

First-of-Its Kind Psychedelic Research Center Debuts at Johns Hopkins

With \$17 million in private funding and a full panel of planned studies, Johns Hopkins investigators in September launched the Center for Psychedelic and Consciousness Research.

The center, believed to be the first such research center in the country and the largest of its kind in the world, will focus on how psychedelics impact brain function and mood in both healthy individuals and those affected by conditions such as Alzheimer's disease and anorexia nervosa.

"Psychedelics are a fascinating class of compounds," said **Roland Griffiths**, founding director of the new center and a professor of psychiatry and of neuroscience, during a press briefing announcing the center's debut. "They produce a unique and profound change of consciousness over the course of just several hours."

For nearly 20 years, Griffiths and colleagues in the Behavioral Pharmacology Research Unit have investigated the effects of psilocybin, the naturally occurring psychedelic compound found in so-called "magic" mushrooms, in over 350 study participants and healthy volunteers. These include studies of psilocybin on anxiety and depression in people with life-threatening cancer and in those with tobacco addiction. A recently completed trial in depression will be published this fall.

The new center will build on previous work and "expand

research on psychedelics to develop new treatments for a wider variety of psychiatric and behavioral disorders," Griffiths says. It also will expand research in healthy volunteers, he notes, "with the ultimate aspiration of opening new ways to support human thriving."

The center has a number of clinical studies planned, says psychiatry researcher **Matthew Johnson**, associate director of the new center: "We plan to focus on how psychedelics affect behavior, brain function, learning and memory. We also plan to explore the mechanisms by which psychedelics can contribute to general wellness."

- Johnson will lead two clinical trials. One will examine psilocybin for the treatment of opioid addiction, while a second will study psilocybin for treating post-traumatic stress disorder (PTSD).
- Psychiatry researcher **Frederick Barrett**, director of neurophysiological mechanism and biomarker assessment for the center, will lead a trial treating alcohol use disorder in people with major depression. He will also continue brain imaging studies to determine how psilocybin affects brain activity and to identify genetic and other biomarkers in the blood that can help predict the brain's response to psychedelics.
- Psychiatry researcher **Albert Garcia-Romeu** will lead two clinical studies, one

testing psilocybin in the treatment of anxiety and depression in people with Alzheimer's disease, in partnership with the Johns Hopkins Memory and Alzheimer's Treatment Center. The other will explore psychedelics in the treatment of emotional and behavioral symptoms of post-treatment Lyme disease syndrome, in partnership with the Johns Hopkins Lyme Disease Research Center.

- Psychiatrist **Natalie Gukasyan**, medical director of the new center, will lead a study of psychedelics as a therapy for anorexia nervosa, in partnership with the Johns Hopkins Eating Disorders Program.
- Griffiths will lead two studies exploring psychedelics in the betterment of healthy individuals. One will examine the effects of taking very small doses of psilocybin. The second will study the effects of psilocybin on creativity. "Overall, I see psychedelics as a paradigm-shifting game-changer in the treatment of mental health disorders, and as tools for understanding the brain's connection to mind and behavior," says Johnson.

The center is backed entirely by philanthropy. ■

Professorship Honors Legacy and Supports Future of Psychedelic and Consciousness Research

Judy Yin Shih had a diverse career in clinical psychology and health program evaluation and research, working in settings including the Johns Hopkins Children's Mental Health Center and the psychiatry department's Office of Behavioral Health Care. Along the way, she learned of research with psychedelic drugs and their potential to facilitate psychotherapy and enhance creativity.

Now retired, Shih has been active in philanthropic support of programs in education, health care and the arts. Her latest effort is providing for an endowed professorship at Johns Hopkins to support psychedelic research.

The Oliver Lee McCabe, III, Ph.D. Professorship in the Neuropsychopharmacology of Consciousness is named for a longtime Johns Hopkins faculty member who, before his affiliation with Johns Hopkins, conducted "pioneering, federally funded investigations using LSD as an adjunct to psychotherapy with patient populations often associated with poor prognosis, including chronic heroin addicts," says Shih. **Roland Griffiths**, founding director of the new Johns Hopkins Center for Psychedelic and Consciousness Research, has been nominated as the first recipient.

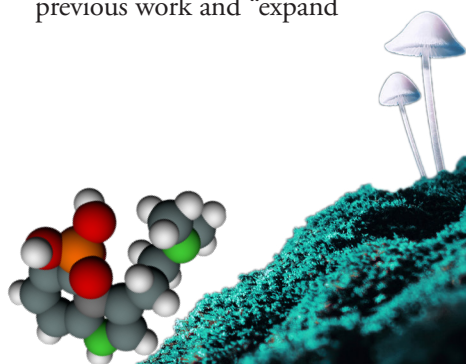
While McCabe and colleagues "were unable to continue their early psychedelic research at the Maryland Psychiatric Research Center in the 1970s, due to regulatory, political and societal factors," says Shih, she sees the endowed professorship aligning their former interrupted research with the contemporary efforts of Griffiths, "who, perhaps more than any other, is responsible for the resurgence of scientific study of these drugs, most notably psilocybin."

"I am very impressed by the rigor that Dr. Griffiths brings to his work," Shih says. "The findings have been so very positive, and appear to hold considerable promise in treating addiction as well as other mental health issues."

"The department and the School of Medicine are deeply grateful for Dr. Shih's generosity in creating this endowed professorship, which, because it constitutes funding in perpetuity, reflects a long-term commitment to this area of resurgent and promising research," says Jimmy Potash, director of Psychiatry and Behavioral Services.



Oliver "Lee" McCabe



Matthew Johnson and Roland Griffiths are leading research on psilocybin, a naturally occurring psychedelic compound found in certain mushrooms. Its molecular structure (left) allows it to penetrate the central nervous system.





Jimmy Potash, M.D., M.P.H.

Breaking New Ground While Upholding Traditions

In the midst of this frigid season, I thought I'd tell you about some cool things happening in the department. Newly installed Kogod Professor of Mood Disorders **Peter Zandi** recently received NIH funding to lead a 50-site worldwide consortium to study genetic predictors of response to electroconvulsive therapy (ECT) — the cleverly named “Gen-ECT-ics Consortium.” It is exciting to see us leading the way in this major new initiative.

Another area in which we're playing a key role internationally is psychedelic psychiatry. The new center described in this issue has been featured on *60 Minutes*, the *Today* show and National Public Radio, as well as in the *New York Times*, *Science* magazine and the *Journal of the American Medical Association*. With the center's new projects, we are helping to usher in the next generation in psychiatry by doing studies to clarify the potential role of psilocybin in treating several disorders.

At the same time, our strong foundations in exceptional clinical care and in training talented young people are alive and well. These were highlighted in October, when we hosted a farewell reception for **Dr. John Lipsey**, who oversaw the training of residents for many years. The event reunited 17 former chief residents, including some from as far away as California and Texas. Dr. Lipsey became legendary as a clinician for sweating every detail, working late into the night and leaving no stone unturned. He taught his trainees what it means to practice psychiatry the Johns Hopkins way: with rigorous thinking and total devotion. One former chief resident said that whenever he has a difficult patient situation, he still asks himself: “What would Dr. Lipsey do?”

While we strive to inspire and create the next generation in psychiatry and maintain our strong foundations, we also aim to uphold our social obligations to our community, especially the underserved. Geriatric psychiatrist **Jin Joo** recently received an NIH grant focused on using peer mentors to support elderly, low-income, minority adults with depression. Her project will determine whether this innovative approach to reaching people who sometimes fall through the cracks can make a difference.

Using Big Data to Decode Alzheimer's Disease

Johns Hopkins molecular biologist **Vasiliki Machairaki** is studying Alzheimer's disease by creating models of patient brains in her lab. **Dimitrios Kapogiannis**, a Johns Hopkins neurologist as well as a clinical investigator for the National Institutes of Health, is studying patient's exosomes, the vessels that carry proteins and DNA from one cell to another.

The two basic scientists are combining their findings with large amounts of data from patients in the Johns Hopkins Memory and Alzheimer's Treatment Center, including information gathered from brain imaging, genetic testing and performance on cognitive assessments.

The goal of this data collection and analysis is to better understand the disease and its subgroups, in hopes of developing treatments tailored to individual patients. For example, some forms of the disease might respond to anti-inflammatory treatment, while others do not, and some people might experience quicker progression than others do.

According to the Alzheimer's Association, an estimated 5.8 million Americans have the disease, a number expected to rise to nearly 14 million by 2050.

As more people live with the debilitating disease, psychiatric epidemiologist **Peter Zandi** is determined to change the status quo. “The Alzheimer's disease treatments we currently have are pretty limited and generally target the whole population of people with the disease,” says Zandi, who is collecting clinical information for the Alzheimer's team. “Our hypothesis is that different people may respond to different treatments. Can we learn about these different subtypes and change their clinical course?”

Johns Hopkins Medicine recently created a Precision Medicine Center of Excellence (PMCOE) for Alzheimer's disease to explore these approaches. The PMCOE designation, launched by Johns Hopkins in 2017, recognizes the power of data to understand disease. It creates teams of clinicians, researchers and data experts who work together, using high-powered data storage and analytics. The team gathers and studies information about patients and diseases, without compromising patient privacy.

About a dozen PMCOEs have been established at Johns Hopkins so far, including ones dedicated to studying prostate cancer and multiple sclerosis.

Leading the Alzheimer's effort is **Constantine Kostas Lyketsos**, director of psychiatry and behavioral sciences at Johns Hopkins Bayview Medical Center. The team

includes

Zandi, Machairaki

and Kapogiannis;

psychiatrists **Milap Nowrangi** and **Paul**

Rosenberg; biostatistician **Jeannie-Marie Leoutsakos**;

brain imager **Gwenn Smith**; geriatric medicine specialist

and associate director of the Memory and Alzheimer's

Treatment Center **Esther Oh**; radiologist **Kenichi Oishi**;

geneticist **Dimitrios Avramopoulos**; and data experts

Anil Mathur, Alan Coltri, Diane Koher and **Diana**

Gumas.

Lyketsos and his team are collecting data from tens of thousands of patient medical records, looking for demographic and genetic influences that determine how the disease progresses over time.

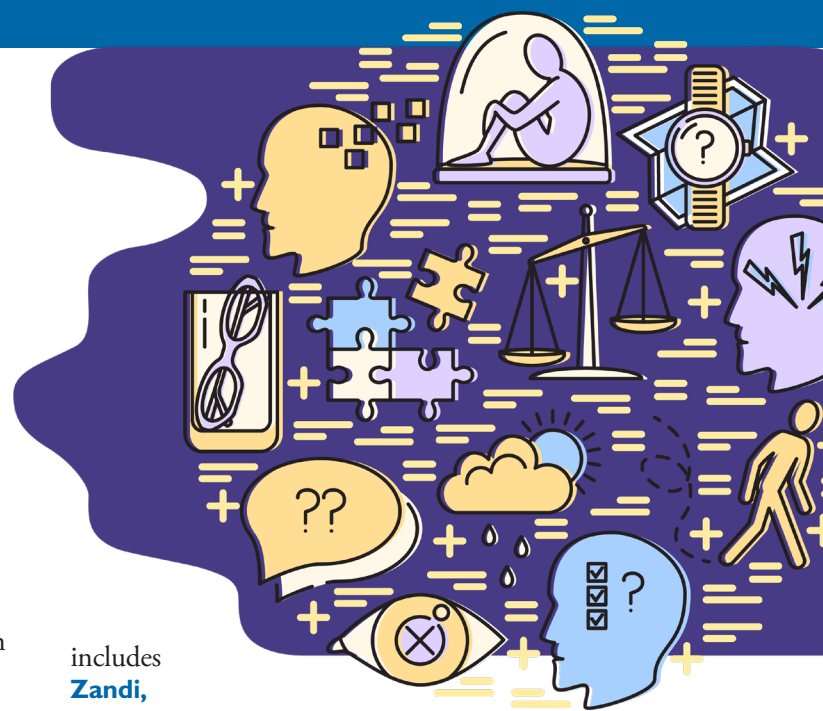
At the same time, basic scientists Avramopoulos, Machairaki and Kapogiannis are studying disease biology, seeking biomarkers in brain cells and exosomes that can help clinicians identify different types of the disease.

“Our idea is that Alzheimer's is not one disease, but rather a family of diseases,” says Machairaki. Her research uses blood samples from patients in the Johns Hopkins Memory and Alzheimer's Treatment Center to create models of that patient's brain, through a process that reprograms the adult cells to become induced pluripotent stem cells, which can then be coaxed into becoming brain neurons, astrocytes and microglia.

These models can be used to study cell behaviors and test potential therapies, says Machairaki. “Alzheimer's is a degenerative disease, so we want to study the development of the disease in vitro and the role of different brain cell types in the pathogenesis of the disease,” she says. “We now have the opportunity to test different hypotheses.”

As a basic scientist, Machairaki spends hours in her lab, tending her stem cell cultures and her 3D cell organoids (“mini brains”), which require several months to develop. Now, she's also collaborating with clinicians as part of the Precision Medicine Center of Excellence team.

“We are combining our expertise,” she says. “I think that's the future.” ■



Kostas Lyketsos and his team are collecting data from tens of thousands of patient medical records, looking for demographic and genetic factors that determine how the disease progresses over time.



Why Defining Impulsive/Reactive Aggression in Youth Matters

As an undergraduate, **Andrea Young** taught a summer school course to youth in Washington, D.C. She worked to build relationships with her students, some of whom appeared to be experiencing mood symptoms and behavior problems. “It got me wondering,” recalls the child and adolescent psychologist: “Where does aggression come from, and how can we change it?”

Young has been probing the topic ever since. The trouble with aggression, she says, is that “it tells us something is wrong, but it’s not specific to a single diagnosis.” She points out that the more impulsive and reactive type of aggression doesn’t have a distinct diagnostic home in the *Diagnostic and Statistical Manual of Mental Disorders* nor in the International Classification of Diseases. Yet, as the leading cause of referrals to outpatient mental health providers, aggression contributes to a host of public health problems, including emotional distress, property damage and incarceration.

In a recent paper published in the *Journal of Clinical Child & Adolescent Psychology*, Young and her colleagues shared results of a study that aimed to develop a data-driven definition of impulsive/reactive aggression (“AIR”—an acronym she and her collaborator have coined) in children ages 5 through 18. They set out to establish distinctions between impulsive/reactive aggression and other common childhood symptoms, such as rule-breaking behavior, depression and mania.

The study builds on research from a 2007

investigation by Jensen and others, who conducted secondary analysis on data drawn from a sample of youths seeking outpatient mental health services in academic medical centers and community clinics to assess bipolar disorder. Young replicated the methods from Jensen and others in three separate analyses with three different datasets. She and her colleagues enlisted the help of three experts, who independently rated items from several widely used scales that assess AIR. Items selected by the raters were then analyzed, along with symptoms of other common childhood problems, using principal component analysis. This analysis identified five dimensions of symptoms, including impulsive/reactive aggression, depression, mania, self-harm and rule-breaking behavior.

“It wasn’t enough to say what we think,” says Young. “We wanted to back it up with data. We’re breaking new ground in identifying a rational, data-driven definition of AIR across three datasets.”

Some kids, she explains, seem more inclined toward acts of aggression, often overreacting to things that appear trivial to others, but have no evidence of a mood disorder. Others have components of mood disorders. “We set out to better define the more reactive kind of aggression.” She explains: “*You stepped on my toe, so I’m going to step on yours*” might be more characteristic of a child with AIR.

The study covered children with large age differences across the datasets. There were many

“We’re breaking new ground in identifying a data-driven definition of the disorder.”

— ANDREA YOUNG



shared measures, as well as distinctions that could affect how aggression was represented in the study. “It was very exciting to find the AIR components in all three datasets,” says Young.

The next step, says Young, is to take children’s scores across dimensions, including AIR, depression and mania and — based on where they fall — determine whether they point to distinct subgroups of youth; e.g., kids who scored high on AIR but low on depression.

Ultimately, Young hopes that better characterization of AIR will lead to improved assessment, treatment and outcomes for children with these symptoms. In addition, she sees a role for school systems to identify those showing signs of AIR. “I’m very excited,” she says, “because it has the potential to change lives.” ■

NEURON CONNECTIVITY

Gene Reveals Itself As Key Epigenetic Regulator in Neurodevelopmental Disorders

A hallmark of neurodevelopmental disorders — including intellectual disabilities, autism spectrum disorder or even schizophrenia — seems to be a disconnect in signaling between different areas of the brain, says psychiatrist-researcher **Atsushi Kamiya**. This is sometimes accompanied by structural alterations in the corpus callosum, a band of nerve fibers joining the right and left hemispheres.

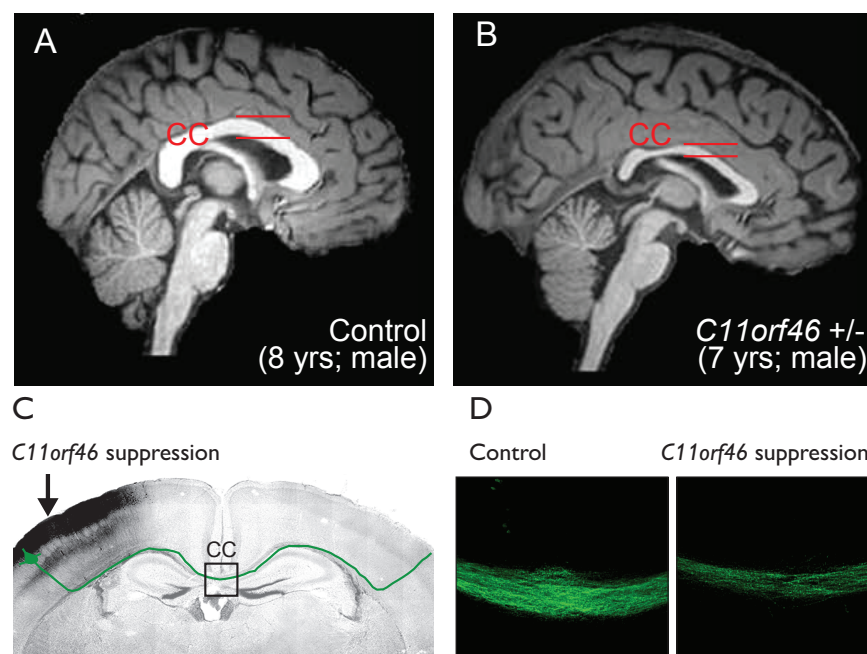
For 10 years, Kamiya has studied the molecular and circuit mechanisms underlying the development of psychiatric disorders, investigating how genetic risk factors and environmental factors lead to impairment of brain function regulating cognitive and mood-related behaviors.

“It’s no surprise that the formation of connections across brain hemispheres is a highly orchestrated, multistep process, with numerous opportunities for error,” says Kamiya. Copy number variations — duplications or deletions in the genome — are associated with neurodevelopmental disorders and abnormal neuron connectivity. In

new research studying the underlying mechanisms of genes involved in impaired connectivity between the hemispheres, his group has found that the gene *C11orf46* — located on chromosome 11 and associated with intellectual disability and other conditions — encodes a protein that is an important epigenetic regulator of neuron connectivity through the corpus callosum.

C11orf46 is highly expressed in developing neurons, and regulates the development of axons, the part of the cell that conducts impulses. It also, with histones (proteins in cells that organize DNA), is part of a molecular structure called the SETDB1 complex. Mutations to *C11orf46* impair its ability to bind to SETDB1 and negatively affect the transmission of neurons across the hemispheres.

The SETDB1 complex is involved in biological mechanisms that switch target genes’ expression on and off, called epigenetic mechanisms, or the epigenome. Suppressing *C11orf46* resulted in altered expression of *Sema6a*, a gene that regulates the



***C11orf46* plays critical roles for transcallosal neural connectivity.**

(A, B) Sagittal MRI images of a control human case (A) and a case with chromosome 11p13 haploinsufficiency, including *C11orf46* region (B). Red lines indicate thickness of corpus callosum (CC).

(C) Scheme of *C11orf46* suppression by in utero electroporation on mouse brain.

(D) *C11orf46* suppression causes CC hypoplasia.

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ability of neurons to transmit signals, leading to impaired callosal neuronal connectivity. But using a sophisticated epigenome editing tool called dCas9-SunTag, Kamiya, research associate **Atsushi Saito** and colleagues targeted the *Clorf46* protein to the promoter region of *Sema6a* on chromosome, a region key to turning the gene on, which restored the expression of *Sema6a* and, in turn, the ability of neurons to cross the corpus callosum. A description of their study, conducted with researchers at Mount Sinai's Icahn School of Medicine in New York, the National Institutes of Health and the University of Tennessee Health Science Center, was published in September in the journal *Nature Communications*.

The study, while preliminary, shines a light on a direction for future therapies that could use chemical activators or proteins to reshape the neural connections in the brain, says Kamiya.

In addition, he says, "Many drugs for histone modulation,

such as HDAC inhibitors used in cancers, have concerning side effects like nausea, diarrhea and a lowered number of platelets in the blood. If we can indirectly control histones by modulating regulator genes, like we did here, we may be able to avoid side effects while normalizing developmental abnormalities."

Copy number variations associated with neurodevelopmental disorders may affect not only neurons, but other cell types, such as microglia, brain cells that act as immune system defenders, says Kamiya. His group will next study copy number variation-related epigenetic mechanisms underlying brain development, with a focus on cell interactions between neurons and brain immune cells. ■



Atsushi Kamiya

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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Hopkins **BrainWise** WINTER 2020

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



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