Neuroscience, Clinical Evidence, and the Future of Psychiatric Classification in DSM-5

In the initial stages of development of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), we expected that some of the limitations of the current psychiatric diagnostic criteria and taxonomy would be mitigated by the integration of validators derived from scientific advances in the last few decades. Throughout the last 25 years of psychiatric research, findings from genetics, neuroimaging, cognitive science, and pathophysiology have yielded important insights into diagnosis and treatment approaches for some debilitating mental disorders, including depression, schizophrenia, and bipolar disorder.

In *A Research Agenda for DSM-V* (1), we anticipated that these emerging diagnostic and treatment advances would impact the diagnosis and classification of mental disorders faster than what has actually occurred. This optimism was not wasted, however. First, it stimulated a series of international research planning conferences supported by the National Institutes of Health that formed the basis of early deliberations by the DSM-5 task force and work groups. For example, one conference provided a detailed examination of the heterogeneity and overlap of disorders characterized by fear and avoidance, including posttraumatic stress disorder, panic/agoraphobia, social phobia/social anxiety disorder, and specific phobias (2). Though these are phenotypically heterogeneous, neuroimaging and neuroanatomy data from human and animal model studies suggest a shared membership in a "stress-induced and fear circuitry spectrum," which is conceptually and clinically distinct from other anxiety disorders, such as generalized anxiety disorder, obsessive-compulsive disorder, and impulse control disorders. This new conceptualization has important implications for assessment, treatment, and research.

The review of neuroscientific evidence for establishing groups of disorders with shared criteria, and possibly shared etiologies, also bolstered broader discussions on the overall organization of diagnostic categories across DSM-5. The role of neuroscience research findings in shaping these "metastructure" talks was most prominent in the proposal for 11 external validators (3) to help define and group diagnoses. Among these validators are shared genetic risk, familiality, shared neural substrates, and shared biomarkers. Furthermore, our recognition of the significance of neuroscience and genetics in psychiatric diagnosis has supported DSM-5's novel integration of neurobiologic findings, such as inclusion within the text that accompanies diagnostic criteria sets the potential role of these factors in shaping risk and prognosis. While not central to the criteria themselves, this information is nonetheless useful and informative for helping DSM provide a more precise picture of the clinical realities of psychiatric diagnosis.

The seminal article by Robins and Guze (4) on diagnostic validity, which proposed a classification of psychiatric illnesses based not on psychodynamic, a priori hypotheses but rather on external, empirical indicators, built a direct pathway to DSM-III. Their proposed classification steps included identifying core clinical features, conducting differential diagnosis to separate the condition from similar disorders, gathering laboratory data, assessing temporal stability of the diagnosis, and determining familial aggregation of the disorder. The resultant explicit criteria featured in DSM-III and subsequent editions have significantly improved our understanding of psychiatric disorders, but they did not come without a price (5). While diagnostic reliability has thrived, large-scale epidemiological studies have underscored the inefficiency of DSM's criteria in accurately differentiating diagnostic syndromes, especially in community samples.

With reification of the criteria through revised editions of DSM-III-R and DSM-IV, proliferation of diagnostic comorbidities and overreliance on the "not otherwise specified" category have continued.

We realized from our *Research Agenda* (1) conference series that we would not be able to accomplish by DSM-5's deadline all of the things we set out to and, in fact, that portions of that agenda related to advances in neuroscience were already being addressed in other arenas. A logical extension of those discussions, as detailed in our *Research Agenda* (1) articles, is the Research Domain Criteria (RDoC) initiative recently launched by the National Institute of Mental Health (NIMH). A commentary by Insel and colleagues (6) introduced readers to the working principles behind the RDoC, whose proposed reclassification of mental disorders for research purposes is predicated on a neuroscience-based framework that can contribute to a nosology in which disorders are grouped by underlying pathophysiological similarities rather than phenomenological observations. This NIMH objective is consistent with our research planning conferences and conclusions, which underscored our commitment to examining evidence from neurobiology and assessing the readiness of proposed revisions for DSM-5. We are pleased with the work on RDoC that is being undertaken, and we believe this initiative will be very informative for subsequent versions: DSM-5.1, DSM-5.2, and beyond.

Beyond keeping pace with the science of psychiatry, many of DSM-5's proposed changes represent an opportunity to improve the field from clinical and public health perspectives. The proposal for a single "autism spectrum disorder" category that would include the current DSM-IV diagnoses of autistic disorder (autism), Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified was born from data suggesting that these disorders share a pathophysiological substrate. Changes in the wording of the criteria, however, help clarify symptom manifestation and provide diagnosticians with a more accurate example of how these children actually appear in clinics. Similarly, a proposal from the Psychotic Disorders Work Group for an "attenuated psychosis syndrome" diagnosis was developed largely because of the sizable body of literature on psychosis risk and vulnerability factors detailing structural and functional imaging, neurocognition, and genetic outcomes. Clinically, this proposal may aid clinicians in early detection and intervention for help-seeking individuals at risk for a future psychotic disorder. Our current thinking about criteria specifically and the classification of diagnoses in DSM-5 as a whole is consistent with observations from research on heritability, treatment similarity, and shared genetic risk factors among disorders, including neurodevelopmental disorders, mood disorders, anxiety disorders, and schizophrenia spectrum disorders (7), while also supporting our philosophy that DSM-5 remains first and foremost a tool for clinicians.

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It is important to emphasize that DSM-5 does not represent a radical departure from the past, nor does it represent a radical separation from the goals of the RDoC. As we gradually build on our knowledge of mental disorders, we begin bridging the gap between what lies behind us (presumed etiologies based on phenomenology) and what we hope lies ahead (identifiable pathophysiologic etiologies). It is difficult to assess how quickly progress will come about because the thresholds we have set for replication and usability must be as applicable to clinical purposes as they are to research ones. We may be able to examine, for instance, schizophrenia through a genetic framework in terms of researching risk factors and developing treatments, but genetic data are clearly not yet ready for clinical applications (8). Can we ask psychiatrists to use genetic markers to assist in diagnosing a patient with schizophrenia? At this point in time, the answer

is no, but the point at which such data can be meaningfully used by clinicians is soon coming, and in the meantime we must be prepared to accept and incorporate genomics and "personalized medicine," which is now used in diagnoses and therapies for cancer and coagulation disorders.

One way in which the authors of DSM-5 are preparing for the future is in proposed changes to the text within each diagnostic chapter. In addition to current subheadings about disorder prevalence, subtypes, specifiers, and differential diagnosis, we propose that DSM-5 also include sections on genetic and physiologic risk factors, gender and cultural aspects of presentation, and clinical expressions across the lifespan. These will not be applicable equally for all disorders. Mood disorders, schizophrenia, Alzheimer's disease, and attention deficit hyperactivity disorder are among the diagnoses that may hold the most immediate promise for the use of this information for clinical purposes. These processes will be facilitated by one of the new, core features of DSM-5—the ability to exist as a "living document" that can be readily updated to reflect changes in our understanding of neuroscience and pathophysiology in a world of (sometimes) rapid and dramatic neuroscience discovery. We have no doubt that future editions will greatly benefit from continuing to incorporate information generated by the RDoC initiative.

The evolution of ideas occurs incrementally, with occasional "off the scale" breakthroughs, and when we consider how far psychiatric neuroscience and nosology have come, those hard-fought inches of incremental scientific advances taken cumulatively add up to miles. DSM-5 is a work in progress, and we must await the outcome of several proposed changes before ascertaining their true impact on the field. This includes, for example, the possibility of improving assessments with a uniaxial approach that combines psychiatric and general medical diagnoses but still separately conveys important information about social and environmental contextual factors and disability. While it is clear that the forthcoming version of the manual cannot exhaustively address the limitations and questions posed by the current nosology, progress is our constant goal, and we look forward to working alongside our colleagues in basic and clinical research on this endeavor.

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