OPINION

Can neuroscience be integrated into the DSM-V?

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Abstract | To date, the diagnosis of mental disorders has been based on clinical observation, specifically: the identification of symptoms that tend to cluster together, the timing of the symptoms' appearance, and their tendency to resolve, recur or become chronic. The Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Disease, the manuals that specify these diagnoses and the criteria for making them, are currently undergoing revision. It is thus timely to ask whether neuroscience has progressed to the point that the next editions of these manuals can usefully incorporate information about brain structure and function.

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), *fourth edition, text revision* (TR)[1] and the *International Classification of Disease* (ICD), *tenth edition*[2] (chapter V) are the two diagnostic systems that list the currently recognized mental disorders and the criteria for diagnosing them. The American Psychiatric Association produces the DSM, and the World Health Organization produces the ICD. The ICD covers all medical diagnosis, with chapter V being dedicated to mental and behavioural disorders; the DSM is concerned only with mental disorders. The DSM-IV and the ICD-10 share their intellectual underpinnings and are therefore similar, but they differ in some important details. The DSM system is used far more widely in research, and will thus be the focus of this Perspective, but similar considerations are relevant to the ICD. Both the DSM-IV and the ICD-10 are currently being revised, in processes that involve large numbers of researchers from around the world; it is thus an opportune time to ask whether neuroscience is ready for the DSM-V and the ICD-11, and whether they in turn are ready for neuroscience.

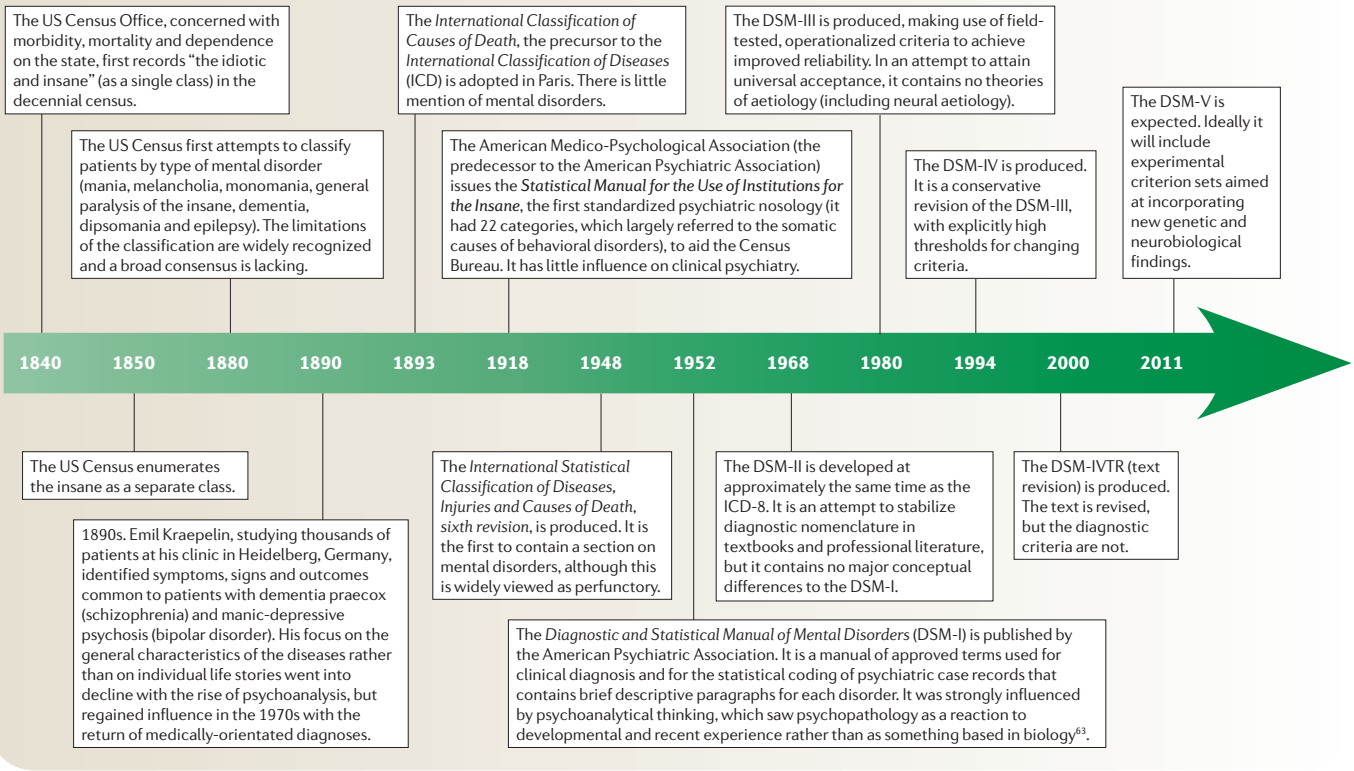
The substantial gaps in our knowledge of the neurobiology that underlies mental disorders derive in large part from the difficulty of characterizing the circuitry and mechanisms that underlie higher brain function, the complexity of the genetic and developmental underpinnings of normal and abnormal behavioural variation, and the unsatisfactory nature of current animal models of mental disorders. The existence of only a small number of well-validated biomarkers and the early stage in which our understanding of neurogenetics and pathophysiology finds itself have, reasonably enough, impeded the incorporation of neuroscience into psychiatric diagnosis to date. However, neuroscience provides much that is relevant and useful — even if it currently falls short of providing a basis for individual diagnoses. Indeed, I will argue that neurobiological information can, along with clinical observations and family and genetic studies, help to shape a reconsideration of the important aspects of the DSM system. Moreover, the DSM-V should be structured to allow the incorporation of well-replicated findings from neuroscience and genetics as they emerge — without forcing us to wait a decade or more for the DSM-VI. In this Perspective, I begin with a brief history of diagnosis and discuss some of the shortcomings of the current diagnostic systems. I then argue for experimentation within the DSM-V that would facilitate the incorporation of data from neuroscience and genetics as they emerge. The ultimate goal is a diagnostic classification system for mental disorders that is based not only on clinical symptoms but also on the aetiology and pathophysiology of the disorders.

Defining mental disorders

Mental disorders are a diverse group of brain disorders that primarily affect emotion, higher cognition and executive function. The boundary between mental and neurological disorders is arbitrary, reflecting the partly different and partly overlapping practice patterns of the two medical specialities that treat disorders of the nervous system. Neurology has tended to focus on disorders that have well-defined lesions, and on those that affect sensation and movement. However, both neurologists and psychiatrists treat disorders of higher brain function, such as autism, attention deficit hyperactivity disorder (ADHD), Tourette's disorder and Alzheimer's disease. In addition, as the neural circuits that are involved in mental disorders are identified, treatments such as deep brain stimulation, which were once reserved for neurological disorders with focal pathologies (for example, Parkinson's disease), are now also beginning to be applied to mental disorders, such as depression[3]. The term 'mental disorders' is an unfortunate anachronism, one retained from a time when these disorders were not universally understood to reflect abnormalities of brain structure, connectivity or function. Although the central role of the brain in these disorders is no longer in doubt, the identification of the precise neural abnormalities that underlie the different mental disorders has stubbornly defied investigative efforts.

The earliest attempts to standardize medical diagnoses derived from the needs of policy makers to have statistical reporting that would be meaningful across localities. Historically, the first detailed classifications focused on causes of death, and only later on the causes of morbidity and disability, including mental disorders. A count of the institutionalized 'insane' was added to the United States census in the mid-nineteenth century as part of an attempt to quantify individuals who were dependent on the state (TIMELINE). Mental disorders

Timeline | **The development of a diagnostic classification system for mental disorders**



were added to international classifications in the 1940s, partly as a result of the recognition of the toll of psychiatric casualties in World War II, and partly as a result of the acknowledgement that mental disorders had a major impact on a person's overall health status. In the United States, these factors contributed to the publication of the DSM-I by the American Psychiatric Association. The DSM-I and the DSM-II reflected the dominant psychoanalytical ideas of their time, and so they emphasized the suggested roles for experience in psychopathology and down-played the role of biology. The impetus for the more detailed, medically orientated approaches to psychiatric diagnosis that characterize the DSM-III[4] arguably arose following the birth of psychopharmacology.

With the availability of a diverse range of efficacious treatments, including stimulants, lithium, antipsychotic drugs, multiple classes of antidepressants, benzodiazepines and, later, cognitive–behavioural psychotherapies, it was clearly important to be able to make diagnoses that would give precision to the selection of patients for clinical trials and, subsequently, to clinical treatment decisions. The seminal paper of Robins and Guze[5] conceptualized the diagnosis of schizophrenia as an exemplary mental disorder, in terms of the approaches that characterized the mainstream medicine of the day. They argued that a valid diagnosis of schizophrenia and, by extension, of other mental disorders, would result from a clinical description that identifies clusters of symptoms that occur together, from laboratory studies, from a clear separation of one disorder from another, from long-term follow-up studies to establish the stability of the diagnosis over time, and from family studies. This approach provided the intellectual basis for the DSM-III and its successor editions. The individual diagnoses were accompanied by diagnostic criteria, in order to make it possible for different observers to make diagnoses with adequate reliability.

Validity and reliability of the DSM

The diagnostic criteria contained within the current DSM (DSM-IVTR) may increase the reliability of diagnoses compared with the situation before DSM-III[6]. However, gains in validity were far less substantial[7], owing to the lack of adequately replicated information regarding specific genetic or non-genetic risk factors, anatomical substrates and pathophysiology, or any objective medical tests for mental disorders. This is not to say that the definitions of the major mental disorders as they appear within the DSM-IVTR are arbitrary. On the contrary, there are striking cross-cultural similarities in the symptoms of major disorders such as autism, schizophrenia, bipolar disorder, major depression and obsessive–compulsive disorder (OCD) and, based on family and twin studies, there is substantial evidence for the heritability of these major mental disorders. Such observations suggest that the current criteria, at least for the major disorders, pick out something real, even if they do so imprecisely. Consistent with this picture, current diagnoses can be used to select treatments, but the drugs do not respect the boundaries of the disorders as defined in the DSM. Thus, antidepressants can treat many DSM-IVTR anxiety disorders, as well as OCD and depression, and antipsychotic drugs can treat schizophrenia and bipolar disorder, as well as many other disorders.

The main stumbling block to the development of valid diagnoses is the complexity of the disorders' underlying biology. However, the structure of the DSM classification itself may also have contributed to the problem. For example, a fairly arbitrary decision was made to favour 'splitting' symptoms over 'lumping' them, which resulted in the creation of a large number of disorders. In addition, all disorders in the DSM system were defined as categorical, that is, as states that can be qualitatively separated from

the state of being 'well'. There is evidence, however, that many mental disorders might be better conceptualized as dimensional traits. Dimensional or quantitative traits that are continuous with the 'normal' state are consistent with the polygenic mode of inheritance that is thought to characterize most mental disorders. The number or expression pattern of risk gene variants carried by a given individual, and the interaction of these variants with non-genetic factors of varying strength, might produce more or fewer symptoms of greater or lesser severity. Mental disorders that might be captured well by dimensional approaches include depression[8], schizophrenia[9,10,11], autism[12], personality disorders[13] and ADHD.

Considering the above points, it should not be surprising that in the clinic a large percentage of patients do not fit the DSM-IVTR criteria with precision; the DSM-IVTR copes with this problem by including, within groupings of similar disorders, a catch-all category termed 'not otherwise specified' (NOS). Among many families of disorders, such as pervasive developmental disorders (PDDs) and eating disorders[14,15], the NOS diagnosis is often more commonly used than any of the specifically named disorders. The disparity between the actual clinical presentations of disorders and their criteria in the DSM-IVTR is greatest for children[16,17], but it also occurs frequently in adults.

An additional problem is that a large fraction of patients with any DSM-IVTR diagnosis qualifies for multiple diagnoses — this situation is termed 'co-morbidity'[17,18]. Throughout medicine, there are situations in which one illness is a risk factor for others; for example, diabetes mellitus is a risk factor for retinal disease, renal disease, cardiovascular disease and neuropathy. This may also be the case for some mental disorders; for example, bipolar disorder appears to be a risk factor for substance use disorders[19]. However, co-morbidity might also reflect different patterns of symptoms that result from shared genetic risk factors. Thus, DSM-IVTR-defined cases of major depression and generalized anxiety disorder may co-occur at high rates because they represent different faces of the same underlying risk genes[20], and thus perhaps the same underlying disease processes. Co-morbidity could also be an artefact that arises from errors in the lumping and splitting of symptoms, so that a single pathophysiological process can cause symptoms that meet the criteria for multiple DSM-IVTR entities. This appears to be the case for many personality disorder diagnoses[21].

Overall, there is evidence that the current diagnoses and their corresponding sets of criteria fall short of mapping nature[22,23]. Nonetheless, one should not be excessively critical of the DSM system: throughout medicine, common, genetically complex diseases are being further categorized into new entities with different risk genes, ages of onset, outcomes and treatment responses[24]. For example, in lung cancer, specific somatic mutations predict different treatment responses[25]. Similarly, in depression, the response to a treatment may be predicted by a single nucleotide polymorphism (SNP) in the *FKBP5* gene, which encodes a chaperone that has a role in glucocorticoid receptor regulation[26]. From the point of view of revising diagnostic criteria in the near future, however, there is a major difference between our ability to apply such findings to cancer and our ability to apply them to depression. With lung cancer, there is a nosological framework based on the direct pathological examination of human tumours which increasingly includes analysis of patterns of gene expression and of somatic mutations. Thus, for example, mutations in the epidermal growth factor receptor have been sequenced in the tumours of multiple individuals with lung cancer and correlated with risk factors, cell types and treatment responses. In depression, the nosological framework is based on clinical observation of symptoms, and the significance for diagnostic subtyping of the FKBP5 biomarker is difficult to establish. For the time being, I would propose that replicated findings that are potentially relevant to psychiatric diagnosis be evaluated by a committee, perhaps one appointed by the organizations that publish the diagnostic manuals. If this committee, by using transparently enunciated criteria, finds such biomarkers to be adequately convincing, they can be posted as candidates for inclusion in subsequent revisions of diagnostic criteria. The goal would be to encourage relevant research in appropriate ill and well populations.

What has neuroscience taught us?

Owing to the limited understanding of the biological underpinnings of mental disorders that neuroscience and genetics could provide at the time, the diagnoses within the DSM-III and the DSM-IV[27] have necessarily been based on clinical observation. Despite the optimism of Robins and Guze, laboratory tests for the major, common psychiatric disorders have not yet materialized. Yet excessive pessimism is not warranted. Despite the challenges that are detailed below, progress in neurogenetics, neuroimaging and other areas of neuroscience is beginning to yield significant insights into mental disorders.

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Neurogenetics of mental disorders. Twin studies[22,28,29] and, where they have been performed, adoption studies[30–32], have demonstrated that genes exert a significant influence on the risk for many mental disorders, including autism, schizophrenia, bipolar disorder, depression and addictive disorders. However, specific risk genes have not yet been identified with adequate certainty to warrant their inclusion in the highly influential diagnostic manuals. The difficulty in identifying risk genes for mental disorders results partly from the lack of objective tests to narrow populations for genetic study and, in large part, from the complexity of genetic risk[33].

What we now call a single disorder might result from the interaction of a large number of common genetic variants, with no variant proving either necessary or sufficient for developing the disorder[34]; this situation is thought to characterize the common forms of mental disorders. Alternatively, the disorder might result from diverse individual mutations, and thus actually represent a large family of rare Mendelian diseases with a similar pathophysiology, such as in retinitis pigmentosa[35]. A more recent hypothesis is that some disorders might result from new germline mutations that may act against certain genetic backgrounds, as has been suggested for some cases of autism and schizophrenia[36]. In addition, twin studies have demonstrated that heredity has a significant role in the major mental disorders, but that non-genetic factors also play a part. Indeed, there is no common mental disorder for which monozygotic twin pairs are 100% concordant. Environmental risk factors for mental illness have been difficult to establish with certainty[37], and where they have been established (as in the case of stress or negative life events), they may be risk factors for multiple disorders (a situation shared with

many disorders in general medicine, where, for example, smoking and obesity may be risk factors for many disorders).

Older genetic linkage methodologies that have been applied to mental disorders lack the power to find risk genes of small effect[33], although they have identified positional candidate genes, such as the neuregulin 1 gene in schizophrenia[38], that provide promising leads. In addition, 'biological' candidate genes have been proposed based on findings from neuroscience and pharmacology; thus, the gene that encodes the serotonin (5-HT) reuptake transporter (5HTT), which is the molecular target of many antidepressant drugs, has been proposed to be a candidate gene for depression and for other conditions in which selective serotonin reuptake inhibitor antidepressants are efficacious[39]. SNPs and other forms of DNA sequence variation in both positional and biological candidate genes have been used to investigate possible associations with disease phenotypes[22,39]. The combination of specific variants within candidate genes (such as the 5HTT gene) and environmental factors (such as life stress) have also been tested as risks for depression[40] and other disorders.

For many candidate genes there has been both replication and non-replication of findings[22,39]. This is not surprising given the complexity of the genetic risk for mental disorders, but it should make the research community conservative about using individual SNPs to revise official diagnoses. However, there is a more subtle problem for the use of individual genetic variants to define diagnostic categories: single candidate genes provide only a narrow window on disorders that may prove to be polygenic. If genetic findings are to influence diagnostic categories, there must be a more complete context in which to place them. We must be able to determine whether a specific genetic variant contributes to the definition of a disorder, a subgroup within a disorder, a symptom that might be shared across multiple disorders, or if it is interpretable only in the context of other genetic findings.

This challenge is illustrated by studies of the gene that encodes catechol-*O*-methyltransferase (COMT), an enzyme that is involved in the metabolism of catecholamine neurotransmitters (including dopamine). This gene lies on the q11 region of chromosome 22, along with many other genes. A microdeletion of this region produces a complex syndrome (velocardiofacial syndrome) that manifests with schizophrenia-like symptoms (among others). Thus, the *COMT* gene was thought to be a candidate gene for schizophrenia, based on both biological and positional information. A common variant within the *COMT* gene results in there being either a valine (Val) or a methionine (Met) within the enzyme. The Val allele results in higher enzyme activity, suggesting that individuals with this variant would have lower levels of dopamine in their prefrontal cortex, and perhaps also diminished cognitive performance. An initial study reported an association of the Val allele with schizophrenia[41]; subsequent studies and a meta-analysis questioned this association[42]. Associations have also been reported and disconfirmed for bipolar disorder[43]. Several association studies that examined prefrontal cortex-dependent cognitive performance have found poorer performance in healthy subjects, schizophrenics and unaffected siblings of schizophrenics who have the Val allele. Other studies have failed to replicate such findings on some or all cognitive tests, or else have found complex relationships between the dosage of Val or Met variants and performance in both healthy and ill subjects[43]. Even if we look past the non-replications, complex questions remain as to what this variant might mean for nosology. Is it a risk factor for one or several disorders? Does it define subgroups in schizophrenia, bipolar disorder or schizoaffective disorder? Does it influence cognition in all individuals, and thus modify the symptom pattern when it also happens to occur in schizophrenic subjects?

Despite the genetic complexity of mental disorders, it is reasonable to hope that new technologies, such as high-density whole-genome association studies with very large sample sizes, will provide increasingly complete information about genetic risk factors. This is already the case for other genetically complex disorders such as diabetes mellitus type II and inflammatory bowel disease[44,45]. In this context, genetic epidemiologists will be better able to team-up with cognitive neuroscientists, clinical neuroscientists and pharmacologists to define the biological significance of genetic variants alone and in combination. This will be a long process, but in the end it will contribute enormously to disease classification, predictors of outcome and selection of treatments.

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Neuroimaging studies. Both structural and functional neuroimaging have provided important tools for the investigation of mental disorders. Structural MRI has begun to convincingly demonstrate patterns of grey-matter thinning in individuals with schizophrenia[46], as well as longitudinal patterns of grey-matter loss over time in patients with childhood-onset schizophrenia[47]. This increasingly clear demonstration of anatomical abnormalities in schizophrenia is likely to have significant implications for studies of pathophysiology and, as will be discussed below, for future diagnostic classifications.

Functional imaging studies have already contributed to experimental therapies for individuals with treatment-resistant depression. Studies that used positron emission tomography (PET) suggested that severely depressed individuals exhibited excessive activity in the subgenual cingulate cortex[48]. With successful antidepressant treatment, this activity returned towards normal[49]. Inducing sadness in normal subjects activates this same region of the cingulate cortex[50]. Based on this body of findings, patients with depression who did not improve with medication, psychotherapy or electroconvulsive therapy had electrodes placed in the subgenual cingulate cortex and received deep brain stimulation. In the initial series, four of six patients had sustained responses[3]. Perhaps the most important implication of this experimental treatment is that it is possible to identify the specific neural circuits that are involved in depression and use them as a treatment target.

Non-invasive neuroimaging cannot yield information as precise as that derived from direct examination of a diseased tissue or from the culture of a disease-causing microorganism. Thus, findings from neuroimaging will probably prove most useful for diagnosis when they are combined with other types of information, including clinical data, genetic information and cognitive testing.

How might neuroscience improve DSM-V?

Despite the kinds of advances described above, it is clear that our understanding of mental disorders is still limited. Patients and families, clinical trials and epidemiological research would all benefit from an improved DSM that has firm diagnostic criteria, but

they will be harmed if the new criteria rely on putatively objective tests that are not validated to a high standard. Thus, it is necessary to state a caveat: it will be important to avoid premature inclusion of genetic or neurobiological findings in the DSM, no matter how interesting they are, if they are not adequately replicated or if their relationship to behavioural or disease phenotypes cannot be established with clarity. At the same time, a slavish adherence to the current classification system would impede progress in research that is investigating the aetiology of mental disorders and identifying new treatments for them. If the current criteria have not effectively "carved nature at the joints", then there is a risk that genetic, imaging and other disease-related studies will be confounded by the inclusion of heterogeneous populations[23,33,51].

The term 'endophenotype' has become popular for describing putatively simpler, or at least objectively measurable phenotypes, such as neuropsychological measures that might enhance diagnostic homogeneity. I find this term less than ideal, because it implies that the current diagnostic classification is basically correct, and that all that is lacking is objective markers for these disorders. If, however, the lumping and splitting of symptoms that gave rise to the current classification was in error, then the search for biological correlates of these disorders will not prove fruitful. Instead, we should create circumstances in which new information from genetics, cognitive neuroscience, brain imaging, animal studies and so on can contribute to a reconsideration of the boundaries of disorders.

Considering the above, how might neuroscience help us to craft a better DSM-V? One way in which neuroscience could contribute to the creation of better diagnostic criteria without prematurely disrupting the current relatively reliable but certainly imperfect (because of their limited validity) clinical diagnoses is through the creation of experimental diagnostic criteria for research purposes that could shadow the 'official' criteria in the DSM-V. Experimental criteria need not be produced for all disorders or all groupings of disorders, but only where there is enough evidence to warrant them. Such experimental criteria could be reconsidered at intervals and updated by appropriately constituted committees as new information emerges from neuroscience and genetics, without the need to wait for an overall revision process that would lead to a new DSM volume. There is a precedent for such criteria: the DSM-IVTR contains a section entitled 'criteria sets and axes provided for further study'. However, at present this section has received little attention, as evidenced by PubMed searches for studies in which these sets and axes were applied. Thus, a special effort would have to be made to encourage the exploration of such criteria sets by the research community, perhaps through supplements to existing research grants, especially in such areas as genetics, and through meetings of key investigators that are focused on the use of new diagnostic groupings.

Box 1 | **Symptom clusters in schizophrenia**

- Positive symptoms: psychological phenomena that do not occur in healthy people, such as hallucinations and delusions
- Negative (deficit) symptoms: symptoms that arise from deficits in normal functions. Examples include asocial behaviour, impoverished content of thought and speech, blunting of emotional responses, and loss of motivation.
- Cognitive symptoms: impairments in working memory and executive functions.

Experimental approaches towards a novel classification of mental disorders could take three different forms, depending on the situation: dimensional approaches; the identification of clinically significant symptom clusters for which there are compelling hypotheses about the underlying neural circuits; and the abandonment of fine-scale splitting of disorders to yield larger 'spectrum' disorders, the constituents of which are presumed to share pathophysiological features[52]. The use of dimensional approaches is consistent with the second and third of these options. In each of these approaches, measures could be incorporated that are based on findings from genetics, cognitive neuroscience, structural and functional neuroimaging or other neurobiological studies.

The introduction of diagnostic experiments runs some risk of creating confusion that could interfere with the replication of research. This concern notwithstanding, the reification of the current diagnoses and criteria may be the greater evil: the acceptance of the current system has too often led grant review committees, journal referees and researchers to channel their efforts into the study of entities that may, in some cases, be blind alleys. The proposed approaches can be illustrated briefly by reference to a few example disorders.

Example disorders

Schizophrenia. Schizophrenia is a serious and disabling disorder that generally begins in the late teen years or in early adulthood; it runs a chronic course that is typically punctuated by episodes of severe psychotic symptoms such as delusions and hallucinations. A great deal of research supports the division of the symptoms of schizophrenia into three clusters: positive, negative and cognitive symptoms that might reflect different aspects of the pathophysiology and possibly different genetic risk factors, and that respond differentially to current antipsychotic medications (BOX 1). Like all disorders in the DSM-IVTR, schizophrenia is defined as a category, and inclusion within this diagnostic class requires the presence of certain symptoms (the DSM-IVTR does not require cognitive symptoms), a deterioration of functioning, and a rather arbitrary requirement for 6 months of illness (this is supposed to establish that schizophrenia is a chronic illness).

In their classic adoption studies of schizophrenia, Kety *et al.*[30] found that the biological families of individuals with schizophrenia contained members who did not have psychotic symptoms, but who nevertheless exhibited less dramatic schizophrenia-like symptoms such as social isolation, suspiciousness, eccentric beliefs and magical thinking. When such symptoms are chronic and impairing, the DSM-IVTR calls for the diagnosis of schizotypal personality disorder. Oddly, this is classified as a personality disorder, and is not grouped with schizophrenia, even though subsequent studies have confirmed a genetic relationship between the two[10]. More recently, multiple studies have found that 'unaffected' monozygotic twins of patients with schizophrenia exhibit cognitive abnormalities similar to those observed in individuals with schizophrenia. These include deficits in spatial working memory and divided-attention tasks that demand cognitive control[53]. Milder deficits can be observed in discordant dizygotic twin pairs and in 'unaffected' siblings who are not co-twins[54,55]. Structural MRI studies of co-twins have also shown thinning of the dorsolateral prefrontal cortex, which is the brain region that is most important for working memory. The thinning is more severe in monozygotic than in dizygotic co-twins, which may reflect the degree of DNA sharing with the affected co-twin. The co-twins with schizophrenia had additional grey matter deficits, the severity of which generally correlated with the severity of the symptoms[46]. In addition to the structural abnormalities of the dorsolateral prefrontal cortex, there are functional

abnormalities in activation that can be detected by PET or by functional MRI in response to working memory tasks. Abnormalities in activation generally correlate with impairments in task performance[56,57].

In summary, findings from family and genetic studies, cognitive neuroscience and structural and functional imaging suggest that some important components of schizophrenia form a continuum, with less severe conditions observed in blood relatives. Moreover, the greater the genetic relatedness to an affected individual, the more severe the deficits are in unaffected family members. In addition, family and genetic studies suggest that many individuals who are diagnosed with schizophrenia, bipolar disorder or less well-defined states such as schizoaffective disorder, may share vulnerability genes[22].

Based on observations of this kind, and given a probable polygenic mode of inheritance, it has been suggested that genetic and neurobiological studies of schizophrenia would be improved if study subjects could be selected using a dimensional approach[10,11,51], rather than the categorical approach currently favoured by the DSM-IVTR. It has been proposed that dimensions could be defined using quantitative scales for positive, negative and cognitive symptoms. In the future, it might be possible to develop a meaningful quantitative scale based on grey-matter thickness, perhaps in some region of the prefrontal cortex. Insofar as dimensions could be measured objectively using cognitive tests in the laboratory or through structural and functional neuroimaging, such an approach would improve diagnostic reliability as well as address concerns about validity. The use of quantitative scales would also give potential clinical status to symptoms that are now considered subsyndromal and therefore not worthy of treatment, just as physicians might intervene in mild hypertension before waiting for the condition to become severe.

A second possible approach is to 'deconstruct' DSM-IVTR disorders such as schizophrenia into related symptom clusters (or quantitative dimensions). This would permit investigators to focus on those symptoms for which there are promising neurobiological leads. In the case of schizophrenia, it might be possible to make substantial progress in research on the cognitive symptoms without having to focus on the neural underpinnings of delusions or hallucinations (about which little is known to date). Relevant to cognitive symptoms, there is much research on the neural circuitry that underlies working memory and executive function, and this has informed functional imaging research on schizophrenia[56,57]. Attempts are also being made to find associations between structural (grey-matter thinning) and cognitive (specific forms of memory impairment) phenotypes with genetic markers in schizophrenia[43,58].

An approach such as this, which focuses on the neurobiologically tractable aspects of disorders, clearly has limitations for nosology. A focus on the structural and functional abnormalities in the circuitry that underlies the cognitive functions that are abnormal in schizophrenia will not, by itself, provide a complete picture of a disorder that also has symptoms such as hallucinations (a positive symptom) and avolition (a negative symptom). Yet this type of 'neural circuit' approach to mental disorders should have substantial benefits for treatment development. If the treatment target is categorical DSM-IVTR schizophrenia, then research is hampered by the lack of animal models. If, instead, treatment development is focused on the neural circuits that are involved in working memory and cognitive control, then a great deal of relevant neurobiology and pharmacology can be brought to bear[59]. Similar neural circuit approaches could be taken with aspects of other disorders. Much is known about reward circuitry, which is relevant not only to addiction and other impulse control disorders, but also to depression, which is often characterized by anhedonia. As will be described below, the amygdala-based fear circuitry is increasingly well understood. Mapping the symptoms of anxiety disorders to such circuits is already an important area of research, and it could have substantial implications for treatment development. Perhaps more speculative is the mapping of the obsessive–compulsive disorder spectrum (including Tourette's disorder and body dysmorphic disorder[52]) to frontal-striatal-thalamic circuits.

The third possible approach to the classification of psychiatric disorders is to think in terms of larger spectrum disorders. For the

Glossary

Anhedonia
An inability to experience pleasure.

Candidate gene
A gene implicated as one that confers an increased phenotypic risk, and which is thus deserving of further investigation (for example, in an association study). Candidate genes can be identified based on biological hypotheses, or as a result of their lying within a region of interest identified by a linkage study or a chromosomal break point (a so-called 'positional candidate').

Categorical diagnosis
A disease state that is qualitatively separable from the state of being 'well', for example, tuberculosis or leukaemia.

Diagnostic classification
A listing of diagnoses clustered by relatedness, for example, cancers, metabolic diseases, infectious diseases and unintentional injuries. The ICD was first developed to allow statistical reporting across countries, initially of mortality and later of morbidity.

Diagnostic criteria
The rules for making diagnoses. The DSM-IV and the ICD-10 (Chapter V) provide both classifications and diagnostic criteria.

Dimensional diagnosis
A diagnosis based on states that are defined as above-threshold on one or more quantitative scales or dimensions and that are continuous with the normal state. For example, hypertension is defined in terms of two dimensions: systolic and diastolic blood pressure.

Disorder
A term generally used instead of the term 'disease' for medical conditions in which the causative factors or pathophysiology remain unknown.

Nosology
The classification of diseases.

Reliability
A diagnosis is reliable if the same conclusion is reached by two diagnosticians who examine the patient at approximately the same time (inter-rater reliability), or if a patient receives the same diagnosis if examined more than once within reasonably close time intervals (test-retest reliability).

Single nucleotide polymorphism
(SNP). The most common form of variation in human DNA sequences. It occurs when a single nucleotide (for example, thymine) replaces one of the other three nucleotides (for example, cytosine).

Spectrum disorders
A group of disorders that are thought to be related through the sharing of risk genes or pathophysiological mechanisms.

Syndrome
A cluster of symptoms that can result from different disease processes. For example, cough and fever can result from bacterial, viral or fungal infections, or from autoimmunity, with very different treatments and outcomes.

Valid diagnosis
A diagnosis that picks out a real entity based on aetiology or pathophysiology.

Validity
The extent to which a variable measures what it is intended to measure.

'schizophrenia' spectrum, this might include at least schizotypal personality disorder and the non-affective psychoses in the DSM-IVTR (such as the rather questionable DSM-IVTR entity 'schizophreniform disorder'). The clear disadvantage for research that uses larger spectrum diagnoses is the greater heterogeneity of the study populations. The advantage of such lumping is that it encourages inductive, bottom-up re-analysis of phenotypes based on factors such as familial aggregation of symptom clusters and the segregation of symptoms across generations. It could be asked how frequently cognitive symptoms (which would ideally be measured dimensionally) co-segregate with positive or negative symptoms, or with other symptoms such as depression or mania. It could also be asked how measures of regional grey-matter thinning correlate with quantitative measures of symptoms' dimensions. Symptoms, structural findings and functional neuroimaging findings could be correlated with genetic risk alleles as they emerge. The results will be quite different from those that would emerge from attempts to define subtypes of DSM-IVTR schizophrenia, because there is a high likelihood that this category has artificial boundaries with related disorders.

Anxiety disorders. Anxiety disorders are another type of disorder that could illustrate how new approaches to disorder classification could be used. The DSM-IVTR category of anxiety disorders currently includes generalized anxiety disorder, simple phobias, post-traumatic stress disorder (PTSD), panic disorder and social phobia as discrete anxiety disorders. Yet co-morbidity among the anxiety disorders and with depression is common. In addition, all of these disorders respond to antidepressants. Moreover, neuroimaging research suggests that hyperactive responses within the fear circuitry, as evidenced by hyperactive amygdala responses to fearful stimuli, may be a general characteristic of some of these anxiety disorders[60,61].

How might the use of dimensions and the deconstruction and lumping of disorders apply to research on anxiety disorders? An attempt to define dimensions seems warranted because the thresholds for anxiety disorder diagnoses in the DSM-IVTR seem arbitrary; moreover, there is much symptom overlap between disorders. It might facilitate research to define quantitative dimensions, such as responsiveness to fear-inducing stimuli (or some other measure of learned or conditioned fear), and measures of anticipatory anxiety, and of distress and dysphoria. Much research in both animals and healthy humans has helped to elucidate the circuitry that is involved in fear conditioning[62]. The mapping of symptom dimensions onto an amygdala-based fear circuitry, as is already happening in some research programmes, could facilitate treatment development by moving the focus from behaviourally defined syndromes to specific circuits, cells and synapses. Finally, the lumping of disorders that involve conditioned fear as a central symptom dimension (namely simple phobias, PTSD, panic disorder and social anxiety disorder), followed by the type of re-analysis described above for schziphrenia, might lead to a redrawing of the boundaries of these disorders that is more consistent with genetic risk factors, neural circuits and pathophysiology.

Although I have, in the interest of brevity, provided heuristic examples from schizophrenia and anxiety disorders, I could just as well have discussed dimensional, neural circuit and 'spectrum re-analysis' approaches related to the OCD spectrum[52], to impulse control disorders or to mood disorders.

Conclusions and future directions

It is probably premature to bring neurobiology into the formal classification of mental disorders that will form the core of the DSM-V. However, it is not too early to use neurobiology as a central tool to rethink the current approach to mental disorders, and to begin some careful experiments that could liberate science from the unintended consequences of reifying the current diagnoses that probably do not mirror nature. Not all disorders are equally susceptible to the kinds of experiments that I have suggested. It is my hope that the committees that are working on the DSM-V can develop and begin testing dimensional criteria for several groups of disorders, and that they can define 'larger groupings' or 'spectra' for a smaller group of disorders based on existing knowledge of symptom clustering, familial transmission, genetics and pathophysiology. The goal of creating larger groupings is to encourage re-analysis in the way I described above for the schizophrenia spectrum. I hope in addition that mechanisms can be created to post and evaluate relevant new findings, be they genetic markers or neuroimaging results, and that there can be interim processes to adjust the experimental criteria long before it is time to start thinking about DSM-VI.

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Competing interests statement

The author declares competing financial interests: see web version for details.

DATABASES

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