**116,200 ways to diagnose ADHD: is this what clinicians really need?**

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According to the Diagnostic and Statistical Manual of Mental Disorders-5th edition (DSM-5)1 criteria, the diagnosis of ADHD is based on a polythetic approach. This means that none of the symptoms listed in the diagnostic criteria is essential for the diagnosis and individuals with the same diagnosis might or not share a number of symptoms. More specifically, in children/adolescents, DSM-5 criterion A requires the presence of at least 6 out of 9 symptoms of inattention *and/or* 6 among 9 symptoms of hyperactivity/impulsivity. As such, a child with 10 impairing symptoms (5 of inattention and 5 of hyperactivity/impulsivity) would not meet the criteria for a formal diagnosis. For individuals 17 years and above, the threshold has been set at 5 symptoms. Other essential criteria require the childhood onset, the pervasiveness and impairing nature of the symptoms, and the exclusion of other mental health conditions that can better explain the presence of the ADHD-like symptoms.

Due to the polythetic approach, it has been calculated that, theoretically, there are 116,200 different combinations of symptoms to achieve the threshold required by the DSM-5.2 A recent study3 drawing on two samples of Brazilian children found that, out of the 116,200 possible combinations, a total of 173 different symptomatic profiles were present in the 189 children with ADHD in both samples. Of note, only 16 (8.4%) children with ADHD had a shared profile of symptom combination with another child. In addition, only four out of the 173 combinations were found in both samples (2.3%).

Unfortunately, this is not the only source of heterogeneity in the ADHD phenotype, as it is currently conceptualised. There is also heterogeneity related to comorbidity. Around 70 to 80% of children with ADHD in population-based and clinical samples have a comorbid condition.4 In addition, parents and teachers report differently about ADHD symptoms in the same child. Importantly, there is also a developmental heterogeneity. The phenotype in adolescence tends not to be the same as it was in pre-school years. However, whilst a different threshold of required symptoms is set for adults, the same approach has not been implemented for the other extreme of the lifespan, i.e., the pre-school age. It could be argued that, since hyperactivity, impulsivity and inattention are, to some extent, normative in pre-schoolers, a higher threshold would be needed for caseness. One option would be to establish a different symptom threshold for pre-schoolers below a certain age. Another possibility would be to consider a normative model approach, which has been recently advocated to model individual neurobiological differences of individuals with ADHD.5 Normative models provide estimate of centiles of variation within the population, such as the centiles for height or weight commonly used in auxology. Future studies could test normative models providing different thresholds of symptoms needed for the diagnosis according to different ages.

 Considering this level of heterogeneity, it is not surprising that recent attempts to disentangle the ADHD neurobiological underpinnings through neuroimaging and GWAS have needed thousands of cases to find subtle differences in the ADHD brain6 and no more than 12 gens associated with the disorder.7

 Potential areas of improvement in the characterisation of ADHD phenotype go beyond heterogeneity. For instance, current criteria assume that each of the 18 symptoms listed in the criteria has the same weight in the diagnostic algorithm. In other words, it is assumed, without any evidence, that all symptoms have the same power to capture the latent construct of ADHD. To make it clearer, this is like assuming that sleep problems, one of the several criteria for diagnosing Major Depression, have the same weight to capture the latent construct of depression as a suicide attempt. Indeed, recent evidence has challenged this notion. In the multi-centre IMAGE (International Multicentre AD/HD Genetics) sample (1497 children/adolescents with ADHD and 291 unaffected individuals),8 each of the 18 ADHD symptoms contributed significantly and independently to the diagnosis of ADHD and predicted impairment. However, not all items carried equal weight in terms of severity. This has been replicated in different samples using statistical approaches like item response theory.9 Interestingly, depending on sample characteristics, different studies found different symptoms to be the ones mostly associated with severity or impairment. Thus, how to prioritize symptoms for diagnostic purposes is not an easy task and should be a major area of research for ADHD diagnosis.

But are the current diagnostic criteria derived from research settings tuned with the diagnostic procedures implemented in the real world, outside very specialized research facilities? In the daily clinical practice, to establish a diagnosis of ADHD, usually busy clinicians do not count the number of symptoms. Rather, they may tend to use a prototypic approach, whereby they assess to which extent the issues presented by the individual referred to consultation fit with the “prototype” of the specific disorders they have in mind. Based on this perspective, the ICD-11 is considering abandoning the polythetic nature of the classification system in favour of a prototypic approach.10 Thus, a real and important challenge is to disentangle how to make operational diagnostic criteria for ADHD something with clinical value in real clinical settings.

To conclude, it seems that the current diagnostic approach based on 116,200 permutations is not everything that clinicians need in order to diagnose ADHD across the lifespan in the daily clinical practice. We look forward to the work of the committees that will be in charge of revising the current ADHD criteria and we hope that the aspects highlighted in this Commentary will be taken into due account.

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