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**The Medicine and Psychiatry Interface: Beyond co-morbidity**

At Brigham and Women’s Hospital (BWH), we have both a deep tradition and an exciting future in advancing the interface of medicine and psychiatry. By looking at mechanisms of disease, pathophysiology, and brain circuits that mediate perception, cognition, emotion, and behavior, we are understanding that many co-morbid medical and psychiatric illnesses are intricately linked by shared underlying disease processes.

Our focus on this interface is providing us with new insights, diagnostic biomarker capabilities, therapeutic targets, and a foundation for innovative personalized medicine approaches. Our goals include tailoring more therapies based on the profile of a patient’s brain activity, genotypic, epigenetic changes, metabolomics, and proteomics. Stratifying subgroups of patients likely to benefit from particular treatments – including pharmacologic therapies, brain stimulation, and cognitive therapies – will enable us to more effectively treat patients with fewer side effects.

We also are embedding psychiatric services in primary care, women’s health, specialty clinics, and many other areas. Our subspecialists span the spectrum of areas defining contemporary medical psychiatry.

An integral part of the BWH Institute for the Neurosciences, we collaborate with a multidisciplinary team to address psychiatric aspects of brain disorders. In addition, we serve as an expert neuropsychiatric referral source for complex and refractory cases requiring integrated diagnostic evaluation and therapeutic intervention.

I am pleased to present you with our latest issue of *Psychiatry Update*. This issue includes just a few examples of our extensive clinical, research, and educational endeavors.

David A. Silbersweig, MD
Chair, Department of Psychiatry
Co-Director, Institute for the Neurosciences

**Psychiatry Residency Program Offers Myriad of Opportunities**

Psychiatry residents at Brigham and Women’s Hospital (BWH) have a vast array of clinical and research opportunities in many subspecialized areas in psychiatry.

As part of the Harvard-Longwood Psychiatry Residency Training Program, 15 residents each year (total of 60 residents over a four-year period) rotate between BWH, Brigham and Women’s Faulkner Hospital, Beth Israel Deaconess Medical Center, Boston Children’s Hospital, and the Massachusetts Mental Health Center.

“We provide residents with a deep understanding of the biological and psychological basis for psychiatric illnesses and ways psychiatrists can interface with other specialists to better treat illnesses overall,” said Charles W. Surber, MD, Director of Resident Education and Training in the Department of Psychiatry at BWH and Brigham and Women’s Faulkner Hospital and Co-Director of the Harvard-Longwood Psychiatry Residency Training Program.

In addition to the core rotations, the residency program provides many opportunities at BWH, including:

- Brain stimulation in psychiatry—ECT, transcranial magnetic stimulation, deep brain stimulation, etc.
- Neuroimaging of psychiatric illnesses;
- Women’s mental health;
- Consultation-liaison psychiatry;
- Psychiatry services as part of the medical home;
- Geriatric psychiatry;
- Neuropsychiatry/behavioral neurology;
- Psychodynamic and behavioral psychotherapy;
- Substance abuse;
- Concurrent participation in research.

“Our program has trained some of the nation’s current leaders in psychiatry, and we continue to educate many of tomorrow’s leaders,” said Dr. Surber.

Charles W. Surber, MD
Director, Resident Education and Training
Addressing Depression and Acute Stress in Parents of NICU Babies

Brigham and Women’s Hospital (BWH) psychiatrists are providing support and services to Neonatal Intensive Care Unit (NICU) staff and mothers and fathers of NICU babies at BWH, ultimately striving to improve the wellbeing of the mother-infant dyad.

“Mothers of NICU babies, in particular, have been determined in preliminary studies to be at higher risk for post-partum depression, acute stress disorder, and post traumatic stress disorder,” said Leena P. Mittal, MD, Director of the Reproductive Psychiatry Consultation Service, part of the Women’s Mental Health Division within the Department of Psychiatry at BWH and Brigham and Women’s Faulkner Hospital. “We are working to help our NICU staff to facilitate communication and best support the parents, as well as offer psychiatric consultation and care directly to parents of NICU babies as needed.”

Psychiatry and NICU Collaboration

Each week, in concert with NICU Medical Director Robert M. Insoft, MD, Dr. Mittal meets with social workers, nurses, and other members of the NICU staff to discuss cases and offer strategies and approaches, as well as identify parents with signs of post-partum depression, bipolar disorder, and other psychiatric illnesses that should be referred for care. The Level-3 NICU at BWH cares for approximately 3,600 infants each year.

As part of the collaboration, BWH psychiatrists:

- Participate in regular rounds with Obstetrics and NICU staff;
- Provide guidelines for the screening and treatment of perinatal mood disorders;
- Facilitate communication among treatment team members about patients at high risk for depression;
- Offer educational programming about perinatal depression and other mental health issues;
- Deliver psychiatric services, including quick referral and ease of access to services in the same building as the NICU to ease parent burden;
- Address issues related to substance misuse, abuse and addiction, including prescription of buprenorphine for opioid dependent perinatal patients;
- Advise in situations of suspected domestic violence;
- Develop therapeutic interventions to help improve outcomes;
- Will implement screening for depression and acute stress disorder for mother of babies with long stays in the NICU.

“We believe that our novel collaboration with obstetrics and neonatology has the potential to provide patients with consensual, rather than potentially contradictory, guidance around treatment and neonatology planning and mutual education of best practices, while maintaining a focus on the mother-infant dyad,” said Dr. Mittal. “Additionally, this multidisciplinary approach allows colleagues to educate each other in best practices from our respective backgrounds and provides opportunities for the provision of primary and secondary preventive measures.”

Continuity of Care

The Women’s Mental Health Division, led by Laura Miller, MD, delivers services ranging from pre-conception through the post-partum period, providing a continuity of care for patients. The Division encompasses the Women’s Mental Health Services at Brigham Psychiatric Specialties and at the Fish Center for Women’s Health, the Infertility Mental Health Clinic at Brigham and Women’s Faulkner Hospital, the Reproductive Psychiatry Consultation Service, and services at other ambulatory care locations. Together, these programs offer diagnostic evaluation, preconception planning, consultation and stabilization, and psychopharmacologic and psychotherapeutic treatment for women throughout pregnancy and the postpartum period, as well as women undergoing infertility treatment.

Leena P. Mittal, MD
Director, Reproductive Psychiatry Consulting Service
Enhancing the Understanding and Treatment of Psychogenic Non-epileptic Seizures

Psychiatrists and neurologists at Brigham and Women’s Hospital (BWH) are collaborating to outline the psychological and neurobiological mechanisms of psychogenic non-epileptic seizures (PNES) and improve outcomes for patients with PNES.

Earlier Diagnosis
David A. Silbersweig, MD, Chief of the BWH Department of Psychiatry, neuropsychiatrist Gaston C. Baslet, MD, and other psychiatrists, are working closely with the BWH Division of Epilepsy, EEG, and Sleep Neurology, including Barbara Dworetzky, MD, Chief of the Division, and psychiatry-neurology resident David L. Perez, MD, to advance early detection, diagnosis, and engagement of treatment in patients with PNES.

“Early recognition of PNES is important, as these patients frequently utilize health care resources – including emergency rooms – and suffer symptoms for an average of seven years before proper diagnosis,” said Dr. Silbersweig. “A quarter of patients who undergo long-term EEG monitoring are ultimately found to have PNES.”

Dr. Dworetzky, Dr. Perez, and their colleagues retrospectively reviewed and compared preictal, ictal, and postictal heart rate differences in patients with PNES and complex partial seizures (CPS) who were electively admitted for video/EEG monitoring in order to further characterize PNES autonomic patterns (Epilepsy Behav. 2012 Jan;23(1):68-70). Statistically significant preictal heart rate increases and postictal heart rate reductions normalized to baseline were identified in subjects with PNES compared with CPS. Ictal heart rate, however, was not found to differentiate between PNES and CPS events.

“We determined that pre- and postictal heart rate distinguishes complex partial and psychogenic nonepileptic seizures and that the pattern of pre-event heart rate increases and post-event heart rate decreases in patients with PNES, compared with those with CPS, suggests potential frontolimbic neural circuit dysfunction,” said Dr. Dworetzky. “These findings may provide early clues to the underlying biological basis of PNES.”

Customizing Treatment and Improving Adherence
Dr. Baslet is characterizing subgroups of patients with PNES based on the psychological mechanisms behind the expression of symptoms in order to customize therapies and more successfully alleviate symptoms in patients (Neuropsychiatr Dis Treat. 2012;8:585-98). Dr. Baslet was the senior author of a recent study of 55 PNES patients who underwent neuropsychiatric evaluation, including self-report questionnaires that measured difficulties in emotion regulation, psychopathology severity, and quality-of-life (Epilepsy Behav. 2012 Mar;23(3):364-9). The study determined that understanding profiles of emotion regulation in PNES can be beneficial in characterizing subgroups of PNES patients and may inform psychotherapeutic interventions.

Figure 1
Brigham and Women’s Hospital researchers established the importance of perigenual anterior cingulate and posterior parietal cortices in disease pathophysiology.
Improving Long-term Success in Patients Undergoing Bariatric Surgery

Brigham and Women’s Hospital (BWH) psychiatrists and psychologists are collaborating with bariatric surgeons at BWH to improve long-term success among patients undergoing bariatric surgery.

“Weight regain following bariatric surgery is one of our most significant challenges,” said Scott Shikora, MD, FACS, Director of the BWH Center for Metabolic Health and Bariatric Surgery. A collaborative new research program between the BWH Department of Psychiatry and the BWH Center for Metabolic Health and Bariatric Surgery is identifying modifiable predictors of success that can be optimized to enhance weight loss maintenance among bariatric surgery patients. In addition, multi-level analyses, including the examination of neurobiological, behavioral, and cognitive-affective pathways, along with surgical outcomes, will help to better define the trajectory of changes among bariatric surgery patients.

“Current indicators of success in bariatric surgery overemphasize unchangeable factors, like demographics, or inconsistent psychiatric and substance use diagnoses,” said clinical psychologist Megan Oser, PhD. “We are focusing on strategic areas where we can intervene with cognitive behavioral treatments, or even pharmacotherapy to increase the likelihood of long-term success.”

These studies are being supported by a comprehensive database derived from the pre-operative psychiatric assessments of 1,100 BWH bariatric surgery patients, completed by BWH psychiatrist Florina Haimovici, MD. Data includes present and past psychiatric history, medical history, substance abuse history, social history, family history, eating habits, patient support, and self-report patient questionnaire information.

Trans-diagnostic Psychological Vulnerability Factors

Dr. Oser is evaluating psychological vulnerabilities that are common among various psychiatric disorders and behavior change efforts in order to better inform and refine cognitive behavioral interventions for bariatric surgery patients. Part of this research program will include acceptance-based therapy (ABT) approaches as it relates to body mass index and sustained weight loss. ABT has been found to be more effective than emotional control-based strategies (e.g., distraction or cognitive reframing) in managing food cravings, as well as offering significantly greater reductions in eating disordered behavior, body dissatisfaction, weight-related experiential avoidance (i.e., avoiding or altering unpleasant and unwanted thoughts, feelings, images, emotions related to weight), and improvement in quality-of-life.

Alcohol Use Disorders after Bariatric Surgery

BWH psychiatrist Joji Suzuki, MD, recently published a study that found that individuals undergoing bariatric surgery have a lifetime prevalence of alcohol use disorders (AUD) comparable to the general population, though they may be at increased risk for relapsing to alcohol use after surgery. (Obes Surg. 2012 Feb; 22(2):201-7). He is currently proposing to research several areas surrounding AUD and bariatric surgery, including:

- Screening for alcohol use using the AUDIT, a 10-question survey regarding current drinking status, before and after surgery at regular intervals;
- Comparing changes to alcohol pharmacokinetics in RYGB and LAGB patients;
- Use of motivational interviewing (MI) pre- and post-operatively to help prepare patients to change behavior.

A Look at Neurobiological Pathways

Using functional MRI (fMRI) imaging, BWH developmental psychologist Laura Holsen, PhD, is examining neural and hormonal factors mediating mood dysregulation as predictors of bariatric surgery outcomes. As part of a previous collaboration, Dr. Holsen and colleagues at the University of Missouri-Kansas City and University of Kansas Medical Center examined changes in brain activity before and 3 months after adjustable gastric banding surgery (Surg Obes Relat Dis. 2012 Sep-Oct; 8(5):602-8). They found increases in brain activation in regions associated with inhibitory processing and decreases in reward circuitry. In addition, changes in brain activity in response to food pictures were related to greater decreases (from pre- to post-surgery) in endorsement of disinhibited eating behavior.

Building on these findings, Dr. Holsen plans to broaden her focus to explore the relationships between critical factors, in particular, brain activity, appetite hormones, and psychiatric co-morbidities (disturbed mood and eating behaviors), which may influence treatment outcomes among bariatric surgery patients.
Identifying Modifiable Risk Factors for Late-Life Psychiatric Conditions

Brigham and Women’s Hospital (BWH) geriatric psychiatrist Olivia Okereke, MD, MS, is researching modifiable risk factors, including health conditions and lifestyle factors such as diet, for late-life cognitive decline and depression.

“The onset of cognitive decline and depression are both common later in life and can be extremely debilitating,” said Dr. Okereke. “By using large, population-based studies to identify modifiable risk factors for these and other mental conditions, we can potentially create ways to intervene and prevent development of poor mental health in the older adult population.”

Insulin, Insulin-related Markers, and Late-life Cognitive Decline

Dr. Okereke and her colleagues have determined that both middle-aged men and women who had high insulin levels or insulin biomarkers consistent with pre-diabetes, but were not diabetic, were more likely to develop cognitive decline in their later years.

In a study published in Neuroepidemiology in 2010 (Neuroepidemiology. 2010;34(4):200-7.), Dr. Okereke and her colleagues measured fasting plasma insulin and C-peptide (insulin secretion) levels in over 1,300 non-diabetic men, aged 60-92 years, from the Physicians’ Health Study II. These men also took part in telephone-based cognitive testing an average of 3.3 years later. Results of the study demonstrated that higher fasting insulin was associated with a greater decline in tests of global cognitive function and verbal memory.

Two separate studies published in 2008 (Neuroepidemiology. 2008;30(3):174-9. Psychoneuroendocrinology. 2008;33(4):455-61) measured fasting plasma insulin and C-peptide (an insulin biomarker) levels in over 1,000 mid-life, non-diabetic Nurses’ Health Study II participants, who also completed cognitive testing that began 10 years later. Over four years, three assessments of multiple domain of cognitive function were administered. Both studies found that higher fasting insulin and insulin marker levels were associated with a faster decline in general cognitive functioning and verbal memory.

Dr. Okereke, in collaboration with Dennis Selkoe, MD, Co-Director of the BWH Center for Neurologic Disease, and others at BWH, also have examined the associations of insulin and insulin-related factors with plasma amyloid beta (Aβ) – the central abnormal protein in the plaques of Alzheimer’s disease. Plasma Aβ42, Aβ40, and fasting insulin and C-peptide were measured in approximately 500 women who were without diabetes and in their early to mid-60s on average. They first illustrated that higher plasma Aβ40 to Aβ42 ratios in midlife, and greater increases in Aβ40 to Aβ42 ratios over the subsequent decade between mid- and later-life, were significantly associated with greater decline in global cognition at later-life (Arch Neurol. 2009;66(10):1247-53.). This finding is consistent with the concept that increased brain sequestration of Aβ42 (relative to Aβ40) is connected to worse cognitive decline over time. In a later study, they showed that insulin-related factors appear associated with lower levels of the plasma Aβ42 to Aβ40 ratio, and of Aβ42, at midlife (Alzheimer Dis Assoc Disord. 2012;26(1):50-4.).

“These and other studies suggest that intervening to control insulin among people without diabetes but with high insulin levels, beginning in midlife, may be a possible strategy to prevent dementia later in life,” said Dr. Okereke.

Dietary Fat Types and Cognitive Decline

In work funded by a Career Development Award from the National Institutes of Health (NIH), Dr. Okereke and her colleagues published results in 2012 of a study relating the intake of different major fatty acids – saturated (SFA), monounsaturated (MUFA), polyunsaturated (PUFA), and trans-unsaturated fatty acids – to late-life cognitive trajectory among over 6,000 older participants in the Women’s Health Study (Ann Neurol. 2012;72(1):124-34.). Serial cognitive testing, conducted over four years, began five years after dietary assessment. The study found that higher intake of SFA (found in foods such as red meat and butter) was associated with worse global cognitive and verbal memory trajectories, whereas higher intake of MUFA (found in olive oil, fish, and avocado) was related to better trajectories. “We determined that different consumption levels of the major specific fat types, rather than total fat intake itself, appeared to influence cognitive aging,” said Dr. Okereke.

Late-life Depression

Funded by the NIH, the VITamin D and OmegA-3 Trial (VITAL) Study at BWH is a large-scale randomized trial testing the role of vitamin D and omega 3 (EPA+DHA) fatty acids in the prevention of cancer, cardiovascular disease, and a wide range of other conditions, including depression, among 20,000 men and women (above age 50 and 55 years, respectively) nationwide.

Dr. Okereke is collaborating with JoAnn Manson, MD, DrPH, Principal Investigator of VITAL and Chief of the BWH Division of Preventive Medicine, on a separately NIH-funded ancillary to the study, called VITAL-DEP (Depression Endpoint Preven-
tion), which will examine the effects of vitamin D and omega-3 on depression prevention. “Older patients often have treatment-resistant depression, which can impact other medical conditions, physical status, and overall quality-of-life,” said Dr. Okereke. “Preventing depression is important to the overall health of this population.”

The VITAL-DEP study is a first-of-its-kind study because it is simultaneously looking at universal, selective, and indicative prevention of depression. Participants are randomized to one of four groups: vitamin D and placebo, omega-3 and placebo, vitamin D and omega-3, or double placebo. The VITAL-DEP study will determine whether Vitamin D, omega-3 fatty acids, or both influence mood or impact risk of developing either new-onset or recurrence of depression over the five-year study period of VITAL.

“Rigorous testing of the role of vitamin D and omega-3 fatty acids in disease prevention has been limited,” said Dr. Manson. “The VITAL study will provide long-awaited concrete data regarding effects of these nutrients in the prevention of depression and many other illnesses.”

Enhancing the Understanding and Treatment of Psychogenic Non-epileptic Seizures … continued from page 4

“PNES patients present with heterogeneous psychiatric and medical backgrounds, and there are currently no standard treatment guidelines for this population,” said Dr. Baslet, “Because the underlying mechanisms are varied, it is critical to tailor the approach to the individual patient.”

Dr. Baslet also is researching predictors of engagement in treatment for PNES to improve adherence, which is traditionally low. He led a recent study, to appear in an upcoming edition of The Journal of Neuropsychiatry and Clinical Neurosciences, measuring treatment retention in PNES. The study found that a multidisciplinary approach, with integration of mental health services, improves treatment retention in PNES.

Uncovering Neurobiological Mechanisms of PNES

Psychiatrists and neurologists at BWH are using functional neuroimaging studies to help uncover biological mechanisms of PNES and are studying patients with PNES to also help elucidate the greater pathophysiology of functional neurologic disorders, also known as conversion disorders. Together, they are probing brain regions involved in perceptive and emotional awareness and motor control.

“Functional neurologic disorders are very poorly understood and are quite prevalent,” said Dr. Perez. “Our collaboration in PNES and use of functional neuroimaging are helping us to develop a conceptual framework to better understand functional neurologic disorders overall.”

Dr. Silbersweig and Dr. Perez, along with Kirk R. Daffner, MD, Chief of the BWH Division of Behavioral Neurology, and psychiatrist Arthur J. Barsky, III, MD, recently authored a paper (J Neuropsychiatry Clin Neurosci 24:2, Spring 2012) outlining neural and clinical parallels between lesional unawareness disorders and unilateral motor and somatosensory conversion disorder, emphasizing functional neuroimaging and disease correlates. They found that functional-unawareness, mediated by right hemisphere lateralized, large-scale brain network dysfunction, may play a significant role in the neurobiology of conversion disorder. The perigenual anterior cingulate and the posterior parietal cortices are detailed in the paper as important in disease pathophysiology (Figure 1).

Dr. Perez and Dr. Baslet will further collaborate to prospectively collect neuroimaging data on patients diagnosed with PNES, and retrospectively explore neural predictors of treatment response to psychotherapy.

“This approach can help stratify subtypes of PNES and direct patients towards the type of intervention that will prove most efficacious for a given individual,” said Dr. Perez. “It’s also a strategy that is currently becoming increasingly used in many other areas as well, including PTSD and major depression.”

Referral Assistance/Physician Liaisons

Physician Liaisons Ellen Stewart (617-582-4733) and Tom Anderson (617-582-4760) provide direct assistance with patient referrals and consultations with our specialists.