



**National Center for
Research Resources**

NATIONAL INSTITUTES OF HEALTH

Advanced Medical Imaging Developments and Applications for Neuroscience Research

**National Institutes of Health
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Final Meeting Report

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I. Abbreviations Used

AD	Alzheimer’s Disease
ASL-MRI	Arterial Spin Labeling MRI technique to access CBF
BBB	Blood Brain Barrier
CBF	Cerebral Blood Flow
CEST-MRI	Chemical Exchange Saturation Transfer MRI
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	X-Ray Computed Tomography
dEEG	Dense-array EEG
dMRI	Diffusion MRI
DTI	Diffusion Tensor Imaging for brain tractography
EEG	Electroencephalography measuring electrical activity of the brain
FDG-PET	A PET technique using F18 labeled glucose to track glucose metabolism
fMRI	An MRI method to access brain activation
HCP	Human Connectome Project
MEG	Megnetoencephalography
MEMRI	Manganese Enhanced MRI
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
ND	Neurodegenerative Diseases
PET	Positive Emission Tomography
RF	Radiofrequency
R-fMRI	Resting state fMRI
SPECT	Single-Photon Emission Computed Tomography
SPIO	Super-Paramagnetic Iron Oxide
T1	Longitudinal relaxation of protons in a magnetic field
T2	Transverse relaxation of protons in a magnetic field
T2*	T2 enhanced by field non-uniformities (more pronounced in high-field MRI)
T-fMRI	Task-evoked fMRI

II. Executive Summary

About the Symposium

This symposium entitled *Advanced Medical Imaging Developments and Applications for Neuroscience Research* took place at the National Institutes of Health (NIH) Lister Hill Center Auditorium on June 9, 2011. The meeting was co-organized and sponsored by the National Center for Research Resources (NCRR), National Institutes on Drug Addiction (NIDA), National Institute of Mental Health (NIMH) and National Institute of Biomedical Imaging and Bioengineering (NIBIB). Twelve invitees, eight speakers with medical imaging expertise and four discussants with cross-boundary expertise, participated in this one-day symposium. The audience consisted of NIH program staff, imaging scientists and neurobiologists at different stages of their research careers from within and outside the NIH. The meeting had two sessions, a morning session focused on technical aspects of medical imaging and an afternoon session on the application of medical imaging to address crucial questions in neuroscience. Each session was followed by a panel discussion and questions from the audience.

Background

Neurobiologists have utilized advanced molecular biological assays and immunohistochemistry to identify the cause and progression of neurological diseases and disorders. However, those techniques are often limited because they can only be performed on biopsied or postmortem brain samples and, therefore, lack longitudinal applicability. Medical imaging modalities such as MRI/MRS, PET, CT and optical imaging, as well as their co-modalities, have enabled real-time visualization of the central nervous system (CNS) in live subjects. Because they do not require brain samples, most of these technologies are routinely used in clinics and offer minimally-invasive means to detect structural, metabolic and physiologic processes of brain function for research and diagnostic purposes. The development of novel imaging technology requires strong knowledge and background in chemistry, physics and engineering. For example, chemists synthesize specialized radiopharmaceuticals, contrast agents and probes to improve image contrast and detect cellular targets. Engineers design coils/sensors with different geometry to maximize signal-to-noise for specific areas of interest. Physicists develop specialized pulse sequences and data processing algorithms to acquire and interpret data with good image resolution in order to gain insights into neural structure, function and activity. Numerous collaborative research efforts between neurobiologists and imaging scientists have shown promise solving neuroscientific problems. With such cross-disciplinary involvement, the success of collaboration relies heavily on the understanding, communication, and respect among the investigators. There is value in bringing together neurobiologists and imaging scientists to talk about working together as a team to better understand brain function in healthy and disease states.

Focus of Meeting

This symposium brought together medical imaging scientists and neurobiologists to 1) explore state-of-the-art medical imaging capabilities and their applications in

neuroscience research, 2) identify obstacles and problems associated with the collaborative efforts between the two disciplines, and 3) discuss ways to tackle these challenges. Presentations were geared toward neurobiologists who have working knowledge about medical imaging capabilities.

III. Purpose and Objectives of the Symposium

- 1) Provide an update on the state of the current medical imaging technology for neuroscience research: presentations aimed to give an overview of the development and basic principles of state-of-the-art methodology used to image anatomy, function, connectivity and molecular activities in human brains. The goal was to expose neurobiologists to the field of medical imaging and to equip them with sufficient knowledge and vocabulary to better communicate with the imaging scientists.
- 2) Highlight medical imaging opportunities and application in neuroscience research: presentations aimed to showcase the broad applications these technologies can offer to detect brain diseases and disorders. This provided an opportunity for neurobiologists to evaluate potential imaging applications they can leverage to enhance their research.
- 3) Explore and encourage better coordination and communication for synergistic research collaboration between imaging scientists and neurobiologists: discussion with the speakers and discussants occurred during the Panel Discussion Sessions which included questions on the robustness as well as limitation/pitfalls of medical imaging technologies and personal experience in this type of interdisciplinary collaboration. The objective was to create a dialogue and common ground between these two research groups for better collaborative efforts.

IV. Summary of Presentations and Discussion

Morning Session: Nuts and Bolts of Medical Imaging Technologies

MRI for Brain Anatomy, Physiology and Functions

This presentation provided an overview of the contributions to MRI methodology developments at the National Resource for Quantitative Functional MRI at Kennedy Krieger Research Institute and the Johns Hopkins University School of Medicine. Topics included:

- Principles and applications of diffusion tensor imaging (DTI), white matter fiber tracking, and the development of the first human white matter atlas. This includes the first *in vivo* fiber tracking and the subsequent application to human disease. In addition, the DTI technology has been further developed to generate deformable brain atlases to investigate brain development from infants to adults and to assess white matter changes in different pathologies. Such noninvasive technology could be applied

in conjunction with genetic analysis in animal models and patients to establish possible linkage between genes and brain disorders.

- Development of methodology to non-invasively measure cerebral blood volume. Arterial Spin Labeling MRI is one technique in which the proton spins of the blood were “labeled” by an RF pulse before entering the brain for MR detection.
- Development of protein/peptide imaging first in animals and subsequently in humans. Recent applications to image ischemia and brain tumors and to separate the effects of tumor treatment from those of recurrent tumors were demonstrated.
- The advancement of high magnetic fields human MRI in clinical application. The highest MRI field strength approved for clinical usage is 3 tesla. More recently, 7-tesla MRI scanners have become available for pre-clinical studies in human. These MRI scanners have provided higher-resolution, enhanced-contrast imaging capabilities to delineate micro vasculature of the brain, which was not detectable by clinically-approved MRI scanners. Some examples of whole-brain high-resolution MRI were presented together with some early illustrations of applications to multiple sclerosis and Huntington’s disease.

Dense-array Electrophysiology Technology for Neural Connectivity

This presentation showcased an electrophysiology technique called dense-array EEG (dEEG) to measure functional activity of human cerebral networks with millisecond temporal resolution. Key points were:

- Unlike conventional EEG technology with limited number of electrodes affixed to the scalp, dEEG technology provides a network of 256 sensors (Geodesic Sensor Net) covering the entire head surface.
- The capability of dEEG technology in locating electrical activity with anatomical accuracy is enhanced by enclosing the subject in a photogrammetry system for geometric information of the skull.
- Based on skull information, advanced linear inverse methods with statistical standardization can generate dense maps of brain electrical activities with anatomical brain coordinates.
- The alignment of cortical source patches with DTI tractography is now feasible, and it promises new approaches to uncovering the dynamic functional networks of the human brain. Being compatible with MRI, Geodesic Sensor Net provides an additional source of connectivity information in the Human Connectome Project.
- This technology has also been used to investigate the source of depression, neural mechanism of expert perception, as well as to locate the abnormal brain activity in patients with epilepsy in preparation for neurosurgery.

Contrast-Enhanced MRI for Molecular Imaging

The presentation provided a basic introduction to contrast enhanced Magnetic Resonance Imaging (MRI) for molecular imaging and potential applications in neuroscience research. Key points were:

- As defined by the Society for Nuclear Medicine in 2007, molecular imaging is the visualization, characterization and measurement of biological processes at the molecular and cellular levels in humans and other living systems.
- Molecular MRI requires the use of contrast agents to enhance the image contrast of the structure of fluids within the body.
- MR contrast agents are categorized into T1 and T2 agents. T1 agents appear bright in T1-weighted images and, therefore, are called positive contrast agents. T2 agents appear dark in T2-weighted MR images and are called negative contrast agents.
- Gadolinium has been used clinically as a T1 agent to detect blood brain barrier leakage as the result of tumor or neurological diseases.
- Manganese Enhanced MRI (MEMRI) uses manganese ion (Mn^{2+} , an analog to Ca^{2+}) as a T1 agent to delineate neuronal tracts and detect calcium transport and neuronal activation. These studies have been performed in rodents and non-human primates.
- Super-paramagnetic iron oxide (SPIO) nanoparticles have been used to assess blood volume changes associated with brain activities. SPIO has been used to label antibodies against Amyloid protein in mouse Alzheimer's disease (AD) model to evaluate AD progression.
- However, the caveat of these exciting molecular detection capabilities is the limitation of contrast agents' delivery across the BBB. Methods to safely and reversibly open the BBB to deliver the contrast agents are needed.

PET for Molecular Imaging

New developments in positron emission tomography (PET) continue to yield unique information on biochemical transformations and the distribution and movement of drugs directly in the living human brain and other organs.

- The advancement of PET requires innovation in radiotracer chemistry, particularly in the development of methods for introducing the short-lived isotopes into chemical compounds and which are targeted to specific cellular elements. The development of PET for neuroscience research that utilizes animals requires tracers that can be rapidly synthesized and that have well defined kinetics and predictable bioavailability in animal models.

- Fluorine-18 labeled glucose (FDG) is an accepted radiotracer used in the clinic to track glucose metabolism associated with brain activities.
- Radioligand technique targeting dopamine receptors has helped in understanding the involvement of the brain dopamine pathway in drug addiction and obesity. PET studies showed that manipulating brain dopamine receptors reversed the addictive behavior in animals and could potentially be applicable in humans.
- PET imaging in humans provides the opportunity to measure relationships between genotype, brain chemistry and personality. An example was given on the study of monoamine oxidase (MAO), an enzyme that oxidizes neurotransmitters. Inhibitors of MOA have been used to treat depression and Parkinson's disease. Low MAO A (a subtype of MAO) genotype was implicated with antisocial behavior. Using radiotracer targeting MAO A, PET studies found that it is the protein product of MAO, not the genotype, which predicts trait aggression.

Afternoon Session: Applications of Medical Imaging Technology in Brain Research

MRI in Neurodegenerative Disease Research

During the past decade, there has been an explosion in research using brain MRI, PET and SPECT scanning to investigate changes in the brain that occur during normal aging and progression of neurodegenerative diseases (ND). These technologies have also been used in other conditions, such as depression and post-traumatic stress disorders. Key points of this presentation were:

- There is currently no effective treatment that slows the progression of ND. The only acceptable method to accurately diagnose ND is based on postmortem brain staining.
- MRI methodologies have been used to identify ND markers in living subjects. Current methods include T1, T2 and T2*-weighted imaging for anatomical structure; DTI for neural integrity; ASL for blood perfusion; and fMRI (such as T-fMRI and R-fMRI) for brain functions.
- Group studies of structural MRI have found potential structural AD markers in certain parts of the brains such as 1) reduced volumes in the cortex and hippocampus, 2) low blood perfusion, and 3) DTI abnormality (as the result of disorganized fibers).
- Many PET and SPECT imaging methodologies have been used to detect molecular alteration in AD. FDG-PET has been used to detect brain hypometabolism that is associated with AD's dementia. Several novel radio-tracers have been used to detect AD in humans such as 1) Pittsburgh Compound-B (PiB) for amyloid burden, 2) PK11195 for microglia activities, and 3) THK523 for tau tangles.

- Standardization in imaging methodologies for multi-site image acquisition and image data sharing will accelerate our understanding in the progress of AD and other neurodegenerative diseases.

The Human Connectome Project

The Human Connectome Project (HCP) is an effort funded by NIH to characterize the “macro-connectome” in the brain and its variability in healthy adults. Key points of this presentation were:

- Connectome is a “comprehensive” map of neuronal connections.
- A consortium of investigators at Washington University, University of Minnesota, University of Oxford and six other institutions recently began a five-year project to characterize the human connectome in a large cohort of twins and their non-twin siblings.
- Imaging technologies used in the HCP include dMRI, R-fMRI, T-fMRI and MEG/EEG.
- The key challenges of this enormous undertaking are individual variability in brain structure, functions and connectivity. Information from these studies needs to be mapped to high-resolution structure MRI for group studies.
- Understanding human brain circuitry in health and disease is a grand challenge for the 21st century. Using advanced computational methods, the HCP investigators conduct group studies to relate brain circuitry to behavioral capacities as well as genotypic data.
- A “complete connectome” at the level of microscopic features is well outside our grasp at the present time.

Application of Molecular MRI to Studies of Brain Function

Molecular indices for neuronal activation include gene expression, as well as intracellular and extracellular signalling. Novel MRI sensors allowing the detection of brain function by accessing perturbation of the molecular indices such as proteins, neurotransmitters and ions are used in an emerging field called “molecular fMRI.”

- Among many MRI sensors developed thus far, protein-based sensors offer special advantages due to of the applicability of powerful protein engineering strategies.
- The development and optimization of a neurotransmitter sensor using a P456Bm3 heme domain that binds to dopamine for MRI detection of dopamine release was discussed.

- The development and optimization of a magnetic nanoparticle-based MRI sensor that detects intracellular calcium signalling associated with neuronal activation was discussed.

PET in Addiction Research

PET neuroimaging techniques have led to significant advances in our understanding of the neurobiology and treatment of drug addiction in humans. The capability to conduct parallel studies in nonhuman primates and human subjects provides a powerful translational approach to link findings in human and animal research.

- PET has been used to define the *in vivo* biodistribution and pharmacokinetics of drug abuse and relate these findings to the time-course of behavioral effects associated with their addictive properties.
- Although dopaminergic systems have been extensively studied, other neurotransmitter systems known to play a critical role in the pharmacological effects of abused drugs have been largely ignored in nonhuman primate PET neuroimaging.
- Recently, there has been some success in implementing pharmacological fMRI in awake nonhuman primates.
- Nevertheless, the unique versatility of PET imaging will continue to complement the systems-level strengths of fMRI, especially in the context of nonhuman primate drug abuse research.
- Collectively, the results of PET neuroimaging studies have enhanced our understanding of the neurobiological basis of stimulant addiction and could have a significant impact on efforts to develop medications to treat stimulant abuse.

V. Meeting Findings

The following points were made by the attendees, program staff, speakers and discussants during the symposium.

- Neurobiologists have difficulty in keeping up with the rapid progression in medical imaging technology due to disparate expertise in the two fields.
- There is a communication barrier between imaging scientists and neurobiologists owing to a lack of understanding, critical evaluation and/or appreciation between the two disciplines.
- Image scientists present intricate images without a sufficient validation that would require the input of a neuroscientist.
- Imaging research laboratories and centers need standardized computer-generated interpretations of physiological phenomena based on image signals.

- Long scans are needed to acquire high-resolution images with sufficient signal-to-noise; patients are asked to stay still in the scanner for an extended period for image acquisition. Such long scans have restricted cutting-edge, high-resolution imaging methodologies from being available to routine clinical applications.
- The current state of molecular imaging is dominated by relatively conservative approaches such as PET due to its proximity to human applications. Conversely, molecular MRI is progressing slowly because of its limited application to humans.
- Minimally-invasive optical imaging techniques, although limited in depth penetration, have led to major advances in our knowledge of intracellular and multi-cellular signaling processes in brain.
- There is a need to develop sensitive and target-specific probes in other imaging modalities that can be used to image molecular events in the brain noninvasively.
- The Blood Brain Barrier remains a formidable obstacle to overcome in advancing molecular imaging research for clinical application and in drug discovery for brain diseases.

VI. Conclusion

Medical imaging technology encompasses many modalities and allows *in vivo* visualization of structure, function and physiology of the brain. Methodology developments for these modalities rely on in-depth understanding of chemistry, physics and engineering. Recent advances in medical imaging technology have brought our view about how the whole brain works to a new level as demonstrated by our speakers.

The presentations in this one-day symposium did not comprehensively cover the complexity of medical imaging technology and the underlying principles. We hope these overviews encourage neurobiologists and imaging scientists to work as teams to understand healthy and diseased brains.

VII. Contact Information

Christina Liu, Ph.D., P.E.
 Division of Biomedical Technology
 National Center for Research Resources
 Phone: 301-435-0905
 E-mail: christina.liu@nih.gov

For more information about NCR, please visit ncrr.nih.gov.

Appendix 1: Symposium Agenda

- 7:45 – 8:15 a.m. **Registration**
- 8:15 – 8:20 a.m. **Welcome Remarks**
Barbara Alving, M.D., director, National Center for Research Resources
- 8:20 – 8:30 a.m. **Introduction**
Christina Liu, Ph.D., P.E., National Center for Research Resources
- Session I: Nuts and Bolts of Medical Imaging Technologies**
Chair: Da-Yu Wu, Ph.D., National Institute on Drug Abuse
- 8:30 – 9:10 a.m. **MRI for Brain Anatomy, Physiology and Functions**
Peter van Zijl, Ph.D., Johns Hopkins University and National Resource for Quantitative Functional MRI
- 9:10 – 9:50 a.m. **Dense Array Electrophysiology Technology for Neural Connectivity**
Don Tucker, Ph.D., University of Oregon and Electrical Geodesics, Inc.
- 9:50 – 10:05 a.m. **Break**
- 10:05 – 10:45 a.m. **Contrast-Enhanced MRI for Molecular Imaging**
Robia G. Pautler, Ph.D., Baylor College of Medicine
- 10:45 – 11:25 a.m. **PET for Molecular Imaging**
Joanna Fowler, Ph.D., Brookhaven National Laboratory
- 11:25 a.m. – 12:15 p.m. **Panel Discussions**
Moderator: Yantian Zhang, Ph.D., National Institute of Biomedical Imaging and Bioengineering
- Panel Members:
Allan Reiss, M.D., Stanford University
Vinod Menon, Ph.D., Stanford University
Eng Lo, Ph.D., Massachusetts General Hospital/Harvard Medical School
Scott Small, M.D., Columbia University
- 12:15 – 1:00 p.m. **Lunch**
- Session II: Applications of Medical Imaging Technology in Brain Research**
Chair: Michael F. Huerta, Ph.D., National Institute of Mental Health
- 1:00 – 1:40 p.m. **MRI in Neurodegenerative Disease Research**

Michael Weiner, M.D., University of California, San Francisco and National Center for Imaging of Neurodegenerative Diseases

1:40 – 2:20 p.m.

The Human Connectome Project

David Van Essen, Ph.D., Washington University in St. Louis

2:20 – 2:35 p.m.

Break

2:35 – 3:15 p.m.

Application of Molecular MRI to Studies of Brain Function

Alan Jasanoff, Ph.D., Massachusetts Institute of Technology

3:15 – 3:55 p.m.

PET in Addiction Research

Leonard Howell, Ph.D., Emory University and Yerkes National Primate Research Center

3:55 – 4:40 p.m.

Panel Discussions/Closing Remarks

Moderator: Christina Liu, Ph.D., P.E., National Center for Research Resources

Panel Members:

Allan Reiss, M.D., Stanford University

Vinod Menon, Ph.D., Stanford University

Eng Lo, Ph.D., Massachusetts General Hospital/Harvard Medical School

Scott Small, M.D., Columbia University

Appendix 2: List of Participants (in alphabetical order)

Speakers and Discussants

<u>Name</u>	<u>E-mail</u>
Joanna S. Folwer, Ph.D.	fowler@bnl.gov
Leonard L. Howell, Ph.D.	lhowell@emory.edu
Alan Jasanoff, Ph.D.	jasanoff@mit.edu
Eng H. Lo, Ph.D.	lo@helix.mgh.harvard.edu
Vinod Menon, Ph.D.	menon@stanford.edu
Robia G. Pautler, Ph.D.	rpautler@bcm.edu
Allan L. Reiss, M.D.	areiss1@stanford.edu
Scott A. Small, M.D.	sas68@columbia.edu
Don Tucker, Ph.D.	dtucker@egi.com
David C. Van Essen, Ph.D.	vanessen@wustl.edu
Peter C.M. van Zijl, Ph.D.	pvanzijl@jhu.edu
Michael W. Weiner, M.D.	Michael.Weiner@ucsf.edu

Organization Committee Members

<u>Name</u>	<u>E-mail</u>
Michael F. Huerta, Ph.D.	mhuert1@mail.nih.gov
Christina H Liu, Ph.D., P.E.	christina.liu@nih.gov
David Shurtleff, Ph.D.	dshurtle@mail.nih.gov
Da-Yu Wu, Ph.D.	wudy@nida.nih.gov
Yantian Zhang, Ph.D.	yantian.zhang@nih.gov