National Institutes of Health
Advisory Committee to the Director (ACD) Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative Working Group 2.0
Workshop #1: Human Neuroscience | August 24, 2018 | Harvard University

EXECUTIVE SUMMARY

The Advisory Committee of the NIH Director (ACD) enthusiastically endorsed *BRAIN 2025: A Scientific Vision* as the strategic plan for the NIH BRAIN Initiative. 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. As with WG 1.0, WG 2.0 reports to the full ACD, which provides recommendations to the NIH Director. 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 (comments are due by November 15, 2018). In addition to the August 24, 2018 workshop "Human Neuroscience" held in Cambridge, Massachusetts, the upcoming workshops include:

- Workshop #2 (Friday, September 21, 2018, Chicago): "Looking Ahead: Emerging Opportunities" University of Chicago Knapp Center for Biomedical Discovery | 900 E 57th Street Chicago, IL 60637
- Workshop #3 (Thursday, October 4, 2018, Houston) "From Experiments to Theory and Back" Onstead Auditorium, MD Anderson Cancer Center | 6767 Bertner Ave Houston, TX 77030
- Society for Neuroscience Town Hall and Networking Session (Sunday, November 4, 2018 6:30 PM-9:00 PM Pacific Time)

Workshop #1 Invited Presentations – Human Neuroscience: What is the State of the Science?

Models and technology were two broad themes that emerged from presentations and surrounding discussion during and after Workshop #1's four speaker sessions (Recording and Stimulation, Functional Imaging, Brain Connectivity, and Translation from Mouse to Human). A brief, thematic description appears below, followed by session summaries.

Models
More models are needed to link theory and experiment in humans. Multimodal approaches, in particular, will enhance the reach of research in human patients but are currently hampered by disparate levels of resolution for data access and analyses. Access to non-cortical brain areas and relative lack of precision restrict the number of brain regions – and thus disorders – amenable to research using recording devices. Neuroethical considerations are paramount, especially for interventions involved with cognitive and emotional plasticity, and for any type of chronic monitoring. It may be necessary to consider ethical standards and risk/benefit ratios for different neurological diseases and disorders. Animal electrophysiological models, in particular

non-human primates, are likely to continue to be important for a range of reasons. Most brain diseases are not monogenic and are thus not likely to be amenable to gene-editing approaches. Possibly, "reverse engineering" of human disease states can lead to more authentic disease models beyond organoids: Profiling human patients may guide development of in vitro experiments and tools – such studies will help define and understand functional units of the brain.

Technology

Merging data across imaging and other experimental platforms – across scales – is extremely difficult but required for the next generation of understanding and exploration of the human brain. Uptake of BRAIN imaging tools by the research community has been slow, for various reasons. These include incompatibility with two extremes of existing commercial models (large industry vs. small-business NIH grants). Intermediate solutions are needed to adapt and push out advances (including user-friendly software) to neuroscientists and clinicians treating brain disorders. Increased research-clinic interactions may also make better use of new technologies toward optimizing them and gathering new types of data from clinical scenarios and for expanding the number of brain regions currently accessible. Defining data standards should be a larger component of BRAIN going forward. Although the Brain Cell Data Center and R24-funded storage archives are organizing all data generated from the BRAIN Initiative Cell Census Network, it is likely that more effort and resources are needed to ensure effective presentation of data, tools, and knowledge facilitates scientific progress and community adoption.

Session I: Recording and Stimulation featured presentations on modulation of the human brain using modalities that vary in their level of invasiveness and which may be paired with the use of biomarkers to guide placement and/or monitor effect. Many are currently used in the context of treatment for diseases such as epilepsy and Parkinson disease. Better technologies and improved interactions with regulatory agencies are likely to be necessary to expand use of these approaches – ideally in an integrative fashion between research and care. Hybrid, milestone-driven models that focus primarily on a clinical problem but adopt a science-based approach (and thus mitigate risk/benefit) may advance knowledge even if trials don't reach their clinical endpoints. Currently, no human-brain recording/stimulation model can stimulate network dynamics. Intentional mixing of engineering, control theory, and neuroscience offers an opportunity to learn about biology and pathology through dynamic modeling, which may be useful for interrogating complex psychiatric disorders that are highly dimensional networks in which encoding is distributed. New BRAIN investments in the recording/stimulation arena might include overcoming technology-restricted hurdles to understudied brain regions, addressing neuroethical issues needing attention and guidance, and funding increased use of animal models for both exploratory and confirmatory studies.

Session I speakers included **Aysegul Gunduz, Ph.D.** (University of Florida); **Sameer Sheth, M.D., Ph.D.** (Baylor College of Medicine); and **Maryam Shanechi, Ph.D.** (University of Southern California).

Session II: Functional Imaging featured presentations on the state of the science in human imaging. fMRI is currently not routinely used in patients because fMRI sessions are time-consuming and difficult with current technologies. Future efforts should aim to make fMRI imaging faster, and less cumbersome, since this research will be critical for finding biomarkers for neuropsychiatric disorders. Other technologies, such as functional near-infrared spectroscopy (fNIRS) may offer some advantages in various settings including neuroimaging in natural environments and to study brain development in children (with thinner skulls than adults), as well as monitoring of patients in the operating room and at the bedside. However, fNIRS lacks depth sensitivity, is unable to distinguish signals from scalp-based artifacts and lacks standardization of data analyses. Increased resolution and sensitivity are needed to map brain activity to quasi-cellular resolution, and multimodal approaches are likely to be the next transformative step in advancing understanding of the human brain as well as defining new treatments for a range of neurological disorders and neuropsychiatric diseases. New BRAIN research investments might include i) those addressing engineering methods (sensor development, fundamental signal-processing research, and neuroscience-dedicated instruments) to expand the number of accessible brain regions, ii) computational approaches including machine learning, artificial intelligence, and deep learning, iii) convening people from different backgrounds (technology developers and technology users). Uptake of BRAIN imaging tools by the research community has been slow, for various reasons, including incompatibility with two extremes of existing commercial models (large industry vs. small-business NIH grants). Intermediate solutions are needed to adapt and push out advances (including user-friendly software) to neuroscientists and clinicians treating brain disorders. Increased research-clinic interactions may also make better use of new technologies toward optimizing them and gathering new types of data from clinical scenarios.

Session II speakers included **Larry Wald, Ph.D.** (Harvard Medical School), **Jack Gallant, Ph.D.** (University of California, Berkeley), and **Maria-Angela Franceschini, Ph.D.** (Harvard Medical School/Massachusetts General Hospital).

Session III: Brain Connectivity featured updates on approaches to map and measure brain connectivity. Some brain-machine interfaces now allow direct, chronic recording of populations of neurons, in daily sessions, for years in a variety of disease settings including spinal-cord injury, stroke, multiple sclerosis, amyotrophic lateral sclerosis, and Duchenne muscular dystrophy. Striking clinical successes, such as with paralyzed patients, have been documented. However, nearly all of these operate at the level of the cortex, leaving many subcortical and other brain regions unstudied. Comparative connectomics, like comparative genomics, is likely to reveal patterns and conserved evolutionary rules for both neuronal structure and function. Another significant barrier to progress in understanding and manipulating brain connectivity is traversing scales – different approaches provide data at variable levels of resolution/precision, making it difficult to combine approaches and analyze data. New BRAIN research investments might facilitate novel data-science approaches, in particular those that employ deep learning, machine learning, and artificial intelligence, to interrogate massive data sets acquired through diverse methodologies. Other BRAIN investment opportunities might include enabling NIH-

funded researchers to conduct large-scale science through U24-like mechanisms and other interactions with private-sector entities such as research institutes.

Session III speakers included **Richard Andersen** (*California Institute of Technology)*, **David Van Essen, Ph.D.** (*Washington University in St. Louis)*, and **Jeff Lichtman, M.D., Ph.D.** (*Harvard University)*.

Session IV: Translation from Mouse to Human discussed opportunities to advance knowledge from BRAIN 1.0 research cataloging cell types and creating new technologies to scaling this work into a human cell atlas. New BRAIN investments can facilitate this large-scale effort, but challenges remain. Effective and efficient delivery of reagents and therapeutics into the brain invites various challenges based on the blood-brain barrier, diffusion as the main mode of transport in brain tissue, tissue heterogeneity, and compartmentalization. Human 3-D brain models can be useful to study brain development and disease. To date, however, few if any head-to-head comparisons have been accomplished between animal/mouse- and human organoids. At present, transplantation studies are more reliable tools to study in vivo neuronal processes compared to 3-D/in vitro models, although hybrid approaches show promise. Genetic engineering in the brain using gene-editing methods may be able to develop novel therapeutics for neurological diseases, but there is still a long road ahead to insure lack of off-site and other undesirable effects. Aside from CRISPR/Cas9, there may be additional "programmable" proteins that already exist in nature. These might include RNA-guided nucleases, antibodies, or other types of adaptive immunity to recapitulate for research or clinical use. However, most brain diseases are not monogenic and are thus not likely to be amenable to gene-editing approaches. Profiling human patients may guide development of in vitro experiments and tools – such studies will help define and understand functional units of the brain.

Session IV speakers included **Ed Lein, Ph.D.** (*Allen Institute for Brain Science)*, **Junghae Suh, Ph.D.** (*Rice University)*, **Sergiu Pasca, M.D., Ph.D.** (*Stanford University)*, and **Feng Zhang, Ph.D**, (*Broad Institute)*.