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Collective analytics: advancing the neuroscience of ADHD

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Neuroimaging has affected our understanding of psychiatric illnesses by shifting conceptualisations towards brain models of disease. However, this process has not unfolded without missteps along the way, and serious concerns about replicability continue to plague the field.^{1,2} From these concerns, researchers strive to find new ways to improve science, and over the years, a key takeaway point has become clear—as long as studies with small samples remain the standard, the field will continue to struggle with false positives, adding more noise to an already complex and unharmonious science. Because it is often financially unfeasible to include large samples within a single study, new data-sharing approaches are needed to address the concerns surrounding such endeavours, including maintaining data integrity and academics' misgivings about curtailing professional advancement by prematurely releasing data. The study by Martine Hoogman and colleagues³ in the ENIGMA collaboration laudably embodies the collaborative spirit of data sharing and the type of science that the field should strive to make commonplace.

Hoogman and colleagues assessed differences in the subcortical structures and intracranial volume of 1713 individuals with attention deficit hyperactivity disorder (ADHD) and 1529 unaffected controls across 23 sites. Their results show reduced volumes in the accumbens, amygdala, caudate, hippocampus, putamen, and intracranial volume in individuals with ADHD compared with healthy controls in the mega-analysis. Reduced volumes were detected in childhood, but were not present by adulthood. Theirs is the largest study of its kind and well powered to detect small effect sizes. Large sample sizes are particularly important in the study of ADHD because of the heterogeneity of the disorder both in the biological cause and clinical manifestation.⁴

The study replicates previously documented volume reductions in the caudate and putamen in individuals with ADHD, yet also makes a novel contribution by being the first meta-analysis, to their knowledge, to document accumbens, hippocampal, and amygdala differences in their mega-analysis. The amygdala, which showed the largest effect size of the subcortical structures tested, has important implications for emotion regulation,^{5,6} and thus, the authors take this finding as support for the inclusion of emotion dysregulation in the core ADHD phenotype. Amygdala volumetric reductions in ADHD are consistent with the importance of emotional dysregulation in the clinical phenotype, yet by itself, this finding is not sufficient to rule out the possibility that dysregulation is a correlated yet separate event, or that it comprises a distinct type of ADHD.⁷ Further studies will need to identify whether

shared environmental or genetic risk factors drive the overlap between ADHD and emotional dysregulation. Understanding of the nature of the overlap is of enormous consequence to our conceptualisation of the disorder. If, in fact, emotional dysregulation is a core component of attention deficit hyperactivity disorder, the field will need to decide whether ADHD should continue to be understood as a purely cognitive disorder, or should also be examined through the lens of a mood disorder.

The finding that subcortical volumetric reductions are not present in adults with ADHD highlights the need for the use of longitudinal samples. Epidemiological studies^{8–10} support the existence of adult-onset ADHD and suggest that this disorder might have a biological cause and a developmental trajectory distinct from that of child-onset ADHD. Adult samples in the present study might have included both child-onset and adult-onset ADHD, and thus, within-group heterogeneity might be responsible for the failure to detect volumetric differences from controls. Longitudinal imaging studies will be necessary to answer this question and to delineate early markers for the different developmental pathways of ADHD.

The authors did not find any relationship between previous medication and subcortical volumetric reductions in ADHD. This result is somewhat surprising given findings from previous meta-analyses^{11,12} suggesting normalisation of basal ganglia volumes in individuals with ADHD who received psychostimulant treatment. However, non-randomised sampling might introduce selection bias that confounds analyses of medication effects. To overcome this limitation, Biezonski and colleagues¹³ used a randomised, placebo-controlled design with pretreatment and post-treatment imaging to show psychostimulants' hypertrophic effects on basal ganglia volumes in a rodent model. Similarly designed studies in human beings are needed to robustly test for volumetric effects of psychostimulants.

The clinical implications of large imaging studies will be directly proportional to the quality of protocols used. Standardised data acquisition and analysis procedures are a promising approach, but differing inclusion and exclusion criteria and clinical assessments across sites still present enough variance to introduce reasonable doubt regarding the specificity of study findings. In the present study, ADHD assessment protocols included ratings scales, semi-structured interviews, and an algorithm system that incorporated both. The absence of an association between brain volumes and clinical symptoms is perhaps not surprising given the varied clinical protocols used across the ENIGMA sites. Future studies will require standardised clinical assessments that, in light of this study's amygdala finding, include emotional dysregulation assessments.

This study represents an important contribution to the field by providing robust evidence to support the notion of ADHD as a brain disorder with substantial effects on the volumes of subcortical nuclei. Future meta-analyses and mega-analyses will need to investigate medication effects as well as the developmental course of volumetric differences in this disorder.

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