EXPLORING UNCHARTED TERRITORY: THE ORIGINS OF PSYCHIATRIC DISORDERS
This edition of *Discovery* demonstrates some of the depth and breadth of research at McLean Hospital. With hundreds of hardworking researchers who hail from all parts of the world, our robust research program has all the tools to bring research from the bench to the bedside.

There is much more transformative research that we couldn’t include in this issue, including the ongoing work in the Center for Depression, Anxiety and Stress Research to help understand the neural circuit mechanisms of mood disorders and investigations at the McLean Imaging Center focused on human brain activity and connectivity underlying many psychiatric disorders.

Our dozens of scientists in the Mailman Research Center continue to make groundbreaking basic science discoveries that will one day impact new treatments for neuropsychiatric disorders ranging from neurodegeneration to stress-related disorders and addiction. Finally, throughout the hospital, our clinical research programs are embedded in clinical care, helping us to better understand best practices in treatment, suicide prevention, and digital phenotyping approaches to the behaviors and physiological processes that underlie mental illness.

Thank you again to all the donors who help fund this critically important research.

Last year, we published our inaugural edition of *Discovery*, and I am pleased to report that the feedback was tremendously positive. I hope you find this year’s publication to be similarly valuable and compelling.

If you would like to provide feedback about *Discovery* or if I can be of service to you in any other way, please do not hesitate to contact me directly at kressler@mclean.harvard.edu.

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Kerry J. Ressler, MD, PhD
BLOOD VESSEL DEVELOPMENT’S ROLE IN PSYCHIATRIC DISORDERS

For decades, scientists have known that gamma-aminobutyric acid (GABA) is a key factor in the development of neuropsychiatric disorders. But recent discoveries in the Angiogenesis and Brain Development Laboratory of Anju Vasudevan, PhD, who is pictured above, have literally opened a new pathway.

Disruptions in prenatal brain development can lead to disorders such as epilepsy, autism, schizophrenia, and anxiety. The Vasudevan laboratory, established in 2011, investigates key events in that development, with the long-term goal of ensuring that early brain development remains on track.

Today, one in four people worldwide suffer every year from some form of neuropsychiatric illness, often the product of abnormal early brain development. Drugs currently used in psychiatry, however, only treat symptoms, as there is still a lack of insight into how these diseases develop.

Research has traditionally focused on GABA and its role in the prenatal development of neurons. But Vasudevan is looking at what she believes is the equally important development of blood vessels.
“Brain development is like a gem that is cut with many facets that sparkle,” she said. “What is new here is that we are saying there is an alternate GABA pathway in blood vessels, and if you disturb that pathway, this too results in neuropsychiatric disorders. It’s like two sides of a coin.”

GABA is a neurotransmitter that blocks impulses between nerve cells in the adult brain. But in the embryonic brain, its function is reversed, exciting impulses crucial to the development and maturation of nerves and serving as a key player in building the cortical network.

Working with experimental mouse models and using techniques involving developmental biology, genetics, cell biology, biochemistry, and imaging, Vasudevan’s lab discovered that angiogenesis (development of blood vessels), also plays a role in the development of nervous system disorders.

By deleting genetic components from endothelial cells that transport and receive GABA in the developing blood vessels, Vasudevan’s team discovered “a whole new perspective for the disease itself,” she said, explaining that when these genes are deleted, blood vessels don’t form normally prenatally and in turn, disturb the development of neurons.

Angiogenesis drugs now commonly used clinically for diseases such as heart attacks and strokes could eventually play a role in the prenatal stages to “rescue” blood vessel development and “restore the postnatal behavior,” she said. “We have medications to delay strokes or to protect against strokes or heart attacks, but we have not thought of that perspective when it comes to psychiatric diseases. By tapping into the right gene pool, we can use angiogenesis to prevent or treat psychiatric disorders.”

Vasudevan estimated that her lab may be two to three years away from producing the laboratory results needed in mice before transitioning to research that could impact humans. Such clinical research would likely involve a test to determine the potential impact on postnatal treatment.

In addition, Vasudevan and her group study embryonic brain endothelial cells in depth. These have considerable potential for intervening in the adult brain to bring about positive outcomes for repair and regeneration of new brain cells.

“The potential of embryonic cells is that they are better at everything,” she said. “They are more plastic, they can proliferate more, they can migrate better. These are characteristics that are lost in the adult brain. When you look at children, they learn faster. As you get older, it gets more difficult to learn new stuff. You lose that plasticity. Embryonic cells have a lot of potential if used correctly in the right scenario. They can serve as a great means for repair and regeneration.”
The human cortex possesses a reconfigurable dynamic network architecture that is disrupted in psychosis

Maternal and early postnatal immune activation produce dissociable effects on neurotransmission in mPFC-amygdala circuits

Serine racemase and D-serine in the amygdala are dynamically involved in fear learning

The thalamic reticular nucleus in schizophrenia and bipolar disorder: role of parvalbumin-expressing neuron networks and oxidative stress

Perineuronal nets in the adult sensory cortex are necessary for fear learning

Metabolic control of primed human pluripotent stem cell fate and function by the miR-200c-SIRT2 axis

Dopaminergic enhancement of striatal response to reward in major depression

The effects of childhood maltreatment on brain structure, function and connectivity

Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity

Successful function of autologous iPSC-derived dopamine neurons following transplantation in a non-human primate model of Parkinson’s disease
Ross J. Baldessarini, MD, originally thought he wanted to be an industrial organic chemist, not a doctor.

The prospect of medical school didn’t thrill the Williams College chemistry major. He found it to be more like a trade school than an academic endeavor, not to mention it being “cutthroat and nasty.” But after a company he worked for one summer laid off 80 percent of its scientists following a corporate acquisition, he decided to rethink his future.

That decision took him to the Johns Hopkins University School of Medicine and a physiology course taught by neuroscientist Vernon B. Mountcastle, which led to a career that has included groundbreaking work in psychopharmacology and looking at the molecules and chemistry of bipolar disorder.

Mountcastle asked the Western Massachusetts native to work in his neurophysiology lab after what he felt was an impressive delivery of an in-class lecture. That led to the National Institutes of Health (NIH), an internship at the former Boston City Hospital, a stint with the Public Health Service, and then back to Johns Hopkins for clinical training in psychiatry.

So, when Seymour S. Kety, a mentor at NIH and Johns Hopkins, was looking for someone to help him establish the Laboratories for Psychiatric Research (LPR) at Massachusetts General Hospital in 1969, Baldessarini signed on. He took on the director’s role following Kety’s retirement—and the LPR’s move to McLean Hospital in 1977.

“I was in the right place for all the wrong reasons,” he said recently from his office in the Mailman Research Center on McLean’s Belmont campus, a structure he helped to design after the lab was lured from Boston.

In addition to his research tasks, he took on the challenge of teaching psychopharmacology, which at that time was so fledgling a specialty there were no textbooks. After relying on a colleague’s very scholarly text, he took it upon himself to write one of his own—on a regular subway ride from Newton.

“I scribbled and scribbled on yellow legal pads for a year, and at the end of it, a textbook popped out,” he said.

Following the commute, the bulk of his day was spent in the lab, working to figure out the rules by which nerve terminals took up, stored, and released neurotransmitters, important to understanding the clinical effect of psychotropic drugs on psychiatric diseases.

Bipolar disorder is characterized by unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. Although first described in AD 150 by the Greco-Roman physician Aretaeus, bipolar disorder didn’t make its way into the Diagnostic and Statistical Manual of Mental Disorders until the third edition in 1980.

Yet, said Baldessarini, bipolar disorder “is about as close to a disease as we have in psychiatry. It has the genetics, it has very stereotyped clinical presentations, it has unique treatments that don’t work in other conditions.”

While studying the pharmacology of neurotransmitters in bipolar disorder, he and his lab zeroed in on the biochemical causes of a widely recognized phenomenon—a high risk of relapse after stopping psychotropic medication.

Case reports showed disease could return within weeks, rather than a more common one-year cycle. The findings were extended to the impact of stopping antipsychotic drugs such as sedatives and antidepressants. The studies determined the optimal time to wean a patient off psychotropic drugs with minimal impact was two weeks.

Since closing the lab a decade ago after turning 70, Baldessarini has taken a more clinical approach to his research, looking for clues that may foretell how a patient’s illness may progress. For example, someone whose first episode involves depression is likely to experience that as the “predominate polarity,” as opposed to someone whose first incident is mania.

He has also focused on “mixed features,” in which a person can be both manic and depressed at the same time. This pattern was first recognized by Aretaeus, but not really studied until taken up by German psychiatrists Emil Kraepelin and Wilhelm Weygandt in the late 1890s.

Today, mixed features are recognized in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), and Baldessarini is looking at data that shows clinical outcomes, including higher suicide rates, are worse in mixed feature cases than in more traditional cases. That has led to new treatments that use “soothing agents,” like anticonvulsants and antipsychotic drugs, rather than antidepressants.

“We are at the beginning of a new era of subtyping of mood disorders for prognostic purposes, for better clinical care, to try to prevent suicide...”

– Ross J. Baldessarini, MD
ROSS J. BALDESSARINI, MD:

CELEBRATING

A PIONEER
Imagine if depression or obsessive compulsive disorder (OCD) could be treated with non-drug therapies, such as those currently being used to tackle Parkinson’s disease and other movement disorders. Suzanne Haber, PhD, is working toward that goal in her labs at McLean Hospital and the University of Rochester Medical Center.

For the moment, the research focus is “to understand how the brain is structurally connected,” said Haber, a visiting professor of psychiatry at McLean. Using imaging to identify the movement of blood and water molecules through the brain, she and her team are working to understand the “wiring” that controls our thoughts and movements.

The “wires” are axons, the threadlike part of a nerve cell along which impulses are conducted from the cell body to other cells. By tracking the flow of these molecules, she hopes to clearly identify “who actually talks to who in the brain.”

The work targets the basal ganglia, a group of subcortical nuclei responsible primarily for motor control as well as for other roles, such as motor learning, executive functions and behaviors, and emotions. Disruption of this neural network forms the basis for movement disorders such as Parkinson’s.

Tools such as functional and diffusion magnet resonance imaging allow scientists to “create some of the complex networks and be fairly sure that these are the structural bases for some of these networks,” she explained. When combined with animal studies, imaging results from people with and without disease provide insights about which connectivity profiles are normal and where therapies might be effective.

One of those therapies is deep brain stimulation (DBS), in which neurosurgeons target specific areas of the brain with electrodes with the goal of reducing the symptoms and impact of Parkinson’s and other motor function disorders. Work is also underway with transcranial magnetic stimulation, a non-invasive therapy that is already being used to treat depression—and which is in clinical trials for treating OCD.

The current focus of her work, Haber said, is the subthalamic nucleus, a part of the basal ganglia system that has been identified as an effective area for Parkinson’s treatment.

“We have some ideas from the imaging studies about what brain regions seem to float to the top in terms of depression and OCD,” said Haber. “Our work has been interested in some of those connections and how that network might be put together.”

The ultimate goal is to translate the basic research to create models to determine the best location to place the electrode and the contacts on that electrode to activate a positive response.

How does it work? “Nobody really knows,” she said, adding the basal ganglia is “a very complex set of interactions, and the lack of dopamine causes problems and that stimulation helps.”

One of the key issues that needs to be addressed would be to define ongoing benefits from a treatment like DBS, she said, explaining the relief in Parkinson’s is immediate, and symptoms return once the stimulation is turned off.

“We know a lot about the pharmacology” for treating depression and OCD, but “there isn’t a clear motor system like with Parkinson’s.”

There are clinical trials currently underway in the United States and Europe, but treatments may still be somewhat farther down the road.

For Haber, the near-term future of her work is clear: “The goal is to understand the normal human brain and how things are wired up...”

– Suzanne Haber, PhD
The transition out of an inpatient psychiatric setting is never easy—for the patient or the clinician. And the challenge escalates after the day program ends, and the patient returns home. Now, clinicians at McLean Hospital's Behavioral Health Partial Hospital Program (BHP), a day program that integrates psychotherapy and pharmacotherapy, believe they have a way to improve on that transition. A smartphone app.

“Our patients struggle mightily,” said Thröstur Björgvinsson, PhD, ABPP, director of the program that annually serves approximately 850 patients. “Most are diagnosed with mood and anxiety disorders and participate in up to five group sessions daily over an average of eight days. About half are in transition from an inpatient level of care. The rest need extra help while outpatients. But we have to re-hospitalize just under 10 percent of our patients.”

Clinicians have long used written assessments to gauge a patient’s progress over the first two weeks post-discharge, but “when you give someone a questionnaire and ask how their day was, it’s totally biased by how they’re feeling in that moment,” she added.

That is where ecological momentary assessments (EMAs) come in. Five times a day, a patient’s smartphone is pinged, and they are asked to answer a short series of multiple choice questions or checklists.

The day’s first questionnaire is a traditional daily symptom measurement, followed by four random checks between 10am and 8pm where questions focus on topics ranging from who they are with and whether that person is a family member, friend, acquaintance, or stranger to what stresses they may be facing and how they may be using the learned coping skills. A manuscript currently in process on this first-of-its kind study in the post-acute period will report that 90 percent of the 114 participants in a two-week EMA saw their depression symptoms remain relatively low and stable. The other 10 percent experienced an increase of symptoms in the first week before a drop in the second week.

The most common external stressors were interpersonal, followed by daily living, “other” or work-related stress, housing or financial issues, and school-related stress. The most common internal stressor was mental health related, followed by physical health.

The ability to use a tool available in virtually every pocket or purse offers great promise for future personalized treatment. “The phone can be with you when your therapist cannot. It’s very important to deliver these in-the-moment interventions rather than coming to the therapist’s office once a week, said Beard. “The promise and potential of smartphones to be able to extend our treatment outside of the BHP is amazing.”

Those group sessions teach cognitive behavior therapy skills, such as how to initiate and engage in activities that are known to have a powerful effect on depression. They also teach dialectical behavior therapy skills, such as mindfulness.

As with many medical conditions, the first 30 days after discharge are usually most critical, because “whatever episode or life episode precipitated their hospitalization is still going on,” added Courtney Beard, PhD, the program’s assistant director of clinical research. “Usually it is an interpersonal or psychosocial episode like divorce or dropping out of school.”
KAUFMAN RECEIVES AWARD FROM SOCIETY FOR THE STUDY OF TRAUMA AND DISSOCIATION

McLean Hospital’s Milissa Kaufman, MD, PhD, was honored with the 2018 Cornelia B. Wilbur Award from the International Society for the Study of Trauma and Dissociation (ISSTD) for her work in the assessment and treatment of acute stress disorder, post-traumatic stress disorder (PTSD), and dissociative disorders. The ISSTD is an international professional association that develops and promotes “comprehensive, clinically effective, and empirically-based resources and responses to trauma and dissociation.”

In her ongoing work, Kaufman focuses on women with experiences of childhood trauma and seeks to understand the subjective experience and brain mechanisms underlying complex PTSD and dissociative disorders.

“I wanted to do this research because these conditions are understudied, underfunded, and undertreated,” she explained. “We want to dispel myths and destigmatize complex PTSD and dissociative disorders. Our work is helping to familiarize the scientific community about these issues—and get individuals who often are excluded as participants in trauma studies to become part of the research.”

RESEARCH REVEALS HOW BRAIN CIRCUITS ARE AFFECTED BY INFECTIONS IN MOTHERS AND NEWBORNS

McLean neuroscientists have found that immune system activation during pregnancy and right at birth can cause alterations in an offspring’s brain neural circuits during young adulthood that are consistent with behavioral symptoms common in autism spectrum disorder (ASD) and other developmental conditions.

“Mounting evidence suggests that immune activation, such as prenatal viral infections and postnatal bacterial infections, can impact later-life brain development in humans,” said Vadim Bolshakov, PhD, director of the Cellular Neurobiology Laboratory at McLean Hospital. “While previous studies at McLean and elsewhere have focused on the behavioral symptoms produced by such immune activation, this study goes deeper, going to the cellular level to show how the brain’s neural circuits are affected.”

The researchers induced either maternal or postnatal immune activation, or gave both treatments, in groups of pregnant mice and their offspring. Behaviorally, the researchers found a strong connection between immune activation and symptoms of enhanced anxiety-like behavior and decreased social interactions. Correspondingly, they found that neural circuits in the brain that contribute significantly to the control of anxiety and social interactions were significantly affected in the immune-activated mice.

NATIONAL EATING DISORDERS BRAIN BANK LAUNCHED

The Foundation for Research and Education in Eating Disorders and the Harvard Brain Tissue Resource Center at McLean Hospital announced earlier this year the establishment of the first and only national brain bank dedicated to research in eating disorders.

The National Eating Disorders Brain Bank is a resource to help advance studies to find the causes of eating disorders which, in turn, will drive breakthroughs in the search for treatments that are desperately lacking for these neuropsychiatric illnesses. The brain bank will also provide researchers with the opportunity to examine the impact of altered nutrition on the brain.
McLean Hospital is honored to be ranked #1 in psychiatry by U.S. News & World Report

BY THE NUMBERS:
WHERE WE ARE FROM

As an international leader in neuropsychiatric research and discovery, our scientists hail from all over the globe—including six continents and nearly 30 countries. Below is a list of just some of the nations we represent.

Australia  Brazil  Canada  Chile  China  Crete  England  France  Germany  Greece
Iceland  India  Ireland  Israel  Italy  Iran  Jamaica  Japan  Mexico  Pakistan
Portugal  Russia  South Africa  South Korea  Sweden  Switzerland  Taiwan  Turkey  United States