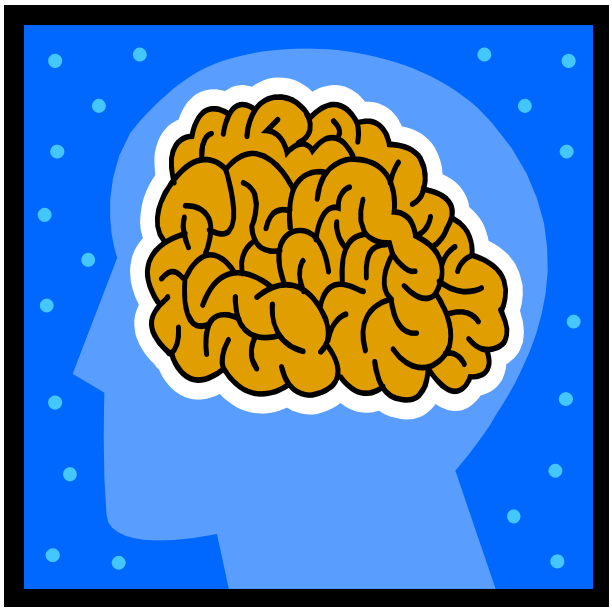
Physical and Mathematical Principles of Brain Structure and Function Workshop

Sponsored by the National Science Foundation and the Kavli Foundation

Holiday Inn Arlington at Ballston
Arlington, Virginia

May 5th to 7th, 2013

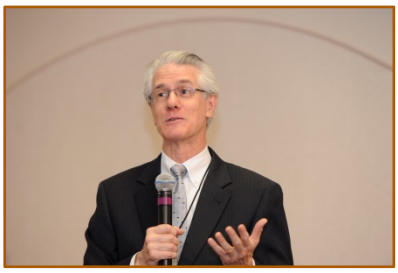


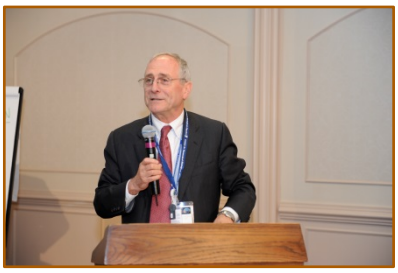
National Science Foundation
WHERE DISCOVERIES BEGIN

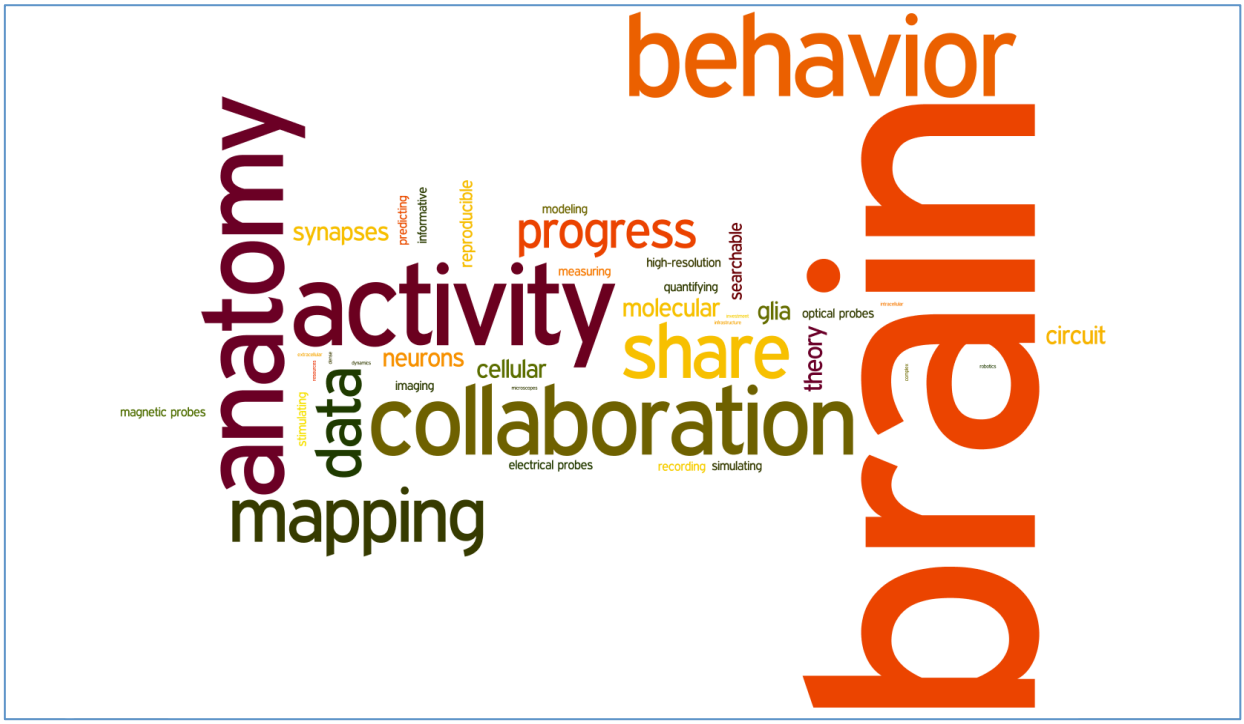
THE KAVLI FOUNDATION

A meeting report prepared by Parizad M. Bilimoria, Conte Center at Harvard University

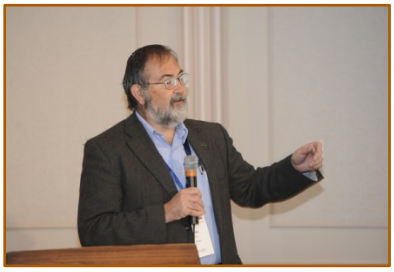
With rapporteurs Narayanan "Bobby" Kasthuri, Arjun Krishnaswamy, Vivek Venkatachalam, Yun Zhang, Bob Datta, Mala Murthy, Joshua T. Vogelstein, Daniel Colón-Ramos, Misha Ahrens, Marta Zlatic and Forrest Collman











The President of the United States recently announced a grand challenge for the scientific community, termed the BRAIN initiative (Brain Research through Advancing Innovative Neurotechnologies). The BRAIN initiative calls for historic investments in neuroscience research that "give scientists the tools they need to get a dynamic picture of the brain and better understand how we think, learn, and remember."[1]

Sponsored by the National Science Foundation and the Kavli Foundation, the Physical and Mathematical Principles of Brain Structure and Function Workshop held on May 5th, 6th and 7th, 2013, brought together over 100 leading neuroscientists to discuss the BRAIN initiative and identify a common set of priorities for researchers and funding agencies participating in this project.

All photographs courtesy of Rice University.
Word art created using www.wordle.net

TABLE OF CONTENTS

EXECUTIVE SUMMARY

On April 2, 2013, President Obama, building on earlier comments in his State of the Union address, announced a grand challenge for the scientific community termed the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative. This new 'big science' project calls for government agencies, private foundations and others to join hands for a historic investment in brain research—in many respects aiming to accomplish for neuroscience what the Human Genome Project did for genetics.

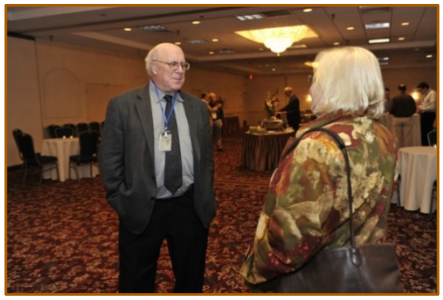
Soon after the President's announcement, on May 5th-7th 2013, the National Science Foundation and the Kavli Foundation jointly sponsored the *Physical and Mathematical Principles of Brain Structure and Function Workshop* in Arlington, VA. Bringing together over 100 esteemed neuroscientists, this workshop identified key priorities in basic neuroscience research and technology development that should be addressed in order to move forward with the BRAIN initiative's overarching goal of giving scientists "the tools they need to get a dynamic picture of the brain and better understand how we think, learn, and remember."[1]

The BRAIN initiative grew out of a proposal originally developed at a series of meetings sponsored by the Kavli and Gatsby Foundations and Allen Brain Institute, named the Brain Activity Map (BAM). The BAM proposal sought to map the activity patterns of all the brain's neurons, arguing that the emergent properties of neural circuits cannot be understood by recording from single neurons or small subsets of neurons alone.

The BRAIN initiative is essentially an expanded version of BAM, acknowledging that activity alone is not the answer to understanding how the brain works –rather, activity measurements must be placed in the context of structural and behavioral maps. What's more, there must be innovations in the sociology of science and infrastructure for data-sharing in addition to tool development.

To identify common priorities, scientists attending the current workshop were asked to submit short white papers describing what they each believe to be the most significant obstacle in neuroscience research today.





A group of rapporteurs reviewed these materials and organized the topics for discussion into nine categories, falling under five major thematic windows. Following two days of breakout sessions, a number of key aims were identified in each of the nine categories:

(i) Brain Structure

- High-Resolution Anatomy

(ii) Brain Activity

- Pan-Neuronal Recording using Electrical Probes
- Pan-Neuronal Recording using Optical and Magnetic Probes

(iii) Animal Behavior

- Quantifying and Simulating Behavior

(iv) Linking Brain Structure & Activity to Animal Behavior

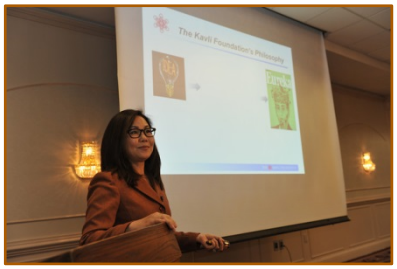
- Different Model Organisms
- Multiscale and Multimodal Approaches
- Theories of Brain Function

(v) Facilitating 'Big Science' in Brain Research

- Collecting, Curating and Disseminating data
- Research Systems, Funding and Incentives



EVOLUTION OF THE BRAIN INITIATIVE



Miyoung Chun, Kavli Foundation

- In September 2011, a workshop organized by the Kavli Foundation together with the Allen Brain Institute and Gatsby Charitable Foundation, *Opportunities at the Interface of Neuroscience and Nanoscience*, led to discussions regarding the need for large scale mapping of activity patterns in the brain, also known as "functional connectomics"

- Following this, a white paper was written by a small group of workshop participants and presented to NIH, DARPA and OSTP and an article describing the Brain Activity Map (BAM) project was published in *Neuron* in June 2012

- In his January 2013 State of the Union address, President Obama discussed the return on investment Americans have received from the Human Genome Project and alluded to funding a new, large-scale brain mapping project

- In March 2013, a Perspectives piece on the BAM project was published in *Science* and a detailed article on nanotools for neuroscience and the BAM project was published in *ACS Nano*, both by attendees of BAM-related workshops and meetings

- On April 2, 2013, President Obama formally announced the BRAIN Initiative at a White House press conference

- Since then the NIH has announced a BRAIN Working Group of the Advisory Committee to the Director, charged with seeking input from the scientific community at large and developing a final report on high-priorities areas for funding by June 2014

- On May 5-7th, 2013 the NSF and Kavli Foundation co-sponsored the *Physical and Mathematical Principles of Brain Structure and Function Workshop* to discuss priorities for the BRAIN initiative

- On May 13, 2013, leaders of the NIH published a PolicyForum article in *Science*, outlining the NIH's vision for the BRAIN initiative

- In August 2013, a Commentary summarizing the deliberations of the Physical and Mathematical Principles of Brain Structure and Function Workshop was published in *Nature Methods*

- On September 16, 2013, the NIH's BRAIN Working Group issued an interim report identifying high priority research areas that should be considered for BRAIN initiative funding in 2014

PRIORITIES FOR PROGRESS IN BRAIN SCIENCE

Prior to the *Physical and Mathematical Principles of Brain Structure and Function Workshop*, participants were asked to submit one page white papers describing what they felt were the major obstacles impeding progress in brain science today. Over 80 white papers addressing this weighty question were received. The rapporteurs then reviewed these papers and used them to develop topics of discussion for the workshop's breakout sessions, detailed below:

(i) Brain Structure

The human brain, with close to 100 billion neurons and trillions of synapses, is the most complex and least understood of all the organs in our bodies. While ailments affecting other parts of the body often leave recognizable signs of pathology, it is notoriously difficult to identify a structural basis for many common brain disorders, including neurodevelopmental or psychiatric disorders. This is because it is hard to understand what goes wrong in brain disorders when we do not even have high resolution structural information about the 'normal' brain.

Since the BRAIN initiative seeks to elucidate how we think, learn and remember—broadly speaking, how our brains function—the results of pan-neuronal recording experiments must be overlaid upon a high resolution physical map of the brain. Put another way, the meaning of patterns of activity in a circuit cannot be gleaned without simultaneously considering the patterns of connectivity underlying that circuit.

High-resolution anatomy

Attendees of this breakout session discussed the value of different scales and methodologies for anatomical investigations of the brain. The following key ideas emerged:

- Anatomical insights are needed at many different scales
    - At the synaptic level, key techniques include electron microscopy reconstructions, viral methods and light level techniques
    - At the cellular level, single cell transcriptomics, protein level descriptions, and the barcoding of individual neurons for sequencing may help identify and map the different cell types of the brain
    - At a broader scale—mapping connectivity between different brain regions—anterograde and retrograde tracers can be used
    - An alternative to these tracers is diffusion magnetic resonance imaging (dMRI), particularly useful for measuring connectivity in intact animals
- Insights from functional measurements can be enhanced by studying the activity between anatomically defined cells. Likewise, insights from connectivity measurements can be enhanced by studying the connections between functionally defined cells

- All levels of analysis would be well served by improvements in automation and high throughput techniques
- Currently there are many individual labs using technologies that they have customized and are unique to their location. More concerted efforts are needed to regularize anatomical studies so that data is easily transferrable and methods are reproducible

A number of big picture anatomy questions emerged as well:

- What scale is most important for understanding brain function?
- What is the definition of a cell type?
- How can we combine molecular data with functional signals obtained through neuroimaging?
- How can we ensure that glial cells are not left out of the effort to obtain high resolution anatomical data?
- How can we combine anatomical information across different scales and methods?
- Is it possible to use electron microscopy techniques to measure long range connections?
- Many structural measurements are not possible *in vivo*. Should this point be taken into consideration when deciding what experiments to conduct in model organisms, since the ultimate goal is to obtain high resolution anatomical information about the human brain?

While there was a diversity of opinion regarding specific methods and milestones to focus on, there was some consensus regarding the following technical recommendations:

- Consider making the reconstruction of a whole mouse brain with 20 nanometer isotropic resolution one of the milestones of the BRAIN initiative
- Do not forget the importance of the brain's myeloarchitecture—keep in mind what resolution is ideal for imaging white matter
- Try to distinguish excitatory versus inhibitory connections whenever possible
- Also try to overlay anatomic data with genomic data whenever possible
- Identify promoters unique to specific cell types, as these cell types can then be selectively targeted through optogenetics
- Employ confocal optical imaging to bridge the gap from EM to MRI
- Use diffusion spectrum imaging (DSI) over diffusion tensor imaging (DTI)

Summary

While attendees had a range of views regarding the best methods for anatomical studies, most agreed that tools for making synapse-level anatomical maps of the whole brain would be of tremendous value. After raw data of this type is acquired for model organisms, it could be made available online—so that the broader neuroscience community can contribute to the massive job of analyzing such data, and zoom in on a variety of different circuits of interest.

There was clear consensus that these anatomical maps would have considerably greater value if overlaid with molecular and functional information—yielding a rainbow per vowel, with data on cell and synapse type available for integration with data from activity maps.

MAJOR GOALS

- Synapse-level anatomical maps at the whole brain scale
  (20 nm isotropic resolution reconstruction of mouse brain could be a key milestone)
- Online resources that make raw anatomical data available to the entire community
- Multidimensional resources that allow investigators to overlay molecular and functional maps on top of the anatomical maps

(ii) Brain Activity

Electrical signals control the flow of information in the nervous system. On a fundamental level, neurons communicate with each other via action potentials, or quick bursts of activity in which the membrane potential of a neuron rises momentarily and then falls. At chemical synapses, such 'firing' of the presynaptic cell results in a release of neurotransmitter which then modulates the firing patterns of the postsynaptic cell. On a much broader scale, there are entire neuronal ensembles in the cortex that display synchronized oscillations in their firing patterns, with different frequencies being signatures for different states of sleep or wakefulness.

Neuroscientists have gained some understanding of the electrical dynamics between pairs of connected neurons using physiological methods and, working at much broader scales, the dynamics of activity in different brain regions using functional neuroimaging. However, it remains difficult to simultaneously record from large numbers of neurons. The BRAIN initiative aims to address this problem by fostering innovations in electrical, optical and magnetic approaches to pan-neuronal recording. This is important because elucidating the emergent properties of circuits is thought to be central to understanding brain function.

Pan-neuronal recording using electrical probes

Attendees of this breakout session discussed the purpose of improving pan-neuronal recording techniques that utilize electrical probes, as well as some strategies for making the desired improvements. The following are some key questions that emerged:

- Currently we can record from hundreds, possibly even thousands of neurons. How can we move towards recording from even more neurons simultaneously?
  - Need advancements in materials sciences, engineering
  - Consider collaborations with industry

- Why do this? What is the ideal number of neurons we need to record from at the same time to understand the emergent properties of various neural circuits?
- What type of damage is induced in brains when long term recordings are carried out? Is there a way to ameliorate this damage?
- What is the role of electrical probes as optical probes become more and more prevalent?
- What lessons have been learned from the prospect of pan-neuronal recordings of activity in C. elegans, where all 302 neurons have been identified?
- How might advances in electrical probes lead to improvements in therapies for neurological conditions?
    - Electrical probes are not just for recording and studying endogenous patterns of neural activity. They can be used to stimulate neural activity in ways that restore functionality to disordered or damaged circuits
    - People with hard to treat depression or amputated limbs may benefit, for instance, if probes were:
        - Smaller and denser
        - Less likely to cause tissue damage
        - More resilient to biologically-induced decay
        - Designed for use with easier—maybe wireless—forms of telemetry

Summary

Attendees considered multiple types of electrical dynamics in the brain, including stimulus driven vs. spontaneous neural activity and spatially localized vs. widely distributed neural activity. The major challenges in electrical recordings fell into three categories: (1) need to reduce invasiveness and increase durability of probe arrays, (2) need to access several brain regions at the same time, and (3) need to standardize and streamline experiments.

A key point of interest in terms of therapeutics was the idea that improvements in electrical probes could be used in deep brain stimulation protocols and neural prosthetics.

MAJOR GOALS

- Electrode arrays that are denser, less invasive and more durable
- Distributed methods of recording that allow researchers to simultaneously measure neural activities in many different brain regions, each with single cell resolution
- Automated methods (e.g., robotics) to perform these experiments in a reproducible way from animal to animal and lab to lab

Pan-neuronal recording using optical and magnetic probes

In addition to directly measuring changes in current or voltage using electrical probes, neuroscientists employ optical and magnetic probes to assess changes in neural activity in other ways. Attendees of this breakout session discussed the potential to improve pan-neuronal recording techniques involving these probes, focusing on the following key questions and strategies:

- What do we expect to gain from pan-neuronal recordings that use optical and magnetic probes?
    - Is the main aim to record from "all neurons" at the same time?
    - If so, what exactly does this mean? What is the minimal unit of neurons needed to understand the emergent properties of a neural circuit?
    - Optical and magnetic probes are generally considered 'non-invasive' – but what exactly does this mean?
- We may need different probes for experiments conducted at different scales, as there is likely to be a tradeoff between resolution and speed
- We may need to develop new probes
    - Quantum dots don't bleach, but they are hard to get into cells
    - Consider new probes that interact with magnetic fields or sound waves? Unexplored spectral regions? Metalloproteases?
    - Consider new sensors as well (think about voltage and speed of sensors)
- We may also need to develop new imaging technologies
    - Is there a way to obtain higher resolution information from non-invasive imaging techniques such as PET or MRI scans?
    - Deeper imaging is possible with three photon technology, at approximately two millimeters depth – are there new approaches that would allow even deeper imaging?
    - How fast do we need to image activity? Maybe consider selective plane illumination microscopy (SPIM)
    - What is the role of connectivity in informing imaging across dispersed regions?

Summary

Attendees concluded that it would be beneficial to develop a wide range of electromagnetic probes, from multicolor fluorescent voltage indicators to probes for comprehensively identifying neurochemical or metabolic changes or conducting magnetic imaging in humans. It was widely agreed that developments in probe technology should be accompanied by advances in microscopy—allowing faster, deeper tissue imaging in a wide range of model organisms.

Ultimately, the goal of the activity arm of the BRAIN initiative is to observe the input-output relationships of neural circuits at multiple spatiotemporal scales. Optical approaches offer the advantage of naturally linking functional measurements to other areas of interest, such as the precise spatial location of specific activities, the connectivity of the neurons involved, and/or their molecular identities.

MAJOR GOALS

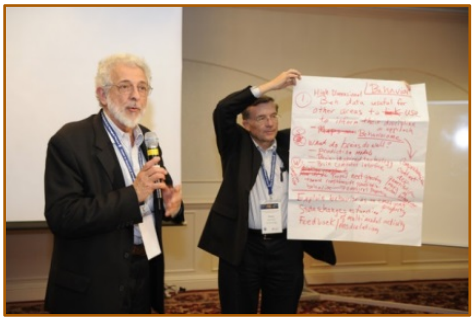
- A wide range of new or improved optical and magnetic probes that record brain activity across all relevant dimensions
- New microscopes that enable faster and deeper brain imaging and can be used in a wide range of model organisms, from nematodes to primates

(iii) Animal Behavior

The quest to understand human behavior is the fundamental driving force behind basic neuroscience research. Questions about the morphology and molecular identities of neurons, the organization of synapses, and patterns of spiking and circuit dynamics are ultimately all part of bigger inquiries—such as the desire to understand why we think, feel and act the way we do.

Yet, unlike anatomy and activity, behavior remains hard to study in a precise manner, with thorough multivariate quantifications and simulations. Additionally, it is challenging to ensure that studies of animal behavior in the laboratory are yielding insights relevant to natural behaviors. Therefore advances in the study of animal behavior are likely to plan a central role in the BRAIN initiative, and essentially in any effort to understand how the brain functions.

Quantifying and simulating behavior



Attendees of this breakout session discussed the value of advancing behavioral analysis as part of the BRAIN initiative—complementing the high resolution anatomy and activity mapping projects. The following are some of the key ideas and questions stemming from this discussion:

- Why, from the perspective of better understanding how neural circuits work, is behavioral analysis so important?
    - Behavior is the final common output of the nervous system and its circuits
    - It is also a reflection of an organism's internal state (taking into account modulators that may regulate how the same circuit functions in different circumstances)
    - Behavioral analysis can help us understand circuit diversity across phyla
    - The reduction in dimensionality from circuits to behaviors could facilitate modeling
- What is the taxonomy of behavior?
    - Innate vs. learned behaviors
    - Naturalistic vs. artificial behaviors
        - Active sensing of natural stimuli vs. passive sensing of stimuli presented in lab
    - Trained vs. "over-trained" behaviors

- What are some key parameters to measure when characterizing common animal behaviors in the lab?
    - Muscle activity (kinematics, dynamics)
    - Motion (egocentric and allocentric, without consideration of actuators)
    - Precision of behavioral control
- Style of reporting is also an important consideration –in experiments with humans in particular, there can be cognitive or perceptual reports of behavior, which are very different from measurements of muscle activity or motion (essentially, more subjective)
- The ideal measurement of behavior might have the following properties:
    - Objective
    - Comprehensive
    - Long-term
    - Conducted at multiple timescales
    - Respect for context
    - Consideration of prior history
- Put another way, we want to bring the precision of circuit analysis to behavioral analysis… how exactly can we hope to achieve this?
    - Advancements in machine vision
    - Advancements in statistical methods, data mining techniques
    - Using both supervised and unsupervised classification methods
    - Integrating engineering and computer science approaches into biological labs
    - Collaborations between academia and industry
- Much of this is already happening, as part of the Human Behaviorome project

Summary

Behavior is the final output of the nervous system, representing a drastic reduction in dimensionality that can be measured via video, audio and muscle recordings. Behavior should be studied at high resolution, on multiple spatiotemporal scales and in ethologically natural, yet dynamically controllable settings. One goal is to develop large databases of context-specific behavioral reperotoires for various model organisms. Unsupervised machine vision and data mining methods will then hopefully reveal quantitative links between behaviors and their underlying neural circuits.

MAJOR GOALS

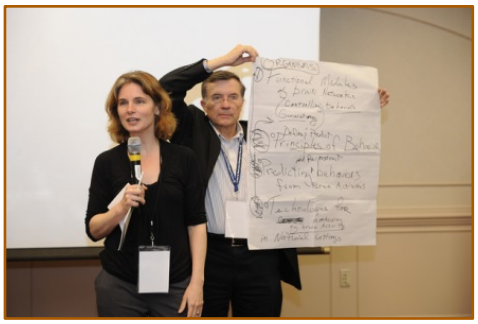
- Advances in unsupervised machine vision, machine learning and data collection methods that allow researchers to characterize whole animal behavior using video, audio and muscle recordings
- Multilevel methods to link brain dynamics with behavioral dynamics
- To generate these tools, increased involvement of engineering, computer science, mathematics and statistics in behavioral studies

(iv) Linking Brain Structure and Activity to Animal Behavior

Just as patterns of activity must be interpreted in the context of a physical map of the brain, both the activity and anatomy of neural circuits must be interpreted in the context of animal behavior if we hope to truly improve our understanding of brain function. Choosing 'simple' model organisms can facilitate this sort of integration, making it feasible to work across multiple scales and experimental modalities.

It is also important to develop a theoretical framework for working with the data that emerges from the three different worlds of anatomy, activity and behavior. Studies in model organisms that reveal the smallest units of the nervous system required for particular behaviors can provide building blocks for elucidating principles of neural circuits that may be broadly applicable. These observations, coupled with what we learn about the emergent properties of neural circuits using pan-neuronal recordings, can generate theories of brain function, which can then be used to make and test predictions regarding the convergence of structure, activity and behavior—and then the cycle continues, with the results of such efforts further refining the theories and allowing for new predictions.

Different Model Organisms



Model organisms allow researchers to glean insights into the inner workings of the nervous system in a manner that is simply not possible in human studies. In this breakout session, attendees reviewed a variety of ways in which the choice of model organism impacts data collection and utility:

- It is extremely important to fund studies of simpler model organisms (such as nematodes, fruit flies, zebrafish larvae, rodents, and birds) because:
    - Information gleaned from studies of simple model organisms can serve as building blocks for understanding brains in more complex organisms
    - Studies in simple model systems can reveal the smallest units of the nervous system—be it numbers of neurons or patterns of activity—required for particular behaviors
    - Certain model organisms offer incredible optical access. For instance, in C. elegans or zebrafish one can use fluorescent labeling methods to watch the dynamics of living nervous systems in real time
    - Lots of excellent reagents are already available, and there is potential to develop low cost methods for circuit reconstruction
- Studies of non-traditional model systems should be funded too, especially because there are now technologies that allow the use of genetically-encoded sensors in organisms that are not yet genetically well-characterized
    - For instance, transcription activator-like effector nucleases (TALENs) and clustered regularly interspaced short palindromic repeats (CRISPRs)
- Despite the value of studying simpler model organisms, there remain a number of questions and cautions to keep in mind:

- How well will findings in simpler systems translate to more complex systems?
- How challenging will it be to move technologies across systems?
- Even the simple model organisms can be surprisingly complex

Summary

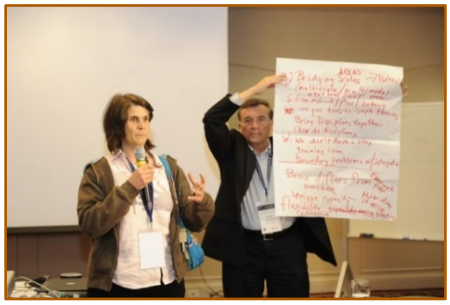
Attendees agreed that research on 'simple' model systems should be encouraged under the BRAIN initiative, as these systems offer the unique opportunity to directly link brain activity and wiring diagrams to behavioral outputs, across a range of experimental paradigms. To study these systems more fully, we should encourage the development of methods that permit remote monitoring of animal behavior under naturalistic conditions. Also, we should recognize that principles of neural circuit function in model organisms may represent "functional modules" for behavior that are conserved across species.

Finally, and perhaps most importantly, we should appreciate that research in model organisms provides the unique opportunity to manipulate neural activity patterns and subsequently test the resulting effects on behavior—thereby establishing causal relationships between brain activity and behavior.

MAJOR GOALS

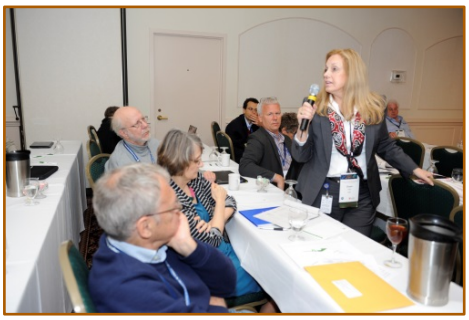
- Increased nervous system research in model organisms like nematodes, fruit flies, zebrafish larvae, rodents and birds

Multiscale and Multimodal Approaches



To understand how neuronal connectivity and activity patterns underlie specific behaviors, it is necessary to work both vertically and horizontally—connecting information at various scales within each sphere of study and also across different spheres. Attendees of this breakout session discussed the following key ideas and questions surrounding multiscale and multimodal approaches:

- The motivating force for multiscale approaches is being able to explain what happens at one level of brain function in terms of what happens in the levels below, and through the integration of data across scales eventually be able to manipulate the brain at lower levels and make accurate predictions about the impact on upper level phenomena. Examples of the different scales include:
    - Behavioral – For example, if we were interested in understanding what happens when a person catches a ball, at the behavioral level we'd want to make high resolution measurements of their movements in three dimensional space, with as fine a time scale as possible.



- Circuit – We'd also need to understand the morphology and activity patterns of a variety of interrelated circuits, from those in the visual system that allow the person to see the ball and track its path to the intracortical circuits that process information from visual areas and activate motor areas in response, and then the pathways carrying signals from the motor cortex down to individual muscles.
- Cellular – To understand each of these circuits, we'd need to know their cellular composition—what different types of neurons and glial cells they contain. And then, for each cell itself, we'd need to know its connectivity with other cells, its morphology (for neurons, the patterns of axon and dendrite arborizations) and its physiological properties (baseline activity, firing patterns in response to presynaptic inputs, forms of cellular plasticity exhibited etc).
- Synaptic - To understand each neuron's output, we'd need to know the number and type of synapses made onto that neuron (whether they are electrical or chemical synapses, excitatory or inhibitory, dendritic or somatic, etc), as well as the relative strength of each synapse.
- Molecular – To understand how a specific synapse works, we'd need to know what neurotransmitter receptors and ion channels are present, the kinetics of their activation, and what molecular trafficking events and transcriptional, translational or posttranslational changes ensue in response to synaptic activity.

- Multiscale integration can be pursued using both bottom-up and top-down approaches at the same time
- Beyond conducting experiments at multiple scales, it is important also to create theories and models that extend across levels
  - Computational neuroscience is thus vital to the BRAIN initiative
  - How do we know when we're 'done'?
    - When we have models with predictable power and testable hypotheses
    - When we can manipulate one level and have predictable effects on others
    - When we can design bio-inspired devices
- Most likely one of the greatest difficulties will be the black box between neuronal population dynamics and cognitive function
- Within the sphere of human physiology, where there are so many different gradations of spatial and temporal resolution, now may be the time to focus on mesoscopic levels of analysis—methods that fill the void between focused microelectrode recordings and broader scale methods such as EEG, fMRI, PET and lesion studies

- The motivating force for multimodal approaches is the idea that the greatest progress can be achieved in systems where different kinds of information can be combined. Examples include:
    - Genetically defined cell types with known transcriptomes
    - Detailed knowledge of the morphology of various circuit elements, and the connectivity patterns between these circuit elements
    - Genetic tools that allow manipulation of individual circuit elements
    - Precise, high-dimensional behavioral classification
    - Activity patterns of identifiable cell types in freely behaving animals
    - Models with predictive power and clearly testable predictions
- Ideal model systems for multimodal approaches include C. elegans, Drosophila, leech, and defined modules of the vertebrate nervous system (such as amygdala, cortical column, central pattern generator in spinal cord)
- Collaboration across labs is vital. It is unlikely that one lab alone will possess expertise in all relevant modalities
- The hope is that many of the principles discovered in the 'simple' model systems ideal for multimodal approaches will be conserved in more complex systems
- In addition to integrating data across different scales and modalities for each organism, and across the various model organisms, we must strengthen efforts to bridge the divide between animal and human studies

Summary

The ideal 'big brain' dataset includes: (1) morphological and molecular characterization of circuit elements, (2) connectivity patterns of the circuit elements, and (3) activity patterns of a large portion of identifiable neurons and synapses within the circuit, correlated with (4) high resolution measurements of behavioral output.

MAJOR GOALS

- Approaches that enable researchers to acquire datasets on the anatomy of brain circuits, their molecular makeup and their dynamical activities during behavior in naturalistic settings—all in the same model organism
- Development of a theoretical and computational framework that bridges levels from molecules to cells, cell to circuits, circuits to activity patterns, and ultimately activity patterns to behavior
- Based on this framework, the ability to predict the effects of nervous system manipulations at any level (molecular, cellular or circuit) on animal behavior

Theories of Brain Function

The goals of the BRAIN initiative cannot be met by collecting data alone, no matter how voluminous or multifaceted the data is. To understand how the brain functions, researchers must be able to build and test theories based on the data gathered. Attendees of this breakout session discussed the following ideas regarding the role of theoretical neuroscience in the BRAIN initiative:

- Theoretical neuroscientists seek to understand how the activity patterns of groups of neurons arise, and how these patterns relate to behavior
- There are two main flows in theoretical work:
    - Using theory to construct experiments (theory → data)
    - Using experiments to construct theories (data → theory)
- There are many different fields involved in constructing theories:
    - Engineering (e.g. control theory)
    - Physics (e.g. statistical physics)
    - Statistics (e.g. theories of wiring)
- One important point to consider when constructing models is the difference in dimensionality between neuronal activity and animal behavior—at present, activity is measured in many more dimensions than behavior
- Experiments examining links between neuronal activity and connectivity are relatively 'straightforward.' Theoretical work linking patterns of neuronal activity to neural codes is 'good enough.' Connecting theoretical work on neural codes to network-level theories, on the other hand, remains a significant challenge
- To bridge the gaps between theories, simulations and data, we need better statistical characterization of the data (one needs to be able to take the results of a simulation and quantify how well they fit to the actual biological data)

Summary

Attendees agreed that the need to discover principles of neural computation is one of the biggest challenges in neuroscience today, and advances in engineering, physics, statistics and mathematics will be essential for tackling this challenge. The future of neuroscience has a distinct role for professional theorists who will work at many levels of inquiry, from building detailed computer simulators of brain activity to constructing high-level principles of neural structure and dynamics.

MAJOR GOALS

- Theories of dynamical systems constrained by experimental data sets
- Theories of biological computation, perhaps inspired by computer science

(v) Facilitating 'Big Science' in Brain Research

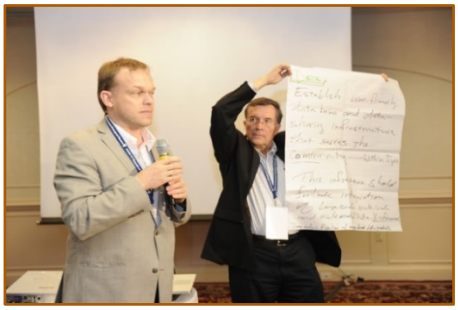
The aims of the BRAIN initiative are ambitious and multifaceted. Putting together the priorities detailed in many of the breakout sessions above, these aims would be:

(1) To map patterns of connectivity across the brain,
(2) To map the activity of all the brain's neurons,
(3) To be able to quantify and simulate a large array of animal behaviors, and
(4) Finally, to build bridges between and integrate these three spheres of research, with theoretical as well as experimental work.

Considering these goals, the BRAIN initiative will most certainly produce vast—even unprecedented—amounts of data. Ensuring that this data is collected in standardized formats and made freely available and broadly analyzable will be critical to the initiative's progress. It's not just having sequenced the human genome that has revolutionized genetics—it's the fact that sequence data is publicly available and relatively easy to tap into when searching for variants associated with particular traits or medical conditions that has truly changed the field.

Beyond organization and accessibility of data, the research systems, funding and incentives in place for the BRAIN initiative will be intmately tied to the project's health and success. In order to collaborate on a large scale—freely sharing results, taking risks, thinking big and crossing the traditional boundaries of their disciplines—neuroscientists need innovations and improvements in research infrastructure, grant awarding mechanisms and career opportunities as much as they need new experimental tools.

Collecting, curating and disseminating data



Attendees of this breakout session outlined the needs and challenges related to managing the data deluge expected to arise from the BRAIN initiative:

- Sharing data on a large scale, and creating the infrastructure to do so, is absolutely essential. As one attendee said, *"To collect data is heroic; to share data is divine."* Or, put another amusing way, *"Share until it hurts"*
- Neuroscientists need to develop scalable software and hardware systems that incentivize and support data sharing
- A number of challenges are involved:
    - Protecting young investigators who share data—making sure they receive credit in ways that matter, such as hires and grants
    - Storing and sharing data in formats amenable to diverse analyses
    - Facilitating stastical analyses on data-intensive computer clusters
    - Integrating data across scales and modalities
    - Managing both raw and derived data, from multiple species
    - Ensuring that databases can be easily searched

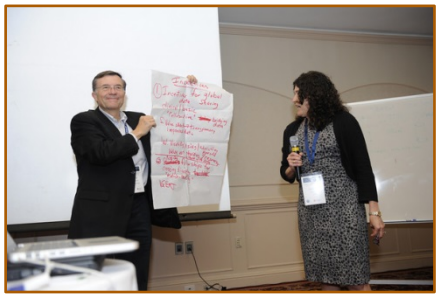
Summary

There was a strong consensus among attendees that there is a pressing need to establish a user-friendly infrastructure for sharing, processing, and analyzing 'big brain' data—hopefully ready to serve the greater scientific community within five years.

MAJOR GOALS

- Investment in information theories that link together the complex web of data describing brain structure, brain function and animal behavior
- Cybernetics infrastructure that makes these data reproducible, searchable and shareable across the scientific community

Research Systems, Funding and Incentives



Attendees of this breakout session discussed the following needs and solutions regarding research systems, funding and incentives for the BRAIN initiative:

- Deciding what areas of brain research to prioritize funding-wise is critical in moving forward with the BRAIN initiative
- The full set of ideas that emanated from this Workshop is extensive, and important decisions must be made to prioritize these goals within the context of finite resources by continuing to engage the scientific community
- Encouraging younger, less established principal investigators is essential—so funding agencies should offer more seed grants
- Funding for risky projects must also be increased
- Individuals with expertise in quantiative studies, including those trained in mathetmatics, physics and computer science, must be recruited for BRAIN projects. Ways to do this include:
    - Designing nationally-available online courses in relevant areas
    - Providing multi-disciplinary training and funding education for 'hybrid talents,' through more programs like the Integrative Graduate Education and Research Traineeship (IGERT)
    - Making career opportunities in neuroscience known to students trained in quantitative fields (this is not common at the moment, according to at least one attendee's personal experience)
- Sharing data is a cultural as well as computer systems issue. We must train neuroscientists to think in terms of their data being reproducible and useable by others, even accessible by

machines when possible. Also, data deposits should be obligatory and linked to publication in major scientific journals

- We need to address worries regarding the BRAIN initiative's impact on smaller, investigator-initiated neuroscience projects and programs

Summary

Attendees felt that more financial and professional incentives could be established at the laboratory, institutional and agency levels to promote data and code sharing practices. They also agreed that more training to support cross-disciplinary endeavors (especially related to quantiative methods) – via online courses and summer workshops, for example – would accelerate brain research.

MAJOR GOALS

- Increased data and code sharing (through mechanisms that protect young as well as established investigators)
- Enhanced cross-disciplinary training opportunities, perhaps via summer workshops and online courses
- Genuine, deep-seated collaborations between laboratories in different disciplines

WORDS OF INSPIRATION AND CAUTION

Huda Zoghbi,
Baylor College of Medicine/HHMI

In addition to the breakout sessions and white paper discussions that comprised the majority of the workshop, words of inspiration and caution were formally offered by scientific leaders from various disciplines. Neurobiologist Huda Zoghbi (Baylor College of Medicine/HHMI) delivered the opening address, followed by perspectives from chemist George Whitesides (Harvard University), physicist Robert Laughlin (Stanford University), and biophysicist William Bialek (Princeton University). The areas discussed included lessons from the Human Genome Project and 'big science' ventures in other fields, the sociology of collaborative science, and the value of and best strategies for engaging the public. A number of these themes resonated throughout the meeting and were discussed informally in many of the breakout sessions as well. The following are some key points of advice that repeatedly emerged in these discussions:

- Think carefully about the best way to share problems and progress in brain science with non-experts. Make sure that the general public understands why the BRAIN initiative is important, and is kept abreast of advances along the way
- Set clear goals, with both long-term and short-term milestones or 'deliverables'
- Don't overpromise results, especially with regard to treatments for brain diseases
- Openly share data on the web as soon as it is available and organize it in user-friendly databases that make it easy for individual laboratories to deposit, search, download, or integrate information
- Foster cross-talk between government funding agencies and private foundations, and academia and industry

George Whitesides,
Harvard University

- Involve experts from a diverse range of fields, including computer scientists, physicists, mathematicians, engineers and others outside of traditional life science departments
- Remember that the training, development and funding of young investigators is absolutely vital to the success of both this initiative and science in general
- Guard against the tendency for one research paradigm to dominate over others
- Don't forget that the brain includes a diverse array of glial cells in addition to neurons

CONCLUSIONS

The BRAIN initiative calls for historic investments in collaborative neuroscience research and tool development that ultimately seek to advance our understanding of the activity, structure and function of the human brain. The Physical and Mathematical Principles of Brain Structure and Function Workshop brought leading neuroscientists from across the country together to share and synthesize their visions for this initiative. The following major priorities in five thematic areas were identified:

(i) Brain Structure

High-Resolution Anatomy

- Synapse level anatomic maps at the whole brain scale, perhaps with a key milestone being the reconstruction of a whole mouse brain at 20 nm isotropic resolution

(ii) Brain Activity

Pan-Neuronal Recording using Electrical Probes

- Electrode arrays that are denser, less invasive and more durable, coupled with distributed methods of recording that allow simultaneous measurements from different brain regions

Pan-Neuronal Recording using Optical and Magnetic Probes

- A variety of new or improved optical and magnetic probes
- New microscopes that enable faster and deeper brain imaging

(iii) Animal Behavior

Quantifying and Simulating Behavior

- Unsupervised machine vision, machine learning and data collection methods that allow researchers to objectively and repeatedly characterize whole animal behavior

(iv) Linking Brain Structure & Activity to Animal Behavior

Different Model Organisms

- Increased investment in model organisms like nematodes, fruit flies, zebrafish larvae, rodents and birds

Multiscale and Multimodal Approaches

- Approaches that enable researchers to integrate anatomical, molecular, behavioral and electrophysiological data sets

Theories of Brain Function

- Theories of dynamical systems constrained by experimental data sets
- Theories of biological computation, perhaps inspired by computer science

(v) Facilitating 'Big Science' in Brain Research

Collecting, Curating and Disseminating Data

- Investment in information theories that link together structural, functional and behavioral data
- Cybernetics infrastructure that makes these data reproducible, searchable and shareable

Research Systems, Funding and Incentives

- Increased data and code sharing
- Mechanisms to protect young investigators and encourage taking risks
- Enhanced cross-disciplinary training opportunities

APPENDIX 1: REFERENCES

1. BRAIN initiative infographic on White House website. Accessed 06 June 2013.
http://www.whitehouse.gov/infographics/brain-initiative

All photographs courtesy of Rice University.

APPENDIX 2: WORKSHOP AGENDA

Sunday, May 5th

5:00-8:00pm **Registration and Reception**
The Holiday Inn- Arlington at Ballston
4610 N Fairfax Drive
Arlington, VA 22203

Monday, May 6th

8:30-8:45am **Introduction**
Denise Caldwell, NSF, Division Director of the Physics Division in MPS

8:45-9:00am **Welcome**
F. Fleming Crim, NSF, Assistant Director, Mathematical and Physical Sciences Directorate

9:00-9:15am **Remarks**
Miyoung Chun, Kavli Foundation

9:15-9:45am **Opening Address**
Huda Zoghbi, Baylor College of Medicine/HHMI

9:45-11:00am **Overview of the Submitted Materials**
Session Chair, Herbert Levine, Rice University

11:00-11:30am Coffee break

11:30-12:10pm **Overview of the Submitted Materials (continued)**

12:10-12:30pm **Talk: Perspective, George Whitesides, Harvard University**

12:30-2:00pm Lunch

2:00-5:00pm **Breakout Sessions**

5:00-5:30pm Coffee break

5:30-6:30pm **Breakout Session Reports by Rapporteurs**

6:30pm **Dinner & Speaker**
Robert Laughlin, Stanford University
The Westin Arlington Gateway Hotel
801 N. Glebe Road
Arlington, VA

Tuesday, May 7th

9:00am-9:30 **Opening Remarks**
William Bialek, Princeton University

9:30-12:30pm **Breakout Sessions**

12:30-1:30pm Lunch

1:30-2:30pm **Synthesis and Discussion**

2:30-3:00pm Coffee break

3:00-4:00pm **Synthesis and Discussion**

4:00-4:15pm **Closing Remarks**
John C. Wingfield, NSF, Assistant Director of the Biological Sciences Directorate

APPENDIX 3: WORKSHOP ORGANIZERS AND ATTENDEES

Workshop Organizers

Winfried Denk, Max Planck Institute for Medical Research

Herbert Levine, Rice University

Partha Mitra, Cold Spring Harbor Laboratory

Aravi Samuel, Harvard University

Terry Sejnowskil, The Salk Institute

Van Wedeen, Harvard Medical School

Workshop Sponsor Contacts

Krastan B. Blagoev, NSF/Physics of Living Systems Program

James Deshler, NSF/Integrative Organismal Systems, Neural Systems Cluster

Diane Witt, NSF/Integrative Organismal Systems, Neural Systems Cluster

Miyoung Chun, The Kavli Foundation

Workshop Coordinator

Sara Bradley

Rapporteurs

Narayanan “Bobby” Kasthuri, Harvard University

Arjun Krishnaswamy, Harvard University

Vivek Venkatachalam, Harvard University

Yun Zhang, Harvard University

Bob Datta, Harvard University

Mala Murthy, Princeton University

Joshua T. Vogelstein, Duke University

Daniel Colón-Ramos, Yale University

Misha Ahrens, Janelia Farm/HHMI

Marta Zlatic, Janelia Farm/HHMI

Forrest Collman, Stanford University

Attendees

Elad Alon, UC Berkeley

David Anderson, Caltech/HHMI

Richard Andersen, Caltech

Dora Angelaki, Baylor College of Medicine

Giorgio Ascoli, George Mason University

Peter Bandettini, NIMH

Helen Barbas, Boston University

Cori Bargmann, Rockefeller University

Peter Basser, NIH

Eshel Ben Jacob, Tel Aviv University/Rice University

Ted Berger, USC

Bill Bialek, Princeton University

Ed Boyden, MIT

Kevin Briggman, NIH

Emery Brown, Harvard Medical School/MIT

Randal Burns, Johns Hopkins University

Gyorgy Buzsaki, NYU

Carmen Canavier, LSU

Jose Carmena, UC Berkeley

Ted Carnevale, Yale

Catherine Carr, UMD-College Park

Edward Chang, UCSF

EJ Chichilnisky, Salk

Mitya Chklovskii, Janelia Farm/HHMI

George Church, Harvard University

Tom Clandinin, Stanford University

Avis Cohen, UMD-College Park

Daniel Colon-Ramos, Yale University

Carina Curto, University of NE-Lincoln

Karl Deisseroth, Stanford University

Winfried Denk, Max Planck

James DiCarlo, MIT

John Donoghue, Brown University

John Doyle, Caltech

Florian Engert, Harvard University

Bard Ermentrout, University of Pittsburgh

Michale Fee, MIT

Joe Fetcho, Cornell University

David Fitzpatrick, Max Planck-Florida

Ralph Greenspan, UCSD

Sten Grillner, Karolinska Institute

Melina Hale, University of Chicago

Matti Hamalainen, Harvard Medical School/MGH

Moritz Helmstaedter, Max Planck

Harald Hess, Janelia Farm/HHMI

Sean Hill, INCF

Vladimir Itskov, University of NE-Lincoln

Harvey Karten, UCSD

David Kleinfeld, UCSD

Nancy Kopell, Boston University

Alan Koretsky, NIH

Bill Kristan, UCSD

Robert Laughlin, Stanford University

Herbert Levine, Rice University

Anthony Lewis, Qualcomm

Jeff Lichtman, Harvard University

Loren Looger, Janelia Farm/HHMI

Daniel Lopez, Argonne National Labs

Eduardo Macagno, UCSD

Peter MacLeish, Morehouse

Michel Maharbiz, UC Berkeley

Eve Marder, Brandeis University

Maryann Martone, UCSD

Mayank Mehta, UCLA

Karen Mesce, University of Minnesota

Stefan Mihalas, Allen Institute for Brain Science

Partha Mitra, Cold Spring Harbor Laboratory

Michael Naughton, Boston College

Bill Newsome, Stanford University

John Ngai, UC Berkeley

Richard Normann, University of Utah

Arto Nurmikko, Brown University

Yoshio Okada, Harvard Medical School

Bruno Olshausen, UC Berkeley

Hongkun Park, Harvard University

Vincent Pieribone, Yale

Jonathan Pollock, NIH

Raj Rao, University of Washington

Bruce Rosen, Harvard Medical School/MGH

Douglas Rosene, Boston University

Michael Roukes, Caltech

Todd Sacktor, SUNY Downstate

Aravi Samuel, Harvard University

Josh Sanes, Harvard University

Terry Sejnowski, UCSD

Michael Shadlen, Columbia University

Mikhail Shapiro, UC-Berkeley

Eric Shea-Brown, University of Washington

Ken Shepard, Columbia University

Stephen Smith, Stanford University

Sara Solla, Northwestern

Fritz Sommer, UC Berkeley

Charles Stevens, UCSD

Michael Stryker, UCSF

David Tank, Princeton University

Wilson Truccolo, Brown University

Doris Tsao, Cal Tech

Robert Turner, Max Planck

Kamil Ugurbill, University of Minnesota

David Van Essen, WA University, St. Louis

Van Wedeen, Harvard Medical School

Paul Weiss, UCLA

George Whitesides, Harvard University

Rachel Wilson, Harvard Medical School

Chris Xu, Cornell University

Rafael Yuste, Columbia University

Tingting Zhang, University of Virginia

Huda Zoghbi, Baylor College of Medicine

National Science Foundation

Mary Ann Asson-Bates

Krastan Blagoev

Denise Caldwell

Clark Cooper

F. Fleming Crim

James Deshler

Mary Ann Horn

Bill Miller

Michael Mishkind

Kamal Shukla

Greg Warr

Ken Whang

John C. Wingfield

Diane Witt

The Kavli Foundation

Miyoung Chun

Chris Martin

Nick Pici

National Institutes of Health

Thomas R. Insel, Director of NIMH

Story C. Landis, Director of NINDS

Gregory Farber, NIMH

Marlene Guzman, NIMH

Kathy Hudson, NIH

Lyric Jorgenson, NIH

Kip Ludwig, NIH

Ned Talley, NINDS

Government Representatives

Reza Ghanadan, Program Manager, Defense Sciences Office, DARPA

Philip Rubin, Principal Assistant Director for Science, OSTP

Journals, Media and Science Writers

Rebecca Alvania, Neuron

Peter Bandettini, Neuroimage

Brigitta Gunderson, Nature Neuroscience

Erika Pastrana, Nature Methods

Elizabeth Quill, Smithsonian

Parizad Bilimoria, Conte Center at Harvard

Helen Shen, Nature

APPENDIX 4: WEB RESOURCES

(i) Meeting Website

Homepage:
http://physicsoflivingsystems.org/brainstructureandfunction/

Agenda:
https://docs.google.com/file/d/0B9eDULFfT0lbTGM5cmhmWFNPOFk/edit?pli=1

Collection of White Papers:
https://docs.google.com/file/d/0B3wJfwGdhfvEOUpYZ2V4R29QcVE/edit?pli=1

Transcript of Opening Address by Professor Huda Zoghbi:
https://docs.google.com/file/d/0B9eDULFfT0lbd2pkSEVJRmhsVHc/edit?pli=1

(ii) Meeting Coverage

Meeting Organizers on Twitter as @nsfBRAINpols
Comments with hash tag #nsfBRAINmtg
https://twitter.com/search?q=%23nsfBRAINmtg&src=hash

See also #nsfBRAINmtg synopsis by Joshua Vogelstein of @OpenConnectome

Nature News Blog: Neuroscientists brainstorm goals for US brain-mapping initiative
By Helen Shen
http://blogs.nature.com/news/2013/05/neuroscientists-brainstorm-goals-for-us-brain-mapping-initiative.html

(iii) Sponsor Websites

National Science Foundation
http://www.nsf.gov/

NSF Physics of Living Systems
http://physicsoflivingsystems.org/

Kavli Foundation
http://www.kavlifoundation.org/

(iv) BRAIN Initiative Websites

White House BRAIN Initiative Webpage: http://www.whitehouse.gov/infographics/brain-initiative

NIH BRAIN Initiative: http://www.nih.gov/science/brain/
Advisory Committee: http://www.nih.gov/science/brain/acd-roster.pdf
Feedback: http://brainfeedback.nih.gov/

Kavli BRAIN Initiative Homepage: http://www.kavlifoundation.org/brain-initiative
Timeline of Brain Activity Map Project: http://www.kavlifoundation.org/BAMTime/BAMindex.html

NSF BRAIN Initiative: http://www.nsf.gov/news/news_summ.jsp?cntn_id=127477

DARPA Announcement: http://www.darpa.mil/NewsEvents/Releases/2013/04/02.aspx

Allen Institute Announcement:
http://www.alleninstitute.org/Media/documents/press_releases/2013_0402_PressStatement_BRAINInitiative.html

(v) Articles about the BRAIN initiative in scientific journals

The brain activity map project and the challenge of functional connectomics.
Alivisatos AP, Chun M, Church GM, Greenspan RJ, Roukes ML, Yuste R.
Neuron. 2012 Jun 21;74(6):970-4.
http://www.sciencedirect.com/science/article/pii/S0896627312005181
[Earlier, Longer Version: http://academiccommons.columbia.edu/item/ac:147969]

Neuroscience. The brain activity map.
Alivisatos AP, Chun M, Church GM, Deisseroth K, Donoghue JP, Greenspan RJ, McEuen PL, Roukes ML, Sejnowski TJ, Weiss PS, Yuste R.
Science. 2013 Mar 15;339(6125):1284-5
http://www.sciencemag.org/content/339/6125/1284.long

Nanotools for neuroscience and brain activity mapping.
Alivisatos AP, Andrews AM, Boyden ES, Chun M, Church GM, Deisseroth K, Donoghue JP, Fraser SE, Lippincott-Schwartz J, Looger LL, Masmanidis S, McEuen PL, Nurmikko AV, Park H, Peterka DS, Reid C, Roukes ML, Scherer A, Schnitzer M, Sejnowski TJ, Shepard KL, Tsao D, Turrigiano G, Weiss PS, Xu C, Yuste R, Zhuang X.
ACS Nano. 2013 Mar 26;7(3):1850-66.
http://pubs.acs.org/doi/full/10.1021/nn4012847

Research priorities. The NIH BRAIN Initiative.
Insel TR, Landis SC, Collins FS.
Science. 2013 May 10;340(6133):687-8.
http://www.sciencemag.org/content/340/6133/687.full

Science Priorities for the BRAIN Initiative.
Samuel A, Levine H, Blagoev KB.
Nat Methods. 2013 Aug;10(8):713-4.
http://www.nature.com/nmeth/journal/v10/n8/full/nmeth.2565.html