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New Approaches to Psychiatric Diagnostic Classification

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Recent findings in psychiatric genetics have crystallized concerns that diagnostic categories used in the clinic map poorly onto the underlying biology. If we are to harness developments in genetics and neuroscience to understand disease mechanisms and develop new treatments, we need new approaches to patient stratification that recognize the complexity and continuous nature of psychiatric traits and that are not constrained by current categorical approaches. Recognizing this, the National Institute for Mental Health (NIMH) has developed a novel framework to encourage more research of this kind. The implications of these recent findings and funding policy developments for neuroscience research are considerable.

Introduction

There has been no major advance in psychopharmacology for over 40 years. Moreover, repeated and expensive failures have resulted in many pharmaceutical companies scaling down drug discovery in psychiatry or abandoning it altogether (Abbott, 2011). This is generally attributed to our poor understanding of disease mechanisms. The complexity and inaccessibility of the brain compared to other organs, and the difficulties inherent in modeling complex human systems and behaviors experimentally, certainly pose challenges. On the other hand, advances in genomics, stem cell biology, and neuroscience potentially place us in an unprecedentedly strong position to tackle major psychiatric disorders such as schizophrenia, bipolar disorder, attention-deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) (McCarroll and Hyman, 2013).

But researchers hoping to understand these disorders face another challenge. This arises from the fact that, because we understand so little about disease mechanisms, our approach to diagnosis remains largely descriptive and syndromic; what we recognize as disorders are actually syndromes: constellations of signs and symptoms that tend to occur together. Recognition of these syndromes helps clinicians constrain the range of likely outcomes, choose treatments, and communicate with each other and with patients and their families. As far as research is concerned, it has generally been assumed that current diagnoses, imperfect as we suspect them to be, are nevertheless the best basis we have for understanding etiology and pathogenesis. As we acquire new knowledge from epidemiology, genetics, and neuroscience, so the argument goes, we will be able to refine these categories and develop new treatments, diagnostic tests, and biomarkers that will place psychiatry on a par with other branches of medicine. But recently another view has been gaining support. Perhaps our tendency to view research findings through the primitive syndromic lens of current diagnoses is actually impeding progress. Perhaps we need to try new ways of classifying psychiatric disorders if we are ever going to benefit from advances in neuroscience and develop more effective treatments.

Psychiatric Diagnosis: Reliability at the Expense of Validity

Current approaches to psychiatric diagnosis grew out of the appreciation in the early 1960s that the rate with which schizophrenia was being diagnosed in the US was 5–20 times greater than that in the UK (Cooper et al., 1972). Work over that decade showed that this reflected diagnostic differences rather than real differences in prevalence and pointed to the need for diagnostic standardization. This led to the development of operationalized classifications that were designed to provide a reliable way of assigning a patient with a particular constellation of signs and symptoms to a diagnostic category (Allardyce et al., 2007). This works by defining a set of inclusion and exclusion criteria for each category. A "polythetic" approach is taken such that multiple positive features are identified but none is regarded as essential; in order to make a diagnosis it is simply necessary to check the clinical features against the list of criteria. The main benefit of this "Chinese menu" approach is to greatly improve diagnostic reliability. In other words, different clinicians should make the same diagnosis of a given case assuming that they have been equally assiduous in eliciting the signs and symptoms. These approaches were developed to remedy a lack of diagnostic reliability and in this regard their introduction has had many benefits to clinical practice and to the collection of data on prevalence and incidence (Kendell and Jablensky, 2003). However, in the absence of a solid understanding of pathophysiology, the majority of diagnostic categories chosen were by necessity largely descriptive and syndromic in nature. They are in effect an operationalization of expert consensus of the best descriptors of the clinical syndromes recognized by psychiatrists; they were not, nor were intended to be, valid descriptors of disease entities. The precise meaning of the concept of validity as applied to psychiatric diagnosis has been debated (Kendell and Jablensky, 2003), but for current purposes we can consider it as referring to the degree to which a diagnostic construct delineates a group of cases that share common underlying etiological and/or pathogenic processes (Allardyce et al., 2007). Applying this test, few diagnostic categories in psychiatry

would generally be accepted as valid. Many of these designate causes of intellectual disability or dementia such as Down syndrome, phenylketonuria, Huntington's disease, and Jakob-Creutzfeldt disease (Kendell and Jablensky, 2003). In the case of the majority of psychiatric disorders, where etiology and pathogenesis remain largely unknown, the validity of the syndromic concepts that form the basis of current diagnostic criteria is questionable (Kendell and Jablensky, 2003; Craddock and Owen, 2005; Allardyce et al., 2007).

Most western clinicians use either the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM) (American Psychiatric Association, 2013) or the International Classification of Diseases (ICD) of the World Health Organization (International Statistical Classification of Diseases and Related Health Problems, 1992). These are updated every decade or so but, while hopes are frequently expressed that diagnoses will be modified on the basis of new insights into etiology and pathogenesis, the weight of evidence has largely been insufficient to justify radical overhaul. Lack of validity was widely recognized when these operationalized systems were developed, but their convenience and reliability were such that this significant shortcoming soon became overlooked. This has led to a process of "reification" whereby researchers, practitioners, and regulators have come to regard psychiatric diagnoses as valid categories defining distinct illnesses with their own characteristic underlying etiology and pathogenesis (Kendell and Jablensky, 2003; Hyman, 2010).

Psychiatric Diagnoses Are Both Too Broad and Too Narrow

The limitations of classifying psychiatric disorders using this categorical and syndromic approach have become increasingly apparent in recent years (Craddock and Owen, 2010). Indeed, many current diagnoses would appear to have the unusual property of being simultaneously both too broad and too narrow. They are too broad in the sense that patients with the same diagnosis can vary widely in symptoms, severity, course, and outcome. For example, people with quite widely different symptom profiles can satisfy DSM5 criteria for schizophrenia (American Psychiatric Association, 2013). Moreover, a diagnosis of schizophrenia is associated with a wide range of outcomes ranging from essentially full recovery to chronic symptoms and disability (van Os and Kapur, 2009). It is often assumed that, with further research, it will be possible to resolve this heterogeneity into specific, valid disease subtypes. Yet, repeated attempts to do this convincingly using a variety of features have failed. Current diagnoses are too narrow because many diagnoses have symptoms in common and the boundaries between disorders are frequently indistinct and to a great extent arbitrary as are the boundaries between disorder and wellness. For example, psychotic symptoms, particularly delusions and hallucinations, as well as episodes of affective disturbance, are commonly seen in both schizophrenia and bipolar disorder (Craddock and Owen, 2005). The overlap of symptoms between diagnostic categories means that it is often difficult to assign an individual to a single specific category, and the diagnosis given to a particular patient may change over time (Craddock and Owen, 2005). One approach to this problem has been to recognize "interforms," such as "schizoaffective disorder," in which features of schizophrenia and severe mood disorder occur in the same individual (Heckers, 2009). A second approach is to recognize "comorbidity," whereby a patient is diagnosed with more than one disorder. This may be clinically useful but raises questions about the validity of the diagnostic categories being employed. Moreover, comorbidity is often obscured in research studies by the use of diagnostic hierarchies or exclusions. For example, until the most recent edition of DSM (DSM5) was published (American Psychiatric Association, 2013), it was not possible to diagnose ADHD and autism in the same individual. Yet in population studies these two syndromes frequently co-occur (Simonoff et al., 2008; Lee and Ousley, 2006). Finally, not only are the boundaries between established diagnostic categories indistinct at best, but so also are the boundaries between illness and wellness (Narrow and Kuhl, 2011). This might seem obvious in instances such as depression and anxiety that are widely recognized at different degrees of severity in many of us. However, there is increasing realization that even psychotic symptoms, such as auditory hallucinations and paranoid thinking, occur in attenuated form in the 5%–8% of the healthy population (van Os et al., 2009).

Impact of Recent Genetic Findings: Complexity and Pleiotropy

Genomic analysis of psychiatric disorders remains a work in progress; much genetic risk is still unexplained at the level of the genome, and progress has been greater for some disorders, in particular autism and schizophrenia, than others (Sullivan et al., 2012). However, empirical findings from those disorders with sufficient data now support a general framework for the genetic architecture of psychiatric disorders. As expected from genetic epidemiology and population genetics, it appears that a spectrum of allelic risk underlies complex psychiatric traits as for other common diseases (Sullivan et al., 2012). There are contributions from alleles that are common in the population but whose effect sizes tend to be small due to the effects of natural selection, as well as from rare alleles, some of which can have a large effect on disease risk pending their removal from the population by selection (Sullivan et al., 2012; Gaugler et al., 2014). The precise genetic architectures of different psychiatric disorders remains to be determined pending larger and more detailed studies. However, findings to date are sufficient to yield two important implications for classification and for psychiatric neuroscience more widely. The first of these is that the disorders are highly polygenic with hundreds of risk variants involved at a population level (Sullivan et al., 2012). In schizophrenia, where the largest samples have been studied and our understanding is therefore greatest, genome-wide association studies (GWAS) have identified to date over 100 distinct genetic loci harboring relatively common alleles of small effect at robust, "genome-wide" levels of statistical significance (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Furthermore, studies looking at the en masse effects of common risk alleles that are not individually supported at genome-wide levels of statistical significance have estimated that relatively common small-effect alleles account for at least 25% of total liability to schizophrenia (about 33% of genetic