

Current State of Psychiatric Nosology

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Abstract

Psychiatric classifications categorize how patients present to mental healthcare professionals and are necessarily utilitarian. From the clinician's perspective, the most important goal of a psychiatric classification is to assist them in managing their patients' psychiatric conditions by facilitating the selection of effective interventions and predicting management needs and outcomes. Due to the field's lack of understanding of the neurobiological mechanisms underlying the psychiatric disorders in both the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD), diagnosis and treatment are only loosely related, thus limiting clinical utility. Both DSM and the chapter on mental and behavioral disorders in ICD adopted a descriptive atheoretical categorical approach that defines mental disorders according to syndromal patterns of presenting symptoms. This chapter discusses the fundamental challenges that underlie this decision. It then reviews the Research Domain Criteria (RDoC) project, a research framework established by the U.S. National Institute of Mental Health (NIMH) to assist researchers in relating the fundamental domains of behavioral functioning to their underlying neurobiological components. Designed to support the acquisition of knowledge of causal mechanisms underlying mental disorders, RDoC may facilitate a future paradigm shift in the classification of mental disorder.

Introduction

Nosology (from the ancient Greek “noso,” meaning *disease*, and “logia,” meaning *study of*) is a branch of medicine that address the classification of diseases. The need to establish a classification of diseases reflects the natural human predilection to categorize for the purpose of simplifying and organizing the wide range of observable phenomena and experiences that one is confronted with so as to facilitate both their understanding and their predictability. Psychiatric nosology, with its focus on the presentations of mental and behavioral symptoms, dates back to antiquity. The first recorded depiction of mental

illness dates to 3000 BC Egypt, with a description of the syndrome senile dementia attributed to Prince Ptah-hotep (Mack et al. 1994).

While some classification systems, like the periodic table, are a direct reflection of natural objective phenomena that clearly exist in nature, psychiatric classifications classify the ways in which patients present to mental health-care professionals. They are necessarily utilitarian, and their success depends on how well they fulfill practical needs. Psychiatric classifications are used in a variety of contexts and settings (e.g., clinical, research, administrative, and educational) and thus must fulfill a variety of practical needs, including helping clinicians diagnose and treat patients, assisting researchers in selecting populations for study, facilitating administrators in their collection of health statistics, and teaching students how to recognize presentations of mental disorders. Although the original purpose of psychiatric classifications was for the collection of statistical information about institutionalized patients, the primary purpose of modern-day classifications, such as the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) and the Mental Disorders Chapter of the International Classification of Diseases (ICD), is to assist mental health professionals in providing clinical care for their patients.

For the clinician, a psychiatric classification system needs to assist them in managing their patients' psychiatric conditions: it needs to facilitate the selection of effective interventions and be able to predict management needs and outcomes. For this, a clear understanding is needed of the neurobiological mechanisms that underpin psychiatric disorders; otherwise, diagnosis and treatment will only loosely be related in psychiatry and psychology, as is the case in DSM and ICD. Most currently available treatments have been found to be helpful in managing a wide range of disorders. Selective serotonin reuptake inhibitors, for example, have been shown to be useful in the treatment of depressive disorders, panic disorder, social anxiety disorder, obsessive-compulsive disorder (OCD), generalized anxiety disorder, posttraumatic stress disorder (PTSD), gambling disorder, early ejaculation, bulimia nervosa, and borderline personality disorder (Vaswani et al. 2003; Tang and Helmeste 2008). Similarly, for each diagnostic category, a wide range of treatments, both psychopharmacological and psychotherapeutic, have demonstrated efficacy (APA 2000).

Nonetheless, determining the patient's psychiatric diagnosis does provide the clinician some assistance in treatment selection and determining prognosis. Consider, for example, a patient with no premorbid psychiatric history, who presents with the very recent onset of a severe depression. Determining that the depressive symptoms arose in the context of that person having recently stopped his regular use of cocaine (which would be diagnosed as a cocaine-induced depressive disorder in DSM) has profound implications for the prognosis and management of that individual. Similarly, determining whether the symptomatic presentation of a patient with recurrent episodes of grandiose

delusions and accompanying hallucinations meets the definitional requirements of bipolar disorder versus schizophrenia can be very important in clarifying both the potential role of lithium in the management of the patient (useful in bipolar disorder but not in schizophrenia) and future course.

Both DSM and the chapter on mental and behavioral disorders in ICD use essentially the same fundamental approach: they provide descriptive atheoretical categorical classifications that define mental disorders according to patterns of presenting symptoms. There are, of course, other possible approaches to implementing a psychiatric classification, namely having the classification based on etiological and pathophysiological factors as opposed to being descriptive, or adopting a dimensional approach instead of one that is categorical. In this chapter, I discuss the fundamental challenges that underlie the decision for the DSM and ICD to adopt a descriptive atheoretical approach and then describe the Research Domain Criteria (RDoC) system, created by the U.S. National Institute of Mental Health (NIMH), which is not actually a nosology or classification per se but is instead best viewed as a framework for conducting research in terms of fundamental circuit-based behavioral dimensions that cut across traditional diagnostic categories.

Approaches to Classification

Etiological versus Descriptive

Ideally, the organization and definition of conditions in any medical classification should be based on an understanding of the underlying etiology and pathophysiology, given that a classification system based on etiology and pathophysiology is most likely to be useful in helping clinicians determine disease prognosis and select the optimal treatment. For example, given that the type of infectious agent is essential for selecting the proper treatment, the diagnostic groupings in the infectious diseases chapter in ICD reflect the underlying infectious agents, starting with the intestinal infectious diseases, which are subdivided into the different bacterial, amoebic, protozoan, and viral agents that cause intestinal diseases, then the various forms of tuberculosis infections (e.g., respiratory, neurologic, etc.), and so on.

While most of the chapters of the ICD strive to follow this organization principle (Table 8.1), there are some areas of medicine (e.g., rheumatological conditions, various forms of headache, psychiatric disorders) for which a deep knowledge of the underlying etiology and pathophysiology remains elusive. For these areas, the main classificatory strategy, sometimes referred to as a “descriptive approach,” is to define disease entities in terms of “syndromes”; that is, groups or patterns of symptoms which appear together temporally. The symptoms comprising a syndrome are assumed to cluster together because

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Table 8.1 Organizational principles of ICD by chapter.

Disease type:	Classified by:
Infectious	Anatomic location (e.g., intestinal infectious diseases) Type of organism (e.g., protozoal diseases) Mode of transmission (e.g., infections with a predominantly viral mode of transmission)
Neoplasms	Nature of neoplasm (e.g., malignant neoplasms, <i>in situ</i> neoplasms, benign neoplasms) Malignant neoplasms subdivided by anatomic location (e.g., malignant neoplasms of the lip, oral cavity, and pharynx)
Blood and blood-forming organs; certain disorders involving immune mechanism	Etiology (e.g., nutritional anemias) Pathophysiology (e.g., coagulation defects)
Endocrine, nutritional, and metabolic	Anatomic location (e.g., disorders of thyroid gland) Clinical presentation (e.g., diabetes mellitus, malnutrition) Etiology (e.g., metabolic disorders subclassified by cause such as disorders of aromatic amino acid metabolism)
Nervous system	Pathophysiology (e.g., inflammatory diseases of the central nervous system) Clinical presentation (e.g., extrapyramidal and movement disorders, headaches) Anatomic location (e.g., nerve, nerve root, and plexus disorders)
Eye and adnexa	Anatomic location (e.g., disorders of eyelid, lacrimal system, and orbit) Pathophysiology (e.g., glaucoma) Clinical presentation (e.g., visual disturbances and blindness)
Ear and mastoid process	Anatomic location (e.g., diseases of middle ear and mastoid)
Circulatory system	Pathophysiology (e.g., ischemic heart diseases) Anatomic location (e.g., diseases of arteries, arterioles and capillaries)
Respiratory system	Pathophysiology (e.g., influenza and pneumonia) Anatomic location (e.g., other diseases of the upper respiratory tract)
Digestive system	Anatomic location (e.g., diseases of esophagus, stomach, and duodenum) Pathophysiology (e.g., noninfective enteritis and colitis)

Table 8.1 (continued)

Disease type:	Classified by:
Skin and subcutaneous tissue	Etiology (e.g., infections of skin and subcutaneous tissues) Clinical presentation (e.g., dermatitis and eczema) Anatomic location (e.g., disorders of skin appendages)
Musculoskeletal system and connective tissue	Pathophysiology (e.g., infectious arthropathies) Clinical presentation (e.g., systemic connective tissue disorders) Anatomic location (e.g., disorders of muscles)
Genitourinary system	Anatomic location reflecting pathophysiological location (e.g., glomerular diseases) Anatomic location in general (e.g., diseases of male genital organs), by clinical presentation (e.g., renal failure)

they are associated in some clinically meaningful way, presumably reflecting a common etiological process, course, or treatment response.

It is important to understand that these two classificatory strategies are not in opposition. Classifying disorders based on etiology and pathophysiology is universally regarded as the preferred approach, for the reason stated above. The syndromal “descriptive” approach is viewed as a clinically useful but temporary way station on the road to a future etiologically and pathophysiologically based classification.

The intuitive appeal of etiologically based classification systems is evidenced by their historical predominance, which goes back to Hippocrates and his classification of personality types based on whether there is excess or deficiencies in the four “humors” (blood, yellow bile, black bile, and phlegm). The problem, of course, with basing a classification on etiological principles is that their ultimate value is constrained by lack of validity of the hypothesized etiological factors. In the sixteenth century, for example, the Swiss physician Paracelsus developed a classification system in which he divided psychotic presentations into three types of disorders based on their presumed etiology. The first category, *vesania*, was for disorders caused by poisons and is analogous to current-day substance-induced disorders. The second, *insanity*, for diseases caused by heredity, is analogous to modern disorders such as schizophrenia and bipolar disorder, which appear to have a strong familial component. His third category, *lunacy*, described a periodic disturbance influenced by the phases of the moon. This lack of validity of the notion that the phases of the moon directly cause psychopathology severely compromises the utility of such a classificatory scheme.

In recognition of the problems inherent in basing a psychiatric classification system on unproven causal theories, an alternative approach which

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concentrated on careful observation of symptomatic presentations was proposed by Emil Kraepelin in the 1880s, who provided exceedingly detailed descriptions of disorders seen in inpatient settings at the turn of the century. While Kraepelin's classification viewed mental illness in terms of disease entities akin to medical disorders, his nosology was firmly based on the methods of descriptive psychiatry. Kraepelin strongly advocated that "psychiatrists should avoid postulating etiologies to make a diagnosis and should stick to the course of the illness, attend to the final state, and do follow-up studies where possible" (Decker 2007:340).

Both DSM and ICD have followed these Kraepelinian principles in their adoption of a descriptive "atheoretical" approach in which disorders are defined according to their symptomatic presentation, rather than according to unproven theories regarding underlying etiology. As noted in the introduction to DSM-III (the first edition of the DSM to adopt such an approach):

The approach taken in DSM-III is atheoretical with regard to etiology or pathophysiological process except for those disorders for which this is well established and they are included in the definition of the disorder....The major justification...is that the inclusion of etiological theories would be an obstacle to use of the manual by clinicians of varying theoretical orientations (APA 1980:6-7).

It is important to understand that the decision to adopt a descriptive approach was not motivated by some aversion to having a classification system organized around etiology per se, but rather an aversion toward defining disorders according to unproven and potentially invalid etiological hypotheses. Thus, those psychiatric disorders in DSM for which the etiology is known (or presumed) are defined according to etiology. Such disorders include the substance-induced mental disorders and disorders due to a general medical condition, which are, by definition caused by the direct physiological effects of substance use or general medical conditions on the central nervous system, as well as disorders included in the DSM-5 diagnostic grouping Trauma and Stress-Related Disorders, each of which include exposure to a traumatic or stressful event as a required diagnostic criterion. Furthermore, given that one of the main goals of a psychiatric classification is to facilitate communication among mental health clinicians, defining disorders according to one particular theory would hinder its utility for clinicians who do not subscribe to that theory.

Although the descriptive DSM approach has been widely lauded because it established a common diagnostic language and improved diagnostic reliability, both researchers (Clark et al. 1995; Goldberg 1996; Cloninger 1998; Parker 2005; Widiger and Samuel 2005; Mellsop et al. 2007) and clinicians (McHugh 2005) have expressed great frustration with the approach taken by the DSM. As noted above, descriptive classification systems define disorders in terms of syndromes that reflected years of clinical observations regarding common cross-sectional symptom presentations and longitudinal courses. The presumption had been that, as in general medicine, the phenomenon of symptom

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covariation could be explained by a common underlying etiology and pathophysiology. Although based largely on expert consensus, there was a general understanding that the DSM-III syndromal definitions would be continually revised in subsequent editions of the DSM with the goal of improving diagnostic validity based on new research findings, ultimately culminating in the identification of the underlying disease processes. The process by which the validity of the DSM and ICD diagnostic categories would be iteratively refined was proposed by Robins and Guze in 1970 and entailed using five types of validity studies: studies that established clinical description, laboratory studies, studies that established differentiation from other disorders, follow-up studies, and family studies (Robins and Guze 1970). Such studies relied on the assumption that there was a one-to-one mapping between the syndromes in the DSM and ICD and their underlying disease processes.

Unfortunately, in the more than three decades that have elapsed since the publication of DSM-III, it has become increasingly clear that the DSM and ICD categories are not “carving nature at the joints” and do not represent true disease entities (Hyman 2010). Despite the discovery of many promising candidates over the years, not one single laboratory marker has been shown to be diagnostically useful for making any DSM diagnosis (Charney et al. 2002). Epidemiological and clinical studies have demonstrated extremely high rates of comorbidities among the disorders, undermining hypotheses that the DSM-defined syndromes have distinct etiologies. Twin studies have also contradicted many of DSM’s assumptions that separate syndromes which have a distinct underlying genetic basis; evidence suggests, for example, that major depressive disorder and generalized anxiety disorder have the same genetic risk factors (Kendler 1996).

To reflect the observed symptomatic heterogeneity which characterizes the way patients present to clinical care, virtually all of the categories in DSM and ICD are defined polythetically; the diagnosis is made by choosing among different combinations of specific operationalized criteria defining a disorder (e.g., five out of a list of nine symptoms are required for a diagnosis of a major depressive episode). While clinically sensible, this approach has led to tremendous diagnostic heterogeneity, both in terms of symptomatic presentation (i.e., two patients with the same diagnostic label may have only one or two clinical features in common) and prediction of treatment response and prognosis. For example, the prognostic power of the diagnosis of schizophrenia for a specific patient is limited by the wide range of observed functional outcomes associated, which can range from relatively superior functioning (e.g., John Nash, winner of a Nobel Prize in mathematics) to extremely poor functioning (e.g., an individual who requires lifelong institutionalization). This heterogeneity is almost certainly a consequence of the fact that the DSM and ICD diagnostic labels, like schizophrenia, include a number of distinct diseases with different etiologies and pathophysiological mechanisms under a single diagnostic rubric.

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These numerous limitations with the DSM and ICD descriptive approach sparked aspirations that DSM-5 would be able to abandon the DSM-IV descriptive approach and replace it with an etiologically and pathophysiologically based diagnostic system. Consequently, in 1999, the American Psychiatric Association initiated a DSM-V¹ research planning process, under joint sponsorship with NIMH, to focus on establishing a research agenda that would allow the DSM to move beyond the descriptive approach. Indeed, a stated goal of the DSM-V Research Agenda was “to transcend the limitations of the current DSM paradigm and to encourage a research agenda that goes beyond our current ways of thinking” (Kupfer et al. 2002:xix), with the ultimate goal of adopting an “etiologically and pathophysiologically based diagnostic system” (Charney et al. 2002:35).

The hope that neurobiological findings could play an important role in the development of the DSM-5 definition of disorders is exemplified by the inclusion within most of the DSM-V research planning conferences of at least one presentation (if not several) that explored whether neurobiological or genetic findings might be incorporated into the DSM-V diagnostic criteria. For example, The Stress-Induced and Fear Circuitry Disorders Conference included a presentation titled “The role of neurochemical and neuroendocrine markers of fear in the classification of anxiety disorders” (Andrews et al. 2009). In every case, however, the presentations concluded that the diagnostic utility of such tests remains too limited to be of use in making a psychiatric diagnosis in an individual patient. Indeed, Hyman, in a 2007 commentary that raised the question of whether neuroscience can be integrated into the descriptive DSM, concluded that “it is probably premature to bring neurobiology into the classification of mental disorders that will form the core of DSM-V” (Hyman 2007:731).

Ultimately, the quest to make DSM-5 more reflective of our current understanding of neuroscience and genetics is only evident in changes made to the DSM-5 “metastructure” (i.e., the grouping of diagnostic categories in the classification). In DSM-IV, diagnostic groupings were largely based on superficial descriptive symptomatology, with disorders sharing common presenting symptoms included in the same diagnostic grouping. For example, in DSM-IV the anxiety disorders grouping included panic disorder, the phobias, generalized anxiety disorder, OCD, and PTSD, reflecting the fact that patients with these disorders typically present with anxiety. Although not enough is known about the underlying causes of mental disorders to base their definitions on etiology and pathophysiology, enough is known about the underlying neurocircuitry, familial inheritance, risk factors, comorbidity patterns, and treatment response of OCD and PTSD to move them into their own separate groupings:

¹ The designation of the revised edition changed from DSM-V to DSM-5 during the revision process to accommodate future plans for the implementation of a continuous revision model, so that the next edition could be called DSM-5.1.

obsessive-compulsive and related disorders; trauma and stressor-related disorders. The entire structure of the DSM-5 classification was thus reorganized along these lines, grouping disorders together that share putative common underlying factors (e.g., internalizing versus externalizing) and underlying vulnerabilities.

Categorical versus Dimensional

Another long running debate in nosology is whether psychiatric illness is best conceptualized as categorical versus dimensional constructs. Classification systems such as DSM and ICD define disorders categorically; that is, diagnostic definitions are provided that indicate whether an individual's clinical presentation either meets, or does not meet, the definitional requirements for a particular disorder. This method of classification is similar to what is used in the rest of medicine (i.e., a patient either has or does not have pneumonia, mitral valve prolapse, etc.). This tendency to define illnesses in terms of categories undoubtedly reflects basic human thought processes, embodied by the use of nouns in everyday speech to indicate categories of "things" (e.g., chairs, tables, dogs, cats).

In principle, however, variation in symptomatology can be represented by a set of dimensions rather than by categories. Take blood pressure, for example, which is measured along a continuum from low to high. It only becomes a categorical construct when the diagnostic label "hypertension" is applied to indicate that a patient has a significant elevation in blood pressure above a defined cut-off point that puts him or her at risk for developing serious illness in the future.

Dimensional approaches to representing psychiatric symptomatology have been proposed as well. For example, Wittenborn, Holzberg, and Simon (1953) developed a multidimensional representation of the phenomena of psychotic illness over sixty years ago, and since then others have developed dimensional models to portray the symptomatology of depressive and anxiety disorders, schizophrenia, personality disorders, and even the entire range of psychopathology (Mineka et al. 1998; Peralta and Cuesta 2000; Peralta et al. 2002; Clark 2005; Krueger et al. 2005; Watson 2005). While a categorical approach to psychiatric classification has important heuristic appeal, it may not represent the true state of things. Implicit in the categorical approach is an assumption that mental disorders are discrete entities, separated from one another, and from normality, either by recognizably distinct combinations of symptoms or by demonstrably distinct etiologies. While this has been shown to be the case for a small number of conditions (e.g., Down syndrome, fragile X syndrome, phenylketonuria, Alzheimer and Huntington diseases, and Jacob–Creutzfeldt disease), there is little evidence supporting the applicability of this model for most other psychiatric disorders. Indeed, in the last 35 years, the validity of the categorical approach has been increasingly questioned as evidence has

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accumulated that so-called categorical disorders, like major depressive disorder and anxiety disorders as well as schizophrenia and bipolar disorder, seem to merge imperceptibly both into one another and into normality with no demonstrable natural boundaries (Goldberg 1996; Widiger and Samuel 2005).

Dimensional approaches have some clear advantages. First, the commonly observed phenomena of excessive comorbidity (i.e., an individual receiving multiple simultaneous DSM diagnoses) is arguably a direct result of having a categorical system with more than 250 narrowly defined discrete categories. (First 2005b). A dimensional representation might characterize an individual's psychopathology by indicating the extent of his or her psychiatric symptomatology across a number of dimensions, virtually eliminating artifactual comorbidity. For example, consider an individual who presents with depression, anxiety, and social avoidance. Using the DSM-5 categorical system, criteria might be met for three diagnoses (i.e., major depressive disorder, social anxiety disorder, and generalized anxiety disorder) and thus give the appearance that the individual has three separate diagnosis. A dimensional approach, on the other hand, would simply indicate that the person has elevated values on the depression, anxiety, and social avoidance dimensions. Another advantage of the dimensional approach is that it avoids setting particular (and inevitably arbitrary) thresholds for distinguishing between pathology and normality. Thus, rather than categorically saying that an individual has major depressive disorder only if the threshold of five depressive symptoms is met or exceeded, a dimensional approach might simply say that the person is high on the depression dimension.

Dimensional approaches have other advantages as well. Research studies using dimensional scales as end points have much greater power to detect differences in groups than do studies which focus on changes in dichotomous categories (Cohen 1983; Kraemer et al. 2004). Furthermore, continuous dimensions more closely model the lack of sharp boundaries between disorders, as well as between disorder and normality, and can be developed using empirical methods that would facilitate research into the underlying etiology and pathophysiology of mental disorders (Goldberg 1996; Smoller and Tsuang 1998). Finally, dimensions can be helpful in indicating the severity of the disorder, which is relevant to making treatment decisions. For many disorders in the DSM-5, the range of appropriate treatments is related to the severity of the disorder (Andrews et al. 2007). For example, although either cognitive therapy alone or antidepressant medication alone are both reasonable options for the treatment of mild to moderate major depressive disorder, cognitive therapy by itself would not be an appropriate option for the treatment of severe forms of major depressive disorder. In such cases, treatment options would include one or more antidepressant medications or electroconvulsive therapy.

There are significant practical problems, however, with the use of a purely dimensional approach to classification (First 2005a). First, clinicians are accustomed to thinking in terms of diagnostic categories, and the existing

knowledge base about the presentation, etiology, epidemiology, course, prognosis, and treatment is based on these categories. Furthermore, decisions about the management of individual patients (e.g., whether to treat, what type of treatment) are also much easier to make if the patient is thought of as having a particular disorder (with its associated prognostic and treatment implications) rather than as a profile of scores across a series of dimensions. Finally, although clinicians certainly appreciate the dimensional nature of psychiatric disorders in terms of their variable severity, the value of dimensions in terms of communicating information from one clinician to another is likely to be quite limited. As Phillips noted in his review of “The Conceptual Evolution of DSM-5” (Regier et al. 2011):

[O]ne clinician communicates with another by saying something like, this is a bad case of depression and so far intractable to treatment, not by saying, on dimensional scales x , y , and z the patient has such and such scores (Phillips 2013:829).

Indeed, one of the greatest challenges for psychiatric classification is to craft dimensional approaches that have sufficient clinical utility to warrant the increased complexity (First and Westen 2007). In recognition of the limitations of the categorical aspects of the DSM-IV, a major emphasis of the DSM-5 revision process has been on the introduction of a dimensional component to DSM-5. During the revision process, the DSM-5 workgroups were asked to develop severity measures (clinician-administered or self-report) or to suggest existing severity measures for each DSM-5 disorder (First 2013). In addition, a disability measure, the World Health Organization Disability Assessment Schedule (WHO 2012), and a modification and enhancement of the psychiatric symptom measures from the National Institute of Health’s Patient Reported Outcome Measurement Information System initiative (Irwin et al. 2010; Pilskonis et al. 2011) were proposed for inclusion in DSM-5 and tested in the DSM-5 field trials. However, because of concerns about their clinical utility, reliability, and validity, the published DSM-5 ended up relegating all of these dimensional measures to Section III, the section for proposed elements of the DSM for which “the scientific evidence is not yet available to support widespread clinical use” (APA 2013:24).

An Alternative to the Descriptive Categorical Approach: The Research Domain Criteria Project

When syndromal definitions for the various mental disorders were first introduced into DSM-III in 1980, it was widely assumed that it was only a matter of time before researchers, using the DSM definitions to select patient populations for study, would elucidate their underlying neurobiological mechanisms and pathophysiology. Although the lack of progress in understanding

the causes of mental disorders stems mostly from the fact that the problem of trying to understand the underlying etiology and pathophysiology of mental disorders has turned out to be much more complex and challenging than originally anticipated, it is likely that the categorical descriptive DSM system itself is at least partly to blame. Scientists attempting to discover the neurobiological or genetic underpinnings of psychiatric illnesses have all too often treated the man-made psychiatric constructs in DSM as if they were “natural kinds,” looking for the gene for schizophrenia or the neurocircuitry underlying major depression as if they were real disease entities (Hyman 2003, 2007, 2010). Perhaps whatever specificity there is between biological findings and behavioral correlates is being obscured by employing the DSM categories as if they were phenotypes, rather than focusing on more fundamental behavioral elements that cut across the various extant DSM categories.

The intent of the NIMH-sponsored RDoC project is to establish “a framework for creating research classifications that reflect functional dimensions stemming from translational research on genes, circuits, and behavior” (Insel and Cuthbert 2009:989). The RDoC project is a direct consequence of one of the aims of the NIMH 2008 strategic plan; namely, to “develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures” (National Institute of Mental Health 2008). Using DSM categories as the basis for selecting research subjects invites researchers to seek a one-to-one relationship between putative mechanisms and clinically defined disorder categories. The goal of the RDoC project, instead, is to shift researchers toward a focus on dysregulated neurobiological systems as the organizing principle for selecting study populations.

The initial stage of the RDoC project is to specify basic dimensions of psychological functioning and their implementing brain circuits, which have been the focus of neuroscience research over the past several decades.

Since the ultimate goal of the RDoC project is to link dysfunctions in neurocircuitry with clinically relevant psychiatric conditions, a priority in the selection of domains is that they can be related to problem behaviors found in the symptom lists of conventional disorder categories (Sanislow et al. 2010). The RDoC matrix² focuses on five major domains of functioning, each containing multiple, more specific constructs: *negative valence systems*, which includes constructs for fear, distress, and aggression; *positive valence*, which includes reward seeking and learning and habit formation constructs; *cognitive systems*, which includes constructs for attention, perception, working memory/executive function, long-term memory and cognitive control; *systems for social processes*, including separation fear, facial expression regulation, behavioral inhibition, and emotional regulation constructs; and *arousal/regulatory systems*, which include systems involved in sleep and wakefulness.

² <http://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml> (accessed July 8, 2016).

It is important to understand that the RDoC project is not intended to function as a diagnostic classification system in the way that DSM and ICD do. Unlike the DSM, ICD, and other medical classifications, which are designed to exhaustively describe and delineate the different ways that psychiatric patients might present symptomatically in terms of conceptually high-level concepts such as disease or disorder, the RDoC project is primarily a research framework to assist researchers in relating the fundamental domains of behavioral functioning to their underlying neurobiological components. As such, for each of the constructs in the RDoC matrix, the current state-of-the-art measurements/elements at several different units of analysis are to be listed, including genes, molecules, cells, circuits, behavior and self-report (Cuthbert and Insel 2010). Thus, in concrete terms, the RDoC framework is being implemented as a matrix, with the constructs forming the rows and the various units of analysis forming the columns.

The RDoC approach represents a true paradigm shift in the classification of mental disorders. It moves away from defining disorders based on descriptive phenomenology and focuses instead on disruptions in neural circuitry as the fundamental classificatory principle. Whether RDoC ultimately bears fruit in terms of eventually improving clinicians' ability to predict prognosis or treatment response will depend on how well this new approach performs for research (Insel et al. 2010), something that will take years or even decades to realize fully.

Conclusion

From both a clinical and research perspective, the most useful nosologies in medicine are constructed around an understanding of the underlying disease mechanisms. Those areas of medicine in which the disease mechanisms remain unknown, like psychiatry, must necessarily define disorders according to symptomatic presentation. It should be noted that despite the shortcomings of the current DSM and ICD categorical descriptive systems, the major disorders which make up these classifications (e.g., schizophrenia, bipolar disorder, autism, major depressive disorder, and obsessive-compulsive disorder) pick out highly replicable features of psychopathology (Hyman 2010). Many disorders have been shown, for example, to have a high degree of familial aggregation (Kendler et al. 1997), with symptom clusters cohering both within and across generations. Twin studies (Kendler 2001) and adoption studies (Kety et al. 1971) suggest that much of this familial aggregation is explained by heredity. If DSM-defined major disorders were simply arbitrarily defined constructs created by expert consensus, the high levels of familial aggregation and heritability would be difficult to explain.

Ultimately, an improved understanding of the underlying disease mechanisms of mental disorders will result in the development of a classification

system that will be more valid and more useful. Hopefully, paradigm-shifting research frameworks, such as the RDoC project, will push the research effort onto the right track and yield significant breakthroughs in our understanding of disease mechanisms. In the meantime, incremental efforts to improve the current categorical descriptive systems, as is being done with the DSM and ICD, should help refine these classifications by incorporating clinically relevant empirical data.