RESEARCH REPORT

Pain

Pain, Anesthesia, Acupuncture, Neuroimaging, fMRI, Neural Signal, Neurons, Brain Imaging, Placebo, Brain Chemistry...
Pain Research at MIT

This survey by MIT’s Industrial Liaison Program identifies research and faculty/researcher expertise related to the area of pain. This survey captures information dated between 2008 and July 2009.

For more information, please contact MIT’s Industrial Liaison Program at +1-617-253-2691.

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RESEARCH IN THE AREA OF PAIN

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http://hst.mit.edu/public/people/faculty/facultyBiosketch.jsp?key=Brown_EN
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http://users.neurostat.mit.edu/enb/

Neuroscience Statistics Research Lab (NSRL @ MIT)
http://www.neurostat.mit.edu/

Understanding General Anesthesia
General anesthesia is a neurophysiological state in which a patient is rendered unconscious, insensitive to pain, amnestic, and immobile, while being maintained physiologically stable. General anesthesia has been administered in the U.S. for nearly 160 years and currently, more than 50,000 people receive anesthesia daily in this country for surgery alone. Still, the mechanism by which an anesthetic drug induces general anesthesia remains a medical mystery. A new research direction in my laboratory is to use a systems neuroscience approach to study how the state of general anesthesia is induced and maintained. To do so, we are using fMRI, EEG, neurophysiological recordings, microdialysis methods and mathematical modeling in interdisciplinary collaborations with investigators in HST, the Department of Brain and Cognitive Sciences at MIT, Massachusetts General Hospital and Boston University. The long-term goal of this research is to establish a neurophysiological definition of anesthesia, safer, site-specific anesthetic drugs and to develop better neurophysiologically-based methods for measuring depth of anesthesia.

Neural Signal Processing Algorithms
Recent technological and experimental advances in the capabilities to record signals from neural systems have led to an unprecedented increase in the types and volume of data collected in neuroscience experiments and hence, in the need for appropriate techniques to analyze them. Therefore, using combinations of likelihood, Bayesian, state-space, time-series and point process approaches, a primary focus of the research in my laboratory is the development of statistical methods and signal-processing algorithms for neuroscience data analysis.

We have used our methods to:

• Characterize how hippocampal neurons represent spatial information in their ensemble firing patterns.
• Analyze formation of spatial receptive fields in the hippocampus during learning of novel environments.
• Relate changes in hippocampal neural activity to changes in performance during procedural learning.
• Improve signal extraction from fMR imaging time-series.
• Characterize the spiking properties of neurons in primary motor cortex.
• Localize dynamically sources of neural activity in the brain from EEG and MEG recordings made during cognitive, motor and somatosensory tasks.
• Measure the period of the circadian pacemaker (human biological clock) and its sensitivity to light.
• Characterize the dynamics of human heart beats in physiological and pathological states.

RANDY L GOLLUB
Harvard-MIT Division of Health Sciences and Technology (HST) Affiliated Faculty; Associate Professor in Psychiatry at Harvard Medical School; Assistant in Neuroscience in Radiology at Massachusetts General Hospital; Director Biomedical Imaging Core (BIC) at Harvard Catalyst at MGH; MIT/MGH Athinoula A Martinos Center for Biomedical Imaging
http://www.nmr.mgh.harvard.edu/martinos/people/showPerson.php?people_id=64
http://hst.mit.edu/servlet/ControllerServlet?handler=PeopleHandler&action=viewOne&id=HST002121

Dr. Gollub is Assistant Director of Psychiatric Neuroimaging at MGH and an Assistant Professor of Psychiatry at HMS. She is a board-certified psychiatrist with over 15 years of research experience spanning all levels of neuroscience investigation from intracellular interneuron electrophysiology to clinical neuroimaging in humans. Dr. Gollub oversees the day-to-day operation of the BIC and assists in the interface of the BIC with the main GCRC. She has 10 years of imaging experience at the Martinos Center and is available for consultation with investigators to ensure that GCRC resources fully support their imaging studies. Her involvement with Biomedical Informatics Research Network (BIRN) enhances her ability to bring technological advances in image data acquisition and analysis to investigators at the GCRC.

Dr. Gollub works in close collaboration with many investigators within the Psychiatric Neuroimaging Research Program, the Athinoula A. Martinos Center for Biomedical Imaging and across the country to advance the imaging technologies and their application to neuropsychiatric disorders. She participates in a several multi-site consortium projects; each aimed at advancing biomedical imaging and associated bioinformatics technology. Most of her independent research projects focus on the investigations of the neural mechanisms underlying pain perception and its modulation by expectancy, placebo, and acupuncture treatment. A critical long-term goal of this work is to develop the capability to use functional neuroimaging as adjunct assessment in clinical evaluation of individual patients with chronic pain disorders. Gollub also is deeply committed to the training and education of the next generation of research scientists.

fMRI and PET Opioid Imaging Investigation of the Expectancy Component of Acupuncture Analgesia in Health and Disease

Principal Investigator: Dr. Randy L Gollub
Other Investigator: Dr. Bruce R Rosen
Depts/Labs/Centers: MIT/MGH Athinoula A Martinos Center for Biomedical Imaging

We propose to use quantitative brain imaging methods (fMRI and PET [11C]diprenorphine opioid receptor binding) to investigate the neurobiological mechanism of acupuncture analgesia, placebo analgesia and their interrelationship.
The initial approach is to study healthy subjects using a well tested method to manipulate their expectation of pain relief from treatment. We combine this manipulation with acupuncture analgesia and sham acupuncture analgesia to create a 2 X 2 neuroimaging comparison of verum (real) acupuncture and sham acupuncture each paired with positive and negative expectancies. We measure fMRI signal changes caused by application of calibrated painful stimuli and subsequent evaluation of pain intensity after the different treatments. The patterns of fMRI signal changes will identify critical brain networks involved in acupuncture and placebo analgesia.

We hypothesize that expectancy (placebo) analgesia, will produce analgesia by activating descending endogenous opioid systems as well as by activating what we have called the selective pain intensity evaluation distortion process. The first mechanism may also be shared with acupuncture analgesia; however, the second mechanism should be unique for placebo analgesia.

We are developing methods to extend this experimental paradigm to a cohort of chronic low back pain patients with specific controls for psychiatric co-morbidity. We are also using PET [11C] diprenorphine opioid receptor binding changes to investigate the role of endogenous opioid neurotransmission in mediating acupuncture analgesia.

This project completes the requirements to allow our research group to study the mechanisms of acupuncture in animal models, healthy and chronic pain subjects. This forms a beneficial cycle and provides a powerful model for acupuncture research.

Laboratory for Neuroimaging Applications to Pain, Acupuncture and Placebo Research

Division of Neuroscience Research & Neurotherapeutics, Massachusetts General Hospital
Randy L. Gollub, M.D. Ph.D., Director, Neuroimaging Training Curriculum and Education
http://www2.massgeneral.org/allpsych/psychneuro/labfunctionalstructural.asp

The Laboratory works in close collaboration with many investigators within the Psychiatric Neuroimaging Research Program, the Athinoula A. Martinos Center for Biomedical Imaging and across the country to advance the imaging technologies and their application to neuropsychiatric disorders. The Laboratory participates in a several multi-site consortium projects; each aimed at advancing the enabling aspects of imaging and associated bioinformatics technology. Within the Laboratory, most research projects focus on the investigations of the neural mechanisms underlying pain perception and its modulation by expectancy, placebo, and acupuncture treatment. A critical long-term goal of this work is to develop the capability to use functional neuroimaging as adjunct assessment in clinical evaluation of individual patients with chronic pain disorders. The laboratory also invests heavily in the training and education of the next generation of research scientists.

Ongoing Projects:

1. Neuroimaging studies of expectancy, placebo and verum acupuncture analgesia: This project uses quantitative brain imaging methods (fMRI and PET [11C]diprenorphine opioid receptor binding) to investigate the neurobiological mechanism of acupuncture analgesia, placebo analgesia and their interrelationship.
2. Test-retest reliability of acupuncture induced changes in fMRI measures of brain activity: There is much debate in the literature regarding the neuronal networks that are activated during acupuncture treatment. This project uses a simple calibration paradigm to study the consistency of fMRI signal changes in response to acupuncture needle manipulation and sensorimotor controls across a cohort and within single subjects over repeated scan sessions.

3. Effect of psychiatric co-morbidity on the efficacy of acupuncture analgesia: Concurrent psychiatric illness associated with poor response to treatment for chronic pain. This study aims to determine whether psychiatric co-morbidity also diminishes measures of acupuncture induced analgesia to the application of calibrated noxious stimuli. This study is a close collaboration with Dr. Wasan.

External Collaborative Projects:

The Lab has major leadership responsibilities in:

1. MIND clinical imaging consortium project. A joint study of first episode and chronic schizophrenia. This multi-institutional clinical consortium study of first onset and chronic schizophrenia seeks to identify the neural markers for disease onset and progression by using functional, structural, and diffusion weighted imaging combined with clinical characterization, neuropsychological evaluation and genomic analysis.

2. Morphometry Biomedical Informatics Research Network (M-BIRN). This multi-site project focuses on the calibration, analysis, visualization and integration of quantitative structural MRI in large-scale, multi-site studies of Alzheimer's Disease, Minimal Cognitive Impairment and Depression. The technical goals include developing a distributed network infrastructure to support a federated structural MRI database and query tools. The clinical objective is to use the technology developed to answer fundamental questions about brain function in health, diseases that cause memory impairment and normal aging.

3. National Alliance for Medical Image Computing (NAMIC). The goal of this interdisciplinary, multi-institutional center is to create, develop, integrate, and deploy computation tools for the analysis and visualization of medical image data. The goal of the Training Core is to develop and provide a rich educational program that supports these aims for trainees and post-doctoral fellows involved in the project and to the broader scientific community.

The Lab participates in:

1. Functional Imaging Research of Schizophrenia Test Bed, Biomedical Informatics Research Network (FIRST BIRN). This multi-site project focuses on the development and validation of fMRI in large-scale, multi-site studies of schizophrenia. The technical goal involves developing a distributed network infrastructure to support a federated fMRI database and to identify sources of measurement variation. The clinical objective is to use the technology developed to answer fundamental questions about brain function in schizophrenia.
For the past thirteen years, I have successively used anatomy, histology, Positron Emission Tomography (PET), functional Magnetic Resonance Imaging (fMRI), Diffusion Tensor Imaging (DTI), electroencephalography (EEG), magnetoencephalography (MEG) as well as behavioral methods to study the normal and the diseased brain.

My dissertation was based on anatomical studies of the human visual cortex, and examined the callosal connections between different areas of the human brain. As a postdoctoral fellow, I have used PET to address the issue of crossmodal matching between touch and vision, and was able to show communication between modality specific areas through the claustrum.

Since I came to the MGH/HMS/MIT-Athinoula A.Martinos Center for Biomedical Imaging, I have been using different method of brain imaging (fMRI, EEG, MEG) to better characterize the different functional components of our visual system. Using fMRI, we discovered and characterized the area of the brain responsible for color vision. With this knowledge of the basis of the functional organization of the brain, the next issue I have been concentrating on is the interaction between these different areas, both in normal subjects and in people with medical conditions such as migraine, focal brain damage and developmental disorders such as autism. I now share my time between the Martinos Center in Boston and the Brain and Mind Institute at EPFL, Lausanne, Switzerland.

Migraine is a very common yet poorly understood phenomenon. In about 20% of patients, the headache is preceded by a visual phenomenon called the aura. For the first time, our group was able to show that the aura of migraine was a phenomenon similar to cortical spreading depression, invalidating the old vascular theory of migraine and opening new perspectives in the treatment of this common and debilitating disorder. Presently, our group is working on extending our understanding of the pathophysiology of migraine, and examining the long-term consequences of this disease on the brain.

Neurological syndromes following focal lesions provide a way to better understand the functional organization of the brain. We have been using this approach to investigate the network of areas involved in face recognition. Examining the responses of lesioned brains to stimuli characterized in normal controls can cast light on the potential plasticity and help identify appropriate strategies to adopt for rehabilitation.

Autism is a neurodevelopmental disease that affects 1:166 children. The etiology of this syndrome is still not well understood, and the correlations between autism behavioral deficits and their biological substrate is only starting to emerge. Based on our previous studies of the organization of the visual system, we were able to demonstrate that "low level" visual processing is normal in individuals with autism, ruling out a bottom-up deficit. Moreover, our group was the first to provide data disproving a popular theory stating that individuals with autism are lacking the brain area devoted to face identification, opening new hypotheses on the etiology of some of the
behavioral aspects of autism potential new therapeutic strategies. We are actively pursuing projects of multimodal imaging of neurodevelopmental disorders.

Emotion perception has been studied using functional imaging for several years, but to date has been concentrated primarily on processes associated with viewing facial expressions. However, from an evolutionary perspective, investigations of expressive body movements may be just as important for understanding the neurobiology of emotional behavior. We published the first functional study on the perception of body expression of emotion in normal subjects, and we are using this new and fascinating model of emotion perception to examine neurodevelopmental disorders and intend to explore this aspect of emotional cognition in autism.

PROF. RICHARD J WURTMAN
Cecil H Green Distinguished Professor of Neuropharmacology and Health Sciences and Technology
http://web.mit.edu/bcs/people/wurtman.shtml
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Areas of Interest and Expertise:
Neural and Endocrine Regulation
Control of Glandular Functions and Bodily Metabolism of the Brain
Effects of Light, Food, and Other Environmental Factors on Mammalian Regulatory Systems
Brain Neurotransmitters and Behavior: Their Responses to Drugs, Nutrients, and Hormones
Melatonin and the Pineal Gland
Weight Loss
Obesity; Binge Eating
Alzheimer's Disease, Chemical Pathology of Alzheimer's Disease
Sleep
Depression
Molecular and Cellular Neuroscience
Interactions of Brain Dopamine and Serotonin Membrane Synthesis
Neurochemistry
Pharmacology

Richard J. Wurtman, M.D. is Cecil H. Green Professor at MIT and Director of MIT's Clinical Research Center. He took an undergraduate degree in philosophy at the University of Pennsylvania, then an M.D. at Harvard Medical School, after which he was an intern, resident, and fellow at the Massachusetts General Hospital, and a research associate at the National Institutes of Health. He came to MIT in 1968. His major research interests have been: neurotransmitters; catecholamines; serotonin; acetylcholine; amino acids; peptides; adenosine; phospholipids and neuronal membranes; melatonin and the pineal gland; nutrition, the brain and behavior; neurodegenerative diseases; light and biologic rhythms; and appetite disturbances. Dr. Wurtman has been the recipient of numerous awards, and a member of various advisory panels, including the Board of Overseers of the Boston Symphony Orchestra. He has published about 920 research articles, and has authored or co-authored 18 books. He lives in Boston with his wife, Dr. Judith Wurtman, a research scientist specializing in nutrition and obesity.
Effects of Drugs, Foods and Diseases on Brain Neurotransmitters and Behavior:
The goal is to discover safe and effective treatments for brain diseases. I do this by (1) doing fundamental research to identify a previously-unsuspected control mechanism involving brain chemistry; (2) confirming that this mechanism also works in the human brain; (3) identifying a disease in which this mechanism seems not to be operating properly; and (4) doing pilot studies to see whether a possible new treatment, based on these discoveries, actually works. Examples of fundamental principles we have discovered are the facts that (1) certain food constituents affect the chemistry of the brain, and (2) melatonin is a hormone, which is secreted at nighttime, and which promotes sleep. New treatments that have been based on this "translational research" include: (1) melatonin to promote sleep; (2) REDUX (dexfenfluramine) to treat obesity; (3) PROZAC (fluoxetine) to treat the premenstrual syndrome; (4) Citicoline- which is currently in large-scale, Phase III testing, to treat strokes; and (5) a protein/carbohydrate mixture to enhance the efficacy of L-dopa in treating Parkinson's Disease.

The Wurtman Lab of Neuroendocrine Regulation
http://wurtmanlab.mit.edu/home.php

The Lab's goal is to discover safe and effective treatments for brain diseases. We do this by:
1. doing fundamental research to identify a previously-unsuspected control mechanism involving brain chemistry
2. confirming that this mechanism also works in the human brain
3. identifying a disease in which this mechanism seems not to be operating properly, and
4. doing pilot studies to see whether a possible new treatment, based on these discoveries, actually works.

CENTER FOR ACUPUNCTURE NEUROIMAGING
Principal Investigator: Dr. Bruce R Rosen
Other Investigators: Anders M Dale, Bruce Fischl, Randy L Gollub, David N Kennedy, Kenneth K Kwong, Mark G Vangel
MIT/MGH Athinoula A Martinos Center for Biomedical Imaging
http://www.nmr.mgh.harvard.edu/acupuncture/PPG/

The Center of Excellence for Research on Complementary and Alternative Medicine is a Regional Resource located at the Athinoula A. Martinos Center for Biomedical Imaging at the Massachusetts General Hospital.

The central goal of this new Center of Excellence is to investigate the “Neural Mechanisms of Acupuncture” and to develop a more rigorous understanding of the mechanisms of acupuncture’s effect. The Resource is sponsored by National Center for Complementary and Alternative Medicine (NCCAM) of the NIH.

For the healing art of acupuncture to be fully integrated into mainstream medicine, it needs to be examined within the evidence-based framework of the scientific method. To attain this goal, all three projects will investigate the possible brain pathways and circuitries involved in acupuncture.
Two projects will study healthy human subjects and patients, while another project will use animal models to complement human neuroimaging data by studying the underlying neurochemical processes.

**NEUROIMAGING AND MOLECULAR ANALYSIS OF ACUPUNCTURE ACTIONS IN ANIMALS**

Principal Investigator: Kenneth K Kwong  
Other Investigator: Dr. Bruce R Rosen  
http://www.nmr.mgh.harvard.edu/%7Ephilipp/PPG/projects/project2.php

In this project, we will use animal models of rats and monkeys to study the effects of electroacupuncture (EA) on neurochemical brain circuitries, with a special emphasis on the dopaminergic system.

We hypothesize that with EA manipulation, dopamine will play a role in modulating brain circuitries as well as the release of other neurochemicals.

Aim I will study the response of the whole brain circuitry to EA manipulation, relating animal data to collected human data.

Aim II will study on EA’s action on the basal-ganglia circuitry: the cortico-striato-thalamo-cortical (CSTC) feedback loop.

Aim III will study the gene-controlled enzyme-activity level of the COMT enzyme that inhibits dopaminergic activity. Our tools include using blood volume functional MR imaging (fMRI) and pharmacological MRI (phMRI) to assess the neuronal activity.

MRI results will be validated and supported with 1) PET measurements of receptor binding potential; 2) microdialysis to correlate intra-cranial neurochemical concentrations; 3) microdialysis to measure the tempo-dynamic relationships among neurochemicals; and 4) a behavioral analysis of EA response.

This multi-modality integration will obtain a more complete picture of the acupuncture action associated with various brain circuitries and enhance the interpretability of the human data collected in other Projects.
PROF. EDWARD S BOYDEN
Benesse Career Development Assistant Professor of Biomedical Engineering; Head, Synthetic Neurobiology Group; Associate Member, McGovern Institute for Brain Research (MIBR)
http://bcs.mit.edu/people/boyden.html
http://edboyden.org/
http://www.media.mit.edu/people/esb
http://web.mit.edu/be/people/boyden.shtml
http://mcgovern.mit.edu/principal-investigators/ed-boyden

Ed Boyden became an Associate Member of the McGovern Institute for Brain Research in July 2007. In 2006, he joined the MIT Media Lab as a visiting scientist, where he is now an Assistant Professor (jointly with the Department of Biological Engineering).

Synthetic Neurobiology Group
http://syntheticneurobiology.org/

The Group is inventing new tools for analyzing and engineering brain circuits. We are devising technologies for controlling specific neural circuit elements, to understand their causal contribution to normal and pathological neural computations. Our inventions include 'optogenetic' tools we developed for activation and silencing of neural circuits with light, and noninvasive devices using novel physical principles to control neural activity.

We are using our inventions to enable systematic approaches to neuroscience, revealing how entire neural circuits operate to generate behavior, and empowering new therapeutic strategies for neurological and psychiatric disorders. Our entrepreneurial approach to tackling clinically and philosophically important problems will hopefully yield a better understanding of the nature of human existence, and enable the ability to engineer improvements thereupon. More at http://www.syntheticneurobiology.org/projects

Silencing the brain with light
MIT neuroengineers find a new way to quickly and reversibly shut off neurons with multiple colors of light, which could lead to new treatments for epilepsy and chronic pain.
Anne Trafton, MIT News Office, January 7, 2010

Giving epilepsy patients an electric jolt to shut off out-of-control neuron firing during seizures is being explored as a way to treat the chronic brain disorder. New research from MIT now raises the possibility of silencing those seizures with light instead of electricity.

A team led by neuroengineer Edward Boyden has found a class of proteins that, when inserted into neurons, allow them to be turned off with rays of yellow-green light. The silencing is near instantaneous and easily reversible.

This kind of selective brain silencing, reported in the Jan. 7 issue of Nature, could not only help treat brain disorders but also allows researchers to investigate the role of different types of neurons in normal brain circuits and how those circuits can go wrong.
“We hope to enable a broad platform of molecular tools for controlling brain activity, thus enabling new general therapeutic tools, and new ways of studying brain function,” says Boyden, the Benesse Career Development Professor in the MIT Media Lab and an associate member of the McGovern Institute for Brain Research at MIT...

Boyden's group, working with the Desimone lab at the McGovern Institute at MIT, is now performing pre-clinical testing of this approach in non-human primates, to assess its safety as a potential therapy for epilepsy, chronic pain and post-traumatic stress disorder. The team has also developed, in collaboration with other groups at MIT, hardware for optical neural stimulation, which could be valuable for neural prosthetic purposes...