Brain Research through Advancing Innovative Neurotechnologies® (BRAIN)

Multi-Council Working Group Teleconference

May 16, 2017

On May 16th, the Multi-Council Working Group (MCWG) for the National Institutes of Health (NIH) Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative® held its seventh meeting as a teleconference. The MCWG is an external group of scientific experts who provide oversight of the long-term scientific vision of the Initiative at NIH. The group was joined by directors and staff from the 10 NIH Institutes and Centers supporting the Initiative, and open to the public via WebEx.

Welcome

Dr. Susan Weiss, the newly appointed designated federal official of the MCWG, initiatied the meeting. Dr. Weiss is the Director of the Division of Extramural Research at the National Institute on Drug Abuse (NIDA), which oversees NIDA's extramural programs, research training, operations planning, and trans-NIH initiatives, such as the Adolescent Brain Cognitive Development (ABCD) study. Dr. Weiss is also a senior science advisor to the NIDA Director.

Brief Overview and Budget

Drs. Joshua Gordon (Director, National Institute of Mental Health/NIMH) and Walter Koroshetz (Director, National Institute of Neurological Disorders and Stroke/NINDS) provided an update on the NIH BRAIN Initiative. The fiscal year (FY) 2017 federal budget passed in early May appropriated an additional $110 million (M) to BRAIN, which includes $10M from the 21st Century Cures Innovation Funds, bringing the total investment to $260.4M. In FYs 2022–2024, there may be large funding increases in BRAIN due to the Cures Funds, which may enable leveraging scientific opportunity to rapidly advance an area and/or devote additional funds to one of the BRAIN Initiative priorities, particularly costly goals. For FY 2017, there were 30 BRAIN Funding Opportunities issued, which span the seven priority areas of the *BRAIN 2025* report. NIH will initiate an assessment of BRAIN that includes revisiting *BRAIN 2025* and gathering input on the fundamental questions about the brain the Initiative could/should focus on, given the newly developed tools and technologies and evolving neuroscience landscape. To date, there are over 190 publications that have emerged from the NIH BRAIN Initiative. Finally, efforts to draft *Neuroethics Guiding Principles*, a roadmap to anticipate neuroethics questions associated with BRAIN research, are underway. The Neuroethics Division will complete these guiding principles through focused discussions of particular areas of interest, such as the recent May 11th workshop on organoids and research with *ex vivo* human brain tissue, hosted by Neuroethics Division member Nita Farahany. If there are any MCWG members interested in serving on the Neuroethics Division, they should let the MCWG co-chairs know.

Fiscal Year 2018 Concept Clearance

1. **Tools for Non-Neuronal Cells**

The meeting proceeded with clearances of FY 2018 funding concepts. Dr. Olivier Berton (NIDA) presented the first concept, "Tools to enhance studies of non-neuronal cells," with a goal of stimulating

grant applications that develop cutting-edge technologies tailored to study non-neuronal cells, such as glial cells, vascular cells, and neuro-glio-vascular interactions. Non-neuronal cells represent the majority of the cells in the nervous system but are understudied by neuroscientists, partly due to a lack of adapted tools. Their interactions with neurons impact many key functions, and tools developed for neurons (e.g., sensors, viral vectors) are often not directly applicable to non-neuronal cells. Although previous BRAIN funding opportunity announcements (FOAs) never formally excluded non-neuronal cell types, none of the existing tool development and census activities, thus far, have covered non-neuronal cells. Examples of tools include:

- New genetic and non-genetic tools for delivering genes, proteins and chemicals to cells of Interest.
- New tools for identifying and classifying non-neuronal cells (molecular profile, morphology).
- New tools for manipulating and monitoring their specialized functions and investigate their contribution to normal and abnormal neural network function.
- Intersectional approaches that target specific cell types during developmental periods or specific microdomains at the neuro-glio-vascular interface (e.g., endfeet).

Dr. Story Landis suggested that this potential FOA would need to be focused on circuits and not other neuroscience areas (e.g., stem cells, development, disease models), to avoid moving the NIH BRAIN Initiative off its established goals. Dr. Richard Huganir agreed that the main focus for this proposal should be to determine how non-neuronal cells affect circuit function. Dr. Koroshetz suggested that they could focus the FOA to the role of glia on brain circuits. Dr. Andrea Beckel-Mitchener (NIMH) indicated that this FOA would be in the context of the cell census activity, and the FOA can incorporate specific requirements as necessary. ***The MCWG voted to approve this funding concept for a new Tools for Non-Neuronal Cells FOA.***

2. Tools for Electron Microscopy/Micro-connectomics

Dr. Michelle Freund (NIMH) presented the next funding concept, "Tools to facilitate high-throughput microconnectivity analysis." The second priority area in the *BRAIN 2025* report is, "Maps at Multiple Scales: Generate circuit diagrams that vary in resolution from synapses to the whole brain", where it is mentioned that "it is important to focus now on developing technologies that will drive down the cost of connectomics." The proposed FOA would address:

- Techniques for tissue sample preparation and image acquisition.
- Methods for incorporating multi-modal information into microconnectivity assays, including information on cell types, gene expression, and synaptic phenotypes.
- Tools for enhancing and scaling automated image processing, connectivity analysis, and data interpretation, including algorithms, information extraction routines, and user interfaces.
- Datasets to serve as ground-truth for algorithm development and testing.
- Proof-of-principle integration of structural microconnectivity with functional data at the cellular, synaptic or neural system levels, for understanding whole circuits from micro- to macro-scales.

Dr. Mark Schnitzer indicated that this potential FOA may engage a very small body of researchers and wondered if the focus would be on electron microscopy (EM). Dr. Freund replied that they hope to reach the broader research community, which is why they removed "EM" from the original title. Dr. Huganir mentioned that there might be many computational individuals interested in this FOA.

Dr. Schnitzer suggested that this FOA could be written in a manner to help optical approaches advance to be competitive with connectomics. For instance, lower resolution light microscopy techniques have yet to achieve a resolution for imaging true synaptic contacts (like EM), but improvements might be made to the lower resolution technologies by combining them with optical labels, cell types, macromolecules, etc. to provide suitable pre- and post-synaptic markers that allow for mapping synaptic point-to-point contacts.

Dr. Eve Marder agreed with Dr. Schnitzer, and added that there are volumes of EM data that can be used and that while there is tremendous value in EM connectomics, high quality, high resolution light level could also be very useful. Dr. Schnitzer commented that using the light microscopy techniques would allow for multiple brains to be studied and not simply one mouse – to which Dr. Marder agreed completely. Dr. Marder asked if electrical synapses and gap junctions would be included, and Dr. Freund said that they can be incorporated in the announcement. ***The MCWG voted to approve this funding concept for a new Tools for Micro-connectomics FOA.***

3. Biophysics of Neuromodulation

Dr. Nick Langhals (NINDS) presented the third funding concept, "Biophysics of Neuromodulation" that aims to: 1. Understand the basic biophysics or "mechanisms of activation" of how modulating technologies used to probe neural dynamics affect cells, and 2. To sufficiently characterize, model, and validate the fields produced by neuromodulation technologies. The proposed FOA is supporting *BRAIN 2025* goals: Section III.4, p. 83 - "New and improved perturbation technologies suitable for controlling cells that have been specified by type, wiring, location, and other characteristics. Perturbation technologies in this context could include tools for stimulation, inhibition, or modulation that mimic natural activity, and could span optical, chemical, electromagnetic, biochemical, and other." This proposed FOA aligns with existing efforts in BRAIN, including: New Concept for Recording and Modulation (R21), New Tools/Optimization for Recording and Modulating Technologies (U01), Non-Invasive Neuromodulation – New Tools, Mechanism and Dose/Response (R01), and Next Generation Invasive Devices for Modulation in Human CNS (UG3/UH3).

Dr. Marder indicated two points of potential confusion, noting neuromodulation means different things to different communities. For instance, the cellular community might not understand this FOA. Additionally, when referring to studies in small models (e.g., slice preparations), the scientific community must consider whether the data that is gathered will generalize to other model systems (mouse, humans, etc.). Dr. Langhals thanked Dr. Marder for her points, and agreed that it is unclear how the data will scale/generalize, which further highlights the gaps in the field and how this FOA could help fill those gaps in knowledge. Dr. Holly Lisanby (NIMH) added that the community is currently implementing tools with an absence of knowledge of mechanisms at the biophysical level, so this FOA will help us learn from what we are currently funding today.

Dr. Larry Abbott mentioned that the current language suggests biophysics, but not systems-level, researchers, and he suggested that the language be revised to be more inclusive of different fields. Dr. Schnitzer agreed, pointing out that BRAIN is focused on circuitry and tools for stimulating circuits, yet this FOA seems distinct in the goal to understand differences between cell types and general application of field without regarding the specificity that can be achieved with current state-of-the-art tools and technology. Dr. Langhals answered that they are not trying to exclude specificity/micro-circuitry and/or

selective tool application, with Dr. Lisanby explaining that the intent is to avoid overlap with a pre-existing FOA for macro-circuits.

Dr. Gordon suggested the term "neurostimulation" might avoid the semantics issues that "neuromodulation" might cause. Dr. Marder acknowledged that, to her, it would be less confusing to use "neurostimulation" instead, or at least acknowledge the fact that certain researches might interpret something completely different depending on their expertise. She explained that researchers, for instance those who use optogenetics, need to include the right controls and measurements, and she was still cautious about the generalizability of the results. She can imagine several proposals coming into this FOA, having read it with very different optics, all with legitimate rationales. Dr. Landis suggested that program staff should consider these points and revise this concept. ***MCWG agreed to re-examine this funding concept at the next MCWG meeting in August.***

4. Brain-Behavior Quantification

Dr. Lisanby presented the fourth funding concept, "Brain-Behavior Quantification." Discovering how the brain produces behavior is a central theme in the *BRAIN 2025* report, and understanding the brain "at the speed of thought" requires matching the temporal resolutions of brain and behavioral measures. Currently, there is only one BRAIN-funded human project that integrates real-time behavioral measurement with simultaneous neural recording. The proposed FOA would be the first BRAIN FOA to focus on behavior and address this identified gap. The goals of the proposed FOA are:

- Develop, utilize, and link quantitative, temporally-dense behavioral measures to neural circuit activity.
- Establish linkages between behavioral methodologies and neural recording/stimulation technologies.
- Integrates behavior: real-time capture of temporal dynamics of behavior; brain-behavior linkage on the same time-scale; incorporates chronobiology and state-dependency; ability to interrogate circuit function via neuro-modulation technologies.

Dr. Lisanby explained that behavior quantification tools and measurements include motion sensing (GPS location, accelerometer, gyroscope, actigraphy), physiology (EEG, real-time fMRI, pupilometry, NIRS Smart-bandage), video sensing (facial expression, body movements, eye position), social/environmental sensing (call/texting frequency, vocal patterns, language environment analysis), and symptom assessment (symptoms at pre-determined intervals). She provided several examples of currently available tools, such as Google Watch for health metrics and 2D/3D video recordings for facial expressions used in autism research. Dr. Lisanby indicated that they are proposing a staged plan:

- Supplement (FY17): Encourage active BRAIN grantees to add these types of behavioral methodologies to existing studies via supplement requests.
- Meeting (FY17): Hold a webinar/workshop to bring the researchers that are involved in "deep phenotyping" and invasive human recordings into the same space.
- Release the Brain-Behavior Quantification Initiative FOA (FY18).

Dr. Rafael Yuste said that he was uncomfortable with this proposal, as well as the glial and neuromodulation proposals. He believes these proposals seem to be more incremental for what NIH can support, and that they might lose focus of the Initiative, which aims to build tools. The original vision of

the BRAIN Initiative was to be a "game changer" and – similar to physical sciences – to have large teams and cores, bringing other sciences into neuroscience to broaden perspectives. Specifically, he believes that the Brain-Behavior FOA is not right for the BRAIN Initiative. Dr. Lisanby agreed with Dr. Yuste in that BRAIN should attract innovators, but indicated that portfolio analyses showed only 1 grant in this area of research – a BRAIN grant. This FOA will be groundbreaking in that it will advance behavioral experiments to the state-of-the-art with the same temporal resolution as brain activity. The seventh priority area in the *BRAIN 2025* report is, "From BRAIN Initiative to the brain: Integrate new technological and conceptual approaches produced in goals [priority areas] #1-6 to discover how dynamic patterns of neural activity are transformed into cognition, emotion, perception, and action in health and disease." Dr. Lisanby maintained that we cannot achieve this goal unless we measure brain activity in conjunction with behavior, action, emotion, and perception.

Dr. James Eberwine mentioned that he believes that this concept is an appropriate use of BRAIN Initiative funds, but is concerned that aspects lack focus (e.g., privacy issues), suggested linking it to a neuroethics request for applications (RFA). Dr. Lisanby agreed and said they will associate this proposed FOA with a neuroethics RFA.

Dr. Schnitzer concurred with Dr. Yuste's remarks, in that this concept notably broadens the scope of BRAIN. He noted that Silicon Valley contains an active environment of start-ups and companies working on these issues, and wondered if this is work of the BRAIN Initiative or the NIH, broadly. All of these research topics are worthwhile, but determining whether or not they align with the BRAIN Initiative is the question.

Dr. Brad Hyman said that this proposal has the potential for making an enormous impact in the field and highlighted the idea that translating our understanding of circuits into human behavior is critical. This FOA would be transformative and include psychological studies, translational studies, and clinical trials – he believes this is a great proposal, and Dr. Hank Greely concurred. Dr. Landis suggested that they could move forward with the supplement and the workshop and bring the FOA proposal back to MCWG after being informed by these activities. ***The MCWG voted to approve the supplement and meeting for FY17 and to re-examine the funding concept for a Brain-Behavior Quantification FOA at a later date.***

The meeting proceeded in a closed session of MCWG and federal staff to discuss FY 2018 pay plans.