**Bring to Light**

*Researchers are unearthing the biological roots of psychiatric disorders*

A century or two ago, if a patient developed a persistent cough, physicians could only approximate the cause and offer a suppressant. Today, a deeper understanding of the many distinct biological origins of cough, combined with better diagnostic and treatment tools, allow doctors to zero in on a patient’s specific problem—be it asthma, an infection, or lung cancer—and prescribe the remedy that targets the underlying pathology.

While fields such as cardiology and oncology have made similar strides, psychiatry has lagged behind. Researchers haven’t yet pinpointed the biological causes of major psychiatric and neurodevelopmental disorders, including schizophrenia, bipolar disorder, and autism spectrum disorders. There are no physical tests to diagnose or chart the course of these conditions. With the roots unknown, treatments can address only symptoms. Change now brightens the horizon. Equipped with sophisticated tools and an ever-greater understanding of the human brain, researchers are at long last identifying biological phenomena—including gene variants, molecules, cell types, neural circuits, and inflammatory and metabolic processes—that may underlie some of the more vexing maladies of the mind.

“Psychiatry still has a reputation as being fuzzy and only Freudian,” says Kerry Ressler, an HMS professor of psychiatry, chief scientific officer at McLean Hospital, and former president of the Society of Biological Psychiatry. “Many people don’t appreciate how much progress we’ve made even in the past few years in understanding the biological basis of behavior and how that goes awry in what we call mental illness. We’re in a transformative period in neuropsychiatry, and we now believe that these problems, though enormously complex, are finite and solvable.” Unmasking biological contributors promises to improve the classification, diagnosis, prognosis, screening, and treatment of psychiatric disorders and open the door to prevention and treatment. It could also reduce the stigma that has beleaguered people with mental illness and neurodevelopmental disorders for centuries.

If researchers are able to provide physiological explanations and, crucially, translate them into more effective care, hundreds of millions of people worldwide could benefit. Nearly 20 percent of adults, roughly 65 million people, in the United States live with a mental illness, according to the National Institute of Mental Health. About one-quarter of those cases constitute serious psychiatric illnesses: disorders of thinking, behavior, or feelings that significantly impair function. Mental illnesses cause more disability and death in people under age 50 than any other group of disorders, reported Thomas Insel, former director of NIMH, in New Scientist in 2015.

Biological insights won’t tell the complete origin stories of psychiatric and neurodevelopmental disorders. Traumatic experiences, grief, stress, substance use, and an array of other environmental and cultural factors play important roles as well. The onset of post-traumatic stress disorder requires an external trigger, but differences in genetics, biochemistry, or neural circuitry may explain why some people develop debilitating fear after a traumatic event while others do not. Similarly, treatments that follow from biological discoveries are expected to complement rather than replace other effective strategies. Studies might indicate which patients would benefit most from combining talk therapy with medications, ideally those developed from newly identified molecular targets.

“We haven’t developed any drugs for schizophrenia that represent a different molecular target or pathway than the drugs that were discovered in the fifties and sixties,” says Aswin Sekar, a former HMS genetics graduate student who will rejoin the community in July as a hematology-oncology fellow. “It’s hard to change that situation without understanding the biological mechanisms underlying the disease.”

**A million tiny pieces**

Studies in twins have led researchers to estimate that schizophrenia, bipolar disorder, and autism spectrum disorder are 60 to 80 percent heritable, meaning that across a population, the majority contribution to these conditions comes from parental DNA sequences or expression patterns. PTSD is thought to be 30 to 50 percent heritable in those who have experienced trauma. For all these conditions, the remaining percentage encompasses everything else, from spontaneous gene mutations to differences in brain anatomy to individual traumatic experiences.

Although genetics can contribute substantially to psychiatric disorders, finding and acting on the culpable variants or mutations has been difficult. That’s in part because there is no single driver like the HTT gene mutation known to cause Huntington’s disease. Instead, there are a variety of genes that each raise risk a small amount. Several hundred gene locations have been implicated in schizophrenia so far.

In 2016, Sekar, then a member of the lab of Steven McCarroll, the Dorothy and Milton Flier Professor of Biomedical Science and Genetics in the Blavatnik Institute at HMS, found a gene variant that raises a person’s risk for schizophrenia from about 1 percent to 1.25 percent. Researchers also want to know how such genes influence disease. McCarroll’s team determined in postmortem human brain tissue that different common variants (alleles) of the gene *C4*make different amounts of a protein called C4A and that the variants that make C4A were all more common among people with schizophrenia. Then, in work in mice, McCarroll’s colleagues Beth Stevens, an HMS associate professor of neurology at Boston Children’s Hospital, and Michael Carroll, an HMS professor of pediatrics at Boston Children’s, showed that *C4* tags synapses for pruning during brain development. Taken together, the findings suggest that schizophrenia involves excessive synaptic pruning via C4A and perhaps other such proteins.

The study was hailed worldwide, with some scientists saying it offered an explanation for why people with schizophrenia have thinner tissue in the prefrontal cortex and thus difficulties with behaviors governed by this region, such as executive function, social behavior, emotional response, and personality expression. Furthermore, because synaptic pruning occurs as people mature from adolescence into adulthood, the findings could illuminate why schizophrenia typically manifests in the teens or early twenties.

Building on such findings will be no easy task, considering that many diseases with much simpler genetics still lack treatments. Still, McCarroll, who is also the director of genomic neurobiology in the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, says having many small risk factors offers an opportunity. “What excites me isn’t ‘small,’ it’s ‘many,’ ” he says. “You may not have one big genetic shove, but you can investigate whether multiple nudges act on the same cell populations or cellular processes. I think that’s what will teach us how these illnesses work and how to treat them.”

**Scent trail**

Gene variants aren’t all that can be inherited when it comes to psychiatric disorders. As part of his research into normal and disordered fear learning, Ressler has found that not only do mice that repeatedly experience a mild shock combined with a scent react with fear when later exposed to the scent alone but so do their offspring and their offspring’s offspring. He discovered that areas of the mice’s brains involved in olfaction undergo structural and functional changes that get passed down as well.

Further experiments indicated that the mouse version of exposure therapy—smelling the scent ninety times over three days without any shocks—reduces the fear response and reverses the neural changes in their brains as well as potentially in their offspring.

Ressler and colleagues hope this line of inquiry will ultimately inform treatment for patients with PTSD who suffer extreme reactions to scents associated with traumatic memories, such as the cologne worn by someone who once abused them.

Parallel efforts are uncovering molecules, signaling pathways, cell types, and neural circuits involved in the creation, suppression, and overall plasticity of fearful memories. Researchers, including Ressler, are exploring ways to prevent new memories from being encoded with excess fear after a traumatic event by taking advantage of a brief window of malleability before the memory consolidates. For established memories, the researchers are testing drugs that enhance neuroplasticity so clinicians can better help patients with PTSD gradually disentangle excess fear from traumatic recollections

**Outside influence**

Of increasing interest in many disorders is the potential role of inflammation, the body’s immune response to perceived threats.

Epidemiological studies suggest that pregnant women hospitalized for infections are more likely to give birth to children with certain psychiatric disorders, such as schizophrenia and major affective disorder, as well as with neurodevelopmental abnormalities, including autism spectrum disorder. The type of infection—influenza, rubella, bacterial pneumonia, toxoplasmosis—doesn’t seem to matter.

How maternal inflammation might lead to such issues in children, or whether the occurrences are coincidental, remains unclear. Among those trying to connect the dots is Jun Huh, an assistant professor of immunology in the Blavatnik Institute at HMS. Using a mouse model of autism, Huh has implicated a particular type of immune cell and found a missing link in an unexpected place: the gut microbiome.

Huh discovered that provoking immune responses in pregnant mice can alter brain structure and neuronal activity in offspring. The changes resemble lesions seen in the prefrontal and temporal cortices of autistic children, although in the mice the changes occur in the primary somatosensory cortex. Many of the offspring also behave in ways analogous to autism, Huh found, such as spending less time socializing with other mice and more time engaging in repetitive acts such as burying marbles. The problems manifest in offspring only if infection occurs during a narrow window late in the first or second trimester. Huh’s research further revealed that if certain gut bacteria known to promote the biogenesis of T helper 17 immune cells are present in pregnant mice, infection can cause these immune cells to become overstimulated and produce an excess of cytokine IL-17a. Noting that fetal mouse brains have receptors for IL-17a, Huh postulates that activation of these cells starts the observed structural and behavioral changes. Blocking Th17 cells, or IL-17a or its receptor, reversed those changes.

To find out whether similar variations in the human microbiome drive at least some cases of autism, Huh is setting up collaborations with clinicians worldwide to analyze stool samples from women who were or were not sick during pregnancy and who have children with autism. He envisions a day when individuals hoping to become pregnant can be screened for risk of adverse immune reactions and, if found at risk, provided either a currently available Th17 cell blocker or a new immunotherapy to prevent any reactions.

“I think inflammation plays a larger role than people have appreciated,” says Huh. “I hope our studies get people excited to focus on the maternal side as well as on children.” High on the list of caveats for studies like these is the question of how well mouse or other animal behaviors reflect the actions and experiences of people with neurodevelopmental and psychiatric disorders. “Is what we’re seeing in our model comparable to autism?” asks Huh. “Probably, but only time and further research will tell.” Limitations in animal models have hampered research into psychiatric disorders that involve issues of interiority or occur in evolutionarily advanced parts of the brain. As Sekar points out, some experiences may be uniquely human.

**Collected wisdom**

Although many findings in biological psychiatry still lie within the realm of correlation, that might be enough to move ahead.

“We don’t have to know the whole sequence of events in order to intervene,” says Dost Öngür, MMSc, the HMS William P. and Henry B. Test Professor of Psychiatry and chief of the Psychotic Disorders Division at McLean Hospital.

“Psychiatry is full of successes like that. We don’t actually have the explanation for why people with depression have a serotonin deficiency, but SSRIs still work for many people.”

Before Ressler came to McLean, he helped build a cohort of more than 12,000 residents of inner-city Atlanta to study civilian trauma and PTSD. In one study that followed a subset of this cohort, Ressler’s team found that people with chronic PTSD who take blood pressure medications that act on the hormone angiotensin have less intense psychiatric symptoms. Curious, Ressler and colleagues went on to uncover angiotensin receptors in the amygdala, the brain’s fear center, leading them to propose that angiotensin joins adrenaline and cortisol in managing the body’s stress response. Bolstered by mouse studies and genetic analyses, he’s now testing losartan, a common angiotensin-receptor blocker, as a PTSD treatment in a multisite randomized controlled clinical trial funded by the U.S. Department of Defense.

Using magnetic resonance spectroscopy, Öngür has documented significant metabolic problems in the brains of people with schizophrenia and bipolar disorder: the synthesis of the energy storage molecule ATP is slower by 22 percent than in healthy brains and generates excess “exhaust fumes” in the form of oxidative stress molecules. Although it isn’t clear if the problems, which have been spotted in other diseases such as Alzheimer’s and epilepsy, are effects of or contributors to psychotic disorders, Öngür thinks addressing them could improve patients’ cognitive load. Now he’s translating those findings into a clinical trial.

The imaging work represents one way that researchers are trying to transform traditional, arguably subjective, gauges of psychiatric illness into more quantitative measures. “We currently have no way to measure the neural basis of psychopathology,” says Ressler.

Another strategy involves seeking biomarkers that can help distinguish different stages and courses of illness. Solid results could allow psychiatrists to offer prognoses, whereas now it’s impossible to predict how a patient will progress. For instance, no one knows why some people diagnosed with schizophrenia do well while others follow a “relentless downhill course,” says Öngür. Both at McLean and as part of the Massachusetts Psychosis Network for Early Treatment, he is helping to tackle the problem by collecting, standardizing, and analyzing data from patients with psychosis starting from their first episode.

**Taxonomy**

By illuminating differences within and among psychiatric and neurodevelopmental disorders, biological insights could also inform the way these illnesses are classified, a perennial thorn in psychiatry’s side. Much as cancers were once defined by the organs where they first appeared but are now more accurately diagnosed and treated based on molecular characteristics, what clinicians currently call schizophrenia or autism may prove to be collections of disorders distinct enough to require different approaches. Conversely, there may be unforeseen connections between disorders assumed to be unrelated. “Do we even know what these disorders are?” asks Öngür. “Nobody thinks schizophrenia is one thing. Nobody thinks our diagnostic categories are great, but nobody has anything better.”

Large-scale efforts such as NIMH’s Research Domain Criteria project are gathering genomic, cellular, imaging, and behavioral information from people with mental illnesses and running analyses in an attempt to let categories arise from the data. Such projects remain in the early stages. Genomic analyses, meanwhile, are turning up overlaps and divergences that alternately support and challenge standard classifications as researchers seek the disorders’ underpinnings. A 2013 study led by Jordan Smoller, MD ’92, an HMS professor of psychiatry at Massachusetts General Hospital, found that autism, schizophrenia, bipolar disorder, depression, and attention-deficit hyperactivity disorder share gene variants, while a 2018 analysis by UCLA researchers found that although bipolar disorder is characterized as swings between mania and depression, its gene-activity patterns in the cortex resemble schizophrenia more than depression.

Studies of brain circuitry offer refinements as well. Researchers comparing the neural patterns of people with and without schizophrenia have seen abnormalities in the circuit connecting the auditory cortex to other parts of the brain, suggesting why people with the disorder are more likely to have trouble distinguishing which voices come from their own thoughts versus the outside world. By studying the same circuits within schizophrenia, comparing patients who experience auditory hallucinations to those who don’t, Öngür and colleague Ann Shinn, MMSc ’11, an HMS assistant professor of psychiatry at McLean, tied those abnormalities to the group with hallucinations. They replicated their findings in bipolar disorder.

“This is something that travels with hallucinations, not with a diagnosis,” says Öngür.

**Arc of discovery**

Researchers like Öngür and McCarroll see themselves in the nascent stages of understanding the roots of psychosis, while scientists like Ressler who work on more primitive and well-studied phenomena believe they’re near the middle of an arc that ends in effective, biologically informed treatments.

Scientists are both optimistic and braced for a hard road ahead, given the complexity and mystery of behavior and cognition. How does a malfunctioning circuit contribute to the ineffable phenomenon of delusion? As Siddhartha Mukherjee, MD ’00, when writing about the *C4* gene discovery in *The New Yorker*, asked: How does synaptic over-pruning beget emotional emptiness?

Will we ever know? Do researchers first need to crack the age-old question of how the body gives rise to consciousness, to self?

Of course, when it comes to causes, mechanisms, and treatments, the field is firmly rooted in the body. Because postmortem brain samples from people with bipolar disorder or autism don’t present the same striking anatomical abnormalities as the plaques in Alzheimer’s disease or the loss of medium spiny neurons in Huntington’s, says Sekar, uncovering the biological mechanisms of psychiatric and neurodevelopmental disorders may require a deeper look.

“We believe as biologists that if it’s an illness with an organic, molecular cause, then the information must be in the tissue somewhere,” says McCarroll. “The molecular secrets are probably still hidden.”