Rethinking Mental Illness

Thomas R. Insel, MD
Philip S. Wang, MD, DrPH

In the first 2010 issue of *Nature*, the editor, Philip Campbell,[1] suggested that the next 10-year period is likely to be the "decade for psychiatric disorders." This was not a prediction of an epidemic, although mental illnesses are highly prevalent, nor a suggestion that new illnesses would emerge. The key point was that research on mental illness was, at long last, reaching an inflection point at which insights gained from genetics and neuroscience would transform the understanding of psychiatric illnesses. The insights are indeed coming fast and furious. In this Commentary, we suggest ways in which genomics and neuroscience can help reconceptualize disorders of the mind as disorders of the brain and thereby transform the practice of psychiatry.

Compelling reasons to look for genes that confer risk for mental illness come from twin studies demonstrating high heritability for autism, schizophrenia, and bipolar disorder.[2] Although there have been notable findings from linkage and genome-wide association studies, with candidate genes and specific alleles identified for each of the major mental disorders, those that have been replicated explain only a fraction of the heritability.

Where is the missing genetic signal for mental illness? The discovery that large (>1 megabase) structural or copy number variants, such as deletions and duplications, are 10-fold more common in autism and schizophrenia is an important clue.[3,4] Copy number variants are individually rare, sometimes restricted to a single family or developing de novo in an individual. Although "private mutations" are rare (reminiscent of Tolstoy's dictum that "each unhappy family is unhappy in its own way"), they are in aggregate remarkably common, spread across vast expanses of the genome, and ultimately could explain more genetic risk than common variants. Although many of the genes implicated are involved in brain development, copy number variants do not appear to be specific for illnesses in the current diagnostic scheme. Within families, the same copy number variant may be associated with schizophrenia in one person, bipolar disorder in another, and attention-deficit/hyperactivity disorder in yet another. The genetics of mental illness may really be the genetics of brain development, with different outcomes possible, depending on the biological and environmental context.

The same twin studies that point to high heritability also demonstrate the limits of genetics: environmental factors must be important for mental disorders. The advent of epigenomics, which can detect the molecular effects of experience, may provide a powerful approach for understanding the critical effects of early-life events and environment on adult patterns of behavior. Epigenomics can now map changes across the entire genome with unbiased, high-throughput technologies and point to the mechanisms by which experience confers enduring changes in gene expression and, ultimately, changes in brain activity and function. Epigenomic modifications that alter transcription may also be a mechanism for mental illness, even in the absence of common or rare structural variants. For instance, a rare copy number variant detected in autism deletes the oxytocin receptor gene. In many individuals with autism who do not have this deletion, epigenomic modifications appear to silence this gene.[5]

Genomics and epigenomics already point to diverse molecular pathways that confer risk of mental illness. What binds these diverse molecular mechanisms together to yield clusters of symptoms recognized as the syndromes of psychiatric disorders? Increasingly, clinical neuroscientists are identifying specific circuits for major aspects of illness. But just as the genetic variants do not map selectively onto current diagnostic categories, so, also, circuits seem to be associated with cognitive and behavioral functions, without a one-to-one correspondence to diagnosis. For instance, the neural basis of extinction learning, which was first mapped in the rat brain, appears to be conserved in the human brain, with key nodes including ventromedial prefrontal cortex, amygdala, and hippocampus.[6] Rather than defining the biology of a single illness, extinction is an important feature of posttraumatic stress disorder, obsessive-compulsive disorder, and various phobias.

Two noteworthy points are emerging from systems neuroscience. First, there seem to be emerging relationships between genetic variation and development of neural circuits that mediate complex cognition and behavior, from reward to emotion regulation. Second, the current diagnos-

Author Affiliations: National Institute of Mental Health, Bethesda, Maryland.
Corresponding Author: Thomas R. Insel, MD, 6001 Executive Blvd, Room 8235, NIMH/NIH, Bethesda, MD 20892 (tinsel@mail.nih.gov).

tic categories, based on clinical characteristics, do not seem to align well with findings from genetics and neuroscience. The National Institute of Mental Health recently launched the Research Domain Criteria project to reformulate psychiatric diagnosis according, in part, to emerging biology rather than the current approach, which is limited to clinical consensus.[7]

Reconceptualizing disorders of the mind as disorders of the brain has important implications for how and when to intervene. From the study of neurodegenerative disorders such as Parkinson disease, Huntington disease, and Alzheimer disease, it is known that behavioral and cognitive symptoms are late events, occurring years after initial signs of neuronal damage. Although mental illnesses are more likely neurodevelopmental rather than neurodegenerative disorders, the behavioral and cognitive manifestations that signify these as "mental" illnesses may be late stages of processes that start early in development. In medicine, the best outcomes are rarely observed from treatments initiated in late phases of an illness. If genetics and neuroscience could provide rigorous, specific, early detection years before psychosis or depression, these illnesses might be redefined in terms of a trajectory. As a result, interventions, rather than being ameliorative or rehabilitative, could become preemptive or even preventive. But this transformation in diagnosis and treatment, which can be informed by recent progress in cardiovascular disease and cancer, will depend on an intense focus on the genetics and circuitry underlying mental illness to ensure new approaches to detecting risk, validating diagnosis, and developing novel interventions that may be based on altering plasticity or retuning circuitry rather than neurotransmitter pharmacology.

Recent examples illustrate how these genetic and basic neuroscience discoveries can rapidly lead to new clinical innovations that will make such a transformation in practice possible. For example, elucidation of the roles that genetic and downstream effects on protein synthesis play in the pathogenesis of fragile X syndrome[8]—an important cause of autism and inherited mental retardation—has quickly opened the door to clinical trials of pharmacologic treatments for that disorder's debilitating cognitive impairments. Likewise, advances in understanding the circuitry underlying extinction learning have led to promising new behavioral approaches for blocking previously learned fear responses.[9] Even as new interventions are developed for anxiety disorders, recent discovery of genetic variants associated with efficacy of existing behavioral treatments suggests new ways to tailor their use.[10] Such examples provide strong bases for hope that insights emerging from genetics and neuroscience will be translated into rational development of new robust and personalized treatments.

A "decade for psychiatric disorders" cannot come too soon.[1] With no validated biomarkers and too little in the way of novel medical treatments since 1980, families need science to provide more than hope. Genetics and neuroscience finally have the tools to transform the diagnosis and treatment of mental illness. But first, it is time to rethink mental disorders, recognizing that these are disorders of brain circuits likely caused by developmental processes shaped by a complex interplay of genetics and experience.

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