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Voices

Understanding the biological basis of psychiatric disease: What's next?

Psychiatric disease is one of the greatest health challenges of our time. The pipeline for conceptually novel therapeutics remains low, in part because uncovering the biological mechanisms of psychiatric disease has been difficult. We asked experts researching different aspects of psychiatric disease: what do you see as the major urgent questions that need to be addressed? Where are the next frontiers, and what are the current hurdles to understanding the biological basis of psychiatric disease?

Conor Liston
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Toward mechanism-guided psychiatric therapeutics

The early 1950s saw the serendipitous discovery that monoamine-targeting drugs, which were being studied as treatments for other diseases, had potent antidepressant properties. Nearly 7 decades later, most antidepressant medications work on the same principle. Yet they are fully effective in only 1 in 3 individuals, and depression remains a leading cause of disability worldwide. Today, the field is poised for a second transformation focused on developing fundamentally different, mechanistically informed treatment strategies, driven by new technologies. First, there is an urgent need for identifying new treatment targets. Toward this end, massive genome-wide association studies involving tens of thousands of individuals have identified dozens of genetic risk variants implicating unexpected signaling pathways, and single-cell sequencing technologies are identifying cell-type-specific treatment targets. Second, there is a growing understanding that, in most people, depression is a consequence of dysfunction in complex brain circuit networks. Rapid advances in optogenetics, neuronal activity sensors, and mesoscale imaging tools are enabling investigators to record and manipulate neuronal activity with exquisite precision across circuits and networks, opening new avenues to develop more effective, rationally directed, circuit-targeting therapeutics. Finally, depression is a highly heterogeneous syndrome, with different forms of depression potentially requiring different treatments, but defining those subtypes has been an elusive goal for the field. The growing availability of large-scale neuroimaging datasets—aided by the maturation of functional magnetic resonance imaging (fMRI) and machine learning tools for analyzing them—is beginning to reshape how we diagnose and treat depression. In the longer term, these approaches have the potential to yield new models for matching individuals to the treatments most likely to benefit them—an urgently needed form of precision medicine for psychiatry.

Angela Roberts
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A pathway to translation

There has been a dearth of new treatment strategies for psychiatric disorders despite increasingly sophisticated human brain imaging technology and neural pathway elucidation in rodents using viral mediated precision targeting. The latter promised to uncover the neurobehavioral mechanisms underpinning the symptoms of psychiatric disorders, but this approach has not delivered new treatments so far, highlighting the potential difficulties of cross-species translation. This is particularly true for studying higher-order cortical association regions, like the prefrontal cortex, that are dysregulated in psychiatric disorders. Research in non-human primates has the potential to bridge the translational divide between rodents and humans, but first, methodologies need to be extended. Fortunately, we are now on the cusp of a new wave of studies that could transform translational psychiatry. Many scientists around the world are developing novel research programs using a new world monkey, the common marmoset, which is small in size and relatively easily bred, and their social and biological needs are easily met in a laboratory setting. The organization of their brain, and the prefrontal

cortex in particular, resembles that of humans far more so than rodents. Moreover, its relatively small size and smooth cortical surface makes it highly suitable for applying state-of-the-art viral mediated techniques for targeting cortical and subcortical pathways. Complementary intervention studies in rodents and marmosets using comparable cognitive and behavioral tasks, in combination with neuroimaging that can be applied across rodents, monkeys, and humans, will provide enormous insight into the similarities but also, importantly, the differences in cognitive and affective neural networks across species. Together, they have the potential to bridge the current translational gap and advance our mechanistic understanding of network dysregulation underlying the core symptoms of psychiatric disorders.

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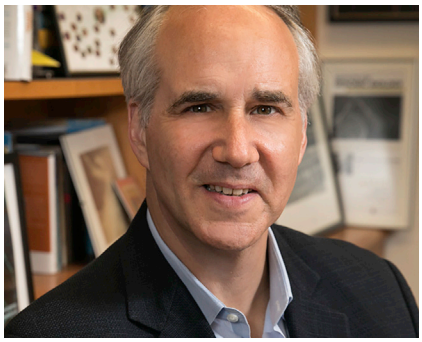
Data meet data science

The last decade has given rise to an explosive development of tools to measure brain activity with unprecedented spatial and temporal resolution. Now combined with rich behavioral quantification and novel analytical methodologies based in machine learning, these tools have guided neuroscience to the precipice of revealing fundamental codes that link complex patterns of neural activity with emotions. Discovery of these codes will undoubtedly transform our understanding and management of emotions in health and psychiatric dysfunction, in the same way that the electrocardiogram transformed cardiology practice.

Several of these early emotional codes appear to be shared across individuals, while others provide insights into why only some people exhibit strong emotional responses when they encounter a given situation. Yet, others appear to predict how individuals with psychiatric diagnoses will respond to different classes of treatments.

As our data quantification and analysis methodologies/pipelines continue to expand, the integration of these neural codes into medical practice may ultimately rewrite the entire diagnostic framework for psychiatric disease. Furthermore, these codes may reveal new neural targets for intervention, based on direct stimulation of the brain, psychopharmacology, psychotherapy, or some personalized combination of the three.



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It's simple: Embrace genetic complexity

Although luck has played a role in many major advances in medicine, as Louis Pasteur observed, "in the fields of observation chance favors only the prepared mind." However, because human biology and medicine lack the strong theoretical framework of mathematics and physical sciences, the identification of key disease mechanisms and treatments has often been hamstrung in the inability to prioritize many possible competing hypotheses. As a result, while performing hypothesis-driven research researchers often stick to what is most familiar. We are now the beneficiaries of extraordinary advances in technology, exemplified by computing and genetic/genomic technologies. These developments enable us to rely on systematic, highly parallel, discovery-based studies (rather than serial, single hypothesis-driven investigations) to elucidate the mechanisms of disease. Indeed, genetic findings in neuropsychiatric disorders have opened new windows that have begun to clarify the causes of these disorders. This provides enormous hope for understanding mechanisms and developing new treatments. At the same time, these studies reveal further complexity, exemplified by genetic heterogeneity and polygenicity. This complexity must be embraced, not dismissed, if we are to move forward. Rather than acting in isolation, gene products are components of complex regulatory and interaction networks. By integrating genetic data into networks, we can provide an organizing framework that can vastly simplify what initially might appear to be a list of genes or jumble of data. I have always believed that the best way to gain new perspectives on neural function in health and disease is by organizing and integrating comprehensive "ome-wide" data with other systematically collected data types (e.g., systems biology). More and more, research at the intersection of genetics, genomics, and neuroscience supports this perspective.

Susanne E. Ahmari
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Tailoring treatments using patient biology

During residency, I learned that the modern practice of psychiatry is grounded in neuroscience. My PhD studying the mechanisms underlying synapse formation served me well when working with patients, as a framework for discussing how strengthening or weakening synaptic connections can facilitate new behavioral strategies. I also learned that disruption of delicately balanced neural networks can lead to neuropsychiatric illness. Consistent with this understanding that psychiatric symptoms are rooted in biology, modern pharmacotherapies are developed to engage specific molecular targets. But although the treatments we prescribe are biologically based, psychiatrists deploy them blind to our patients' biology. That blindness results in a succession of randomly selected treatments, often guided almost exclusively by qualitative data and subjective self-report. This leads to precious time lost for patients and their loved ones, unnecessary side effects, discouragement, and—perhaps most importantly—continued progression toward end-stage illness. To make meaningful change, we need to match treatments to the specific biology of people receiving them. This is a hard problem that requires breakthroughs to enable predictive stratification, including development of non-invasive measures of brain state, and objective measures of treatment response. Emerging results hold promise in these areas, most notably the identification of "biotypes" derived from resting-state fMRI connectivity and cerebral spinal fluid (CSF) metabolite levels. But it is crucial to push forward and integrate across siloed levels of investigation to understand the biological complexity that underlies heterogeneous psychiatric illness and see the patient's biology as a tool to identify tailored treatments.

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Translating modern circuit neuroscience

In the early 2000s, the introduction of channelrhodopsin combined with the recently introduced genetically encoded calcium indicators to birth modern circuit neuroscience. Neuroscientists could now observe and control the activity of genetically defined neurons. A decade and a half later, the optogenetic toolbox has become versatile, including sensors with a wide range of kinetics and affinities reporting activity or, most recently, the concentration of transmitter. Accentuators can excite or inhibit neurons and diverse viral vectors allow for projection and cell-type specificity.

Although circuit models in rodents can only reflect core components of psychiatric disease, they have nonetheless opened the doors for mechanistic insight into behavioral disorders. We now have detailed knowledge of circuits causing an individual to overeat, feeling the helplessness of defeat or compulsion to consume drugs. Optogenetic manipulations can also relieve symptoms in rodents via correction of aberrant activity or reversal of pathological synaptic plasticity. Translation of these findings puts modern circuit neuroscience in a unique position to help develop better treatments. Successful optogenetic restoration of neural function in rodent disease models has shifted the challenge from figuring out what to do to now figuring how this can be achieved in humans.