Grand Challenges in Mapping the Human Brain: NSF Workshop Report

Bin He*, *Fellow, IEEE*, Todd Coleman, *Senior Member, IEEE*, Guy M. Genin, Gary Glover, Xiaoping Hu, *Fellow, IEEE*, Nessa Johnson, Tianming Liu, Scott Makeig, Paul Sajda, *Fellow, IEEE*, and Kaiming Ye, *Senior Member, IEEE*

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***Abstract*—This report summarizes the outcomes of the NSF Workshop on Mapping and Engineering the Brain, held at Arlington, VA, during August 13–14, 2013. Three grand challenges were identified, including high spatiotemporal resolution neuroimaging, perturbation-based neuroimaging, and neuroimaging in naturalistic environments. It was highlighted that each grand challenge requires groundbreaking discoveries, enabling technologies, appropriate knowledge transfer, and multi- and transdisciplinary education and training for success.**

***Index Terms*—Brain mapping, biomedical imaging, modeling, neural engineering, neuroimaging, neuromodulation.**

I. Introduction

THE past decade has witnessed an explosive growth in our ability to observe and measure brain activity in animals and humans. The ability to "understand the brain" has been the key to progress in neuroscience, to promote and protect brain health, and to develop treatments for restoring, regenerating, and repairing diseased and/or deteriorated brain functions. Currently available techniques are limited in their ability to map brain activity with both high spatial resolution and high temporal resolution, or are limited by the invasive nature of the approaches. Thus, there is a strong need to develop novel and paradigm shifting technologies and methodologies that allow us to collect data about the spatiotemporal activation of the brain across different scales dynamically and with high resolution. Though vast amounts of data have been generated using various techniques at multiple scales, there has been only limited progress in integrating functional data across the molecular, cellular, and systems levels. It is therefore important to develop principled methods, models, and technologies that focus on the integrated picture of the data obtained at these various scales, to understand brain function as a whole. This challenge is fundamentally one in the domain of neurotechnology and neuroengineering disciplines intersecting engineering sciences with neuroscience.

The development of methods capable of building an integrated picture of the multiscale functional networks within the brain will have a marked impact on our understanding of the healthy, diseased, and aged brain. Functional mapping techniques can be used to discern both the origin, as well as the direction, of information propagation within the cortex and can be used to analyze the complex pattern of interconnected neuronal networks. Characterization of these complex neural circuits and networks will enable a deeper understanding of the mechanisms by which the brain operates, leading to improved diagnoses for neuropathologies, such as stroke and epilepsy, better surgical planning, and the development and improvement of neural prostheses in cases of injury or disability. Such advancements could also lead to better management of pain as well as other brain disorders, such as schizophrenia, Alzheimer's disease, and depression. Innovative systems engineering theories, imaging tools, sensors, informatics, algorithms, and models are needed to tackle the grand challenges in human brain research.

This report summarizes the outcomes of the NSF Workshop on Mapping and Engineering the Brain, held at Arlington, VA, during August 13–14, 2013. Thirty-three workshop participants from academic institutions around the country (see the complete list of participants at the end of this report) met over the course of two days to discuss the grand challenges in mapping the brain. Attendees participated in one of four breakout sessions: spatiotemporal brain mapping, multiscale neuroimaging of brain activation and function, engineering challenges in

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*B. He is with the Department of Biomedical Engineering and Institute for Engineering in Medicine, University of Minnesota, Minneapolis, MN 55455 USA (e-mail: binhe@umn.edu).

T. Coleman is with the Department of Bioengineering, University of California, San Diego, CA 92093 USA (e-mail: tpcoleman@ucsd.edu).

G. M. Genin is with the Department of Mechanical Engineering and Materials Science and Department of Neurosurgery, Washington University, St. Louis, MO 63130 USA (e-mail: gening@seas.wustl.edu).

G. Glover is with the Department of Radiology, Stanford University, Stanford, CA 94305 USA (e-mail: gary.glover@stanford.edu).

X. Hu is with the Coulter Department of Biomedical Engineering, Georgia Tech and Emory University, Atlanta, GA 30332 USA (e-mail: xhu3@emory.edu).

N. Johnson is with the Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN 55455 USA (e-mail: joh02102@umn.edu).

T. Liu is with the Computer Science Department, University of Georgia, Athens, GA 30602 USA (e-mail: tliu@cs.uga.edu).

S. Makeig is with the Institute for Neural Computation, University of California, San Diego, CA 92093 USA (e-mail: sscott@sccn.ucsd.edu).

P. Sajda is with the Department of Biomedical Engineering, Columbia University, New York, NY 10027 USA (e-mail: psajda@columbia.edu).

K. Ye is with the Department of Bioengineering, State University of New York, Binghamton, NY 13902 USA (e-mail: kye@binghamton.edu).

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brain mapping and data analysis, and neurotechnologies for maintaining and augmenting the healthy brain. Following the breakout group discussions, the overall group discussed the grand challenges identified by each breakout session and agreed by consensus on a comprehensive list of grand challenges. Three grand challenges were identified (see Fig. 1), as outlined later, and it was emphasized that each grand challenge requires groundbreaking discoveries, enabling technologies, appropriate knowledge transfer, and multi- and transdisciplinary education and training for success. In addition to the three grand challenges, several other challenges were identified by the breakout discussions, and are described following discussion of the three grand challenges.

II. Grand Challenge 1: High Spatiotemporal Resolution Neuroimaging

Functional imaging at high spatiotemporal resolution was identified as a technology central to enabling breakthroughs in understanding the human brain. Modalities considered included functional magnetic resonance imaging (fMRI), electrophysiological neuroimaging such as electroencephalography (EEG), magnetoencephalography (MEG), and electrocorticography (ECoG), as well as functional near-infrared spectroscopy (fNIRS) and positron emission tomography (PET). Of these imaging modalities, fMRI has relatively high spatial resolution but low temporal resolution, while electrophysiological methods have high temporal resolution but limited spatial resolution. One of EEG's great advantages is that it can enable wireless, ambulatory measurements, with very fine time resolution and modest spatial resolution at a small fraction of the cost of most other functional brain imaging systems. fNIRS has the ability to measure both oxyhemoglobin and deoxyhemoglobin and can also be portable or wearable, allowing experiments in naturalistic environments for extended periods, yet it does not offer whole-brain coverage and has limited spatial and temporal resolutions. Therefore, participants agreed that a multimodal array of technologies is essential to develop, so that complementary data can cover a wide spectrum of spatiotemporal brain dynamics.

A. Challenges in Higher Resolution Hemodynamic and Electrophysiological Imaging

Increasing the resolution and enhancing the capabilities of fMRI and electrophysiological neuroimaging are important challenges that are necessary in order to achieve high spatiotemporal resolution functional brain images.

1) Higher Resolution fMRI: fMRI is widely utilized for neuroscience research and has high potential for benefiting from advances in technology. It plays a significant role in improving our multimodal imaging capability. The present resolution of 3 T fMRI typically used for cognitive neuroscience studies and clinical applications is 3–4 mm spatially (voxel size) and 1–3 s temporally (volume sampling interval, TR). This level of spatiotemporal resolution has been used for the bulk of the fMRI research conducted in the past decade. Increasingly, however, more complex questions are being asked about brain function, and it is essential to move beyond these basic acquisition parameters.

One example of the need for high spatial resolution is the study of cortical regions responsible for discriminability within sensory functions, such as retinotopy and cortical columns in visual systems [1], tonotopy in audition [2], and organization of the homunculus in sensorimotor systems. In translational applications, detailed knowledge of these and other sensory systems is crucial for brain–computer interface (BCI) applications used for prosthetic control; therefore, the study of neural dynamics at high spatial resolution is critical.

A second class of studies requiring high spatial resolution is in the delineation of function in highly heterogeneous brain regions such as the thalamus, each half of which is on the order of 25 mm in width. The thalamus serves as a signal relay station for sensory and motor information, regulates functions such as consciousness, sleep, and alertness, and is broadly connected with the neocortex. It is a highly heterogeneous structure consisting of at least 13 nuclei; therefore, study of its specific functions necessitates a voxel size of 2 mm or smaller. Many of these nuclei have been implicated in specific diseases and serve as targets for deep brain stimulation (DBS), such as the ventral intermediate nucleus in essential tremor and central lateral nucleus in disorders of consciousness [3]. Robust functional imaging of these thalamic nuclei could be of importance in guiding the surgical placement of DBS electrodes [4], [5].

With respect to temporal resolution, recent advances in accelerated fMRI have enabled volume-sampling rates as high as 10 Hz (although with compromised spatial resolution and signal-to-noise ratio (SNR) not capable of exploring high-frequency spontaneous brain activity) [6], [7]. Such advances have demonstrated high-frequency spontaneous oscillations in the brain using the blood-oxygen-level-dependent (BOLD) signal, which are poorly understood in light of the slow biophysics of the hemodynamic basis for BOLD contrast. In addition, recent studies have demonstrated rapid (50–100 ms latency) fMRI signal changes accompanying interictal electrical discharges in epilepsy patients [8]. Again, the neurobiological mechanism by which the magnetic resonance imaging (MRI) signal magnitudes paradoxically increase during these events has yet to be elucidated. Therefore, development of novel fMRI methods that can achieve higher temporal resolution while maintaining high spatial resolution can lead to a tool of exceedingly high value for research leading to advances in both basic and clinical neuroscience.

The physics of fMRI dictates tradeoffs between spatial resolution, temporal resolution, and SNR. Recent advances in gradient and radiofrequency technologies have enabled the exploration of ever higher tradeoff limits, based on more efficient and faster k-space trajectories that are sampled sparsely, combined with multicoil arrays of receiver coils and iterative reconstruction algorithms. Furthermore, fMRI contrast-to-noise ratio benefits directly from the SNR advantage of higher magnetic field strength; thus, the use of 7 T and still higher field scanners will be critical for achieving the highest possible spatial imaging resolution.

In advanced fMRI and diffusion tensor imaging (DTI) systems to map connectivity between brain regions,

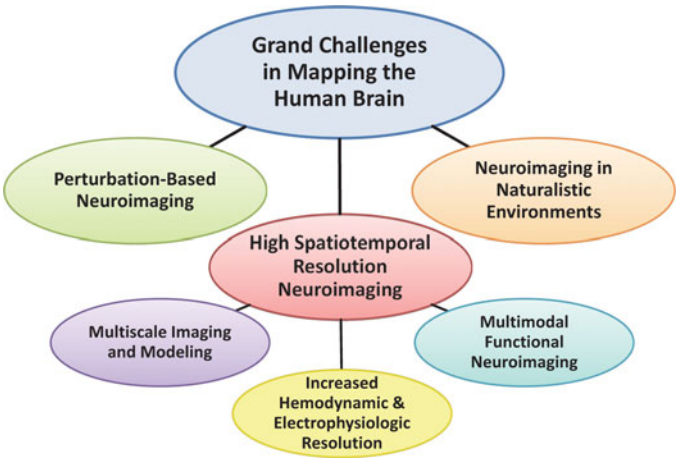

Fig. 1. Illustration of grand challenges in mapping the human brain.

high-performance gradients [9] will be critical to achieving higher spatiotemporal resolution. This likely means inserting gradient coils whose spatial extent is short enough to avoid peripheral nerve stimulation. Radio frequency receiver coils and electronic subsystems with much higher channel counts ($\geq$128) than presently deployed [9] will be crucial. Novel reconstruction methods will be needed to make optimal use of multichannel sampled data and correct for artifacts due to off resonance, such as seen in a recent example for ultrahigh-resolution DTI [10]. Enhanced data management systems will be required because of the high data rates and computational complexity of new iterative image reconstruction methods, especially for concurrently acquired multimodal studies.

2) Higher Resolution EEG Source Imaging: Over the past two decades, innovations in source imaging have turned EEG from a 1-D sensing or 2-D mapping technique into a 3-D source imaging modality for mapping dynamic distributed brain activity, primarily from the cortex with high temporal (ms) and increasing spatial (5–10 mm) resolution. The availability of dense array EEG mapping systems has offered opportunities to sense the spatiotemporal distributions of brain electric activity over the scalp. Numerous investigations in cognitive neuroscience, clinical neurology, psychiatry, and neurosurgery have revealed the power of EEG source imaging in providing dynamic brain activity [11].

The speed and portability of EEG systems, as well as their dramatically lower cost relative to fMRI and MEG, offer unique capabilities for functional brain imaging. However, the EEG (and MEG) modality is limited in its spatial resolution to image brain activity due to the head volume conduction effect. Advancements in the field of EEG source imaging have benefited significantly from using stable anatomic information available through high-resolution T1-weighted MRI. Such anatomic constraints, first introduced in late 1980s by means of the boundary element method [12], [13], have played a significant role in improving the spatial resolution of EEG (and MEG) source localization and imaging. Furthermore, anatomic and functional constraints introduced by the cortical current density models [14] have greatly enabled the capability of imaging source distributions through solving a linear inverse problem. Another line of advancement has come from the introduction of statistical methods to identify maximally distinct sources of information in high-density EEG (or MEG), separating out many nonbrain processes (including eye, muscle, heart, and line noise activities) that also contribute to these scalp recordings [15], or extracting desirable brain processes among multiple ongoing brain activities [16].

Recent advances in EEG source imaging have significantly improved performance in localizing event-related brain activity from event-related potentials in healthy human subjects, and from interictal spikes in epilepsy patients [11]. Advanced EEG source imaging techniques have also demonstrated the ability to image oscillatory brain activity at various frequencies, for example, in human subjects performing motor imagery for BCI applications and for directly imaging oscillatory seizure activity in patients suffering from epilepsy [16]. Applications to psychiatric and neurological research and practice are also a clear opportunity.

A unique feature of EEG source imaging is the intrinsic ability of EEG to be used for mobile imaging; thus, it is suited for studying brain activity in a naturalistic environment [17] or mapping spontaneous pathological brain conditions [16]. EEG has become the major modality for developing direct BCIs in human subjects, and continues to be used to study human cognitive functions. Applications introducing cognitive monitoring into human–computer interfaces could soon appear in the workplace including transportation and plant monitoring, in classrooms and computer learning environments, and even in computer gaming and communication.

One of the important challenges in EEG source imaging is to further develop imaging techniques for modeling and interpreting ongoing, spontaneous, distributed cortical activity without the need for predesigned events. Such spontaneous source imaging is important to further advance the fundamental ability of EEG source imaging, especially with regard to naturalistic environments. Another challenge in EEG source imaging is the development of high-density wearable sensing arrays that can detect and measure rich information contents about the underlying brain activity, with or without the simultaneous use of other imaging modalities such as fMRI, transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), etc. A unique advantage of scalp EEG recording is the information it provides about distributed dynamics in cortex, in that it represents synchronized network activities reflecting overall brain functions instead of activity from a single neuron. More work is needed on adequate methods for detecting, modeling, and understanding the role of distributed EEG activity in cognition and behavior.

A limitation associated with current EEG source imaging techniques is that its spatial resolution is limited by the lack of detailed information regarding the electrical properties of the head, skull, and brain. Therefore, it will be important to foster advances in other neuroimaging techniques using magnetic resonance electrical property tomography or magnetoacoustic-based methods to provide subject-specific, high-resolution conductivity and permittivity maps. These electrical properties can then be used to better inform EEG inverse solutions.

3) High-Resolution μECoG: ECoG is a means of monitoring and mapping brain activity in selected patients undergoing surgical planning by implanting electrodes over the cortical surface. It offers direct capability of measuring brain electric activity in the vicinity of such activities and is well used in clinical applications, including aiding presurgical planning in epilepsy patients. Recent advancement in micro-ECoG (μECoG) has demonstrated the ability to map brain activity at a very fine spatiotemporal scale over broad areas in animal models [18]. Through solving important engineering challenges, this approach can be brought to use in humans, vastly expanding our ability to understand brain network dynamics at high spatial and temporal resolutions, when such an invasive procedure is needed. In addition, ECoG can serve as an important validation for the findings of noninvasive approaches, including EEG and fMRI. However, challenges exist in developing flexible electronics for high-density μECoG mapping and solving the inverse source imaging from ECoG measurements to map the underlying brain activity. Another challenge associated with μECoG is the limited applicability, since ECoG is currently only used for patients already undergoing either a presurgical evaluation or another surgery. Hence, the use of advanced μECoG techniques would be limited to patient populations requiring surgery or active invasive monitoring. However, taking full advantage of this unique clinical window of opportunity for observing human brain dynamics across spatial scales, with high time resolution, should allow new insights into distributed multiscale brain dynamics, albeit in a limited patient population.

B. Challenges in Multimodal Functional Brain Imaging

Despite recent improvements in fMRI, there remains the necessity for its combination with electrophysiological and/or optical methods that have inherently high temporal resolution, in the millisecond range [19]. Such combinations exploit the complementary physics to high advantage. For example, fMRI can be used to provide submillimeter spatial resolution and tissue specificity by compromising the temporal resolution to maintain SNR, while concurrently acquired EEG can be used to inform the fMRI reconstruction with millisecond temporal features. Similarly, the high spatial resolution fMRI can be used to aid in constraining EEG (or MEG) source imaging [11]. Finally, simultaneous acquisition of EEG and fMRI enables one to relate the trial-to-trial variability of the electrophysiological signals with that of the hemodynamics, in a way that is not possible with either modality alone [20].

However, these combination methods require refinement, because fMRI is inherently a scalar measure of hemodynamic activity and flow in the brain, indexing finely tuned hemodynamic compensation for local energy depletion, while EEG recordings reflect a vectoral combination of volumetric and intercellular currents arising from neuronal activation. Therefore, the inverse solution of EEG (and MEG) recordings may differ in depiction of source locations from that of fMRI activity, and more complex understanding of how to best integrate the various concurrently acquired data types is needed. Additional challenges exist regarding obtaining simultaneous neuroimaging data from two or more techniques, as one modality often results in significant artifacts in another. For example, with simultaneous EEG/fMRI imaging, gradient, cardio ballistic, and other artifacts are recorded in the EEG signal and must be removed effectively to extract any information from the EEG. Thus, additional research should be conducted to optimize experimental and signal processing techniques to allow for concurrent measurements from multiple modalities, as well as to develop mathematical and statistical methods for more optimally isolating and combining information about brain dynamics contained within signals from concurrent recording modalities.

Experimental data have suggested correlation between BOLD signals and electrophysiological events via neurovascular coupling [11], [20]. However, challenges exist in delineating the correlations between BOLD signals and the direct electrophysiological measurement of neuronal activation via EEG, including further development of multimodal imaging devices and methods that can integrate the hemodynamic and electrophysiological measurements in a principled way. Such research shall lead to further improvement in integrated fMRI–EEG multimodal neuroimaging.

Efforts have also been made to develop non-BOLD-based fMRI techniques for mapping brain functions, including contrast-based techniques. Moreover, with multimodal functional imaging, electrical, hemodynamic, and/or metabolic components can allow quantitative interpretation of both resting-state [21] and task-induced [22] fMRI data in terms of specific neuronal (i.e., excitatory and/or inhibitory) activities. Understanding the neurophysiological basis of both resting-state and task-induced fMRI signal changes will greatly improve interpretation of the neuroimaging data.

PET has been applied broadly to high resolution in vivo mapping of brain function, including vascular flow, metabolism, and receptor binding [23]. The method requires the injection of positron emitting, short (∼10–100 min) half-life isotopes, such as ^{11}C, ^{15}O, or ^{1}8F. Although crossing the blood brain barrier is a challenge, advances such as the development of the glucose analog 2-deoxy-2-(^{18}F)fluoro-D-glucose have enabled the very sensitive measurement of glucose metabolism. Additional tracers currently exist for a range of brain function including cerebral blood flow, oxygen metabolism, dopamine handling, and microglial activation. However, the means to connect PET measurements to those acquired through other modalities does not yet exist, and the range of tracers available covers only a small part of brain function. More work is needed in both of these areas.

Beyond these approaches, additional imaging modalities that capture the full range of the normal and pathological function of the brain are needed, as are tools for linking these to state-of-the art modalities. Underlying this is the need to treat a range of diseases that can be attributed to dysregulated feedback in the homeostatic control systems that define brain function. Approaches for developing easily measurable biomarkers capable of capturing the onset of neuropathology are desired for both therapeutic and neuro-evaluation purposes. The typical methods for monitoring the brain described earlier extract information about its anatomy, hemodynamic responses, or

electrophysiology. However, the dynamic ebb and flow of biochemical reactions underlying blood flow, perfusion, pressure regulation, etc., cannot be observed with the aforementioned methods. As an example, Alzheimer's disease is currently believed to involve a dysregulation of the clearance of a protein that can form plaques within brain parenchyma [24]. New technologies to measure nonequilibrium steady-state rate constants associated with cellular, tissue, and organ-wide nonequilibrium steady states can provide novel information about brain function, dysfunction, and therapeutic responses. In many situations, the rate constants of these reactions might be different and this cannot necessarily be directly observed using hemodynamic or electrophysiological methods. Attractive alternatives are magnetic resonance-based methods for measuring metabolism, and other techniques for measuring nonequilibrium steady-state rate constants in living organisms.

C. Challenges in Multiscale Imaging and Modeling

While neuronal function starts at the molecular and cellular level in the time scale of microseconds to milliseconds, the brain functions as a result of the action and interaction of billions of neurons, as well as nonneuronal brain cells (glia), and of multiple circuits and systems within the brain. Therefore, the imaging of brain activity and function has to be performed at multiple levels and scales both in space and time. To date, a variety of techniques are available for imaging the brain at different spatial and temporal scales as described earlier. One of the challenges that remains, however, is to develop a more integrated understanding of how different mapping modalities, at different spatial and temporal scales, relate to one another, given the assumptions underlying these measurements and sources of noise and error. There was substantial discussion on the need to develop multiscale modeling and imaging approaches to quantitatively link currently used brain mapping methodologies in terms of the anatomical/physiological/biological information they measure and the scales at which they measure this information. Also, it is essential to develop and validate quantitative representational maps of common brain architectures that are reproducible and predictive across individual populations and can serve as the structural substrate for integrating multiscale multimodal data.

1) Development of Multiscale Neuroimaging Methods: fMRI is widely utilized for neuroscience research and has high potential for benefiting from advances in technology. There has been remarkable progress in neuroimaging methods at individual scales. For instance, at the microscale, the recently introduced serial two-photon tomography is capable of high-throughput fluorescence imaging of mouse brains [25] and made it possible for the Allen Institute for Brain Sciences to produce the first Mouse Brain Connectivity Atlas. At the macroscale, the latest MRI techniques used in the Human Connectome Project have produced fMRI and DTI datasets with unparalleled spatial resolution [26], [27]. These new neuroimaging methods have significantly advanced our understanding of the structural architecture of the brain at drastically different spatial and temporal scales. However, there are currently very few facilities in the country that allow one to obtain multiscale measures simultaneously and to obtain the same measures at different scales, making multiscale modeling and imaging particularly challenging for human brain mapping. In addition, the current analytical methods for deriving relevant information regarding neural circuitry/networks and functional maps at multiple scales are lacking.

Regarding temporal scales, the chemical, electrical, and physiological processes in the brain are time varying and multiscale in nature. For example, the temporal durations of neuronal oscillations in brain networks vary over a factor of at least 10^4—across the range of 0.05–500 Hz [28]. It will be useful to image such activities and processes as comprehensively as possible to more completely understand the temporal dynamics of the brain. However, to link neuroimaging data at different temporal scales together is nontrivial and may itself be considered a major challenge. For example, at the macroscale, it has been challenging to link EEG electrophysiology data with fMRI hemodynamic data recorded on different temporal scales. At the microscale, it is challenging to perform simultaneous patch-clamp neural recordings and calcium imaging in neuronal networks. It is even much more difficult to perform simultaneous high spatiotemporal resolution imaging of chemical, electrical, and physiological processes across more than two scales and to link them for computational modeling and interpretation.

There are several major issues and challenges for the development of multiscale neuroimaging methodologies. The first is the lack of neuroimaging methods for evaluating multiscale neural circuits/networks. There are multiple ongoing efforts for connectome imaging and mapping, including the Open Connectome Project at the cellular scale and the Human Connectome Project at the millimeter scale. However, it is very challenging to link such projects into a multiscale connectome map. For instance, even for the simple situation of investigating structural connection patterns between the gyri and sulci of the cerebral cortex, imaging and mapping the brains of multiple species across different scales have proven to be a difficult, if not impossible, task.

Second, it is challenging to develop neuroimaging/bioimaging methods to study the same aspect of the brain from molecular to subcellular, to tissue, and to system levels. For instance, mutation of genes could alter brain structure and function at multiple scales [29], and it is nontrivial to develop neuroimaging techniques that are capable of generating imaging data at multiple scales to be used for characterizing phenotypes and genotype effects.

Third, it is important yet challenging to perform simultaneous acquisition of multimodality data at multiple scales. For instance, simultaneous acquisition of EEG/fMRI data has seen substantial advancement in the past years but acquisition of high quality data for both modalities is still hampered by cross contamination.

2) Quantitative and Predictive Models That Link Different Scales of Neuroimaging Data: In both the microscale bioimaging and macroscale medical imaging data analysis, there have been tremendous advances in computational modeling methodologies and software tools. However, most previous efforts in modeling and quantifying neuroimaging data were carried out

on a single scale, and the potential of linking different scales of neuroimaging data has not been widely explored. Therefore, the development and experimental validation of quantitative and predictive models that can integrate and interpret multiscale neuroimaging data have significance and great potential to lead to novel discoveries, despite several challenges associated with such models. First, it has been challenging to derive the most relevant measures at the proper scales of neuroimaging data. For example, there have been a variety of quantitative metrics for DTI and higher angular resolution diffusion imaging datasets [30], but it is still not clear what is most correlated with the neuronal tracing data at the microscopic level. It was also noted that it is equally challenging to link relevant measures by multiscale registration. Second, based on the relevant and meaningful measures of multiscale neuroimaging data, it is essential, but challenging, to construct realistic and generative computational models to predict measures at other scales. Construction and validation of such computational models will entail the effective integration of brain science knowledge, the availability of high-quality multiscale neuroimaging data, and the development of novel computational algorithms and methodologies, a difficult endeavor. Third, a major challenge is to model the functional activities/interactions across multiple spatial/temporal scales. For example, due to the intrinsic complexity of temporal dynamics, it has been difficult to computationally or statistically model the functional interactions and dynamics of resting state networks and connectomes [31]. It will be even more challenging to link such functional activities/interactions across multiple spatial and/or temporal scales.

III. Grand Challenge 2: Perturbation-Based Neuroimaging

The second grand challenge identified is to develop perturbation-based neuroimaging methods, which will open novel pathways for neuroimaging by combining neuromodulation with high-resolution neuroimaging to delineate active brain networks by temporarily altering them in controlled ways. Much of the understanding of structure-function relationships in the brain has depended on awaiting clinical cases of focal brain dysfunction (e.g., stroke, lesions, cancer, trauma, etc.) to inform the relevance of these structures on higher level cognitive functioning. Brain stimulation allows one to artificially and temporarily produce changes in neuronal activity specific to a brain region or network [32]. Such stimulation can be applied invasively or noninvasively using magnetic, electrical, or acoustic energy. The results of the stimulation can be measured using a variety of neuroimaging techniques including EEG, fMRI, and MEG, in addition to electromyography muscle responses and behavioral measures.

The ability to perturb the brain in a controlled fashion and measure the result using neuroimaging will allow for several important advances. First, it will allow one to better interpret the functional implications of data obtained with observational techniques. For example, one can determine whether a region activated by a task is actually necessary for the task by inhibiting the activated region, repeating the task, and comparing task performance before and after stimulation. Similarly, one can determine whether correlations observed in observational data actually predict the causal influence of one brain region on the other. In this way, perturbation-based neuroimaging can be used to define causally connected brain networks by generating activity with a spatially and temporally defined source and tracking the propagation of the induced activity throughout interconnected brain areas. This type of brain mapping will serve as an important complement to anatomical and functional mapping from observational techniques. Finally, perturbation-based neuroimaging is likely to prove critical for understanding the therapeutic mechanism of brain stimulation therapies. Both invasive therapies, such as DBS, and noninvasive therapies, such as TMS and tDCS/tACS, are seeing increased therapeutic use. However, we are just beginning to understand the network-level changes that underlie these therapies, an area of investigation that is critical for treatment improvement and optimization.

Noninvasive neuromodulation methods have shown promise for perturbing and modulating the brain in order to manage pathological brain conditions. These include delivery of external magnetic energy (TMS) [33], electrical energy (e.g., tDCS) [34], and acoustic energy (focused ultrasound) [35]. The use of such neurostimulation techniques offers tools that, together with high-resolution mapping of the brain, allow testing of hypotheses otherwise inaccessible in humans. Alternatively, the perturbation may also be an integrative part of new imaging modalities, such as photoacoustic tomography, magnetoacoustic tomography with magnetic induction, etc. Such perturbation also includes selective modulation of brain activity, enabling closed-loop control of brain activity in real-world contexts and human social interaction. In addition, portable optical imaging could be integrated with genetic engineering tools being developed in animal models to probe or control neural circuits optically.

There are several challenges associated with combining neuromodulatory and neuroimaging techniques. First, work is often needed to ensure that the physics of the two techniques are compatible, such as placing an electromagnetic TMS coil inside of an MRI scanner. Second, when applied concurrently, neurostimulation may result in significant artifacts in the neuroimaging data. Sophisticated analysis and experimental techniques are required to minimize and remove the resultant artifacts. Third, the precise mechanisms of neuromodulation including TMS and tDCS remain unclear and the stimulation may involve nonfocal areas of the brain. There is a need to further develop innovative noninvasive neuromodulation techniques to improve the spatial resolution, and elucidate their neural mechanisms. The availability of such techniques will not only enhance the capability of perturbation-based neuroimaging, but also the ability to manage and treat various brain conditions. Finally, advanced modeling and analysis methods will likely be needed to best understand and subsequently predict the impact of brain stimulation on brain networks.

IV. Grand Challenge 3: Neuroimaging in Naturalistic Environments

The third grand challenge identified is to develop new noninvasive methods to image the human brain while it is interacting with its natural environment. The challenge lies in developing adaptive neurotechnology that will allow an unobtrusive seamless link with the living system. Such imaging methods would be mobile or wearable, and would ideally measure neural activity in three dimensions. In addition to imaging, brain stimulation and neuromodulation techniques could be brought to bear and integrated into closed-loop systems enabling real-time feedback. The integration of neuromodulation techniques would also enable sequential experimental design for mapping human brain activity representative of brains interacting in real-world contexts, for example, in social interaction such as casual and/or personal meaningful conversation/interaction. For addressing this challenge, significant advancements will be required in the design and development of novel neurotechnology.

As medical practice reimbursement increasingly incentivizes ambulatory monitoring for preventative care, in-home monitoring is moving at a rapid pace; however, in-home brain monitoring has been primarily limited to low-level neural signals for use in entertainment devices, such as game playing. To transcend this hurdle, low-cost portable technologies for extracting useful information are needed. Wearable technology has the potential to provide increasingly rich information about the context of the users and their experience in their environment. A challenge is to develop immersive brain monitoring systems for "natural" dynamic settings in concert with novel analytical approaches for characterizing how neural signals covary with environmental dynamics. This could help understand predictive changes in brain dynamics that could be used for providing outpatient suggestions on changing therapies pertaining to cognitive impairment or for rehabilitation purposes.

Translating neurotechnologies out of the laboratory or clinical setting to study and benefit a broader population requires development of brain imaging techniques that are wearable. The unwieldy size and confinement of an MRI equipment restrict the range of natural cognition, including direct social interactions, which can be studied with fMRI, prompting further interest in developing wearable techniques. This includes new opportunities for functional electrophysiology (dense array EEG) and fNIRS. These techniques hold promise to monitor the human brain in a naturalistic environment, and guide users to adapt within the contexts of education, training, and neuropsychiatric treatment.

One of the challenges associated with imaging of ambulatory individuals is difficulty of obtaining reliable signals given the elasticity of the brain. The brain not only stretches significantly ($>5\%$) in normal physiologic motion [36], but also displaces significantly (mm to cm) relative to the skull [37]. This motion is a normal part of physiologic brain function that needs to be mapped and understood, and minimized or accounted for when interpreting functional readings from ambulatory individuals. An additional challenge associated with monitoring in naturalistic environments is the potential for signal corruption due to environmental electrical and magnetic noise. Thus, the development of novel and robust sensing and denoising techniques will be required to obtain reliable data in such naturalistic environments.

Wearable neuroimaging technology is also of importance for maintaining and augmenting the healthy brain. Impactful lines of research would include BCI "orthoses" for tracking user intent and/or brain state to customize and manage information delivery [38]. Such research could also be applied to track degradation in perception, cognition, and memory, which might be a result of the normal aging processes. By enabling a continuous and natural tracking of such brain states, interventions could be prescribed to mitigate deterioration of cognition, for example, neurofeedback to mitigate age-related memory loss. Applications to improve workplace efficiency and safety and enhance learning and communication appear possible. In all cases, it was believed this line of research must include research into the ethical and moral concerns, which are clearly apparent when one considers measuring, tracking, and recording latent intent [39]. Also, care must be taken to investigate the risk that closed-loop brain monitoring and modulation systems can lead the brain, and thus the participant, unwittingly into abnormal regimes, with potential negative as well as positive consequences.

V. Other Challenges

A. Neuroimaging in Patients With Implanted Devices

A challenge associated with high-resolution neuroimaging is the fact that many patient populations that could benefit in some way from higher resolution neuroimaging are inherently not candidates for neuroimaging techniques, such as MRI, due to the presence of implanted devices. Thus, in addition to developing MR-based imaging techniques with higher spatial and/or temporal resolution, an emphasis must be placed on both developing new implantable devices that are compatible with MR-based imaging techniques and developing alternative imaging techniques for individuals with implanted devices. Neuroimaging with implantable devices remains a challenge in the industry and, if solved, could lead to a wealth of diagnostic and treatment-related information. This should not necessarily be treated as a focus only for the medical device companies developing such implanted devices, but also for the neuroimaging community in general. Even at low magnetic field strengths, the energy absorption of implants and specific absorption rate (SAR) becomes an issue in patients with implanted devices, often because such systems include wires that can pick up and focus the MRI's radiofrequency energy. Thus, not only is it important to develop compatible neuroimaging devices and implantables, but also SAR imaging itself requires development to enable subject-tailored monitoring of energy absorption and heating with implanted devices.

Enhancements in alternative imaging techniques such as fNIRS or EEG could also alleviate the challenges of imaging with implantable devices. In addition, biophotonic techniques could allow for the visualization of the neurovasculature and blood flow, as well as oxygen saturation. The challenge is to enhance multimodal imaging that takes advantage of combining

these techniques with fMRI and EEG to provide a comprehensive picture of the functional brain activity.

B. Multispecies and Multiscale Data Integration

In the past few decades, there has been tremendous advancement in imaging and mapping the brains of individual model species such as C. elegans, drosophila, zebrafish, mouse, monkey, chimpanzee, and the human. For instance, microscale imaging via optical and electron microscopy techniques of drosophila and mouse brains has seen remarkable progress in terms of mapping a large population of neurons and their connections [40], [41]. At the same time, at the macroscale, neuroimaging techniques such as DTI and fMRI have revolutionized our understanding of the brains of rodents and primates [42], [43]. Specifically, with regard to the wide applications of resting-state fMRI in clinical populations, there needs to be superior neurophysiological understanding of the fluctuating signals (i.e., electrical, hemodynamic, metabolic). The neurophysiological basis of the so-called resting or baseline state will allow mechanistic understanding of what is reflected macroscopically in the resting-state fMRI data down to the microscopic level of neuronal (i.e., excitatory and/or inhibitory) and astrocytic functions, thereby allowing quantitative interpretation of the data from the Human Connectome Project. Each species could have its unique advantages and a combined study across multiple species and scales could lead to a deeper understanding of brain activity and function. However, there are several significant challenges to overcome to achieve such a combined study of multispecies neuroimaging data.

First, generalizing the imaging data and brain mapping results from one species to another is multiscale in nature and is not trivial given the biological differences between species. For example, one cannot assume that the number of resting state functional brain networks identified in humans is the same in macaque monkeys and chimpanzees. Second, effectively dealing with the intrinsic variability across individuals and species could be a major challenge. For instance, the similarity and variability of cortical folding patterns of primate brains are still not well understood [43]. Without effective representation of common brain architectures [44], it is difficult to quantitatively compare and integrate multiscale neuroimaging data across species and make meaningful interpretation of such data. Third, different species have variable life spans, and the age dependence of structural and functional properties of the brain of different species could be considerably different. Thus, identification of the appropriate life stages across species for cross-species multiscale imaging and data integration is another challenge.

C. Developing Models and Theories and Building Infrastructures for Better Understanding and Analyzing of Brain Data

Because of the unique complexity of brain function, advances in device engineering require advances in modeling of brain dynamics and behavior. Such advances include computational, mathematical, and statistical methods for identifying information contained in the increasingly large and diverse data sets provided by brain/behavioral imaging methods. A clear challenge for the community is to develop new algorithms to archive, process, and analyze data, and more innovative and comprehensive models for relating measured neural data to behavior and cognition. This could range from development of models relating brain maps to cognitive correlates in the human brain to specialized hardware to inform and simulate these models efficiently. Success in developing such models and theories would ultimately enable development of synthetic brain-based cognitive systems. Current methods for modeling and analysis tend to investigate first-order relationships between neural activity and cognitive correlates. A challenge is to develop new theories and mathematics to enable higher level, nonlinear relationships to be captured and analyzed. There is a clear need for brain-informed cognitive models that can predict and learn in complex stochastic environments. A common theoretical language for describing the brain, particularly across scales, would also be highly impactful in terms of understanding the brain. An example is network-/graph-based theory [45], which is being employed at the macroscale, mesoscale, and even microscale to describe and analyze neural connectivity. Ultimately, such theories and models need to be tested, for example, via simulation, and the challenge of developing specialized hardware for enabling such simulation was seen as an important aspect of the challenge. These platforms need to go beyond traditional Von Neumann architectures and instead adopt hardware designs better suited to the "wet ware" approach. Finally, these theories, models, and simulations would be most impactful if they could unify molecular- and cellular-scale processing with systems scale function, information processing, and ultimately perception and cognition.

A related challenge is to reduce "Big Data" to "Small Data." Low-dimensional measures that are robust and predictive within or across individuals are needed to apply effective therapeutic, assistive, or augmentative devices for use by therapists, patients, or healthy individuals. Such systems might also guide or abet behavioral interventions. Ideally, they may provide objective metrics of mental health, a problem now recognized as foremost to the field of psychiatry. Model-based procedures and algorithms are needed that can distill succinct, predictive, and descriptions of physiology. This need brings forth interesting opportunities for the study of cellular, multicellular, and mass action brain systems for control theory and statistical information processing.

Also of importance for data management and data sharing is standardization of storage formats, collaboration across centers (or countries), the ability to store and reuse data long-term, and patient privacy and security.

D. Training and Educating a Workforce for the Future

An important challenge is the development of a broadly educated and well-trained workforce that can lead future efforts in research and development for mapping and managing brain health through neurotechnologies. Many physical therapists, neuropsychologists, and rehabilitation experts do not have the technical background to understand data from emerging brain

imaging modalities. They are also not trained in analytics associated with interpreting neural signals measured from the brain. Developing educational tools for a neuroimaging ready workforce is an important priority. Similarly, many engineers trained in traditional disciplines may not have the neuroscience background to identify challenges that will be of significance for brain sciences. Integrative training and education of the workforce at all levels, ranging from undergraduate, graduate, postdoctoral, and resident levels are needed.

VI. Participants

The following colleagues from a number of academic institutions participated in the NSF Workshop on Mapping and Engineering the Brain and contributed to the discussions and identification of grand challenges summarized in this report: Bin He (Workshop Chair), Philip Bayly, Kwabena Boahen, Ed Boyden, Truman Brown, Todd Coleman, Tom Cortese, Mingzhou Ding, Michael Fox, Jack Gallant, Guy Genin, Gary Glover, James Hickman, Xiaoping Hu, Fahmeed Hyder, Nessa Johnson, Ranu Jung, Seong-Gi Kim, Alexander Leonessa, Mo Li, Wen Li, Tianming Liu, Scott Makeig, Dave Meaney, David Mogul, Lilianne Mujica-Parodi, Banu Onaral, Peter Saggau, Allen Song, Paul Sajda, Olaf Sporns, Ramesh Srinivasan, and Jonathan Viventi. In addition, a number of program officials from NSF (including Kaiming Ye and Ted Conway) and other federal government agencies participated in the workshop.

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