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DSM-5 and RDoC: progress in psychiatry research?

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Abstract

Neuroscience studies into psychiatric disorders generally rely on disease definitions that are based on the influential *Diagnostic and Statistical Manual of Mental Disorders* (DSM), the fifth edition of which (DSM-5) was released earlier this year. Designed as a purely diagnostic tool, the DSM considers different disorders as distinct entities. However, boundaries between disorders are often not as strict as the DSM suggests. To provide an alternative framework for research into psychiatric disorders, the US National Institute of Mental Health (NIMH) has recently introduced its Research Domain Criteria (RDoC) project. In the RDoC, five 'domains' each reflect a brain system in which functioning is impaired, to different degrees, in different psychiatric conditions. *Nature Reviews Neuroscience* asked six leading investigators for their thoughts on how DSM-5 and the RDoC will influence neuroscience research into psychiatric disorders.

Competing interests statement

The authors declare competing financial interests: see Web version for details.

Have neuroscience and genetic findings contributed to DSM-5 (the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders)?

B. J. Casey and Francis S. Lee

DSM-5 is a revision from the previous edition of the DSM, which was published in 1994. Despite advances in neuroscience and genetic research during the past two decades, there are still few genetic or other biomarkers that reliably guide the diagnosis of psychiatric disorders. Thus, a DSM-informed psychiatric diagnosis is based mainly on self-reports of feelings and experiences by patients with diverse backgrounds and on clinicians' understanding of psychiatric terms or observation of behaviour. Such subjective impressions of complex phenomena can lead to diagnostic inconsistencies across patients and practitioners. Moreover, diverse and sometimes contradictory phenomena are included in some DSM-5 diagnoses. For example, a diagnosis of major depressive disorder consistently requires depressed mood or loss of pleasure to be present, but some combination of four of seven other symptoms are required as well, and these can include both increases and decreases in sleep or appetite. This means that studies into major depression (for example, genetic studies) often involve subjects with different clinical presentations of the disorder. The phenomenological heterogeneity that characterizes the DSM means that a diagnostic category likely encompasses a large number of biologically distinct entities. This makes it difficult to link a specific disorder to a specific circuit or gene, and in this context, neuroscience and genetic findings have had a limited impact on the revised manual. The one notable exception is a change in the section on sleep–wake disorders, where the definition and diagnostic criteria of narcolepsy now include low cerebrospinal fluid hypocretin (also known as orexin) levels. Narcolepsy is thereby distinguished from other forms of hypersomnolence — a direct result of a better understanding of the molecular mechanisms underlying this disorder.

Nick Craddock

Unfortunately, they have had very little impact. Those developing DSM-5 had originally hoped that neuroscience and genetics would shape developments. The reality has not lived up to the hope. The problem is that the scientific knowledge has not yet advanced enough to make the latter realistic.

Steven E. Hyman

Neuroscience and genetics have contributed little to DSM-5 for three main reasons. First, despite significant progress in neuroscience and genetics, information about psychiatric disorders remains fragmentary and early — not ready for prime time; second, DSM-5 is central to clinical practice, insurance reimbursement, determinations of disability and service eligibility, among others. Thus, stability in diagnostic categorization has great value, and significant changes require substantial validation. Third, the DSM system has itself impeded progress in the areas of neuroscience relevant to psychiatric disorders. If to obtain a grant or to publish a paper, one has to select study populations according to a system that is a poor mirror of nature, it is very hard to advance our understanding of psychiatric disorders.

Kerry J. Ressler

I think that the primary conflict in the creation of DSM-5 was the wish to reflect (and demonstrate) progress in our understanding of the biological underpinnings of mental illness pitted against the reality that the brain–mind–behaviour problem is, of course, much more complicated than the field had hoped in the 1990s — during the heyday of the Human Genome Project and the Decade of the Brain — when the next DSM was being planned. Unfortunately, owing to the time pressure to move forward with DSM-5, combined with relatively limited progress with mechanistic biomarkers to date, neuroscience and genetics have contributed very little to the diagnostic framework. Notably, such findings are considered in the text discussions that accompany the DSM-5 framework, which mention that DSM-5 could be updated as new information from neuroscience or genetics studies becomes available, along with recent reviews of the work[1,2].

Will the changes in DSM-5 influence research into the aetiology and pathophysiology of disorders?

B.J.C. and F.S.L

By defining the clinical phenomena that comprise a disorder, DSM-5 sets the benchmark for biomarker discovery and further refinement of diagnostic criteria in clinical studies of the aetiology and pathophysiology of disorders. In this sense, DSM-5 makes further advances in refining the clinical phenomena but is not a qualitative advance from DSM-III and DSM-IV.

N.C

As a clinician and researcher, it is important that I state very clearly that we do need a diagnostic system for psychiatric disorders — even if it is not perfect — to serve as a provisional, agreed method for describing, communicating and making sense of previous experience and research. We must always be aware of its limitations and be ready to move towards a better system when the evidence shows that this will be beneficial. For DSM-5, my view has always been that it is the wrong project at the wrong time. I do not see it as a helpful development for research or for clinical care. It is tinkering at the edges. What is needed for psychiatry is a game-changer: a truly new approach to diagnostic classification that better reflects the underlying functions and dysfunctions of the brain and that, hence, maps more readily onto the experiences of patients. DSM-5 does not provide that. Rather, it exemplifies the shortcomings of the current, descriptive method and highlights the need for different approaches in the future.

S.E.H

I see no substantial change from DSM-IV. It is critical that scientists are freed from the epistemic blinders and administrative strictures (for example, in grant review) that are imposed by widely accepted but fictive diagnostic categories such as those in the DSM. The price for freedom from the DSM — pending the elaboration of new frameworks such as the Research Domain Criteria (RDoC) project — is that scientists will have to describe the nature and logic of their sampling criteria with great precision and clarity so that their work is replicable.

K.J.R

It is not clear to me that the new DSM-5 nosology will markedly differ from DSM-IV in its influence on aetiology and pathophysiology research. There are a few exceptions where further division of symptom clusters in DSM-5 (for example, the separation between avoidance symptoms versus negative cognition symptoms in post-traumatic stress disorder (PTSD)) may help to clarify research questions. The primary influence, again, will remain in the 'small print' of the discussion for the different diagnostic divisions but not in the framework outline per se.

How about the discovery and testing of potential new treatments?

B.J.C. and F.S.L

DSM-5, as well as the other major categorical classification system (Mental and Behavioural Disorders section of the International Classification of Disease (ICD)), are classification systems that were designed primarily for clinical purposes, specifically to provide a common language in the diagnosis and treatment of patients with psychiatric disorders. Future revisions of these classifications will reflect advances in research into the aetiology of these disorders, as in the case of the diagnosis of narcolepsy in DSM-5, and may include specific tests for a diagnosis. There have already been some significant advances in the treatment of psychiatric disorders that resulted from research using categorical classification systems. For example, on the basis of basic neuroscience findings — specifically, functional neuroimaging of cortical connectivity in patients with major depression — Mayberg has developed and tested deep brain stimulation of the subcallosal cingulate region (Brodmann area 25) as a treatment for patients with treatment-resistant depression.

N.C

I see the issue of new treatments as being intimately related to, and dependent upon, our understanding of aetiology and pathogenesis. So, my answer to this question is the same as my answer to the previous question.

S.E.H

Attempts to model the cognitive and behavioural symptoms listed in DSM-IV and now DSM-5 have been problematic for preclinical research. There has been a tacit assumption, even with genetic mouse models constructed with penetrant human disease genes, that there is enough evolutionary conservation for the resulting mouse behaviour to be reminiscent of human symptoms. However, as psychiatric disease often affects evolutionarily more recent circuits (for example, those involving lateral prefrontal cortex), modelling DSM-5 symptoms in animals becomes far less relevant. I hope to see genetic disease models (which will be really challenging for polygenic disorders) in human neurons *in vitro* as well as animal models that focus on the molecular, cellular and developmental effects of a disease mutation and that use behaviour (in a way that is agnostic to the DSM) only as one among many readouts.

K.J.R

I think most will agree that DSM-5 is incremental, and not transformative, compared to prior versions. Its reclassification of some diagnoses (for example, obsessive-compulsive disorder and PTSD as separate from anxiety disorders) may lead to the consideration that the neural circuitries underlying these conditions are likely to be different from panic attacks or generalized anxiety. However, overall, it is not clear if any significant conceptual advances are made in DSM-5 that would change how a translational behavioural neuroscientist, neuroimager or neuropharmacologist would approach research questions.

Is the dimensional approach of the RDoC project more useful than the categorical approach of the DSM?

B.J.C. and F.S.L

The RDoC project is a very different classification system from the DSM and ICD that is intended not for diagnostics but mainly to facilitate the translation of basic neuroscience research findings to clinical diagnosis and treatment. The RDoC thus provides a complementary way of classifying mental illness — namely, on the basis of behavioural and neurobiological measures that are dimensional in nature — that is not intended to replace the DSM and ICD.

N.C

Yes, without any doubt. For research, it is absolutely essential that we use a broader approach to measurement of the clinical phenotype. Dimensions are useful because they help to capture the enormous complexity of higher brain functions that we encounter in psychiatric practice. It is, however, important to acknowledge that categories are immensely useful to facilitate communication and decision making in psychiatry. My expectation is that future psychiatric practice will use both dimensional and categorical diagnostic measurements.

Bruce N. Cuthbert

The US National Institute of Mental Health (NIMH) has endorsed dimensional approaches to psychiatric disorders through Strategy 1.4 of the 2008 NIMH Strategic Plan, which charges the Institute to: “develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures.” (REF. 3) Further, the dimensions in the RDoC do not simply represent levels of disorder severity, but rather are to encompass “the full range of variation, from normal to abnormal, among the fundamental components to improve understanding of what is typical versus pathological.” (REF. 3) This approach follows the current trend of regarding diseases as complex traits that are extremes on a spectrum of normal functioning (for example, diabetes), but it has other goals in addition. First, as more validated dimensional measures become available, it may be feasible to establish cut-off points for various levels of dysfunction that require different types of interventions. Further, the RDoC project could facilitate research into risk factors, as in the RDoC, subsyndromal levels of pathology (that is, potential disease risk factors) are quantified on the same scales as those used to quantify

different levels of defined (that is, syndromal) pathology. Finally, the availability of quantitative scales means that cutoff points for disease risk and various levels of disorder severity can be changed as data from ongoing clinical and epidemiological studies become available — as has been done for disorders such as hypertension.

S.E.H

Like essentially all heterogeneous, polygenic illnesses, psychiatric disorders are poorly captured as categories (which assume significant discontinuities between ‘well’ and ‘ill’ conditions and between any two disorders). DSM categories have the bizarre property of being both too broad (in the sense that they identify remarkably heterogeneous populations) and too narrow (in the sense that, given the large number of arbitrary DSM diagnostic silos, many if not most patients with a single DSM diagnosis actually qualify for two or more.) The RDoC project is clearly on the right track by emphasizing dimensions both within and across disorders. Indeed, the spectrum concept implemented for autism in DSM-5 (which begins to resemble the RDoC approach) may be the manual’s most important advance.

K.J.R

Yes, I believe that the RDoC approach will be more useful for bridging neuroscience and genetic approaches with behavioural neuroscience and human behavioural phenotypes[4]. That said, it has the opposite problem of the DSM conundrum — in that the neuroscientifically informed, and thus much more readily translatable, phenotypes in the RDoC do not clearly map onto the diagnostic clusters that the mental health disciplines have used for the better part of a century. Whether this transition can be made smoothly or whether it will require a schism of some sort remains to be seen.

How will the RDoC influence neuroscience research into psychiatric disorders?

B.J.C. and F.S.L

The basic strategy of clinical neuroscience research before the RDoC project has been to study patients with and without a psychiatric disorder, assess if and where they differ in brain and behaviour, and then try to understand the biology underlying these differences. A main way in which the RDoC project will influence neuroscience research is that rather than taking a diagnostic group and attempting to discover its underlying neurobiological basis, the RDoC approach uses our current understanding of behaviour–brain relationships as the starting point and relates these to clinical phenomenology. The RDoC project uses different levels or units of analysis (molecular, circuit, behaviour and symptom levels) to define constructs that are presumed to underlie core symptoms of mental disorders.

N.C

The RDoC project is an important development, and the US NIMH is to be congratulated on championing this approach. The move to use RDoC will force researchers to think differently. This is very welcome. However, it is important that researchers are not rigidly constrained in their methods or thinking by having to adopt just this one system — that

would merely recapitulate the problems associated with the dominance of the DSM in psychiatry over the past couple of decades. The key is that we need to use methods of measurement that map onto brain functions and dysfunctions as they occur in the human population. It is important to have one common set of measurements that everyone adopts, but it is desirable that we can accommodate and encourage richer phenotypic characterization and thinking.

B.N.C

The US NIMH has announced that it will be 're-orienting' its clinical research grants away from research based on DSM categories in favour of RDoC-based research. (Preclinical studies are not affected, although various aspects of the RDoC constructs, which are heavily based on basic research findings, may continue to interest this community.) This does not mean that the Institute will stop funding DSM-oriented research altogether — particularly for large-scale services research — but resources will increasingly be directed towards RDoC-based studies. However, this shift is not expected to alter the overall amounts of support that will be directed to clinical research. The US NIMH will give priority to applications that include primary diagnoses that cut across current categories. For example, the investigator might study all patients in a particular type of clinic (for example, a mood disorders clinic or a serious mental illness service) without having to exclude subjects who have a primary diagnosis outside the target category, a co-morbid disorder, a NOS (not otherwise specified) diagnosis or a *forme fruste* condition (that is, one that has some, but not all, of the criteria required for a diagnosis of a specific disorder) — so that the investigator can obtain a subject sample that provides appropriate variance along a dimension of interest. (Note that this approach may facilitate subject recruitment, as fewer subjects will be excluded.) Applications that use a single DSM category could also be candidates for funding if they examine a dimension or particular subgroups within the disorder, whereas applications with traditional designs — comparing one DSM category (treated as a unitary disease entity) to controls — will be given a lower priority. The hope is that investigators will be encouraged to think in terms of dimensions that align better with data from basic research studies on fundamental behavioural constructs and the neural systems that implement them; in turn, this perspective can open the door for more powerful translational studies — studies that integrate genetic risk architectures, patterns of neurodevelopment and their interaction with environmental factors to investigate how they result in various types of dysfunction (or resilience).

S.E.H

When I was Director of the US NIMH (from 1996 to 2001), I had feared that study section demands for DSM criteria in grant applications would, despite enhancing replicability, preordain some projects to be stillborn before they had even started. However, systems neuroscience, cognitive neuroscience and human genetics at the time seemed to be too nascent to anchor an entirely new diagnostic framework. I also worried (and still do) about separating scientific from clinical disease definitions. The RDoC project is in an early stage, but it exploits scientific advances of the past decade, will motivate new research and I hope will provide scientists with a far better framework for research.

K.J.R

If successful, the RDoC project does have the potential to catalyse a shift in our thinking and in our approaches to translational research. Historically, 'translation' to the clinic has mostly been given lip-service in basic research, because in psychiatric disorders in particular, it has been hard to translate findings to the clinic in a truly meaningful way. By starting on the relatively solid ground of well-established behavioural neural circuits and then working both top-down (to understand the molecular mechanisms of these circuits) and bottom-up (to identify human phenotypes and pathologies related to these circuits), real progress may be possible.

What is the best way forward for neuroscience research into psychiatric disorders?

B.J.C. and F.S.L

A vertically integrative approach in which basic neuroscientists coordinate studies with psychiatric researchers would be the best way to use the considerable advances in neuroscience to inform our understanding of psychiatric disorders. The framework of the RDoC project allows for such an integrative approach. For example, the effects of mutations found in humans in key candidate genes could be studied in rodents, and circuit-based and behavioural tests in rodents could then be optimized and validated for the human condition. This would allow translation of the rodent findings to humans with and without psychiatric disorders. Moreover, this integrative approach can build bridges between, on the one hand, the relevant but complex and imprecise phenomenology of human behaviour and, on the other hand, the solid findings from rodent neurobiology, which can be difficult to extrapolate to human behaviour and disease. We have recently used this approach to study a common human genetic single-nucleotide polymorphism (SNP) in the gene encoding brain-derived neurotrophic growth factor (BDNF). The effects of this common variant on extinction learning of fear memories were analysed in knock-in mice containing the human variant *BDNF* as well as in behavioural and functional imaging studies in humans with this variant gene[5]. These studies have begun to suggest that the presence of the *BDNF* SNP may be a potential biomarker for treatment response in patients with PTSD[6]. This work illustrates how a dimensional approach that uses different levels or units of analysis can provide insights into core symptoms of mental disorders and, more importantly, their treatment.

In addition, this integrative approach can be used to investigate the neurodevelopmental aspects of psychiatric disorders (many of which emerge in childhood or adolescence): the developmental trajectories and sensitive periods (restricted windows of development when the effects of particular experiences have a strong influence on brain and behaviour) of different brain systems are beginning to be better understood in rodents and humans, and the effects of experimental manipulations during different periods of brain development in rodents can inform our understanding of the developmental aetiology of psychiatric disorders. Such animal studies also allow for longitudinal investigations across the entire lifespan in much shorter periods of time than equivalent studies in humans, which would require years to decades.

N.C

In the past, progress has been impeded both by the lack of adequate neuroscientific tools and the complexity of clinical phenotypes of psychiatric disorders. Happily, we are moving rapidly towards appropriately powered twenty-first-century tools but have been struggling with what are essentially nineteenth-century diagnostic approaches. We need to combine the new tools with more open-minded approaches to the clinical phenotype. Some of the early findings from psychiatric genetics are giving new insights into the pathogenesis of mood and psychotic disorders (as well as autism and Alzheimer's disease), and are revealing unexpected biological relationships between disorders. Such findings will help to refine our understanding and our definitions of clinical phenotypes and to inform new approaches for treatment. While one must never underestimate the challenge ahead, I am very optimistic that we can deliver better outcomes for future generations of patients by being able to offer quicker, more accurate diagnoses coupled with more personalized and effective treatments.

B.N.C

The heterogeneity of individual disorders in the current (DSM) categories is widely cited as a major reason for the withdrawal of pharmaceutical companies from drug development for mental disorders. That is, if the mechanism of action of a given compound is relevant only to about half of the patients for a potential indication (that is, a given diagnostic category), it may be expected that this will result in many failed trials and an inconsistent pattern of trial outcomes. A goal of the RDoC project for treatment development is to identify particular symptoms that can be related strongly to dysfunction in a particular neurobehavioural system; this would provide a more homogeneous clinical target and thus a higher probability of success for a compound directed towards a particular mechanism or symptom that, notably, may occur in more than one disorder (for example, disrupted reward valuation, hallucinations of a particular type or excessive fear reactivity). In addition to pharmaceutical compounds, this same approach holds for other treatment modalities, such as psychosocial and behavioural interventions or devices (for example, transcranial magnetic stimulation). Obviously, many aspects will need to be worked out, but the US NIMH is already funding early trials in this mode that show the promise of the concept.

S.E.H

The genomic revolution has provided the first real molecular clues to the pathogenesis of genetically complex but highly heritable psychiatric disorders. As recently as 2007, the number of genetic loci that could be associated with certainty to schizophrenia was zero; the number is now greater than a hundred. Protein-damaging mutations have been confidently associated with rare monogenic forms of autism, and progress is being made on more common polygenic forms. An exciting challenge for neuroscience is to convert this emerging genetic information into useful biology: information about molecular pathways, identification of relevant cell types and circuits (which can be investigated with new technologies such as optogenetics) and an understanding of pathogenesis that can be exploited to develop treatments.

K.J.R

Scientific progress seems to most often occur when one aspect of a question is well grounded in solid, mechanistic, testable phenomena while uncharted territory is examined with quantitative tools. A potential argument for the delay in understanding psychiatric phenotypes is that even our best psychological tools to explain the phenomena were surrounded by black boxes and not grounded in biological mechanism. Therefore, I think our best hope is to work to understand neuroscience phenomena in model systems in which we can thoroughly dissect the structural, functional and biochemical aspects of a behavioural neural circuit, followed by translating this to the parallel circuit biology and behaviour in humans across the normal to 'pathological' spectrum.

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*Listed in alphabetical order.