

Report to the National Science Foundation

2014 Workshop on Noninvasive Imaging of Brain Function

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Introduction

An understanding of the functional architecture of the human brain is among the most profound and far-reaching scientific challenges of our time. Such insight holds the promise of new treatments for disorders of brain function and development, fundamental discoveries about mechanisms of thought and behavior, and impactful applications of neuroscience to more intelligent computational systems, brain-machine interfaces, and neural simulation. Recently, a national initiative, Brain Research through Advancing Innovative Neurotechnologies (BRAIN Initiative) was launched to “accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought.”

Techniques for imaging the structure and function of the *in vivo* human brain are of particular value because they can reveal connections between neurological activity within specific regions of the brain and corresponding perceptions, thoughts or behaviors. To advance imaging in humans, potentially outside a laboratory setting, there is a great need for techniques that are noninvasive, in contrast to the emerging and complementary class of brain imaging techniques that include *ex vivo* whole brain imaging of cleared brain structures and optogenetic imaging of cell-scale neuronal activity in animals.

New capacities to image brain function or structure noninvasively could revolutionize the way we understand the connections between brain physiology and human behavior. Limitations of existing techniques include constraints on subject motion during imaging, requirements for elaborate electromagnetic shielding from the environment, requirements for active cooling of imaging system sensors, and system resolution that is much coarser (millimeter to centimeter scale) than that required to detect activity corresponding to individual neuronal signaling.

In the summer of 2014, Professor Thomas Bifano of Boston University was awarded a grant to organize and host an NSF Workshop on Noninvasive Imaging of Brain Function. The workshop committee invited recognized national experts to discuss three main aspects of in noninvasive imaging of brain function: imaging modalities, sensors and nanoreceptors, and algorithms and computational approaches. The workshop was held on July 23-24, 2014 at the Westin Arlington Gateway Hotel in Arlington, VA, and included 70 invited participants (Appendix I), most of whom were affiliated with federal agencies, national laboratories, or academic institutions. The workshop agenda included fourteen technical presentations, a moderated panel of government agency representatives, and an extended breakout session to discuss enabling research directions in each of the workshop’s three themes (Appendix II).

This report was prepared by the technical session chairs of the workshop, and is intended to summarize fundamental research challenges and promising research directions. It is provided to NSF to assist in planning future programs in noninvasive imaging of brain function.

Summary of workshop findings

The workshop focused on identifying current limitations in our ability to image brain function *in vivo* and on discussing emerging technologies that could expand the reach of noninvasive human functional brain imaging.

Current State and Limitations of Noninvasive Brain Imaging

Existing technologies for imaging the functioning human brain are powerful and have yielded core insights about the architecture and dynamic function of the brain. Computed Tomography (CT) and magnetic resonance imaging (MRI), including functional MRI, perfusion imaging, diffusion imaging, spectroscopic imaging, and MRI-based molecular probes offer not only exquisite structural but functional information in the awake, intact human brain. Electroencephalographic (EEG) and magnetoencephalographic (MEG) technologies record electromagnetic signals from the surface of the head, allowing fine temporal resolution of brain activity with improving spatial selectivity. Nuclear medicine techniques such as Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT), combined with advances in radiopharmaceuticals allow imaging of functional brain metabolism and specific molecular-scale neurochemistry. Optical technologies such as Functional Near-Infrared Spectroscopy (fNIRS) allow potential for imaging brain function in more organic environments. And both imaging and nondestructive perturbations may be achieved by such techniques as High-Frequency Ultrasound (HIFU) and Transcranial Magnetic Stimulation (TMS).

Throughout the course of the workshop, areas of common ground were identified from among speaker presentations that highlight limitations in current abilities to noninvasively image the brain. Such capability gaps in existing technologies constrain clinical diagnostic imaging and scientific research on brain function and represent opportunities for investment in strategies to mitigate these limitations. Four perceived gaps discussed at the workshop included the need for portable, low-cost imaging solutions, the limitation of imaging neural populations at the sub-millimeter to millimeter spatial scale, the integration of existing technologies into more functional combined or hybrid techniques, and the information-theoretic challenges of multiscale visualization, management of large imaging datasets, and large network modeling.

Gap 1: Portable, Low Cost Noninvasive Imaging Solutions in Organic Environments

Many of the most useful technologies for noninvasive brain imaging are constrained by bulky, fixed hardware that preclude imaging of the functioning brain in organic environments inhabited by awake, interacting, behaving humans. Although clever reductionist paradigms have made strides toward deducing brain function in highly controlled laboratory environments, the high cost of imaging machines has limited the scope and duration of imaging that can be performed. Next generation imaging modalities that can offer mobile, wearable hardware at lower cost could allow more flexible and longer epochs of brain imaging. Wireless telemetry between sensors and data recording devices could remove constraints on activities and interactions during which imaging could be performed. Such imaging solutions could accelerate timing and availability of clinical diagnostics, probe human brain function in natural environments, and expand the scope of brain imaging beyond what can affordably be obtained with existing higher-cost techniques.

Gap 2: Imaging Between Cellular and Macroscopic Scales

There was great enthusiasm among attendees that existing optical and molecular imaging techniques have rapidly developed to allow imaging of synaptic, single-neuron, and small circuit dynamics, and that whole-brain imaging modalities allow capacity for functional imaging of macroscopic brain tissue. Bridging these domains to allow multiscale modeling and imaging will require improved technologies for noninvasive imaging at spatial scales between one hundred micrometers and a few millimeters while providing precise information about electrical, molecular and/or cellular function. Ideally, such imaging would combine millisecond-scale temporal resolution for imaging that can resolve cortical columns and small subcortical nuclei. Although the grand challenge of the BRAIN initiative has been to record activity from single neurons, workshop attendees were in general agreement that imaging neural populations at higher levels of organization and larger spatial and temporal scales (up to millimeters and seconds, respectively) may also yield important insights into mechanisms of behavior, perception, and cognition, given the modular organization and functioning of the brain at those scales, especially if it carries highly precise information about electrical signaling, neurotransmission, intracellular signaling and gene expression. Part of this gap is due to inadequate molecular reporters for non-invasive imaging (in contrast to optical imaging).

Gap 3: Development and Accessibility of Hybrid and Multimodal Imaging Devices

Among existing imaging techniques, each modality offers unique strengths and is limited by differing operational resolutions, environments, and interaction modality with the brain. There is underutilized potential for combining these techniques into hybrid devices that can take advantage of the strengths of each modality. Solutions such as PET/CT and fMRI/EEG are examples of such devices that have allowed improvements via contemporaneous imaging. Attendees expressed optimism that new combinations of imaging devices may allow noninvasive imaging combined with brain functional probes such as TMS or HIFU or may expand combined temporospatial resolution with improvements to or development of MRI/EEG, MRI/MEG, EEG/MEG, or other combination devices. There is a need for software tools to facilitate image coregistration, visualization, source localization, and integration of signals in such combined devices that can address artifacts and promote ease of use that can expand the user base of such devices beyond a highly specialized core of researchers.

Gap 4: Multiscale Visualization, Image Data Management, and Large Network Modeling

As imaging techniques continue to advance in resolution and capacity, larger datasets are routinely acquired that stretch the abilities of researchers and clinicians to analyze and interpret. There is increasing need for tools that combine information across spatial and temporal scales in the brain to make predictions or model behavior and cognition. Approaches for visualization of multidimensional and high-resolution datasets must be enhanced to take advantage of existing and emerging tools. Flexible data storage solutions for image processing and analysis must take advantage of continuing advances in mobile, high-performance, and distributed computing. Algorithms and approaches to modeling emergent properties of large circuits of neural populations are needed to integrate the information that can be obtained from next-generation imaging strategies.

Sensor, Probe, and Algorithmic Technologies for Filling Imaging Gaps

The workshop included discussions of emerging sensor, probe, and algorithmic technologies that may address the limitations in imaging capabilities discussed above. A number of approaches involved development of improved magnetometers or magnetometer arrays that could record magnetic signals from the surface of the brain at room temperature, transmit information via wireless telemetry, and offer improved spatiotemporal imaging resolution. Such approaches included atomic magnetometers, multiferroic magnetometers, high temperature superconducting quantum interference devices (High T_c SQUIDs), and nitrogen vacancy quantum diamond sensors. To facilitate improved resolution with arrays of sensors more closely spaced on the surface of the head, efforts on new type of magnetometers and improvement in sensitivity of existing sensors are needed.

Ultra-low-field MRI may allow more portable MRI devices that can image in less-constrained environments and identify novel signal sources such as free radical imaging. Advances to obtain functional brain information in addition to structural brain imaging in ultra-low-field or zero-field MRI are needed. Approaches to direct neural current MRI measurement may include both high-field and ultra-low-field strategies as well as hybrid imaging devices.

Intrinsic and extrinsic molecular imaging probes may expand capabilities of existing and emerging technologies by allowing imaging of novel physiological processes or visualization of neurochemical information not accessible to conventional imaging techniques due to sparsity or insufficient contrast of signal sources. Magnetic resonance, optical, sonographic, and emission imaging strategies may be combined with such probes to image new types of functional brain information on physiological and neurochemical processes. Improved capabilities for dynamic imaging of brain chemistry would represent an important advance in noninvasive brain imaging.

Hybrid image devices such as MRI/MEG (including both ultra-low-field and high-field MRI), improved MRI/EEG, TMS/MEG, fNIRS/MEG, HIFU/MRI and HIFU/MEG may allow improved portability or combined temporospatial resolution of brain imaging, and continued hardware and software advances for such techniques are needed to attain impactful accessibility and performance.

Improved capabilities in source signal localization, multiscale visualization, multimodal imaging, and large network modeling require both computational and algorithmic advances. Algorithmic and information-theoretic tools are needed to improve performance of brain imaging sensors, imaging modality systems, and the interpretation of data produced by these tools. Software that can extend visualization and analysis capabilities to larger a user base and imaging population will increase the rate at which emerging technologies can be translated into clinical and scientific advances.

Imaging Modalities

The development of traditional noninvasive brain imaging modalities based on external sensing (optical, MRI, fMRI, EEG, MEG, PET, CT and ultrasound) has resulted in enormous advances in both the understanding of the human brain and also the ability to diagnose, and in some cases treat, brain disease. However, all existing modalities used individually fall short of

the “ideal”: real-time, non-invasive recording of functional neural signals with millisecond temporal resolution and neuron-level spatial resolution; see Figure 1. In addition, existing brain imaging systems with a spatial resolution below a few millimeters are large and cumbersome, expensive to operate and currently not suitable for widespread deployment outside dedicated hospital facilities.

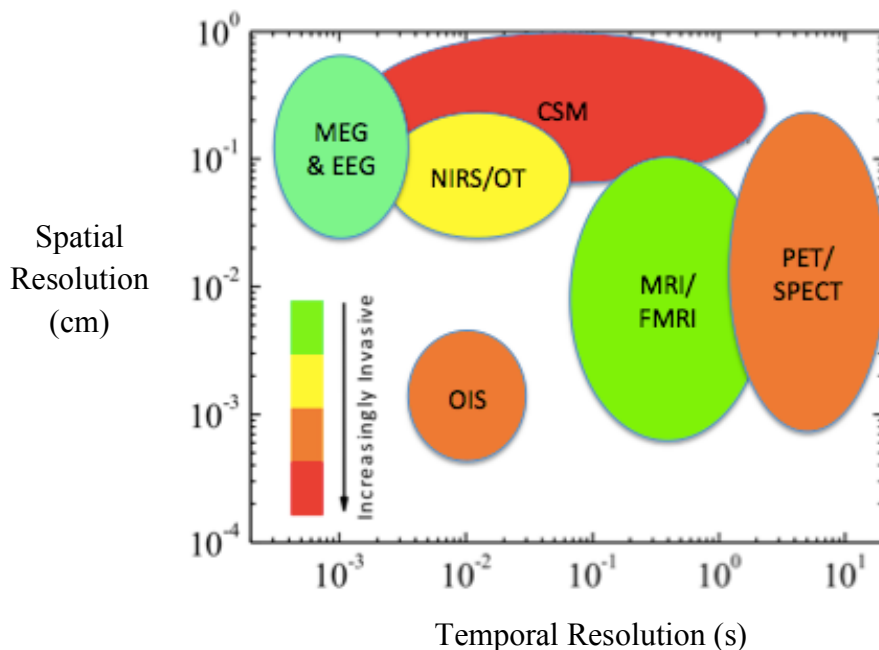


Figure 1. Spatial and temporal resolution of existing conventional imaging modalities. (Adapted from [1]). MEG: Magnetoencephalography; EEG: Electroencephalography; OT: Optical tomography; NIRS: Near-infrared spectroscopy; CSM: Cortical stimulation mapping; US: Ultrasound; CT: Coherence tomography; PET: Positron emission tomography; SPECT: Single-photon emission computed tomography; fMRI: Functional MRI; OIS: Optical imaging of intrinsic signals.

The limitations of existing imaging technology are largely inherent to the modality and it is unlikely that vast improvements will be made through incremental advances in any one technology. Conventional magnetic resonance imaging gives structural or chemical information about the brain, not information on direct neuronal currents, and is typically limited to time scales slower than one second. Magnetoencephalography faces the fundamental non-uniqueness of the inverse problem in reconstructing current sources inside the brain from external measurements. Electroencephalography relies on the propagation of electrical signals through a conducting medium, which limits its spatial resolution for non-invasive detection of these signals. Cryogenic systems are likely to continue to be needed in the future for both high-field superconducting MRI coils and the operation of highly sensitive SQUID magnetometers in MEG.

Emerging Opportunities

The workshop explored many novel approaches to future brain imaging technology and systems. Low-field magnetic resonance imaging techniques, in which superconducting magnets are not needed, may lead to robust, widely deployable systems with high diagnostic impact. New magnetic detector technologies that operate at low frequencies and do not need cryogenic cooling have been developed and are now achieving sensitivity levels suitable for MEG. And multi-modal imaging approaches that combine the best features of one or more individual approaches are being tested [2, 3]. Taken together these advances offer significant opportunity for future progress in understanding brain function and diagnosing and treating brain disease using entirely non-invasive techniques.

A number of new sensor technologies are emerging as replacements for SQUID or coil-based detectors of magnetic fields. SQUID detectors require cooling to (usually) liquid helium temperatures while coils are not sensitive to DC magnetic fields. Figure 2 illustrates the tradeoff between field sensitivity and size for a number of important magnetic sensor technologies. Until the last decade, atomic magnetometers, based on the precession of the spins of alkali atoms in a magnetic field, had not achieved the sensitivity levels needed for the measurement of brain fields. The use of suppressed spin-exchange collision relaxation [4, 5] has enabled atomic magnetometers based on cm-scale alkali atom vapor cells to achieve sensitivities well below 1 fT/ $\sqrt{\text{Hz}}$ [6] over a broad frequency band and reaching 0.16 fT/ $\sqrt{\text{Hz}}$ at some frequencies. These improvements in sensitivity have enabled the detection of MEG signals from humans for the first time with atomic magnetometers [7-10]. The use of microfabrication techniques has enabled electrode-sized versions of these sensors [11, 12] that might ultimately lead to portable, unshielded measurement of brain magnetic fields. These improvements in sensitivity have enabled the detection of MEG signals from humans for the first time with atomic magnetometers. The use of microfabrication techniques has enabled electrode-sized versions of these sensors [11, 12] that might ultimately lead to portable, unshielded measurement of brain magnetic fields. The enhancement of the signal strength made possible by the closer proximity of the sensors to at least shallow sources in the brain [12] may lead to lower localization error. The limitation of many of the highest performing atomic magnetometers that they be operated in low magnetic fields (typically below a few nT) has been relaxed by the recent demonstration of suppressed spin-exchange relaxation in a scalar magnetometer configuration at high fields [13]. Outstanding challenges going forward include continual improvements in detector sensitivity, the development of high-rejection gradiometers and operation on mobile platforms without magnetic shielding.

The long coherence times of electron spins associated with nitrogen-vacancy (NV) color centers in diamond [14] has recently been exploited to enable magnetic sensors with extremely high spatial resolution, below 1 micron [15]. The close proximity to sources that can be achieved with these sensors enables very high dipole moment sensitivity even with only modest field sensitivity [16]. Applications relevant to brain imaging include single-molecule NMR [17], high-resolution magnetic imaging of in vitro cellular cultures and possible simple (small) animals and intracellular monitoring of local environments, such as temperature [18, 19].

High-Tc SQUID magnetometers are also improving, with sensitivities of 5fT/ $\sqrt{\text{Hz}}$ [20] in the frequency band between 10 Hz and 1 kHz. These may be well suited to be coupled with superconducting coils for transcranial magnetic stimulation allowing impulse-response magnetic experiments with high spatial and temporal resolution using only liquid nitrogen cooling.

Low-cost, room-temperature multiferroic magnetic sensors based on ferromagnetic-piezoelectric composites may have the potential for use in MEG [21, 22], but many challenges for their use are to be addressed. Sensors made of Metglas-piezofiber with sensitivities in the range $1\text{-}5\text{pT}/\sqrt{\text{Hz}}$ @ 1Hz [21], FeCoSiB/AlN miniature cantilevers with sensitivity of $\sim 3\text{pT}/\sqrt{\text{Hz}}$ at mechanical resonance [22], and nano-electromechanical multiferroic sensors [23] have been demonstrated in recent years. Efforts are needed for sensitivity enhancement, self-biasing technology, noise reduction, fabrication of arrays, and signal conditioning electronics [21].

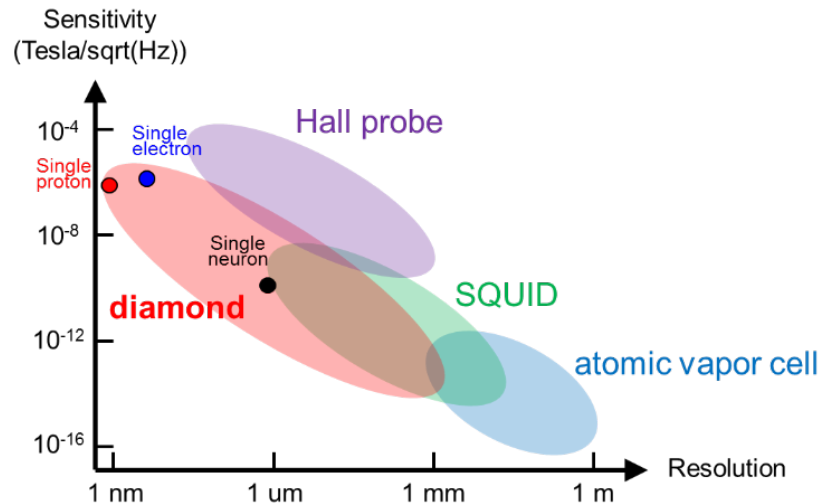


Figure 2. High-performance magnetic sensors illustrating the tradeoff between spatial resolution and performance (Adapted from workshop presentation by R. Walsworth, Harvard University).

Magnetic resonance imaging at low magnetic fields avoids the need for large superconducting magnets but has traditionally suffered from poor signal-to-noise ratios resulting from the associated low polarization fractions. However, hyperpolarization techniques such as spin-exchange optical pumping [24, 25], parahydrogen-induced hyperpolarization [26], and dynamic nuclear polarization [27] allow orders of magnetic improvement in the thermal polarization fraction and hence improves the sensitivity of low-field techniques considerably [28, 29]. As discussed below, molecular probes compatible with hyperpolarization and low-field MRI could broaden the application of these technologies in neural imaging. In addition, sensitivity to endogenous compounds such as, for example, free radicals, may allow detection of some types of brain disease associated with oxidative stress injury [30]. The sensitivity of magnetic resonance imaging to chemical composition is a considerable strength of this technique. Low-field MRI also allows coregistered structural imaging with functional magneto-encephalography using SQUID detectors implemented on a helmet for both imaging modalities [2]. Such multimodal systems combine the advantages of each modality individually; in the case of MEG/MRI systems the high spatial resolution of the structural MRI image can constrain the variability inherent in the non-unique MEG source reconstruction. Neuronal current MRI is an appealing alternative to conventional techniques, potentially giving high spatial and temporal resolution while being directly sensitive to neuronal activity, although its physical feasibility remains to be established.

At present there are no non-invasive imaging modalities that are able to resolve electrical activity of single neurons on time scales typical of neural signaling. While such “ideal” information would be useful in many situations, modeling large systems at this level of resolution rapidly progresses to impossible levels of complexity. Considerable understanding of high-level brain function and behavior may be possible with measurements with much coarser spatial resolution over aggregate neuron populations. Opportunities exist for combining information over a large range of length scales to deepen understanding of brain function. Cross-scale coupling and emergent behavior will be important to connect neuron-level dynamics to large-scale behavior.

Imaging Modality Recommendations

Guided by the assessment of emerging brain imaging technologies made at the workshop, an important opportunity was identified for unshielded and/or mobile brain imaging. EEG already achieves the compact form factors but better telemetry is needed along with better forward head modeling and inverse source imaging algorithms for enhanced source localization. Compact, low-power fiber-optically coupled or stand-alone magnetic sensor arrays for MEG or portable low-field MRI systems may allow imaging of the brain in disruptive environments not previously possible. The dominant clinical application for MEG is localization of epileptic activity before surgery and is usually carried out by monitoring interictal neural spiking. Mobile neural magnetic recording might enable direct recording of neural activity during a seizure similar to EEG and lead to correspondingly better localization and treatment. Novel imaging algorithms to localize and image seizure sources from EEG and MEG (with mobile MEG recording capability to be developed) will significantly enhance our ability to image seizure generating tissues noninvasively. Low-field MRI might be implemented at low-cost in doctors’ offices or other in-field environments. The panel recommends future investment in these and other areas, taking advantage of new sensor technologies new imaging modalities and low-power electronics and telemetry.

Imaging reporters to enhance non-invasive imaging modalities

A major limitation of non-invasive brain imaging is the relatively narrow scope of information non-invasive modalities are able to provide about neural signaling. In particular, EEG and MEG are limited by fundamental physics to measuring concerted, large-scale electrical activity involving thousands to millions of neurons, while MRI, ultrasound and PET are mostly limited to imaging anatomy, hemodynamic responses or metabolism indirectly reflecting underlying neuronal excitation. Thus, while non-invasive imaging techniques can probe deeply inside the brain, they fail to capture the vast majority of specific cellular and molecular signaling events comprising neural activity.

In some respects, the present state of non-invasive imaging is similar to that of optical microscopy before the proliferation of chemical dyes and genetic reporters. While the microscopic observation of unlabeled cells and tissues enabled some seminal discoveries in organismal anatomy, it was not until chemical dyes were invented that microscopy could provide information about specific cell types and molecular signals involved in the function of organs and organisms. The observation of neural function in particular was revolutionized by

environmentally-sensitive fluorescent compounds capable of reporting real-time concentrations of calcium or membrane potential [31]. And more recently, the development of genetically encoded optical reporters (such as those based on green fluorescent protein, GFP) has enabled optical imaging of specific molecular signals in targeted cells [32-35]. Today, genetically encoded calcium indicators such as GCaMP dominate the interrogation of neural function in translucent model organisms or surgically accessed brain regions. Notably, the advent of fluorophores both enabled optical imaging to obtain maximal information about biological systems and stimulated advances in the imaging technology itself. Fluorescent imaging, confocal and multiphoton microscopy (including, recently, 3-photon imaging approaching 2 mm penetration [36]), are all active areas of technology development co-evolved with the advent of chemical and genetic reporters.

Following the example of optical imaging, how can non-invasive imaging technologies go beyond endogenous signals to obtain more specific molecular and cellular information? What will be the MRI and ultrasound equivalents of GCaMP? This is a key scientific question and opportunity for technology breakthroughs.

Targets for non-invasive imaging: beyond electricity

To develop precise reporters for non-invasive imaging of neural activity, it is important to define the targets for such imaging. Although historically both invasive (electrode recordings) and non-invasive (EEG, MEG) brain imaging methods have focused on the electrical activity of neurons, it is now known that much of the information content corresponding to brain function is contained in chemical signals such as neurotransmitters, second-messenger cascades, gene expression and protein trafficking (Figure 3). In fact, neurons interact with each other primarily through chemical, rather than electrical means. Thus, being able to monitor the chemical function of the brain as well as its electrical signals non-invasively would enable major advances in neuroscience.

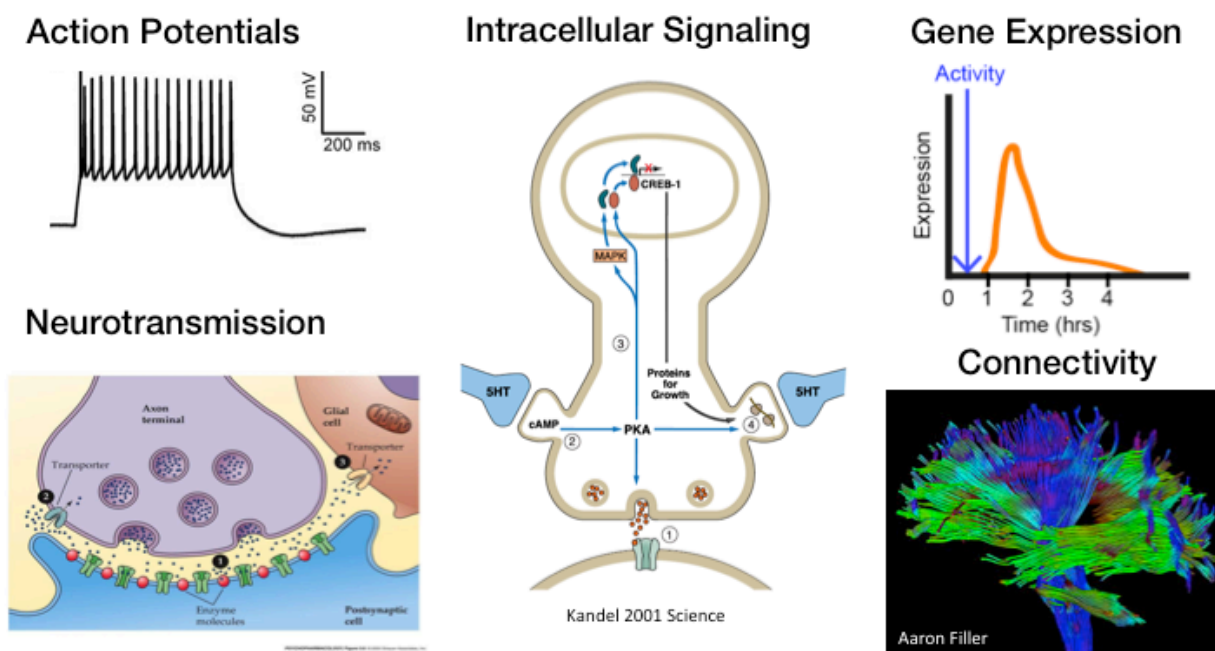


Figure 3. Targets for noninvasive neural imaging

Classes of imaging reporters

Reporters developed to enhance the information content of non-invasive neural imaging may be organic chemicals, reporter genes, inorganic nanostructures or microscale devices (Table 1). Each type of reporter offers potential advantages for imaging brain activity. Chemical contrast agents for MRI have been developed based on organic compounds chelating paramagnetic ions such as gadolinium(III), which shorten the longitudinal relaxation of aqueous proton nuclei [37]. Such agents have been configured to respond dynamically to signals such as calcium with changes in contrast [38]. However, as large, charged compounds they have been difficult to introduce into cells and the brain from systemic circulation due to the blood-brain barrier, limiting their utility for neuroscience studies. New chemical imaging agents are needed that have chemical properties enabling them to cross the BBB. Potential approaches could include more lipophilic chemical scaffolds and functionalization with “Trojan horse” ligands or antibodies mediating active uptake into the brain [39].

A second category of imaging agents has been developed based on nano- and micro-materials. For MRI, these agents include magnetic nanoparticles (MNPs, typically comprising an iron oxide core and organic shell) that produce contrast by shortening transverse relaxation [40]. MNPs have been functionalized as dynamic reporters of calcium and other analytes [41, 42], but have not been used in neuroscience experiments because of the difficulty of delivering them into the brain and into cells. Contrast agents for ultrasound have been developed based on microbubbles – gas bubbles of 1-5 μm diameter stabilized by a protein or lipid shell [43]. Microbubbles are challenging to use inside cells and in the brain because their micron size typically confines them to the circulation. Nanoscale ultrasound imaging agents have been

developed based on perfluorocarbon liquid nanodroplets [44] and biogenic protein nanostructures [45]. However, these have not yet been employed in neuroscience.

Recently, non-invasive imaging agents have been developed based on genetically encoded biomolecular structures that can be targeted to cells as genes. The genetically encoded approach has been spectacularly successful in optical imaging due to the fact that genes can be targeted to specific cell types in defined regions of the brain (e.g. using cell type specific promoters) and allow cells to continually express the reporter inside the cell for long-term imaging [46]. The reporter itself can be large and chemically complex without compromising delivery because it is made *in situ*. Instead, the task of delivery is transferred to gene targeting, a routine capability in animal studies and a rapidly developing area of clinical research [47, 48]. Several genetically encodable imaging agents have been proposed for MRI, including reporters based on metalloproteins and peptides with labile proton pools [49]. Protein-based reporters have been engineered to sense neurotransmitters such as dopamine and serotonin [50, 51], but have not yet been delivered genetically. A major issue with current MRI reporter genes has been their poor molecular sensitivity, with a detection limit in the 10-30 μ M range[52], which is too high for many imaging targets of interest. For ultrasound, the first genetically encoded imaging agents were reported in 2014 [45]. These agents are based on gas vesicles – gas-filled protein nanostructures from buoyant microbes. So far, these agents have only been expressed in their native organisms (haloarchaea and cyanobacteria) and *E. coli* [45, 53]. If genetically encoded MRI or ultrasound imaging reporters could be developed to robustly report neural signaling, this would represent a major breakthrough in neuroscience.

Finally, microscale devices offer the potential to provide a high-bandwidth link between deep brain function and external receivers. Although such microscale devices would need to be implanted, perhaps through a minimally invasive approach, they would couple with non-invasive imaging modalities to provide more precise information about neural signaling. For example, 100 μ m-sized “neural dust motes” have been proposed that could be powered and communicate with an implanted ultrasound transducer, which in turn communicates wirelessly with an external receiver[54]. Microscale transducers could also be engineered for detection directly by external magnetic sensors or radiofrequency transmission.

Table 1 – Classes of Imaging Reporters

	Electrical	Optical	Magnetic	Acoustic	Nuclear
Endogenous Signals	Neuronal E	Hemodynamic Chemical	Neuronal B Hemodynamic Connectivity Chemical	Hemodynamic	
Chemical Transducers		Environment-sensitive dyes (Ca ²⁺ , V _m)	Contrast agents, Hyper-polarized molecules		PET agents (e.g. glucose)
Nanomaterial Transducers	Nanowires	Quantum dot, Nanodiamond	Magnetic nanoparticles	Nanodroplets	
Genetic Transducers		GECI (Ca ²⁺), GEVI (V _m), Luciferase	Metallo-proteins, Gas vesicles	Gas vesicles	
Micro-device Transducers	Several		Micro-resonators	“Neural dust”	

Opportunities for breakthroughs

Opportunities to advance the capabilities of non-invasive brain imaging through the use of imaging agents include the development of non-conventional chemical reporters, genetically encoded sensors and advances in implantable, wirelessly-addressable microscale devices.

For chemical imaging in MRI, a major area of opportunity is hyperpolarization, an approach whereby imaging agents are pre-polarized to a highly magnetized state and introduced into the body [26]. These agents can then be directly detected and provide information about their chemical state. For example, the hyperpolarized metabolite pyruvate and its conversion to lactate, alanine and bicarbonate, were recently used to directly image the metabolism of prostate tumors in human patients [55]. Could hyperpolarized metabolites directed to the brain be used to monitor chemical metabolism related to neural function? Alternatively, hyperpolarized nuclei such as the biocompatible noble gas xenon can be used as the magnetic resonance substrate for chemical reporters, enabling such reporters to be detected at nanomolar or lower concentrations [56]. Xenon is particularly attractive due to its ability to dissolve in blood and delivered to the brain via inhalation, pulmonary uptake and circulation [57]. To be useful for neural imaging, new functional contrast agents are needed to convert neuronal signals such as neurotransmission or gene expression into Xe-MRI contrast. Among the potential advantages of hyperpolarized MRI is that it could work well at low fields, making it compatible with low-cost, ambulatory low field MRI scanners. Furthermore, operating at low fields would allow imaging approaches that involve electron spins instead of, or in addition to, nuclear spins. For example, Overhauser-enhanced MRI allows chemical imaging agents containing stable free radicals to dynamically hyperpolarize nearby nuclear spins, effecting hyperpolarization *in situ* [30]. If appropriate free

radical agents could be developed as reporters of neural signaling, this would provide another avenue to imaging brain chemistry non-invasively using low-field MRI.

Another major area of opportunity is the development of more sensitive genetically encoded reporters for MRI and ultrasound. A key focus for MRI is overcoming the sensitivity limitations of first-generation agents. This may be accomplished by using more strongly paramagnetic proteins, including manganese-containing enzymes, as starting points for sensor design. Established protein engineering and directed evolution approaches can be used to adapt such paramagnetic proteins into sensors of specific neurochemical analytes. More radical advances in sensitivity may be possible by developing reporter genes compatible with hyperpolarization. For example, genetically encoded gas nanostructures were recently used as imaging agents for hyperpolarized xenon MRI, providing a 2-5 order of magnitude improvement in molecular sensitivity [53]. Could such agents could be used to image neuronal gene expression connected to activity or plasticity? Similarly, genetically encoded reporters could make a major impact in brain imaging with ultrasound [45, 58].

A third major area of opportunity is the continuing development of implantable microscale devices. As described above, such devices could be engineered to interact with external magnetic, RF or ultrasound receivers, providing information about local neural signals. This approach requires progress on some fundamental challenges, including efficient RF and ultrasonic communication at penetrant frequencies with microscale receivers (which naturally resonate at frequencies too high for efficient transmission through the brain). Another fundamental challenge for RF and magnetically detected devices is spatial localization [59].

Algorithmic and computational approaches

Dominant non-invasive structural and functional brain imaging modalities such as MRI, fMRI, MEG and EEG technologies have matured in recent years, with continued increases in resolution and fidelity of these methods. These advances have been enabled whole brain acquisition with sufficient spatial and temporal resolution and sensitivity not only by novel hardware and acquisition schemes but also by algorithmic and computational approaches. Notably, the field of non-invasive imaging has emerged from examining whole brain activity to whole brain structural and functional connectivity and the dynamics of connectivity both within and across isolated spectral frequency bands, and the relationship of activity and connectivity to human behavior. Blood-oxygen-level dependent (BOLD) fMRI has advanced from examining brain activations to examining brain networks and their connectivity, mainly through computational and algorithmic approaches. MEG imaging has emerged as a powerful tool for human neuroscience, allowing for mesoscopic imaging with high spatial, temporal and dynamic connectivity enabled by algorithms. Integration of MEG and FMRI, as well as other structural/functional imaging data remains an active area of research that relies strongly on development of algorithmic and computational approaches.

The challenges and future developments are thought to lie in the area of multimodal imaging data integration - either simultaneous collected data or non-simultaneous fusion of information across multiple modalities - potentially enabling extracting robust information in an individual subject rather than having to fuse data across subjects for noise reduction and generalization. As novel sensor based imaging modalities emerge, and current multiple modalities of structural and functional brain imaging have matured, there is great need for algorithmic and computational

approaches to fully harness the potential of these imaging modalities. Algorithms and computational approaches have paved for “super-resolution” reconstructions in many fields, including non-invasive brain imaging and it is fully expected that they will continue to do so. In addition to enabling whole brain imaging capabilities, algorithmic approaches can also enable non-invasive imaging at a microscopic scale through imaging of single neuron activity by adaptation and application of advances in whole brain image analysis techniques to optical imaging with or without novel probes.

Algorithmic and computational approaches can augment capabilities at the four levels: 1) Data acquisition, 2) Post-processing image analysis and reconstruction, and 3) Single subject and group level statistical inference, and 4) interactive visualization of data. At the workshop, Dr. Eric Wong who demonstrated that algorithms impact post-processing reconstructions through modifications in data collection in the context of fMRI that can result in significant acceleration of image acquisition time with little tradeoff in resolution. As a second example, Dr. Aude Oliva, demonstrated how high-level models of computer vision can be tested with multimodality neuroimaging data using novel analytical approaches such as representational similarity analyses. Furthermore, Dr. Srikantan Nagarajan, who showed that machine learning algorithms can significantly enhance the fidelity of magnetoencephalography (MEG) based imaging. Many other workshop participants also demonstrated in white papers and in posters how algorithmic and computational approaches significantly augment imaging modalities to enable deeper insights into brain function and connectivity.

Algorithmic approaches can enhance the capabilities of novel sensor technologies. They can also help determine limits on performance of specific imaging modalities. Key challenges will involve integration between teams of computational scientists and sensor and imaging modality developers. At the level of data acquisition, algorithms can be used to reduce single and multiple sensor level noise and interferences through novel selective signal cancellation and enhancement methods that can be implemented in hardware. One such challenge is dealing with non-stationary signal and noise environments. Additionally, within MRI algorithmic approaches like compressive sensing are already showing the potential to revolutionize acquisition speeds with no reduction in SNR.

Harnessing mobile and miniaturization technologies for computation at the level of data acquisition can enable taking devices and systems outside of a laboratory setting. Algorithmic and computational approaches can also inform the design of novel imaging modalities as demonstrated in work of Drs. Matti Hamalainen and Kensuke Sekihara who have examined design criteria and trade-off for next generation MEG systems. For instance, computational analyses have revealed that significant benefits in spatial resolution and signal-to-noise ratio in MEG systems, can be achieved with having sensors closer to the scalp surface than existing SQUID-based systems, as is possible with new sensor-technologies such as Atomic magnetometers (AMs).

Within the realm of post-processing of sensor data, there already exist tremendous efforts that involve algorithmic and computational approaches for image analysis. These include unimodal and multimodal imaging analyses, statistical inferences, incorporating experimental design features, leveraging theoretical and experimental data across multiple scales and modalities, leveraging information from quantitative and qualitative models. There needs to be continued efforts in developing and sustaining pipelines for image analysis that will enable

widespread use of novel imaging technologies, and challenges involving visualization of multidimensional data.

Visualization challenges include the ability to interactively interact with high-dimensional functional imaging data (8 or 9-dimensions such as space, time, frequency or activity, cross-space connectivity and cross-frequency coupling). Such interactivity does not exist even in current technologies and are important. Furthermore, the ability to include statistical inference within visualization environments is also important and currently lacking. There is need for flexible visualization platforms that harness cloud-computing and visualization across multiple client platforms. A related problem for image analysis and visualization is the lack of a consistent data format standards. This may be important to establish for the next generation of non-invasive imaging modalities so that results across labs can be easily compared etc. This point can be addressed within pipeline development and maintenance.

A subsequent problem in non-invasive imaging modalities is the facile explosion of data volumes. Computational approaches can help address big data challenges within this field, especially as we move in the regime of multimodal imaging data fusion. Here to, leveraging advances in machine learning can be used to successfully integrate information across multiple modalities to develop convergent information about brain function. This is especially important because various brain imaging modalities often provide complementary information about brain function and therefore necessitating integration of information across multiple modalities.

In particular, there was some consensus in the workshop that to advance next generation of non-invasive imaging modalities, there needs to significant investment in teams that include multidisciplinary scientists including expertise in algorithmic and computational approaches. Furthermore, in addition to development of general purpose imaging modalities, there could also be investment in teams solving specific neuroscience problems that harness non-invasive imaging modalities, leveraging algorithmic and computational approaches.

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Appendix I: Invited Attendees

<u>Last Name</u>	<u>First Name</u>	<u>Affiliation</u>
Achim	Catalina	National Science Foundation
Anderson	Jeff	University of Utah
Athale	Ravindra	Office of Naval Research
Bandettini	Peter	National Institutes of Health
Barbic	Mladen	Howard Hughes Medical Institute
Barth	Daniel	University of Colorado at Boulder
Bates	Sara	National Science Foundation
Bifano	Thomas	Boston University
Brown	Truman	Medical University of South Carolina
Buckius	Richard	National Science Foundation
Budinger	Thomas	University of California, Berkeley
Conroy	Richard	National Institutes of Health
Dean	Heather	National Science Foundation
Duyn	Jeff	National Institutes of Health
El-Ghazaly	Samir	National Science Foundation
George	John	Los Alamos National Laboratory
Goldstein	Lee	Boston University
Gonzalez	Cecile	National Science Foundation
Grant	Steven	National Institutes of Health
Haddad	George	National Science Foundation
Hämäläinen	Matti	Harvard Medical School/MGH
Hamburg	Arlene	National Science Foundation
Han	Xue	Boston University
Haxby	Jim	Dartmouth College
He	Bin	University of Minnesota
Johnson	Cort	Draper Laboratories
Kaul	Anupama	National Science Foundation
Khargonekar	Pramod	National Science Foundation
Kitching	John	National Institute of Standards and Technology
Knappe	Svenja	National Institute of Standards and Technology
Luo	James	National Institutes of Health
Maharbiz	Michel M.	University of California, Berkeley
Makeig	Scott	University of California, San Diego
Mathisen	Beth	Boston University
Montague	Read	Virginia Polytechnic Institute and State University
Nagarajan	Srikantan	University of California San Francisco
Okada	Yoshio	Harvard Medical School, Boston Children's Hospital
Oliva	Aude	Massachusetts Institute of Technology
Pantazis	Dimitrios	Massachusetts Institute of Technology
Parra	Lucas	The City College of of New York
Pawlyszyn	Stephanie	Boston University
Piestun	Rafael	University of Colorado at Boulder
Priya	Shashank	National Science Foundation

Puyana Barcha	Carolina	National Science Foundation
Raja	Sruti	Boston University
Rastegar	Sohi	National Science Foundation
Romalis	Michael	Princeton University
Rosen	Matthew	Harvard University
Rubin	Philip	White House Office of Science and Technology Policy
Sajda	Paul	Columbia University
Sambanis	Athanassios	National Science Foundation
Schwindt	Peter	University of New Mexico, Sandia National Laboratories
Shapiro	Mikhail	California Institute of Technology
Soriano Molla	Jesus	National Science Foundation
Srinivasan	Gopalan	Oakland University
Sun	Nian	Northeastern University
Tabib-Azar	Massood	University of Utah
Talley	Edmund	National Institutes of Health
Traub	Roger	IBM T.J. Watson Research Center
Van Hartesveldt	Carol	National Science Foundation
Varshney	Usha	National Science Foundation
Verstynen	Timothy	Carnegie Mellon University
Vettel	Jean	Army Research Laboratory
Wakai	Ron	University of Wisconsin
Walsworth	Ronald	Harvard University
Wang	Grace	National Science Foundation
Wilson	Tony	University of Nebraska
Wong	Eric	University of California San Diego
Xu	Chris	Cornell University
Yoon	Euisik	University of Michigan
Zavada	John	National Science Foundation

Appendix II: Workshop Agenda

Schedule

2014 NSF Workshop on Noninvasive Imaging of Brain Function

Overview
Background
Organizers
Call for Whitepapers
Speakers
Schedule
Hotel
Registration
Sponsors

23-July		TENTATIVE SCHEDULE	
8:00 - 8:20 am		Breakfast	
8:20 - 8:40 am		Welcome Remarks	Shashank Priya, Pramod Khargonekar, Samir El-Ghazaly, Grace Wang
8:40 - 8:50 am		Introduction and Overview	Thomas Bifano
		Technical Session 1: Imaging Modalities	
8:50 - 9:00 am		Topic Introduction	John Kitching
9:00 - 9:30 am		New directions in noninvasive studies of brain function	Yoshio Okada
9:30 - 10:00 am		Dynamic imaging of multi-scale neural system	John George
10:00 - 10:30 am		Low-field MRI for Non-invasive imaging of brain function	Matthew Rosen
10:30 - 11:20 am		Coffee Break and Poster Session (20-25 to bring posters)	
11:20 am - Noon		Related Topic Guest Speaker - The depth and speed limitation of in vivo, non-invasive optical imaging of mouse brain	Chris Xu
Noon - 1:10		Lunch	
		Technical Session 2 : Sensors and Nanoreceptors I	
1:10 - 1:20 pm		Topic Introduction	Mikhail Shapiro
1:20 - 1:50 pm		Noninvasive imaging of brain function & think quantum	Ronald Walsworth
1:50 - 2:20 pm		Nanofabricated magnetolectric sensor arrays for room temperature magnetoencephalography	Nian Sun
2:20 - 2:50 pm		Molecular engineering for noninvasive imaging of brain function	Mikhail Shapiro
2:50 - 3:30 pm		Coffee Break and Poster Session	
3:30 - 5:00 pm		Breakout sessions and debrief	Session Leaders
		Imaging Modalities	John Kitching
		Sensors and Nanoreceptors	Mikhail Shapiro
		Algorithms and Computational Approaches	Srikantan Nagarajan
5:30 - 7:30 pm		Dinner Talk: Technologies for controlling neural circuit dynamics	Xue Han
24-July			
8:00 - 8:30 am		Breakfast	
8:30 - 8:40 am		Summary of Day 1, Goals for Day 2	Thomas Bifano
		Technical Session 3: Sensors and Nanoreceptors II	
8:40 - 9:10 am		Towards noninvasive high-resolution and whole-brain neuroimaging: can it include constituents not native to the brain?	Cort Johnson
9:10 - 9:40 am		Microfabricated atomic magnetometers for next-generation brain imaging	Svenja Knappe
9:40 - 10:10 am		Sub-femtotesla scalar atomic magnetometers for magnetoencephalography	Michael Romalis
10:10 - 10:30 am		Coffee Break	
10:30 am - Noon		Government Panel	Moderator: Read Montague, Panel: George Haddad (NSF), Sohi Rastegar (NSF), Shashank Priya (NSF), Richard Conroy (NIH), Steven Grant (NIH)
Noon - 1:10		Lunch	
1:10 - 1:50 pm		Related Topic Guest Speaker - Mechanisms of mild traumatic brain injury and chronic traumatic encephalopathy	Lee Goldstein
		Technical Session 4: Algorithms and Computational Approaches	
1:50 - 2:00 pm		Topic Introduction	Srikantan Nagarajan
2:00 - 2:30 pm		Beyond Voxels: Direct imaging of functional networks	Eric Wong
2:30 - 3:00 pm		High temporal, spatial and algorithmically explicit representation of the human brain: When, where and what of visual recognition	Aude Oliva
3:00 - 3:30 pm		Machine learning algorithms for next generation MEG and EEG systems	Srikantan Nagarajan
3:30 - 3:50 pm		Coffee Break	
3:50 - 4:30 pm		Summary and Workshop Outcomes Discussion	

Workshop point of contact: Thomas Bifano, 617-353-8908, tgb@bu.edu

Workshop Date
July 23-24, 2104

Location
The Westin Arlington Gateway
801 North Glebe Rd.
Arlington, VA 22209
Tel. 703-717-6200
www.westin Arlingtongateway.com

Website
tinyurl.com/NSF-Brain

Important Dates

June 20, 2014
Notifications of invitation

July 2, 2014
Hotel booking deadline

July 11, 2014
Workshop registration deadline

Announcement

