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Department of PSYCHIATRY UPDATE

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Functional Neuroimaging Researchers Probe Mechanisms Underlying Psychiatric Disorders

Striving to better inform diagnosis and treatment and lay the foundation for new therapeutics, researchers in the Functional Neuroimaging Laboratory at Brigham and Women's Hospital (BWH) are using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) to pinpoint the biological mechanisms underlying a wide range of psychiatric disorders.

"Functional imaging has revolutionized the study of brain-mind function and dysfunction in the setting of disease," said Emily Stern, MD, Director of the Functional Neuroimaging Laboratory. "By characterizing brain function and activity changes in patients with psychiatric disorders and symptoms, patients with neurological disease and healthy subjects, we are able to identify brain circuitry abnormalities in mental health conditions."

Important aspects of the Lab's approach include:

- Symptom-level analyses across a broad range of psychiatric disorders to examine abnormalities that are common across these disorders and those that are distinct;
- Development of new methods to improve image acquisition, including the reduction of susceptibility artifact at the base of the brain;
- Development of new methods of multivariate image analysis to identify relevant profiles of integrated brain activity;
- Development of activation tasks to probe targeted neuropsychological functions and circuits.

Selected Findings

Studies in the Functional Neuroimaging Laboratory are focusing on circuitry in the ventromedial prefrontal cortex, medial temporal structures – including the amygdala and the hippocampus, and ventral striatal regions, integrating results from preclinical studies with translational research. Significant findings from studies in the Lab include:

- **Paranoia in schizophrenia** – Findings from a recent study in the Functional Neuroimaging Laboratory further characterize dysfunction in the evolutionarily preserved fear and threat circuitry in patients with schizophrenia and paranoid delusions;
- **Differences in panic disorder and post-traumatic stress disorder** – Panic disorder (PD) and post-traumatic stress disorder (PTSD) are both considered anxiety disorders, but in one the threat is internal/somatic-autonomic, and in the other, it is external/trauma. An instructed fear probe with fMRI has demonstrated a dissociation of activity in core basal forebrain and brainstem regions that can underlie these clinical-phenomenological differences;
- **Menstrual cycle emotional processing changes in premenstrual dysphoric disorder** – In the analysis of functional images obtained during pre- and postmenstrual phases, premenstrual dysphoric disorder (PMDD) subjects in the premenstrual phase,

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David A. Silbersweig, MD, Co-director of the Functional Neuroimaging Laboratory and Chairman of the Department of Psychiatry, and Emily Stern, MD, Director of the Functional Neuroimaging Laboratory, are leading research using fMRI and PET to pinpoint biological mechanisms underlying psychiatric disorders.



HARVARD MEDICAL SCHOOL
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as compared with asymptomatic subjects, showed an increased amygdala response to negative versus neutral stimuli and a decreased ventral striatum response to positive versus neutral stimuli. PMDD subjects' failed to show the asymptomatic subjects' patterns of increased medial and decreased lateral orbitofrontal cortex (OFC) response to negative versus neutral stimuli in the premenstrual vs. postmenstrual phase. This decreased premenstrual medial OFC response to negative stimuli in PMDD subjects was further enhanced in the context of behavioral inhibition. These findings help provide a systems-level neurobiological basis for the emotional bias and reactivity in PMDD patients.

Findings Help to Inform Treatment

Researchers in the Lab are now extending their findings related to abnormal circuitry in specific psychiatric disorders to examine treatment-related changes in these disorders, including:

- Identifying mechanisms of treatment, such as cognitive behavioral therapy (CBT) for PTSD, which is preliminarily associated with enhancement of dorsal anterior cingulate and dorsolateral prefrontal cortex function and decreased reactivity of amygdalar function to negative stimuli, supporting enhanced, top-down modulatory function, and pharmacologic approaches that target the ventral striatum in major depression;
- Utilizing brain imaging results to refine brain stimulation targets for neuropsychiatric disorders such as depression, schizophrenia, and Alzheimer's disease;
- Guiding treatment with imaging, such as using the imaging results to develop predictive models of response to guide the selection of therapies that are most likely to be effective in a particular patient. The team's recent research suggests, for example, that there are particular patterns in patients with borderline personality disorder (BPD) that are predictive of whether BPD symptoms will improve with insight-focused psychotherapy;
- Combining imaging studies with other physiologic and clinical measures. Examples include stress hormones, such as cortisol, and genetic analyses, where imaging can be used as a bridge between the genotype and the phenotype in stratifying patient populations based upon mechanism.

"Our approach is a shift from the traditional model based on the Diagnostic and Statistical Manual of Mental Disorders," said David A. Silbersweig, MD, Co-director of the Functional Neuroimaging Laboratory and Chairman of the Department of Psychiatry. "Using biology and domains of function to characterize psychiatric disorders, we are able to contribute to a

more biologically-based foundation for the care of patients with many psychiatric disorders."

Benefits of Mindfulness

BWH Functional Neuroimaging Laboratory psychologist David R. Vago, PhD, has evaluated the role of meditation for the treatment of many conditions. His early work included the evaluation of the perception of pain and emotion regulation in patients with fibromyalgia, specifically looking at their perceptual and cognitive biases. When given a task to look at pain-related words, for example, the patients' perceptual systems were found to quickly notice words as threatening and avoid them as part of their emotion regulation process. At a cognitive level, they tended to ruminate and overprocess when confronted with this information. "Using meditation practices, we were able to substantially reduce both of these biases," said Dr. Vago. "This is just one example of how meditation can be beneficial across many chronic conditions."

Drs. Vago and Silbersweig recently published an integrative theoretical framework and systems-based neurobiological model that explores the mechanisms by which mindfulness reduces biases related to self-processing and emotional reactivity, and promotes resilience. (*Front Hum Neurosci.* 2012 Oct 25;6:296.). The model characterizes neural circuits and neuro-behavioral functions that underlie self-awareness, self-regulation, and self-transcendence. Current mindfulness-based meditation studies in the laboratory are testing this model.

(For more information on functional neuroimaging studies, contact Emily Stern, MD, at estern3@partners.org.)



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eBehavioral Health Initiatives Enhance Mental Health Care Delivery and Outcomes

Brigham and Women's Hospital (BWH) psychologist David K. Ahern, PhD, is leading research in patient-facing technologies in mental health care and evaluating ways to leverage technology to improve quality of mental health care delivery. He and his collaborators have outlined specific challenges and potential solutions to implementing computer-based distance therapy and self-guided treatments in the United States (*Harv Rev Psychiatry* 2010; Volume 18, Number 2). Dr. Ahern and his colleagues also provided a framework for organizing patient-facing technologies into categories of meaningful use in order to improve health care quality, safety, and population health management (*Am J Prev Med* 2011;40(5S2):S162-172.).

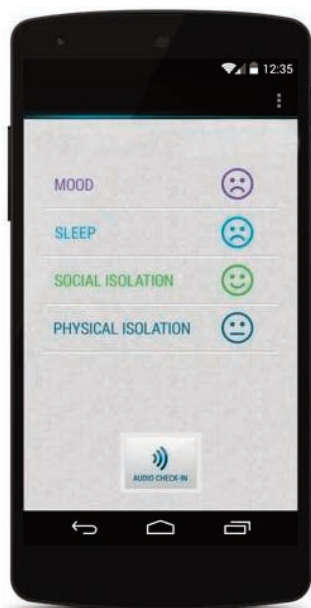
"Patient-facing technologies are likely to play a critical role in supporting patients to become more informed, activated, and involved in their own care," said Dr. Ahern.

Smartphone Application Integration in the Patient-Centered Medical Home (PCMH)

Dr. Ahern is co-leading a new National Institutes of Mental Health-funded research project using a smartphone-based application within BWH's South Huntington Advanced Primary Care Associates, a medical home primary care model located in Boston. Data will be collected from approximately 300 study participants who have one or more co-morbid behavioral health conditions and are receiving medical care in the clinic. The smartphone application uses passive sensors to track location, call schedule, call and text patterns, and other important behavioral indicators that may be related to the participant's mental health status.

The data will be available to patients for self-monitoring and delivered in a clinically-designed Cogito mobile sensing platform to co-located behavioral health providers, including social workers and psychiatrists, in the practice so that they can monitor changes in patients' behavior patterns over time. The study will commence recruitment in July 2015.

Prototype view of the home page of the patient-facing mobile research application



"This study will provide valuable information about a patient's status outside of the practice, including changes such as reduced communication with family and friends and more time spent at home that are early warning signs in patients with high-acuity mental health conditions," said Dr. Ahern. "This data can enable a proactive and preemptive response to these early changes that may avoid emergency room visits and hospitalizations in these patients, not only enhancing efficiency of care but also reducing costs."

Study measures will include:

- Patient satisfaction and usage;
- Routine clinical measures of depression, anxiety, and mental health state;
- Changes in the trajectory of behavioral indicators;
- Effectiveness as part of the process of care delivered by social workers in the practice.

Connected Health Clinical Trial

The Life Balance Program was developed by BWH in collaboration with Blue Cross Blue Shield of Massachusetts (BCBSMA) in response to stark differences in health care services usage data from a large cohort of members with a behavioral health diagnosis and a comorbid medical diagnosis (such as cancer, cardiovascular disease, or degenerative joint disease) compared with usage data from members with the same medical diagnoses and no behavioral health diagnoses.

Dr. Ahern, Arthur J. Barsky, III, MD, Vice Chair for Research in the BWH Department of Psychiatry, and Megan Oser, PhD, Director of Behavioral Medicine in the BWH Department of Psychiatry, worked with BCBSMA over a two-year period to design and implement a 12-session intervention as part of a clinical trial using a protocol that they developed.

The sessions are delivered via telephone by nurse coaches trained in the intervention, with the goal of more effectively managing symptoms and utilization of services. Standard scales are employed to measure perceived stress, disruption of functions, and management of medical symptoms among study participants. Over the past two years, more than 1,000 individuals have been enrolled in the Program. Pre- and post-data is now available for approximately 250 patients who have completed all 12 sessions.

"We have seen statistically significant improvement in the participants' perceived stress scale, disruption of functioning

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index, and management of medical symptoms scale, with results similar to patients who have received cognitive behavioral therapy in face-to-face sessions,” said Dr. Ahern.

Preliminary review of the medical claims data suggest that participants in the Program have fewer emergency room visits, hospital admission, and hospital days than the cohort who were eligible but not enrolled. Further controlled analyses are planned as more data are collected. In an effort to integrate additional technology into the Program, planning is underway to create a more interactive version of the workbook that will be accessible online and a smartphone application that will be used to collect survey responses. These will be used in conjunction with telephone-based coaching from the nurses.

Optimizing Mental Health Care Delivery in Oncology

Dr. Ahern is currently serving as a Special Advisor in the Health Communications and Informatics Research Branch (HCIRB) of the National Cancer Institute, where he is assisting in developing a research agenda in communication science and behavioral informatics to enable enhanced care across the cancer care continuum. As part of this role, he is participating in the President’s Cancer Panel on this year’s topic of Connected

Health. In addition, he is working with Ilana Braun, MD, Chief of the Division of Psychosocial Oncology at Dana-Farber/Brigham and Women’s Cancer Center, to promote development of guidelines on oncology informatics in the United States, including electronic survey-based depression screening in oncology patients – a practice that is currently in place at Dana-Farber/Brigham and Women’s Cancer Center.

“Ultimately, technology can augment but not replace the role of humans in clinical care,” said Dr. Ahern. “The best outcomes are achieved using a high-tech, high-touch approach.”



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For More Information

Our Physician Liaison Ellen Steward can provide assistance if you would like more information on these topics and ongoing research within the Department of Psychiatry. Ellen can be reached at **(617) 582-4733** or via email at esteward@partners.org.



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