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Categorical diagnosis: a fatal flaw for autism research?

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The use of autism as a diagnostic category guiding translational research is fraught with so many problems that the validity of research conclusions is suspect. Neuroscientists would benefit from attending to nosological difficulties to formulate meaningful research bridging basic biological systems and human disease. I propose a diagnostic schema that could translate more efficiently between the clinical and the neuroscience perspective as a step to improve the effectiveness of this type of research.

The problem of categorical diagnosis in psychiatry

Studying brain disorders 'bench to bedside', one must consider levels of complexity from the molecular to the whole organism as a social entity. Diagnoses from the Diagnostic and Statistical Manuel (DSM), the sanctioned diagnoses used by psychiatrists, are often used by neuroscientists despite their being considered poor reflections of nature by many in the psychiatric community. For this reason, the National Institute of Mental Health (NIMH) is supporting research that transcends current diagnostic categories with the Research Domain Criteria (RDoC). Incorporating genetics, imaging, cognitive science, and other information, it will lay the foundation for new classification systems. The goal is to have more biological validity through improved correlation between clinical criteria and neuronal pathways [1].

Until 1980 there were no universally recognized criteria for psychiatric diagnosis. This unacceptable situation was remedied by the introduction of DSM third edition (DSM-3). The DSM-3 provided reliability of diagnosis, but without attention to etiology or pathophysiology. The DSM-3 was created by utilizing the 'wise professor model' [2], with one influential physician describing and classifying his patients and, from that, creating categorical diagnoses. Efforts to validate these diagnoses have been disappointing.

Nosological constructs such as phenotype, diagnosis, and syndromes are manmade tools that can be useful for various tasks but should not be thought of as absolute truth. Diagnoses are names given to clinical observations to create a shorthand for physicians to describe a complicated entity that is present in nature. The diagnosis 'strep throat' provides accurate and reliable information to the physician. A psychiatric diagnosis, by contrast, is rarely as informative. The DSM diagnoses frequently tell us little about etiology, lack biological markers, have widely varying and poorly predictable prognoses, have multiple comorbidities (often outweighing the clinical significance of the original diagnosis), merge into other disorders or into neurotypicality and therefore lack clear boundaries between disease and health or between disorders, lack rigor in their description of symptoms, and are not predictably responsive to treatments [3].

Perhaps more pernicious is the widespread reification (making something real, absent of evidence) of these diagnoses, creating premature closure of debate on the quality of the diagnosis and facilitating false premises on which research is conducted [4]. Many have forgotten the warnings of the DSM's framers that the categorical diagnoses chosen were to be way stations until better, more neurobiologically correct diagnoses could be formulated. Unfortunately, we are not there yet. Despite a neurobiological revolution, psychiatric disease treatments have progressed little over 50 years [5]. The pace of psychotropic drug discovery was dizzying in the 1950s and 1960s; however, progress has now slowed to a virtual halt [6]. Why might this be? Clinical trials, using DSM diagnoses, have heterogeneous groups of patients labeled with the same diagnosis, which could doom a trial from the start. In large genetic studies, phenotypic data collections were limited to fit the DSM diagnosis as if they 'were natural kinds that would map onto the human genome'. Hyman notes that using the DSM is often enforced by National Institutes of Health (NIH) study sections, as well as regulatory agencies including the FDA, which takes the DSM to represent the scientific community's consensus on valid indications for the approval of new treatments [4].

Autism: a singular disorder or a collection of diverse brain anomalies?

Kanner's original description of autism as extreme aloneness and an obsessive desire for the preservation of sameness, as well as current descriptions of autism, are better characterized as a 'behavioral complex' found within many diagnoses and also in the neurotypical population. An alternative way of conceptualizing autism and the related disorders is that they are diverse manifestations of anomalous brain development rather than a 'special' category.

Until recently, the DSM defined autism to comprise three symptoms or factors: (i) social impairment; (ii) communication impairment; and (iii) repetitive interests, behaviors, and activities (RIBAs). These three factors correlated weakly with each other (for a given symptom, only 20–40% have two of these symptoms), leaving many with

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only one or two of these three symptoms. This and the independence of the course of the three symptoms led Happe *et al.* [7] to recommend that researchers give up searching for causes of autism as a whole and focus on the individual factors. The DSM fifth edition (DSM-5) has partially addressed this challenge by combining social and communication deficits into one factor and adding social–communicative disorder as a separate diagnosis, but it failed to remedy the larger problem, retaining the assumptions that only Kanner's original symptoms define autism and that it remains a category in nature. This leaves no entry point for other, coexisting symptoms to be considered central to a given person's brain pathology.

Symptom descriptions remain vague, nonspecific, and difficult to define. RIBAs, as a case in point, comprise stereotyped motor movements, repetitive manipulation of objects, repetitive self-injurious behavior, specific object attachments, compulsions, rituals and routines, an insistence on sameness, repetitive use of language, and narrow and circumscribed interests. Several studies have shown that RIBAs fall into (at least) two clusters: the 'lower-order motor actions' (stereotyped movements, repetitive manipulation of objects) and the 'higher-order behaviors' (compulsions, rituals, insistence on sameness, and circumscribed interests) [8]. In addition, the DSM-5 adds hyper- or hyporeactivity to sensory input and unusual interest in sensory aspects of the environment as a component of the RIBAs. From a neuronal systems viewpoint, the development of the RIBAs represents diverse brain processes, diverse mechanisms, and diverse brain circuitry and could not possibly be a single phenomenon [9]. The other core symptom of autism – social–communicative impairment – is even harder to characterize, leaving diverse concepts such as social anxiety, social interest, social skills, and social cognition somewhat undefined and certainly overlapping.

The boundary of autism from neurotypicality is unclear. The broader autism phenotype (BAP) is found in relatives of autistic individuals. They have symptoms of autism, although milder in severity, often not reaching clinically relevant levels. Population-based studies have found that autism traits are continuously distributed in the population with no natural boundary between normality and psychopathology. A population-based twin study of autistic traits [10] compared four cut-off scores of autism symptoms representing the diagnosis, the broader phenotype, and the tenth and 15th percentiles of the population, both of which are well outside the range of clinical diagnosis. All four had similar heritability factors, suggesting that autistic disorder and autism traits have similar genetic susceptibilities rather than different genes mediating the disorder as opposed to the traits. Concordant with several similar studies, this supports the hypothesis that autism spectrum disorders (ASDs) represent the extreme end of a distribution of traits in the population, placing doubt on the validity of autism as a discreet entity.

When studying the categorical diagnosis against controls, a continuous trait creates less power as many in the control group almost meet case status. Being a continuous trait might explain the dramatic changes (greater than tenfold increase in a few years) in the prevalence of autism noted in epidemiological studies where a change in cut off could significantly impact the prevalence. Autism's variability in intelligence quotient (IQ) scores ranges from profoundly cognitively impaired to genius. With many etiologies and presentations of autism, authors are using the term 'autisms' or ASDs, implying multiple disorders and looser boundaries.

Comorbidities

The term 'comorbidity' was coined to mean any other diagnosis or symptom or a physiologically normal state, such as pregnancy, that is other than the indexed disease. The term took hold in the late 1980s, coinciding with the DSM-3 [11]. This concept developed in response to the DSM, which artificially split complex clinical conditions into several pieces. If demarcations are made where they do not exist in nature, several diagnoses are needed to describe an individual case, explaining the proliferation of comorbidities. This is the case throughout psychiatric diagnosis; for example, 90% of patients diagnosed with schizophrenia have at least one other diagnosis. Comorbidity is a vague term implying a disorder or symptom that may be: (i) coincidentally related to the indexed disorder; (ii) causally related to the disorder (that is, one condition leads to the other); or (iii) causally and indirectly related (that is, an underlying condition/impairment leads to both the indexed disorder and the comorbid disorder). To a neuroscientist, these distinctions are critical, yet little attention has been paid to these possibilities. Labeling conditions as comorbidities devalues their centrality to the condition being studied.

Over 60% of individuals with autism had one co-occurring diagnosis and another 26% had two or more co-occurring diagnoses, leaving 15% with none [12]. Autism is comorbidly present in over 50 specific diagnoses comprising other genetic and medical conditions. Of 16 medical symptoms examined in one study, only three (blood diseases, neoplasms, and genitourinary disease) were not significantly associated with higher rates in autism compared with population-based controls. Below are three examples of important autism-related comorbidities and their inherent problems.

Motor disorders: an excluded symptom

The authors of a meta-analysis of 51 studies [13] determined ASDs to be associated with significant and widespread alterations in motor performance and concluded that motor abnormalities should constitute a core symptom of ASD. Other than the RIBAs, motor symptoms are labeled as associated symptoms or comorbidities and are not recognized as central to autism. Motor symptoms are often not looked for and not treated and are rarely central to autism research. For various reasons research on motor systems might be a superior way of studying autism.

In one study, 'simple minor neurological dysfunction' has been found in as many as 95% of a group of normal-IQ individuals with autism, including posture and muscle tone dysfunction (87%), cranial nerve dysfunction (39%), fine manipulative disability (75%), dyscoordination (60%), and excessive associated movements (40–45%). Abnormalities in motor development as early as 3 months have been