



# Department of **Psychiatry**



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## Chair's Report 2023



We devoted our energies to delivering the best care possible, developing enhanced interventions, and conducting research that has the potential to be truly transformative.

The year 2022 was a productive and prolific one for our department. We launched the Center for Disease Neurogenomics—one of the few in the world with access to brain tissue and population-level datasets. Our Women’s Mental Health Center has expanded, investigating how infection and medication affect mental health during pregnancy and postpartum, as well as long-term behavioral outcomes.

In addition, the Blau Center, established in 2021, hit the ground running with a study looking at

10 very rare genetic mutations associated with schizophrenia. We found 61 patients with these mutations through Mount Sinai’s BioMe™ biobank, and we have high hopes for subsequent insights into new treatment approaches.

These undertakings reflect the fundamental focus and strength of our department: We are in the people business. Our people are the patients who look to us for our diagnostic and treatment expertise. Our people are also the clinicians who deliver exceptional care to our patients, and the researchers who continually advance knowledge in our field. And our people are the new generation of psychiatrists and psychologists whom we train to set new standards of excellence in care and research.

Finally, we devoted our energies to delivering the best care possible, developing enhanced interventions, and conducting research that has the potential to be truly transformative. We believe genetics holds the key to achieving successful interventions among patients. And we will continue to lead the effort to identify genes that are associated with an increased risk for psychiatric illnesses for the benefit of our patients.

As proud as we are of our achievements, we are even more excited about what we can accomplish next for the people we serve—with the support of the people who make our progress possible.

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# Precision Psychiatry Through Genetics and Genomic Sciences: The New Center for Disease Neurogenomics



Panos Roussos, MD, PhD, and John Fullard, PhD, Director of the Multiomics Technology Group.

Identifying the genetic variants and underlying mechanisms that cause neuropsychiatric disease is the key to personalized therapy. But achieving that goal requires an interdisciplinary team of experts, and access to population-level data sets. Mount Sinai's Department of Psychiatry's new Center for Disease Neurogenomics is in the unique position of having both.

As researchers continue to make significant inroads in the investigation of genetics, genomic sciences, and precision medicine in the fields of cancer and cardiovascular disease, Mount Sinai's Panos Roussos, MD, PhD, MS, is looking to make similar breakthroughs in neuropsychiatric disorders by establishing the Center for Disease Neurogenomics (CDN).

"The human brain is a complex and vast field of study, with billions of cells, thousands of cell types, and many different brain regions," says Dr. Roussos, Professor of Psychiatry, and Genetics and Genomic Sciences, at the Icahn School of Medicine at Mount Sinai, and member of The Friedman Brain Institute and the Icahn Genomics Institute.

"Furthermore, the brain is not a static organ but a dynamic, evolving entity as it ages. Our goal is to understand how genetic liability affects this developmental process, determine which cell types and molecular markers are affected as disease progresses, and use those insights to enable effective, personalized therapeutic approaches."

Launched in 2022, the Center's exploration of the genetics of neuropsychiatric disorders has the potential to predict the severity of clinical phenotype, optimal treatment, and outcomes for each patient. These spell significant benefits for a broad swath of the population. For instance, more than 6 million Americans are living with Alzheimer's disease, and this number is projected to rise to nearly 13 million by 2050. But the Center's work would also benefit millions who live with, or are caregivers to someone who has, schizophrenia, Parkinson's disease, bipolar disorder, depression, and other neuropsychiatric and neurodegenerative diseases.

"We are interested in how genetics can be used for the benefit of patients, specifically in identifying therapeutic approaches that would work best for them," Dr. Roussos says. "Ideally, we would not treat every schizophrenic patient with the same medication; instead, through our research, we could use their genetic profile to identify the most effective treatment for each person. However, finding effective drug targets for neuropsychiatric disease is challenging because there are no reliable biomarkers and the effect of each genetic risk factor is very small."

## Two Key Ingredients: Interdisciplinary Expertise and Access to Population-Level Data

To overcome those challenges, the Center is taking an interdisciplinary approach that brings together computational scientists, biomedical scientists, psychiatrists, and genomic scientists. Many of its researchers are cross-trained and have advanced knowledge in key areas that span "omics" technology, single-cell biology, data integration using artificial intelligence, and statistical genetics.

That breadth and depth of genetic expertise will further benefit from the Center's unparalleled access to brain tissue and datasets that reflect the population-level sample sizes necessary to conduct such vital research. Data sources include biorepositories, such as the Million Veteran Program, the Mount Sinai BioMe BioBank program, the UK BioBank, and psychEMERGE. Relationships with brain banks, neurosurgeons, and health care systems are also providing access to fresh brain tissue, which is advantageous to study cells that are critical for Alzheimer's disease.



Panos Roussos, MD, PhD, during a presentation of his team's findings.

These data are enabling researchers to conduct large-scale studies—including groundbreaking multi-ethnic studies—that are leading to a deeper understanding of risk variants and genetic liability. And findings from those studies are fed through Mount Sinai's supercomputer Minerva, a powerful resource that enables analysis and management of data. Combined, they create a solid foundation for innovation in neuropsychiatric disorder investigation that has already resulted in the development of several groundbreaking techniques to meet the Center's objectives, including:

- Innovative methods to isolate human brain cells to perform cell-type specific assays and generate large-scale functional omics;
- New computational and machine-learning approaches to analyze large scale functional omics and understand cellular and molecular mechanisms in disease perturbation; and
- Novel predictive models to assess gene expression, disease manifestation, and treatment outcomes

"I'm energized by this team's enormous productivity in just six months," Dr. Roussos says. "We are functionally validating our findings in cell-type specific contexts. And we are translating these discoveries to uncover new drug targets, repurpose existing drugs for neuropsychiatric diseases, and optimize treatment for each individual based on their genetic profile—which is the ultimate goal of precision psychiatry, and will pave a new era in patient-centric care."



# Two Leading Brain Scientists Elected to the National Academy of Sciences

Yasmin Hurd, PhD, and Helen Mayberg, MD, have paved new paths in addiction and depression research by opening new lines of inquiry into treatment approaches: the therapeutic potential of CBD, and a specific target for deep brain stimulation.



In May 2022, two Mount Sinai researchers—Drs. Yasmin Hurd and Helen Mayberg—were elected to the National Academy of Sciences (NAS), which recognizes individuals for their distinguished and continuing achievements in original research. Drs. Hurd and Mayberg are among six Mount Sinai faculty members who have achieved such recognition—one of the highest honors a scientist can receive.

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Helen Mayberg, MD

A Pioneer in Mapping Molecular Mechanisms of Depression



The idea of studying a psychiatric disorder as a neurological one was novel, if not heretical, when Mount Sinai researcher Helen Mayberg, MD, began her training in neurology. But thanks to her pioneering work in integrating imaging techniques to map the molecular mechanisms of depression in the brain, it has become commonplace.

That innovative thinking, and the advances Dr. Mayberg has made over the past 35 years both in understanding abnormal brain circuits in depressed patients and how different treatments work, has been recognized with her election to the National Academy of Sciences (NAS).

As Mount Sinai Professor in Neurotherapeutics, Dr. Mayberg began her path toward neurological innovation with clinical training in neurology at Columbia University, followed by a research fellowship in nuclear medicine and functional imaging at Johns Hopkins University in Baltimore. Prior to joining Icahn Mount Sinai, Dr. Mayberg held cross-disciplinary appointments in neurology, psychiatry, radiology, neurosurgery, and neuroscience at institutions such as Johns Hopkins, University of Texas Health Science Center in San Antonio, University of Toronto, and Emory University in Atlanta.

It was Dr. Mayberg who first identified the critical role of Brodmann area 25 of the brain, a region of the cingulate cortex, in negative mood among healthy individuals and as a common target of various antidepressant treatments. She subsequently hypothesized that deep-brain stimulation

(DBS)—delivering electrical stimulation to area 25 and its white matter connections using implanted electrodes—could offer an effective therapeutic approach for patients with treatment-resistant depression. Mapping studies she conducted in the 1990s enabled her to conduct a test of that theory in 2003, with a majority of participants demonstrating long-term benefit.

Believing that transdisciplinary collaboration is foundational to her work, Dr. Mayberg became the founding Director of the Nash Family Center for Advanced Circuit Therapeutics in 2018. The center brings neurology, psychiatry, neurosurgery, imaging, physiology, engineering, and behavioral health under the same roof to explore the potential of using DBS to treat circuit disorders such as Parkinson's disease, depression, and obsessive-compulsive disorder.

Advances in technology are enabling researchers at the center to further enhance this therapeutic approach by personalizing their treatment with precision imaging-based targeting through mechanistic studies to better understand why and how DBS works, and through biomarker studies to identify patients who are most likely to respond to a particular DBS treatment. Researchers are also interested in exploring questions such as whether DBS repairs brain circuits by promoting circuit or global brain plasticity.

"My work has had the same basic thread over the course of 35 years: what is the neurology of depression and how do we optimally treat it, not just generally, but in individual patients," Dr. Mayberg says. "Mount Sinai is the ultimate place for this work, with a committed set of clinicians, scientists, and engineers who share this transdisciplinary vision."

Yasmin Hurd, PhD

Exploring New Avenues in Translational Addiction Research



When Mount Sinai researcher Yasmin Hurd, PhD, began exploring the therapeutic uses of cannabidiol—a component of cannabis that is also known as CBD—few people had heard of it, much less thought it could have any efficacy in treating substance use disorders. Today, CBD not only is recognized for its therapeutic potential but also has become a popular add-on option on coffee shop menus.

That shift in thinking about CBD is, in large part, the result of Dr. Hurd's pioneering work that, in combination with her other transformative research, has resulted in her election to the NAS.

The Ward-Coleman Chair of Translational Neuroscience and Director of the Addiction Institute of Mount Sinai, Dr. Hurd focuses her research on the neurobiology of drug addiction and various psychiatric disorders, spanning both basic science research and translational work in humans. She says that having evidence in both non-clinical and clinical settings enables her research to inform treatment and health policy. "Producing research that actually has impact to our society was important to me," Dr. Hurd says.

By focusing on the molecular impacts of prenatal to adulthood exposure to substances, including pioneering studies of the human brain, Dr. Hurd discovered milestones about the developmental and transgenerational effects of exposure to cannabis and its therapeutic potential for treating substance use disorders, such as those involving opioids.

Her work progressed even as the prevailing wisdom held that cannabis was a benign drug with no long-term impact on the brain. "My research into the developmental effects of cannabis as well as

potential therapeutic aspects of cannabidiol made people take another look at cannabis and has shaped the questions people are asking today," she says. Her foundational research created a path on which numerous other researchers are now working.

That research received a crucial endorsement shortly after Dr. Hurd joined Mount Sinai in 2006. Recognizing the potential importance of Dr. Hurd's research in advancing her preclinical studies from animal models to live human beings, Dennis Charney, MD, Anne and Joel Ehrenkranz Dean of Icahn Mount Sinai and President for Academic Affairs of the Mount Sinai Health System, knew that Mount Sinai would be an ideal place for her to conduct these clinical trials. That support also propelled Dr. Hurd to explore the role of epigenetics in addiction, specifically the potential to use knowledge about epigenetic dysregulation to develop targeted interventions that reverse addiction.

"When I started in this field, there was the pervasive stigma of the common phrase 'Once an addict, always an addict,'" she says. "After studying this for such a long time, I know it's not true. The effects may be long-lasting, but they are not locked in perpetuity."

Enduring stigmas about addiction still pose challenges even for funding many aspects of Dr. Hurd's research. But the progress she has made to date provides the fuel for her to take on those challenges, further her work, and have an impact on the lives of thousands of people with substance-use disorders. "With broader support, I know we will continue to make a difference and create real solutions," she says.



# Growing Our Understanding of Genes Strongly Linked to Autism

A study of more than 150,000 people identified genes strongly linked to autism and neurodevelopmental disorders. Joseph D. Buxbaum, PhD, is furthering that work to gain insights into how mutations might result in developmental disorders and provide potential targets for treatment.



Joseph Buxbaum, PhD,  
with graduate student  
Lauren Dierdorff.

Autism spectrum disorder was first understood to have links with genetics 20 years ago. Looking back, Joseph D. Buxbaum, PhD, marvels at his and his colleagues' naiveté and what they thought of the condition.

“For good reason, we thought there were a handful of genes that, if we found them, would enable us to understand the biology of autism,” recalls Dr. Buxbaum, Director of the Seaver Autism Center for Research and Treatment at Mount Sinai, and Professor of Psychiatry, Neuroscience, and Genetics and Genomic Sciences, at the Icahn School of Medicine at Mount Sinai.

Today, he says, an estimated 1,000 genes—approximately 5 percent of our genes—are thought to contribute to autism risk if mutated. The fact that so many genes are disrupted, many of which may play key roles in defining who we are and building our social lives, creates a need to identify these mutations.

Dr. Buxbaum is furthering these efforts through a new genetic sequencing study by the Autism Sequencing Consortium (ASC), which he co-founded in 2010 and co-leads, involving more than 50 institutions. The study involved an international team of researchers who collected and analyzed 63,327 participant samples, 20,000 of which were from individuals with autism, making it the largest

undertaking of its kind to date. In addition, the study leveraged additional participant samples for individuals with motor, cognitive, and language delay.

The study, whose findings were published August 18, 2022, in *Nature Genetics*, identified 185 genes strongly associated with the condition. The Seaver team, using the Swedish National Patient Register, has now shown that those genes provide a key for making a genetic diagnosis in 30 percent of individuals with autism.

“We know there are many genes that, when mutated, contribute to autism, and through this study we were able to bring together multiple types of mutations in a wide array of samples to get a much richer sense of the genes and genetic architecture involved in autism spectrum disorder,” Dr. Buxbaum says.

The Seaver team is now leveraging CRISPR gene editing technology for a better understanding of the biology of autism and identification of shared pathways. They are using CRISPR to mutate the top autism genes in nerve cells to understand the biological impact. This would open the door for drug discovery and development for autism spectrum disorder. But Dr. Buxbaum cautions that the sheer number of genes being identified will likely necessitate a precision medicine approach.

“A precision medicine approach is typically necessary when we encounter a condition or illness that is biologically very complex,” he explains. “What we have shown with this study is that autism is biologically very complex, and there will not be one therapeutic agent that is going to benefit everyone.” That said, the genes being identified create the potential for stratification, identifying pathway convergence, and pursuing novel therapeutics, he adds.

## Uncovering Links Between Autism and Developmental Delays

The research team also explored genes, mutations, and cellular expression patterns that are shared among individuals with autism and developmental delays, typically cognitive and motor delays.

They found that there is overlap among most autism and developmental delay risk genes, but that some of these genes are more likely to be mutated in autism while others are more likely to be mutated in developmental delay. Furthermore, genes associated with developmental delay were more likely to influence earlier nerve cell development, while those associated with autism were more likely to influence later nerve cell development.

Additionally, in an analysis of more than 20,000 samples from individuals with schizophrenia, researchers found that genes strongly associated with autism were more likely to be associated with genes that increase risk for schizophrenia.

The goal for Dr. Buxbaum now is to continue discovering genes, interpret their significance using data sets such as the Swedish National Patient Register, and use those clinical findings to facilitate drug discovery and development. At Mount Sinai, faculty members are investigating genes that are of top interest through clinical trials with existing and novel compounds, and Ana Kostic, PhD, recruited from the pharmaceutical industry, has been tasked with leading the effort to identify novel compounds as Director of Drug Discovery at the Seaver Autism Center.

“We are already gaining insights on which treatments work, and there is no question in my mind that we will see something come to the fore in the realm of precision medicine in autism in the next four to five years,” Dr. Buxbaum says.

*“We know there are many genes that, when mutated, contribute to autism, and through this study we were able to bring together multiple types of mutations in a wide array of samples to get a much richer sense of the genes and genetic architecture involved in autism spectrum disorder.”*

— Joseph D. Buxbaum, PhD



# Exploring Social Interactions’ Links to Mental Health Through Computational Science

Adaptation to new social situations depends on brain computations. But what happens when those computations break down? That is the question computational scientist Xiaosi Gu, PhD, is attempting to answer. Through digital phenotyping, computational modeling, and neural recording, she is gaining insights on how the brain encodes social information and how that may impact mental health.

Every day, the human brain makes a series of computations that enable us to learn and adapt to new social situations. At Mount Sinai’s Center for Computational Psychiatry, Xiaosi Gu, PhD, is interested in the psychiatric ramifications of breakdowns in those computations.

“Many psychiatric disorders are associated with problems with how the software of the brain is programmed to handle complex situations, such as social interactions,” says Dr. Gu, Director of the Center, and Associate Professor of Psychiatry, and Neuroscience, at the Icahn School of Medicine at Mount Sinai. Her team is developing paradigms and models that can capture real-life social behaviors among healthy individuals and those who have a psychiatric diagnosis. This enables better understanding of the neurocomputational mechanisms at play in those behaviors and how any alternation in those mechanisms can contribute to mental health symptoms. Findings from their efforts were published October 29, 2021 in *eLife*.

Dr. Gu is applying a combination of neuroscience, cognitive science, and behavioral economics expertise to explore how our beliefs, emotions, decision-making, and social interactions are affected by these mechanisms in states of mental health and illness. She is particularly interested in “social controllability”—the degree of control we have over our relationships—in the context of mental health. This research has become more vital given the impacts of COVID-19 and other issues such as global warming and geopolitical challenges on mental health.

“The social world we live in has become more chaotic,” Dr. Gu explains. “Many of the core symptoms or triggers of mental health issues stem from the sense that we have too little—or too much—control over our lives or relationships.”



Daniela Schiller, PhD, and Xiaosi Gu, PhD.

## The Illusion of Control

Using large-scale digital phenotyping, computational modeling, and neural recording, Dr. Gu and her research team have launched studies on how the human brain encodes social information and how that might affect mental health.

In one study, they explored whether people used forward thinking in situations to try to influence others or exert “social control.” Forty-eight participants played different versions of the “ultimatum game,” a well-known bargaining exercise in which the subjects are asked to split \$20 with an opposing team. In one “controllable” version of the game, participants could affect the amount of money they were offered in each round. In the “uncontrollable” version of the game, participants were offered a random amount each round.

Using functional magnetic resonance imaging, Dr. Gu observed that the choices made by the study’s participants were driven by neural activity in the ventromedial prefrontal cortex—a decision-



making center that is known to be involved in forward thinking. This, she says, suggests that the participants were able to think a few steps ahead in social interactions. Interestingly, participants reported a sense of control even during the “uncontrollable” version, beyond what they actually had. In a subset of participants who played games against a computer instead of teams, the reported sense of control was 60 percent regardless of the version or the fact they received higher offers in the “controllable” version.

The initial study involved healthy controls to establish social controllability as a paradigm and the neural mechanism involved. A subsequent study involving people with a high sense of delusion further explored the mental health relevance of social controllability.

In the latter study, Dr. Gu observed that people with a high degree of delusion were able to influence their partners in controllable interactions just as well as participants without delusion. But individuals with a high degree of delusion both attempted to exert control and reported a higher sense of control in situations that were uncontrollable, suggesting they had an illusion of control.

“We knew that illusory beliefs were central to delusion, but did not know how they came about,” Dr. Gu says. The study provided initial proof that there was a mismatch between the controllability of the environment and how people perceive such controllability in delusion. But the only way to truly understand the causal effect between delusion and those mental computations requires longitudinal studies, she says.

Dr. Gu is conducting similar studies among cohorts with drug addiction, eating disorders, personality disorders, and autism spectrum disorders. She is also interested in applying her social cognition paradigms to assess the efficacy of treatment through neuromodulation—an interest that has led to several collaborations with Helen Mayberg, MD, founding Director of the Nash Family Center for Advanced Circuit Therapeutics at Mount Sinai and Mount Sinai Professor in Neurotherapeutics.

“Although neuromodulation is currently limited to a small percentage of the patient population, given that it involves brain surgery, it offers a unique opportunity for us to understand the direct, causal relationship between neurobiology and behavior,” Dr. Gu says. “This will eventually help us design better evidence-based treatment for all patients based on their individual biology and needs.”



# Understanding the Molecular Mechanisms Involved in Psychosis and Schizophrenia

The Jeff and Lisa Blau Adolescent Consultation Center for Resilience and Treatment is studying 10 rare genetic mutations that are implicated in schizophrenia. The Center found 61 patients with these mutations in the Mount Sinai BioMe biobank, and has launched a study to engage these patients and their families for insights on those genetic changes and potential therapeutic approaches.

Looking through Mount Sinai’s BioMe biobank for patients with 10 rare genetic mutations implicated in psychosis and schizophrenia, Alexander Charney, MD, PhD, found 61 individuals. Intriguingly, he noted that approximately five of them had a defective variant of GRIA3, a glutamate receptor that, when coded improperly, has known links to schizophrenia.

“We were not expecting to find that,” says Dr. Charney, Associate Professor of Psychiatry, Genetics and Genomic Sciences, Neuroscience, and Neurosurgery at Icahn School of Medicine at Mount Sinai. The Schizophrenia Exome Sequencing Meta-Analysis (SCHEMA) consortium, in which Mount Sinai participated, had identified the 10 rare mutations through sequencing more than 24,000 and more than 97,000 controls worldwide. Of the variants, GRIA3 was assessed to hold among the highest odds ratio for schizophrenia risk (48), and among the lowest allele frequency in the general population (approximately 1x10<sup>-5</sup>).

It was a surprise that a single biobank had this many people with the GRIA3 variant, but even more so that they were all members of the same family. “This is a family that has some members who have both the variant and have psychosis or intellectual disabilities and other members who have the variant but have no signs of disease,” Dr. Charney says. “That creates an opportunity to ask powerful questions about the molecular mechanism of psychosis so we can gain insights on the risk factors for disease development and potential therapeutic interventions.”

Understanding those molecular mechanisms is a key focus of both the Jeff and Lisa Blau Adolescent Consultation Center for Resilience and Treatment and its executive director, Dr. Charney, who leads the Center in tandem with its founding director, Rene S. Kahn, MD, PhD, Esther and Joseph Klingenstein Professor and System Chair of Psychiatry.

## A ‘Population-Driven’ Study

The family-based genetic study Dr. Charney is conducting is also looking at these mutations from a population perspective based on shared characteristics. The 61 patients he identified with the mutations came from genome sequencing of 50,000 patients in the biobank. The initial plan was to study the patients to see how these mutations play a role in schizophrenia, says Dr. Charney. “Based on what we found, we developed a new protocol to study each patient and their extended families to gain insights as to why some people who have this mutation develop disease and others do not.”

The goal is to enroll as many family members of the 61 patients as possible. Each participant will undergo a standard psychiatric interview to assess whether there are conditions that might disqualify them from a schizophrenia diagnosis. Participants will also undergo a blood draw and skin biopsy, and the collected cells will be reprogrammed to create human pluripotent stem cells, which have the potential to grow into any cell or tissue in the body.

Using a process called directed differentiation — a bioengineering method in which specific growth factors or small molecules are administered to the pluripotent stem cells — Deepak Kaji, MD, PhD, a resident and instructor in the Department of Psychiatry, will grow the stem cells into brain organoids. These organoids recapitulate the brains of study participants and will enable him to look at how genetic mutations factor into the pathophysiology of psychosis and schizophrenia.

“Essentially, this technology enables us to subject a patient’s brain to a battery of electrophysiological tests without having to open the skull,” says Dr. Kaji. “Our hypothesis is that we will see differences in the synaptic connectivity of neurons in patients with rare variants. Deleterious changes in brain connectivity tend to play a significant role in psychiatric diseases such as schizophrenia. If we see that a certain mutation changes the way



Alexander Charney, MD, PhD, with lab technician Vibhuti Patel.

neurons conduct ion currents, we could consider therapeutic agents that force neurons to conduct currents as they would under normal physiological conditions.”

This undertaking has the potential to enable examination and characterization of the genes implicated in schizophrenia to an extent never before possible — and Mount Sinai is already developing a bigger database to advance that work. An effort is underway to enroll 1 million people to profile their genomes, vastly increasing the opportunities to study the molecular mechanisms associated with schizophrenia.

Given that Mount Sinai serves a racially and ethnically diverse population, this database will be broad enough to enable studies that address disparities in mental health research. That, Dr. Charney indicates, could have a significant translational impact.

“We have people who have made donations to Mount Sinai’s biobank to further our research, and we want to be able to offer them something in return for that, such as access to an experimental therapeutic that could result in positive outcomes for them,” Dr. Charney says. “We need to translate the knowledge we are gaining on molecular mechanics into new treatments.”



# Breaking Down Barriers in Access to Mental Health Treatment

The rate of mental health treatment remains low among Black and Latinx communities due to longstanding barriers and inequities. Mount Sinai’s Sidney Hankerson, MD, MBA, hopes to change that through a community engagement approach that is making support and services available where people live.



Sidney Hankerson, MD, MBA, (center) with pastor Michael Walrond Jr. (left) and Lena Green, DSW, LCSW (right) at First Corinthian Baptist Church in Harlem.

For years, the rate of mental illness treatment among Black and Latinx people has remained disconcertingly low. Many barriers have contributed this trend, including lack of access to culturally sensitive care, costs, and a legacy of poor outcomes that have led to distrust among these communities.

These are the barriers that Mount Sinai’s Sidney Hankerson, MD, MBA, is seeking to break down. Through Community Partnered Participatory Research, a documented model of community engagement developed by Kenneth Wells, MD, MPH, Professor of Psychiatry and Biobehavioral Sciences at the

David Geffen School of Medicine and Professor of Health Services at the UCLA School of Public Health; and Loretta Jones, MD, ThD, Assistant Professor at Charles R. Drew University of Medicine and Science, he is exploring opportunities to partner with community-based organizations to deliver mental wellness services and supports to Black and Latinx people in their neighborhoods.

The program involves a “community coalition,” an advisory board consisting of clinicians, researchers, policymakers, and people who have experience with mental health challenges. “They will serve as boots on the ground for access to a whole

host of psychiatric services,” says Dr. Hankerson, Associate Professor and Vice Chair for Community Engagement in the Department of Psychiatry at the Icahn School of Medicine at Mount Sinai, and Director of Mental Health Equity Research at Mount Sinai’s Institute for Health Equity Research.

One key stakeholder is the church, which has historically played a foundational role in Black communities. Dr. Hankerson has partnered with First Corinthian Baptist Church and its pastor, Michael Walrond Jr., on the Healing On Purpose and Evolving (HOPE) Center, a clinic that has been delivering therapeutic services to the community of Harlem since 2016. It offers 10 free evidence-based psychotherapy sessions to approximately 200 individuals each year, as well as affinity group therapy sessions, meeting the specific needs of diverse demographics such as LGBTQ+ community members and pregnant mothers. The HOPE Center also delivers a suicide-prevention intervention for Black and Latinx teenagers in Harlem and conducts a bi-annual Wellness Fair that gives access to a myriad of therapeutic resources such as yoga, arts, and mindfulness meditation. Last year, it reached more than 20,000 people worldwide through a virtual wellness initiative.

Dr. Hankerson is looking to integrate Mount Sinai psychiatry residents into the clinic to provide direct psychiatric services to low-income New York City residents free of charge. “In doing so, we can train the next generation of psychiatrists in a curriculum that talks about the impact of structural racism on psychiatric care delivery and show them how to engage different community-based entities, all of which we hope will contribute to improved clinical outcomes,” he says. He is working with the American Psychiatric Association Foundation to replicate this community-based engagement model for training and embedding psychiatry residents nationwide.

## Engaging Community Partners

However, Dr. Hankerson acknowledges that there are limits to what can be achieved through faith-based engagement. For example, houses of worship are not always welcoming of the LGBTQ+ community or individuals with mental illness, and there are individuals who are not religious. Thus, he is exploring opportunities to engage other entities and institutions such as barbershops, schools, and sports leagues.

“The first step is having informal and formal meetings with key stakeholders and leaders in these organizations,” Dr. Hankerson says. “These meetings create an opportunity to ask them to recommend other individuals whom we should engage.”



Sidney Hankerson, MD, MBA, at the HOPE Center.

The HOPE Center also delivers a suicide-prevention intervention for Black and Latinx teenagers in Harlem and conducts a bi-annual Wellness Fair that gives access to a myriad of therapeutic resources such as yoga, arts, and mindfulness meditation.

Through this outreach process, Dr. Hankerson hopes to make progress in addressing another pressing concern: mental health outcomes among young people. With funding from the American Foundation for Suicide Prevention (AFSP), he has launched a church-based youth suicide-prevention initiative. The AFSP grant extends Mount Sinai’s reach in New York State through a collaboration with the New York State Office of Mental Health; Sherry Molock, PhD, from George Washington University; and Peter Wyman, PhD, from the University of Rochester.

Dr. Hankerson is looking at sports leagues, specifically basketball and tennis, as a way to reach youth, and is cultivating partnerships with community colleges and universities to connect with college-age students. Additionally, he is serving as a consultant with the New York State Office of Mental Health to address stigma and deliver support through community engagement

“I believe the field of psychiatry can benefit from embracing the principles of community engagement, whether that is basic science, clinical services, or education and training,” Dr. Hankerson says. “My vision is to integrate those principles across the department and make Mount Sinai the preeminent location for community-informed psychiatric practice and research.”



# Addressing Knowledge Gaps About Mental Illness in Pregnancy and Postpartum

While people who are pregnant can easily learn how to safeguard their physical health and that of their babies, information about mental health concerns is scarcer. Researchers at Mount Sinai’s Women’s Mental Health Program are attempting to address that gap through studies that are providing new insights on how infection and medication may impact both mental health during pregnancy and postpartum, and long-term behavioral outcomes among children.

Although 10 percent to 16 percent of people who are pregnant are estimated to experience some form of mental illness, according to the World Health Organization, significant knowledge gaps remain about the impacts of these diseases and their treatments on the health and well-being of both the parent and child.

These are the gaps that Veerle Bergink, MD, PhD, and her colleagues are attempting to address. As Director of the Mount Sinai Women’s Mental Health Program, she is working with researchers in the Departments of Obstetrics, Gynecology and Reproductive Science, and Psychiatry, on studies focused on the role of medication in maintaining mood stability during pregnancy; the impact of parental mental illness on the brain and behavior of the child; and the etiology and treatment of severe mental illness immediately after delivery, such as postpartum psychosis.

“Individuals who are pregnant or postpartum have traditionally been excluded from most clinical studies to protect this population from any unforeseen risks,” says Dr. Bergink, Professor of Psychiatry, and Obstetrics, Gynecology, and Reproductive Science, at the Icahn School of Medicine at Mount Sinai.

“As a result, clinicians and pregnant individuals lack data to make informed health care decisions specifically related to mental health. Our diverse research program is intended to address that.”

## Generation C and Beyond

The program launched Generation C, a large-scale, prospective, multidisciplinary study, in April 2020 to examine the impact of SARS-CoV-2 infection, and the ensuing immune response, during pregnancy on gestational parent and child health outcomes. Collected samples and established collaborations have spawned recent follow-up efforts.

The first follow-up effort to receive National Institutes of Health funding is “Cerebrospinal fluid (CSF) and peripheral markers of the neuropsychiatric sequelae of COVID-19: The Generation C-SF pregnancy study.” This study is using cerebrospinal fluid samples collected during epidurals to investigate the long-term impact of the immune response to SARS-CoV-2 infection on neuropsychiatric outcomes among 600 patients recruited from the Generation C cohort.

Obtaining brain fluid during delivery is notable, as it has not been routinely done during other studies in pregnancy, says M. Mercedes Perez-Rodriguez, MD, PhD, Associate Professor of Psychiatry and Director of the Affective and Cognitive Therapeutics Lab at Icahn Mount Sinai.

“It creates a unique opportunity to investigate whether the immune response is related to behavioral changes in the pregnant and postpartum patient,” says Dr. Perez-Rodriguez.

The team is also exploring the impact of immune expression in the placenta and is following children who were exposed to SARS-CoV-2 in utero to see if there are any differences in behavioral outcomes or brain development versus children who were not prenatally exposed to the virus. Anna-Sophie Rommel, PhD, Assistant Professor of Psychiatry, is leading the effort to study behavioral outcomes of children born into the Generation C cohort. She is assessing behavior based on 900 responses to caregiver questionnaires; in a subset of 300 children, she will conduct a clinical assessment involving electroencephalogram.

Dr. Rommel’s work creates the first time point for possible ongoing follow-ups with these children over the long term, while exploring the merit of future follow-ups. “My goal is to investigate whether these children are impacted in a similar way to what we have observed when we look at other types of infection during pregnancy,” she says.



From left to right: Mercedes Perez-Rodriguez, MD, PhD, Thalia Robakis, MD, PhD, Veerle Bergink, MD, PhD, and Anna Rommel, PhD.

## Managing Medication During Pregnancy

The Women’s Mental Health Program also looked at the impacts of psychotropic medication on pregnancy and offspring. Dr. Bergink and her colleagues found that discontinuation of antidepressants before or during early pregnancy does not appear to be associated with an increased risk of adverse psychiatric outcomes and is beneficial for avoiding adverse outcomes such as postnatal adaptation syndrome and pulmonary hypertension among neonates — both of which are only associated with antidepressant use late in pregnancy. Findings were published in three journals in 2022.

Dr. Bergink characterized long-term child outcomes as reassuring, with any adverse mental health outcomes in the child likely attributable to the underlying parental psychopathology rather than antidepressant exposure.

“Given that the use of antidepressants has significantly increased in recent years, these insights are vital in addressing questions about the impacts of continuing medication during pregnancy,” Dr. Bergink says, adding that her team is planning additional clinical studies and data collection focused on antipsychotics and stimulant medication.

Dr. Rommel is also conducting a study to assess whether acetaminophen use during pregnancy has any long-term behavioral impacts on children.

“Although this is the one pain medication that is allowed during pregnancy because it is thought not to cause any birth defects, acetaminophen is very similar to endocrine-disrupting chemicals,” Dr. Rommel explains. The study will examine the relationship

of prenatal exposure to acetaminophen with inattention and social responsiveness among children ages three to four. The assessments will be based on caregiver reports and EEG data collection.

The program is generating vital guidance on best practices for mental health treatment during pregnancy, but the team hopes to make more headway, especially for individuals with severe mental illness, who have very high risk of relapse after delivery, or children at higher risk of developing illness.

“That is something that is really important to figure out in a targeted way,” says Thalia Robakis, MD, PhD, Associate Professor of Psychiatry at Icahn Mount Sinai. “The research on illness and therapeutic agents has largely been siloed. We are looking to secure funding so we can explore these things holistically and identify the relative risks versus benefits of medication among gestational parents and their children in a systematic and all-encompassing way.”



# Assessing a Novel Target for the Treatment of Major Depressive Disorder

An estimated one in three patients diagnosed with major depressive disorder does not respond to existing therapeutics. But James Murrough, MD, PhD, has identified a novel therapeutic target that, based on his studies, has the potential to change that paradigm and the lives of millions of patients worldwide.



When Mount Sinai researcher James Murrough, MD, PhD, heard that ezogabine—the first and only therapeutic agent that targets the KCNQ2/3 potassium channel in the brain for partial-onset seizures—was being withdrawn from the market for commercial reasons in July 2017, he knew he had to act fast.

At the time, Dr. Murrough was preparing to launch a National Institutes of Health (NIH) funded randomized clinical trial to assess ezogabine's impact on reward circuit activity and clinical symptoms in depression. Available preclinical and clinical data, which led to the NIH grant, suggested that the KCNQ channel could be a novel target for the treatment of depression, but in the absence of placebo-controlled human trial results, it was not

possible to predict whether this approach would be successful. The only way he could proceed with the study was to purchase all available supplies nationwide. Against the odds, he managed to secure enough ezogabine to administer 900 milligrams a day for five weeks to a cohort of 45 patients—an effort that yielded remarkable positive outcomes. Treated patients showed significantly larger improvements versus the placebo cohort in their symptom scores, such as the Montgomery-Åsberg Depression Rating Scale and Snaith-Hamilton Pleasure Scale.

Surprised to see such an impact on multiple clinical outcomes relevant to depression, Dr. Murrough considered the trial a success on a clinical level. Although the study's primary neuroimaging endpoint—the numerical increase in ventral striatum response to reward anticipation—

showed a trend towards separation between active and placebo, it did not reach statistical significance between the two cohorts.

“It would be ideal to demonstrate target engagement because that is important for the progress of science,” says Dr. Murrough, Professor of Psychiatry, and Neuroscience, and Director of the Depression and Anxiety Center for Discovery and Treatment at the Icahn School of Medicine at Mount Sinai. “But if you ask patients which is more important—that their brains demonstrated a specific signal or that they are experiencing relief from their symptoms of depression—they will say it is symptom relief.”

## An Accidental Clinical Outcome

Dr. Murrough had not intended to demonstrate clinically that ezogabine improves symptoms of depression; instead, he was testing a hypothesis that the KCNQ family of potassium channels offers a valid target for treating patients with major depressive disorder (MDD). It is estimated that one in three patients diagnosed with MDD—a leading cause of disability worldwide according to the World Health Organization—is not responsive to existing therapeutics. By exploring the molecular mechanisms involved in depression, Dr. Murrough hopes to identify therapeutic targets, such as KCNQ, that differ from existing treatments and have the potential to be game changers.

Dr. Murrough's interest in KCNQ builds upon previous research conducted by Mount Sinai researchers. It was Ming-Hu Han, PhD, Professor of Neuroscience, and Pharmacological Sciences, at Icahn Mount Sinai, who first identified the potential of these channels, based on research initiated by Eric J. Nestler, MD, PhD, the Nash Family Professor of Neuroscience, Director of The Friedman Brain Institute, and Dean for Academic and Scientific Affairs at Icahn Mount Sinai, and Chief Scientific Officer of the Mount Sinai Health System.

In a study involving a social defeat stress model, Dr. Han noted that mice that did not show depressive behavior naturally exhibited increased expression of KCNQ receptors in their brains. He subsequently showed that when these channels were blocked, the mice became depressed. Based on those findings, Dr. Han looked at the impact of activating these channels by injecting a class of compounds known as positive allosteric modulators (PAMs) directly into the reward circuits of mice that exhibited depressive behavior.

“PAMs are known to bind to KCNQ receptors and cause them to stay open, effectively functioning as if there are more of them,” Dr. Murrough explains. “Overall, these therapeutics are known to calm brain cells.” Dr. Han found that mice that exhibited signs of depression paradoxically had an overactive reward circuit wherein the dopamine cells were on overdrive. The hypothesis is that they are not responding to environmental cues and stimuli, which leads to behavioral depression. “Dr. Han showed that if you use PAMs to open the KCNQ channels in the reward circuit, it has an antidepressant effect,” Dr. Murrough says.

## Finding a Path Forward

What Dr. Murrough observed in his study, which was published in *The American Journal of Psychiatry* in March 2021, mirrored Dr. Han's findings. Although he concluded KCNQ warranted further research, the withdrawal of ezogabine made further work with the compound unviable. That changed in 2019 when Dr. Murrough discovered that a Vancouver-based company, Xenon Pharmaceuticals, had developed a more selective, better-tolerated KCNQ channel opener, XEN1101, which was undergoing human clinical trials for efficacy in treating seizure disorders, and had shown promising preclinical results in animal models of depression.

Dr. Murrough engaged the company and is now in year one of a three-year randomized control trial that will explore the impact of this pharmaceutical agent on adults with major depression. The study will enroll 60 patients, half of whom will be administered two 10-milligram capsules of XEN1101 each day for eight weeks. Neuroimaging and symptom effects from this cohort will be compared against those from the placebo cohort. In parallel, the company is conducting a proof-of-concept trial using clinical endpoints to measure an improvement of depressive symptoms in approximately 150 subjects.

Replicating the symptom improvements observed in the previous study or achieving statistical significance in neuroimaging findings in the ongoing trial would be exciting, Dr. Murrough says. Either outcome would provide compelling evidence that KCNQ is a worthwhile therapeutic target for pharmaceutical development. There is also the possibility that the study will provide insights for predicting which patients are more likely to respond to KCNQ channel openers.

“That is an important future direction for us—not just exploring the efficacy of these therapeutics but also the opportunity to examine why they perform better among certain patients,” he says. “That would open the door to more personalized medicine approaches. Regardless, the more we know about the brain, the more likely we are to move the needle in terms of identifying or developing effective treatments for patients who have this debilitating illness.”

**Note:** Neither Dr. Murrough nor Mount Sinai has any financial interests in Xenon Pharmaceuticals. However, Dr. Murrough is an inventor on a pending patent application filed by Mount Sinai for the use of KCNQ channel modulators for mood disorders and related conditions. If KCNQ channel activation is shown to be an effective treatment for depression, both Mount Sinai and Dr. Murrough (as a faculty inventor) could benefit financially.



# PTSD in Veterans: The Potential of Psychedelic-Assisted Psychotherapy

Rachel Yehuda, PhD, is exploring whether psychedelics can effectively treat PTSD. Her journey began with a study on MDMA in veterans and is expanding to psilocybin.



From left to right: Miryam Sperka, PhD; Heather Bader; Amy Lerner, PhD; Rachel Yehuda, PhD; and Tamar Glatman Zaretsky, PsyD.

Mount Sinai researcher Rachel Yehuda, PhD, knows that the concept of treating post-traumatic stress disorder (PTSD) with psychedelics has its share of skeptics. She used to be among them.

But Dr. Yehuda has seen the potential efficacy of this approach through her own training and research. She is conducting a groundbreaking study to assess the effects of administering 3,4-methylenedioxy-methamphetamine (MDMA) to 60 veterans as part of psychotherapy at the Mount Sinai-affiliated James J. Peters VA Medical Center. This treatment modality consists of three eight-hour guided therapy sessions, pre-administration consultations, and post-administration integration.

In prior studies, two-thirds of participants who received MDMA-assisted psychotherapy no longer had PTSD. But veterans often respond differently to conventional treatments because of the sheer complexity and nature of the trauma they have experienced, as well as its aftermath.

The clinical trial at the VA is an exciting development, but Dr. Yehuda's study has an additional component that could be a real game changer in this relatively nascent field of research. Using

functional magnetic resonance imaging and blood samples collected from participants, Dr. Yehuda and her team are looking for prognostic biomarkers and brain signals that demonstrate recovery — enabling the identification of patients who are more likely to respond to this treatment modality.

“It is still very early to talk about our observations in combat veterans, but we have not seen anything so far that suggests we should not continue,” says Dr. Yehuda, Director of Mount Sinai’s Center for Psychedelic Psychotherapy and Trauma, Mount Sinai Professor in Psychiatry and Neuroscience of Trauma at the Icahn School of Medicine at Mount Sinai, and Director of Mental Health at the James J. Peters Veterans Affairs Medical Center.

## Skepticism and Resistance

Although Dr. Yehuda has been leading trauma research at the VA for 30 years, her entry into studying psychedelics was gradual. It began with a friend who had been asked to donate to the Multidisciplinary Association for Psychedelic Studies (MAPS), a nonprofit that has been exploring the mental wellness benefits of psychedelics since 1986. Although the concept struck Dr. Yehuda as strange, a literature

review revealed a small clinical study that did suggest there was therapeutic potential for administering psychedelics among patients with PTSD. But it took an invitation to participate in an MDMA therapy-training program in Israel from Rick Doblin, the executive director of MAPS, to transform Dr. Yehuda’s interest into action.

“It was around the time that the FDA declared breakthrough status for MDMA,” she recalls. “Being a neuroscientist with a focus on PTSD, I was open to learning more, but I did not know how it would work and was concerned about potential adverse effects of putting someone in an altered state.”

Dr. Yehuda attended the training session and was reassured to find the therapy had been developed by people who were very knowledgeable about PTSD and how to treat it. “I asked Rick Doblin why we were not studying its potential at the VA, and he said he had not been able to have a protocol approved there. I took that as a personal challenge,” she says.

Dr. Yehuda overcame the VA’s disinclination to administer a compound that has received the Drug Enforcement Administration designation of “potentially harmful and without therapeutic benefits” by establishing an FDA-approved protocol that provides the utmost protection for veterans with PTSD and providing education about how, when used in the context of psychotherapy, MDMA can have promising results. Now, Dr. Yehuda is working to achieve the same goal among her peers.

## Leading in Clinician Training

To date, Mount Sinai’s center has trained approximately 100 therapists. The goal of the training, Dr. Yehuda stresses, is not just to engage physicians who want to develop psychedelic therapy protocols but also those who want to work with patients attempting psychedelic-related therapy on their own.

“Most physicians might not know what to say or do to help a patient who had an intense experience with a psychedelic and now wants to talk more about that. The clinician might refer that individual to a substance abuse program,” she says. “Clinicians also need to know the principles of harm reduction and to understand the kind of changes that can occur in someone who has taken psychedelics, whether in a safe and legal way or underground. The more physicians who are trained in that ability, the less mysterious or scary this therapeutic modality is.”

Dr. Yehuda is also ensuring that a new generation receives training in, and performs the needed scientific research on, psychedelic-assisted psychotherapy through the introduction of two two-year research fellowship programs — an MD and a PhD. This program



Rachel Yehuda, PhD, and Iouri Makotkine, MD, PhD.

has been made possible through a grant from the Bob & Renee Parsons Foundation.

The first two fellows have been selected and will participate in a first-ever phase II clinical trial to assess the therapeutic efficacy of administering psilocybin to patients with PTSD. Twenty participants will be recruited for this open-label trial, which is being conducted in partnership with Kings College in London. “Although people have indicated that psilocybin is effective for addressing trauma, there has been no clinical trial of it for PTSD,” Dr. Yehuda says. “Because psilocybin is a more classical psychedelic, patients may be less likely to talk about the experience during the session, but may need to talk more during integration. Based on the initial findings, we hope to proceed to a larger placebo-controlled trial.” The fellows will also participate in research to determine the mechanism of action of both psilocybin and MDMA-assisted psychotherapy.

## Looking Ahead

There are additional studies that Dr. Yehuda is interested in conducting, such as assessing symptom reduction and life changes at 6 and 12 months post-therapy among participants in the MDMA study, examining the efficacy of MDMA-assisted psychotherapy in the context of a group, and the efficacy of MDMA-associated therapy among patients with intergenerational trauma. These hinge to some extent on whether the FDA approves MDMA for trauma. For now, Dr. Yehuda continues to collect data, develop manuscripts, and encourage and equip other academics to conduct their own research.

“There are many developments that could hinder or accelerate this work. However, we are fortunate to have the funding in place to begin to investigate some of the important questions,” she says. “The question is whether our efforts will become a brief chapter in the history of psychiatry or will continue to fuel more investigation. We hope it will be the latter.”