

# ADVANCES IN PSYCHIATRY

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## The Role of Ketamine in Treatment-Resistant Depression

For much of his career, **J. John Mann, MD**, has sought to understand the molecular mechanisms of antidepressants in order to design medications that work better and faster for patients. “All FDA-approved antidepressants still take weeks to work, and it is very difficult to predict which antidepressant is going to help a patient,” says Dr. Mann, the Paul Janssen Professor of Translational Neuroscience in the Departments of Psychiatry and Radiology at Columbia University Irving Medical Center and Director of Molecular Imaging and the Neuropathology Division at the New York State Psychiatric Institute. “This trial-and-error approach to treatment selection leaves the patient sometimes feeling depressed for many weeks until we find the right dose of the right antidepressant or combination of antidepressants. Given how painful and disabling depression is as an illness, this is a big problem.”

Some 15 million Americans suffer from an episode of depression every year, and by 2030, it is estimated that depressive illness will account for more disability than any other illness worldwide –



Dr. J. John Mann

more than cancer, cardiovascular disease, malnutrition, and infectious diseases. In addition, mood disorders are the most common cause of suicide, which is the second leading cause of death in people between the ages of 15 and 25 and accounts for about 45,000 deaths per year in the United States.

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## Defining Unique Subtypes in Depression

Learning how to diagnose depression during his medical training, **Conor Liston, MD, PhD**, remembers being puzzled. “I thought I must be missing something in that people with such different symptoms can get the same diagnosis,” says Dr. Liston, a neuroscientist and psychiatrist in the Feil Family Brain and Mind Research Institute and the Department of Psychiatry at Weill Cornell Medicine. “As an example, you can meet one of the

criteria for depression if you’re sleeping too little or if you’re sleeping too much. One patient can have severe anxiety and agitation, sleeping four hours a night, and lose 30 pounds due to no appetite. Another person is sleeping 20 hours a day, can’t get out of bed, has no problems with anxiety, but is profoundly slowed and anhedonic. This person gained 30 pounds and has intense carbohydrate cravings. These people seem like opposites in so many ways, yet they get the same diagnosis and oftentimes the same treatment. In a way, it’s kind of surprising and wonderful that our treatments work as well as they do on these very different people.”

The disparity in behaviors that produced the same diagnosis piqued Dr. Liston’s interest in understanding the neurobiology of mental illness, a key focus of his research today. “How we go about

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“Our approach is driven by a biology-first perspective. What we are trying to do in our research is rethink the ways we diagnose depression that are grounded in biological measures.”

— Dr. Conor Liston



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## The Role of Ketamine in Treatment-Resistant Depression (continued from page 1)

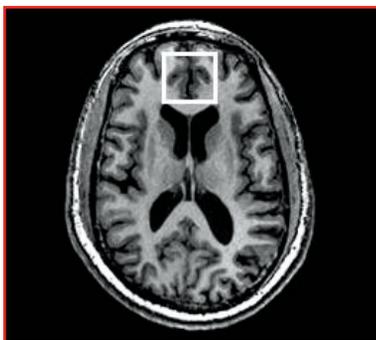
“Figuring out a way to treat depression more reliably and with a quicker response is one of the major medical priorities for the United States and the world,” says Dr. Mann, whose research employs functional brain imaging, neurochemistry, and molecular genetics to probe the causes of depression and suicide.

To that end, Dr. Mann and his Columbia colleagues have been investigating the use of ketamine as a treatment option for rapidly reducing suicidal thoughts in patients with refractory depression. “Ketamine offers a new possibility for treatment because it has been shown in a number of clinical trials – including two large NIH-funded clinical trials conducted here at Columbia – to be an effective antidepressant that produces a generally robust antidepressant effect within hours,” says Dr. Mann.

Ketamine is also known as a party drug due to its hallucinogenic and tranquilizing effects. “It does produce a sense of derealization and some sensory distortions, but it’s transient, when administered intravenously over 40 minutes under medical supervision,” says Dr. Mann.

In their first NIH trial, the Columbia researchers tested ketamine in depressed patients only; their second trial included depressed patients with a history of a suicide attempt or suicidal ideation. According to the researchers, ketamine not only works as an antidepressant, but it also has a profound anti-suicidal effect. “That’s very valuable in patients who are feeling suicidal. Not only do they potentially get better, but the suicidal thoughts can fade dramatically,” says Dr. Mann. “In an occasional subgroup of people treated with regular antidepressants, the depression sometimes begins to improve, and they become energized before the suicidal thoughts go away. Under those circumstances, the risk of suicide increases, paradoxically. That doesn’t happen with ketamine because it has a fast effect on both the depression and the suicidal impulse.”

The full benefit of ketamine lasts for about five to seven days and partial benefit can last for weeks, says Dr. Mann. “We’ve given it to people while they’re taking antidepressants and then we’ve adjusted their antidepressants to what we regard as optimal. We find that the benefits under those circumstances are fully maintained for many weeks.”



*Medial prefrontal cortical levels of glutamate + glutamine (Glx) and  $\gamma$ -aminobutyric acid (GABA) were measured before, during, and after ketamine administration using proton magnetic resonance spectroscopy.*

In a pilot study, Columbia researchers examined the relationship between antidepressant effect and ketamine dose. Eleven depressed patients were given ketamine during proton magnetic resonance spectroscopy. “We knew from animal studies that ketamine produces an increase in the amount of glutamate, the primary excitatory, or activating, neurotransmitter in the brain,” explains Dr. Mann. “At the same time, ketamine blocks one of the glutamate receptors, NMDA, that mediates the excitatory or potentially

neurotoxic action of glutamate. However, it does not block the AMPA receptor, which mediates a brain-trophic effect of glutamate. The increase in these synapses in mice happens within hours. At the end of the hour-and-a-half scan period, the patients were feeling much better. So, we think the two are related.”

In a second double-blind control trial, the results of which were published in the *American Journal of Psychiatry* in April 2018, 80 depressed adults with clinically significant suicidal thoughts were randomly assigned to receive an infusion of low-dose ketamine or midazolam, a sedative. Within 24 hours, those in the ketamine group had a clinically significant reduction in suicidal thoughts that was greater than with the midazolam group. The improvement in suicidal thoughts and depression in the ketamine group appeared to persist for up to six weeks.

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Those in the ketamine group also had greater improvement in their overall mood, depression, and fatigue compared with the midazolam group. Ketamine’s effect on depression accounted for approximately one-third of its effect on suicidal thoughts, which suggests that the treatment has a specific anti-suicidal effect. “The side effects during the infusion, mainly dissociation, were mild to moderate, typically resolving within minutes to hours,” says Dr. Mann.

The number of ketamine infusions varies from patient to patient. “We’ve been using ketamine in either one dose and then putting the patient on regular antidepressants, or sometimes others have used repeated doses,” says Dr. Mann. “A patient might get two doses a week for three weeks, and then one dose a week for a few more weeks, and then one dose a month. Eventually, one tries to manage the depression without using the ketamine at all.”

“As a researcher and clinician who has been treating depression for over 30 years, I’ve seen the painful consequences of untreated depression,” adds Dr. Mann. “Studies like these may help us give more hope to those who are suffering.”

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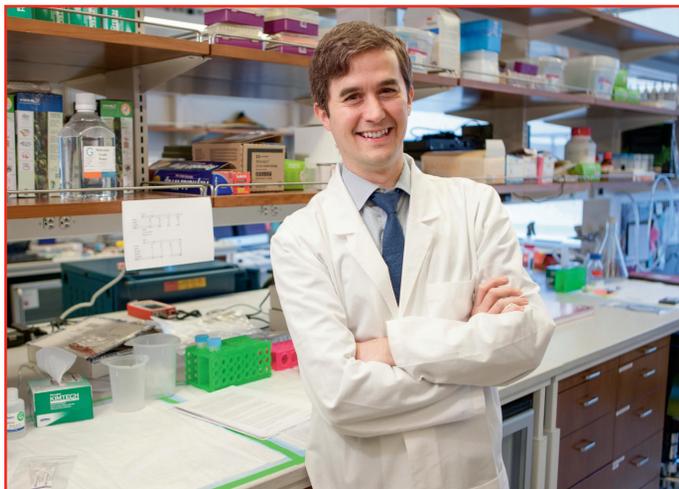
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## Defining Unique Subtypes in Depression *(continued from page 1)*



*Dr. Conor Liston*

diagnosing our patients is a longstanding challenge in psychiatry,” says Dr. Liston. “Unlike other areas of medicine where we have a relatively developed understanding of the biology of organs and illnesses that we’re trying to treat, that knowledge is relatively underdeveloped in psychiatry. Most of our diagnoses are based on clinical interviews that ask people to report subjectively about their experiences, symptoms, and history. The upshot is that our current diagnostic and statistical manual system, which relies exclusively on these self-reports, tends to group people into big, catch-all categories.”

“A great example of that is depression,” continues Dr. Liston. “We diagnose depression today when you have five or more of nine symptoms. That means that there are at least 256 unique combinations of symptoms that a person can present with and get the same diagnostic label.”

Dr. Liston emphasizes that the DSM has been transformative and positive for many individuals, ensuring access to mental health care and providing doctors with a common language for talking about mental illness. “However, one limitation is that the DSM was never designed to map directly onto biological processes. When it first came out in 1980 we had little understanding of the biology of mental illness so we weren’t trying to integrate the two. Our approach is driven by a biology-first perspective. What we are trying to do in our research is rethink the ways we diagnose depression that are grounded in biological measures.”

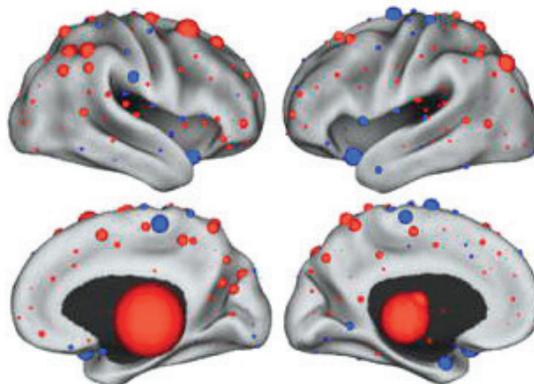
### Mapping Depression through Brain Scans

That approach led to a landmark investigation by Dr. Liston and research colleagues at Weill Cornell in which they showed that patients with depression can be categorized into four unique subtypes defined by distinct patterns of abnormal connectivity in the brain. In the study, the results of which were published in January 2017 in *Nature Medicine*, the researchers identified biomarkers in depression by analyzing more than 1,100 functional magnetic resonance imaging (fMRI) brain scans of patients with clinical depression and of healthy controls. These biomarkers may help physicians to better diagnose depression subtypes and determine which patients would most likely benefit from transcranial magnetic stimulation.

“In our study, we were trying to look for subtypes of depression where patients are more similar to one another and where there is a stronger correspondence to biology,” says Dr. Liston. “Historically, researchers have looked for groups of symptoms that tend to co-occur in subsets of people, great examples being seasonal and melancholic depression. But the fact remains that even these subtypes don’t have a very strong correspondence with biology. We wanted to try something different. Instead of grouping people based on symptoms and then asking if there are biological biomarker correlates of those symptoms, we did the opposite and grouped people based on biology. Then we asked if those groups predict different kinds of symptoms and different patterns of responding to treatments.”

As Dr. Liston explains, the scientists chose resting state fMRI brain scans as a biological measure as they can be sensitized to activity in the brain. “We’re mapping the brain’s connections and seeing which connections are altered,” he says. “The brain is organized into hubs. Connections with these hubs turn out to be very important for supporting the way the brain functions and

### Depression Biotypes Transcend Conventional Diagnostic Boundaries



*Generalized anxiety disorder (GAD) was associated with widespread connectivity differences in resting-state networks that overlapped significantly with those in depression. This figure shows the neuroanatomical distribution of the most discriminating connectivity features for the comparison of patients with GAD versus controls. Red represents increased and blue decreased functional connectivity in GAD. (Nature Medicine. 2017 Jan;23(1):28-38.)*

give rise to our daily experience: learning, memory, attention, emotions. When these connections are altered that can disrupt those processes. We know there are alterations in depression and we are testing whether there might be different alterations in different subgroups of people.”

Collecting data in neuroimaging studies is no easy task, notes Dr. Liston. “We’re still in an era where most neuroimaging studies in depression include only a few dozen people. We knew we would need more data than we could possibly collect ourselves, so I went around the country asking everyone I know, and a lot of people that I didn’t know, to share their data with me. The data were provided to us by a network of scientists and psychiatrists at seven institutions across the country and internationally as well.”

The researchers derived the biomarkers by assigning statistical weights to abnormal connections in the brain and then predicting

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**Defining Unique Subtypes in Depression** *(continued from page 3)*

the probability that they belonged to one subtype versus another. They found that distinct patterns of abnormal functional connectivity in the brain differentiated the four biotypes and were linked with specific symptoms. For example, reduced connectivity in the part of the brain that regulates fear-related behavior and reappraisal of negative emotional stimuli was most severe in subtypes one and four, which exhibited increased anxiety.

The researchers also discovered that the four discrete subtypes vary in terms of their clinical symptoms. "The clinical symptoms the subtypes are associated with are complex, just like depression is," says Dr. Liston. "Our sample of depressed people varied along two dimensions. One had to do with severe anhedonia and a psychomotor slowing with low energy, a loss of interest in the things once enjoyed, and so on. A second dimension was quite the opposite and related to anxiety and insomnia. The different subtypes are basically different combinations of those sets of symptoms."

Just as the patients' clinical symptoms differ, so does their response to treatment. "We found that these subtypes were associated with different likelihoods of responding to transcranial magnetic stimulation," says Dr. Liston. "We could predict with high accuracy whether or not a patient will respond to this therapy, which has been in use for at least 10 years for treating depression. However, like many of our antidepressants, it works for some

people and not for others, and it takes about five weeks to know whether it is working. To be able to predict whether this treatment would work for a patient beforehand is significant."

Going forward, Dr. Liston plans to replicate and confirm the results of this research and work with other investigators to see if objective biological tests can help diagnose subtypes of other mental illnesses, such as psychotic disorders, autism, and substance abuse syndromes. "We are currently seeking funding from the NIH to do a prospective clinical trial to scan patients with depression and try to predict which treatment is best for them," says Dr. Liston. "Then we'll give them the treatment we think is likely to work and then test if those predictions were accurate. If that works out, it could have a big impact on peoples' lives. There are many reasons to be hopeful for big advances in the future."

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