

## Commentary

## Commentary on... the overlapping and distinct resting functional connectivity between autism spectrum disorder and attention-deficit hyperactivity disorder†

Chirag Mehra and Michael Absoud

## Summary

Altered neural connectivity in neurodevelopmental disorders is likely subtle, meaning that neuroimaging literature studying development has produced heterogeneous findings. A recent study, published in this issue, illustrates the translational potential of functional connectivity magnetic resonance imaging findings as a biomarker for attention-deficit hyperactivity disorder and autism spectrum disorder. Importantly, it highlights the overlap between disorders, emphasising the need for transdiagnostic and dimensional approaches in neurodevelopment.

## Declaration of interest

None.

## Keywords

Attention deficit hyperactivity disorders; autistic spectrum disorders; imaging.

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## Introduction – comorbid attention-deficit hyperactivity disorder and autism spectrum disorder

There is increasing evidence that neurodevelopmental disorders, such as autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD), although traditionally categorised as distinct, share aetiological, imaging and clinical features.<sup>1</sup> Approximately one-third of children with ASD have comorbid ADHD. Children with either disorder share symptoms beyond their individual diagnostic criteria, including cognitive and executive function impairments, emotional dysregulation, motor dysfunction and altered sensory perception. Further, there is evidence that both ASD and ADHD are diagnoses that lie at extremes of neurocognitive dimensions.<sup>2</sup> However, it is possible that phenotypic overlaps may partly stem from differing early motivational and cognitive processes. For example, inattention in ASD may be secondary to sensory overload, while impulsivity in ADHD can contribute to apparent social problems.<sup>2</sup> These behavioural similarities and differences are being explored in integrative research, such as human cognitive, genomics and imaging studies, with the hope of eventual clinical translation.

## The neurobiology of ASD and ADHD

Existing literature illustrates that these patterns of behavioural similarities and differences between ASD and ADHD extend to their neurobiology.<sup>3</sup> Imaging genetic studies show that variations in the serotonin transporter (*SLC6A4*) gene and associated functional connectivity changes in emotional regulation constructs have been implicated in both disorders.<sup>4</sup> Meanwhile, disorder specific findings have included the role of oxytocin in ASD and dopamine in ADHD. In this issue, Jung and colleagues add to this sentiment, showing both overlapping and distinct functional connectivity features

between ADHD ( $n = 83$ ) and ASD ( $n = 86$ ), compared with typically developing controls ( $n = 125$ ).<sup>5</sup>

Previous neuroimaging studies have alluded to the utility of studying resting state networks in ADHD and ASD, despite inconsistencies in the literature.<sup>1</sup> Jung and colleagues show that ASD and ADHD are both associated with atypical resting state functional neural connectivity.<sup>5</sup> It is difficult to decipher the particular consequences of the direction of change in connectivity, as both increased and decreased connectivity (compared with typically developing children) were found for each condition, often in the same neural networks. Out of 162 regions of interest compared with typically developing children, connectivity was: increased in 8, while decreased in 2 in ADHD; increased in 72, while decreased in 9 in ASD. Deviations from the typical brain were in both long and local connections. Of note, the study found that increased functional connectivity in the right insula was associated with Social Responsiveness Scale scores in the ASD group. Hyperconnectivity-affected behaviour in a 'dose-dependent' manner, adding validity to this finding. Other studies report that insular abnormalities in ASD correlate with emotion dysregulation and that idiosyncratic functional connectivity in the brain is a hallmark of ASD.<sup>6</sup> Interestingly, in the paper by Jung and colleagues,<sup>5</sup> sensory processing networks (namely, the dorsal and ventral attention, visual and parietal networks) have been implicated in aberrant connectivity. As children with ASD have hyper- or hypostimulated sensory perception, a question for future study could ask if there is any association between neurophysiological changes and brain circuitry in these children.

In ADHD, the altered neural connectivity has been characterised more consistently. Meta-analyses of functional magnetic resonance imaging (MRI) studies have shown alterations in neural networks that mediate executive function, particularly motor response inhibition, working memory, sustained attention, response variability and cognitive switching. Consistent with the paper by Jung and colleagues,<sup>5</sup> aberrant connectivity has been reported in regions also implicated in ASD, including the default mode network, limbic, frontoparietal, visual and ventral attention networks, which might account for comorbidity.<sup>3</sup>

† See this issue.

## Biomarkers: opportunities and challenges for clinical translation

The application of machine learning in neuroimaging has led to a recent surge of literature predicting neurodevelopmental diagnoses in individuals based on their neuroimaging, introducing the exciting prospect of biomarkers in disorders that have historically lacked any. This is an important step forward from finding group differences between participants with different disorders using statistical methods.

This may help advance the case of using advanced imaging for prognostication and personalised medicine approaches.

Authors, including Jung and colleagues, looking for neural biomarkers have used machine learning to recognise discriminating patterns in regions of interest in functional MRI paradigms. Other studies have focused on cortical thickness in structural MRI and fractional anisotropy in diffusion tensor imaging. Modalities used reflect current understanding of pathophysiology: a higher proportion of ASD and ADHD studies used functional imaging than Alzheimer's studies. Using these methods, the mean accuracy of distinguishing children with established diagnoses from traditional developing children currently lies at about 82% in ASD and 76% in ADHD. This is similar to that for schizophrenia, another disorder with neurodevelopmental origins, but less accurate than for the diagnosis of the neurodegenerative Alzheimer's disease (86%). The recognised, reproducible structural abnormalities in Alzheimer's lend themselves to being more accurate neural biomarkers than the subtle, network-based changes in neurodevelopmental disorders.<sup>1</sup>


Further, heterogeneity within disorders may limit the accuracy of a biomarker based on a single imaging modality. Although a biomarker differentiating neurodevelopmental atypicality from neurotypicality is an essential first step, identifying a disorder from a set of differential diagnoses may provide genuine clinical utility. Unfortunately, there is a paucity of literature on this, making Jung and colleagues' contribution a useful addition: they differentiate between 'homogeneous' ASD and ADHD with an accuracy of 79%.<sup>5</sup> However, as they highlight, there are several limitations to generalisability to 'real-life' samples. For example, they only included boys, who had an average IQ and excluded participants with comorbid ASD and ADHD. The latter may also suggest that the shared neural correlates discussed in the study are not those that are responsible for comorbid features.

Improving prognostic information in children presenting with neurodevelopmental difficulties using advanced imaging may hence prove challenging. Recent literature suggests that combining multimodal imaging modestly improves prediction accuracy in ASD and ADHD. Combining imaging findings with genetic risk scores, neurophysiological and neurocognitive measures, as reported for bipolar affective disorder and schizophrenia may also provide opportunities for translational research. This approach could be extended to assessing at-risk populations (such as siblings of a child with autism) before the clinical onset of symptoms.

## Conclusions

Despite the increasing insight on neurobiology and the encouraging prospect of biomarkers in neurodevelopmental disorders, there

remains significant heterogeneity in current neuroimaging literature. Differing methodologies regarding case ascertainment (including age and gender ratios of cohorts), imaging protocols and analysis methods contribute to the inconsistent findings. Longitudinal and developmental psychopathology approaches to account for age-related changes in behaviour and neural connections are uncommonly utilised. Brain imaging biomarkers treat ASD and ADHD as homogeneous and discrete concepts. However, there is established heterogeneity in symptoms, developmental trajectories and neurogenetics in both ASD and ADHD.<sup>4</sup> Furthermore, there is evidence of convergence of symptoms, risk factors and neurobiology spanning across psychiatric disorders. A shift towards the study of endophenotypes in neurodevelopmental disorders is likely to provide new insights that could aid in transdiagnostic treatment approaches (for example treating emotional dysregulation in the context of social impairment). The Research Domain Criteria suggest tools to study endophenotypes in neurodevelopmental and mental disorders, combining behavioural, genomic and neural network approaches. This should be coupled with measuring dimensional symptom severity as opposed to just relying on diagnostic categories. Despite the obvious complexity, the change to investigating comorbid ADHD and ASD using integrative methodologies and advanced statistical methods is welcome as this population has greater impairment in adaptive function and responds less well to pharmacological intervention than the disorders in isolation.

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## References

- 1 Park MTM, Raznahan A, Shaw P, Gogtay N, Lerch JP, Chakravarty MM. Neuroanatomical phenotypes in mental illness: identifying convergent and divergent cortical phenotypes across autism, ADHD and schizophrenia. *J Psychiatry Neurosci* 2018; **43**: 201–12.
- 2 Visser JC, Rommelse NN, Greven CU, Buitelaar JK. Autism spectrum disorder and attention-deficit/hyperactivity disorder in early childhood: a review of unique and shared characteristics and developmental antecedents. *Neurosci Biobehav Rev* 2016; **65**: 229–63.
- 3 Bethlehem RAI, Romero-Garcia R, Mak E, Bullmore ET, Baron-Cohen S. Structural covariance networks in children with autism or ADHD. *Cereb Cortex* 2017; **27**: 4267–76.
- 4 Klein M, van Donkelaar M, Verhoef E, Franke B. Imaging genetics in neurodevelopmental psychopathology. *Am J Med Genet B Neuropsychiatr Genet* 2017; **174**: 485–537.
- 5 Jung M, Tu Y, Park J, Jorgenson K, Lang C, Song W, Kong J. Surface-based shared and distinct resting functional connectivity in attention-deficit hyperactivity disorder and autism spectrum disorder. *Br J Psychiatry* 2019; this issue.
- 6 Mash LE, Reiter MA, Linke AC, Townsend J, Muller RA. Multimodal approaches to functional connectivity in autism spectrum disorders: an integrative perspective. *Dev Neurobiol* 2018; **78**: 456–73.