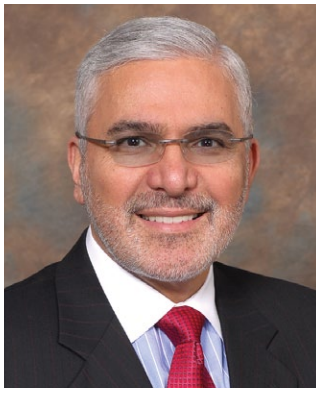

Henry A. Nasrallah, MD
Editor-in-Chief

Is there only 1 neurobiologic psychiatric disorder, with different clinical expressions?

The nearly 1,000-page DSM-5 lists hundreds of psychiatric disorders, with an operational clinical process to distinguish them. Psychiatrists and other mental health practitioners dutifully apply DSM criteria to categorize patients as having a psychotic or mood or anxiety or addictive disorder; most rarely question the veracity of the diagnostic Bible of Psychiatry. But is that dogma about to be slaughtered by scientific research?

In a report of a study that was published recently in a top-tier psychiatry journal,[1] researchers describe a stunning finding that challenges the notion that there is a plethora of psychiatric brain disorders. They conducted a large meta-analysis of 193 published brain imaging studies of people with schizophrenia, bipolar disorder, major depression, obsessive-compulsive disorder (OCD), anxiety, and addiction. They found that those 6 supposedly discrete illnesses are all associated with a varying degree of shrinkage (atrophy or hypoplasia) of the same 3 brain regions:

- **Dorsal anterior cingulate cortex.** This region around the frontal part of the corpus callosum controls rational cognitive processes, reward anticipation, decision making, empathy, impulse control, and emotional response. Francis Crick, the Nobel laureate who first described the structure of DNA, hypothesized that the anterior cingulate sulcus might even be the center of what we call "free will."
- **Left insula and right insula.** The insulae are the cortical regions deep inside the lateral sulcus, which is the fissure that separates the temporal lobe from the parietal and frontal lobes. The functions of the insulae include consciousness, emotions, perceptions, motor control, self-awareness, cognitive functioning, and interpersonal experience. (In addicts, the insular cortex is activated when they are exposed to environmental cues that trigger craving because the insulae are a target for the dopamine system. Notably, it has been reported that, when cigarette addicts suffer a stroke that damages the insulae, they stop smoking completely.)

The 3 regions of the brain, in which pathology extends across 6 DSM-5 diagnoses, work together to manage high-level executive functions, such as working memory, reasoning, and flexible thinking. The degree of dysfunction varies among the 6 clinical disorders, with schizophrenia having the highest severity.

Neurobiological commonality

The idea of shared neurobiological underpinnings among 6 distinct psy-

Can you envision a day when psychiatric disorders are conceptualized as having a common genetic, neurobiological, and clinical core?

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chiatric disorders flies in the face of the entrenched DSM model, in which those 6 disorders are distinct disease entities. Other studies (including the Bipolar Schizophrenia Network on Intermediate Phenotypes) also found prominent biological similarities in varying degrees across schizophrenia, schizoaffective disorder, and bipolar disorder.[2,3] The Research Domain Criteria of the National Institute of Mental Health also embraces the dimensional approach to neurobiological biomarkers across various psychiatric disorders.

A common genetic substrate also is emerging. A recently published genome-wide association study, conducted on 33,332 psychiatric patients and 27,888 controls,[4] revealed that a number of genes are shared by 5 different psychiatric disorders: schizophrenia, autism, bipolar disorder, major depression, and attention-deficit/hyperactivity disorder. The genetic phenomenon of the same genes manifesting in different clinical phenotypes is called pleiotropy, and is consistent with shared neurobiological findings.

Genetic and brain structural commonalities among multiple DSM diagnostic categories might explain some well-known clinical observations:

- frequent comorbidity of certain psychiatric disorders, such as depression and addiction in schizophrenia; anxiety and OCD in bipolar disorder; depression with OCD and addictions; and so on
- the presence of intermediate phenotypes in unaffected family members, such as cognitive dysfunction in the parents of patients with schizophrenia, compared with parents of matched healthy controls[5]
- the much higher rate of psychopathology among family members of patients with a major psychiatric disorder, compared with the general population.[6]

Core inflexible thinking. So what about clinical features across those disorders that share genetic and neurobiologic similarities? Psychiatrists may agree that symptoms of schizophrenia, bipolar disorder, major depression, OCD, anxiety, and addiction appear very different. However, given that reasoning and flexible thinking are functions of the insulae, which are shrunken in all 6 disorders, one can postulate that inflexible thinking (fixed false beliefs also are called psychotic delusions) might be a common feature across all those disorders. Namely:

- schizophrenia is known for paranoid or implausible delusions
- bipolar disorder is characterized by grandiose delusions
- major depressive disorder is associated with a fixed false belief of worthlessness as well as hopelessness
- anxiety patients harbor the fixed false belief of impending doom or death (the plane will crash if they are a passenger on it)
- OCD manifests as ego-dystonic false beliefs (obsessions) that can progress into ego-syntonic delusions
- people with an alcohol or tobacco addiction are in delusional denial that they are not really addicted or that they will not be harmed by their drug of abuse. Pathologic gamblers harbor the false belief that they will soon reverse their fortunes and "win big."

It seems that poor reality testing and impaired reasoning is a common feature of not only all 6 psychiatric disorders with shared neurobiology, but others, too, including anorexia nervosa, body dysmorphic disorder, delirium, and dementia.

continued

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If brain research steers psychiatric nosology in the direction of a common core, we might end up with a 10-page DSM

From a thick volume to… a booklet?

Can you envision a day when psychiatric disorders are conceptualized as having a common genetic, neurobiological, and clinical core, with some variability in phenotype and behavior? If further brain research steers psychiatric nosology in that direction, we might end up with a DSM of 10 pages instead of almost 1,000, with an "Appendix" of genetic, neuroimaging, and other emerging biomarkers.

Bold scientific prophecies often sound delusional—until they come true….

Henry A. Nasrallah, MD
Editor-in-Chief

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