

potheses whose confirmation will be based on RDoC matrices?

And the RDoC approach, if understood in this way, also raises the question of the best way to satisfy Jaspers' requirement that we should not only describe but also try to understand and interpret the meaning of the components of psychopathology in their social, biological and psychological context. The study of dimensions and their measurement are only the beginning of the process of approaching the creation of meaningful prototypes corresponding to individuals in their context. It is to be hoped that the RDoC project has foreseen a way to do this, starting with it in parallel to the acquisition of data about the research domains.

Another issue that should be kept in mind is the emphasis on the collection of data concerning the domains that have been defined on the basis of a consensus of a limited number of experts who met in 2009. The consensus which they reached directed the work of five workshops that followed the first meeting in order to define the dimensions to be included in the domain, provide definitions of these dimensions and specify elements that could be used to characterize each dimension. It is possible that another group of experts would have selected another set of domains which would have oriented the research into another direction. This is particularly true for the domain of "systems for social processes" but also holds, possibly to a lesser degree, for the domains of "positive valence systems" and "negative valence systems". The workshop participants also "nominated and vet-

ted" the various classes of measurement. There is nothing basically wrong with this approach, unless working along those lines uses all the available resources and the approach becomes the dominant theme for the National Institute of Mental Health, which has been such a very important player in the governance of research and its orientation not only in the USA but also globally. Another group might perhaps choose a different set of domains, containing a different set of dimensions, possibly more helpful: there should be room and support for such a project. It will therefore be important to remember that the basic premise of the RDoC project is the consensus of a relatively small group of experts about the area that should be explored.

A third important issue which is not explicitly addressed in the fine paper that Cuthbert has written is that of measuring the development of the units of analysis over time. Physiological indicators related to "acute threat" and any other dimension included in the RDoC change over time, and the longitudinal profile of this change might be just as revealing as its correlation with other factors and characteristics of the individual. To capture the impact of these factors, it would probably be useful to construct a three-dimensional matrix involving domains, manners of investigation, and age, gender and other characteristics of the persons whose dimensions are being measured, all of this along the axis of time and longitudinal development of the phenomenon.

The same argument applies, in a slightly different form, to the decision

to avoid funding research that will be based on DSM or ICD diagnostic categories. Research using categories created on the basis of observations of behavior and the development of the disorder over time is as justified as other approaches. Diagnostic categories have never been more than hypotheses about the nature of the disorder that medical practitioners meet. These hypotheses should continue to be explored and their definitions should continue changing over time and in the light of information about the reaction of the disorders to treatment, about long-term outcome, about brain structures and functions recorded by modern means.

In summary, we should congratulate the National Institute of Mental Health and thank it for deciding to fund work proceeding along a well-defined new avenue of research, hoping at the same time that this departure will not block the funding of alternative ways of examining human behavior and its basis in health and in disease.

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# An integrative approach to psychiatric diagnosis and research

**DAN J. STEIN**

Department of Psychiatry, University of Cape Town, Cape Town, South Africa

Much attention has been paid to revisions of psychiatric classification systems. Nevertheless, there remains sig-

nificant dissatisfaction with the nosology. From a neuroscience perspective, diagnostic criteria have failed to incorporate neurobiological data, and a focus on "circuit-based behavioral dimensions" (1) will improve diagnosis. From a more critical perspective, given

that psychiatric disorders do not represent valid disease entities (1), diagnosis merely medicalizes problems in living.

These specific debates echo larger debates about classification in medicine, in which many emphasize notions of disease, arguing that clinicians must

be scientists who understand physiology, while others emphasize the experience of illness, stating that clinicians must be humanists who understand suffering (2). An integrative medicine and psychiatry arguably recognizes each of these aspects of being a good diagnostician and researcher (3,4).

From an integrative perspective, ongoing work on nosological systems is needed to optimize diagnostic validity and utility. To the extent that the RDoC framework leads to research that allows such progress, it should be supported. However, I worry that many DSM-5 and ICD-11 critics may have unduly high expectations of diagnostic systems. Insofar as the RDoC framework sets unrealistic goals for nosology, caution is needed. Along these lines, I would emphasize the following points.

First, a clear goal of medical and psychiatric classification is clinical utility, which is only partly related to underlying pathophysiology. In medicine, the diagnosis of a syndrome, such as cardiac failure, may provide little information about precise etiology, but nevertheless may help guide treatment (5). In psychiatry, many entities are syndromic. While syndromes may have multiple causes, blurry boundaries, and absent biomarkers, they also are clinically useful.

It may be counterargued that much of medicine focuses on specific etiologically-based entities, e.g., viral pneumonia. Psychiatry too has specific diseases, such as psychosis due to neurosyphilis. But these exceptions prove the rule; many diagnoses in medicine and psychiatry reflect the fact that patients present with variegated symptoms underpinned by multiple mechanisms (6). Some cases of hypertension, headache, and depression are due to single gene variants or other circumscribed pathophysiologies; the majority reflect multiple influences.

Second, given that multiple mechanisms play a role in producing psychiatric signs and symptoms, foregrounding any particular diagnostic validator, such as “circuit-based behavioral dimensions”, has both pros and cons. Science has progressed from Hippocrates’s account of the “humors” to theories

of the neurocircuitry basis of positive and negative valence, but it is possible that, a century from now, circuitry concepts will be considered rudimentary. On the other hand, the construct of depression, which is based on several other validators, may continue to resonate with eons of clinical descriptions.

DSM-5 distinguishes between anxiety and obsessive-compulsive related disorders partly on the basis of the different neurocircuitry underpinning these conditions. But there are also strong arguments for lumping these disorders on the basis of considerations such as response to serotonin reuptake inhibitors and cognitive-behavioral treatments (7). We need to accept that diagnostic systems cannot “carve nature at her joints”. Rather, facts and values need to be continually re-assessed, to try to optimize classifications.

Third, given the multiple mechanisms underlying psychiatric complaints, and the many considerations relevant to treatment decisions, we should be cautious in our expectation that diagnostic criteria or thresholds will ultimately be based on behavioral dimensions or biological markers. Simple assessments, such as blood pressure measurement or mental status examination in medicine and psychiatry, can provide important information. Still, such information is partial. In medicine and psychiatry, deciding on whether and how to intervene necessarily requires a complex assessment of a range of factors, including understanding the function of symptoms, their social context, and the risks versus benefits of treatment.

One set of factors sometimes neglected by critics of nosology emerges from a public health perspective. Psychiatric classifications focus on individual disorders, where underlying “endophenotypes” may be relevant. However, it may be as important to address “exophenotypes”, i.e., societal phenomena, such as interpersonal violence, that crucially contribute to the burden of disease (8). Furthermore, decisions about thresholds for psychiatric intervention may need to include not only facts about underlying neurobiological mechanisms, but also consid-

erations such as the cost-effectiveness of particular interventions.

Given that the RDoC framework encourages research on a broad range of phenomena and mechanisms, it is hard to be overly critical. By adopting a translational approach that encompasses different levels of investigation, RDoC may well contribute to advancing personalized medicine. Still, we need to be cautious of medical strawmen, such as the physician who relies solely on laboratory tests to determine diagnoses, or the public health practitioner who eradicates pathogens using simple interventions such as hand-washing. No matter how many dollars we pour into behavioral neuroscience, we may have to accept that there are few diagnostic biomarkers for psychiatric disorders, and few mosquito nets to combat them (9).

Indeed, given the complexity of medicine, psychiatry provides a number of approaches worth emulating. Thus, a physician faced with a patient with headache should be able, after a careful history and examination, to diagnose a particular headache syndrome (indeed, headache classification takes a DSM-like approach (10)). Then, based on neuroscience knowledge, as well as a range of other considerations, one or another intervention may be chosen. Similarly, a physician faced with a complex public health problem, such as substance abuse, knows that the causes are complex, that a range of responses are needed (and that, as in much of psychiatry, there is no mosquito net).

For the foreseeable future, an integrative approach to psychiatric diagnosis and research ought to incorporate DSM/ICD, RDoC, and a broad range of other constructs.

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# Preserving the clinician-researcher interface in the age of RDoC: the continuing need for DSM-5/ICD-11 characterization of study populations

**MICHAEL B. FIRST**

Columbia University and New York State Psychiatric Institute, New York, NY, USA

For the past 35 years, clinicians and researchers in the United States have utilized essentially the same diagnostic system for the purposes of describing patients' symptomatic presentations.

Having common diagnostic definitions for both research and clinical practice has had a number of advantages. It has made possible the transfer of information between the ever growing clinical research literature and clinical practice. Because the same criteria are used for diagnosing patients in both settings, it is easier to translate findings of a research paper to the diagnosis and treatment of the next patient that one might see in an office practice. This approach also ensures greater clarity of communication within and among areas of psychiatric practice. Most importantly, this approach facilitates the necessary dialogue and mutual influence between clinicians and researchers.

Recognizing the value of operationalized diagnostic criteria for facilitating communication among clinicians and researchers and improving the reliability of diagnostic assessment, in 1980 the American Psychiatric Association adopted diagnostic criteria as the centerpiece of the DSM-III classification. The expectation was that, in addition to improving clinical assessment, they

would be widely adopted by the research community.

Subsequently, most of the psychiatric research literature since DSM-III has been keyed to DSM categories, thus facilitating its application to clinical practice. The hope was that iterative refinement of the diagnostic criteria sets through successive validation studies would eventually elucidate their underlying etiologies (1,2). However, despite years of intensive investigation, researchers using the current DSM paradigm have "failed to identify a single neurobiological phenotypic marker or gene that is useful in making a diagnosis of a major psychiatric disorder" (3, p. 33). While much of this lack of success reflects the enormous complexity and relative inaccessibility of the human brain (4), undoubtedly a major contributor is the fact that the DSM categories are a poor mirror of nature.

Although it has become increasingly evident to researchers over the past 20 years that the DSM categories do not represent valid disease entities, the entrenched hegemony of the DSM system and the conservative nature of review processes has led to researchers being pressured to use the DSM-IV categories "in order to satisfy most grant-making bodies, journal reviewers and editors, and organizers of scientific meetings" (5, p. 156).

One of the main goals of the National Institute of Mental Health's RDoC project is to release the research community

from the shackles of the DSM/ICD categorical system by providing an alternative framework for conducting research in terms of fundamental circuit-based behavior dimensions. Given its role as the premier governmental body funding psychiatric research in the United States, the NIMH is uniquely positioned to incentivize researchers to adopt such a framework and thus it is likely that most NIMH-funded research over the next decade will adopt the RDoC framework.

While this has the potential to be a positive step that facilitates the development of the requisite research literature "to attain groundbreaking nosological approaches in the future that are based upon genetics, other aspects of neurobiology, and behavioral science" (6), it has the potential drawback of impeding clinicians' ability to make clinical sense of such research and apply it to their patients, whose clinical presentations will likely continue for the foreseeable future to be thought of in terms of the DSM/ICD-type categories.

Indeed, one of the central thrusts of RDoC is to discourage the use of the DSM/ICD syndromal constructs by researchers in either research design or subject selection, except insofar as is necessary during the research community's "transition" from the DSM/ICD to RDoC. As noted by Cuthbert, many if not most of the symptoms that form the basis for DSM psychiatric assessment and treatment do not appear in the