Background

The major objective of the BRAIN Initiative®, announced in April 2013, is to develop new tools and technologies and employ them in research aimed at understanding how networks of cells (e.g., circuits) in the brain generate behaviors. The Advisory Committee of the NIH Director (ACD) enthusiastically endorsed BRAIN 2025: A Scientific Vision as the strategic plan for the NIH BRAIN Initiative. Reflecting the thoughtful, scholarly work of the BRAIN (1.0) ACD Working Group (WG 1.0) and incorporating input from public workshops, BRAIN 2025 coalesced support for BRAIN across the neuroscience community and provided the framework for NIH’s implementation of this initiative. Ten NIH Institutes and Centers (ICs) and the NIH Office of the Director (OD) contribute to the BRAIN initiative, through 6 project teams. BRAIN funding is expected to be greater in its second 5-year funding period than in its first 5 years. The projected total spending for the lifetime of BRAIN (through 2026) is $4.9 B, and through 2017, only $548.3M has been spent (~11% of the total, to 345 awardees).

To date, BRAIN funding has focused on 7 high-priority research areas:

1. Brain cell types | Discovering diversity
2. Tools for circuit diagrams | Maps at multiple scales
3. Technology to monitor neural activity | The brain in action
4. Precise interventional tools | Demonstrating causality
5. Theory and data analysis tools | Identifying fundamental principles
6. Advance human neuroscience | Creating human brain research networks
7. Integrate approaches | From BRAIN Initiative to the brain

Overlaying these 7 priority research areas are 7 principles:

1. Pursue human and non-human animal studies in parallel
2. Cross boundaries in interdisciplinary collaborations
3. Integrate spatial and temporal scales
4. Establish platforms for sharing data and tools
5. Validate and disseminate technology
6. Consider ethical implications of neuroscience research
7. Accountability to NIH, taxpayers, and the scientific community

See Appendix I for an estimated timeline of BRAIN 2.0 events and deliverables.

Consistent with the BRAIN 2025 report, in the second 5 years of the BRAIN Initiative, NIH plans to build upon its current emphasis on technology development and has convened a new working group (WG 2.0) to revisit the 2025 report’s priorities through the lens of progress to date, rising scientific opportunities, and the new set of tools and technologies emerging from BRAIN. A companion WG, the NIH ACD BRAIN Initiative Neuroethics Subgroup (BNS), has been charged with developing a neuroethics roadmap for BRAIN 2025, taking into
consideration any proposed updates to BRAIN 2025. Overlapping members of WG 2.0 participate in the BNS WG.

See Appendix II for both rosters. As with WG 1.0, both of these WGs report to the full ACD, which provides recommendations to the NIH Director.

**BRAIN 2.0 Community Input**

Beginning in April 2018, and led by co-chairs Catherine Dulac, Ph.D., and John Maunsell, Ph.D., WG 2.0 members have reviewed the existing BRAIN investment and progress and have considered potential areas for growth and expansion. In so doing, WG 2.0 is soliciting input from the broader neuroscience community and other BRAIN stakeholders through two principal means: i) a series of public workshops held between August 2018 and November 2018 ii) an RFI seeking input (comment period has been extended through March 2019). Workshops included: “From Experiments to Theory and Back” (October 4, 2018, Houston, Texas) “Looking Ahead: Emerging Opportunities” (September 21, 2018, Chicago, Illinois) and “Human Neuroscience” (August 24, 2018, Cambridge, Massachusetts). The group also hosted a Town Hall and Networking Session at the Society for Neuroscience November 4, 2018 meeting.

**BRAIN Neuroethics Investment to Date**

*James Eberwine, PhD (co-chair) - University of Pennsylvania*

The first half of the BRAIN investment has yielded significant discoveries in all 7 BRAIN priority areas, such as three-dimensional maps of cell types and activity-dependent gene expression, high-speed three-dimensional imaging of neural activity, cost-effective applications of remote magnetothermal disruption to modulate biological processes, and a range of novel sensors and probes that use various voltage-dependent and optical-imaging methods. Among BRAIN-funded scientific advances that will likely propel neuroscience understanding and health applications include biosensor/probe development, computational analyses, and data-science approaches such as artificial intelligence (AI), as well as new methods for introducing molecules into specific cells, in particular neurons. Although neuroscience research entails ethical issues that are common to other areas of biomedical science, it entails special ethical considerations. As well, the importance of neuroethics is already well appreciated, as articulated in the BRAIN 2025 report (p.118):

“… 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.”

Shortly after the publication of BRAIN 2025, NIH created a Multi-Council Working Group (MCWG) comprised of nongovernmental representatives from the advisory councils of each of the 10 NIH Institutes or Centers (ICs) that contribute to the initiative, as well as five at-large members. In addition,
the MCWG includes ex officio members from the Defense Advanced Research Projects Agency (DARPA), the Food and Drug Administration (FDA), the Intelligence Advanced Research Projects Agency (IARPA), and the National Science Foundation (NSF) - four of NIH’s federal partners involved in the BRAIN Initiative. The MCWG provides ongoing oversight of the long-term scientific vision of the BRAIN initiative, as endorsed by the ACD, in the context of the evolving neuroscience landscape. Recognizing that neuroethics in the BRAIN Initiative needed close and continuing attention, NIH held a one-time workshop on neuroethics in November 2014 and the following August, MCWG approved the creation of a subgroup, a Neuroethics Working Group, drawn from MCWG membership and that includes other neuroethics experts. As noted, the ACD BRAIN Initiative Neuroethics Subgroup (BNS) has been charged with developing a neuroethics roadmap for BRAIN 2025, taking into consideration any proposed updates to BRAIN 2025. The ACD charge to the BNS is to: “Develop a neuroethics roadmap in anticipation of rapid growth in BRAIN-associated knowledge with particular attention to application of BRAIN neurotechnologies/knowledge in humans.”

INVITED SPEAKERS

Mapping the Global Landscape of Neuroethics
Caroline Montojo, PhD - The Kavli Foundation

The Kavli Foundation operates through an international program of research institutes, professorships, symposia, and other initiatives in the fields of astrophysics, nanoscience, neuroscience, and theoretical physics. Its efforts “ignite and catalyze” international neuroethics projects and collaborations, including the International Brain Initiative (IBI) and others described below. In December 2017, representatives from the world's major brain projects made a formal declaration to establish the IBI, which convened a 2016 meeting that identified neuroethics and societal outreach as high-priority topics and that pointed to ethical questions raised by the use, development, and application of neurotechnologies. They also noted that outreach and communication must be integral to brain research, ensuring an international and humanistic mindset. The meeting led to development and publication of Neuroethics Questions to Guide Ethical Research, and a subsequent global neuroethics summit led to publication of Neuroethics Questions to Guide Ethical Research in the International Brain Initiatives. Kavli sees a great need to integrate neuroscience and neuroethics intentionally, and with the emergence in recent years (since BRAIN was launched) of various global brain projects, better coordination is needed to maximize impact and efficiency, as well as to minimize potential redundancy. In addition to IBI, global neuroethics groups include:

- The Organisation for Economic Co-operation and Development (OECD) Neurotechnology and Society group, which is developing 11 principles to guide neurotechnology applications in health and impacts on individuals and society
- The Institute of Electrical and Electronics Engineers (IEEE) Brain Think Tank is considering implications of closed-loop control of neural activity and is preparing a white paper and technology roadmap to guide research and development
- The International Neuroethics Society is a group of scholars, scientists, clinicians, and other professionals who share an interest in the social, legal, ethical, and policy implications of advances in neuroscience.

Responsible Brain Research and Neuroethics: The Case of the Human Brain Project
Arleen Salles, PhD - Uppsala University

The Human Brain Project (HBP) has several ethical and neuroethical foci: an ethics directorate; an external ethics advisory board; a stakeholder board; a science and infrastructure board; a data-governance working group; a
dual-use working group; a gender advisory committee; and an ombudsperson. In particular, the Ethics and Society subproject (#12 – a core part of the research project, with 4.5% of research budget) promotes responsible research and innovation practices within the HBP. It uses an interactive process and the AREA framework, which Anticipates intended and unintended impacts of brain research; Reflects on research purpose and motivations/assumptions; Engages with external experts, stakeholders, and citizens; and Acts on information gathered to develop policy options and recommendations and to shape research directions. A distinctive feature is promotion of a broad understanding of neuroethics, both applied and conceptual. This approach addresses not only impacts of research but social benefits and limitations – with an eye to societal norms and priorities – to engage public interest and to shape research priorities. Selected issues that have been considered and addressed (including through published opinion pieces) include consciousness, data protection/privacy, dual use, compliance and research integrity, community building, identity, AI, brain research/mental health, and neurotechnologies. Of note, HBP funds research in the humanities and social sciences (including philosophy) as a means to address its intentional focus on reflection.

**Ethics of the Use of Non-Human Primates as Models for Human Brain Disease**  
*Jeffrey Kahn, PhD, MPH - Johns Hopkins University*

Research with nonhuman primates (NHPs) generates substantial interest and concern from various stakeholders of biomedical research as a whole, especially with the emergence of transgenic techniques that enable perturbation of biological processes. Public engagement is thus a highly relevant concept that is not unique to research with humans’ closest relatives but that emerges as a top priority for BRAIN and biomedicine more broadly. The scientific rationale for using NHPs itself presents ethical considerations: NHP models are meant to model human diseases and their symptoms, and that very similarity invokes an obvious question/concern about effects of those same symptoms on the animals. In this context, many questions arise related to “importance” of any given disease, level of “humanization” of an animal model, and others. A [2011 report](#) on the use of chimpanzees in biomedical research offers a potentially instructive historical precedent for consideration; it resulted in [NIH’s 2013 decision](#) to limit experiments in chimpanzees to those that answer questions impossible to answer in humans or that are not ethically feasible in humans, and in [2015](#), to end all NIH support of biomedical research with chimpanzees. A central issue that extends beyond the use of NHPs in neuroscience research is the importance of using appropriate animal models for addressing all research questions of interest. For BRAIN 2.0, potential features of oversight and questions to consider regarding NHPs include: necessity of specialized review expertise and/or centralized review beyond Institutional Animal Care and Use Committee (IACUC); clarity of scientific rationale, as guided by a community of researchers and non-researchers to create consensus-based criteria; and unique features of animal care in modified animals.

**Ethics and Innovation in Neuroscience and Psychiatry: Stakeholder Perspectives**  
*Laura Dunn, MD - Stanford University*

Are there similarities between the BRAIN initiative/neuroethics and the Human Genome Project/ethical, legal, and social implications (ELSI)? Both invoke a balance between scientific/technological excitement and human concern (for privacy, safety). The extraordinary innovation in brain research - organoids, neurostimulation, neuromodulation, and other examples – is difficult to discuss in a thoughtful way with a mixed audience of scientists, non-scientists, and policy makers. Vulnerable populations present a particularly difficult scenario for understanding (and informed consent). Research is underway to give a voice to such individuals – in part through comparative analysis of viewpoints on benefits and harms of neuroscience research. A recently published study analyzed views about the importance of psychiatric...
genetic research as viewed by varied stakeholder groups (people with mental illness, first-degree family members of people with mental illness, a healthy comparison group, a national sample of psychiatric genetic researchers, and a national sample of investigational review board (IRB) chairs) and identified significant differences. Other research is obtaining stakeholder data to enhance understanding of underrepresented voices and to strengthen ecological validity of the overarching neuroethics dialogue. This study, which is employing the Roberts Valence Model of ethical participation in human research, aims to build tools to strengthen ethical rigor and caliber of neuroscience innovation and investigation. A key goal is building public trust for research.

**Discussion – Key Points**

**Public engagement**
- Public engagement underlies nearly all issues relevant to neuroethics, but it is a vague term that affects and invites conversation with a wide array of stakeholders and participants, ultimately on a global scale.
- It should be bidirectional, not one-sided educational delivery of facts or concepts. Reviewing progress in other fields (physics, nanoscience) may be instructive.
- Emphases on anticipation and reflection can address unintended or unexpected consequences of neuroscience research, as well as manage potential hype of scientific data and results. Funding research in the humanities (sociology, philosophy, other) is one potential vehicle.
- The HBP is aligned with a group dedicated to public engagement that conducts surveys and questionnaires and publishes public activities and impact – this type of effort could be more broadly adopted.
- Evaluation of public engagement – how to do it and what to measure? Are efforts being effective and or understood by intended audiences?
- Should neuroethical review/consideration think beyond compliance to anticipatory “what ifs?”
- It is continually important to challenge new assumptions invoked by varied stakeholders, to avoid group thought.

**NHPs**
- Guidance established by government funders can have impacts on other sectors, such as industry.
- Variation in international governance of scientific experimentation creates a quandary for research collaborations (and data sharing) when scientists work across borders.
- The 2011 report on use of chimpanzees in biomedical research may not have been representative for future efforts, as it embarked on asking a singular question and required co-authors of the guidance to be non-committed to either “side” before deliberations.
- What makes chimps special? There is draft Congressional legislation to limit all NHP research; where should the line be drawn? Can a line be drawn?
- A similar NIH issue centered on human-animal chimera research - what about human cells in an animal brain? Humans cannot know what animals are experiencing.

**BNS MEMBER SHORT PRESENTATIONS**

**Ethical Considerations for Human Organoid Research**

*Insoo Hyun, PhD - Case Western Reserve University*

Human organoids are three-dimensional structures grown from pluripotent stem cells or adult progenitor cells that self-organize into organ-specific cell types in culture. They can model structural and functional properties of a wide variety of organs, such as the gut, kidneys, pancreas, liver, retina, and
the brain. Research with organoids generally raises ethical questions related to stem cells and animal models, but brain organoids raise particular issues and potential concerns. An extension of the term brain organoid, brain “assembloid,” connotes spheroid conglomerates of human cells, vasculature, immune cells, and signaling pathways - which have polarity and architecture mimicking a human brain. These multidimensional entities do not possess consciousness, but they do react to signals: thus, do they require moral status (when interests matter morally to some degree for the entity’s own sake)? Moral considerability, on the other hand, may be more applicable due to membership of a group; e.g., an organ representing a human. Future studies that transplant human brain organoids into the brains of large lab animals might require special ethical consideration based upon sensory and motor function conveyed upon the animal. These types of experiments may advance rapidly and thus may invite ethical study sooner than later. Similar issues pertain to organs-on-a-chip.

Does Existing Guidance Suffice for BRAIN Research?
Christine Grady, MSN, PhD - Department of Bioethics, NIH Clinical Center

Through its stated goals, the BRAIN initiative is “creating tools and neurotechnologies to provide access to core mechanisms that underlie human thoughts, emotions, perceptions, actions, identity, and memories, [which] could therefore “… profoundly alter some core human characteristics.” To date, many ethical, and neuroethical, guidelines have been developed and published: are additional guidelines needed?

- The Belmont Report was developed in 1979 by the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research – it specifies three ethical principles underlying the conduct of research: i) respect for persons, ii) beneficence, and iii) justice.
- The IEEE Code of Ethics – outlines ethical and professional conduct for its membership.
- The IEEE Code of Conduct (2014) – outlined more generally expected behaviors for its membership that include: i) respecting others, ii) being fair, iii) protecting (avoid injuring) others, iv) refraining from retaliation, and v) complying with applicable laws.
- The U.S. Presidential Commission for the Study of Bioethical Issues published three relevant documents:
  - New Directions: The Ethics of Synthetic Biology and Emerging Technologies - reported five principles (which overlap with Belmont): i) public beneficence, ii) responsible stewardship, iii) intellectual freedom and responsibility, iv) democratic deliberation, and v) justice and fairness.
  - Gray Matters (Volume 1) – recommended integration of ethics early and explicitly throughout neuroscience research.
  - Gray Matters (Volume 2) – recognized neuroscience as a rapidly growing, multidisciplinary field, encompassing a diversity of scientific and ethical issues and highlighted three topics that illustrate ethical tensions and societal implications: i) cognitive enhancement, ii) consent capacity, and iii) neuroscience and the legal system.
- The Nuffield Council on Bioethics - an independent body that examines and reports on ethical issues in biology and medicine developed a 2013 report, “Novel neurotechnologies: intervening in the brain.” It established an ethical framework based around two fundamental considerations: beneficence (the need for new approaches to treating serious disorders in the absence of other effective interventions) and caution (based on uncertainty about the benefits and risks of novel neurotechnologies due to currently limited understanding of the effects of intervening in the brain). Stakeholder interests pertain to safety, protection risks, impacts on privacy, and promotion of autonomy, as well as equity of access and promotion of trust in neurotechnologies. Ultimately, this
will be achieved through a combination of inventiveness, humility, and responsibility (avoiding hype).

- The Neurotechnology and Ethics Task Force – is made up of neuroscientists, neurotechnologists, clinicians, ethicists, and machine-intelligence engineers. This group developed four ethical priorities for neurotechnologies and AI: i) privacy and consent (with opt-out as default choice for sharing neural data), ii) agency and identity (neurorights as part of human rights), iii) augmentation (national and international limits, including military), and iv) bias (countermeasures for machine learning to combat bias becoming the norm).

- The Neuroethics Guiding Principles for the BRAIN Initiative – developed eight guiding principles framed by two overarching concepts: i) pursuing neuroscience research is an ethical imperative and ii) neuroethics is vital to neuroscience research.

Overall, familiar principles that guide clinical research and clinical care (e.g. respect for persons, beneficence, justice) are relevant and apply to neuroscience/neuroethics, but they are not always specific enough and thus may not suffice. Similarly, principles relevant to emerging technologies (public beneficence, responsible stewardship and prudent vigilance, inventiveness and responsibility) are relevant and apply, but are not specific enough and may not suffice. Specific attention should be paid to possible effects of neurotechnologies and BRAIN research on agency, identity, capacity, and public trust. In addition, particular matters related to “studying ourselves” are critical, including issues concerning augmentation, hype, bias, and misuse.

What Can We Learn from Deep Brain Stimulation? Ethical considerations in innovative neural devices

Karen Rommelfanger, PhD - Emory University

Certain features of neuromodulation technologies suggest special ethical consideration. These include invasiveness, chronic effect, assumed reversibility, newness, and associated uncertainty of side effects and consequences, potential physical and nonphysical harms (e.g., effects on autonomy, decision-making, sense of self). Deep brain stimulation (DBS) is especially relevant since it is here: there are FDA-approved and currently investigated applications for a variety of conditions ranging from motor disorders to psychiatric disorders. DBS thus offers great opportunity for mechanistic work and potential for even more clinical application. Even so, the terrible legacy of psychosurgeries such as lobotomies remain in public memory and urge caution. Neuroethics has the capacity to look forward, to anticipate (and manage) potential ethical roadblocks in brain research and development. Typical ethical principles (patient selection and risk management, long-term follow-up and protection, and consent) need refinement in the context of brain research to address nuanced topics such as personality and identity changes, memory and cognition changes – positive and negative, and consciousness. The distinctions between normal/healthy and abnormal/diseased are morphing into a continuum shaped by increased knowledge of biological processes, brain function, and behavior. Relevant case studies visit scenarios such as unexpected effects of neurostimulation, significant changes in affect that disturb family members, and unintended positive side effects of treatments. Neuroethics research offers many opportunities for clarifying some of these dilemmas and for understanding the human condition and its relationship with health and disease. Two broad types of (neuro)ethical research include empirical and conceptual approaches – both of which can inform policy decisions as well as facilitate a common language between researchers and participant/patients for discussing risks and benefits.

BRAIN 2025 and the Future of Neurolaw

Francis Shen, PhD, JD - University of Minnesota Law School
“Every story is a brain story” might encapsulate the scope of neurolaw, an emerging interdisciplinary field that appears in a growing number of contexts including governance/regulation, courtrooms, legislatures, and legal concepts (e.g., “what is normal/healthy,” what is a “disability?”). Neurolegal concepts are playing out in a range of ways – many of which are outside the scope of BRAIN and health. Nonetheless, law might facilitate or hinder what we know about the brain, and on the other hand, advanced understanding of brain circuitry might fundamentally reshape law. There are obvious distinctions between legal and scientific approaches: the former is concrete/binary, local, adversarial, and precedent-based; whereas the latter is complex/probabilistic, universal, collaborative, and innovative. Neuroscience advances may be legally relevant but clinically irrelevant (e.g., neuroscience of lie detection); clinically relevant but legally irrelevant (neuronal cell census); or both legally and clinically relevant (e.g., dementia research affecting elder abuse/fraud). Neuroscience has transformative potential for law, but only if used judiciously and now is the time to begin these discussions as research progress races forward.

Discussion – Key Points

• What are the most important areas of neuroscience research for law? Some areas include refined governance/informed consent; an opportunity to better understand mental health and illness; and increased connections between “silos” such as education, criminal justice, and health/science.
• Is neurolaw any different from legal aspects of other areas of science, such as genetics? Perhaps, in that brains change but mostly genes don’t.
• There is worry that an “overly scholastic” view of science processes and constructs may trend toward elitism that excludes input and perspectives from people who are non-experts in science but who play important roles in society and who are recipients of health advances.
• Should all neuroscience data be made public? To be considered: potential misuse and unintended consequences. Algorithms/patterns of usage also may have unintended consequences.
APPENDIX II: BRAIN 2.0 WG ROSTERS

WG 2.0

• Catherine Dulac (Co-Chair), Harvard
• John Maunsell (Co-Chair), U Chicago
• David Anderson, CalTech
• Polina Anikeeva, MIT
• Paola Arlotta, Harvard
• Anne Churchland, CSHL
• Karl Deisseroth, Stanford
• Tim Denison, U Oxford
• Kafui Dzirasa, Duke U
• Adrienne Fairhall, U Washington
• Elizabeth Hillman, Columbia
• Lisa Monteggia, Vanderbilt
• Bruce Rosen, MGH
• Krishna Shenoy, Stanford
• Doris Tsao, CalTech
• Huda Zoghbi, Baylor

Ex Officio:

• James Deshler, NSF
• Alfred Emondi, DARPA
• Christine Grady, Bioethics, NIH
• Lyric Jorgenson, NIH
• David Markowitz, IARPA
• Carlos Peña, FDA

BNS

• James Eberwine (UPenn); co-chair
• Jeffrey Kahn (Hopkins); co-chair
• Adrienne Fairhall (U Washington) *
• Christine Grady (NIH)*
• Elizabeth Hillman (Columbia)*
• Insoo Hyun (Case Western)
• Andre Machado (Cleveland Clinic)
• Laura Roberts (Stanford)
• Karen Rommelfanger (Emory)
• Francis Shen (U Minn Law School)

* Member of ACD BRAIN 2.0 Working Group