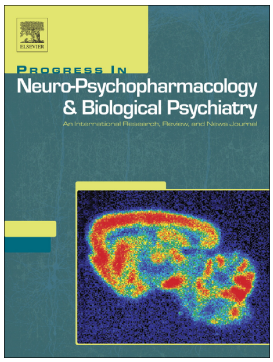

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PII: S0278-5846(20)30441-3

DOI: https://doi.org/10.1016/j.pnpbp.2020.110125

Reference: PNP 110125

To appear in: *Progress in Neuropsychopharmacology & Biological Psychiatry*

Received date: 1 June 2020

Revised date: 21 September 2020

Accepted date: 2 October 2020

Please cite this article as: C. Hyde, I. Fuelscher, E. Sciberras, et al., Understanding motor difficulties in children with ADHD: A fixel-based analysis of the corticospinal tract, *Progress in Neuropsychopharmacology & Biological Psychiatry* (2020), https://doi.org/10.1016/j.pnpbp.2020.110125

Understanding motor difficulties in children with ADHD: a fixel-based analysis of the corticospinal tract

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KEYWORDS: ADHD, fixel-based analysis, corticospinal tract, fine motor skill, white matter

Highlights

- This is the first study to apply a novel fixel-based analysis to examine white matter correlates of fine motor competence in ADHD
- Children with ADHD presented with lower fibre density and cross-section of the corticospinal tract (CST) compared to non-ADHD controls.
- The same children with ADHD showed poorer non-dominant fine motor performance.
- Children with ADHD and reduced fine motor competence demonstrate atypical microstructure within the CST relative to non-ADHD controls.

Abstract:

Aims: Children with attention deficit hyperactivity disorder (ADHD) often present with deficits in fine motor control. The cortico-spinal tract (CST) is critical for voluntary motor control. Although neuroimaging work has identified anomalous microstructural properties in the CST in ADHD, no study to date has attempted to investigate the link between deficits in fine motor performance and microstructural properties of the CST in children with ADHD. This study aimed to address this gap using a novel fixel-based analysis (FBA). **Methods:** Participants were 50 right-handed medication naïve children with a history of ADHD and 56 non-ADHD controls aged 9- 11 years. Fine motor control was assessed using the Grooved Pegboard task. Children underwent high angular resolution diffusion MRI. Following pre-processing, FBA was performed and the semi-automated deep-learning TractSeg was used to delineate the CST bilaterally. Fibre density (FD), fibre cross-section (FC-log), and fibre density/cross-section (FDC) were extracted for each tract. **Results:** Children with ADHD performed significantly worse than non-ADHD children on the Grooved Pegboard task when using their non-dominant hand. They also demonstrated widespread significantly lower diffusion metrics in both CSTs compared to non-ADHD controls. However, no correlations were observed between Grooved Pegboard performance and diffusion metrics for the CST in either hemisphere. **Conclusions:** While we failed to detect a significant relationship between fine motor skill and FBA metrics in either group, this paper extends previous work by showing that children with ADHD and reduced fine motor competence demonstrate atypical microstructure within the CST relative to non-ADHD controls.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by inattention and/or impulsivity/hyperactivity, leading to functional impairment in daily living, academic performance and a child's capacity to develop and maintain interpersonal relationships (Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). Children with ADHD also often present with difficulties engaging in everyday tasks that involve movement (e.g. handwriting, tool use), with up to 50% of children with ADHD presenting with impaired motor skill (viz developmental coordination disorder- DCD: Goulardins et al., 2015; Kaiser, Schoemaker, Albaret, & Geuze, 2015). The negative psycho-social effects of ADHD are exacerbated in the presence of low motor ability (Goulardins et al., 2015), including poorer educational outcomes, and increased ADHD symptom severity, risk of reading disorders, alcohol abuse, and criminal offending relative to ADHD in isolation (Rasmussen & Gillberg, 2000). Despite these findings, very little is understood about the neurobiological basis of motor function in ADHD.

White matter organization in motor networks, including the cortico-spinal tracts (CST), has been shown to be a reliable predictor of motor outcomes in pediatric (e.g. cerebral palsy- Jiang et al., 2020; Mailleux et al., 2020) and adult (e.g. stroke- Puig et al., 2017) patient populations. The CST is responsible for voluntary movements. CST fibres emanate largely from the primary motor cortex (M1), with most neurons crossing the midline in the medulla before projecting to the spinal cord (Welniarz, Dusart, & Roze, 2017) and synapsing with lower motor neurons, which in turn stimulate peripheral muscles. White matter organization of CST differentiates typical and atypical motor competence in otherwise healthy children (Zwicker, Missiuna, Harris, & Boyd, 2012), and early disruption of CST microstructure is associated with compromised motor function (as is observed in cerebral palsy: Mailleux et al., 2020).

A growing body of literature has investigated white matter organization in children with ADHD using diffusion MRI, an elegant method for estimating the macro and microstructural properties of white matter pathways *in vivo* (see Aoki, Cortese, & Castellanos, 2018; Chen et al., 2016; van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012 for reviews). Despite motor difficulties being common in ADHD, only a small number of studies have characterized the microstructural properties of the CST in this group (Bu et al., 2019; Chuang, Wu, Huang, Weng, & Yang, 2013; Hamilton et al., 2008; van Ewijk et al., 2014). In one recent example, drug naïve children with ADHD showed differential microstructural properties of the cerebral peduncle and posterior limb portions of the CST relative to healthy controls (Bu et al., 2019). However, neither this study, nor any prior work to our knowledge, has examined whether atypical CST microstructure in ADHD co-occurs with low motor ability in this group. Thus, despite the prominent role that the CST plays in motor function across the developmental spectrum, it is unknown if, or how, it is associated with the often reported lower motor ability in children with ADHD.

Many previous studies probing white matter microstructure within the CST in children with ADHD have adopted diffusion tensor imaging (DTI). While commonly used, the limitations of DTI have been the subject of much discussion in recent years (Farquharson & Tournier, 2016; Farquharson et al., 2013; Jones, Knösche, & Turner, 2013; Tournier, Mori, & Leemans, 2011). Briefly, DTI adopts a single tensor to estimate underlying white matter fibre-population orientation within a given voxel. Hence, it is unable to reconcile multiple fibre orientations within a single voxel, the latter of which can be found in the vast majority (≈90%) of white matter voxels (Jeurissen, Leemans, Tournier, Jones, & Sijbers, 2013). This limitation can render visual reconstructions of white matter tracts inaccurate or incomplete. Further, classic tensor derived metrics, such as fractional anisotropy (FA) and mean diffusivity (MD), are not fibre specific, making findings difficult to interpret (Jeurissen et al.,

2013; Raffelt et al., 2017). Accordingly, while prior work provides preliminary support for the view that white matter microstructure within the CST may be atypical in children with ADHD, limitations of the tensor model preclude any firm conclusions.

High angular diffusion models, such as constrained spherical deconvolution (CSD), are able to reconcile the 'crossing fibre' issue and offer a more sensitive alternative to the tensor model (Dell'Acqua & Tournier, 2018). A recent analytical advance, fixel-based analysis (FBA), uses the fibre orientation distribution (FOD) signal generated by CSD to model specific fibre populations within a given voxel, even in the presence of multiple fibre orientations (Raffelt et al., 2017). Unlike traditional tensor methods (e.g. DTI), the FBA framework is therefore able to generate quantitative metrics at the fibre-population level within a voxel. These include fibre density (FD), a measure of microscopic differences in density of a given fibre population, measured as the intra-axonal volume of a population of fibres; fibre cross section (FC), a macroscopic measure of the cross sectional region perpendicular to the fibre; and 'fibre density-cross section' (FDC), the product of combining FD and FC. Recent work has shown these FBA derived metrics to be sensitive to modelling white matter organization of the CST in the developmental setting, both cross-sectionally and longitudinally (Dimond et al., 2020; Genc et al., 2018). Accordingly, this highly novel approach offers the ideal method with which to characterize white matter microstructure within the CST of children with ADHD.

The present study is the first to our knowledge to investigate the link between poorer motor competence in children with ADHD and white matter microstructure within the CST. With respect to movement, we opted to focus on fine motor skill as measured by the well-validated 'Grooved Pegboard Task', since movement is multifaceted and fine motor difficulties are consistently observed in ADHD (Kaiser et al., 2015). All children underwent high angular resolution diffusion imaging, from which CSD modelling was conducted. The

bilateral CST were reconstructed using the deep-learning semi-automated TractSeg (Wasserthal, Neher, & Maier-Hein, 2018), FBA conducted, and FD, FC and FDC extracted for each CST (Raffelt et al., 2017). We hypothesized that children with ADHD would perform less efficiently when engaging in fine motor performance, indicated by poorer performance on the 'Grooved Pegboard Task' relative to non-ADHD controls. Given the critical role that the CST plays in supporting voluntary motor control, we also hypothesized that these same children with ADHD would show differential white matter microstructure relative to non-ADHD controls, shown by decreases in fixel-based metrics (e.g. FD, FC and FDC) relative to non-ADHD controls.

2. Method

2.1. Participants

The data presented in this study were collected as part of the Neuroimaging of the Children's Attention Project study (NICAP- Sciberras et al., 2013; Silk et al., 2016). Briefly, children were recruited from 43 socio-economically diverse primary schools in Melbourne, Australia, and ADHD screening surveys were completed by parents and teachers (Conners 3 ADHD Index: Conners, 2008) for children in their second year of school. The NIMH Diagnostic Interview Schedule for Children IV (DISC-IV: Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) was then used to confirm ADHD status. Conversely, non-ADHD controls screened negative for ADHD by both parent and teachers, and did not meet diagnostic criteria on the DISC-IV. At the 36 month follow-up, a subsample of participants completed a detailed neuroimaging assessment in addition to the cognitive and behavioral assessments in a 3.5 hour assessment at The Royal Children's Hospital, Melbourne, Australia. This included a self-report survey, parent questionnaire, diagnostic re-assessment, MRI scan, and a cognitive assessment which included tasks assessing fine motor skill and attentional bias.

Data for the present study relates to Wave 3 (36 month follow-up) of the NICAP cohort study. Currently medicated children and/or those with a known history of ADHD medication were excluded given recent evidence suggesting that ADHD medication may impact motor function (Kaiser et al., 2015). We included only children who self-reported being right-handed (≈90% of total sample), since motor control is lateralized and the number of left handed children at Wave 3 who met inclusion criteria was too small to support sub-group analyses. Exclusion criteria included neurological conditions, severe medical conditions, genetic disorders, and moderate-severe sensory impairment. Consequently, no child presented with a neurological or severe medical condition impacting movement (e.g. cerebral palsy, muscular dystrophy). The final sample consisted of 50 right-handed children with a history of ADHD (met criteria for ADHD at recruitment and/or the 36 month follow-up) (Female= 15; Age $_{Mean}$= 10.38 years, SD = 0.43 years; Age $_{Range}$: 9.60 – 11.31) and 56 right-handed non-ADHD controls (Female= 25; Age $_{Mean}$= 10.49 years, SD = 0.45 years; Age $_{Range}$: 9.58 – 11.86). In addition to those included in the final sample, we had MRI data for a further 8 ADHD and 7 controls, but these children were excluded due to poor diffusion MRI data quality. Exclusion in these cases was due to the presence of venetian blinding, anatomical abnormality or acquisition artefacts (n= 5), or data quality was such that brain coverage was partial, or diffusion masks were incomplete upon generation (n= 10). Chi square test of independence found no association between group and sex [χ^2 (1, N =106) = 2.41, p= .121] of the final sample, suggesting no statistically meaningful difference in the proportion of boys and girls in the ADHD and non-ADHD groups. For a summary of demographic and clinical information, please see Table 1. This study was approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee (HREC #34071). Parents or guardians gave informed consent while participating children assented.

INSERT TABLE 1

2.2. Measures

Intelligence was estimated at the initial recruitment stage using the vocabulary and matrix reasoning sub-tests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Weschler, 2011). Socio-economic status (SES) of participants was determined using the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD), from the Socio-economic Indexes for Areas (SEIFA), a relative measure of socio-economic advantage/disadvantage based on 2011 Australian Census data (Australian Bureau of Statistics, 2011). The IRSAD (M=1000, SD = 100) measures of areas relative socio-economic disadvantage, with lower scores indicating greater disadvantage.

Participants' clinical features were characterized using a combination of the inattentive and hyperactive symptom count, and comorbid internalizing and externalizing disorders as determined by the DISC IV. Children were identified as presenting with an internalizing disorder if they met criteria for depression, dysthymia, separation anxiety disorder, social phobia, generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder, hypomania or manic episode. Further, they were identified as presenting with an externalizing disorder if they met criteria for oppositional defiant disorder or conduct disorder. Finally, ADHD symptom severity was measured using the parent reported Conners 3 ADHD Index.

2.2.1. Fine motor task

Fine motor skill was measured using the Grooved Pegboard test (Lafayette Instruments, Lafayette, IN). Children were presented with a pegboard consisting of 25 grooved holes organized in 5 parallel rows (i.e. 5 x 5 grid). The pegs had a square key along one side,

meaning that participants had to rotate the pegs to fit them in a given hole. Participants completed the task twice, beginning with the right (dominant) hand inserting pegs in the holes from left to right for each row, followed by left (non-dominant) hand performance which involved inserting pegs from right to left for each row. Participants are instructed to put the pegs in the holes as quickly as possible beginning from the top row without skipping any holes, and to continue to the next peg if they dropped one. Timing began once the assessor signalled the beginning of the trial and terminated when the final peg was inserted. The number total time (seconds) and the number of peg drops and total pegs completed were combined and constituted the total score, and was calculated separately for the right and left hand.

2.2.2. Attentional Bias

Based on evidence that children with ADHD may present with a right hemispace attentional bias, we measured attentional bias using the well-validated 'Landmark Task' (Bellgrove et al., 2008; Bellgrove et al., 2005), so as to be able to control for it if necessary. Here, participants are presented with a sheet of paper with a bisected line and are asked to indicate which side of the line is shorter. Participants complete 20 trials: 50% of the lines are bisected exactly in the middle, while the remainder are bisected slightly offset, equally to the left or right. The degree of offset varied with six of the ten trials offset by 1mm (3 right, 3 left), two offset by 2.5mm (1 right, 1 left) and 2 by 5mm (1 right, 1 left). Attentional bias was calculated by the number of bisected lines reported to be shorter in the left minus the number of bisected lines reported to be shorter in the right, divided by the total number of lines (20).

2.3. Image acquisition and processing

Participants initially completed a 30-minute mock scanning session to familiarise the child with the scanning environment and procedure and reduce anxiety. MR scanning was conducted on a research-dedicated 3T Siemens Tim Trio MRI scanner (Erlangen, Germany). High resolution T1-weighted, multi-echo MPRAGE images were acquired in the sagittal plane with in-scanner motion correction (TR = 2530ms, TE = 1.77, 3.51, 5.32, 7.2ms, flip angle 7^{o}, voxel size = $0.9mm^3$). High-angular resolution diffusion imaging (HARDI) data were acquired in the transverse plane with an anterior-posterior phase encoding direction (PE). Sixty gradient directions, b-value = 2800 s/mm^2 and four interleaved b = 0 volumes were acquired (TR = 3200ms, TE = 110ms, echo spacing= 0.69ms, FOV=260mm, multi-band factor = 3 and 2.4mm isotropic voxels). A reverse phase encoded image was acquired to correct for magnetic susceptibility-induced distortions during EPI acquisition.

Diffusion data were pre-processed using the MRtrix3 software package which included denoising, motion, eddy current and susceptibility distortion correction, and bias field correction (Tournier et al., 2019). Following pre-processing, data were upsampled to an isotropic voxel size of $1.30mm^3$. Group average response functions for gray matter, white matter and CSF were then used to generate individual FOD maps using single-shell 3-tissue constrained spherical deconvolution (SS3T-CSD) (Dhollander, Raffelt, & Connelly). FOD images then underwent intensity normalization so that FOD magnitudes were consistent across participants (Raffelt et al., 2017). A study specific population FOD template was generated based on a subset of 60 participants (ADHD: 15 females, 15 male; non-ADHD; 15 female, 15 male), which was then registered to MNI space (necessary for TractSeg, discussed below). The template requires equal numbers of participants from each group (ADHD vs non-ADHD) and sex (females vs male) to reduce bias. The group that had the smallest *n* was females with ADHD group (*n* =15). Accordingly, we then matched 15 participants from each of the other three groups as best as possible (i.e. males with ADHD, males non-ADHD, and

females non-ADHD). This ensured that we had the largest population template possible, whilst appropriately representing relevant groups and controlling for sex.

All 106 participant FOD images were registered to the study specific FOD template. Fixel metrics including FD, FC (log) and FDC were calculated for each participant across white matter fixels. Since FC is commonly skewed, FC (log) was calculated and adopted in subsequent analyses rather than FC to ensure normal distribution of the variable. While we have summarized these metrics in the introduction, they have been described in more details elsewhere (Raffelt et al., 2017).

In order to delineate the left and right CST, we used the automated TractSeg method (Wasserthal et al., 2018) in the population FOD template to segment those voxels that correspond to the bilateral CST in each individual. We adopted this technique since it provides a welcome compromise between the accuracy of manual delineation and the reliability/objectivity of atlas-based tractography (Genc et al., 2020). Here, tract orientation maps were generated for the left and right CST, from which probabilistic tractography was conducted with 10,000 streamlines. The resultant CST tractograms (see Figure 1) were then converted to fixel maps. This was achieved by cropping each participant's whole brain fixel mask to only correspond to fixels that were traversed by streamlines belonging to the left and right CST (using the tck2fixel command in MRtrix3) (see Figure 2). Fixel metrics including FD, FC and FDC were then extracted for each participant for fixels within the left and right CST.

INSERT FIGURE 1 ABOUT HERE

INSERT FIGURE 2 ABOUT HERE

2.4. Study Design and Analysis

To test for the presence of group differences in head motion during the diffusion sequence, the mean and maximum framewise displacement (FWD) was calculated using the FSL Motion Outlier script as a measure of overall movement for each participant during the diffusion sequence (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). From volume to volume over the sequence, FWD reflects the change in rotation and translation motion parameters. Preliminary analyses were then conducted to compare scanner motion metrics across groups via a series of independent-samples *t*-tests. Further, cortical white matter volume and intracranial volume (ICV) were also compared across groups.

We conducted separate independent-samples *t*-tests to compare the fine motor performance of children with and without ADHD, as measured by the total score on the Grooved Pegboard Task, for the right and left hand respectively. An independent t-test was also conducted to determine whether there were significant differences in attentional bias between groups, as measured using the Mean Total Asymmetry on the Landmark Task

To compare microstructural properties of the CST between children with and without ADHD, we used the connectivity-based fixel enhancement (CFE) method to compare groups on FD, FC (log), and FDC in separate analyses (Raffelt et al., 2015). These analyses were conducted for the left and right CST separately. For group comparisons involving FD we covaried for sex, age and FWD. For group comparisons involving FC (log) or FDC, we covaried for sex, age, FWD and ICV, since the latter have shown to be associated with individual differences in FC (log) and FDC (Smith et al., 2019). The CFE is the optimum approach for group wise comparisons, with *p* values provided for each fixel which are permutation-based and family-wise error corrected at the fixel level (Genc et al., 2020; Raffelt et al., 2015). Statistical significance was thresholded at $p<.05_{FWE}$ for group comparisons.

We were then interested in the relationship between fine motor performance and white matter organization within the CST. We reasoned that, if microstructure within the CST were to subserve the decreased motor ability observed in those with ADHD at the group level, the association between fine motor performance and CST white matter organization would be specific to, or magnified in, those regions of the CST where group differences in mircostructure existed between those with and without ADHD. With respect to the latter, we generated a threshold mask for those fixels where significant group difference existed between children with and without ADHD (p<.05 $_{FWE}$). This was then used to crop those fixels within the left and right CST for which group differences were observed. The CFE method was then used to investigate the relationship between fine motor performance on the Grooved Pegboard Task and fixel-based metrics for the left and right CST where group differences had been identified. These correlational analyses were conducted separately for the ADHD and non-ADHD groups. Separate two-tailed analyses were conducted for the non-dominant (left) and dominant (right) hand performance of the Grooved Pegboard Task. As above, where correlations involved FD, we covaried for sex, age and FWD, and where correlations involved FD or FDC, we adjusted for sex, age, FWD and ICV. Again, statistical significance for correlations was set at p<.05 $_{FWE}$. Finally, given the number of correlational analyses conducted, the False Discovery Rate (FDR: Benjamini & Hochberg, 1995) correction was used to correct for multiple comparisons.

3. Results

Preliminary analysis failed to detect a significant difference between children with and ADHD and non-ADHD children for in-scanner motion, white matter volume, or ICV (Table 2).

INSERT TABLE 2 HERE

Independent samples *t*-tests showed that children with ADHD performed significantly worse than non-ADHD controls on the Grooved Pegboard Task when using their non-dominant (left) hand, t (104)= 2.28, p = .025, d = 0.44. We observed that 50% (25 of the 50) of children with ADHD presented with non-dominant hand performance on the Grooved Pegboard task that exceeded the upper 95% CI for the non-ADHD group (i.e. 112- see table 3). No significant group differences were observed for dominant (right) hand Grooved Pegboard Task performance, t (104)= 0.758, p = .450, d = 0.15. Finally, children with and without ADHD did not differ significantly in attentional bias, t (104)= 0.249, p = .804, d = 0.05. See Table 3 for descriptive statistics.

INSERT TABLE 3 HERE

Children with ADHD showed significantly lower FD, FC (log) and FDC in the right CST (p<.05 $_{FWE}$). They also demonstrated lower FDC in the left CST (p<.05 $_{FWE}$). No significant group differences were observed between children with and without ADHD for FD or FC (log) of the left CST (Figure 3). Finally, no significant correlations were observed between Grooved Pegboard performance or CST measures of microstructure in the ADHD group, regardless of the hand of performance of laterality of the CST or direction. Similarly, no such association were observed in the non-ADHD control group.

INSERT FIGURE 3 HERE

4. Discussion

The present study aimed to investigate the association between previously reported poorer fine motor competence in children with ADHD and microstructure within the CST. In keeping with prior evidence (Goulardins et al., 2015; Kaiser et al., 2015), children with ADHD were significantly less efficient in fine motor control relative to their same-age peers. While we failed to detect a significant correlation between Grooved Pegboard task performance and FBA metrics within the ADHD or non-ADHD controls groups, this paper extends previous work by showing that children with ADHD and reduced fine motor competence demonstrate atypical microstructure within the CST, shown by lower FD, FC (log) and FDC in the right CST, and lower FDC in the left CST. These findings, and their implications, are discussed next.

While we observed that children with ADHD were significantly less efficient than non-ADHD controls when engaging in fine motor control, this effect was confined to non-dominant (i.e. left hand). This finding is consistent with prior reports of poorer fine motor competence in children with ADHD, with some studies reporting pronounced deficits to the non-dominant limb (Kaiser et al., 2015). Since no group differences were observed on the Landmark task, it is unlikely that these groups differences can be attributed to differences in the spatial attentional bias that is often reported in children with ADHD.

As predicted, children with ADHD showed significant differences in white matter microstructure of the bilateral CST relative to non-ADHD controls. More specifically, children with ADHD showed lower FD, FC (log) and FDC in the right CST, and lower FDC in the left CST. Since FD is thought to reflect the number, or density, or axons within a voxel, our data potentially suggest a lower number, or diameter, of axons in the CST for those with ADHD (Genc et al., 2018; Raffelt et al., 2017). The lower FC (log), on the other hand, suggests decreased fibre bundle size in those with ADHD, which may reflect a reduction in the speed with which the CST is able to transmit information (Raffelt et al.,

2017). While these findings are in keeping with earlier DTI accounts which reported differences in FA, RD and MD (Bu et al., 2019; Chuang et al., 2013; Hamilton et al., 2008; van Ewijk et al., 2014), a strength of this paper is the use of CSD modelling and subsequent FBA of white matter. In contrast to DTI, the CSD method allowed us to reconcile multiple fibre orientations and to more accurately track fibres through voxels with multiple fibre orientations, which are highly prevalent in the lateral projections of the CST (Farquharson et al., 2013). Further, the FBA analysis we adopted is able to generate fibre specific metrics (Raffelt et al., 2017). Finally, the use of TractSeg to delineate the CST provides a balance between the anatomical accuracy of manual delineation and reliability of atlas-based tractography methods (Genc et al., 2020). In sum, we present a state-of-the-art account of CST macro and microstructure in children with ADHD, with compelling evidence of widespread CST microstructural abnormalities in children with ADHD relative to non-ADHD controls.

Since all of our participants were right-handed and the CST projects from the motor cortices to the contra-lateral limbs (Welniarz et al., 2017), the finding of lower FD, FC (log) and FDC in the right CST of those with ADHD and poorer fine motor performance using the left (i.e. non-dominant) hand theoretically would provide support for the view that poorer motor competence in children with ADHD may be associated with microstructural properties within the CST; however, correlational analyses failed to detect a significant relationship between the efficiency of fine motor performance in children with ADHD and any microstructural measures within the right CST, nor were such effects observed in the control group alone. We consider three plausible explanations for these findings. Firstly, it may be that microstructure within the CST does not explain individual differences in motor ability for children with and without ADHD. However, we argue that this account is unlikely, given the functional role of the CST in motor output, the breadth of prior work demonstrating a link

between white matter organization within the CST and childhood motor outcomes in otherwise healthy children (Zwicker et al., 2012), and developmental work showing that insult to the CST is associated with impaired movement efficiency (Jiang et al., 2020; Mailleux et al., 2020). Still, it should be acknowledged that motor control is a heterogenous construct, and that the structural association between the CST and motor output may very well differ depending on the type of movement, its novelty and environmental demands. Further, while the present study excluded left-handed children due to small sample size which precluded meaningful sub-group analysis, inclusion of a sample of left-handed children of sufficient size to conduct such analyses may shed light on the functional relevance of microstructural differences within the CST of children with ADHD and reduced fine motor performance. To this point, were atypical microstructure within the contralateral CST to contribute to non-dominant fine motor skill, one might expect to see both reduced right hand performance and co-occurring abnormalities within the left CST of left-handed children with ADHD. However, this remains a limitation of the present study and warrants future attention.

Alternatively, while the 'Grooved Pegboard Task' remains sensitive to detecting group level differences in fine motor ability between individuals with and without developmental disorders, a recent review showed that performance stabilizes in early adolescence (e.g. between 10 - 13 years) (Skogan, Oerbeck, Christiansen, Lande, & Egeland, 2018). As such, the Grooved Pegboard Task was likely a relatively basic task for the children in our study, and may not be as effective at discriminating fine motor abilities within group as between group. In support, the Skogan and colleagues review also demonstrated that within group variability generally decreases with age on the task up to this period- consideration of SD values shows that variability in our current sample was comparable to children of a similar age in this earlier review. Were a correlation to exist between individual differences

in CST microstructure and fine motor performance, reduced variability on any measure of fine motor ability (as may be the case in the present study given our participant ages) would decrease the sensitivity of subsequent correlational analyses. Taken together, these effects would explain why we observed co-occurring deficits in fine motor competence in those with ADHD and atypical white matter organization within the CST, yet no correlation was observed between fine motor ability and CST microstructure in either of our groups. Still, while our study demonstrates that group level CST microstructural abnormalities and poor non-dominant fine motor performance co-occur in children with ADHD, it remains unclear if individual differences in CST microstructure predict motor difficulties in this group.

Lastly, some have argued that the low motor ability often observed in ADHD may be, at least partly, a product of the inattention that characterizes the disorder (Goulardins, Marques, & De Oliveira, 2017). Given that non-dominant hand performance places increased demands on sustained attention relative to dominant hand performance (Strenge, Niederberger, & Seelhorst, 2002), this may also explain why we only observed group difference in fine motor ability for the non-dominant hand. Were individual differences in fine motor ability influenced by attention in the present study, this might also explain why we failed to detect a significant relationship between CST microstructure (a tract predominantly implicated in motor output) and motor skill. In order to address the above issues, future work would benefit from adopting a broader battery of standardized fine motor tasks of varying task complexity when probing the integrity of fine motor performance, and its association with white matter microstructure.

Further, while we found significant reductions in FBA metrics within the left CST for those with ADHD, no group differences were observed for dominant (i.e. right hand) performance of fine motor function. This would appear to be inconsistent with the view that atypical microstructure in the CST might be subserved poor fine motor function in those with

ADHD. As noted above, however, the Grooved Pegboard Task may not be of sufficient complexity to detect group differences in fine motor performance between children with and without ADHD. This effect would explain why we observed poorer fine motor performance in those with ADHD when engaging their non-dominant hand, where movement is less likely to be practiced and automated, and place greater demands on motor and attentional processes. It has even been argued that right-handed deficits in motor performance may be, at least in part, moderated by practice, since many day-to-day tasks are reliant of right hand performance (Rommelse et al., 2007). Again, future work would benefit from including a broader battery of fine motor tasks of greater complexity in order to probe the role of atypical microstructure of the CST in dominant hand performance.

To our knowledge, ours is the first study to directly investigate the relationship between fine motor performance and atypical microstructure within the CST in a single sample of children with ADHD. Further, as noted above, our application of FBA to examine white matter organization to achieve this aim is highly novel, with FBA providing fibre specific metrics that cannot be derived from the tensor model adopted by earlier studies investigating the white matter correlates of poor motor skill in ADHD. Nor can fibre specific metrics be derived from non-tensor modelling in the absence of FBA, which we have previously reported on when using CSD to model white matter microstructure of the superior longitudinal fasciculus (SLF) in a cohort of children with ADHD and co-occurring fine motor problems that overlapped with the present sample (Hyde, Sciberras, Efron, Fuelscher, & Silk, 2020). Taken together, the addition of FBA in the current study represents a substantial methodological advance on earlier work, with ours being the first to report that children with ADHD who experience fine motor difficulties also demonstrate reduced fibre density and cross section within the CST. While broader white matter abnormalities have been reported in in children with ADHD (Aoki et al., 2018; Chen et al., 2016; van Ewijk et al., 2012), our

work demonstrates that such disruption may extend beyond the classic fronto-striatal systems associated with the attentional profile of symptomatology, and may contribute to the spectrum of motor difficulties often reported in ADHD.

As noted in the introduction, motor difficulties (*viz* DCD) are known to occur in up to 50% of children with ADHD (Goulardins et al., 2015; Kaiser et al., 2015). Thus, though motor dysfunction is common in ADHD, it is not ubiquitous. Indeed, we found that 50% of children with ADHD in our study presented with non-dominant hand performance on the Grooved Pegboard task that fell above the upper 95% CI (i.e. 112, see table 3) of non-ADHD children. In the absence of a standardized motor battery, this data demonstrates that even though group level analysis suggests that children with ADHD present with low fine motor ability, poor non-dominant fine motor skill impacted roughly 50% of children with ADHD. While this incidence is consistent with earlier accounts, we were unable to formally distinguish between children with ADHD who did, and did not, present with co-occurring DCD, a distinction that may be critical to understanding the clinical significance of the atypical CST microstructure that we report here in children with ADHD, as well its role (if any) in broader ADHD symptomatology. Indeed, were atypical microstructure within the CST to subserve poorer motor function in ADHD, one might assume that the former would be more pronounced in children with ADHD and co-occurring DCD, compared to ADHD in isolation. Our inability to distinguish between those children with ADHD and co-occurring DCD stands as a limitation of the present study, one that could be addressed with the inclusion of a standardized motor assessment battery (e.g. Movement Assessment Battery for Children-2: Henderson, Sugden, & Barnett, 2007).

5. Conclusion

To conclude, the present study is the first to our knowledge to investigate the link between fine motor difficulties in ADHD and microstructure within the CST. While our work is consistent with previous suggestion of poorer fine motor performance in children with ADHD, we also show that the same group of children with ADHD report atypical white matter microstructure within the CST using a state-of-the-art FBA analysis. We failed to demonstrate a relationship between microstructural properties of the CST and fine motor performance in either children with or without ADHD, though we point towards the need for future work to employ a broader battery of complex fine motor tasks in order to best clarify the functional relevance of atypical CST microstructure and reduced fine motor competence in children with ADHD.

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Table 1. Demographic and clinical information for ADHD and non-ADHD groups (standard deviation in parentheses).

	ADHD Mean (SD) or *n* (%)	Non-ADHD Mean (SD) or *n* (%)	*p*
Sex (Female)	15	25	.121
Age (years)	10.38 (.43)	10.49 (.45)	.22
IQ	96.28 (13.34)	102.73 (13.36)	.015
Conners 3 (Parent)	8.72 (6.19)	1.20 (1.97)	<.001
Internalizing disorder	9 (18%)	5 (9 %)	.168
Externalizing disorder	17 (34%)	4 (7%)	.001
IRSAD	1019 (36)	1017 (50)	.856
Inattention symptoms	7.00 (3.02)	1.79 (2.31)	<.001
Hyperactivity symptoms	4.08 (2.96)	.95 (1.30)	<.001

NOTE: Internalizing/ Externalizing disorder and inattention/hyperactivity symptom counts were derived from the DISC-IV interview. IRSAD; Index of Relative Socio-Economic Advantage and Disadvantage; IQ was measured at Wave 1 of the original cohort study, 36 months prior to Wave 3 for which the current data pertains.

Table 2. Motion and volumetric comparisons between children with ADHD and non-ADHD

	ADHD			Non-ADHD				
	n	*M (SD)*	95% CI	*n*	*M (SD)*	95% CI	*t*	*p*
Motion								
FWD_{MAX}	50	2.48 (1.19)	[2.15, 2.82]	56	2.25 (0.81)	[2.03, 2.46]	1.20	.231
FWD_{MEAN}		.984 (0.18)	[0.93, 1.03]		.997 (0.25)	[0.93, 1.06]	-0.31	.760
Volume								
ICV	48	1565 (1175)	[1531, 1599]	56	1583 (1216)	[1551, 1616]	-0.80	.429
WMV		425 (454)	[411, 438]		432 (456)	[420, 444]	-0.85	.400

Note. FWD= framewise displacement; ICV = intracranial volume (cm^3); WMV = cortical white matter volume (cm^3), CI = confidence interval. The T1 images for 2 children with ADHD were excluded from preliminary analyses due to excessive motion during scanning. Accordingly, their data were not included for group comparisons on ICV and WMV.

Table 3. Grooved Pegboard Task and Landmark Test comparisons between children with ADHD and non-ADHD

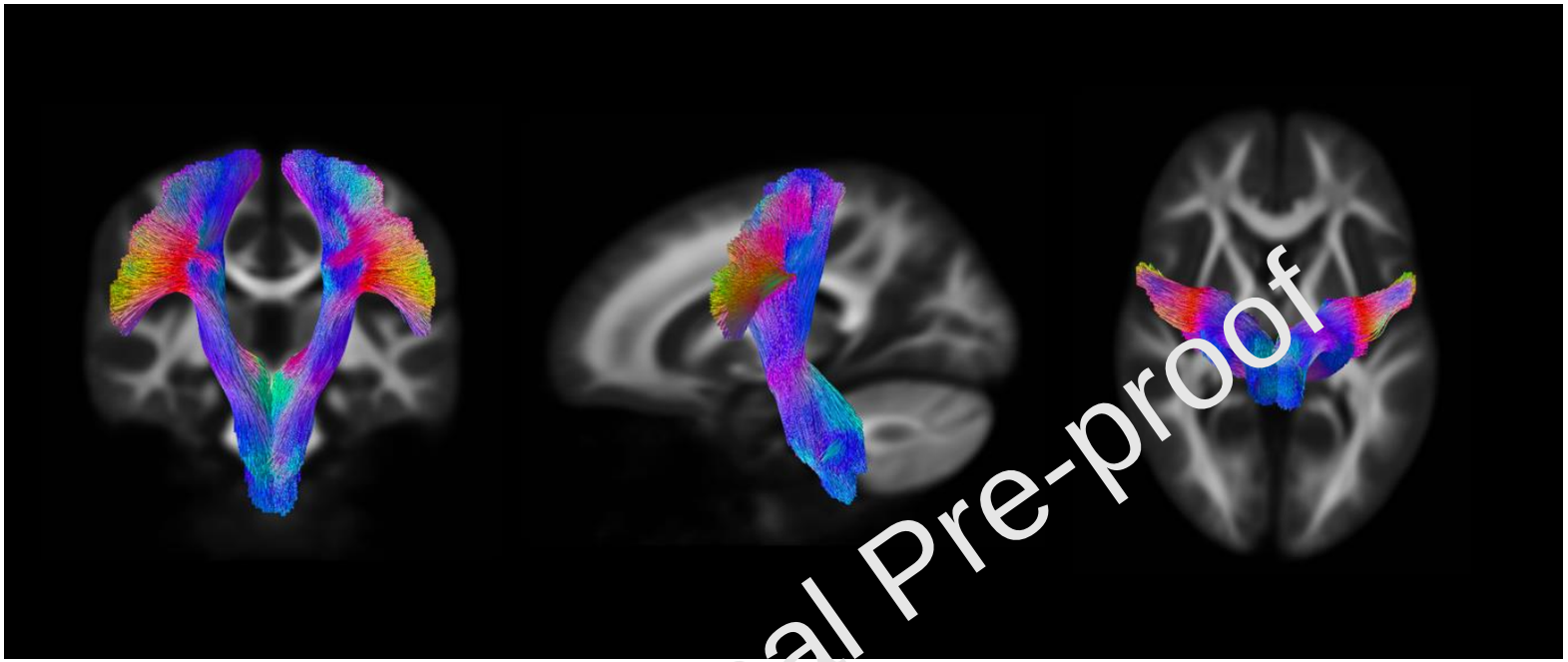
	ADHD			Non-ADHD				
	n	*M (SD)*	95% CI	*n*	*M (SD)*	95% CI	*t*	*p*
Grooved Pegboard								
Total left	50	115 (18)	[110, 120]	56	108 (14)	[105, 112]	2.26	.025*
Total right		104 (13)	[100, 107]		102 (13)	[98, 105]	0.76	.450
Landmark Test								
Asymmetry	50	-0.01 (0.24)	[-0.07, 0.07]	56	-0.01 (0.23)	[-0.08, 0.05]	0.25	.804

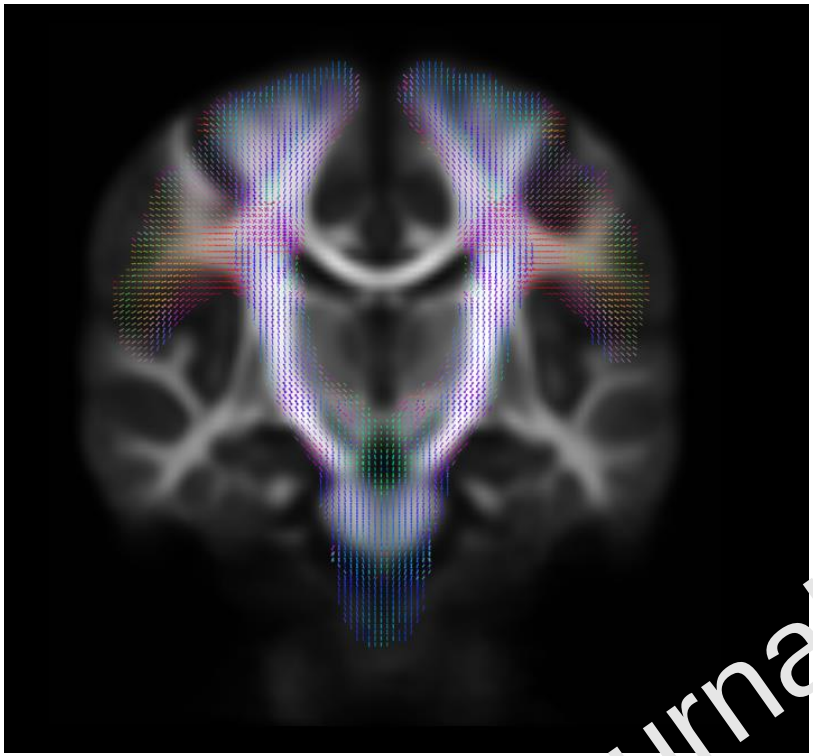
Note. CI = confidence interval.

*$p < .05$ (FDR corrected)

Figure 1. Corticospinal projections reconstructed using TractSeg (applied to the fibre orientation direction population template) and overlaid on a single representative slice for visualisation. Streamlines are colour coded by direction (anterior-posterior: green; superior-inferior: blue; left-right: red).

Figure 2. Fixels belonging to the corticospinal tract overlaid on a single representative slice of the population template for visualisation. Fixels are colour coded by direction (anterior-posterior: green; superior-inferior: blue; left-right: red).





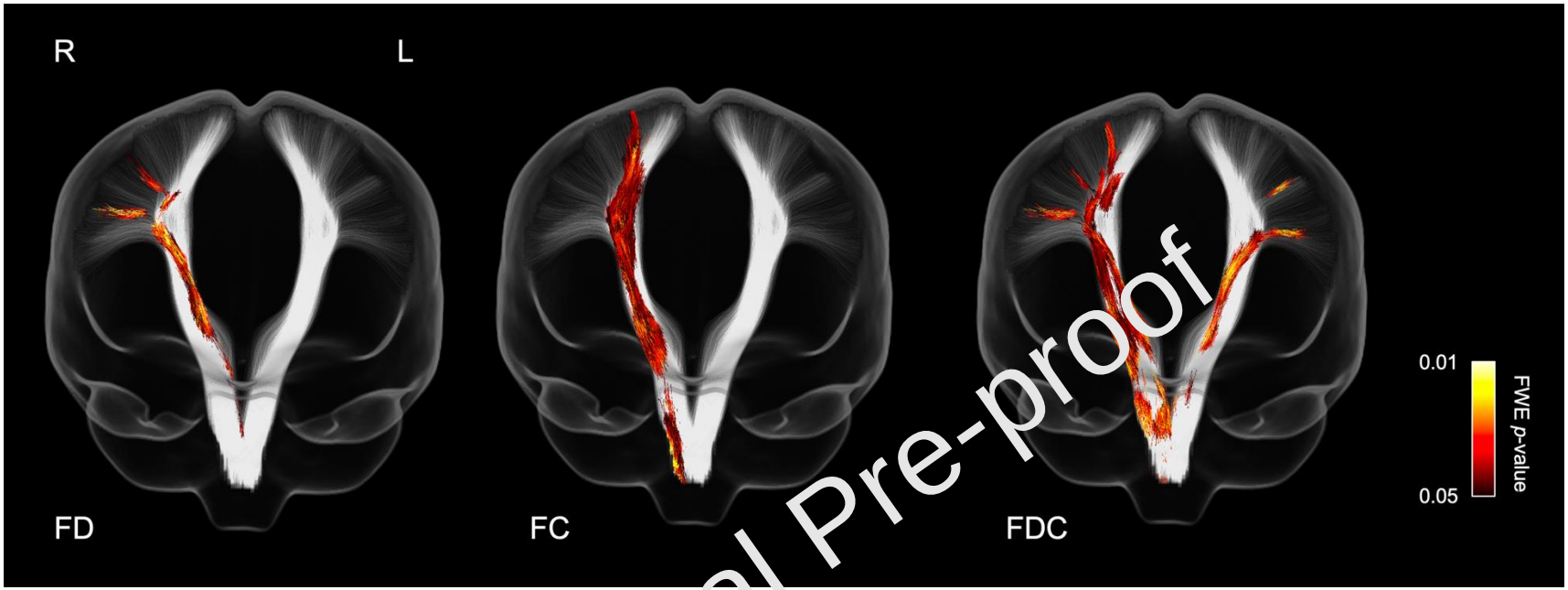


Figure 3. Glass brain representation of tract specific streamline segments that showed a significant (FWE corrected *p*-value < .05) decrease in fibre density (FD), fibre cross-section (FC- log) and fibre density cross-section (FDC) in the ADHD group compared to the non-ADHD group. Streamlines are colour coded by FWE corrected *p*-value. FD values are adjusted for age, sex and framewise displacement. FC (log) and FDC values are adjusted for age, sex, framewise displacement and intracranial volume (ICV).

Author Contributions

CH contributed to the study design, data analysis, interpretation of results, drafting of the work and revising the paper critically for important content. IF contributed to data analysis, interpretation of results and revising the paper critically for important content. ES contributed to data analysis, interpretation of results and revising the paper critically for important content. DE contributed to data analysis, interpretation of results and revising the paper critically for important content. VA contributed to the study design, data collection, interpretation of results and revising the paper critically for important content. TS contributed to the study design, data collection, data analysis, interpretation of results and revising the paper critically for important content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

The authors declare that they have no conflict of interest. All procedures performed in this study were approved by, and conducted in accordance with, the ethical standards of the institutional human research ethics committee. In doing so, they were performed according to the standards of the 1964 Helsinki declaration and its later amendments or comparable standards. Informed consent was obtained from all individual participants included in this study.

Highlights

- This is the first study to apply a novel fixel-based analysis to examine white matter correlates of fine motor competence in ADHD
- Children with ADHD presented with lower fibre density and cross-section of the corticospinal tract (CST) compared to non-ADHD controls.
- The same children with ADHD showed poorer non-dominant fine motor performance.
- Children with ADHD and reduced fine motor competence demonstrate atypical microstructure within the CST relative to non-ADHD controls.

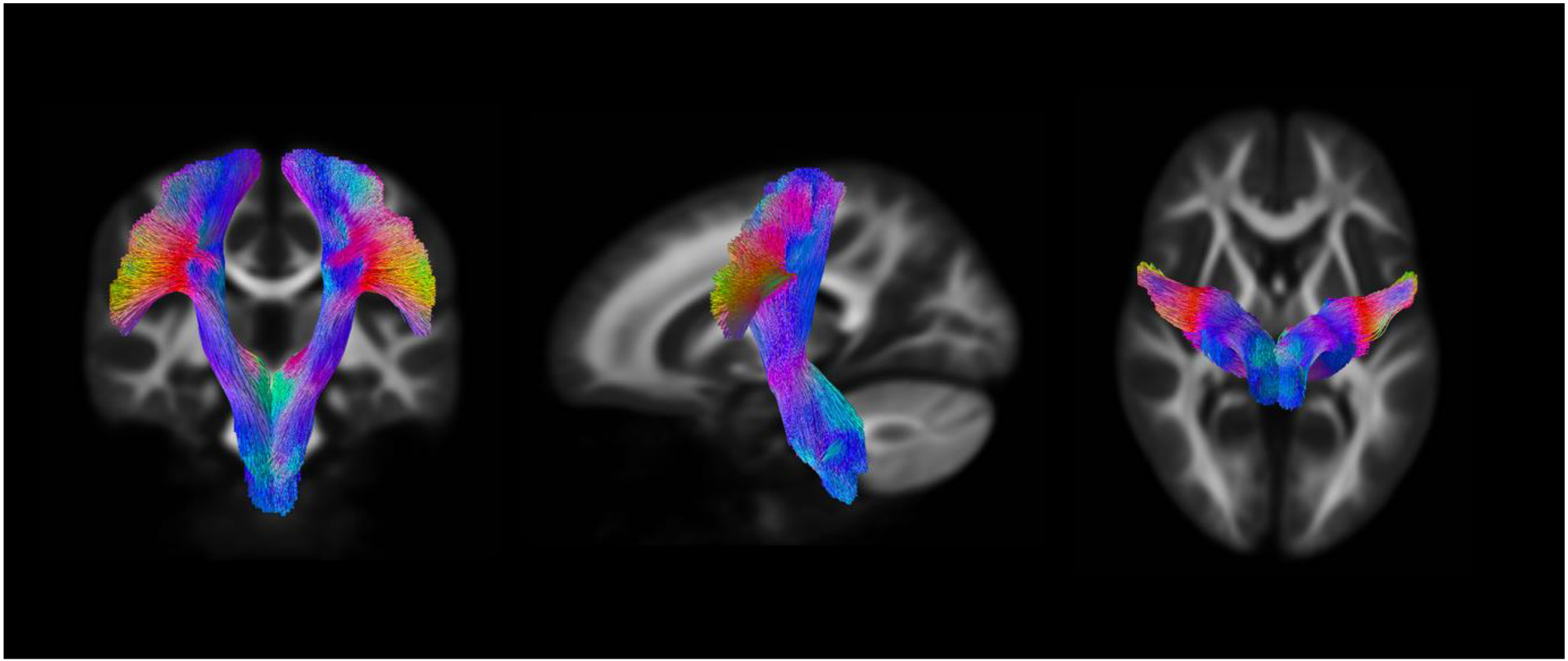


Figure 1

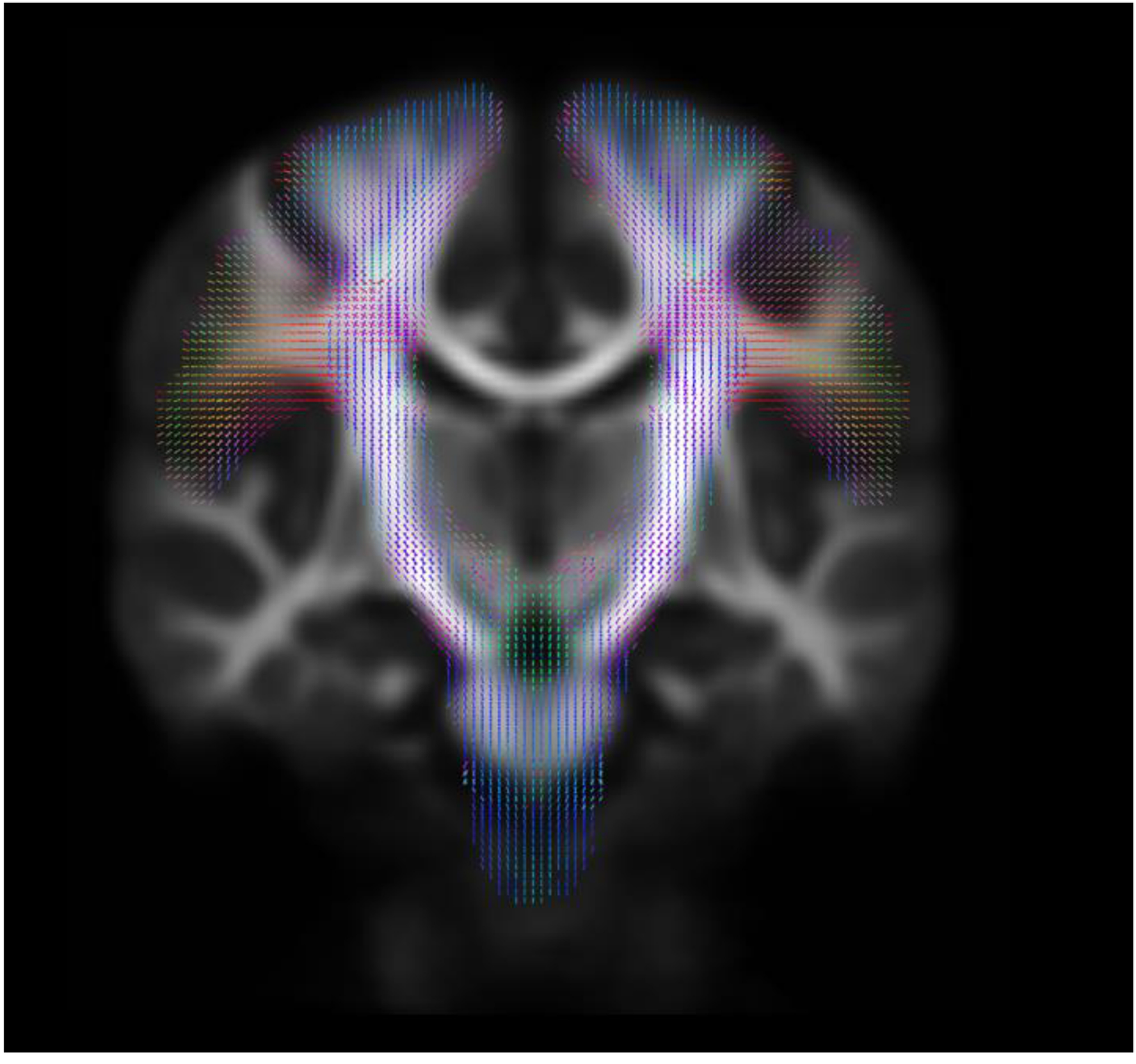


Figure 2

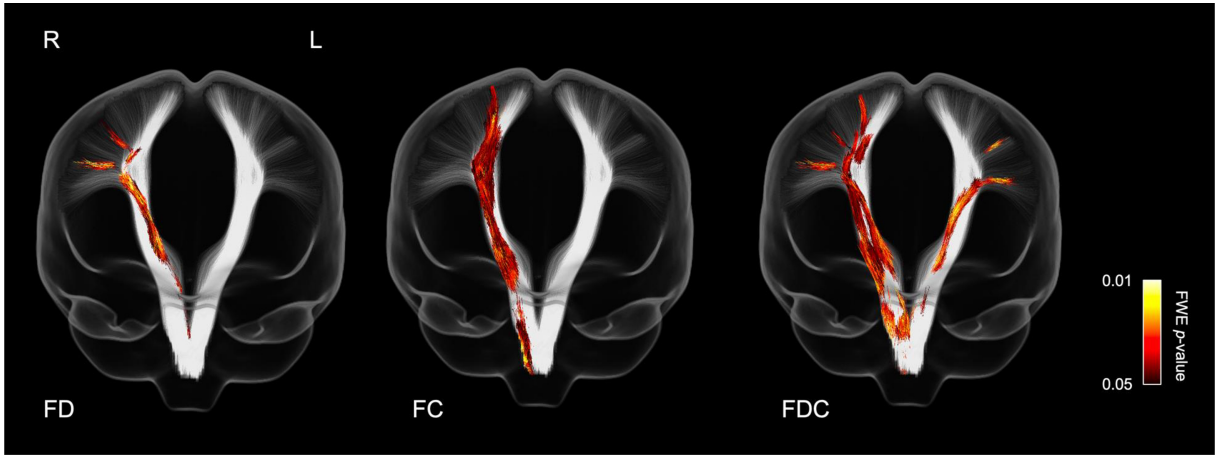


Figure 3