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Frontiers of Medical Research: Brain Science

Icahn School of Medicine at Mount Sinai

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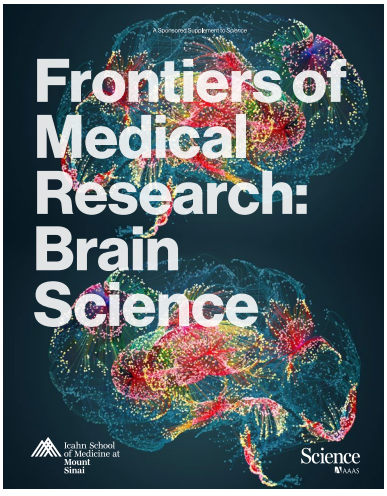

About the Cover:
A graphical rendering of neural networks in human brain activity. Courtesy of Icahn School of Medicine at Mount Sinai

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Odyssey of the mind: Delving deeper into the brain

We have explored the outer limits of our solar system and the depths of our oceans, yet there continues to be much we can learn about our own brains. The human brain consists of approximately 100 billion neurons—about the same as the number of stars in the Milky Way Galaxy. Brain tissue the size of a grain of sand contains 100,000 neurons and over 1 billion synapses.

So, where do we begin? A key goal is identifying brain cells and circuits that might underlie neurological and psychiatric disease. With that information, researchers and clinicians could design better tools to study these disease-triggering cells, as well as develop new treatments. Brain diseases are hard to understand and treat; that is why we need talent from multiple disciplines, each with its own valuable perspective. Through collaborations between neurologists, neurosurgeons, psychiatrists, psychologists, neuroscientists, engineers, and data scientists, the Friedman Brain Institute at the Icahn School of Medicine at Mount Sinai is addressing unmet clinical needs.

This supplement is the third in a series being published in partnership with the Icahn School of Medicine at Mount Sinai. In the first, "The Frontiers of Medical Research," physicians and scientists summarize new developments across 16 fields of medicine. The second supplement, "Frontiers of Medical Research: Cancer," focuses on breakthroughs in cancer research and care, as explained by researchers and clinicians. This latest supplement, "Frontiers of Medical Research: Brain Science," brings together neuroscientists, psychiatrists, and geneticists, among others, to unravel the pathophysiology of brain dysfunction.

The eight articles in this supplement cover cutting-edge research into the causes and treatment of psychosis, depression, drug addiction, autism spectrum disorder, and Alzheimer's disease. Genetics and behavioral phenotyping have led to the discovery of various biomarkers for these brain disorders. The biomarkers allow techniques such as computational modeling, artificial intelligence, and multiomics (genomics, transcriptomics, proteomics) to help create rationally designed drugs. These approaches are revolutionizing brain research and promising much-needed relief for patients.

Whether you are a researcher, clinician, patient, or loved one of a patient, we invite you to launch into these articles. No doubt you will be amazed at all that has been discovered about the brain—as well as all that remains to be.

Jackie Oberst, Ph.D.
Science/AAAS

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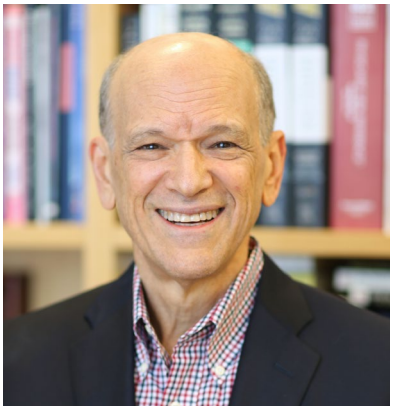

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On the frontiers of brain science

By Dennis S. Charney, Eric J. Nestler, and Paul J. Kenny

Beneath the cerebral cortex's wrinkled landscape of gyri and sulci—its ridges and crevices—is the greatest challenge confronting modern biomedicine. Vastly more complex than any other organ, the brain holds biological secrets within its countless neural pathways—secrets that have been locked since the ancient Greek scientist-philosopher Alcmaeon first postulated that the brain, not the heart, is the seat of intelligence.

This special supplement—the third in a series on "Frontiers of Medical Research" that the Icahn School of Medicine at Mount Sinai has developed in partnership with *Science*—reports on major advances in solving the mysteries of the brain. These advances are urgently needed: Five of the leading causes of disability worldwide are brain disorders, including depression, stroke, dementia, psychosis, and drug addiction.

The speed and accuracy of computer processing has made it possible for us to dramatically improve our understanding of the brain. Thanks to the marriage of artificial intelligence and advances in capturing molecular, cellular, and circuit features of the brain and its behavioral output, neuroscience has arrived at an inflection point. We can now identify vast molecular constituents of individual cells and understand how those constituents determine cell function, as well as how cells work together in a single circuit and more complex composite circuits to generate a specific behavior. We can also establish bidirectional causal connections across cells, synapses, circuits, and behavioral responses. Now we are applying these insights to normal brain function to better understand brain disorders and address associated illnesses.

On the front lines of brain science research, there is new promise of translating our growing knowledge into therapies that will help patients suffering from brain disorders. In this collection of essays, you will read about research progress that provides the foundation for game-changing therapies. These articles explore:

- The genomic revolution that has identified hundreds of genome sequence variations associated with autism spectrum disorder (ASD) and related neurodevelopmental disorders, and that is now paving the way for precision psychiatry, including the development of gene-based therapies for ASD;
- Breakthroughs in the treatment of major depressive disorder resulting from research that has identified changes to the brain's reward pathway and stress-induced epigenetic mechanisms that mediate changes in gene expression;
- The development of brain circuit neuromodulation to deliver low doses of stimulation that can treat not only Parkinson's disease and tremor but also depression, obsessive-compulsive disorder, and other psychiatric conditions;
- Research programs that are mapping the genetic architecture of schizophrenia and bipolar disorder to find more effective treatments for psychoses.

Among the greatest challenges in biomedicine is the effort to find effective treatments for Alzheimer's disease and other neurodegenerative disorders. Many billions of U.S. dollars have been invested into research without yet yielding definitive treatments for these devastating illnesses. We explain why, as brain science continues to gain momentum, this decade will deliver unprecedented progress in translational research and drug discovery for Alzheimer's disease and other dementias.

This *Science* supplement also reports on our growing understanding of brain function, with articles that discuss:

- How computational neuroscience is generating detailed analyses of the brain's circuitry and its ability to store and recall memories;
- Progress in understanding how drugs of abuse impact brain cells and circuits, and in the identification of genetic variations that increase susceptibility to drug and alcohol addiction—essential knowledge for development of new medications to treat substance use disorders;
- New insights into the dynamic and bidirectional dialogue between the brain and the rest of the body.

After reading about the research advances described in these essays, we hope you will share our optimistic view about the future of neuroscience. We firmly believe we are on the path to discovering improved diagnostic tests and new therapies that can effectively treat the most complex brain disorders—perhaps the most ambitious goal of modern medicine.

The science of addiction

Paul J. Kenny[1]*, Rita Z. Goldstein[2], Yasmin Hurd[1,2], Nelly Alia-Klein[2], Ian Maze[1], Paul Slesinger[1], Eric J. Nestler[1,2]

Life expectancy in the United States has fallen for the first time in decades, a shocking trend driven by so-called "deaths of despair" involving drug overdoses, suicides, and diseases attributable to substance abuse and stress. The country is in the midst of a veritable epidemic of opioid use. Over 99% of the world's supply of the powerful opioid drug hydrocodone, the active ingredient in Vicodin, is consumed by the United States. Illicit synthetic opioids such as fentanyl are also flooding across the border. Alcohol sales have increased in recent years, while numbers of individuals testing positive for cannabis, cocaine, and methamphetamine in the workplace are at an all-time high. The U.S. Food and Drug Administration (FDA) has approved several treatments for opioid use disorder (OUD). These include the slow-acting opioid receptor agonists (or partial agonists) buprenorphine and methadone that attenuate the intense cravings for opioid drugs during abstinence, and the fast-acting opioid receptor antagonist naloxone that quickly reverses opioid overdose if used in time. The available medications all share one feature in common—they have limited clinical efficacy for the treatment of OUD. As a consequence, treatment-seeking individuals have considerable risk of relapse to opioid use even when treated with the most effective medications and behavioral approaches available. Individuals attempting to quit cannabis, cocaine, or amphetamines face an equally daunting challenge, as they remain vulnerable to relapse for months or even years, yet there are no FDA-approved medications to help maintain abstinence. Thus, there is a pressing need to better understand the pathophysiology of substance use disorders (SUDs) so that more effective treatments can be developed.

Genetic contributions to addiction

Large-scale human genetic association studies have identified gene variants that influence the risk of SUDs. Many of these variants reside within genes that code for potentially "druggable" proteins, which may represent novel targets for medication development. Allelic variation in the *OPRM1* gene, which encodes the μ opioid receptor (MOR), increases OUD risk (*1*). MORs are the principal receptors through which opioid drugs exert their euphorigenic and analgesic properties and are the major targets for the therapeutic actions of methadone, buprenorphine, and naloxone. Other potentially druggable gene variants that influence risk of OUD include *KCNN1* and *FURIN* (*1*). Allelic variation in the *CHRNA2* gene, which encodes the α2 nicotinic acetylcholine receptor (nAChR) subunit, increases risk of cannabis use disorder (*2*). Other nAChR genes, particularly *CHRNA5* encoding the α5 subunit, regulate vulnerability to alcohol, cocaine, and tobacco use disorders (*3*). Studies using cultured human neurons are identifying functional consequences of these risk-associated gene variants, consistent with their involvement in addiction (Fig. *1*). The adoption of electronic health records (EHRs) by many healthcare systems in the United States promises to revolutionize our understanding of the genetics of SUDs. Linking genetic information to the wealth of data contained in EHRs will help identify genes that influence vulnerability to addiction. Such information may also predict the course of the disorder in individual patients and identify those most likely to benefit from specific therapeutic interventions.

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Neural circuitry underlying addiction

Mesocorticolimbic circuits in the brain have been the major focus of addiction research over the past 30 years (Fig. *1*). However, many addiction-associated genes are expressed preferentially or exclusively in brain regions that have received relatively scant attention in the context of SUDs. For example, the highest concentrations of MORs in the brain are found in neurons of the medial habenula that project to the interpeduncular nucleus (IPN). Similarly, the *CHRNA2* and *CHRNA5* genes that influence vulnerability to SUDs are expressed almost exclusively in the habenula–IPN circuit. Little is known about the function of the habenula–IPN circuit, but emerging evidence suggests that it regulates aversive responses to drugs of abuse that reduce the risk of addiction (*4*), and undergoes striking structural and functional adaptations in response to drug use (*5*). MORs are also densely expressed in other aversion-related brain regions, such as the parabrachial nucleus. Notably, the parabrachial nucleus has been implicated in the respiratory depression that contributes to opioid overdose-related deaths (*6*), but its involvement in the motivational properties of opioid drugs is unclear. Hence, human genetics studies are revealing not just gene variants that influence addiction vulnerability, but pointing as well to novel brain circuits that are likely involved. The emergence of new spatial transcriptomics and barcoding technologies, in vivo brain imaging approaches with single-cell resolution, and sensors that can track neurotransmission with unprecedented spatiotemporal precision will facilitate better understanding of the actions of drugs of abuse on brain circuits. Advances in optogenetics, chemogenetics, and other methods of brain modulation, particularly those that are non-invasive, may enable circuit-based approaches for the treatment of SUDs (*7*). Unique small-molecule drugs that modulate neuronal circuits involved in addiction may provide additional treatment options (*8*).

Molecular and cellular basis of addiction

Drugs of abuse induce striking structural and functional remodeling of neurons throughout the brain, and addiction is largely considered a disorder of neuroplasticity (*9*). The long-lasting alterations in brain function that drive addiction reflect the ability of drugs of abuse to engage complex programs of gene expression that control such maladaptive plastic changes (Fig. *1*). Groundbreaking studies over the past 15 years have revealed crucial roles for epigenetic and noncoding RNA mechanisms in drug-induced neuroplasticity (*9-12*). Remarkably, recent findings suggest that classical neurotransmitters such as dopamine can be covalently appended to histone proteins to influence gene expression in the brains of animals exposed to drugs of abuse (*13*). These findings suggest that molecular machineries that regulate chromatin function may be novel targets for medication development to treat SUDs. Studies exploring drug-induced changes in gene expression have focused almost exclusively on neurons. Over the past 2 to 3 years, single-cell RNA sequencing (scRNA-seq) technologies have shown that non-neuronal cells are of-

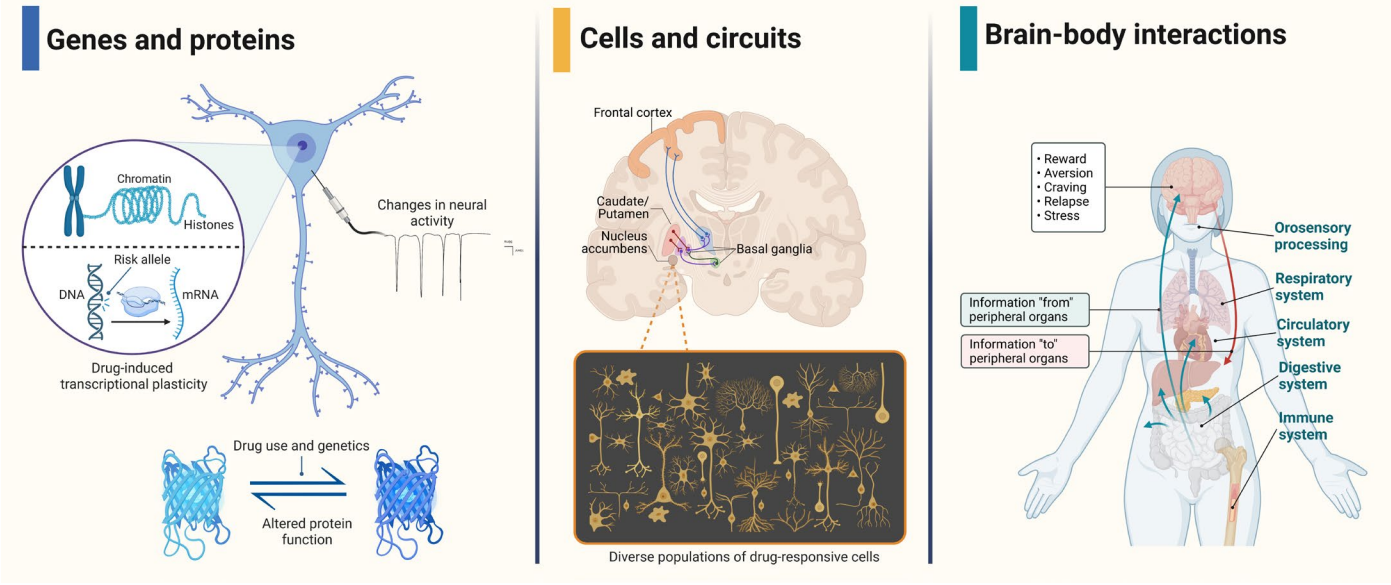

Figure 1. Multiscale actions of addictive drugs drive substance use disorders. Genetic risk factors influence drug-induced changes in gene expression and protein function that precipitate long-lasting alterations in cellular function in the brain (left panel). Drug-induced modifications in the function of neurons and non-neuronal cells alter the activity of brain circuits that influence reward, aversion, and other addiction-related behavioral processes (middle panel). Drugs of abuse remodel addiction-related brain circuits by direct actions in the brain and indirect actions in the periphery (right panel).

ten more transcriptionally responsive to drugs of abuse than neurons, particularly astrocytes and microglia (*14*). Astrocytes maintain glutamate homeostasis in the brain while microglia prune synaptic contacts between neurons and secrete neuroregulatory factors to influence synaptic transmission. Drug-induced perturbations in the function of these glial cells may contribute to the abnormalities in neurotransmission that underlie relapse vulnerability. Intriguingly, scRNA-seq has shown that lesser-studied non-neuronal cells in the brain also demonstrate striking transcriptional responses to drugs of abuse, including periventricular ependymal cells, vascular epithelia, and oligodendrocytes (*14*). Remodeling of these non-neuronal cells may contribute to SUDs through as-yet unknown mechanisms.

Brain–body interactions in addiction

Finally, drugs of abuse can modulate brain function through indirect actions in the periphery (Fig. *1*). MORs, nAChRs, and other addiction-relevant receptors are expressed in peripheral tissues such as the mouth, lungs, and heart that come into direct contact with drugs of abuse before they enter the brain (*15*). Peripheral actions of addictive drugs contribute to their interoceptive properties that influence drug-taking behavior. Nevertheless, remarkably little is known about how drug-related sensory information is routed to the brain and processed by circuits that control drug-seeking (see article in this booklet by Swirski). The emergence of whole-body activity mapping procedures, such as vDISCO, will facilitate better understanding of the peripheral actions of addictive drugs. This may reveal peripherally located targets for medication development, thereby avoiding difficulties associated with getting medications across the blood–brain barrier.

In summary, SUDs and other neuropsychiatric abnormalities are perhaps the least well understood and most difficult to treat of any health affliction. Progress in the development of new treatments depends on the continued incorporation of cutting-edge technologies to better understand the long-lasting molecular, cellular, circuit, behavioral, and whole-body actions of drugs of abuse that cause addiction.

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The origins of psychosis

Panos Roussos[1-4,*], Alexander W. Charney[1,3,4], Hirofumi Morishita[1,3,5], Schahram Akbarian[1,3,4,5], Rene S. Kahn[1,3]

Introduction

Despite its prevalence of 1-3% in the population, schizophrenia and related psychotic disorders are associated with significant health, social, and economic concerns, and schizophrenia is one of the top 15 leading causes of disability worldwide (*1*). While significant advances in precision medicine applications have been made in other fields to improve risk stratification and develop novel drugs based on genetic findings, in schizophrenia no such progress has been made. New clinical insights combined with evolving genetic and neurobiological knowledge as well as advances in artificial intelligence and machine learning offer optimism in translating genetic findings to improved diagnostic tests, more effective treatments, and specific preventive measures for schizophrenia and related psychotic disorders, including bipolar I disorder with psychotic features and schizoaffective disorder.

Uncovering the genetic basis of schizophrenia and related psychotic disorders

A person's genome can increase their risk for schizophrenia and related conditions through both common and rare variations in DNA sequences. To date, over 300 common genetic variants have been implicated in schizophrenia (*2*), and many ongoing studies aim to characterize the mechanisms by which these variants—none of which, on their own, are sufficient to cause disease—exert their effects. In contrast, rare variants can, for a given patient, be causal. To date, 12 genes have been identified that harbor excess rare loss-of-function variants in schizophrenia cases relative to controls (*3*, *4*). Mount Sinai researchers, working as part of the Psychiatric Genomics Consortium (PGC), are now partnering with the University of North Carolina, Cardiff University, the National Institutes of Mental Health, and Regeneron Genetics Center to sequence—as part of the PGC WeSeq Study—the genomes of approximately 150,000 diverse individuals with schizophrenia or related conditions. In addition, Mount Sinai researchers, working as part of the Million Veteran Program (MVP), are collaborating with investigators at the State University of New York and University of Miami to analyze common and rare variants in a cohort of U.S. Veterans that include more than 300,000 diverse individuals with serious mental illness, including schizophrenia (*5*). Collectively, these efforts carry the promise to further elucidate the genetic architecture of psychosis and reshape our thinking about its etiology.

Linking genetic discovery to disease mechanisms

Larger and more powerful genetic studies continue to expand our understanding of the polygenic risk architecture of schizophrenia (*2*, *3*). One of the main challenges is how we map genomic risk loci to disease causal mechanisms. Mount Sinai has long been at the forefront of efforts to elucidate the functional genomic and cellular architecture of schizophrenia and related psychotic disorders, playing a leading role in large national and international consortia, including the CommonMind Consortium (*6*) and psychENCODE Consortium (*7*). The primary focus of these consortia is the orchestrated study of postmortem brain tissue from thousands of subjects diagnosed with serious mental illness, including schizophrenia. These tissue specimens have been extensively profiled for a range of molecular markers, capturing gene expression and epigenetic regulation using high-throughput sequencing technologies. In addition, by applying state-of-the-art single-cell approaches to such large sample cohorts, we are able to better understand the contribution of specific cell types to a range of neuropsychiatric conditions. Through these efforts, molecular changes influencing chromosomal organization (*8*) and the regulatory mechanisms of gene expression (*6*, *9*) have been identified as being altered in schizophrenia. These changes primarily affect neurons, an observation that is concordant with the mapping of schizophrenia risk loci to neuronal regulatory elements. Recent advances in spatial approaches further enhance our ability to examine the impact of these alterations across a range of developmental time points and disease contexts, allowing us to gain a more thorough understanding of the biology underlying these highly complex processes.

Target validation and mechanistic interrogation

Building on the discovery of genetic risks and vulnerable cell types for schizophrenia, it is now essential to uncover the neurobiological function of these genes and circuits to identify functional biomarkers and therapeutic targets. Schizophrenia characteristically begins during adolescence, starting with cognitive impairments followed by psychosis (*10*), and human cellular and organoid models are not technically feasible to study late developmental processes. Rodent animal models are useful experimental systems that enable much-needed investigation of neurobiological mechanisms associated with late developmental trajectory in a living brain. Over the past decade, technical breakthroughs in neuroscience made it possible, for the first time, to establish causal connections across genes, cells, synapses, circuits, and behavioral responses. For example, manipulation and monitoring of specific gene expression or neural circuit activity in behaving animals at specific developmental windows is now possible by applying cutting-edge techniques such as CRISPR-based genome editing (*11*), optogenetics, and chemogenetics. Such approaches revealed key chromatin modulators (*12*), vulnerable developmental windows, and circuits essential for social and cognitive behavior relevant to schizophrenia (*13*, *14*). In coming years, animal studies will continue to shed light on how genetic and environmental risk factors interact with adolescent developmental processes to result in schizophrenia. In parallel, an integration of information from animal models along with analysis of human samples, large human datasets, and human experimental biology will be essential to improve diagnosis, prevention, and treatment of schizophrenia.

Increasing opportunities for translational medicine

Despite the availability of effective pharmacotherapy for the treatment of psychosis for over 70 years, the overall prognosis for schizophrenia has not materially improved. One of the reasons is that some of the core symptoms

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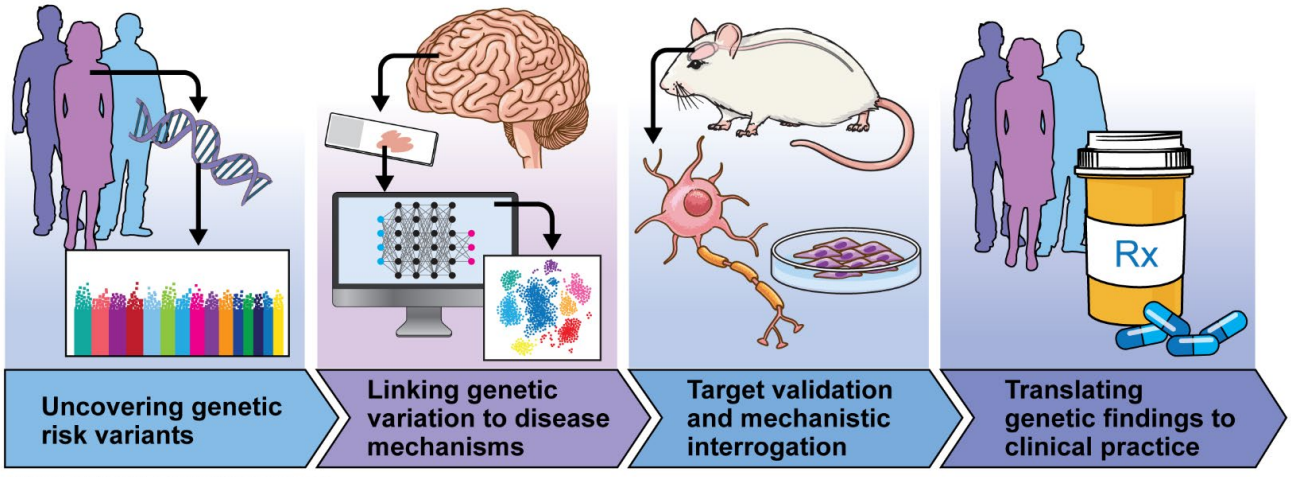

Figure 1. Pipeline for the analysis of variation in individuals' genome to develop clinical applications for patients with schizophrenia and related psychotic disorders.

of this illness, particularly its cognitive deficits, are not ameliorated by currently available antipsychotic medications (*10*). The Blau Center of Mount Sinai has set out to improve this situation and work to develop more effective treatments for schizophrenia. The first step is to better define the phenotypes of this illness, focusing on the heterogeneity of the disorder and on its more refractory symptoms, such as cognitive dysfunction and social withdrawal. One of the major problems in psychiatry, impeding the development of more effective treatments, is the fact that almost all phenotypes are based on subjective assessments with limited reproducibility. At the Blau Center we will harness artificial intelligence (AI) to quantify phenotypes, beginning with verbal and facial expression (*15*), in order to develop objective and reproducible phenotypes that can then be linked to biological markers. In combination with the Mount Sinai Million Health Discoveries Program—through which 1 million consenting patients within the Mount Sinai Health System will be enrolled to study how genetics and environment impact risk for human disease across all organ systems and medical specialties—the program will endeavor to establish a direct link between genes and behavior in schizophrenia. The focus is to discover the genes responsible for increasing risk for schizophrenia and related disorders, or conferring resistance to the illnesses in other individuals. Its findings will be utilized to understand how these genes, acting in conjunction with other factors such as environmental exposures, are responsible for schizophrenia and will form the basis for the development of new medicines to treat this still-intractable illness.

Conclusions

Here we discuss the achievements to date, challenges ahead, and a roadmap for making precision medicine a reality for schizophrenia and related psychotic disorders. These steps are presented in Figure 1. Through continued investment in genetics, neuroscience, AI, phenotyping, and therapeutics, genomic knowledge from each patient will translate to customized therapeutics that will revolutionize the way that we currently diagnose and treat patients, which will dramatically benefit their lives.

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Stress, trauma, and the depressed brain

Scott J. Russo[1,2]*, Ian Maze[1,2], Eric J. Nestler[1,2], Dennis Charney[2,3], James W. Murrough[2,3]

Stress-related disorders, such as major depressive disorder (MDD), are among the world's greatest public health problems. Yet, their etiology and pathophysiology remain incompletely understood, and more than half of affected individuals are not fully treated by available antidepressant medications or psychotherapies. Almost all U.S. Food and Drug Administration (FDA)-approved antidepressants act initially on the brain's monoamine systems, but the mechanisms underlying their delayed therapeutic action remain unknown. Moreover, depression is diagnosed today solely on the basis of behavioral abnormalities, with no biological endpoints yet validated. Considerable evidence supports the view that highly interconnected mesocorticolimbic brain structures are important in regulating cognition, mood, motivation, and related emotional states under normal conditions, as well as the abnormalities in these behavioral domains that characterize depression and other stress disorders such as post-traumatic stress and anxiety disorders. These structures include the nucleus accumbens (NAc), prefrontal cortex (PFC), hippocampus, amygdala, and ventral tegmental area (VTA), among other regions (*1*). Large-scale analysis of neuroimaging datasets combined with blood-based biomarker studies show that depression is a heterogeneous collection of "biotypes" rather than a singular disease. The expectation is that, by defining the underlying biology of these biotypes and by developing diagnostic tests to recognize them, we will develop novel therapeutics tailored to the needs of each patient. From this perspective, we discuss work from animal models and humans that is enabling effective translation to identify these biotypes and generate mechanistically distinct therapeutics (Fig. *1*).

Circuit mechanisms of depression

Alterations within mesocorticolimbic brain structures are observed in a subset of depressed patients. Preclinical stress models have shown that exposure to chronic stress perturbs communication across several regions of this system. As just one example, in a subset of mice that are susceptible to social stress, there is increased activity of dopamine neurons projecting from the VTA to the NAc (*2*) that, by use of optogenetics, we know cause depression-related behavioral symptoms. By contrast, mice that are stress-resilient exhibit active behavioral coping strategies in which they avoid highly stressful situations or engage in behaviors that limit the negative impacts of stress, such as exercise. By doing so, they can avoid depression-related behavioral abnormalities such as social withdrawal, anhedonia, and weight gain. Resilient mice also display normal levels of DA activity, which is due to increased expression of a class of potassium (K^+) channels—KCNQ2/3 (Kv7) channels—that prevent stress-induced increases in VTA activity (*3*). Informed by these preclinical results, clinical trials have demonstrated that an opener of this type of channel, ezogabine, is highly effective in restoring normal activity of the brain's reward circuitry and in decreasing depressive symptoms in MDD patients (*4*).

Chronic stress in mice has also been shown to reduce glutamate signaling between PFC and other mesocorticolimbic regions, such as NAc, leading to the view that disturbances in glutamatergic signaling in specific circuits might define subsets of MDD patients, particularly those that are treatment resistant (*5*). The S-enantiomer of ketamine—"esketamine"—gained FDA approval for treatment-resistant depression in 2019, becoming the first mechanistically novel, non-monoaminergic antidepressant available in the United States. Esketamine is thought to act in part by restoring functional glutamatergic signaling in PFC (*6, 7*). Early work suggests that psychedelic interventions, such as psilocybin, may also act by altering neural activity within the PFC by targeting serotonin signaling. Lastly, novel non-pharmacological digital health interventions for stress disorders (e.g., the Emotional Faces Memory Task) may act by optimizing functional connections between the PFC and other mesocorticolimbic structures, such as the amygdala.

These translational studies, which highlight the importance of animal models to inform human trials, remain our most effective tool in developing new therapeutics for depression and related stress disorders.

Epigenetic and transcriptional mechanisms of depression

Genetic variation contributes only ~35% to MDD susceptibility. As such, it has been posited that genetic predispositions, in concert with exposures to stressful life events, precipitate MDD through "epigenetic" mechanisms, which mediate changes in gene expression that are not based in DNA sequence variation (*8, 9*). These mechanisms include chemical modifications to histone proteins or DNA, perturbed transcription factor activity, regulation of noncoding RNAs, and even changes in the 3D structure of chromatin. Some of these stress-induced epigenetic mechanisms within the mesocorticolimbic system are thought to result in "chromatin scars," which contribute to the protracted nature of MDD susceptibility (*8*). Medications targeting these epigenetic mechanisms are now being explored for a broad range of mood-related disorders, including MDD. Also, this work is defining the biochemical pathways in the mesocorticolimbic cells most important in driving depression, which will further guide novel therapeutics. These studies have yielded surprising findings, including the observation that males and females exhibit mostly different molecular aberrations in these brain regions, which argues for sex-specific treatment discovery programs (*8*). Finally, the field of neuroepigenetics remains in its infancy with respect to novel mechanisms of chromatin regulation that contribute to MDD pathophysiology (*9*). For example, certain monoamine neurotransmitters (e.g., serotonin or dopamine) serve as donors for post-translational histone modifications termed monoaminylation. Given the involvement of monoamines in MDD treatment, it is possible that such modifications may contribute to MDD pathophysiology independent of monoaminergic neurotransmission per se.

In sum, our growing appreciation of the roles for brain epigenetic mechanisms contributing to MDD has been evolving at an exponential pace over the past two decades, and the neuroepigenetics field's embrace of multidisciplinary approaches holds great promise for the future of epigenome-centric pharmacotherapeutic drug development and perhaps even epigenome-targeting approaches for treatment of this pervasive syndrome.

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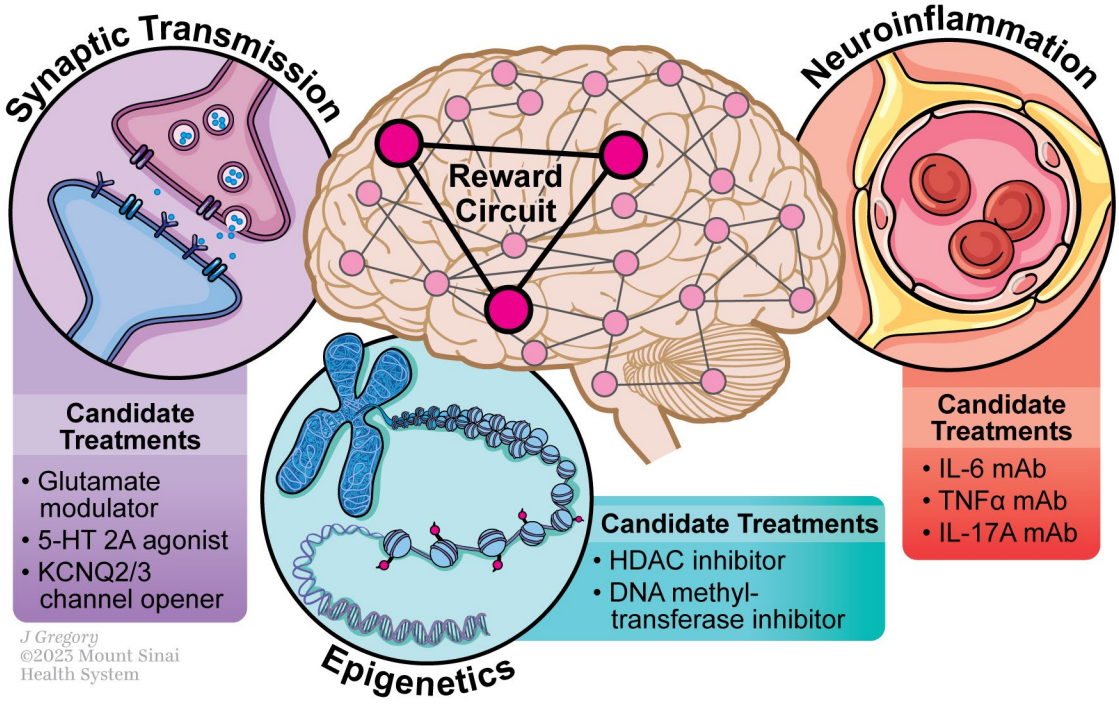

Figure 1. Schematic describing the primary mechanisms thought to underlie major depressive disorder (MDD) along with several promising pharmacological targets being pursued for new MDD treatments

Neuroimmune mechanisms of depression

While much of the focus on MDD pathophysiology revolves around understanding molecular and neural circuit mechanisms, it is becoming increasingly clear that interactions between the periphery and brain play important roles in disease severity and progression (see article in this booklet by Swirski). Interactions between the brain and other organ systems, including the immune system, are tightly regulated. Psychosocial stress profoundly impacts this bidirectional communication, with disruptions in the neuroimmune axis now recognized as a critical factor in the pathogenesis of stress disorders (*10*).

Chronic stress activates the innate immune system, resulting in increased generation of peripheral myeloid cells (i.e., monocytes and neutrophils) and increased production of several pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFa) (*11*, *12*). In humans, a subset of patients with MDD displays a state of chronic low-grade inflammation, characterized by increases in circulating pro-inflammatory cytokines and myeloid cells (*13*). A major question regarding the "immune hypothesis of depression" has centered on how the immune system ultimately affects the brain to control behavioral symptoms in MDD. Recent studies in mice show that stress disrupts the endothelial blood–brain barrier (BBB), allowing greater entry of circulating proteins directly into mesocorticolimbic regions like the NAc (*14*). As a result, clinical studies have focused on testing antidepressant properties of monoclonal antibodies (mAbs) that sequester cytokines in the periphery and prevent them from entering the brain. Recent studies show that these approaches have great potential for use in MDD treatment, although they have also shown that it is critical that patients are stratified based on pre-existing inflammatory status. For example, infliximab, a TNFα mAb, reduced depression symptoms only in patients with heightened systemic inflammation (*15*). Additional cytokine targets being tested in MDD include IL-6 and IL-17A, among others.

These studies, along with those described above, highlight how new approaches to MDD treatment that consider one's unique physiological or genetic predispositions are allowing clinicians to tailor treatment in a more personalized way.

Conclusions

For many decades following the discovery of monoamine-based antidepressants, drug discovery efforts in depression stalled, in part because the field ignored the heterogeneity of depression etiology and focused on developing additional, more selective monoamine drugs with no better efficacy than their predecessors. Research that is being fueled by large-scale unbiased gene and biomarker discovery efforts have increasingly shifted to new approaches that rely on stratification of patients based on underlying biological factors to test more rationally designed approaches for depression treatment. In this brief synopsis, we have highlighted several key approaches, which are revolutionizing the field and promising much-needed relief for patients suffering from depression and related stress disorders.

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Brain–body communication in health and disease

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The body's various systems—nervous, immune, metabolic, hematopoietic, endocrine—are deeply intertwined and interdependent. Although we have known for a long time that the nervous system is essential in many biological processes, the nature of the dialogue between the brain and body has remained elusive. Discoveries over the last few decades, many by Mount Sinai scientists, have shed light on trans-system communication lines integral to both tissue homeostasis and its breakdown. As the central hub for interpreting sensation and eliciting motor responses, the brain is the apex of a layered and heterogeneous tissue, cellular, and molecular ecosystem that keeps us alive (Fig. *1*).

Neural and humoral factors in brain–body communication

The brain utilizes several modes of communication to talk with the rest of the body. The most direct route is the brain's own machinery, a web of neurons innervating major organs (through the autonomic nervous system) and forming a dense communication network (through sensory neurons). This constellation of neural circuitries continuously processes information between our tissues to harmonize organ function (*1*). But information exchange is not limited to neural axons. A vast array of neuropeptides, neurotransmitters, cytokines, and growth factors constitute another layer of communication. These small molecules, peptides, and proteins, once secreted, access the lymph and blood, endowing the nervous system with more reach and depth and thus ensuring even more intimate dialogue between the body's various tissues. The closer we look, the more the borders distinguishing one system from another blur. Perhaps this is most evident when considering the nervous, immune, hematopoietic, and metabolic systems. Plenty of examples abound: Various cytokines, which largely define immune cell function, are secreted by cells that "belong" to the nervous system; immune cells, the products of a dizzying hematopoietic process in bone marrow niches, express neuropeptide and neurotransmitter receptors; and metabolites, essential constituents of biochemical pathways such as glycolysis and the Krebs cycle, modulate immunity and influence neural circuits. This blurring at the borders underscores the profound interdependence of our body systems.

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Among the many brain–body partnerships that exist, somatosensation, a process by which the brain perceives touch, temperature, pain, itch, and proprioception, nicely illustrates the coupling of the nervous and immune systems. Recent advances have shown that cytokines and other immune products decisively modulate sensations such as skin itch (*2*, *3*). The phenomenon relies on specialized subsets of sensory neurons that survey the status of a specific microenvironment by recognizing and interpreting information delivered by type 2 cytokines, leukotrienes, and other immune cell products. Immune-derived neurosensory signals occur across multiple barrier surfaces, like the skin, gut, and lungs, and regulate brain response and neuropeptide release. We are learning that proprioceptive and interoceptive sensory neuron-dependent brain–body communication regulates processes relevant to infection, cancerous growth, and metabolic dysfunction. How exactly the brain and central circuitry integrate, interpret, and respond to these peripheral sensory cues remains a major area of inquiry.

Brain–metabolism links

As a metabolically costly organ, the brain is irreversibly entangled with the metabolic system at large. Epidemiological data have highlighted a bidirectional relationship between glucose homeostasis and brain function, generating intense interest in elucidating how brain circuits respond to and regulate glucose, how they contribute to metabolic disease, and how they can be targeted therapeutically. Recent work suggests that specific central nervous system (CNS) circuits bidirectionally regulate not only food intake, but also blood glucose levels directly via effects on autonomic innervation of metabolically active organs such as the liver and pancreas (*4*). Three-dimensional imaging of cleared pancreata, for example, demonstrates regional neuronal innervation that rapidly remodels during metabolic disease (*5*). Perhaps more intriguingly, the data show that modulating specific pancreatic neural circuits can enhance insulin release to improve glucose control (*6*). Moreover, transcriptional and neuroimaging analyses in people with diabetes have shown profound alterations in the caudate nucleus, hippocampus, and nucleus accumbens—brain regions that regulate mood and reward (*7*). Indeed, insulin controls dopamine release in the nucleus accumbens while insulin sensitivity negatively correlates with response to non-food-related rewards, suggesting that nutritional status is crucial to mood regulation. These neurometabolic insights linking glucose and metabolic control with mental health and behavior motivate the development of neuromodulatory drugs for treating metabolic disease (see articles in this booklet by Kenny and Russo).

Brain–body interactions govern adaptations to the environment

Experimentally, crucial observations on brain–body communication can arise during interventions that disturb homeostasis and force the systems to reset and adapt. Such interventions may include infection, injury, neoplasms, fatty high-calorie diets, or sensitization to auto-antigens. To specifically investigate brain–body communication, disruptions that engage the brain's unique perception capabilities arguably offer the most rewarding insights because they open the possibility for exploring the links between body systems and classical neurological and psychiatric conditions. Altering lifestyle factors is one such intervention; indeed, lifestyle strongly affects brain-body communication. Among these factors, we have learned that psychosocial or psychological stress shapes peripheral immune responses and modulates inflammatory and autoimmune disorders.

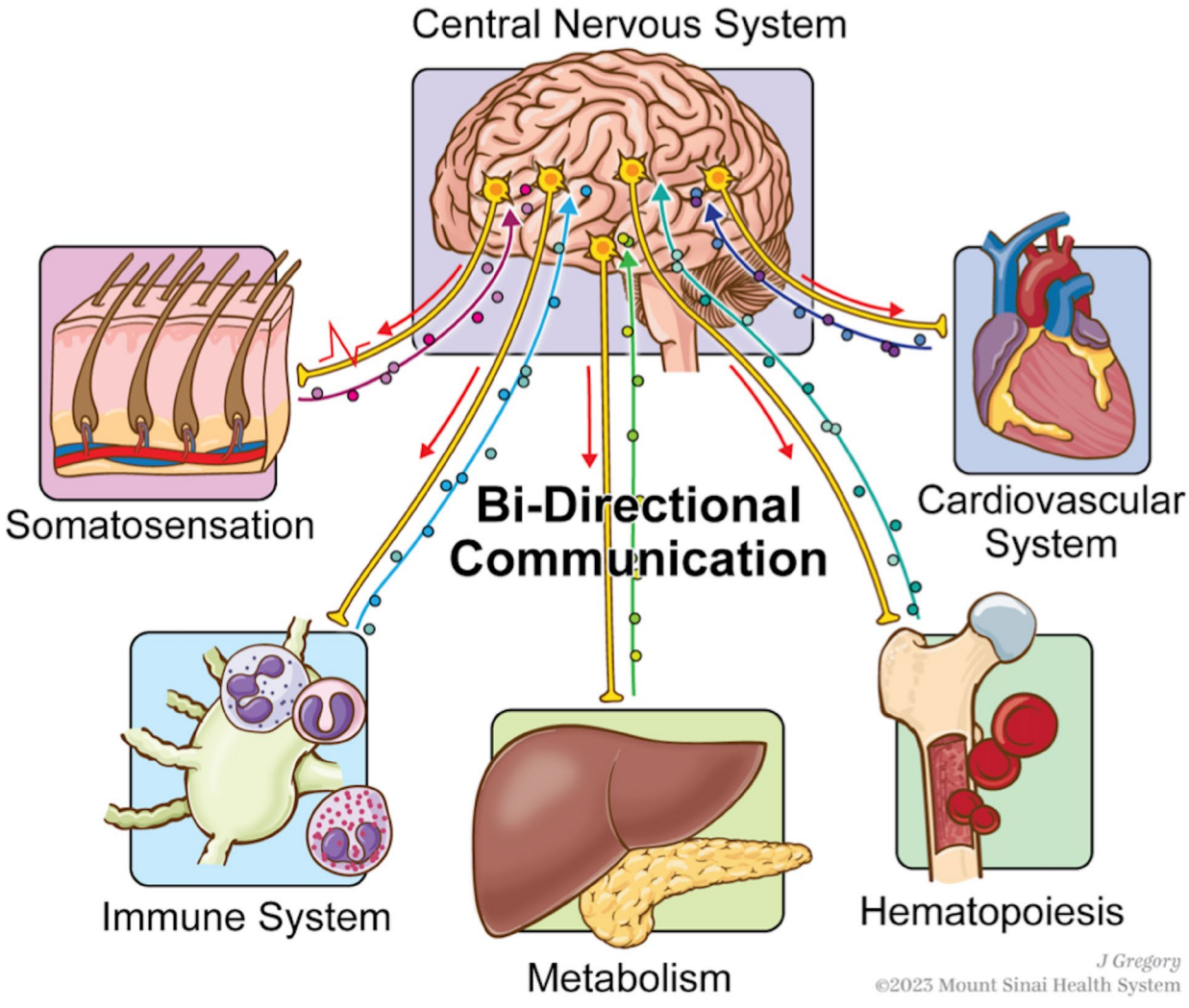

Figure 1. Cartoon demonstrating the various lines of communication between the brain and the sensory, immune, metabolic, hematopoietic, and cardiovascular systems.

Psychosocial stress alters bidirectional communication between the CNS and immune system, leading to severe social avoidance behavior and reduced reward (*8*). On the one hand, chronic psychosocial stress mobilizes peripheral monocytes and induces inflammatory cytokine production through direct sympathetic innervation of the bone marrow, thus aggravating inflammatory and metabolic conditions like cardiovascular disease (*9*). On the other hand, acute psychological stress activates distinct brain regions that orchestrate leukocyte distribution throughout the body (*10*). More specifically, during acute stress, motor cortex rapidly mobilizes neutrophils out of the bone marrow by procuring neutrophil-attracting chemokines, while the paraventricular hypothalamus regulates monocyte and lymphocyte egress from peripheral organs to the bone marrow through leukocyte-intrinsic glucocorticoid signaling. Stress-dependent communication from the body to the brain also occurs by disrupting the endothelial blood–brain barrier to allow more circulating proteins to enter directly into brain reward regions like the nucleus accumbens, a region disrupted in stress-influenced disorders such as depression and Parkinson's disease (*11–13*). These new findings provide important insights into how stress alters peripheral immune responses and how these changes in turn can act locally in the brain to regulate neuronal function and ultimately control complex behaviors relevant to major depressive disorders.

Brain–body communication and sleep

Sleep is another lifestyle factor that illustrates the interdependence of organ systems. Integral to health, sleep is a fundamental biological need that originates in the brain and configures neural circuitry and peripheral function. Insufficient or disrupted sleep rewires the circuitry of sleep-regulating neuropeptides in the hypothalamus, which connects to a seemingly countless number of processes linked to metabolic, immune, and endocrine systems. Recent studies specifically focused on how sleep affects leukocytes have shown that sleep disruption increases hematopoiesis in the bone marrow, leading to monocytosis and worsened atherosclerosis (*14*). Sleep calibrates the epigenetic wiring of peripheral immune cells, programming them for divergent and consequential responses to

inflammatory stimuli (*15*). Peripheral immune dynamics can also signal to the brain to modulate sleep. Many cytokines produced outside of the brain, such as TNFα and IL-1β, engage their receptors on neurons to shape sleep states, timing, and architecture. Sleep, and the circadian rhythm to which it is bound, is thus a key regulator that engages and tunes bidirectional communication between the brain and periphery.

Insights by Mount Sinai researchers, among many other scientists across the globe, point to a remarkably dynamic multi-faceted discourse between the brain and body. New discoveries demonstrate that the brain participates in an exquisite colloquy with distal organs and tissues and has a powerful grip on their biology and function. This bidirectional communication plays a fundamental role in health and disease and therefore offers opportunities for entirely new classes of neuromodulatory therapies.

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Autism spectrum disorder: Leading the way to precision psychiatry

Silvia De Rubeis*, Jennifer Foss-Feig, Hala Harony-Nicolas, Nan Yang, Joseph D. Buxbaum*

Autism spectrum disorder (ASD) describes behavioral characteristics of neurodevelopmental conditions that manifest with an array (*spectrum*) of disabilities. Based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), an individual is diagnosed with ASD when they have: *1*) persistent deficits in social communication and social interaction, and *2*) restricted patterns of behavior, interests, or activities. ASDs often co-occur with other neurodevelopmental disorders (NDDs) affecting brain development, such as intellectual disability, attention-deficit/hyperactivity disorder, or epilepsy. ASD is estimated to affect over 1% of the population, and males are 4-5 times more likely to be diagnosed than females.

The past decade has seen a profound revolution in our understanding of the biology of ASD, with the identification of hundreds of genes that, when mutated, confer high risk for ASD and associated NDDs. As a result, a constellation of rare genetic conditions associated with ASD have emerged (e.g., ADNP syndrome, CHAMP1 syndrome, DDX3X syndrome, FOXP1 syndrome, Phelan-McDermid syndrome [PMS]), with immediate benefits for diagnosis and rapid translation of gene findings into new experimental models and drug discovery. Beyond the impact on therapeutics and clinical care, these genetic findings offer pathways toward an improved understanding of how the human brain develops and orchestrates cognition and social function.

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The hunt for risk genes

In the past decade, increasingly sophisticated and accessible genomic technologies, alongside larger and larger collections of DNA samples from individuals with and without ASD, have made possible the identification of hundreds of new risk genes and genomic loci. In 2012, pioneering genomic studies on the first ~1,000 families with ASD uncovered significant risk associated with rare genetic variation occurring spontaneously in offspring (de novo mutations) and yielded a handful of risk genes. Fast forward 10 years: Through analyses of tens of thousands of DNA samples from individuals with ASDs, we now know at least 185 genes that, if mutated, significantly increase ASD risk (*1*).

Compared with rare and highly penetrant alleles, the discovery of common variations (i.e., variants common in the population that, in concert, increase risk) in ASD lags behind. The largest study so far, involving over 18,000 individuals with ASD and more than 27,900 controls, identified only five loci with genome-wide significance (*2*).

ASD gene discovery is a function of the sample size, and there are more genes to be discovered. Large-scale collaborations (*3*) remain the *conditio sine qua non* for success. Collection, sequencing, and analysis of large-scale patient cohorts have been coordinated through government- and privately funded efforts, e.g., the Autism Genetic Resource Exchange (AGRE), the Autism Sequencing Consortium (ASC), the Hartwell Autism Research and Technology Initiative (iHART), the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) consortium, MSSNG from Autism Speaks, the Psychiatric Genomics Consortium (PGC), the Autism Simplex Collection (TASC), and the Simons Foundation Powering Autism Research for Knowledge (SPARK) (*2*). These massive initiatives, which continue to grow and interact, have provided the substrate for the genomic revolution in autism and provide important new insights into brain development, co-occurrence with other NDDs, and the emergence of precision medicine in psychiatry.

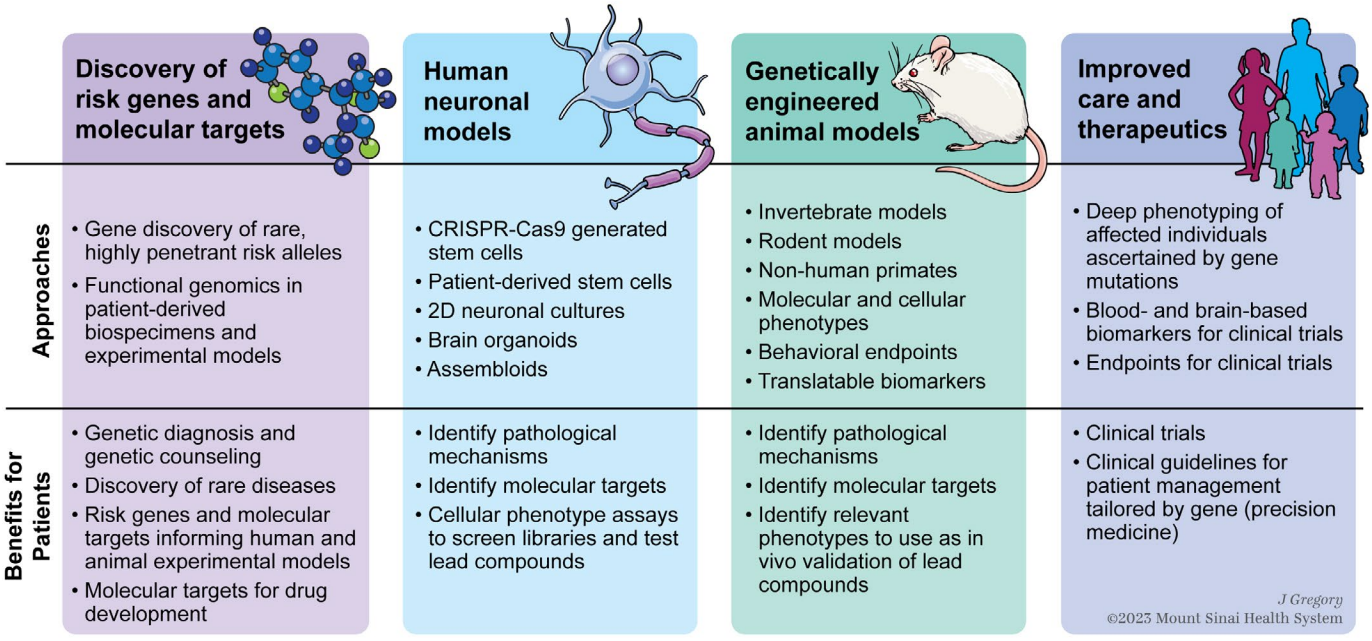

Figure 1. Pipeline for translational research in ASD, from gene discovery and experimental models to better methods for clinical care and therapeutic development.

There is an urgent need to address the overrepresentation of European ancestry in existing sample collections. Ongoing and future efforts must enhance inclusion of diverse ancestries to delineate ASD risk architecture across populations in order to identify the full range of ASD risk genes and to ensure that precision medicine can be tailored for all populations. Common variation is especially impacted by ancestry, and findings to date (*3*) may not be useful across ancestries. Moreover, samples of diverse ancestry are important when considering the interaction between rare and common variation in shaping liability for ASD (*4*).

Genes shedding new light on brain development and circuits

Advances in autism genetics also illuminate the underlying biology. We now know that ASD risk genes converge on two major biological pathways: synaptic function and chromatin remodeling (*5*). Parallel progress in profiling gene expression in human development, even at single-cell resolution, has enabled us to define where and when ASD risk converges (*4,6,7*): Intersection of genetic and gene expression data has pointed to mid-fetal development of the neocortex as a period of great vulnerability (*7*), especially in glutamatergic neuronal populations (*1,6*). Furthermore, genetics have informed development of new animal models with construct validity for ASD-associated mutations, including genetically engineered invertebrates and vertebrates, the latter including rodents and non-human primates (*4*). Parallel developments of optogenetic/chemogenetic strategies now allow fine manipulations of brain circuits. These approaches have unveiled defective circuits in genetic mouse models of ASDs and identified several novel neural substrates of social behavior and their developmental trajectories (*8*). Importantly, while susceptibility for ASD is ingrained in prenatal development, the efficacy of gene restoration in adult mice in alleviating disease-relevant phenotypes (*9*) indicates that certain circuits are still malleable and amenable to therapeutic intervention later in life.

Accessing the inaccessible: New frontiers in stem cell research

The past 10 years have also seen development of human neuronal models that allow access to the biology of the human brain. Since the breakthrough discovery of induced pluripotent stem cells (iPSCs) by Shinya Yamanaka in 2006 (*10*), technological advancements have enabled reprogramming of human iPSCs into functional neurons (*11*) and, more recently, development of human brain organoids and assembloids (*12, 13*). The field has been further boosted by rapidly evolving genome-editing tools that now enable fine-tuning gene expression and introducing clinically relevant mutations. As a result, organoids or assembloids engineered with ASD-associated mutations (*13*) or directly derived from iPSCs from ASD individuals (*12*) have been generated and characterized and are shedding light onto convergent disease mechanisms.

An exciting new avenue promising to bridge the gap between patient-derived human neuronal models and circuits of complex behaviors is a recent transplant technique developed by Pașca and colleagues (*14*). Human iPSC-derived organoids transplanted into the cortex of newborn rats develop into mature neurons that integrate into circuits and can be optogenetically manipulated to modulate behaviors (*14*). Importantly, this approach has already proven effective in assessing the development and physiology of human neurons generated from individuals with Timothy syndrome, a rare genetic disorder (*14*).

Understanding and treating clinical symptoms through the lens of genetics

Genetic advances have already had and will continue to have significant clinical ramifications. Risk genes emerging from genomic analyses have been incorporated in genetic testing, leading to more accurate and timely diagnoses. In addition, cohorts of individuals with mutations in a specific gene have been deeply phenotyped, leading to characterization of rare genetic conditions and genotype–phenotype correlations that help refine guide-

lines for clinical care and patient management (e.g., PMS Neuropsychiatric Consultation Group; https://pmsf.org/neuropsychiatric-consultation-group/). Clinical trials of pharmaceuticals validated in model systems are underway for several genetically defined NDDs. In addition, gene-based therapies are being developed for ASD *(9)*.

Although NDDs show overlap in their genetic etiologies and many ASD risk genes appear to be pleiotropic, cross-disorder analyses are beginning to isolate genetic loci that have greater effect on specific disorders and delineate distinct risk architecture, for example, genes with narrower impact on social behaviors versus those with broader impact on brain development *(1)*. Similarly, a recent study on ASD and ADHD pinpointed seven common variants shared by the two disorders and five with divergent effects (*15*).

Overall, the convergence of genetics-first approaches in clinical characterization and the parallel advancements of experimental models are bringing new hope for the development of precision medicine in ASD, while guiding parallel approaches for other neuropsychiatric disorders (Fig. 1).

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Advances in neurodegenerative disease research: Setting the stage for new therapeutics

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Decades of research have led to the development of pathology-based treatments for Alzheimer's disease (AD). These treatments, such as the recent U.S., Food and Drug Administration (FDA)-approved anti-amyloid immunotherapies implemented in symptomatic individuals, mark the beginning of the disease-modifying therapeutic era in neurodegenerative disorders (*1*, *2*). Recent mechanistic discoveries and novel diagnostic tools have extended understanding of disease beyond amyloid and tau, enabling the construction of "bedside-to-bench and back" pipelines for therapeutics with larger effect sizes. The new toolkit will enable more-efficient identification of drug targets and treatment algorithms and new approaches to assessments in clinical trials. In this brief overview, we highlight some of the tools that contributed to this shift in disease conceptualization and explain why this decade will be historic for translational research and drug discovery in AD and other age-associated neurodegenerative disorders (Fig. *1*).

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Syndromes and pathologies

New technologies for reliable quantification of biological molecules from biospecimens has shifted the premortem classification of neurodegenerative diseases from a purely clinical grouping to one that incorporates molecular neuropathological hallmarks of disease, such as ß-amyloid peptides, hyperphosphorylated tau, TDP43, and a-synuclein (*3*). Research is shifting to unbiased methods for quantification and analyses of molecular networks that capture the classical "proteinopathies," while also uncovering new molecular dysregulations (*4*). As such, the syndromic landscape of AD and other neurodegenerative diseases is shifting to one that includes more precisely grouped subtypes with diverse molecular pathologies, even in the setting of overlapping symptoms. By becoming better at quantifying disease with indices of pathology and using unbiased molecular omics (proteomics, metabolomics, transcriptomics), new biological subtypes of neurodegenerative disease with therapeutic implications are being discovered. A recent study on Mount Sinai Brain Bank samples identified several transcriptomic signatures revealing sub-types of AD (*5*). Combining these approaches with novel insights from the genetic landscape of disease will enable more useful models to be constructed for novel therapeutic developments.

Inherited risk factors for dementia—monogenic and polygenic risk for AD

In the 1990s, genetic studies in monogenic forms of AD led to the identification of causal mutations in three genes: *APP*, *PSEN1*, and *PSEN2* (*6*). Subsequent studies using these mutations in cell and animal models led to the "Amyloid Cascade Hypothesis," the dominant mechanistic hypothesis for the past 30 years. Several therapeutics (aducanumab, lecanemab) based on this hypothesis have now received FDA approval, representing the first treatments to be considered disease-modifying for AD. Observational

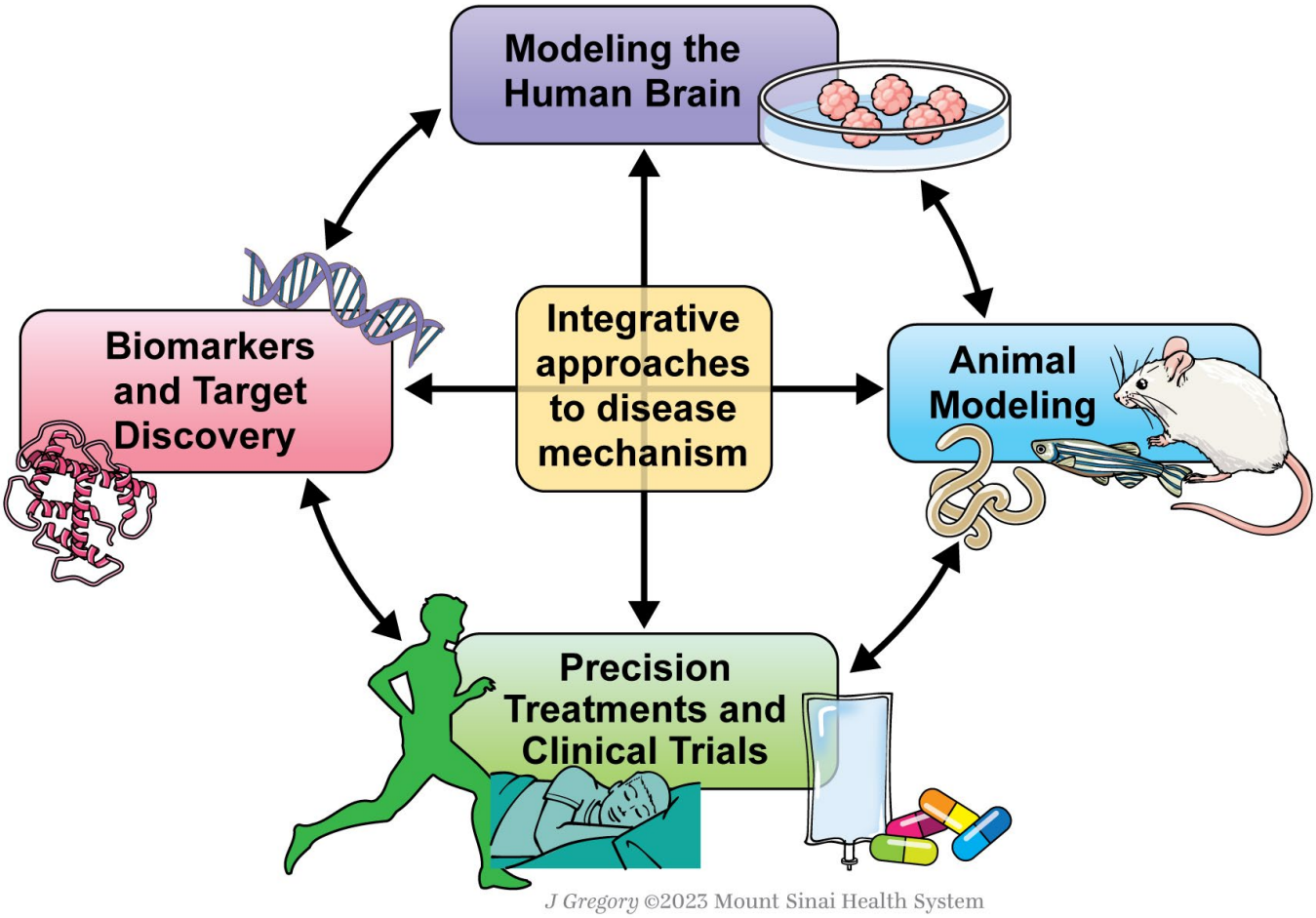

Figure 1. Multi-modal disease modeling for novel drug discovery in Alzheimer's disease and other neurodegenerative disorders.

studies in monogenic forms of AD have provided important insights into disease, including the crucial observation that symptomatic AD is preceded by a prolonged asymptomatic phase in which progressive accumulation of protein aggregates precedes neurodegeneration and symptom onset (*7*).

While these rare inherited forms of AD led to the first molecular insights into disease, most cases of AD result from a mix of genetic and environmental risk factors. In the past decade, genome-wide association studies (GWAS) have identified more than 80 loci that influence risk for AD (*8*). By far the most important is apolipoprotein E (APOE), which contains two common alleles that increase (E4) or decrease (E2) risk and age at onset relative to the major allele (E3). Sequencing studies have also identified several rare protective APOE variants (*6*).

Integrative genomic studies using GWAS data have demonstrated that AD risk alleles are specifically enriched in active enhancers in myeloid cells, rather than in neurons (*9*, *10*), suggesting that disruption in glia-neuron communication is important to AD pathogenesis. Pathway analyses show that these enhancers regulate genes involved in efferocytosis, a biological process characteristic of phagocytic cells, such as microglia that remove apoptotic cells and debris to maintain tissue homeostasis (*6*). Sequencing studies have also identified rare coding variants in microglial-expressed genes *TREM2*, *PLCG2*, and *ABI3* (*6*) that are also part of the efferocytosis pathway, pointing to this disease risk hub as a novel therapeutic target for AD.

While identifying individual gene variants contributes to our mechanistic understanding of disease, each one increases risk by a small amount. Polygenic risk scores (PRS) provide a means to calculate an individual's overall genetic risk for disease by, for example, summing the impact of all AD risk and protective genes. A recent study in the UK Biobank demonstrated heterogeneous effects on the phenome when comparing APOE genotype and AD PRS (*11*).

Modeling disease

The use of cellular and animal models based on insights from human studies continues to improve AD models. Greater access to tissue and fluid biobanks, including ethnically diverse biobanks like BioMe at Mount Sinai, will provide invaluable insights into the pathobiology of AD and other neurodegenerative diseases by combining genetics, biomarkers, and clinical phenotypes in the context of unprecedented patient diversity. Improvements in proteomics-based technologies, such as quantitative mass spectrometry, aptamer-based protein quantification of thousands of proteins, and ultra-sensitive immuno-based assays, alongside advancements in computational methods that capture greater signal over noise, promise to

unlock the potential of tissues and fluids from these biobanks for discovery. The fusion of high-dimensional molecular data with multi-modal clinical data, including structural changes in retina (*12*) and brain or sleep or daytime movement abnormalities (*13*) could uncover molecular-phenotypic associations for drug repurposing or novel therapeutic interventions.

Advances in genomics, proteomics, gene-editing methods, and novel approaches to modeling of disease are disentangling relationships between risk variants, expression, and relevant functional outputs in living systems. AD risk variant models now involve creating patient-derived induced pluripotent stem cell (iPSC) lines with matched isogenic controls, both of which are then converted into disease-relevant cell types and multi-cellular organoid models. Accelerated by the widespread adoption of gene-editing technology, this approach allows researchers to extract early functional insights from putative disease-linked variants relatively easily. For instance, a recent study used iPSC-derived organoids carrying a MAPT mutation associated with frontotemporal dementia to uncover molecular changes that precede neurodegeneration, including changes in splicing and disruption in autophagy associated with loss of glutamatergic neurons (*14*). Advances in organoid biology have also enabled modeling of pathological cell–cell interactions linked with AD risk variants. For example, pericytes, endothelial cells, and astrocytes were modeled in an iBBB (blood–brain barrier) model that identified a role for pericytes in APOE4-associated amyloid accumulation (*15*). Similar studies in 2D cultures demonstrated that APOE4 induces cholesterol and matrisome dysregulation in astrocytes and microglia (*16*).

To advance therapeutic discovery, insights from human biospecimen and clinical models need to be tested mechanistically in vitro (iPSC derived models) and in vivo (new animal models). The new gene-editing methods for iPSCs can now be harnessed to create lines for subsequent engraftment of human cells within the rodent brain. Based on the emergence of many immune-linked AD risk variants in the past decade (*6*), several groups have posited that dysfunction in myeloid cells of the CNS or periphery may be critical to AD pathogenesis. Moreover, recent observations in animals have shown that the brain responds to signals in the systemic environment in the context of aging (*17*) and AD pathology (*18*). Next-generation animal models are poised to explore the role of whole-body immuno-vascular dysregulation in neurodegeneration. Ongoing work at Mount Sinai explores the biological effects of aging in AD and other neurodegenerative disorders and the extent to which a brain exhibiting age-related or AD pathology can be revitalized by modulation of various systemic states. These novel hypotheses and other explorations into the interaction of genes and environment may shape how we develop AD therapies of the future.

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Circuit-based therapies for brain disorders

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Clinical needs drive integrative research

Epilepsy, traumatic brain injury, depression, OCD (obsessive-compulsive disorder), and addiction, among many treatment-resistant brain disorders, place an enormous physical, emotional, and financial burden on individuals, their families, and society. The limited effectiveness of available treatments stems from multiple sources. First, we have an incomplete understanding of the underlying causes of neuropsychiatric conditions, which constrains creation of robust animal models. Second, the variability in disease presentation and symptomology suggests that there is significant inter-patient heterogeneity in their neurobiological basis that is not appropriately targeted with blanket treatments or systemic drug administration. Third, it is becoming increasingly clear that simple behavioral, genetic, biochemical, or region-based biomarkers have important but limited utility. As such, a circuit-based strategy provides unique power for bidirectional, translational studies with robust clinical relevance.

With recent innovations in neurotechnologies, there are now unprecedented opportunities for out-of-the-box thinking to drive the development of circuit-focused therapeutic approaches. By combining observations in the clinic with discoveries from basic neuroscience, and leveraging current surgical and research platforms, transdisciplinary teams at Mount Sinai are working toward next-generation, evidence-based treatments for refractory neuropsychiatric disorders.

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A human brain laboratory

Improving knowledge and therapies for disease states requires vertical integration and translation—from the clinic, to translational and basic human research, to animal models, and back again. This coordinated approach involves investigating the brain at different levels of precision through such bidirectional translation (Fig *1*).

Opportunities for human research in clinical environments classically leverage non-invasive imaging (functional and structural imaging, spectroscopy, and positron emission tomography) and electrophysiological (EEG) recordings, pharmacological manipulations, and investigation of clinical symptomology and behavioral processes in the context of disease. More recently, invasive neurophysiological assessments have emerged as a unique opportunity to both measure high-quality neurophysiological activity and carry out circuit neuromodulation through anatomically precise stimulation. These recordings can be short-term, during implantation surgery, chronic (days to weeks) in specialized in-patient monitoring facilities, and even long-term (months to years) from implanted clinical devices.

Deep brain stimulation (DBS) is the invasive intervention with the longest and most successful track record, especially in the treatment of movement disorders such as Parkinson's disease and essential tremor, and is an example of the promise of circuit-based treatments (*1*). DBS is increasingly being developed to treat psychiatric conditions, such as depression and anxiety disorders and OCD, among others. Foundational to develop-

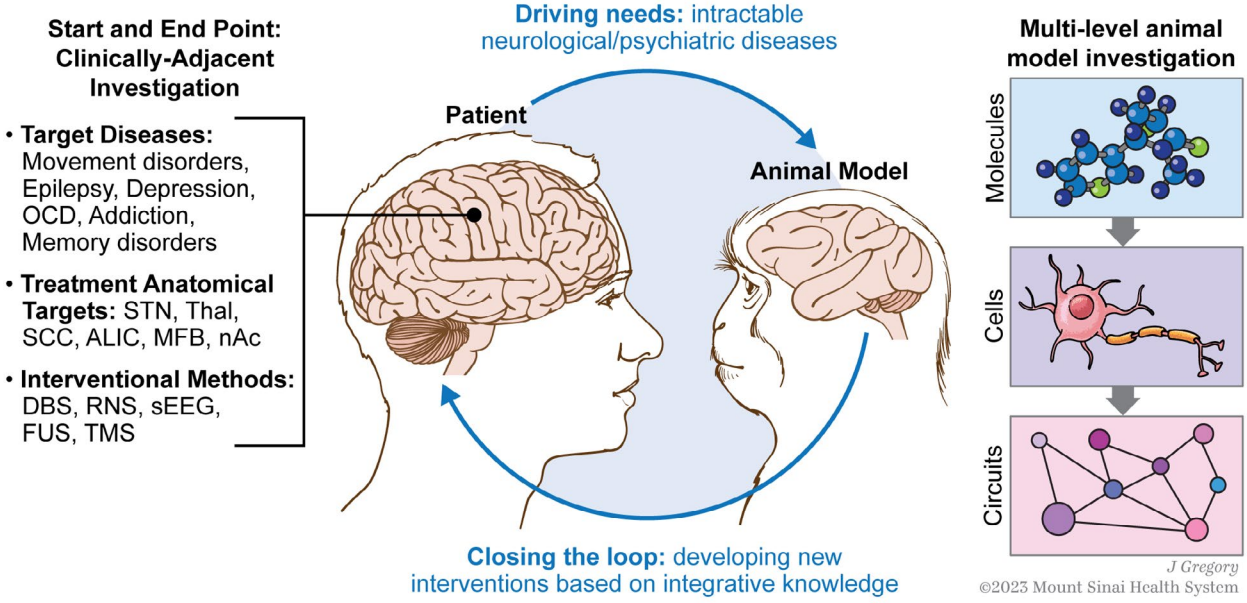

Figure 1. An integrated, need-driven multispecies approach to the development of novel therapeutic approaches for neurological and psychiatric disorders. Clinically adjacent investigation (left) uses a variety of methods to provide an initial description of the relevant disorder, including clinical, behavioral, and computational symptom description, invasive electrophysiological recordings, and anatomical targeting through non-invasive imaging. Complementary research in animal models (right) provides additional detail across multiple biological levels (molecules to cells to circuits), using methods such as multi-region electrophysiological recordings, electrical micro-stimulation, and molecular cellular characterization. Abbreviations: OCD-obsessive-compulsive disorder; STN-subthalamic nucleus; Thal: thalamus; SCC: subcallosal cingulate; ALIC-anterior limb of internal capsule; MFB-medial forebrain bundle; nAc-nucleus accumbens; DBS-deep brain stimulation; RNS-responsive neurostimulation; sEEG-stereoelectroencephalography; FUS-focused ultrasound; TMS-transcranial magnetic stimulation.

ing this novel treatment approach is knowledge about the function of the affected circuits in the human brain—limited in DBS by current clinical single-target strategies. Electrocorticography (ECoG) and stereotactic EEG (sEEG) approaches routinely used in epilepsy centers to pinpoint the origin of focal seizures offer a complementary opportunity. These recordings also provide a unique opening to investigate the function of distinct human brain areas, with access to a greater range of targets, often including prefrontal cortex, medial temporal cortex, and other limbic brain regions. As patients perform complex tasks or respond to emotional situations, the patterns of activity that support cognitive and affective states can be identified (*2*, *3*).

The resulting insights from combined clinical, imaging, neurophysiological, behavioral, and computational approaches can then guide the development of more-precise neuromodulation strategies. These neuromodulatory tools can further incorporate patient-based information to directly treat patients suffering from otherwise intractable disorders (*1*, *4*). This evidence-driven innovation combines clinical and research insights and expertise into patient-tailored treatments that consider each patient's unique disease presentation, anatomy, neurophysiological patterns of activity, as well as behavior—essentially creating personalized treatments, the effectiveness of which can be optimized over the course of therapy (*5*).

Non-human primate models

Despite its promise, this work is constrained by clinical considerations. For instance, human invasive electrophysiology recordings are necessarily limited to areas involved in a patient's disease that are targeted for diagnosis or treatment. Consequently, parallel efforts are essential for reverse translation for questions that cannot be addressed adequately in humans but can be investigated with a high degree of precision using complementary tools in animal models.

Non-human primates (NHPs) are indispensable to understanding how the human brain works in both health and disease. Because NHP brains are similar to human brains, insights from them are more directly relevant to the treatment of human brain disorders. One important avenue is to determine the patterns of neural activity that are associated with complex human cognition using high-density, multi-region electrophysiological recordings with single-neuron resolution in NHPs (*6*). This work is essential for defining neural networks that are engaged in healthy brains, information that is important for correcting dysfunctional activity patterns in human neuropsychiatric disorders. Similarly, by using cutting-edge single-neuron connectomic approaches, the full wiring diagram of the macaque brain is now being built (*7*). This is a foundational step for determining how networks of brain areas communicate. Characterizing the connection patterns in healthy animals and comparing these to developing or aged animals will help reveal the specific neurons that are impacted in neurodevelopmental and neurodegenerative disorders. NHP models are also necessary to test new technologies prior to use in humans—e.g., ultra-thin biocompatible electrodes (*8*) that will provide higher precision neurophysiological information.

Finally, NHP models guide reverse translation. While DBS continues to be a key therapeutic approach for neurological and psychiatric disorders, the mechanisms by which it works are still incompletely known. Functional MRI, diffusion tractography, direct recordings of brain activity, and high-resolution anatomy can track changes that occur after DBS in NHPs, complementing parallel studies in patients. Understanding how DBS affects the brain at multiple scales, from brain-wide circuits to molecular changes at the level of white matter and glial cells, is being used to further refine DBS for depression and other disorders by targeting white matter. It also has the potential to identify new targets in brain for therapeutic intervention.

Closing the loop – Informing new therapeutic strategies

Through unique collaborations among neurologists, neurosurgeons, psychiatrists, psychologists, basic neuroscientists, engineers, and data scientists, the Nash Family Center for Advanced Circuit Therapeutics at the Icahn School of Medicine at Mount Sinai is addressing unmet clinical needs. An area of emphasis leveraging this cross-diagnostic transdisciplinary approach is exemplified by experimental studies of treatment-resistant depression (TRD) involving behavioral assessments, high-resolution imaging, and invasive neurophysiological recordings during chronic therapeutic DBS. Complementary studies optimizing DBS for TRD are being conducted using intracranial recordings in epilepsy patients, combining computational psychiatry and machine learning approaches, and integrating findings across platforms, to further understand the pathogenesis and treatment of depression (*9*). These efforts are complemented by NHP studies outlined above. Such multi-scale investigations inform the development of new devices and therapeutic strategies that can be implemented, tested, and optimized in NHPs before clinical application. The success of this integrative and bidirectional translational research template for TRD is now guiding efforts for other incurable diseases (*10*, *11*). The challenge is vast and there is no shortage of disorders in need of novel treatments where circuit therapeutics is a viable strategy.

The success and traction of a fluid, bidirectional translational model requires creative parallel efforts in patients and animal models, allowing iterative, mutually informative testing of novel therapeutic approaches that leverage the unique strengths of ongoing basic and clinical research. This integrated and synergistic mission enables development and testing of enhanced theories of brain function and dysfunction at multiple levels—cellular and molecular, computational and algorithmic, and circuit- and organism-wide—not possible in human models alone. Such bidirectional translation studies, facilitated by existing and novel neurosurgical (DBS, ECoG, sEEG) and stimulation (DBS) approaches keeps the focus on patient-centric experimental studies that seek to address the underlying urgent need for safe, effective, and sustainable new treatments for a long list of brain disorders (*12*).

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The computational brain

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The brain's hardware

The human brain is populated by diverse cell types, unique in form and function, which have been programmed by millions of years of evolution to assemble into complex networks connected by trillions of synapses. Embedded in this hardware are countless pathways for routing signals from inside and outside the body, and from the resulting symphony emerges our thoughts, feelings, plans, and dreams. One of the most important human endeavors has been to understand how these pathways are organized, what their constituent parts do, and onto which components are imprinted the remnants of our experiences.

Across the animal kingdom, behavior is governed largely by a set of basic drives that further the pursuit of rewards and avoidance of threats, and at times necessitate complex tradeoffs between the two (*1*). To meet these demands, the brain encodes relational information about the external world and the body's own internal state, which under normal circumstances supports adaptive behavioral responses. It is increasingly recognized that deficits in the processing, retention, and updating of this information constitute circuit-based endophenotypes that are invisible to the casual observer but may be a root cause of brain dysfunction (*2*, *3*). Indeed, the National Institute of Mental Health has prioritized this conceptualization of psychopathology over traditional diagnostic criteria (*4*).

Delineating the brain's circuitry

To pinpoint the origins of abnormal circuit activity, researchers must decipher how entire circuits are influenced by the functioning of their parts, which requires that neurons be differentiated based on their anatomy, gene expression, and stimulus-response properties. Fortunately, the field has seen an explosion of technological advances to meet this demand, work that brings the promise of circuit-based therapies squarely into the realm of possibility (see article in this supplement by Saez). Innovation in electrode materials and design (e.g., silicon probes) has enabled electrophysiological monitoring of large neuronal populations at multiple brain sites in rodents and non-human primates, while genetically encoded sensors report neuronal firing and neurotransmitter release with exquisite cellular resolution. With the introduction of microendoscopes, the purview of Ca^{2+}-based imaging has been extended to freely behaving animals, where recordings can be obtained from hundreds of anatomically or genetically defined cells (*5*). Meanwhile, there are a host of chemo- and optogenetic tools for perturbing the activity of discrete cell populations at timescales aligned to behaviorally significant events and thereby causally connecting the functioning of specifically defined circuits to complex behaviors. Given this powerful toolset, it hardly seems like hyperbole to suggest that researchers are poised to crack the neural code, and through open science initiatives like the Miniscope project, they are democratizing the enterprise (*6*).

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Against a backdrop of ongoing technical innovation, the application of new circuit-based approaches is already yielding major returns. In the study of emotions, investigators focused on what was traditionally referred to as the limbic system have defined circuits that respond to survival-based cues and established their potential to restore normal functioning in preclinical models of mood and substance use disorders. A particularly intriguing question stemming from this work has been how, at a basic circuit level, the brain designates the emotional valence of a stimulus as positive (i.e., good) or negative (i.e., bad), an important precursor to motivated behavior. New work is providing clues into how this property is encoded at circuit, microcircuit, and even synaptic levels, independent of other attributes of an experience (*7*).

Some of the most exciting discoveries relate to the circuitry underlying social cognition, which relies on high-dimensional sensory representations whose motivational significance varies profoundly with context and unfolds with the interplay between one animal's actions and another's reactions (*8*). Similarly, cognitive decision-making draws feedback from many sensory modalities to build statistical models for action. While brain loci for these complex mental functions were established long ago, only recently have investigators gained the ability to dissect the signals generated by different components of a task and trace the exact neural pathways through which they are routed (*9, 10*).

How the brain computes

From the perspective of a computational neuroscientist, the floodgates opened by this revolution could provide the raw materials needed to construct a biologically accurate model of the brain. Indeed, machine learning approaches have shown that computers trained on the activity of a large population of cells can reliably predict which stimuli were presented to an animal as well as the response that was executed, confirming that tantalizing insights are within our grasp. Elucidating how these patterns emerge from the integration of many neurons acting in concert is a far more challenging task, but one that will define the future. Toward this goal, new anatomical and electrophysiological approaches are revealing the wiring logic that supports the brain's most basic computational routines, which are likely to be executed by repeating circuit motifs (*11*). These elementary building blocks define the signal processing capabilities of discrete neural pathways and may be important determinants of how relatively subtle alterations in the intrinsic properties of collections of cells can tip the balance between normal and pathological brain function.

Some of the most significant implications of how circuits are organized relate to the mysterious mechanisms by which we learn and remember. While it is believed that the brain assigns this task to sparse neuronal populations, we are only beginning to elucidate how these cells are selected or what enables them to encode information. Through in vivo Ca^{2+} imaging and genetic tagging, it is now possible to identify and track memory-related cells over long periods, permitting extensive inquiries into their stimulus properties and how they are shaped by plasticity. Meanwhile, with surgical precision, an expanding array of optogenetic tools can address the precise behavioral role of this activity. Studies of this type have yielded important and sometimes counterintuitive insights: for example, memory recall can be signaled by neurons that release inhibitory transmitters, which act within specialized microcircuits to activate (rather than inhibit) downstream networks (*12*). Likewise, while intuition tells us that

individual memories are stored separately by the brain, findings indicate that to a surprising degree they rely on overlapping neural ensembles that link different memories together over time (*13*). Experiments like these provide important clues to how memory-related populations influence the networks in which they are embedded, and how the properties of learning may be constrained or facilitated by the available circuit resources.

Ultimately, computational approaches will be useful for validating and extending the concepts derived from these studies but can also play an important role in accelerating discovery. One reason is that in silico experiments provide a more efficient way to test the performance of different circuit components in novel situations. Furthermore, because the activity of a given cell population cannot fully explain behavior, computational modeling will be critical for establishing how many different brain systems must work in concert to generate complex behaviors (*14*). Eventually, the insights gleaned from these studies will provide a blueprint of sorts for novel therapeutic interventions in which dysfunctional circuits are recalibrated through targeted manipulations. To enable such breakthroughs, however, we still need to make a sustained investment in understanding the brain's basic organizational principles.

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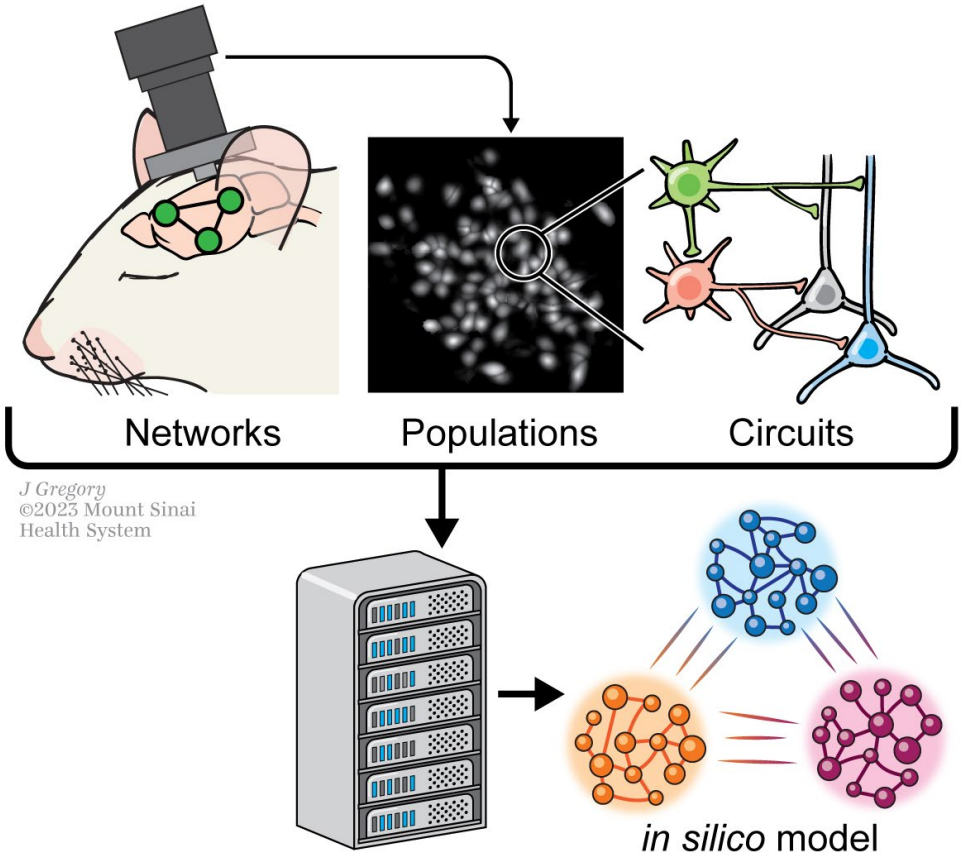

Figure 1. Multiscale analysis of neural processing to establish basic computational principles of normal and abnormal cognition.

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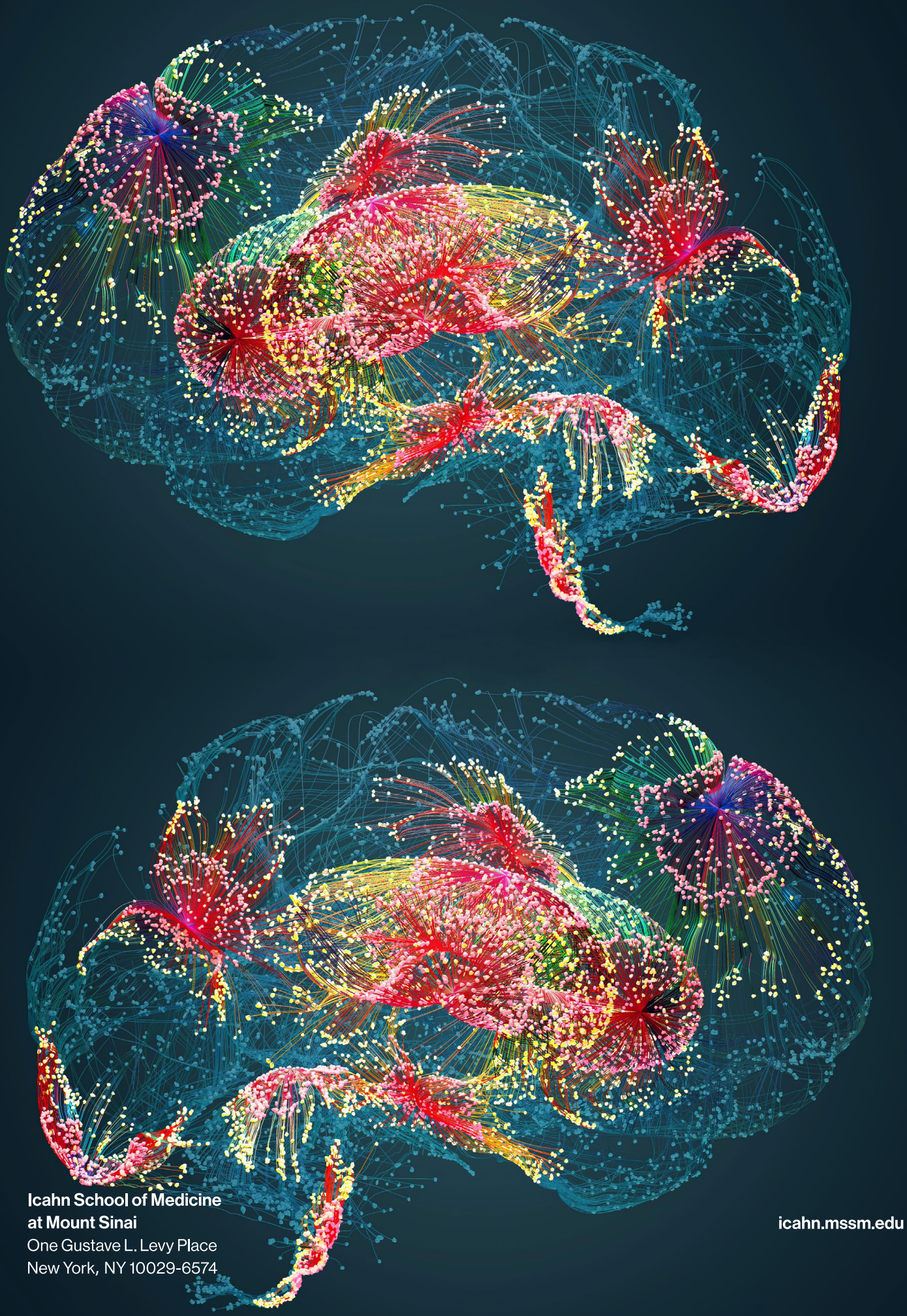

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