRAIN Initiative research facilitates greater use of brain data beyond clinical applications and laboratory research.

### **Advances in neural data collection**

#### *What do we know?*

BRAIN 2025 is ushering in new technologies that will revolutionize the collection and analysis of neural data. For example, ultra-high resolution (>10.5 Tesla) scanning will produce vast amounts of new, more granular, individualized brain data ([Uğurbil, 2018](#)). Even with much lower resolution imaging, neuroscientists have been able to use machine learning techniques and multi-voxel pattern classification to reconstruct visual images based on brain data ([Naselaris et al., 2015](#)). When neural data is combined with real-time data collection from smart phones, social media, and biosensors, “computational phenotyping” of individuals may become possible ([Montague et al., 2012](#)).

These and related advances offer the promise of improved mental health interventions and understanding of brain disease, but they also raise ethical questions about consent, privacy, data collection, data storage practices, and the misuse of this data for discrimination or exploitation.

In addition to new types of data collection and analysis, neuroimaging is also moving into real-world applications. Already researchers are using EEG-based neurotechnology to measure brain activities in real-time – such as while children learn, while athletes play sports, and while people are physically active at work or at play. Researchers are also using functional near-infrared spectroscopy (fNIRS) to assess neurocognitive development in the field ([Lloyd-Fox et al., 2014](#)), and they are developing methods for mobile MRI ([Sarracanie et al., 2015](#)), mobile positron-emission tomography (PET) ([Bauer et al., 2016](#)), and mobile magnetoencephalography (MEG) ([Boto et al., 2018](#)).

Neuroimaging in beyond the laboratory or clinic “flips the script.” Rather than participants and patients traveling to a scanner, the scanner will travel to them. As a result, these technologies will facilitate collection of brain data in real-world settings, including from individuals in groups that are often underrepresented in biomedical research. These include individuals from racial and ethnic minority groups, rural residents, and those from lower-income and lower-education locales. Neuroimaging in the field introduces a host of ethical and legal challenges. These include how to ensure data privacy when data are collected in under-resourced settings, and how to properly deploy artificial intelligence-based algorithms trained on data from groups of brains in the laboratory that are different from diverse groups scanned in the field. Other issues include how to manage return of individual-specific research results and incidental (or secondary) findings, and obligations to geographically dispersed participants who may be far from medical facilities.

#### *What could we learn? Neuroethics research opportunities*

Advances in neural recording may allow for greater use of brain data in sectors such as education, law, and business. For example, simultaneous EEG recording of multiple individuals in real time has been used in a classroom setting ([Poulsen et al., 2017](#)); MRI has been used to scan criminal offenders and examine recidivism rates ([Aharoni et al., 2013](#)); and marketing researchers have explored the validity of fNIRS to measure the effect of product branding on consumers ([Krampe et al., 2018](#)). The use of neurotechnologies in these areas is only beginning, and thus there is much to learn about how they can be deployed ethically and effectively. Basic questions, both theoretical and empirical, need to be explored. Questions include: How are different neurotechnologies being used, what effect are they having in each sector, and what ethical concerns are emerging?

#### *Potential next steps: Implementable goals*

At such an early stage in the use of these technologies, it is important to engage stakeholders across multiple sectors. Brain decoding, computational phenotyping, and neuroimaging in the field raise unique ethical and legal questions because existing policies and frameworks have been largely developed based on older and less-mobile technologies. To address these questions, the BRAIN Initiative could expand its support for embedding neuroethics into technological development; facilitate early-career awards to allow for sustained and robust research in this area; and convene a working group of experts and stakeholders to anticipate research, clinical, and direct-to-consumer use cases and to consider appropriate oversight standards.

### **Brain enhancement**

#### *What do we know?*

As observed by the late psychologist Corneliu Giurgea, “Man is not going to wait passively for millions of years before evolution offers him a better brain” ([Farah, 2015](#)). Whether described as cosmetic neurology, neuroenhancement, brain boosting, cognitive enhancement, or some other term, humans may soon have access to new chemical and electrical interventions to willfully alter their own or others’ brain circuitry to enhance cognitive function, moral decision-making, and mood ([Bostrom and Savulescu, 2008](#)). The neuroethics of enhancement remain in flux both theoretically and empirically. Various forms of enhancement lie across a spectrum that also includes exposure to media, digital technologies, smart phones, and other experiences or devices. These accidental or incidental changes to our neurobiology range considerably in their level of intrusion – from traditional, non-invasive devices to medications to brain surgery.

Direct-to-consumer neurotechnologies are now sold for a variety of purposes, with a projected market of \$3 billion by 2020 ([Wexler and Reiner, 2019](#)). Yet because do-it-yourself devices are not always classified as medical devices, there may be gaps in governance and regulatory oversight ([Fitz and Reiner, 2015](#)). Neurotechnology advances spurred by the BRAIN Initiative will likely accelerate enhancement experimentation, making the need for attention to gaps in oversight even more timely.

#### *What could we learn? Neuroethics research opportunities*

Across this spectrum there remains uncertainty on how to best distinguish enhancement from treatment ([Wolpe, 2002](#)); whether direct-brain enhancement is ethically or legally different from traditional indirect enhancement techniques such as education ([Greely, 2010](#)); and whether and how to distinguish between the many forms of direct-brain enhancement (e.g., caffeine in coffee or soda vs. transcranial direct-current stimulation). Complicating these ethical questions is the lack of reliable and systematic empirical data on how putative neuroenhancers (both drugs and devices) actually work in different types of healthy individuals, as well as their actual usage patterns ([Farah, 2015](#)).

In addition to theoretical research on whether, and in what circumstances, cognitive enhancement should be promoted, two lines of related empirical research are needed. First are carefully controlled studies with healthy research volunteers to evaluate the short- and long-term effects (and side effects) of drugs and devices thought to produce cognitive, moral, and mood enhancement. For instance, would any of these direct-brain interventions produce improvements in classroom or workplace productivity compared to indirect interventions? Second, there is a need for systematic data collection on actual usage patterns of neuroenhancement drugs and devices. Who is already using them and how are they being used? Who is likely to use them in the near future and how might new technological advances change usage patterns? Answering these questions are critical to considering and managing the many emerging neuroethics concerns.

#### *Potential next steps: implementable goals*

A growing body of data informs public perception of key ethical concerns with neuroenhancement – not a concern unique to the BRAIN Initiative but certainly augmented by the expected new technologies. A review of 40 empirical studies found that the most common concerns are safety, coercion, fairness, integrity, and authenticity ([Schelle et al., 2014](#)). Given these public concerns and multiple layers of uncertainty about cognitive, moral, and mood enhancement, there is a need for research into understanding the impact of enhancement in this burgeoning arena will help to identify policy infrastructure and any associated gaps. NIH could develop dedicated training grants and funding opportunities to facilitate research on enhancement.

### **Sector-specific issues**

The missions, stakeholders, incentives, and existing safeguards in many new “neuro-and” fields and areas of industry are different from those in traditional research and medical contexts. NIH-funded neuroscience research is premised upon improving health, but in other sectors the bottom line may be very different. In these other sectors, neuroscience may be used to increase corporate profit, improve national security, reduce systemic equity in criminal justice, and much more.

What oversight mechanisms exist or could be established to address the many beyond-the-bench scenarios introduced by advances in neuroscience and neurotechnology? What role does NIH have in overseeing research with neurotechnologies that are likely to be used beyond the bench? Should other federal and state agencies and private entities be partners in this oversight role? For instance, as illustrated in [Table 1](#), what about the use of brain imaging to determine whether a criminal defendant is guilty? Or the sale of direct-to-consumer neurostimulation devices to healthy adults for mood or cognitive enhancement? In these scenarios, the categories of “patients” or “research participants” no longer apply neatly, if at all. As a result, protections and protocols established for safety, efficacy, and privacy in biomedical research settings may be neither applicable nor feasible.

As policy is developed in these diverse sectors, it will be important for the BRAIN Initiative to meaningfully study the priorities, concerns, and values of relevant stakeholders, such as patients, entrepreneurs, policy makers, and laypeople. Equally important is including perspectives from diverse, marginalized, and vulnerable populations such as children, inmates, and those experiencing mental illness. Strategic engagement of stakeholders outside the research and clinical communities will provide new and informative perspectives.

### **Dual use of BRAIN Initiative neuroscience**

*What do we know?*

“Dual-use” technologies are those that can be used for both peaceful and military purposes ([Ienca et al., 2018](#)). Neurotechnology is a dual-use technology, as possible military purposes might include neuroenhancement for soldiers, reducing the trauma of post-traumatic stress

disorder, brain-computer interfaces, and enhanced interrogation strategies ([Miranda et al., 2015](#); [Canli et al., 2007](#)). Neuroethics analysis of military use of neuroscience suggests that the question is not if the military will use neuroscience, but how – and thus ethical accountability is critical ([Giordano, 2017](#)). For instance, in a [recent report](#), which was informed by receiving citizen feedback collected by public-engagement experts, the Human Brain Project has recommended a path forward to address dual-use issues.

Efforts to frame the debate have arrived at the same general conclusion: more dialogue is needed between the neuroethics community and the public-private partners developing and deploying dual-use technology. Constructive dialogue is only possible, however, if neuroscientists and neuroethicists are engaged with military research initiatives such as those funded by the Defense Advanced Research Projects Agency (DARPA) ([Tennison and Moreno, 2012](#)).

#### *What could we learn? Neuroethics research opportunities*

Most importantly, there is a need for more precise evidence on what types of neurotechnology are actually being developed for military national security purposes. Additionally, greater transparency and collaboration can be developed between the neuroscience and neuroethics communities and the Neuroethics, Legal, and Social Issues Advisory Panel, which was created to address neuroethics issues arising from military research and application ([Greely et al., 2016](#)).

There is an opportunity for neuroethics research to answer questions such as “Which ethical frameworks are being used by the military to evaluate potential uses of neuroscience?” Cross-national comparisons and collaboration would be ideal – though challenging to accomplish. Even if there are restrictions preventing access to actual dual-use research programs, at a minimum there should be access to ethical frameworks and formal procedures in place to evaluate those programs.

#### *Potential next steps: Implementable goals*

First, neuroscientists and neuroethicists should convene to consider the potential for dual use of fundamental BRAIN Initiative-supported research. Balancing an interest in transparency with an understandable need for restricting public access to military neuroscience developments poses a conundrum: It is hard to conduct neuroethics evaluations of projects that cannot be discussed. Important steps forward include efforts such as those led by the Organization for Economic Co-operation and Development to ensure responsible innovation ([Garden et al., 2016](#)). NIH might consider engaging more directly with DARPA, the Department of Defense, and others on joint funding opportunities in neuroethics. Identification of international regulatory gaps, as well as opportunities for expanded international collaboration, would also likely be fruitful.

Second, neuroscientists and neuroethicists should expand dialogue between NIH staff, the NIH-associated neuroethics community and other entities exploring the challenge of dual-use

neurotechnology both domestically and internationally. The NIH-associated neuroethics community can help to shape dialogue by engaging the public and policymakers on challenging dual-use questions. Importantly, this is a particular area where best practices in neuroethics public engagement strategies could be developed and explored. For instance, the European Union-funded Human Brain Project has a division of research dedicated to public engagement, which may provide a valuable collaborative opportunity for best neuroethics engagement practice research.

Finally, more specific guidance should be provided to BRAIN Initiative-funded researchers on potential ways their research could be used for military or national-security purposes. At present, the BRAIN Initiative does not have a formal dual-use education and awareness training program. Development of such materials could be integrated into BRAIN 2.0.

## **Neuroscience and law**

### *What do we know?*

Neuroscience and law are related in multiple ways. For example, regulations and legislation facilitate funding for brain research. In turn, advances in understanding of brain circuitry can reshape legal doctrine and practice. Since the early 2000s, the legal and neuroscience communities have had increasing interactions ([Jones et al., 2014](#)). There has been an increase in the number of legal cases introducing neurobiological evidence ([Farahany, 2016](#); [Denno, 2011](#)), raising questions about criminal responsibility and sentencing, pain and suffering, capacity and competency, juvenile justice, fallibility of memory, brain injury, and bias in decision-making ([Shen, 2017](#)). Neuroscientific perspectives might inform the limits of eyewitness memory and the power of implicit biases to shape behavior. But there remains significant debate about whether neuroscience, given its current limits, is relevant for criminal law ([Morse 2008](#)). The rapid pace of neuroscience discovery has required courts to make evidentiary decisions about whether or not to allow jurors to see particular brain data. For instance, under what conditions should a defendant accused of a violent crime be allowed to argue that a brain abnormality, identifiable in a brain scan, caused the violent behavior? Relatedly, might neuroscience be used prematurely and inappropriately in areas such as developing treatments for offenders and assessing risk of future violent behavior?

Related to concerns about brain privacy are concerns that neuroscientific developments will provide government or private entities with lie-detection and mind-reading capabilities ([Greely and Illes, 2007](#)). The science of fMRI-based lie detection is far from ready for courtroom use ([Bizzi et al., 2009](#)), but a lack of scientific consensus does not prevent social or legal use of a technology ([Langleben and Moriarty, 2013](#)). For instance, there have already been two cases in which a criminal defense expert wished to testify about findings from an fMRI-based lie-detection protocol administered to the criminal defendant ([United States v. Semrau](#), 693 F.3d 510, 2012); [Smith v. State](#), 32 A.3d 59 (2011)). In addition, EEG-based memory recognition protocols have produced a growing body of research suggesting potential forensic use

([Rosenfeld, 2018](#)). An EEG-based procedure has also been used in criminal cases internationally to inform adjudication of guilt ([Parmar and Mukundan, 2017](#)).

### *What could we learn? Neuroethics research opportunities*

It is often difficult to infer from a brain state a legally relevant mental state. For instance, do identifiable plaques and tangles or neurodegeneration in an individual mean that the individual lacks the “capacity” to sign a binding contract? Does the fact that a criminal defendant experienced a traumatic brain injury make that defendant less culpable for a violent act? New questions will arise if implantable brain devices improve in efficacy and are more widely adopted. For instance, if a defendant with a deep-brain stimulation (DBS) device is accused of a crime, must the DBS device’s recorded history of brain activity be turned over to prosecutors? This question, and many others with legal ramifications, could be well informed through NIH-funded empirical research related to decision-making across the lifespan – from development to degeneration. Productive interactions between neuroscientists and legal stakeholders might not only improve health outcomes for those involved in the justice system but might also improve the administration of justice.

### *Potential next steps: Implementable goals*

First, more systematic standards and recommendations for the proper use of neuroscience in law should be developed. Among the challenges to be addressed include how to translate the complex and probabilistic nature of neuroscience findings into simple, often binary legal outcomes (e.g., guilty or not guilty), as well as how to ethically navigate an adversarial legal system.

Second, legal and neuroscientific communities should continue to interact frequently and meaningfully. This is already happening, for instance, as part of the NIH [Helping to End Addiction Long-term](#) (HEAL) initiative – in which scientists, policymakers, legal experts, and community members work together to improve the legal and societal response to the opioid crisis. Similar efforts could involve interactions between stakeholders in the mental-health and legal communities.

Third, expanded partnerships with legal stakeholder groups such as the Department of Justice and the National Institute of Justice may prove fruitful. BRAIN Initiative-funded research is discovering how deficits in human decision-making, including decision-making for those with substance-use disorders, can be understood and improved. The Department of Justice has in recent years made better decision-making a center piece of its offender re-entry programs. Expanding partnerships in this arena could lead to swift and significant improvements in policy outcomes.

## **Neuroscience and education**

### *What do we know?*

Educational neuroscience, also called “mind, brain, and education,” is a burgeoning field of study and practice fueled by the recognition that understanding how the brain learns will lead to better teaching and learning ([Mareschal et al., 2013](#); [Patten and Campbell, 2011](#)). To reach its potential to meaningfully inform educational practice, neuroscience must overcome many challenges ([Bruer, 2015](#); [Bowers, 2016](#)). One concern is that the educational marketplace has ample products marketed as being “brain-based,” when in fact they were not grounded in sufficient research ([Fischer et al., 2010](#)). Other issues center around neurodiversity ([Armstrong, 2015](#)). That is, which types of educational/learning differences should be treated as “disorders” or “deficiencies” to be addressed by the education system, and which educational/learning differences should be accepted and celebrated?

### *What could we learn? Neuroethics research opportunities*

In the United States, 76 million students are enrolled in more than 10,000 school districts in more than 98,000 schools. These 76 million brains are being modified daily by their teachers, peers, and school environments. If neuroscientifically informed educational methods offered even modest improvements in teaching and learning, it could have long-lasting effects across the lifespan of many children. Like other areas of neurotechnology development discussed by the BNS, technology implementation should be assessed by weighing the risks and the benefits – not only for the individual, but for society as well. For example, should medications and/or electrical stimulation to boost test score performance? Schools and educational leaders need knowledge and tools to readily discriminate between effective and ineffective applications of neuroscientifically informed educational methods.

### *Potential next steps: Implementable goals*

First, NIH should engage in neuroethics dialogue with educational neuroscience and coordinate with the Department of Education and other agencies that fund education-relevant research. While progress to date in educational neuroscience has been mixed, there is reason to believe that in the future, brain biomarkers may play an important role in better matching individual students with the most supportive learning environments for their needs ([Gabrieli et al., 2015](#)). Direct integration of brain data into educational practice will raise a host of neuroethics concerns similar to those raised in other sectors.

A second step is to partner with educational stakeholders and institutions at the federal, state, and local levels to explore synergies between neuroethics and educational neuroscience. As one example, neuroscientific perspectives may have implications for policies related to special education, including autism. For example, an NIH-funded study found that differences in white-matter fiber tract development at 6 months old in at-risk infants can predict whether, at 24 months, those infants will develop autism spectrum disorders ([Wolff et al., 2012](#)). While the data remain preliminary, it is likely that in the coming years we will see more examples of biomarker-based predictions with educational relevance. If that occurs, it raises questions about potential stigma (should a 6-month year old infant be labelled as autistic?), resource inequities (who will



pay for intensive interventions at such a young age?), and privacy (with whom will this infant's brain data be shared?). Both conceptual and empirical neuroethics research is needed to address these questions.

## **Neuromarketing**

### *What do we know?*

Increasingly, marketing firms see neuromarketing as a viable addition to their work ([Fisher et al., 2010](#)). A variety of neuromarketing tools are currently used, although the effectiveness of specific approaches remains debated. Neuromarketing techniques include gathering brain data during consumer decision-making, allowing firms to better understand neurocircuitry underlying purchasing decisions. Results of neuromarketing studies might lead to increased revenue via targeted branding, selling practices, or product design and placement.

Neuroethics scholars have identified potential concerns about neuromarketing ([Murphy et al., 2008](#); [Levy 2009](#)). These include practical issues about actually doing the research (e.g., what if the study uncovers incidental brain findings affecting health and attaining informed consent?) as well as deeper conceptual worries such as excessive corporate power to manipulate consumers ([Ulman et al., 2015](#)). Does collecting brain data to manipulate consumers (described by some scholars as a “hard” attack on consumer autonomy) differ in ethically relevant ways from the traditional “soft” attacks on consumer autonomy emerging from traditional tools such as focus groups? ([Murphy et al., 2008](#)). Public opinion on the ethics of neuromarketing is contextual, with more perceived support for non-profit organizations using neuromarketing than for-profit firms doing the same ([Flores et al., 2014](#)).

Regulation of neuromarketing labeling to consumers involves the Consumer Product Safety Commission (CPSC), the FDA, and the Federal Trade Commission (FTC). Statutory authority allows these agencies to promote the safety, effectiveness, and ethical marketing of neurotechnologies. The CPSC, FDA, and FTC use a variety of formal and informal mechanisms to engage in neurotechnology oversight, and work with many stakeholders to monitor technological developments and novel uses and marketing of new products. The BRAIN Initiative should continue to build strong partnerships between researchers, clinicians, ethicists, and regulatory agencies, to better inform the development of ethically appropriate guidelines.

In addition, partnerships with private-sector firms can be strengthened. Neuromarketing has attempted self-policing with regards to ethics ([Thomas et al., 2017](#)). In 2012, the newly formed Neuromarketing Science and Business Association (NMSBA) adopted a [code of ethics](#) for its members, but collaborative research is required to better understand how stringently and uniformly this code is enforced.

### *What could we learn? Neuroethics research opportunities*

More research is needed to understand how and whether neuromarketing firms are adhering to appropriate ethical standards, and how regulatory guidance and rules are shaping those standards. For instance, how many firms are members of the NMSBA, and how are member firms interpreting the organization's code of ethics? How are firms outside of NMSBA navigating informed consent, incidental findings, data privacy, and other ethically relevant issues? Data on these types of questions will be vital to informing neuroethics guidance in this industry.

*Potential next steps: implementable goals*

The neuroscience research community needs to establish mechanisms for more regular and robust engagement with neuromarketing stakeholders. Neuromarketing firms and practitioners are aware of the neuroethics concerns part of their work. These ethical issues overlap substantially with neuroethics issues in other societal domains. Yet there is currently insufficient partnership between neuromarketing and the NIH-associated neuroethics community. For instance, there is little conversation about whether any clients or any types of neuromarketing projects should be ethically off-limits ([Clark, 2017](#)). What if a corporate client asked a neuromarketing firm to investigate the neurobiology of addiction in adolescents so that the client could foster addiction-like consumer behavior for its teenage-focused product? What ethical guidelines could inform the decision to accept or reject this request?

## CHAPTER 6. INTEGRATING NEUROETHICS AND NEUROSCIENCE

Neuroscience has captured the imagination of the non-scientific public and scientists alike because of the rich implications of its findings. As we have shown throughout this report, neuroethics is integral to the neuroscientific endeavor based upon unique ethical issues that arise in conjunction with assumptions and beliefs about the role of the mind and the brain's connection to it. Neuroethics helps guide neuroscience advances and discoveries toward positive social outcomes – in medical or non-medical settings. In turn, the numerous impacts of neuroscience and neurotechnologies on individuals and populations have significant and broad-reaching ethical implications. In this chapter, we provide suggested concrete steps for integrating neuroethics into the study and practice of current and future neuroscience research.

### **Guidance for researchers: The critical role of neuroethics in neuroscience research**

#### *What do we know?*

Neuroethics should be integrated into the entire life cycle of a neuroscience research project – from hypothesis to research design and conduct to dissemination of results and translation of knowledge. Many entities have long-recognized the importance of this interdependence, including at the highest levels of government. For more details, see [Chapter 1. Neuroethics Past, Present, and Future](#).

While neuroethicists can work independently from neuroscientists, neuroethics expertise is most relevant with shared intimate knowledge of the science and its context. Including an ethicist on a research team can lead to fruitful inquiry and provide an opportunity for ethicists to not stall, but accelerate, good neuroscience by anticipating and addressing ethical issues before they arise. Such ongoing interactions mitigate potential roadblocks that ethical missteps create if not considered early and often.

#### *What could we learn? Neuroethics research opportunities*

Integrating collaborative neuroethicists within research teams has been the subject of several BRAIN Initiative-funded neuroethics research project grants (R01s). For example, one project explored the ethics of research involving brain organoids. Researchers also investigated the informed-consent process associated with invasive brain interventions (such as deep-brain stimulation) for psychiatric conditions or opportunistic research occurring with epileptic patients implanted with electrodes.

What is the best way for neuroethics questions to surface in neuroscientific settings? Neuroscientists and others working in neuroscience related areas need the ability to identify ethical quandaries in the context of their work. Although tides are changing, most neuroscientists do not know enough about neuroethics to navigate these waters. As a result of mandatory training, however, most neuroscientists are indeed aware of basic issues related to the responsible conduct of research. We have learned through such efforts to educate

neuroscientists about neuroethics (particularly in preliminary conversations through the NIH BRAIN Neuroethics Working Group) that neuroscientists typically welcome a resource to help them explore the ethical, social, and legal implications that may arise uniquely because their subject of study is the brain. The Neuroethics Questions and the Neuroethics Guiding Principles (see [Chapter 1. Neuroethics: Past, Present, and Future](#)) help to serve this role. In addition, the international brain community has committed to addressing neuroethics issues in formal and informal ways. In a [special issue on neuroethics in the journal \*Neuron\*](#), each of seven large-scale brain research projects demonstrates how they are currently or are planning to integrate neuroethics into their research projects.

## **Neuroethics scholarship and training**

Do neuroscientists and those performing neuroscience-related work have enough training to understand ethical implications of their research? Are there established practices for professional conduct in highly innovative areas in which neurotechnological capabilities are surfacing rapidly?

*What do we know?*

Culture change is a key component to fully integrating neuroethics into neuroscientific practice. The next step will be to establish formal opportunities for established scientists and trainees conducting neuroscience research to learn about neuroethics, and for neuroethicists to learn more about neuroscience. Some of this training may fit well into core principles already articulated by the BRAIN 2025 report, stating the need for crossing boundaries to promulgate interdisciplinary research. To facilitate these interactions, the NIH BRAIN Neuroethics Working Group has held multiple meetings and workshops bringing neuroscientists and neuroethicists together to address important issues.

To motivate true scholarly partnerships, institutional support and incentives are needed— a structure, with resources supplied for both groups. Dedicated support may encourage such collaboration and give collaborating ethicists time to engage in co-developing neuroscience. These efforts could also help meet the BRAIN Initiative’s goal of breaking down “silos” between fields of study.

*What could we learn? Neuroethics research opportunities*

Use of the Neuroethics Guiding Principles and the NeQN set provides both neuroscientists and ethicists a springboard to discuss the design, conduct, and translation of neuroscience research. For example, in [NeQN1](#), scientists are prompted to consider how the questions they choose to study in the laboratory might amplify existing biases. Thus, considering these questions might lead them to reconsider designing a tool that uses a skewed mix of research participants (such as all males) as a normal population – a decision that may confound results. Interpreting such results will have implications for defining fundamental qualities of personhood associated with the brain, so choosing an appropriate study population is vital. Using [NeQN4](#)

and [Guiding Principle 2](#), scientists are prompted to consider how brain interventions might affect autonomy. Researchers can respond to this question by designing technologies that enable ways an affected individual could override the machinery. Alternatively, researchers might also evaluate a neurotechnological design as impractical, by running down a battery, for example.

All true partnerships are two-way streets. While neuroscientists as well as those performing neuroscience-related work, can benefit from learning more about ethics, ethicists must also keep apprised of current principles and trends in scientific and engineering research to have a better sense of how to navigate the ethical challenges. Having neuroethicists collaborating at the formative stages of BRAIN Initiative-funded research study design facilitates not only ethical neuroscience, but also provides more opportunities to speak a common language. There are also many disciplines that intersect with BRAIN Initiative-funded research. A mutually informing dialogue could facilitate consideration of particular clinical issues in neuroethics that include clinicians, health care providers, and others. This dialogue can assist in exploring farther-term ethical issues associated with translation of research into clinical use and even potential non-medical expectations of patients ([Chatterjee, 2004](#)) Finding common ground will undoubtedly add fresh perspectives to conceptualizing, conducting, and translating research for the broadest number of people.

*When should neuroethics education be integrated?*

Among the neuroethics-related short-term goals outlined in BRAIN 2025 are i) to establish training grants for human research/ethics and ii) to establish neuroscience/ethics training programs, meetings, and interactions to establish guidelines and principles for human neuroscience research.

Ideally, as noted in [Gray Matters Volume 1](#), exposure to ethics, and neuroethics, should happen early and often in a scientist's professional development:

“Early ethics education in academic settings is critical to prepare future scientists to integrate ethical considerations into their work – including future research in neuroscience. Professional development for experienced investigators is equally important and can serve multiple ends, contributing not only to their individual knowledge, but to the knowledge of the students and young scientists that they mentor as well. Ethics education has a better chance of informing action when it is continually reinforced and connected to practical experience. (11, p.28)

and

“One foundational approach to integration is pairing science and ethics education at all levels of education. Early ethics education in academic settings is critical to prepare future scientists to integrate ethical considerations into their work – including future research in neuroscience. Professional development for experienced investigators is equally important and can serve multiple ends, contributing not only to their individual knowledge, but to the knowledge of the students and young scientists that they mentor as well.” (11, p. 44)

Some of this work has already begun – the NIH BRAIN Neuroethics Working Group has hosted workshops on invasive and noninvasive neurotechnology involving human research participants as well as research with ex vivo brain tissues and other salient topics. The BRAIN Initiative has also established an internal NIH neuroethics program team and has funded neuroethics grants, including fellowships for postdocs, but has not yet developed training grants. Additional training grants would provide an opportunity for more formalized neuroethics training as well as for setting up exportable models of training for graduate students and postdocs. Such training grants might also set up a mentoring cascade in which faculty train/mentor postdocs who then train/mentor graduate students who then train/mentor undergraduate students. Critically, most effective education and training in this space should move beyond online modules and will be most valuable if formulated as in-person and interactive exercises. Training opportunities are also scalable and could exist as modules or complementary to existing scientific and clinical training or as professional development opportunities for more established researchers and clinicians.

### **Professional/Institutional support**

Since the field of neuroethics is relatively young (about 15 years old, but with a growing community of experts), new approaches are needed to capture talent while also nurturing existing neuroethics scholars – and cultivating cross-fertilization with neuroscience experimentalists. The cultural shifts required to achieve these goals require both top-down and bottom-up methods. Thus, explicit funding opportunities for neuroethics research and for interdisciplinary scholarship are both essential. Research partners are most likely to contribute fully when each is considered an equal participant in the design and conduct of the research – not an “add-on” that is expected to volunteer expertise. To date, the BRAIN Initiative has awarded two rounds of neuroethics research project grants (R01s), and it has included/expanded neuroethics language in predoctoral and postdoctoral training programs.

As awareness of these unique opportunities increases, the program will grow. BRAIN-Initiative support for neuroethics grants should be further continued and expanded in order to anticipate future issues and challenges in BRAIN research as the science progresses.

### *Committing resources*

As a public, taxpayer-funded investment, the BRAIN Initiative aims to promote innovative fundamental science and has a responsibility to assure that the research will be done with integrity and adheres to the highest ethical standards. The BRAIN 2025 report mentions neuroethics as a means to “maximize value” of the neuroscience research investment. In the first few years, leadership of the BRAIN Initiative has increasingly emphasized neuroethics as central – it is our conclusion that this emphasis should not only remain but could also grow over the course of the second half of the BRAIN Initiative. A renewed commitment from the BRAIN Initiative to neuroethics principles and neuroethics research amid this ongoing work requires sufficient, dedicated resources to ensure scientific and ethical rigor.

For comparison, the Human Brain Project (HBP), another similar, large research effort, dedicates about 4 percent of its budget to ethics projects – similar to the proportion allocated for ethics in a wide array of biomedical investigations (as in the commitment of up to 5 percent for ELSI research in the National Human Genome Research Institute (NHGRI)). Applying this focus, from its inception, the HBP continues to conduct a sophisticated and interdisciplinary ethical, societal, and philosophical exploration of how neuroscience could and would inform the question, “What makes us human?” This research endeavor has created a number of sophisticated mechanisms for neuroethics integration and partnerships between ethicists and scientists. For example, the HBP has an ethics advisory board, and each member of this board is partnered with a designated scientist from each project, an “ethics rapporteur.” The board and rapporteurs meet regularly to discuss updates about ethical concerns. The HBP’s Ethics and Society subproject features prominently at the annual HBP meeting and as part of the organization’s progress review.

While the BRAIN Initiative is well underway and now into its second phase, there is still significant opportunity to create additional formal mechanisms to enhance rigorous neuroethics inquiry in neuroscience research that will last beyond the formal structure of the BRAIN Initiative. NIH should provide stable and devoted funding for neuroethics research and activities, commensurate with the importance of ethics research in NHGRI and other international brain projects. Funding should increase, over time, with the aim of approaching 5 percent of the overall BRAIN Initiative annual budget. In addition to the suggested activities through this roadmap, others may include, but are not limited to:

- Using career-development awards to help support neuroethics researchers
- Employing institutional awards to stimulate hiring people with neuroethics expertise
- Funding grants for brain science akin to the NIH Centers of Excellence in Genomic Science
- Associating center awards supporting neuroethics research with researchers; look at NIH portfolio for opportunities (the NIH BRAIN Neuroethics Working Group already does this)
- Including neuroethics attention/training in relevant training grants
- Consider requiring a neuroethics section on each BRAIN application, in which the applicant describes the neuroethics issues raised by the proposed research.
- Facilitating the matching of a bioethics mentor for certain BRAIN projects to recognize and integrate neuroethics issues and enhance the project

#### *Next-generation focus*

Neuroscientists need knowledge beyond what they receive during scientific training to be able to recognize neuroethics issues as well as to conceive neuroethics inquiry in consultation with focused neuroethicists. Focusing on trainees and the next generation of leaders in neuroscience is already happening in the biomedical arena. For example, in collaboration with the International Brain Initiative, professional societies such as the International Brain Research Organization and the Institute of Electrical and Electronics Engineers have partnered with neuroethicists on neuroethics-focused educational modules for in-person and online learning.

The International Brain Initiative's Neuroethics Workgroup is currently designing a neuroethics short course to be shared and offered across the seven existing and emerging large-scale brain projects. Given the vitality of neuroethics training and awareness to the BRAIN Initiative, NIH and other BRAIN-Initiative partners should consider adding additional neuroethics training opportunities within existing responsible conduct of research (RCR) training requirements for neuroscientists. Alternatively, or in addition, the BRAIN Initiative could offer neuroethics-training opportunities associated with funded research at both the trainee- and established-investigator levels, some of which is already being done via administrative supplements. The NIH BRAIN Neuroethics Working Group has also held several public workshops at which experts considered issues related to BRAIN Initiative-funded research on invasive and noninvasive neural devices, as well as with ex-vivo models of the human brain ([Farahany et al., 2018](#)).

Beyond the formal structure of the BRAIN Initiative, scientists might work with their local institutions to develop in-house programming featuring integrated neuroethics discussions. Such forums could generate exportable models for informal and formal neuroethics education. Several dedicated neuroethics centers and programs throughout the world, including many in the United States, have modeled undergraduate- and graduate-student neuroethics training and also host neuroethics short courses and regular programming. Some of these institutions offer neuroethics in the context of interdisciplinary training, while others have dedicated neuroscience-training programs. The BRAIN Initiative could offer incentives to academic institutions to offer neuroethics training for neuroscientists, or to join neuroethics training programs between neuroscience and humanities departments, bolstering neuroethics as a part of the neuroscientific enterprise. One opportunity for research might be to survey these institutions for successful strategies for developing neuroethics training programs for neuroscientists. For example, in one case, an undergraduate neuroscience-and-society course offered to neuroscience majors not only increased knowledge of neuroethics, but also improved overall moral judgment and reasoning skills ([Abu-Odeh et al., 2015](#)). Additional research and evaluation would be valuable to inform future programming and to identify the full benefits of neuroethics education for neuroscientists. Additional BRAIN Initiative funding opportunities might support universities to help establish infrastructure to promote training and mentoring at all levels.

Given the international make-up and reach of neuroscience research, research within (and sponsored by) the United States benefits from multinational and multicultural participation and leadership. This point is especially important given the need for cross-cultural neuroethics educational models that acknowledge the varied cultural aspects of both ethics and science. There is also an opportunity to prioritize and incentivize cultivating a diverse and inclusive neuroethics community, which be more adept at anticipating and addressing concerns representative of a richer diversity of perspectives.

## **Global stage for neuroethics**

*What do we know?*



In an era of global science/neuroscience, publishing, and communication – in which both knowledge and the fruits of science transcend geographic boundaries – it has become increasingly apparent that addressing a variety of value frameworks and perspectives is essential for fulfilling the goals of the BRAIN Initiative. Ethical values, assumptions about the role of science, and about the types of science that should be pursued actually dictate what science is pursued. This pattern has become clear in the case of the not-so-gradual move of most NHP research outside of the United States and Europe. Differing values about the conduct of research – along with which and how much data can be collected – have a profound impact on collaboration and data sharing. Questions such as [NeQN2](#) and [Guiding Principle 3](#) (see [Chapter 1. Neuroethics: Past, Present, and Future](#)) encourage researchers to carefully consider global standards of data collection, as well as to consider potential violations of neuroprivacy and how conceptions of privacy may vary around the globe.

#### *What could we learn? Neuroethics research opportunities*

[NeQN3](#) encourages scientists to consider ethical issues that arise from innovative models of neural circuitry. One example is that posed by brain organoids/assembloids that are engineered to model human brain development, cortical regions, and diseases. While closer approximations to human brains afford richer opportunities to gain deeper insights into the human brain and behavior, these models will also raise concerns about the appropriateness of their use (including transplantation into laboratory animals) given their similarity or similar capacity to human brains. A similar debate has arisen in the context of the use of CRISPR-modified NHPs to study autism ([Tu et al., 2019](#)).

It is also important to consider the inevitable use of laboratory-generated technologies for purposes beyond their original intent. (see [Chapter 5. Beyond the Bench: Real-World Translation of Neuroscience Research](#)). This possibility is recognized in [Guiding Principles 4 and 5](#) (see p. see [Chapter 1. Neuroethics: Past, Present, and Future](#)), but needs additional attention. One recent Human Brain Project Opinion covered the topic of dual-use research, referring to uses and applications of research beyond the initially conceived hypothesis. These Opinions are drafted and published by the Human Brain Project with input from an interdisciplinary group of ethicists, philosophers, and social scientists, including from the project itself. These well-researched reports are generally informed by both science as well as public-engagement research on specific topics.

[NeQ2](#) asks researchers to explore ethical standards of biological material and data collection as well as how they relate to those of global collaborators. As the culture around data collection is moving toward one of sharing and openness, researchers around the globe will need to be aware of also-shifting tides of acceptability and regulation of animal research, particularly as these models attempt to become closer approximations of human disease and suffering ([Tu et al., 2019](#)). The BRAIN Initiative should provide active leadership and collaboration in conversations on how to reconcile conflicting standards across geographic regions as well as justice challenges which are not unique to BRAIN, but will apply to BRAIN as it addresses

equitable access to neurotechnologies and ensuring equitable distributions of not just the benefits, but also the risks to participants in BRAIN Initiative-funded studies.

### **Public engagement: Meaningful and bidirectional**

The modern consensus on how to approach and achieve public engagement for scientific pursuits is quite different from past strategies that focused on increasing public knowledge of science. The latter, mostly unidirectional methods mirror the information-deficit model of science communication – a model that has fallen from favor in both the science-communication and educational communities. Instead is the recognition that individuals within the public arena make conscious choices about what they want to know and learn, as well as how those efforts align with personal and societal values.

#### *What do we know?*

Both scientists in training and non-scientists alike take great interest in neuroscience, based upon the anticipation that advances and discoveries in brain research will affect how we understand ourselves as well as how we engage with the world. Neuroethics is thus a common entry point to neuroscience for everyone. Meaningful public engagement is critical to the success of neuroscience, as articulated by two of the BRAIN Initiative’s Neuroethics Guiding Principles:

- Principle 6: Identify and address specific concerns of the public about the brain
- Principle 7: Encourage public education and dialogue

The BRAIN Initiative also communicated the importance of public involvement and engagement, “Stakeholders should be engaged through a variety of additional mechanisms, including academic research in bioethics, training programs for a broad array of practitioners and students in the medical professions, conferences targeted to audiences with different levels of scientific expertise, and media outreach.” The return on investment from publicly funded research rests on the strength of the public’s trust in individual scientists and with the scientific enterprise. Like many new technologies and scientific advances, neuroscience advances are frequently subject to hyperbole. Importantly, we cannot only blame the media for such hype. Scientists as well as ethicists must appreciate their own responsibility to communicate their work to general audiences clearly and effectively – while retaining its genuine interest and excitement.

#### *What could we learn? Neuroethics research opportunities*

Communicating science with non-scientists via a deficit model that assumes the public is wholly ignorant of science is not only dismissive but also unlikely to be successful ([Stilgoe and Lock, 2014](#)). Skilled communication and effective engagement will likely require resources to connect scientists with experts in public engagement. While it is not uncommon for public engagement to be explicitly required as a component of conducting research projects, rarely are sufficient

resources devoted to rigorous interdisciplinary collaborative work in this area. Scientists of tomorrow (and today) must be prepared to address the reality that science is being communicated, formally and informally, through a relentless 24-hour, 7-day media cycle. In summary, scientists should learn to be adept at public scholarship and engagement.

Some important considerations for the BRAIN Initiative related to engagement opportunities, particularly in neuroethics, include principles and lessons learned from the societal experience with human-genome editing. As noted in the 2017 National Academies of Science, Engineering, and Medicine's Human Genome Editing: Science, Ethics, and Governance:

“We need to engage the public in a more open and honest bidirectional dialogue about science and technology and their products, including not only their benefits but also their limits, perils, and pitfalls. We need to respect the public's perspective and concerns even when we do not fully share them, and we need to develop a partnership that can respond to them ([Leshner, 2003](#)).

The authors of this report noted that high-quality engagement is marked by systematic exploration of the full range of risks and benefits of technology that go beyond simply those that are technical and medical, but that include perspectives and knowledge from all interested and affected parties ([Stern and Fineberg, 1996](#)). Other important considerations include assessing quality outcomes from engagement work that explores policy and regulatory issues – those that consider both facts and values, as well as how anticipated societal effects will affect the things people value ([Dietz and Stern, 2008](#)). Legitimate engagement practices are those participants view as transparent, fair, and competent ([Hadden, 1995](#)) and which truly interrogate the values and interests of the people who will be using these technologies or otherwise affected by them. On a practical note, engagement work cannot be done successfully without administrative efficiency, which requires dedicated resources. To this end, the BRAIN Initiative could consider supporting neuroethics research that assesses public opinion as well as develops best practices for public engagement (recognizing the plurality of science-engagement strategies) around neuroethics issues. In order to design engagement projects, teams will need to clearly define goals, audiences, and metrics for success.

Many challenges are inherent in attempting public engagement in the modern world. We live in a global society in which information access and spread is rapid and distributed – sometimes without proper context. Thus, it is critical to consider engagement activities internationally, requiring a broad definition of stakeholders that extend beyond English-speaking countries. This is especially important given that individuals across the world may use neurotechnologies. The Internet, social media, and other creative electronic and in-person formats are powerful tools for public engagement, but they carry significant risk for distributing unvetted information and/or unsubstantiated claims, in a manner that is difficult to control. It should also be recognized that there will be appropriate times for one-way communications that aim to broadcast and inform audiences about scientific findings, but these opportunities must also be balanced with approaches that enable knowledge exchange between public audiences and scientists. Engagement opportunities in neuroethics should also involve assessing priorities and values of

a breadth of relevant stakeholders in BRAIN Initiative-funded research, such as scientists, patients, entrepreneurs, policy makers, and the general public. This can be done empirically (e.g., with surveys and public groups to assess opinions on goals for neurotechnology development and future concerns) and through other innovative interactive educational activities to raise awareness.

A particularly vexing challenge is translating outcomes of science and related engagement activities into changes in policy and practice. Success requires controlling two key levers: i) support from those empowered to make decisions to incorporate public views and values; and ii) transparent, justifiable, and monitored pathways for those actions. Bias and ulterior motives can also be a concern: What about when decision makers use engagement activities toward achieving predetermined outcomes? In summary, effective public engagement is highly collaborative and requires input from individuals and groups responsible for funding, doing, and measuring such activities.

There are solid examples of what works, such as public-expert interactions that can produce meaningful communication about neuroscience as provided by the National Information STEM Education (NISE) Network, which balance understanding and engagement for various topics, assimilating and integrating the different ways public and scientific individuals and audiences interact. The NISE Network published a 2018 conference report, "[Public Engagement with Neuroscience and Society](#)," which notes that sustained public engagement will benefit from leveraging existing strengths of the current neuroscience outreach ecosystem. Components include BRAIN Initiative-funded neuroscience research, a comprehensive educational content framework (e.g., BrainFacts from the Society of Neuroscience), museums with broad reach that use evidence-based engagement approaches, and employing as ambassadors volunteer experts (e.g., Brain Awareness Week and activities therein).

#### *Next steps: implementable goals*

Integrating neuroethics and neuroscience is occurring, but to fully reap the benefits of the BRAIN Initiative, closer alignment is needed to ensure scientific and ethical rigor – and also to share both the sense of amazement and practical outcomes from this groundbreaking large-scale, cross-sector project. Key concepts toward achieving this goal include fostering side-by-side professional interactions between neuroethicists, neuroscientists, and other expertise to enrich addressing neuroethics issues, extending to neuroscientists knowledge and appreciation of neuroethics principles embedded in basic neuroscientific inquiry, offering formal neuroethics training at various career levels, continuing to support neuroethics research, and truly embracing public engagement as an opportunity to fortify the research investment. Specific possibilities include:

- Establishing (continue to offer, via supplemental funding and neuroethics R01s) and expanding formal mechanisms and incentives to embed (neuro-)ethicists within neuroscience research projects
- Supporting trainees and the next generation of leaders in neuroscience and neuroethics

- Establishing formal opportunities for established scientists and trainees to learn about neuroethics – and for neuroethicists to learn about neuroscience
- Using published principles and guidelines such as the [NeQNs](#) and [Guiding Principles](#) to provide both scientists and neuroethicists a springboard to discuss the design, conduct, and translation of neuroscience research
- Establishing a neuroethics network resource, consisting of people to consider issues on an ongoing basis for a range of stakeholders (neuroscience researchers and trainees, IRBs, health care providers, non-scientific public)
- Developing NIH BRAIN Initiative mechanisms for institutional support and incentives to conduct collaborative, interdisciplinary neuroscience research, perhaps through funding centers and/or joint applications
- Create training grants and other funding strategies to explore more formalized neuroethics training, which may also yield exportable models of training for undergraduate students, graduate students, and postdocs
- Partnering with public-engagement experts, including those using innovative methodologies
- Investigating the relevant neuroethics concerns of BRAIN investigators and of the public
- Developing and evaluating neuroethics educational programs and assessments
- Identifying successful strategies and models for effective neuroethics engagement

## NEUROETHICS TRANSFORMATIVE PROJECT

### Revolutionizing BRAIN: Understanding the Bases of Consciousness: Intersection of Neuroscience and Neuroethics

The BRAIN Initiative aims to “revolutionize our understanding of the human brain” through using new tools to measure biology at “the speed of thought.” Learning how to use these tools should help prevent and treat brain disorders – and ultimately, inform, influence, and challenge definitions of our human nature at the most fundamental level. BRAIN Initiative research is intimately tied to concepts such as consciousness, thought, agency, free will, and identity (see [Chapter 2: Studying Ourselves: The Uniqueness of Neuroscience](#)).

As a transformative project for the second phase of the BRAIN Initiative, we propose a large-scale, concerted interdisciplinary neuroscience/ethics centric project that would result in neuroscience revolutionizing long-held philosophical notions of features once thought privileged to humans or comprising humanness, specifically:

- How could the enterprise of neuroscience challenge or inform long-held assumptions about the meaning of such qualities such as sentience and the mind?
- How would neuroscience successfully operationalize such qualities for study in the laboratory?

The public – including scientists – may assume a shared meaning of these ideas; however, there may be very different interpretations depending on one’s world view. While there are many approaches to defining and understanding methodologies of neuroethics inquiry, one strength of neuroethics is that the field relies on a methodology to systematically unearth cultural assumptions about such socially laden terms. Neuroscience has also become part of the culture defining these terms: the “mind,” for example, is often being conceptualized as a neuroscientific phenomenon with neurological underpinnings.

One common term shared in philosophical and neuroscience discussions of sentience and the “mind” is consciousness. Consciousness and other phenomena are now being understood as complex properties of the brain that emerge from the functioning and coordinated interactions of many brain regions and that help define personhood.

When framed as an emergent property, consciousness is thought to represent a greater entity than the sum of its component biological parts ([Crick and Koch, 1998](#)). Some neuronal substrates of elements of consciousness have been defined and tested in the laboratory. These investigations have involved anatomical approaches, pharmacological modulation and theoretical and mathematical models ([Fekete et al., 2016](#); [Rees et al., 2002](#); [Tononi and Koch, 2008](#); [Tononi et al., 2016](#)), rendering consciousness an emergent feature with biologically tractable neuroscience including behavior ([Edelman et al., 2011](#); [Boly et al., 2013](#)). Advances from the BRAIN Initiative investment presage the ability to understand how millions of cells connect and interact both biochemically and anatomically to create functional circuits. It is experimentally feasible to selectively alter cells within these circuits – and connections between

them – in a specific and multigenic manner. It is not understood how such alterations might affect consciousness, nor is it known whether altering consciousness approaches moral limits to biomedical research. These are important and interesting questions.

**Goal:** Understanding consciousness as a point of study for how brain activity elicits causality at a systems level in a human is a bold undertaking. These higher-order properties have been the focus of extensive philosophical and neurobiological inquiry. The goal of this transformative research project is to explore to what extent a functional or operational definition of the emergent phenomena, like consciousness, can best be explored in the laboratory. In the process, the project would aim to develop neuroethics and neuroscience tools to determine criteria for defining and detecting and understanding consciousness.

Ethicists and scholars from a variety of disciplines, including the humanities, would explore assumptions of what consciousness is, how it might be measured and operationalized in the laboratory – and how such measures could be applied in real-world settings – and more broadly, how these neuroscientific insights might inform societal views and policy in areas such as health care, law, and other realms.

This project builds upon already existing plans of BRAIN Initiative-funded research to advance tool development to measure and intervene with brain activity but in a more precise and directed manner with the goal to understand how brain activity causes complex emergent behavioral outputs which is an important component of neuroethics concern and study. Using BRAIN priorities for research, this project would endeavor to identify molecular, biochemical, and physiological differences/correlates of consciousness in selected brain region(s) and understand function via measuring these correlates in multiple experimental model systems. Moving scientific investigation strategically between model systems and relevant species could advance the goal of understanding core elements of human consciousness. Looking across models (e.g., the social behavior of bees, which is quantifiable and manipulatable, and other model systems including mammals and humans) could be used to assess the generality of study conclusions. In addition, computational modeling and application of synthetic biology approaches throughout the life of each subproject would be an integral component of this research.

Throughout the research project, neuroethicists and neuroscientists would work together in a laboratory setting to explore the neurobiological underpinnings of consciousness. As the research progresses, further innovative techniques and technologies might be developed to explore particular features of consciousness or perhaps investigate additional biomarkers of consciousness. Finally, these collaborative teams can explore how to best disseminate, ensure proper use and apply study findings.

**Approach:** These experiments can be explored systematically through interdisciplinary collaborations of neuroscientists, ethicists, synthetic biologists, bioengineers, artificial-intelligence experts, and others with relevant expertise and would include not only academic researchers, but also non-scientific participants. Such public engagement aligns with two BRAIN Initiative milestones that may warrant more robust attention in its second phase:

1. Support for data-driven research to inform ethical issues arising from BRAIN Initiative research, ideally with integrated activities between ethicists and neuroscientists.
2. Opportunities for outreach activities focused on engaging government leaders, corporate leaders, journalists, patients and their advocates, educators, and legal practitioners in discussion of the social and ethical implications of neuroscience research.

In addition to how understanding conscious states and levels can influence scientific questions and methodologies, the results of this transformative project could also help to inform fundamental issues related to an individual's capacity to consent or assent, how healthcare providers assess and facilitate quality of life and reduce suffering, and perhaps even how personhood is defined and evaluated. Further defining ways to scientifically measure consciousness could help to define whether it is appropriate to worry about organoids' potential to exhibit consciousness, provide data to help understand when life has ceased and determine the extent to which artificial intelligence merits moral consideration/status. This project will also demonstrate the value of integrating neuroethics throughout the lifecycle of a neuroscience research project. For example, interdisciplinary teams of neuroscientists and neuroethicists can interact with a range of stakeholders to systematically investigate (through both empirical and conceptual neuroethics research) the various assumed meanings and components of consciousness. These data can be used to extract terms used to study consciousness in the laboratory – in established human and animal models as well as in other emerging models of brain circuitry.

Broad participation that invites a diversity of thought, expertise, and experience is necessary for this exploration of consciousness to be successful. From the outset, team members that should include scientists, philosophers, ethicists, experts on artificial intelligence, synthetic biologists and computer scientists would create a cohesive set of questions and metrics with the goal of ultimately providing an operational understanding of consciousness and methods for measuring it.

“Understanding the Bases of Consciousness: Intersection of Neuroscience and Neuroethics” is distinct from prior efforts in several ways:

1. Neuroscientists, neuroethicists, philosophers, synthetic biologists, artificial-intelligence experts, and computer scientists will contribute integrally to development and benchmarking of scientific progress.
2. The BRAIN Initiative has seeded progress of neuroscience research to the point where complex multimodal quantitative biological data in multiple experimental systems can be generated that directly provide insight into emergent systems properties.
3. Methodologies for conducting these experiments are advancing rapidly and becoming easier to implement – making them vulnerable to malign intent and use. Staying at the forefront of this research and the knowledge arising from it may mitigate malign use.



4. There is evolving societal recognition that understanding “ourselves” may enhance human flourishing through improved health. Consciousness is one component of this understanding.

Success of this project presages the possibility for follow-up projects to explore agency, thought, identity, and other aspects of the various attributes that make humans distinctively human. It is an understanding of the totality of our unique nature that comprises the theory of the mind and will be achieved as additional “chapters” in the story of our human experience are explored.

## **CLOSING THOUGHTS: A UNIFIED PATH FOR NEUROETHICS AND NEUROSCIENCE**

The first 5 years of the BRAIN Initiative have demonstrated remarkable scientific progress and introduced stunning new opportunities for deepening knowledge about the brain and for improving health. Such progress is interwoven with its investigation – as humans, we are studying ourselves. Because each of us is unique, the plurality of “ourselves” becomes a challenging concept that calls for careful thought about how to design, conduct, and report neuroscience findings. Through this foundational work, researchers are learning how our brains generate thoughts, emotions, perceptions, actions, identity, and memories. These studies and the neurotechnologies borne of them provoke many neuroethics questions. Not all the questions portend worry; in fact, neuroethics inquiry is growing academic pursuit that aims to answer fascinating questions about how the human brain contributes to humanness – as well as what to do with all the new knowledge pouring out of laboratories across the world.

Neuroscience is increasingly being used in a variety of important social sectors. In addition to important clinical uses of neuroscience and neurotechnologies, all of the following endeavors are well underway and/or trending upward: the availability of direct-to-consumer neurotechnology; investments in military neurotechnology; introduction of neuroscience into legal cases; use of neuroscience in marketing; and use of neuroscience in education. This reality raises a fundamental tension: Neuroscience is being regularly used in our societal structures even though our basic understanding of brain function and structure remains limited in many ways. In each scenario, we can imagine a better future as a result of neuroscience: happier consumers, more efficient and safer combat, a smarter and more morally competent citizenry, better educational methods and tools, and fairer legal outcomes. But in each of these scenarios, we can also see potential for harm: wrongful convictions based on inaccurate brain science; invasions of privacy; inadequate consumer protections; and development of inappropriate dual uses in military settings. Moreover, miscommunication and over-promising what neuroscience can actually do may inappropriately raise hopes about what neuroscience can deliver. An important goal for neuroethics in these domains should be to introduce deliberative structures that allow for neuroscience-based benefit without companion harms.

Moreover, existing protocols and protections outside the laboratory do not adequately integrate neuroethics considerations. As envisioned by BRAIN 2025, the neuroethics community has worked closely with researchers and clinicians to establish consensus procedures and protocols for the collection, use, and storage of brain data. But outside these biomedical and clinical contexts, neuroscience oversight is mixed. With no IRB, FDA, or journal editors to serve as gatekeepers, an attorney who wants to employ brain-based lie detection can do so; an entrepreneur who wants to convince a school board to buy her “brain-based” education tools can make her pitch; and a neuromarketing company can establish its own incidental-findings policy. Regarding military decision-making, neuroethics consultation has been integrated to some extent into neurotechnology development and use, but it is unclear how much structure there is with such ethics inquiry.

Undoubtedly, through research, greater insights into the brain will likely emphasize the blurry line between enhancement and therapy. Neuroscience will challenge how we define and raise questions about who gets to determine what constitutes a “normal” brain and “normal” behavior highlighting the need for careful reflections of the study design, implementation, and translation of BRAIN Initiative findings. A critical aspect of this reflective work should also include elements of public opinion and public-engagement research on these emerging topics. There are many open questions:

- What counts as a relevant social benefit from research with human brains?
- Who bears the duty of providing and distributing these social benefits and to whom are these benefits owed, particularly when neuroscience advances may have potential to further deepen social inequities?

To date, the BNS’ view is that the BRAIN Initiative should take the opportunity to address these crucial questions and there may be unique responses to them compared to similar questions asked about genomics, nanotechnology, and other cutting-edge technologies when they emerged. An expanded ethical framework that elicits, engages, and provides reasonable answers to these difficult questions is necessary and will necessarily involve experts beyond the BRAIN Initiative. This will involve engaging principles that offer room for cross-cultural explorations of topics, such as consciousness. The public and scientists alike imbue these terms with weighty and significant unspoken cultural and scientific assumptions. These issues must be explored integrally in order to have thoughtful design of experimental questions, conduct and interpretation of the research, and understanding of the extent to which those data can inform how we understand those concepts. This work will require deeper, systematic conceptual and empirical work to drive how research that can be so challenging to our brain function and our identities can and should be conducted. The goals of neuroethics and neuroscience are interwoven and benefit from close alliances that provide an unprecedented opportunity to bring neuroscience to society. Ethical neuroscience has a responsibility to ensure that biomedical research is fair, rigorous, and protects the humans and animals that are part of this massive enterprise.

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## APPENDIX 1: ROSTER

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Dr. James Eberwine (Illumina, Inc., Agilent Technologies, Inc., LBS technologies, Inc.)

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Dr. Laura Roberts is the owner of Terra Nova Learning Systems LLC, which develops science-based educational products and is supported by the NIH Small Business Innovation Research program.

Dr. Elizabeth Hillman is a member of the scientific advisory board of System1 Biosciences.

## APPENDIX II: CASE STUDIES

The following case studies were developed to stimulate discussion within the BNS group with regard to neuroethics issues that may arise from anticipated advances in the cell census and circuits components of BRAIN 2.0. These case studies also touch on the use of nonhuman primates (NHPs) in neuroscience research. Further, a suite of other case studies that can be used to elicit neuroethics discussions relevant to these and other parts of BRAIN 2.0 can be found [online](#).

### **CASE STUDY: AMYGDALA-RELATED AGGRESSIVE BEHAVIOR**

Professor Cajal has been studying synaptogenesis and neuronal connectivity in the mouse brain for two decades. Over the past few years, she has been using a combination of novel biosensors, new imaging procedures, and new ultra-high speed cryo electron microscopy (cryoEM) to map presumably all synaptic connections in the amygdala of the fetal and adult mouse brain – the region that coordinates and elicits aggression and other social behaviors. Recently, scientists in her laboratory were surprised to discover that single-cell sequencing highlighted gene-expression patterns correlated with the gradient strength of input from various brain regions that provide synaptic input into the amygdala. This result suggested that strength of amygdala stimulation might be controlled post-synaptically by altering expression of these stimulation-correlated genes. Her laboratory's proposed next step is to determine whether and how such transcriptional regulation affects amygdala-mediated aggressive behaviors. Toward this goal, Cajal's laboratory has created novel viral vectors that can transport whole genes into neuronal cells.

#### *Issues to consider*

By using these vectors, the researchers can control the strength of synaptic input – and therefore aggressive behavior in mice.

- Are there neuroethics concerns about direct manipulation of endogenous neuronal pathways to generate specific behaviors?
- Are there limits to the degree of alteration that should be performed – are there neuroethics issues posed by creating a maximally aggressive animal?
- Are there issues with how these studies are described to the press and lay public? If so, how can fact be distinguished from hype?

In further studies, employing computational analysis of human gene mutations, Cajal found a high density of mutations in many of the human homologues of the mouse genes she identified in her studies with mice. Professor Cajal wants to determine whether the human mutations affect aggressive behavior and wants to employ a CRISPR/Cas-based gene-editing procedure to introduce multiple mutations into the homologous genes in the somatic genomic DNA (nonreproductive) of amygdala neurons in marmosets, an NHP species that is highly social. Such mutations have the potential to alter aggressive behavior in marmosets and potentially change dominance status within social hierarchies.

- Are there concerns about altering “normal” NHP behavior toward more or less aggressive behavior? If so, what are the issues?
- Should social hierarchies that are changed as a result of these somatic genetic manipulations be allowed to persist through generations of marmosets?

As the research progresses, Cajal’s team plans to conduct germline manipulation of these genes to assess the developmental impact of the genes on aggressive behavior in marmosets.

- Are there neuroethics considerations introduced by altering the behavioral development of individual marmosets, essentially changing the agency of a marmoset?
- What are the neuroethics concerns posed by creating a line of marmosets that are hyperactive (or less aggressive) to their resident marmoset colony?
- Are there neuroethics concerns with permitting these colonies to persist throughout generations of marmosets?

The marmoset studies have shown that primate behavior can be altered by manipulation of the genes Professor Cajal originally identified. Due to the known role of the amygdala in human social behavior, there is significant interest in understanding whether these same genes are involved in modulating amygdala-mediated behaviors in humans.

- Are there neuroethics concerns introduced by performing these genetic manipulations in explanted human brain tissue (immediate post-mortem tissue isolation or neurosurgery, such as epilepsy), in which portions of the amygdala are removed? (Interestingly, there is a reported case in which a portion of a woman’s hippocampus including the amygdala was removed and she became “hyper-empathetic” [[Richard-Mornas et al., 2014](#)]).
- While behavior cannot be assessed directly, the newly discovered biomarker correlates can be.
- With improving imaging procedures, it is likely that human brain activity assessing specific connections to the amygdala (that can be altered using Dr. Cajal’s technology) will be possible. If so, are there neuroethics concerns to assessing this behavior in humans?
- Among the genes that Professor Cajal described are several receptors for which a pharmaceutical company has developed interacting drugs. Is there a neuroethics distinction to using biological or chemical compounds to manipulate and monitor human amygdala behavior in humans?
- What are the neuroethics considerations posed by conducting somatic gene alteration of these genes in humans to treat human illnesses associated with amygdala dysfunction?

Cajal’s data related to synaptic connectivity data, gene associations, and genetic manipulations will be published and uploaded into public databases.

- Are there concerns about dual-use of these data? If so, what are these concerns?
- How does a detailed understanding of the biological basis of aggression (and perhaps live brain imaging of the pathways) affect the legal status of criminals on trial for or convicted or

violent crimes? If so, what are the legal issues with regard to having such knowledge for defendants?

- Large information-gathering companies are interested in these data, as they might provide a means to better understand consumer social interactions. Are there concerns about how these data will be used by public data companies?

### **CASE STUDY: RESEARCH WITH HUMAN BRAIN ORGANIDS**

*(adapted from U.S. BRAIN Initiative case study for the 2017 Global Neuroethics Summit)*

#### **BACKGROUND**

The development and growth of brain organoids derived from human stem cells is an emerging area of science that holds great promise for advancing human health and neuroscience ([Di Lullo and Kriegstein, 2017](#); [Qian et al., 2016](#)). Researchers have long sought to understand how the human brain functions in health and disease, with much of their work constrained to studies with animal models and post-mortem or pathological human brain tissue. In contrast, human brain organoids, grown *in vitro* from pluripotent stem cells, offer the potential for closer approximation of dynamic human brain development and function. Brain organoids can generate diverse cell types and self-organize into complex structures that resemble parts of the brain. However, they exhibit heterogeneity in terms of cell types and circuitry, and they do not include all cell types involved in normal brain development ([Di Lullo and Kriegstein, 2017](#)). Scientists are still working to understand brain organoids and to develop this early-stage model system for more widespread use.

Human brain organoids also raise important ethical questions. Knowing that brain organoids are meant to model human brains and aspects of brain development or disease, but cannot develop into full persons, what are the relevant ethical considerations? Presumably these would be related to the development of morally-important human features, rather than the creation of full human life. For instance, might brain organoids develop (either naturally or through bioengineering) morally important features, such as sensory perception, sentience, pain, or cognition ([Munsie et al., 2017](#))? What biological indicators would reveal the development of those features? How can we think about a prospective framework for mitigating ethical risks while not inadvertently stifling promising areas of research inquiry?

#### **CASE STUDY**

Scientists in the Temple Laboratory are growing human brain organoids (generated from skin fibroblast-derived induced pluripotent stem cells) to study the effects of prenatal exposure to viruses on neurodevelopment. This research cannot ethically be performed *in vivo* on human embryos or fetuses. The research could provide valuable insights into the effects and prevention of neurodevelopmental insults. Identifying critical developmental periods of exposure could require maintaining the organoids *in vitro* for extended periods of time. Abby donated skin cells for this research. She hopes that the researchers will learn something that will help babies with microcephaly and other developmental disorders, but she is concerned about “her” organoid. She ponders a series of questions. How much does it resemble her brain? Researchers seem to be interested in brain organoids because they are similar to developing fetal brains. Is that

true? Does this organoid look similar to what her own developing brain looked like? Might it reveal any personal medical information about her? Can it ever be made to sense or think? How long will researchers grow and maintain it in culture? Will they modify it? If so, in what ways? After they expose the organoid to a virus, will it become “diseased”? How long will it be allowed to grow in its “diseased” state? And what will the researchers do with the organoid when they are done experimenting with it?

## Questions

As organoid technology advances (likely through the vascularization and linking of multiple brain regions), it is anticipated that these entities will be able to produce intact neuronal connections and develop “normal” functioning systems.

- What features/functions would warrant neuroethics concern in brain organoids? Are these concerns related specifically to the donor or more to an overarching concept of moral status or other general ethical concepts?
- Given that, unlike a normal human brain, a brain organoid exists in a disembodied state, how would researchers know whether these ethically concerning features are present? And what are the implications of having (or not having) the ability to detect these features/functions?
- Should detection of these features be a requirement for research to go forward, with an eye towards halting the research should it attain a particular “level of neuroethics concern?”
- Is there a moral significance of attainment of neurodevelopmental milestones for brain organoids?
- Should there be a limit to how long brain organoids can be maintained in culture and how complex researchers can make them?
- Should there be limits to the kinds of research activities that can be performed on brain organoids, including connecting brain organoids to non-biological circuitry or apparatuses?
- How should we think about cell or tissue donor consent for research with brain organoids?
- How should human brain organoids be disposed of? Are there issues associated with their human origin that require special disposal?
- Organoids are being used in xenografts to see how the organoids can function in a more normal physiological environment, which may be necessary for more complex development and neuronal functioning to develop.
- Are there neuroethics concerns with regard to transplanting human organoids into rodents?
- Are there concerns with regard to transplanting organoids into animal models closer to humans, such as NHPs? If so, what are they, and how significant of a concern are they?
- As a corollary to these studies, are there neuroethics concerns with regard to NHP brain-organoid implantation into other NHPs?