DSM-5 lends new urgency to brain-based evidence for mental illness

The inclusion of new classifications for such typical childhood behavior as temper tantrums in the upcoming version of the *Diagnostic and Statistical Manual of Mental Disorders* is lending new urgency to research aimed at finding empirical evidence for psychiatric disorders.

The new edition of the manual — known as DSM-5 — due to be published this month, updates the previous 2000 classification of mental illnesses. It creates new categories and updates the symptoms, both those required and those excluded, to make a diagnosis of particular mental illnesses.

The changes have already provoked criticism from a previous editor of the manual and other leading psychiatrists (www.cmaj.ca/lookup/doi/10.1503/cmaj.109-4371). They contend the new edition will pathologize normal emotional reactions. The new manual, for example, opens the possibility for doctors to diagnose grief following bereavement as a depressive disorder.

Although these new categories are promoted as addressing the wealth of advances in neuroscience, other psychiatrists and neuroscientists believe new research can make important contributions to diagnosing mental illnesses that are not based solely on symptoms.

The Research Domain Criteria project at the National Institute of Mental Health (NIMH) in Bethesda, Maryland is one such contender. That project plans to categorize mental disorders based on objective brain abnormalities, using brain imaging. Under the project, groups of people with a heightened or lowered response in the amygdala (an area in the brain partly responsible for emotional regulation) would be categorized as having separate psychiatric diseases, regardless of the symptoms they express (*Am J Psychiatry* 2010; 167:748-51).

"We're always going back to the symptom complexes of the DSM as the gold standard to identify psychiatric disease. But this is very limiting," says Dr. Thomas Insel, the NIMH's director.

Using symptoms to diagnose mental illness is equivalent to making a fever — a common symptom of infectious disease — the "gold standard" for infectious disease, Insel says. "Of course, not everyone with a fever has a positive blood culture."

The DSM-5 relies on symptoms for diagnosis, but some psychiatrists and neuroscientists believe physical evidence, such as biomarkers, and assessing brain abnormalities through brain imaging, can also be used.

"For psychiatry to progress, we need to let go of our current gold standard of symptom-based DSM diagnoses and instead build psychiatric disease diagnoses from the brain up," Insel adds.

Insel, who leads the Research Domain Criteria project, believes better psychiatric disease categories may come from understanding biosignatures, which can be found by incorporating data from brain circuits and vast genomic studies.

One study using this methodology found that five major mental disorders share common genetic origins. Investigators studied 33 332 patients with all five disorders and 27 888 controls. They discovered that people with disorders traditionally thought to be distinct — autism, attention deficit hyperactivity disorder, bipolar disorder, major depression and schizophrenia — were more likely to have pathologic genetic variation at the same four chromosomal sites (*The Lance*t 2013;381:1371-9).

"These results will help us move toward diagnostic classification informed by disease cause," says Dr. Jordan Smoller, director of the Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital in Boston, Massachusetts. Smoller was a coordinator of the study, which the NIMH supported.

A similar brain-circuitry study called the Human Connectome Project plans to map the neural pathways that underlie human brain function. Investigators published a study revealing that the brain's neurons are not the random tangle that some had thought, but are arranged in a tidy grid that resembles a city street map (*Science* 2012;335:1628-34).

These types of large scale biosignature studies "will eventually help researchers discover treatments that target specific pathological biological systems underpinning psychiatric diseases, as opposed to just broad symptoms," says Insel.

The search for brain-based explanations for the causes of neurological and psychiatric illness is becoming a hot political issue as well. The United States government recently announced $100-million to fund the BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies). The project is designed to help researchers find new ways to treat, cure and even prevent various brain disorders, such as epilepsy and Alzheimer disease.

While this brain-based approach may succeed for many mental disorders, it is unlikely to work for all of them, cautions Dr. Randolph Nesse, an evolutionary psychiatrist and professor of psychiatry and psychology at the University of Michigan, Ann Arbor.

"It is kind of surprising, actually. With three decades of unsuccessful results, we have no reliable biomarkers to identify psychiatric disorders," says Nesse. "This should send us a signal that something just isn't working. Maybe we should start looking for other solutions."

Insel also believes it's time for a different approach.

"Biomarkers for mental disorders may not be proteins found in blood tests, but may emerge from neuroimaging," he says. "If these are disorders of brain function, then the visualization of abnormal patterns of brain activity should detect the pathology of these illnesses."

The NIMH's Research Domain Criteria project is not yet ready for clinical application, says Insel. "One can imagine a day where patterns of brain activation following stimulation may be a diagnostic test, just as cardiac imaging during a stress test is now used to diagnose coronary artery disease."

Until that day comes, Dr. Jerome Wakefield suggests physicians need to employ common sense when considering and treating mental illness.

"This is not rocket science. Sadness is an inherent and integral part of the human condition, not a mental disorder," says Wakefield, coauthor of *The Loss of Sadness: How Psychiatry Transformed Normal Sorrow into Depressive Disorder* and a professor of social work and psychiatry at New York University in New York city. "Many times, whether it is because of a lost loved one or job, it is normal for people to be sad, even intensely so. Context is everything. Unfortunately, somewhere along the way, psychiatry has forgotten that." — Paul Kudlow MD, Toronto

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