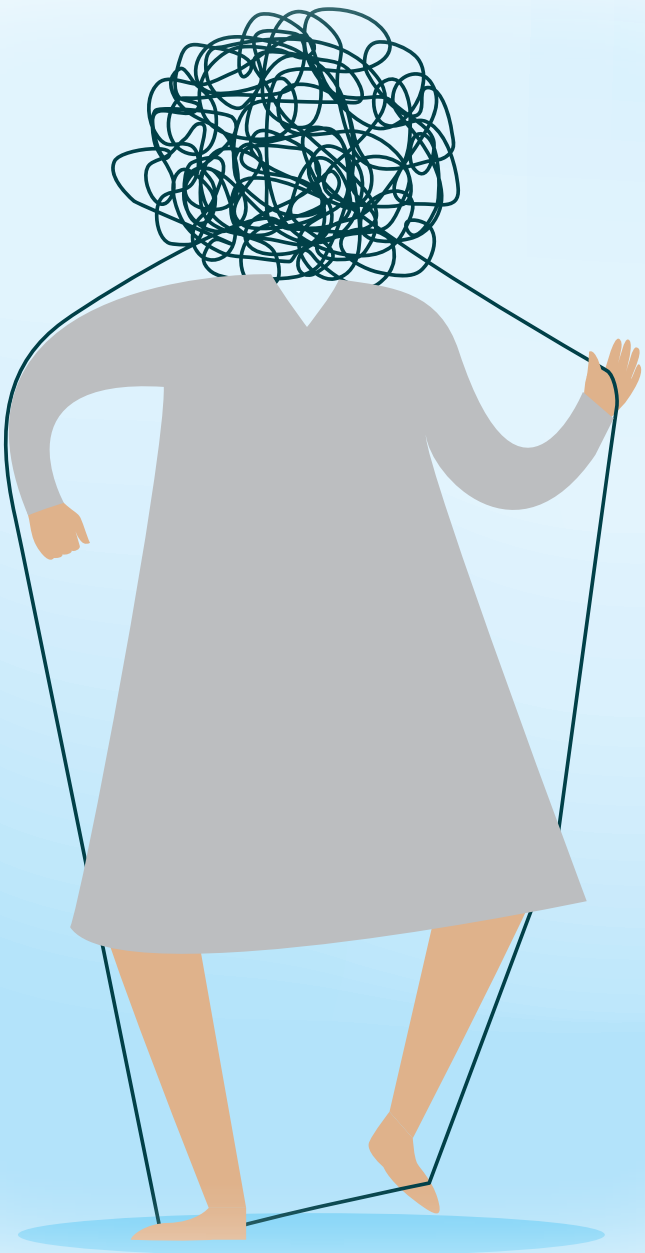
Hopkins BrainWise
THE NEWSLETTER OF THE JOHNS HOPKINS DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES
JOHNS HOPKINS MEDICINE
SUMMER 2015

# TACKLING
## Post-ICU Traumatic Stress



People usually associate post-traumatic stress disorder with those who survive military combat, major catastrophes or assaults. But critically ill patients who survive an intensive care unit stay are at equally high risk for PTSD, says psychiatrist **Joe Bienvenu**.

In a recently published literature review, Bienvenu, pulmonary and critical care medicine fellow **Ann Parker** and colleagues looked at 40 studies of 36 unique patient cohorts with a total of more than 3,000 patients who survived a critical illness and ICU stay. They found that the prevalence of PTSD in the studies ranged from 10 to 60 percent. And, after performing and then repeating a meta-analysis of a subset of the studies, the researchers found that seven to 12 months after being released from the ICU, one in five patients had PTSD.

"These rates are as high as you might see in combat soldiers or rape victims," says **Dale Needham**, medical director of The Johns Hopkins Hospital critical care medicine and rehabilitation program.

The study also found that common risk factors for PTSD among the ICU survivors included being diagnosed with anxiety, depression or other mental health problem before coming in. Another risk factor was having received large amounts of sedation in the ICU, and patients who reported having frightening memories of being in the ICU were at higher risk.

With more than 5 million people annually requiring ICU care and 750,000 Americans needing mechanical ventilation, says Bienvenu, the potential for psychological trauma should not be taken lightly. "PTSD can drastically affect a person's ability to communicate and connect with others, truly interrupting their lives and preventing experiences of joy," he says.

Bienvenu has found that the most effective way to prevent or mitigate PTSD symptoms is for nurses, other clinicians and family members to keep an ICU diary on behalf of patients, a project Bienvenu is piloting in the ICU. Every day, nurses chronicle patients' medical treatments, conditions and behavior changes as a narrative record.

After being released from an ICU, **one in five patients may have PTSD.**

Often, says Bienvenu, patients perceive that they're being tortured or are in prison. "That's understandable," he says. "Many of these patients are fighting for their lives, and their brain dysfunction from critical illness and sedation makes it difficult to determine what is actually occurring." The diaries, he explains, allow patients to process the experience and helps convince them that their visions were not real.

Parker also encourages physicians to call the ICU survivor weekly for eight weeks postdischarge to address psychological and physical hurdles.

These strategies, says Bienvenu, are part of a larger initiative that includes reducing sedation in the ICU, encouraging early mobility and physical therapy, and promoting better sleep habits—"ultimately improving the odds for better long-term mental health." ■

To see a video about the ICU diary project, visit **bit.ly/hopkinsicudiary**.

# Noninvasive Brain Stimulation for Depression After TBI

When **Vani Rao** sees patients who have depression associated with traumatic brain injury, they—and their families—are often desperate for help. Rao, a psychiatrist and director of the department's Brain Injury Program, knows well the urgency to intervene: The risk of suicide in these patients is four times higher than that of the general population.

Depression is the most common psychiatric disturbance following trauma, says Rao, and it's often attributed to psychosocial effects, like loss of identity or employment. But brain pathology, she says, plays a significant role—depending on the injury's site of impact.

"There's dysfunction of the neuropathways in these injuries," says Rao. The most common sites of focal injury, the anterior and inferior frontal regions and the tips of the temporal lobes, sit on bony protuberances, "and we know," she says, "that these regions mediate emotional stability."

In addition, TBI pathophysiology causes mechanical damage, metabolic disturbances, cytotoxic damage and neurotransmitter changes that can persist for a prolonged period and be associated with neuropsychiatric disturbances, says Rao.

The challenge is that there are no FDA-approved drugs to treat TBI-related neuropsychiatric symptoms or syndromes. Now, however, a new pilot study Rao is leading aims to determine whether repetitive transcranial magnetic stimulation (rTMS) may be an effective treatment. The study, funded through a Department of Defense grant, is the first of its kind in the United States.

TMS, a noninvasive method of brain stimulation that relies on electromagnetic induction using an insulated coil placed over the scalp, has been used successfully for some patients with treatment-resistant depression and those who cannot tolerate the side effects of antidepressant drugs. Unlike electroconvulsive therapy, TMS is associated with a low risk for seizures and cognitive deficits or memory loss.

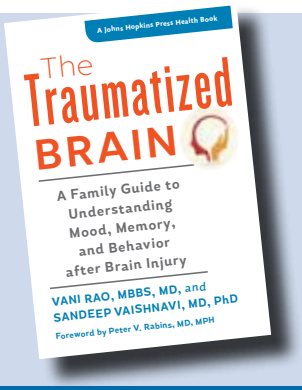
Rao works closely with **Irving Reti**, who directs the Brain Stimulation Program and conducts the treatments. He says rTMS is safe, and there's no need for anesthesia. "Aside from a mild headache in some," says Reti, "patients have no complaints."

The study will include a double-blind placebo-controlled trial of 30 patients with TBI of mild and moderate severity. Patients will come in for a 45-minute session five days a week for four weeks and will be followed for an additional three months. Rao and her colleagues will rate the effectiveness of the treatments at each visit and over time using well-validated psychiatric and cognitive assessments.

As part of the protocol, Rao and Reti are also looking at other TBI-related issues, like sleep problems. They will use diffusion tensor imaging to determine white matter changes. "Trauma to the brain can cause a lot of white matter injury," says Rao, "so we also want to see if electromagnetic stimulation can improve white matter integrity," something, she adds, that's never been done before. ■

**"We hypothesize that repetitive transcranial magnetic stimulation will be superior to sham treatment in reducing symptoms of depression and suicidal thoughts."**

—VANI RAO




## A Resource for Families Affected by TBI

As director of Johns Hopkins' Brain Injury Clinic, Vani Rao has seen hundreds of patients with traumatic brain injury and the toll it takes on families. But, unable to find a book that explains the physical and emotional aspects in plain English, she and her former co-fellow, Sandeep Vaishnavi, decided it was time to write one.

Scheduled for release in October 2015, *The Traumatized Brain: A Family Guide to Understanding Mood, Memory, and Behavior after Brain Injury* addresses mild, moderate and severe brain trauma, with a focus on long-term consequences. The book begins with a primer on how the brain works; explains the emotional, behavioral and cognitive issues that can arise after TBI; and provides targeted tips for coping. "Our aim," says Rao, "is to give voice to this silent epidemic and everyone affected by it."

The book will be available from Johns Hopkins University Press: **bit.ly/RaoTraumatizedBrain**



Scientist-to-be Isaiah Thomas in the lab with Zachary Cordner

# A Winning Experiment on a Mouse Model of Depression

Ever since he first attended the annual research symposium at his high school, Baltimore Polytechnic Institute, Isaiah Thomas wanted to do a study of his own. "I found it amazing that students were doing these interesting, complicated things," he says.

For the next two summers, Thomas participated in a program where he worked with other students to investigate scientific problems. Then in his senior year, he enrolled in a research practicum class that pairs high school students from Poly with researchers in Baltimore science laboratories. The collaboration results in a research paper and science fair project.

Matched with M.D./Ph.D. student Zachary Cordner and psychiatry researcher **Kellie Tamashiro** in the Johns Hopkins Department of Psychiatry and Behavioral Sciences, Thomas started reporting to the behavioral neuroscience lab every afternoon, four days a week, in September 2014.

In addition to performing literature reviews and devising hypotheses and research methods, Thomas worked closely

*(continued on back page)*

Patients with treatment-related cognitive dysfunction, says Tracy Vannorsdall, are increasingly seeking evaluation and tools for dealing with the difficulties they're experiencing.

# Where Oncology Meets Brain Science

Patients who've been treated for cancer often complain that their thinking is different, and not in a good way. They talk about fuzzy thinking and call it "chemo brain," a term that's become part of the lexicon for describing the post-treatment effects of cancer therapies on cognition.

Also called chemo fog or, more formally, cancer-related cognitive impairment, the problem can be short-lived or ongoing. In some breast cancer survivors, effects on thinking have been measured as far out as 20 years.

Johns Hopkins neuropsychologist **Tracy Vannorsdall**, who specializes in the cognitive and psychological impact of major medical treatments, counsels many patients with cancer. "Chemo brain causes some patients significant functional and psychiatric difficulties," says Vannorsdall. "Even people who return to their previous life may say their thinking is less fluid and spontaneous than it was before the cancer and its treatment."

Classic indications of chemo brain include disorganization, fatigue, mental fogginess, loss of attentiveness, trouble recalling conversations, and trouble with memory and mood changes, among other symptoms.

Vannorsdall listens to patients' concerns—which often include descriptions of sleep difficulty, fatigue, anxiety and depression—and provides neuropsychological testing to identify strengths that can be harnessed and challenges for which she can usually recommend a workaround. "For those who feel distressed," says Vannorsdall, "obtaining data about their thinking and personalized advice for improving their functioning can be especially useful."

As patients live longer, continue to work and want a satisfying life, chemo brain is gaining ground as a focus of cancer research. Although cancer itself, surgery, radiation treatment, comorbidities, hormones and even genetic factors could all contribute to chemo brain, little data exist about the neurocognitive effects of different types and courses of cancer treatment.

In vivo and in vitro research involving mice and human cancer cell lines has shown that cancer treatment can cause inflammation, vascular damage, and white and gray matter pathology. The chemotherapeutic agent 5-fluorouracil, for example, can reduce neural progenitor cells by as much as 55 to 70 percent. It also damages myelinated tracts of the central nervous system and alters transcriptional regulation.

Vannorsdall and Johns Hopkins colleague Kristin Redmond in the Department of Molecular Radiation Oncology and Radiation Sciences are looking at ways to prevent injury to regions of the adult brain that house progenitor cells, particularly the hippocampus and the subventricular zone. The hippocampus is involved in learning and memory functions, while the subventricular zone is a known site of active neurogenesis. In their research, they are shielding these regions during prophylactic brain radiation in patients with small cell lung cancer as well as in those receiving treatment for glioblastoma multiforme.

"We need long-term studies like these," says Vannorsdall, "to refine treatment decisions and reduce chemo brain and its emotional consequences." ■


## Keeping the Youngest Patients with Cancer on Track

An estimated 250,000 children in the U.S. are cancer survivors. It's an experience, says Johns Hopkins pediatric medical psychologist **Anna George**, that has the potential to affect their lives in ways that can last a lifetime. Because children and adolescents are still forming their identity, a cancer-related change in functioning can disrupt development at all ages. Many undergo yearslong treatment regimens, and about two-thirds have one or more ongoing medical issues after treatment. Add in the impact of the child's condition on the whole family, and there's fertile ground for emotional, physical, learning and other challenges.

"Many kids tell me they don't feel normal or they feel distressed that they're having problems behaviorally, socially, with learning and with physical skills," says George, who uses principles of cognitive-behavioral therapy and behavior management training to help patients adjust to what might be a "new normal." "Some of these kids had a long stay in the hospital and a long recovery. Our biggest gains come when young patients and their families realize that it's perfectly normal to need extra help for staying on track." ■

**Winning Experiment on a Mouse Model of Depression** *(continued from page 2)*

with Cordner to conduct an experiment as part of a larger project to understand depression in the brain.

"The basis was to use a mouse model of depression that we and others have used in the past," says Cordner, "to figure out if we could treat the mice using an approach called environmental enrichment."

For the first two weeks of the experiment, Thomas conducted a stress-inducing activity that has been shown to cause depressionlike symptoms in mice. He also recorded characteristics about the mice, such as fur quality, body weight and aggressive behavior.

This first part of the experiment was effective, and the mice began to exhibit depressionlike symptoms. "They didn't gain weight or groom themselves as well," says Cordner. "When we gave the mice access to sugar water, something that is normally pleasurable, they didn't have a preference for it."

For the next three weeks, Thomas placed the symptomatic mice in an enriched environment—cages with colorful toys, more bedding, and opportunities for increased activity and exercise. Each day, he evaluated the mice for the same characteristics associated with depression.

By the end of the recovery period, "we were able to reverse the symptoms using environmental enrichment," says Cordner. "It's a novel intervention that could be translated to humans."

After working with Cordner to organize the research, Thomas entered the Baltimore City Science Fair, where he won first place in Biological Sciences and was invited to the International Science and Engineering Fair. He also received prizes from the National Institute on Drug Abuse, the Commissioned Officers Association, and the National Organization of Gay and Lesbian Scientists.

The biggest award of all, however, was Thomas' presentation at his high school's symposium, where he was inspired to do research in the first place. "I've learned so much over the last nine months that is was hard to condense it into a presentation of 10 minutes," he says. "I wanted to say so much more."

Soon, Thomas will have endless opportunities for discussion at Tufts University, where he begins classes in the fall of 2015. ■

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This newsletter is published for the Department of Psychiatry and Behavioral Sciences by Johns Hopkins Medicine Marketing and Communications.
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