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Early diagnosis of autism spectrum disorder using structural connectivity biomarker

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Autism spectrum disorder (ASD) is a multifaceted neurodevelopmental disorder marked by challenges in social interaction, communication, and the presence of repetitive or restricted behaviors (APA, 2013). The disorder exhibits a broad spectrum of symptoms and severity, making it a highly heterogeneous condition. Despite its prevalence, the exact causes of ASD remain largely unknown, while both genetic and environmental factors are implicated in the neuropathology of ASD. In recent years, progress in the development of neuroimaging methods have offered significant understanding into the structural connectivity features associated with ASD. A recent review article summarized the results of 19 studies using diffusion tensor imaging (DTI) to examine white matter integrity in infants and young children (6 months to 12 years) with autism. In most of the reviewed studies, the authors reported an increase in fractional anisotropy (FA) and a decrease in radial diffusivity in various tracts including the corpus callosum, uncinate fasciculus, cingulum, inferior longitudinal fasciculus, and superior longitudinal fasciculus, whereas a decrease in FA and an increase in radial diffusivity were reported in the inferior fronto-occipital fasciculus tract in children with ASD compared to controls (Faraji *et al.*, 2023). These alterations suggest differences in the structural connectivity of the brain in individuals with ASD. Yet, most of these studies were limited by small sample size, and the power of using these DTI features in differentiating ASD from TD remains unclear.

The study conducted by Jiang *et al.* (2023) provides significant insights into the structural changes in the brain associated with ASD. The research aimed to identify potential neural diagnostic indicators for ASD using tractography techniques, especially in young children, during the period when ASD symptoms fully developed. The study used DTI to model brain-wide differences in structural connectivity in children with ASD and typically developing (TD) children. The authors included a reasonable size of discovery cohort of 93 children with ASD and 26 TD children, along with two independent validation cohorts from three distinct cities in China. They measured brain-wide structural connectivity using DTI and constructed a connection matrix for each child. The results were then compared between the ASD and TD groups. The study found 33 structural connections that showed

increased FA in children with ASD compared to TD children. These connections were associated with the severity of autistic symptoms as well as impaired general cognitive development. Most of these connections (29 out of 33) involved the frontal lobe and included five distinct networks related to default mode, motor control, social recognition, language, and reward. The classification model developed from the discovery dataset achieved a very high accuracy rate of 96.77%, and 91.67% and 88.89% in the two independent validation datasets. This suggests that the discovered structural connectivity variations, mainly involving the frontal cortex, can accurately differentiate children with ASD from TD children.

The findings of this study are significant as they may represent a robust early brain biomarker of structural connectivity for ASD. This could potentially address the requirements of differentiating subtypes of ASD at an individual level. Future studies could further explore individual differences within the ASD group because individuals with ASD often exhibit significant variations in the quality and quantity of social-communication deficits, varying from minimal social behaviors to sufficient but atypical social interactions (Lord *et al.*, 2020). Previous studies using neuroimaging techniques have revealed various subtypes of ASD, underscoring the heterogeneous nature of this disorder (Chen *et al.*, 2019; Choi *et al.*, 2022; Guo *et al.*, 2023; Ren *et al.*, 2023; Shan *et al.*, 2022). Such individual differences could affect the comparison of ASD with TD controls or other neurodevelopmental disorders at the group level, hence, accounting for the individual factors may aid more accurately reveal the DTI features of ASD subtypes and further improve the precision of diagnosis of different subtypes of ASD.

Jiang *et al.*'s study offers promising findings in the detection of ASD using DTI biomarkers. However, the specificity of these biomarkers in differentiating ASD from other neurodevelopmental or psychiatric disorders such as developmental delay or attention-deficit/hyperactivity disorder (ADHD) could be further explored. These disorders may share similar symptoms with ASD, such as language delays and communication difficulties in developmental delay (Ventola *et al.*, 2007), or social difficulties in ADHD (Antshel & Russo, 2019), which make differentiating

ASD from these disorders difficult, particularly in young children. Previous neuroimaging studies also showed similarities in functional and structural neuroimaging data between ASD and ADHD (Dougherty *et al.*, 2016; Kangarani-Farahani *et al.*, 2022; Zhao *et al.*, 2022), suggesting those shared symptoms may have common neurological processes. Future neuroimaging studies should therefore consider the inclusion of subjects with neurodevelopmental disorders such as developmental delay and ADHD that shared similar symptoms with ASD as the comparison groups to delineate the DTI features of ASD.

One drawback from Jiang *et al.*'s study is that the comorbidity profile of the studied cohort was unclear. Comorbidity is a prevalent factor that can add complexity to the diagnosis process of ASD. According to DeFilippis (2018), it is estimated that nearly 70% of individuals with ASD experience at least one comorbid psychiatric disorder, and almost 40% may have two or more psychiatric disorders. It is important to note that the reported comorbidity rate can vary across different studies due to the inclusion of diverse population subgroups and methodological differences. However, the average rate of individuals with ASD experiencing at least one comorbid psychiatric disorder remains high (~50%) in children and adults (Hossain *et al.*, 2020). Commonly reported comorbidities of ASD include ADHD, anxiety disorders, depressive disorders, bipolar and mood disorders, schizophrenia spectrum, and conduct disorders (Hossain *et al.*, 2020; Hung *et al.*, 2023). These comorbid psychiatric conditions could potentially influence neuroimaging findings. For instance, shared white matter abnormalities have been reported between ASD and ADHD (Zhang *et al.*, 2023). Additionally, increased functional connectivity between the prefrontal and frontoparietal regions, as well as between the orbitofrontal and occipital regions, has been observed in ASD comorbid with ADHD compared to ASD alone (Lin *et al.*, 2023). These findings highlight the potential impact of comorbid psychiatric disorders on the neuroimaging profile of ASD. Therefore, it would be advisable for future neuroimaging studies investigating diagnostic markers of ASD to consider comorbidity as a potential confounding factor. This consideration could help to ensure more accurate and reliable results in the quest to understand and diagnose ASD.

In conclusion, the work of Jiang *et al.* (2023) is highly commendable for demonstrating the high sensitivity of DTI biomarkers in detecting ASD from TD controls. Their research has significantly contributed to the field and opened up new avenues for understanding ASD. The specificity of these DTI biomarkers for differentiating ASD from other neurodevelopmental disorders presents an exciting area for further exploration. While Jiang *et al.*'s study provides a solid foundation, future research could benefit from considering potential confounding factors such as the heterogeneous nature of ASD, comorbidity with other psychiatric disorders, and the inclusion of other neurodevelopmental disorders for comparison in the study design. Given that shared symptoms are common across neuropsychiatric and neurodevelopmental disorders and ASD, it would be insightful for future studies investigating structural connectivity markers of ASD to shift their focus from disorder-to-brain relationships to symptom-to-brain relationships. This approach could specifically target symptoms unique to ASD, providing a more in-depth understanding of the disorder.

Author contributions

Way K. W. Lau (Conceptualization, Writing – original draft, Writing – review & editing), Mei-Kei Leung (Conceptualization, Writing – review & editing), Kean Poon (Writing – review & editing), and Ruibin Zhang (Writing – review & editing)

Conflict of interest

None declared.

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