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### Authors

Parkkinen, Salla

Radua, Joaquim

Andrews, Derek

et al.

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# Cerebellar network alterations in adult attention-deficit/hyperactivity disorder

Salla Parkkinen, MSc; Joaquim Radua, MD, PhD; Derek S. Andrews, PhD; Declan Murphy, MD; Flavio Dell'Acqua, PhD; Valeria Parlatini, MD, PhD

**Background:** Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition that often persists into adulthood. Underlying alterations in brain connectivity have been identified but some relevant connections, such as the middle, superior, and inferior cerebellar peduncles (MCP, SCP, and ICP, respectively), have remained largely unexplored; thus, we sought to investigate whether the cerebellar peduncles contribute to ADHD pathophysiology among adults. **Methods:** We applied diffusion-weighted spherical deconvolution tractography to dissect the cerebellar peduncles of male adults with ADHD (including those who did or did not respond to methylphenidate, based on at least 30% symptom improvement at 2 months) and controls. We investigated differences in tract metrics between controls and the whole ADHD sample and between controls and treatment-response groups using sensitivity analyses. Finally, we analyzed the association between the tract metrics and cliniconeuropsychological profiles. **Results:** We included 60 participants with ADHD (including 42 treatment responders and 18 nonresponders) and 20 control participants. In the whole ADHD sample, MCP fractional anisotropy (FA;  $t_{78} = 3.24$ ,  $p = 0.002$ ) and hindrance modulated orientational anisotropy (HMOA;  $t_{78} = 3.01$ ,  $p = 0.004$ ) were reduced, and radial diffusivity (RD) in the right ICP was increased ( $t_{78} = -2.84$ ,  $p = 0.006$ ), compared with controls. Although case-control differences in MCP FA and HMOA, which reflect white-matter microstructural organization, were driven by both treatment response groups, only responders significantly differed from controls in right ICP RD, which relates to myelination ( $t_{60} = 3.14$ ,  $p = 0.003$ ). Hindrance modulated orientational anisotropy of the MCP was significantly positively associated with hyperactivity measures. **Limitations:** This study included only male adults with ADHD. Further research needs to investigate potential sex- and development-related differences. **Conclusion:** These results support the role of the cerebellar networks, especially of the MCP, in adult ADHD pathophysiology and should encourage further investigation. **Clinical trial registration:** NCT 03709940

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by inattentive or hyperactive-impulsive symptoms,<sup>1</sup> and is estimated to affect about 4% of adults.<sup>2</sup> Adult ADHD has been associated with increased risk of academic and occupational failure, delinquency, and self-medication with alcohol and substances, as well as high societal costs, mainly related to health care, educational support, and income loss.<sup>3</sup> Stimulants, such as methylphenidate, represent the first-line treatment for ADHD and are effective in reducing core ADHD symptoms, but response rates are lower among adults than children.<sup>4,5</sup> The neurobiological characteristics underlying symptom severity, associated cognitive deficits, and treatment response in adults require further study.<sup>3,6</sup> Imaging studies have iden-

tified alterations in brain anatomy and function among people with ADHD compared with neurotypical controls, although these have mainly focused on children. Observed alterations include reduced volume of the basal ganglia and frontocingulate cortex,<sup>7,8</sup> and hypoactivation of frontostriatal regions during inhibition tasks.<sup>7</sup> Studies investigating brain connectivity are increasingly common.<sup>6,9</sup>

The anatomy of brain connections can be studied using diffusion-weighted imaging, which measures restriction of water diffusivity to identify white-matter bundles and estimate microstructural properties. The most recent systematic review included 129 diffusion-weighted imaging studies of ADHD and reported alterations in diffuse brain connectivity, most consistently in the splenium and body of the corpus callosum.<sup>6</sup> The review highlighted that most studies have focused on frontostriatal networks, in line with a dominant

**Correspondence to:** V. Parlatini, Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 16 De Crespigny Park, SE5 8AF, London, UK; School of Psychology, University of Southampton, SO17 1BJ, Southampton; UK; valeria.parlatini@kcl.ac.uk

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pathophysiological hypothesis of ADHD. Further, only one-fifth of studies restricted recruitment to adults. Among studies that included adult or mixed samples, 17 identified alterations within frontostriathalamic circuits, 11 in the corpus callosum, and 9 in the superior longitudinal fasciculus. These findings primarily focused on reduced fractional anisotropy (FA), a proxy measure of white-matter microstructural organization, among people with ADHD compared with neurotypical controls.<sup>6</sup> Other relevant brain connections, such as the cerebellar peduncles, have remained largely unexplored, especially in adults.

The cerebellar networks likely contribute to ADHD pathophysiology because the cerebellum supports motor, cognitive, and emotion regulation skills that are impaired in ADHD.<sup>10–12</sup> The role of the cerebellum in motor control and learning is well established. However, studies have shown that cerebellar damage may not only cause marked motor disturbances but also attention deficits, impulsivity, anxiety, and aggressive behaviour, especially when damage occurs early during development.<sup>12,13</sup> The cerebellum is connected to other brain structures — such as the cerebral cortex and the basal ganglia — through the cerebellar peduncles, and thus forms part of an integrative brain system that supports planning and execution of complex behavioural sequences.<sup>11,12,14</sup>

In line with these observations, structural and functional cerebellar alterations have been observed among people with ADHD.<sup>15,16</sup> For instance, an early longitudinal study reported persistently smaller cerebellar volumes during childhood and adolescence among people with ADHD compared with controls.<sup>17</sup> Similar alterations were also observed among adults with ADHD.<sup>18–20</sup> A subsequent study showed that reduced volume of the right posterior cerebellar lobe was specific to people with ADHD in comparison to those with autism spectrum disorder.<sup>15</sup> This is of relevance, as the posterior cerebellum primarily supports cognitive functions, such as executive functions, which are impaired in ADHD.<sup>21</sup> Resting-state functional connectivity analyses have also identified differences in frontocerebellar connectivity among both children and adults with ADHD.<sup>22–25</sup> Further, a defective interaction has been observed between cerebellar areas functionally connected to the default mode network, which is associated with mind wandering, and the dorsal attentive network, which supports the voluntary control of attention. The altered interplay between these functional networks has been associated with attentional lapses during cognitive tasks among adults with ADHD.<sup>22,26</sup> The systematic review<sup>6</sup> identified 6 diffusion-weighted imaging studies reporting reduced FA among children with ADHD within the cerebellum or its main afferent pathway, the middle cerebellar peduncle (MCP).<sup>27–32</sup> Among these, only 1 study also investigated the inferior cerebellar peduncle (ICP),<sup>32</sup> and no study investigated the superior cerebellar peduncle (SCP). Two studies focused on adults; 1 observed increased FA in the MCP<sup>33</sup> and the other identified a significant association between cerebellar network organization and symptom severity.<sup>34</sup> Accordingly, alterations in the structural connections of the cerebellum in ADHD and their relation to symptoms are poorly understood, particularly in adults.

Previous diffusion-weighted imaging studies have mostly included people under treatment, resulting in research samples enriched with those who respond to such treatment. The biological differences between those who do and do not respond to stimulant treatment are poorly understood. To date, only 2 diffusion-weighted imaging studies have reported associations between connectivity measures and treatment response in ADHD. These studies separately focused on frontothalamic or frontoparietal connections, either in children<sup>35</sup> or adults with ADHD.<sup>36</sup> The association of cerebellar structural connectivity with ADHD treatment response in adults has not been explored, but this could provide valuable insights into the biological basis of treatment resistance. Overall, a more comprehensive investigation of the role of the 3 cerebellar peduncles in adult ADHD and potential differences between responders and nonresponders to treatment is warranted. Thus, we sought to investigate whether the cerebellar peduncles contribute to ADHD pathophysiology among adults

## Methods

To better understand the potential role of the cerebellar networks in the pathophysiology of adult ADHD, we investigated the anatomy of the cerebellar peduncles in adults with ADHD (including those who did or did not respond to treatment with methylphenidate) and controls. We used diffusion-weighted spherical deconvolution tractography to virtually dissect the cerebellar peduncles. We then compared controls with the whole ADHD sample, and with treatment-response groups in sensitivity analyses. Finally, we analyzed the association between cerebellar tract metrics and clinico-neuropsychological profiles.

### Participants

We recruited adults with ADHD (aged 18–45 yr) from the Adult ADHD Clinic, Maudsley Hospital (London, UK), to take part in a prospective longitudinal study investigating neurobiological associates of treatment response.<sup>36</sup> We determined the sample size based on a power calculation. Considering that around 34% of adults do not respond to methylphenidate,<sup>5</sup> we required 60 participants with ADHD to obtain a third for whom the treatment was ineffective, considering an effect size (*d*) of 0.4 and a statistical power of 80%. To enhance sample homogeneity, we included only males, among whom ADHD is more commonly diagnosed<sup>37</sup> because there is preliminary evidence of sex differences in brain connectivity<sup>38–41</sup> and biological response to stimulants.<sup>42–44</sup> A clinician confirmed the diagnosis of ADHD according to DSM-V criteria.<sup>1</sup> We included participants with an intelligence quotient (IQ) above 70 and no current comorbidities. We mainly recruited medication-naïve participants. No participants received any psychotropic treatment for at least a year before this study. Finally, we matched neurotypical controls on sex, age, and IQ; this group provided baseline scans for secondary comparative analyses.

### Research protocol

This study was part of a larger trial employing a single-blind placebo-controlled crossover design, followed by a longitudinal open-label phase (NCT 03709940). The full protocol has been described previously.<sup>36</sup> The trial tests whether pretreatment brain characteristics were associated with treatment response at 2 months among adults with ADHD. In this specific study, we investigated the anatomy of the cerebellar peduncles and their cliniconeuropsychological correlates. In brief, adults with ADHD completed clinical and behavioural measures under placebo (i.e., baseline) and, 2 days after, under an acute dose of methylphenidate. Participants were blind to the content of the capsules, whose order was reversed for the second half of participants to balance potential practice and expectation effects. Participants also underwent baseline diffusion-weighted imaging. They were then started on the same long-acting formulation of methylphenidate (Concerta XL, titrated up to 54 mg according to standard clinical care). Clinical and behavioural measures were then repeated after 2 months (i.e., follow-up), at which time treatment response was ascertained.

At each time point, participants with ADHD completed the Barkley Adult ADHD Rating Scale-IV (BAARS-IV),<sup>45</sup> which provided 3 scores (ADHD total score, ADHD inattention, and ADHD hyperactivity-impulsivity), and the Quantitative Behaviour (Qb) test (<https://www.qbtech.com>). We selected this test because it measures core ADHD symptoms using a continuous performance task and infrared monitoring of movements, and was granted approval from the Food and Drug Administration to aid treatment evaluation.<sup>46</sup> We considered both summary scores (Qb activity, Qb impulsivity, and Qb inattention) and underlying individual parameters. For instance, the Qb activity score includes parameters measured by motion-capturing device, such as time active (i.e., time the participant moves more than 1 cm/s); microevents (i.e., how many times the participant moves more than 1 mm); distance (i.e., the overall distance, in metres, covered by the marker during the task), and area (i.e., the overall area covered by the marker). Appendix 1, available at [www.jpnc.ca/lookup/doi/10.1503/jpn.230146/tab-related-content](http://www.jpnc.ca/lookup/doi/10.1503/jpn.230146/tab-related-content), provides details on the included parameters. We classified participants with ADHD as responders or nonresponders according to an overall symptom improvement of at least 30% (BAARS-IV total score) at 2 months. We chose this cut-off as it is commonly used in pharmacological trials of ADHD.<sup>5,47</sup> We compared baseline cerebellar metrics between participants with ADHD and controls, and between ADHD responders and nonresponders. We also tested the association between baseline cerebellar metrics and clinicobehavioural measures at the 3 time points.

### Diffusion MRI data acquisition and analysis

We acquired diffusion-weighted imaging scans at baseline. Details on imaging data, preprocessing, and tractography protocols are described in Appendix 1. Tracts were visualized using Trackvis (<http://www.trackvis.org>).<sup>48</sup> We dissected 5 tracts for

each participant, as previously described.<sup>49</sup> Tracts included the left and right SCP, left and right ICP, and the MCP (Figure 1). Of note, the MCP was reconstructed as a single large bundle, as it was not possible to separate the 2 branches at the level of the pontine nuclei. We extracted mean diffusivity, FA, axial diffusivity, radial diffusivity (RD), tract volume, track count, and hindrance modulated orientational anisotropy (HMOA) for statistical analysis (Appendix 1).

### Statistical analysis

We used SPSS software (version 26) to conduct the statistical analyses. We confirmed normality of tract metrics using histograms and Q-Q plots. We used descriptive statistics to analyze the characteristics of the sample and independent-sample *t* tests (2-tailed) to investigate differences in tract metrics between the whole ADHD sample and controls. We applied Bonferroni correction to account for multiple comparisons ( $n = 5$  tracts,  $p < 0.01$ ). For tract metrics that survived correction for multiple comparisons, we ran a sensitivity analysis, using 1-way analysis of variance (ANOVA) and, where appropriate, post hoc *t* tests to investigate potential group differences among controls and the 2 ADHD treatment groups. As we limited the sensitivity analysis to the tract metrics that survived Bonferroni correction, these results were deemed significant at  $p$  less than 0.05. Finally, to ensure that the findings were not confounded by age or total IQ, we repeated the analyses including age and IQ as covariates via multiple regression.

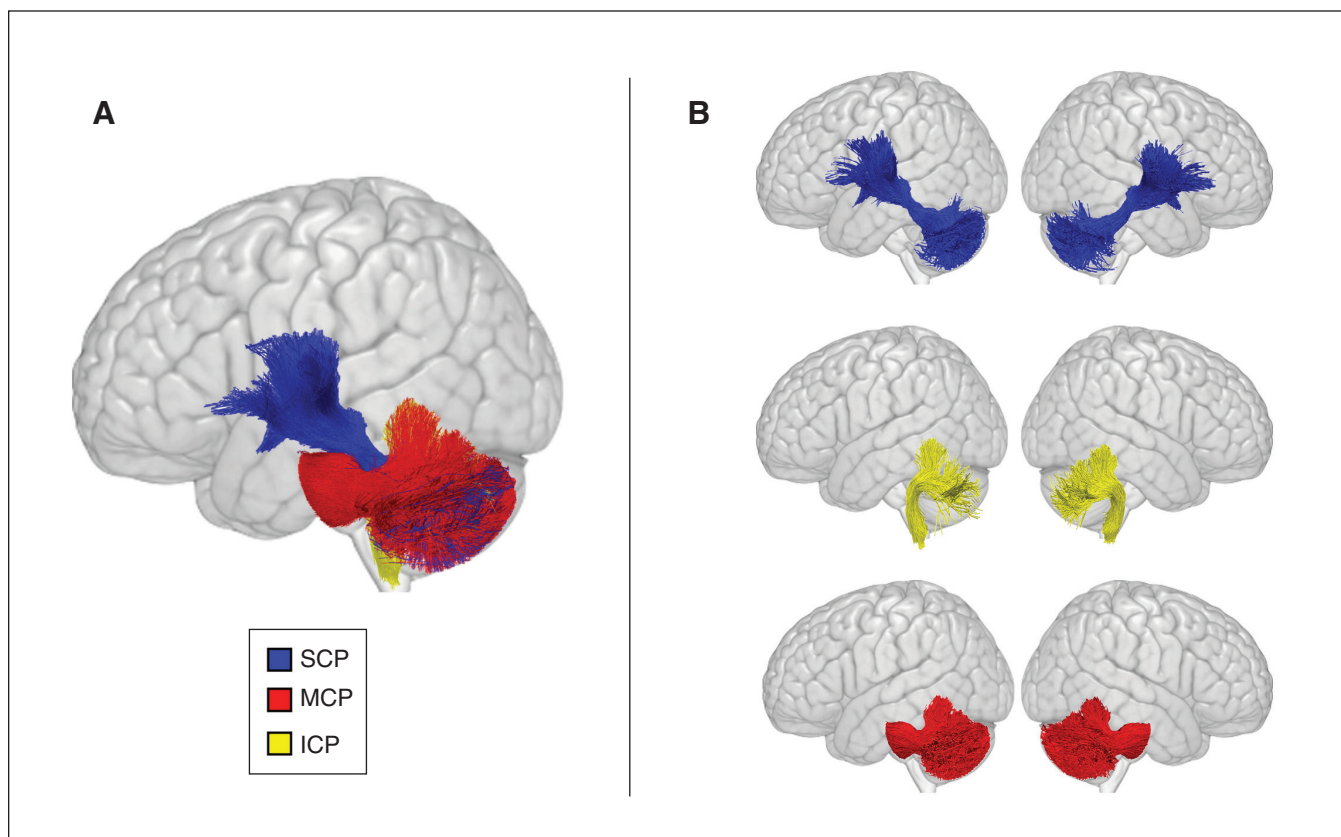
We used correlation analyses to investigate associations between the tract metrics that survived correction for multiple comparisons and cliniconeuropsychological measures in the whole ADHD sample. Specifically, we considered baseline clinical and neuropsychological measures, their change under an acute dose of methylphenidate (compared with baseline), and their change at follow-up (compared with baseline). Here, we applied Bonferroni correction for multiple comparisons by the number of tracts included in the correlation analyses. Effects of age and IQ were controlled through partial correlations.

### Ethics approval

The study was approved by the Camden and Islington Research Ethics Committee (no. 12/LO/0630), and complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration. All participants provided written consent.

### Results

Full details have been reported previously<sup>36</sup> and are summarized in Appendix 1, Table S1. In brief, the sample included 60 male adults with ADHD (58% with combined and 42% with inattentive presentation). Participants with ADHD had a mean age of 28.1 (standard deviation [SD] 7.3) years and an average full-scale IQ of 109.9 (SD 12.3). They were



**Figure 1:** Lateral views of the 5 tracts dissected in each participant, including the bilateral superior cerebellar peduncles (SCPs), the bilateral inferior cerebellar peduncles (ICPs), and the middle cerebellar peduncle (MCP), presented both (A) together and (B) separately.

mostly White British (71.6%), right-handed (78%), and medication-naïve (77%). Twenty controls were matched for sex, age, and IQ (Appendix 1, Table S2); they were mostly right-handed (90%). All participants with ADHD received long-acting methylphenidate. This was titrated up to 54 mg for most participants, as per protocol. The dose was modified in 34% of participants, mainly because of adverse effects. At follow-up, we classified participants into responders ( $n = 42$ ) and nonresponders ( $n = 18$ ), based on their improvement in BAARS-IV total scores. The 2 groups did not significantly differ in ethnicity, baseline clinical severity, handedness, age, total IQ, or methylphenidate dose at follow-up. Characteristics of the whole ADHD sample and responder groups, with comparisons, have been reported previously<sup>36</sup> and are summarized in Appendix 1, Table S1 and Table S2. Among participants who received methylphenidate at a dose lower than 54 mg, 70% were classified as responders.

#### Participants with ADHD v. neurotypical controls

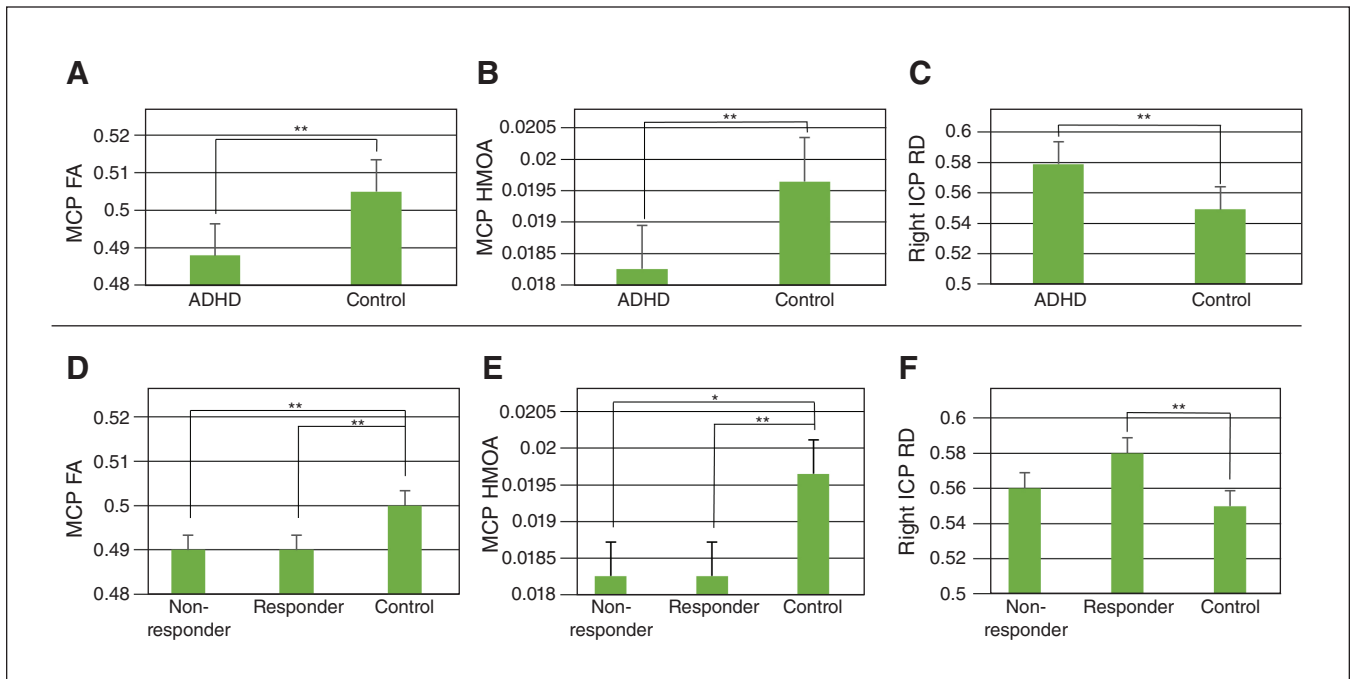
Independent-sample  $t$  tests revealed significant differences between the participants with ADHD and controls in MCP FA ( $t_{78} = 3.24$ ,  $p = 0.002$ ), MCP HMOA ( $t_{78} = 3.01$ ,  $p = 0.004$ ), right ICP RD ( $t_{78} = -2.84$ ,  $p = 0.006$ ), MCP RD ( $t_{78} = -2.44$ ,  $p = 0.017$ ), and right ICP mean diffusivity ( $t_{78} = -2.55$ ,  $p = 0.013$ ). The first 3 metrics remained significant after

Bonferroni correction for multiple comparisons. Multiple regressions showed no effect of age or total IQ on these metrics (Appendix 1, Table S3). These results indicate that MCP FA and HMOA were reduced, while the RD of the right ICP was higher, among participants with ADHD compared with controls (Figure 2). All results are reported in Appendix 1, Table S3.

#### Responders, nonresponders, and neurotypical controls

Sensitivity analyses tested for differences between the treatment-response groups and controls in the 3 tract metrics that survived correction for multiple comparisons. We observed a significant effect of group in MCP FA ( $F_{77,2} = 5.18$ ,  $p = 0.008$ ), MCP HMOA ( $F_{77,2} = 4.46$ ,  $p = 0.015$ ), and RD of the right ICP ( $F_{77,2} = 5.73$ ,  $p = 0.005$ ). Post hoc  $t$  tests indicated that MCP FA was significantly lower among both responders ( $t_{60} = -3.00$ ,  $p = 0.004$ ) and nonresponders ( $t_{36} = -2.76$ ,  $p = 0.009$ ) than controls. Similarly, MCP HMOA was significantly lower in both treatment-response groups than the control group ( $t_{60} = -2.79$ ,  $p = 0.007$  v. responder group;  $t_{36} = -2.30$ ,  $p = 0.027$  v. nonresponder group). Finally, RD of the right ICP was significantly higher among responders than controls ( $t_{60} = 3.14$ ,  $p = 0.003$ ) (Figure 2). We did not observe significant differences between responders and nonresponders in these 3 tract metrics. Group differences in these metrics retained





**Figure 2:** Group differences in cerebellar tract metrics, showing significant differences between all participants with attention-deficit/hyperactivity disorder (ADHD) and neurotypical controls that survived correction for multiple comparisons, including (A) fractional anisotropy (FA) of the middle cerebellar peduncle (MCP), (B) hindrance modulated orientational anisotropy (HMOA) of the MCP, and (C) radial diffusivity (RD) of the right inferior cerebellar peduncle (ICP). Significant differences between ADHD treatment responders, nonresponders, and controls are shown in (D) MCP FA, (E) MCP HMOA, and (F) RD of the right ICP. \*Significant at  $p < 0.05$ ; \*\*significant at  $p < 0.01$ .

significant when we controlled for age and total IQ using multiple regressions (Appendix 1, Table S4). We report the ANOVA results for all tract metrics in Appendix 1, Table S4.

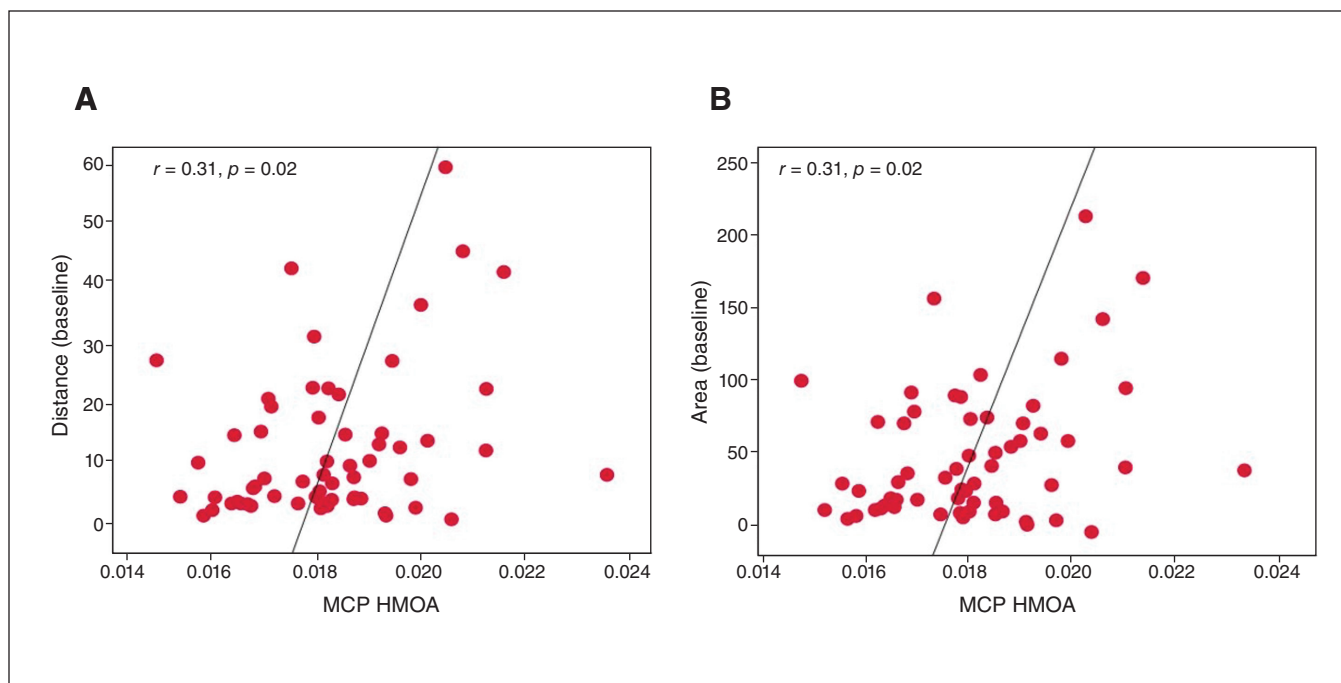
#### Correlations between tract metrics and cliniconeuropsychological profiles

We determined correlations between tract metrics and baseline neuropsychological variables, measured by the Qb test, among participants with ADHD. We found that MCP FA was significantly correlated with distance ( $r = 0.27$ ,  $p = 0.03$ ), and MCP HMOA was correlated with both distance and area (both  $r = 0.31$ ,  $p = 0.02$ ). Further, MCP FA was significantly correlated with change in omission errors under an acute dose of methylphenidate ( $r = 0.29$ ,  $p = 0.03$ ) and at follow-up ( $r = 0.27$ ,  $p = 0.04$ ). These results suggest that microstructural organization of the MCP was associated with increased baseline hyperactivity, as measured by the Qb test, and with improvement in the number of omissions (i.e., inattention) under treatment. Associations between MCP HMOA and baseline hyperactivity measures survived correction for multiple comparisons ( $p < 0.025$ ) (Figure 3 and Appendix 1, Table S5 and Table S6). All the above associations retained significance when controlling for the effects of age and full-scale IQ (Appendix 1, Table S7). For completeness, results of correlations for tract metrics not included in the main analyses are reported in Appendix 2, Table S8, and Appendix 3, Table S9, available at [www.jpn.ca/lookup/doi/10.1503/jpn.230146/tab-related-content](http://www.jpn.ca/lookup/doi/10.1503/jpn.230146/tab-related-content).

## Discussion

We investigated the 3 cerebellar peduncles and their associations with cliniconeuropsychological profiles and response to methylphenidate treatment among adults with ADHD. The results indicate significant reductions in MCP FA and HMOA and increased RD in the right ICP among adults with ADHD. Participants who responded to methylphenidate did not significantly differ from those who did not in these 3 metrics. However, while case-control differences in MCP FA and HMOA were driven by both treatment response groups, only responders had significantly higher RD in the right ICP than controls. In addition, MCP HMOA was significantly positively associated with baseline levels of hyperactivity levels among all participants with ADHD.

Comparisons between our results and other findings are limited, given the paucity and heterogeneity of published studies. For instance, reduced white-matter microstructural organization of the MCP has been reported among children and adolescents with ADHD.<sup>27-31</sup> However, these results are inconsistent.<sup>6,32</sup> Further, only 2 diffusion-weighted imaging studies have reported cerebellar network alterations among adults with ADHD.<sup>33,34</sup> The study that measured the microstructural characteristics of individual tracts reported increased FA in the MCP of participants with ADHD compared with controls.<sup>33</sup> This contrasts with our findings and those of most studies among children.<sup>6</sup> The incongruence between these findings can likely be attributed to sample and



**Figure 3:** Correlations surviving correction for multiple comparisons among participants with attention-deficit/hyperactivity disorder. Hindrance modulated orientational anisotropy (HMOA) in the middle cerebellar peduncle (MCP) was positively correlated with pretreatment hyperactivity levels, as measured by (A) distance and (B) area metrics of the Quantitative Behaviour test.

methodological differences between studies. To our knowledge, only 1 diffusion-weighted imaging study reported reduced FA in the ICP, but included only children with ADHD.<sup>32</sup> No study has investigated the SCP in the ADHD population. Accordingly, our findings of significant differences in MCP microstructural organization and in RD in the right ICP among adults with ADHD fills an important gap in the ADHD literature.<sup>6</sup>

Significant differences between adults with ADHD and neurotypical controls were limited to a few measures among cerebellar peduncles. These findings are in line with those of structural imaging studies, which often observe less prominent anatomic alterations among adults than children with ADHD, especially in the basal ganglia.<sup>8,50</sup> Reductions in ADHD-associated anatomic alterations with time, especially in brain regions involved in the modulation of motor functions, may relate to improvements in hyperactivity and impulsivity symptoms that are often observed among adolescents and adults with ADHD.<sup>3</sup> Taken together, our results and those of previous studies suggest that, although anatomic differences generally reduce with age, subtle alterations in the microstructural organization of the cerebellar networks associated with ADHD, especially of the MCP, may contribute to the persistence of ADHD into adulthood.

The suggestion that the MCP plays a role in ADHD pathophysiology is further supported by the significant correlation between MCP microstructural organization and neuropsychological profiles. We observed that MCP HMOA was positively associated with increased hyperactivity at baseline among participants with ADHD, which is in line with

the role of the cerebellum in modulating motor functions.<sup>10</sup> Very few diffusion-weighted imaging studies have investigated the association between cerebellar white-matter anatomy and cliniconeuropsychological profiles, and these mostly involved children.<sup>6</sup> A study involving adolescents with ADHD reported that reduced MCP FA was associated with executive dysfunction and inattention.<sup>30</sup> Similarly, reduced cerebellar FA was reported to be associated with increased severity of inattentive symptoms<sup>27</sup> and worse performance at the continuous performance task among youth.<sup>51</sup> One study has examined correlations between cerebellar anatomy and clinical measures in adult ADHD. Using a graph-theoretical approach, this study reported associations between the cerebellar network and symptom severity.<sup>34</sup> In contrast, we observed group differences associated with cognitive deficits but not with symptom severity. However, these studies are not methodologically comparable, as the previous study did not separately investigate the 3 cerebellar peduncles.<sup>34</sup> Further, we primarily tested associations for the tract metrics that survived correction for multiple comparisons between participants with ADHD controls. Studies have suggested that associations with symptoms may also be mediated by white-matter characteristics in addition to case-control differences.<sup>52</sup>

We did not identify significant differences between participants with ADHD who did or did not respond to methylphenidate in the 3 metrics that differed between participants with ADHD and controls. However, treatment responders differed significantly from controls in RD of the right ICP. Structural imaging studies involving children with ADHD

reported that nonresponders showed smaller corpus callosum<sup>53</sup> and parieto-occipital white matter,<sup>54</sup> as well as altered developmental trajectories of frontocerebellar regions.<sup>55,56</sup> Two diffusion-weighted imaging studies have reported differences between responders and nonresponders, focusing on frontothalamic tracts in children with ADHD<sup>35</sup> and frontoparietal connections in adults with ADHD.<sup>36</sup> Taken together, the current and previous findings suggest that microstructural characteristics of specific brain connections may contribute to variations in treatment response, although further studies are needed to investigate potential differences between children and adults.

Unfortunately, tractography does not allow the direct investigation of the biological mechanisms through which altered structural connectivity may influence cliniconeuro-psychological profiles or their change under treatment. Functional anisotropy and HMOA are composite measures that reflect several underlying microstructural properties, including altered myelination, axonal density or diameter, or fibre crossing.<sup>57</sup> Although not a direct measure, evidence suggests that RD may be more sensitive than FA or HMOA to alterations in myelination.<sup>58,59</sup> Accordingly, observed differences between adults with ADHD and controls may be indicative of delayed or altered myelination, which has been previously suggested as a pathogenetic mechanism in ADHD.<sup>60</sup> The causes of this putative delayed or altered myelination are unknown, but studies have suggested the involvement of both genetic and environmental factors. For example, genes related to myelination have been identified by a recent genome-wide association meta-analysis of ADHD.<sup>61</sup> In addition, the methylation pattern of these genes, which may reflect environmental insults, has been shown to be associated with the developmental trajectory of ADHD symptoms.<sup>62</sup> Further studies are needed to clarify the exact mechanisms underlying ADHD clinical presentations. However, the current findings support the suggestion that altered white-matter development and resulting structural connectivity may affect the ability of the cerebellum to finely coordinate motor activity and cognitive functions in ADHD.

### Limitations

We included a small percentage of individuals who were previously exposed to ADHD medication. However, most participants were medication-naïve, and previous reports have excluded a normalizing effect of stimulants on brain structure.<sup>63</sup> Further, we included only participants with ADHD who did not have current comorbid conditions, given findings that neuroanatomical differences exist between people with and without comorbidities.<sup>6</sup> For instance, meta-analyses highlighted that people with ADHD and autism spectrum disorder have both shared and specific connectivity alterations.<sup>64</sup> Nevertheless, our results should be validated in clinical samples that include people with comorbidities. Similarly, we included only males, among whom ADHD is more commonly diagnosed,<sup>37</sup> because preliminary evidence showed sex differences in brain connectivity and biological response to stimulants.<sup>40,42–44</sup> However, it is not known how the former

may relate to the latter; thus, we wanted to avoid potential sex-related confounding. Accordingly, studies should be extended to females. In addition, our prospective study design was the most appropriate to identify pretreatment characteristics associated with treatment response but resulted in the inclusion of a relatively small number of nonresponders. This is similar to the proportion of nonresponders identified in previous randomized clinical trials,<sup>5</sup> and is representative of the actual clinical population of adults with ADHD. Similarly, we included a relatively small number of controls, as these were originally recruited for secondary comparative analyses to aid the interpretation of the results of the primary analysis. Thus, although we provided evidence of the involvement of cerebellar peduncles in adult ADHD pathophysiology, our findings need to be validated in larger samples to ensure generalizability. Finally, given limitations of tractography algorithms in areas with multiple fibre crossings, we were unable to separate the right and left components of the MCP. Further investigation in a higher-resolution data set may help resolve limitations related to fibre tracking.

### Conclusion

The present study provided evidence that the cerebellar peduncles play a role in adult ADHD pathophysiology. We observed white-matter microstructural differences between adults with ADHD and neurotypical controls in the MCP and right ICP and found associations between tract metrics and hyperactivity levels. The limited differences between the ADHD and control groups may be reflective of the established age-related improvement of ADHD symptoms, although these findings suggest alterations are still detectable in adults with persistent symptoms. Future studies are needed to clarify potential age-related differences in the role that the cerebral peduncles play in ADHD pathophysiology, including variation in their associations with cliniconeuro-psychological profiles and response to treatment.

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**Affiliations:** From the Institute of Translational Neurodevelopment, Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK (Parkkinen, Andrews, Murphy, Dell'Acqua, Parlatini); the Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK (Parkkinen, Murphy, Dell'Acqua, Parlatini); the Institut d'Investigacions Biomèdiques August Pi i Sunyer, CIBERSAM, Instituto de Salud Carlos III, University of Barcelona, Barcelona, Spain (Radua); the Department of Psychiatry and Behavioral Sciences, The MIND Institute, University of California, Davis, Sacramento, CA, USA (Andrews); the Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK (Dell'Acqua); the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London, Institute of Psychiatry, Psychology and Neuroscience, London, UK (Dell'Acqua); the School of Psychology, University of Southampton, Southampton, UK (Parlatini); the Solent NHS Trust, Southampton, UK (Parlatini).



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