

Tapping into Psilocybin's Potential

From the 1940s to the early 1970s, psychedelic drug research had a heyday, where tens of thousands of people participated in trials exploring multiple basic research questions and therapeutic indications. Then, because of the drugs' association with counterculture and street use, the work fell out of favor.

"It's really unprecedented in pharmacology, and probably throughout science, that you would have an entire research agenda that looked this promising be put on hold for decades," says psychiatry researcher **Matthew Johnson**. Slowly, over time, such studies began again. Johnson and colleague **Roland Griffiths** have been evaluating drugs, including psilocybin—a hallucinogenic substance obtained from certain mushrooms—for more than 13 years.

"There are an incredible number of questions that need to be explored," says Johnson. "These substances tinker with the serotonin system and interact with it in a unique way. What we're understanding now is that regardless of receptor-level pharmacology, the really interesting changes that occur with these compounds are in brain network dynamics—the way different areas of the brain communicate with each other."

Work published last December in the *Journal of Psychopharmacology* demonstrated that a high dose of psilocybin could produce large, sustained decreases in depression and anxiety among cancer patients with life-threatening diagnoses and clinically significant depression and/or anxiety. Another small study published in the January issue of *The American Journal of Drug and Alcohol Abuse* found that psilocybin, when administered with cognitive behavioral therapy (CBT) for smoking cessation, resulted in substantially higher six-month smoking abstinence rates than are typically achieved through other medications or CBT alone. About 87 percent of participants rated their psilocybin experiences among the five most personally meaningful and spiritually significant experiences of their lives.

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—MATTHEW JOHNSON

When administered in carefully controlled settings, says Johnson, psilocybin's effects are often akin to "mystical experiences" that people who are deeply religious or practice meditation report—timelessness, a sense of self dissolved to a larger whole and an overall feeling of positivity. What's more, he adds, "there may be changes in brain network patterns that persist beyond the acute effect, almost like the acute effects may be inducing plasticity and flexibility."

Additional studies being planned at Johns Hopkins will explore psilocybin's effects on depression unrelated to cancer and how meditative states compare with psychedelic ones. Meanwhile, researchers at fellow institutions have found that psilocybin may effect change in areas as varied as inflammatory disease, addiction and obsessive-compulsive disorder.

These studies could offer insight into underlying likenesses among these maladies, Johnson says. While depression and addiction currently are considered different disorders, "there might be more in common than we normally realize," he says. "I think psychedelics are going to be a powerful tool to address those questions." ■



Roland Griffiths, left, and Matthew Johnson frequently visit the research pharmacy in the Johns Hopkins Behavioral Pharmacology Research Unit. There, pharmacists and pharmacy technicians prepare psilocybin capsules that are administered in psilocybin research studies.

PSILOCYBIN CAPSULES

Potential to treat various disorders, including:

- Cancer-related depression/anxiety
- Post-traumatic stress disorder
- Obsessive-compulsive disorder
- Nicotine addiction
- Inflammatory disease



Probing Deep Brain Stimulation for Alzheimer's Disease

When neuropsychologist **Gwenn Smith** was on the faculty at the University of Toronto, she was thrilled to collaborate on a study of deep brain stimulation (DBS) in Alzheimer's disease patients with neurosurgeon Andres Lozano. DBS, in which a medical device is implanted into the brain to stimulate a particular circuit, is well-established for controlling tremors in Parkinson's disease and is under investigation for managing depression and chronic pain, but its application in Alzheimer's was novel.

For their pilot, in which DBS was tested in six patients to target the fornix, a bundle of nerve fibers involved in brain memory circuits, Smith analyzed PET scans to study cerebral glucose metabolism to assess safety of the DBS procedure.

"Usually, over a one-year course of Alzheimer's disease, a decrease in metabolism is observed that correlates with memory getting worse," Smith explains. Instead, their study observed a sustained increase in glucose metabolism of the brain over one year.

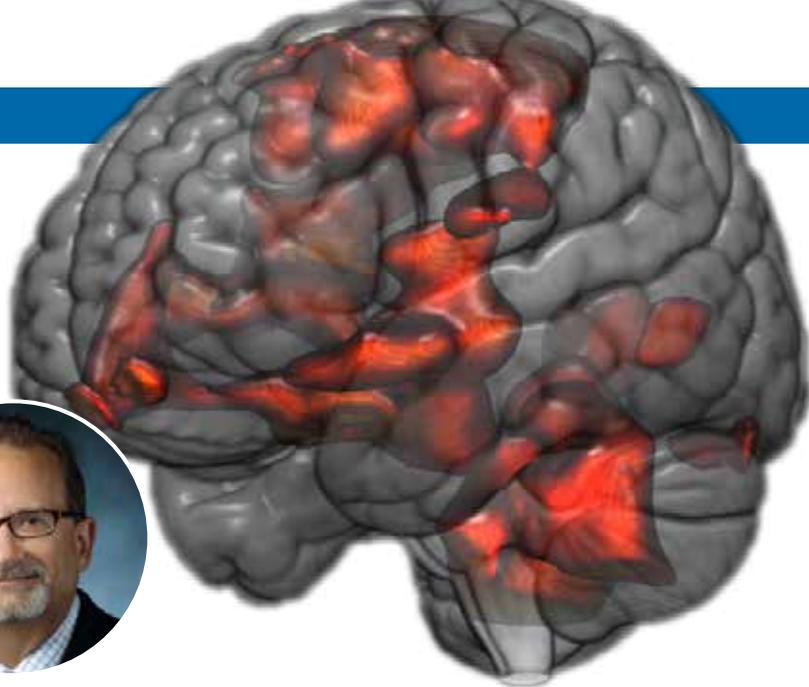
After Smith moved to Johns Hopkins in 2008, she suggested Lozano as the inaugural speaker for the Michael M. Ossoff Visiting Lectureship in Memory Disorders and Alzheimer's Disease, and introduced Lozano to psychiatrist **Constantine Lyketsos**. The trio collaborated on a multicenter phase II study of DBS in 42 Alzheimer's disease patients, further demonstrating safety and a potential benefit for patients over age 65. The study group included an interdisciplinary team of psychiatrists, neurologists, neurosurgeons and neuropsychologists. The work, published last fall in the *Journal of Alzheimer's Disease*, was also presented at the Alzheimer's Association International and Clinical Trials on Alzheimer's Disease conferences in 2015.



Gwenn Smith



Constantine Lyketsos



Early Alzheimer's disease (AD) patients underwent deep brain stimulation (DBS) directed at the fornix—a major fiber bundle in the memory circuit of the brain. Comparisons before the surgery and 12 months after showed significant increases in glucose metabolism (with areas in lighter red/yellow showing the greatest increases). The regional increases in metabolism may be produced by activating the fiber pathways, driving neural activity and modulating the dysfunctional brain networks in AD.

Their study enrolled patients ages 45-85 with mild Alzheimer's disease. All had caregivers who could reliably report their activities and functioning, and all were taking a stable dose of a cholinesterase inhibitor medication. After the participants were implanted with electrodes, half were randomly assigned to receive continuous stimulation for one year, while the other half received no stimulation. Investigators measured cognitive function and cerebral glucose metabolism.

Although there were no differences in cognitive outcomes for participants as a whole, in analyses limiting the sample to those 65 and older, says Smith, "there was a trend for cognitive benefit, or even stability, in the older Alzheimer's patients who were treated with DBS. They showed greater increases in cerebral glucose metabolism, compared with the older patients not treated with DBS. This was not seen in the younger patients." Additional analyses of the data are ongoing, some suggesting that stimulation may cause an increase in the volume of the hippocampus, where early Alzheimer's pathology surfaces.

It's not clear why younger patients didn't fare as well. "We hypothesize that an effect in younger

patients would be more difficult to detect because both glucose metabolism and cognition decline more rapidly than in older patients," says Smith. Still, "the sense is the treatment is still worth pursuing, but we need to learn more about how to optimize DBS for individual patients, as is well-established in Parkinson's."

In Parkinson's disease, clinicians implanting electrodes can determine which contact is more effective by testing the contacts and seeing immediately that if they stimulate in a particular place, tremors stop. In Alzheimer's disease, explains Smith, it's not that simple: "We need to develop methods to detect short-term improvement in memory, which is challenging. We also need to learn more about the mechanisms of action of DBS so that we can develop biomarkers to predict treatment response."

The team is working to define parameters for its next study. ■

PEDIATRIC PSYCHIATRY

A Boon for Children's Mental Health Services

For 31 years, beloved child psychiatrist **James Connaughton** mentored young psychiatrists at Johns Hopkins and taught them the art and science of interviewing children with mental health problems. A trailblazer who advocated for a holistic approach to treatment, Connaughton, in 1981, founded the Children's Mental Health Center, a community psychiatric clinic to treat children with psychological trauma and behavioral problems. He died in 2011, but his legacy will live on, thanks in part to an endowed professorship established by his children.

Pediatrician and psychiatrist Larry Wissow has been named the inaugural recipient of the professorship honoring the late James Connaughton (inset). "He believed in the power of warmth, empathy and connection as a therapeutic tool," says Wissow.

At a time when some people thought of East Baltimore as an area of great danger, Connaughton "doubled down on building relationships and working in the community," says pediatrician and psychiatrist **Lawrence Wissow**, who last November became the inaugural James P. Connaughton, M.D., Master Clinician, Educator and Professor for Child and Adolescent Psychiatry. "He was a terrifically compassionate guy who refused to be distant from the families he worked with. He believed in the



Self-Harming Behavior in Children with Autism: Can Electroconvulsive Therapy Help?

About one in four people diagnosed with an autism spectrum disorder displays serious self-injurious behaviors, such as head banging, scratching or biting. In cases where pharmacologic and behavioral therapies don't sufficiently suppress the behaviors, some families and clinicians have turned to electroconvulsive therapy (ECT), a procedure that induces a seizure in these patients, to break the self-injury cycle.

The therapy "is highly effective," for these patients, says psychiatrist **Irving Reti**, who has treated many children and teenagers referred from the Kennedy Krieger Institute and other centers. "I don't recall having a patient in whom it didn't work, and in some cases the response is remarkable after just one to two treatments," adds

Reti. At Johns Hopkins, ECT has suppressed some self-injurious behaviors by 90 percent.

But the therapy has its drawbacks, he notes: Unlike patients treated with ECT for depression, who can be gradually tapered off the therapy, patients treated for self-injurious behaviors can't be tapered well off of ECT. In fact, some require maintenance ECT treatments as often as every five days, Reti says, "and nobody really knows the long-term effects of ECT at that frequency and started at such a young age." The repeat sessions also pose logistical burdens to patients and their families.

Looking for alternative, nonconvulsive therapies that might be effective and better at maintaining suppression of self-injurious behaviors, Reti and colleagues have been studying mouse models of autistic self-injury. One study, published in the journal *Neuropsychopharmacology*, found that deep brain stimulation (DBS) aimed at the subthalamic nucleus, an area of the brain that holds movements in check, helped suppress excessive self-grooming in two autismlike mouse models.

Reti's team studied two genetically distinct mouse lines that exhibited excessive self-grooming that caused injury as well as deficits in social interactions. The researchers investigated the impact of high-frequency stimulation given via implanted electrodes at the subthalamic nucleus on the animals' grooming and social interactions.

"Unexpectedly, we found that suppression of excessive self-

grooming by the mice occurred acutely when the stimulation was switched on, and less attention to self-grooming was also persistent for several days after it was turned off," says Reti. While it's



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—IRVING RETI

still unclear exactly how the therapy suppresses self-injurious behavior, scientists believe it affects the function of the neurotransmitter gamma-aminobutyric acid, which plays a key role in reducing excitability in the nervous system. The treatment had no effect on social behaviors.

Ongoing studies are evaluating DBS at other brain sites and using optogenetics to learn more about brain circuitry in the mice engaged by DBS. The work could help pinpoint the best targets in the brain to stimulate using DBS or noninvasive, nonconvulsive therapies, like transcranial magnetic stimulation and transcranial direct current stimulation, which stimulate areas of the brain using brief magnetic pulses or direct electrical currents, he says. Such neuromodulation could also prove helpful for patients with less severe behaviors. ■

The Brain Stimulation Program has moved into new, expanded facilities on the 7th floor of the Meyer Building at The Johns Hopkins Hospital. Services include inpatient and outpatient electroconvulsive therapy (ECT), as well as outpatient transcranial magnetic stimulation (TMS). For more information, call 410-614-1732. Learn more: bit.ly/JHMbrainstimulation

power of warmth, empathy and connection as a therapeutic tool, and one for bridging the cultural and socioeconomic divide."

Wissow, who first encountered Connaughton as a pediatric resident in the 1980s, has spent a career working in nontraditional mental health settings, such as Head Start centers and outreach clinics for new immigrants. He has studied psychosocial issues in children and families in different cultures domestically and around the world. Since 2005, he has been part of the pediatric HIV clinic at Johns Hopkins. The endowed professorship offers a chance to take Connaughton's vision to a new level, Wissow says.

"We have a chance to create a real center for thinking and learning about how to do population-based, two-generational work on behalf of kids and families," says Wissow, whose ideas include partnering with after-school tutoring and economic counseling opportunities for children and parents,

"Our goal is to make the clinic into more of a center of excellence...[combining] great family-centered patient care with training and research that will help us better respond to the community's needs."

—EKATERINA STEPANOVA



and working with primary care clinics and school-based programs.

To that end, he has joined forces with **Ekaterina Stepanova**, who in August 2015 became medical director of the Children's Mental Health Center, following a few years in private practice.

"All of our therapists are trained in various aspects of psychotherapy," she says. "The most recent training was in trauma-focused therapy—it's helpful in Baltimore, given that a lot of the kids experience traumatic events." Stepanova would also like to start an intensive outpatient program, where

children with disruptive behaviors and aggression can come after school for rigorous programming. Research projects at the center include validating a blood test for attention-deficit hyperactivity disorder in children and adults.

"The clinic is going to grow," adds Stepanova, "and our goal is to make it into more of a center of excellence, where we can combine great family-centered patient care with training and research that will help us better respond to the community's needs." ■



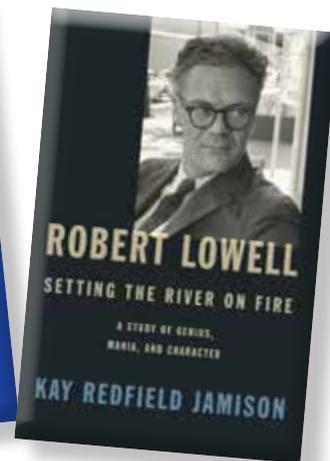
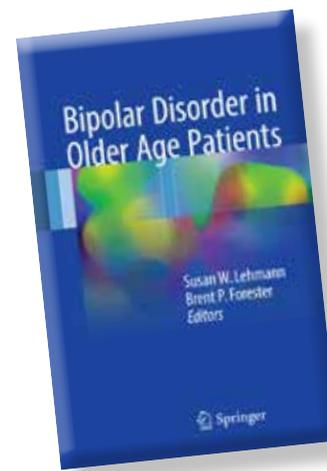
A Sampling of **Brain Research and Thinking** Underway at Johns Hopkins

The challenging experience questionnaire: characterization of challenging experiences with psilocybin mushrooms. **Frederick Barrett, Matthew Bradstreet, Jeannie-Marie Sheppard Leoutsakos, Matthew Johnson, Roland Griffiths.** *Journal of Psychopharmacology* 2016 Dec;30(12):1279-1295.

Oxytocin for the treatment of drug and alcohol use disorders. **Mary Lee, Elise Weerts.** *Behavioral Pharmacology* 2016 Dec;27(8):640-648.

Depression, its comorbidities and treatment, and childhood body mass index trajectories. **Brian Schwartz, Timothy Moran.** *Obesity* (Silver Spring). 2016 Dec;24(12):2585-2592.

Subtle changes in daily functioning predict conversion from normal to mild cognitive impairment or dementia: an analysis of the NACC database. **Milap Nowrangi, Paul Rosenberg, Jeannie-Marie Sheppard Leoutsakos.** *International Psychogeriatrics* 2016 Dec;28(12):2009-2018.



New Books by Faculty

Bipolar Disorder in Older Age Patients
 Edited by Susan W. Lehmann, M.D. and Brent P. Forester, M.D.
 Springer

Robert Lowell, Setting the River on Fire: A Study of Genius, Mania, and Character
 by Kay Redfield Jamison. Knopf

Hopkins **BrainWise**

This newsletter is published for the Department of Psychiatry and Behavioral Sciences by Johns Hopkins Medicine Marketing and Communications. 901 S. Bond St., Suite 550 Baltimore, MD 21231

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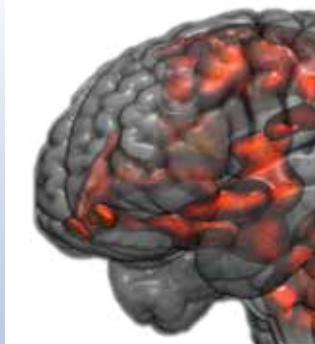
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THE NEWSLETTER OF THE JOHNS HOPKINS DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES



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