National Institutes of Health
Advisory Committee to the Director (ACD) Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative Working Group 2.0
Workshop #2: Looking Ahead: Emerging Opportunities | September 21, 2018 | Chicago, IL

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. 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.

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 and the September 21, 2018 workshop "Looking Ahead: Emerging Opportunities" held in Chicago, Illinois, the upcoming workshops include:

- Workshop #3 (Thursday, October 4, 2018, Houston) "From Experiments to Theory and Back" Baylor College of Medicine, Alkek Building, One Baylor Plaza, Houston, TX 77030
- Society for Neuroscience Town Hall and Networking Session (Sunday, November 4, 2018 6:30 PM-9:00 PM Pacific Time)

Workshop #2: Invited Presentations – Looking Ahead: Emerging Opportunities

Discovery to translation/commercialization and characteristics/external validity of behavioral models were two broad topics of discussion in presentations and surrounding discussion during and after Workshop #2's three speaker sessions (**Developing and Disseminating New Technologies**, **Sensitive Molecular and Cellular Methods to Circuit Analysis**, and **Revolutionizing Circuit-to-Behavior Analyses**). A brief, thematic description appears below, followed by session summaries.

Discovery to translation/commercialization
A recurring issue in any type of technology development is mission misalignment. Academic scientists are not trained in bridging the gap, and they are rewarded for tool innovation - not

tool utility. Resources are needed to help individual labs/tool creators distribute useful technologies. Many academics may prefer not to want to involve industry and/or commercialize their discoveries. It has become apparent that the SBIR mechanism cannot provide sufficient time nor resources to support the development of some neurotechnology applications. Could BRAIN 2.0 "subsidize" larger companies to co-develop complex technologies for research use? Research institutes and companies can provide dedicated resources and staff – akin to project teams – in which "handoffs" of research and product occur in a defined, go/no-go environment. Public-private partnerships should be designed such that therapy development is part of the goal from the outset.

Models: external validity and behavior

There is a pressing need to develop refined animal models with direct relevance to human disease. Patients may be increasingly willing to participate in research, but they should have a say in how the research is designed and conducted: this can be advantageous for both research participants and researchers if done carefully and with attention to solid neuroethical standards. However, addressing a research problem can be done using a range of different model systems. Proper framing for behavioral analysis – using either model systems or humans – requires focus on ethology, the scientific and objective study of animal behavior, especially under natural conditions. To this end, the use of complex behaviors may be preferred since simple behaviors often hide computations due to equifinality. Complex tasks provide more entry points into computations and allow multiple access points for investigation.

Session I: Developing and disseminating new technologies featured presentations on the importance of measurement quality on scientific rigor and outcomes, including translational potential. Measurement science and standards provide industries and innovators with a common language to facilitate trade, simplify transactions, and enable people to work together toward common goals across disciplines and borders. The National Institute of Standards and Technology (NIST) supports the development of standards by identifying areas where they are needed, convening stakeholders, and providing technical and scientific guidance and expertise to help stakeholder groups reach a consensus. Careful metrological considerations, such as employing orthogonal measurements – two or more methods to measure the same phenomenon – help distinguish fact from artifact and can also pave a path from BRAIN technologies that are "exciting engineering" to those that are "useful for neuroscience." An important distinction in deriving new BRAIN technologies is intended use: Publication readiness (a common NIH marker of success) is a markedly different metric from product readiness (a much longer-term process that involves commercialization and user adoption). Many projects that are product-ready involve a substantial financial investment that will continue to grow with distribution and that includes production costs and user support, both of which may be financed through product markup that can erode user adoption rates. In general, discordant incentives, team structure, and resource allocation frustrate the translation of neurotechnologies beyond makers' labs into community use (either clinic or research).

Session I speakers included **Elizabeth Strychalski, Ph.D.** (National Institute of Standards and Technology, NIST); **Tim Harris, Ph.D., Luke Lavis, Ph.D.** (both from Janelia Farm Research

Campus, Howard Hughes Medical Institute, HHMI); and **Florian Solzbacher, Ph.D.** (University of Utah, Blackrock Microsystems).

Session II: Sensitive Molecular and Cellular Methods to Circuit Analysis featured presentations on large-scale identification and characterization of proteins – one of the next required technical leaps for the BRAIN initiative. Many techniques have emerged rapidly toward achieving this goal, including single-cell proteomics; bio-orthogonal chemistry; global in vivo protein conformation analysis; spatial and interactional proteomics; and synaptic-level assessment of interactions of ligands and receptors. However, the level of sensitivity and selectivity in proteomics approaches have not reached that of RNA-based analysis, and unlike RNA-based studies, no approach so far allows spatially aware proteomics. The BRAIN initiative has had a very important impact on technology development that has helped to integrate knowledge of cell types and circuits. As a result, current approaches to cell type-specific access are faster and cheaper; examples include transgenic strategies for combinatorial expression of fluorescent proteins in the nervous system; multiplex genome engineering using CRISPR/Cas systems, and selective optogenetic control of neuronal cells. To date, the BRAIN initiative has made inroads toward understanding glial function and structure, but additional investment is needed to expand this knowledge base. Modulate diseased circuits might present various opportunities for research while also providing symptomatic relief for patients suffering from a range of disorders, and they can be used for conditions whose genetic causes are unknown or complex. Non-typical model systems may provide entry into complex human-like cognitive functions that are difficult to access with more traditional models such as the mouse.

Session II speakers included **John Yates, Ph.D.** (The Scripps Research Institute); **Gül Dölen, M.D., Ph.D.** (Johns Hopkins University School of Medicine); **Cagla Eroglu, Ph.D.** (Duke University School of Medicine); and **Nathaniel Heintz, Ph.D.** (The Rockefeller University).

Session III. Revolutionizing Circuit-to-Behavior Analyses featured presentations related to various models and behavioral analyses in neuroscience. Viable model systems include computer-based approaches: Combining artificial intelligence and deep-learning approaches with transfer learning has enabled the ability to build trained networks that can learn new tasks, and computer-based tools have succeeded in some cases in mapping behavior to anatomy. External validity is a key issue in behavioral studies performed in model systems. Equifinality – the principle that in open systems a given end state can be reached by many potential means – has created difficulty in translating behaviors across species. Comparing circuits across species requires that both species are doing the same computations, not merely the same tasks. Experimental approaches across species can be especially valuable for identifying conserved mechanisms and processes. In addition, use of multiple models may be necessary to address facets of a research problem using a range of tools: imaging, genetic manipulation, electrophysiology, neuroendocrinology, and others. This approach has enabled detailed study of subcortical systems that is not yet feasible in humans. Conducting research with healthy human subjects and clinical populations may offer an opportunity to investigate neuroanatomically distributed brain states using various types of imaging or recording.

Session III speakers included **Mackenzie Mathis, Ph.D.** (Harvard University); **A. David Redish, Ph.D.** (University of Minnesota); **Karen Parker, Ph.D.** (Stanford University); **Yevgenia Kozorovitskiy, Ph.D.** (Northwestern University); **Conor Liston, M.D., Ph.D.** (Weill Cornell Medicine)