

## JAMA commentary: Time to rethink causes, possible treatments of mental disorders

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It is time to reassess mental disorders, recognizing that these are disorders of brain circuits likely caused by development processes, according to a commentary in the May 19 issue of *JAMA*, a theme issue on mental health.

Thomas R. Insel, M.D., Director, National Institute of Mental Health (NIMH), Bethesda, Md., presented the commentary at a *JAMA* media briefing on mental health.

Dr. Insel and commentary co-author Philip S. Wang, M.D., Dr.P.H., Deputy Director, NIMH, write that 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. "Although there have been notable findings from linkage and genome-wide association studies, with [candidate genes](#) and specific alleles [an alternative form of a gene] identified for each of the major [mental disorders](#), those that have been replicated explain only a fraction of the heritability."

The authors add that 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," they write. "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."

The authors note that 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."

Emerging from systems neuroscience are two noteworthy points, according to the authors. "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 diagnostic categories, based on clinical characteristics, do not seem to align well with findings from genetics and neuroscience."

They add that reconceptualizing disorders of the mind as disorders of the brain has important implications for how and when to intervene. 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. "If genetics and neurosci-

ence 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."

The authors add that 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. Examples such as this and others provide strong bases for hope that insights emerging from genetics and neuroscience will be translated into rational development of new robust and personalized treatments.

"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](#)," the authors conclude.

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