Longitudinal changes of ADHD symptoms in association with white matter microstructure: A tract-specific fixel-based analysis

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A R T I C L E  I N F O

Keywords:
Attention deficit hyperactivity disorder
Magnetic resonance imaging
Diffusion imaging
White matter
Microstructure

A B S T R A C T

Background: Variation in the longitudinal course of childhood attention deficit/hyperactivity disorder (ADHD) coincides with neurodevelopmental maturation of brain structure and function. Prior work has attempted to determine how alterations in white matter (WM) relate to changes in symptom severity, but much of that work has been done in smaller cross-sectional samples using voxel-based analyses. Using standard diffusion-weighted imaging (DWI) methods, we previously showed WM alterations were associated with ADHD symptom remission over time in a longitudinal sample of probands, siblings, and unaffected individuals. Here, we extend this work by further assessing the nature of these changes in WM microstructure by including an additional follow-up measurement (aged 18 - 34 years), and using the more physiologically informative fixel-based analysis (FBA).

Methods: Data were obtained from 139 participants over 3 clinical and 2 follow-up DWI waves, and analyzed using FBA in regions-of-interest based on prior findings. We replicated previously reported significant models and extended them by adding another time-point, testing whether changes in combined ADHD and hyperactivity-impulsivity (HI) continuous symptom scores are associated with fixel metrics at follow-up.

Results: Clinical improvement in HI symptoms over time was associated with more fiber density at follow-up in the left corticospinal tract (ICST) (I\text{max} = 1.092, standardized effect(SE) = 0.044, p\text{FWE} = 0.016). Improvement in combined ADHD symptoms over time was associated with more fiber cross-section at follow-up in the ICST (I\text{max} = 3.775, SE = 0.051, p\text{FWE} = 0.019).

Abbreviations: ADHD, attention-deficit hyperactivity disorder; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FA, fractional anisotropy; FBA, fixel-based analysis; FC, fiber cross-section; FD, fiber density; FDC, fiber density and cross-section; FOD, fiber orientation distribution; HI, hyperactivity-impulsivity; IA, inattention; ICST, left corticospinal tract; ISLF, left superior longitudinal fasciculus; MRI, magnetic resonance imaging; SE, standardized effect; WM, white matter.

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https://doi.org/10.1016/j.nicl.2022.103057
Received 22 November 2021; Received in revised form 9 May 2022; Accepted 21 May 2022
Available online 24 May 2022
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Conclusions: Aberrant white matter development involves both ICST micro- and macrostructural alterations, and its path may be moderated by preceding symptom trajectory.

1. Introduction

Although (proto)typically considered a childhood syndrome, clinical trajectories of attention-deficit/hyperactivity disorder (ADHD) vary by individual. Many ADHD-affected adolescents exhibit improvement over time, but approximately two-thirds of them retain impairing symptoms into adulthood (Faraone et al., 2015, 2006; Sibley et al., 2016). The neural substrates that determine this variable clinical course of childhood ADHD have been increasingly investigated through the years, yet the dynamic nature of these mechanisms in relation to maturation remains unclear. Theoretically, symptom remission occurs via brain compensation-reorganization, and/or normalization-convergence, with a possible fixed anomaly ‘scar’ or enduring neurological trait—all of which may concurrently arise in different brain regions (Sudre et al., 2018). In a double dissociative neurodevelopmental model of ADHD, the underlying neural mechanisms that control onset are distinct from those that drive remission (Halperin and Schulz, 2006). Thus, onset can be characterized by dysfunctional subcortical structures remaining static throughout life, while remission may be separately associated with brain (particularly prefrontal cortex) maturation and compensation (Cortese et al., 2013; Shaw et al., 2015; Sudre et al., 2018).

The theory that maturing frontal cortical regions compensate for initial childhood ADHD emergence via top-down regulatory processes, leading to eventual symptom remission, has been supported by magnetic resonance imaging (MRI) studies: Reduced symptom severity throughout development appears to correlate with prefrontal cortex maturation. White matter (WM) development in frontal-temporal areas subserving emotional and cognitive processes indeed continues to mature into early adulthood, coinciding with the typical age range of ADHD symptom remission (Cheung et al., 2015; Clerkin et al., 2013; Franx et al., 2015; Halperin and Schulz, 2006; Lebel and Deoni, 2018; Shaw et al., 2013). Based on this model, it is possible to methodologically differentiate remitted from unaffected brains with MRI. Yet, previous neuroimaging studies have reported inconsistent results—perhaps because of study-specific differences (e.g. analysis methods, cross-sectional cohorts, sample characteristics). Considering this disorder’s neurodevelopmental component, sample age is especially important, making systematic longitudinal studies essential in deconstructing the etiological timeline of brain mechanisms in relation to remission.

Diffusion-weighted imaging (DWI) is an in vivo MRI method which measures the magnitude and direction of water molecules diffusing through brain tissue, reflecting the underlying architecture of axons and their ensheathing myelin. Diffusion tensor imaging (DTI) has been the most commonly used DWI method in ADHD studies, which have usually reported tensor-derived, voxel-wise measures like fractional anisotropy (FA). One follow-up case-control DTI investigation in only men suggested that ADHD is a lasting neurobiological trait irrespective of remission or persistence: Compared to those who did not have childhood ADHD, probands with both remittent and persistent ADHD showed approximately 90% of voxels contain multiple fiber populations, we applied a high angular diffusion model: constrained spherical deconvolution (Jeurnissen et al., 2013). Voxel-based methods that model crossing fibers (e.g. BEDPOSTX) only represent a subset of the full range of possible fiber orientation distributions (FODs), whereas constrained spherical deconvolution represents FODs as spherical harmonics, free to distinguish more or less arbitrary shapes (Tournier et al., 2004). Fixel-based analysis (FBA) applies the constrained spherical deconvolution model and can more accurately reconstruct a continuous FOD in both single- and multiple-fiber voxels—characterizing properties of each “fixel,” or specific fiber population in a voxel (Raffelt et al., 2017b; Schilling et al., 2018; Tournier et al., 2019, Tournier et al., 2013, Tournier et al., 2007). Fixels can be statistically analyzed for fiber-specific indices of underlying physiology: fiber density (FD), a microstructural measure of the within-voxel intra-axonal restricted compartment of a fiber population; fiber cross-section (FC), a macrostructural measure of the area perpendicular to the fiber orientation; and fiber density and cross-section (FDC), a combination of FD and FC (Raffelt et al., 2017b). Less FD can indicate axonal loss, while less FC can indicate macroscopic fiber atrophy (Gajamange et al., 2018; Mito et al., 2018; Rojas-Vite et al., 2019). FBA resolves crossing fibers more accurately as well as characterizes the microstructural and morphological, macrostructural properties of specific fiber populations.

One cross-sectional FBA showed that ADHD-affected children who had reduced fine motor competence also had lower WM microstructure in all three fixel metrics in the CST. These results suggest that cases had fewer and/or thinner CST axons, which may lead to reduced fiber bundle information transmission speed (Hyde et al., 2020). Likewise, compared to controls, children with ADHD had less FD in association and projection pathways subserving behavioral control and motor...
function (Fuelscher et al., 2021). Despite the consistent clamor to resolve crossing fiber regions and FBA’s evident advantages, there have been no other published FBA applications in people with ADHD to our knowledge. Furthermore, besides our prior research, there have been no other DWI studies with multiple follow-up waves in the longitudinal symptom course of ADHD.

In an extension of our previous work in overlapping samples, here we followed 139 people over approximately 15 years. We used a more recent multi-shell DWI fiber model and a new follow-up measurement at an older age range. Because our previous findings were detected in regions of crossing fibers, it is reasonable to expect that, by using more sensitive FBA metrics, we could find an opposite effect between symptom improvement and follow-up white matter microstructure. We aimed to assess the time-lag between the course of ADHD symptomatology and WM microstructure in a priori models and regions-of-interest. Because our smaller sample size at an older age range is not suitable for a data-driven search to discover any new relevant regions or tracts, the present analyses were intended to further understand the nature of our previous results. To compare FBA metrics to our previous FA findings, our first follow-up analysis used the same exact sample as our most recent longitudinal DTI study (Leenders et al., 2021). Our second analysis probed whether those same time-lag associations existed at the newly-acquired later age range. For both analyses, we hypothesized that, like in our earlier findings, symptom improvement would be associated with lower FC, FD, and FDC at follow-up in the ICST and ISLF.

2. Methods

2.1. Participants

Clinical and MRI data were originally collected from probands with childhood ADHD, their first-degree relatives, and healthy families in one initial wave: NeuroIMAGE1 (W1) (von Rhein et al., 2015). After an average of 3.7 years (standard deviation [SD] = 0.5 years), those participants were invited back for a second acquisition: NeuroIMAGE2 (W2). After a mean of 5.1 years (SD = 1.4 years), some individuals returned for another wave, DELTA (W3), which included only people who fulfilled full ADHD diagnostic criteria in at least one previous wave (Table 1). For the analyses here, we only included participants who had clinical data from at least two of the three waves and DWI data from W2 and/or W3 (Fig. 1). For each time-point, there were no differences between the participants included in the current analyses and the complete sample in symptom severity, age, and sex (p > 0.12).

Given our longitudinal design, we did not split our participants into cases versus controls. Through the years, symptom scores and diagnoses varied through time and participant characteristics changed from wave to wave (Fig. 2). Some individuals originally recruited as controls or unaffected siblings developed ADHD at a later time-point and others recruited as ADHD participants remitted, further highlighting the complex, variable course of ADHD. Alternative to a case-control categorization, ADHD can be operationalized as a continuous trait (Lahey and Willcutt, 2010; Marcus and Barry, 2011). In a previous cross-sectional study, we systematically showed that, compared to categorical diagnoses, continuous symptom measures are more sensitive to diffusion-
2.2. Clinical symptom measures

According to our previous report, we used raw combined Conners Continuous Rating Scale (CPRS) scores from W1 and W2, and Conners Adult ADHD Rating Scale (AAAS). Symptom scores in W1 and W2 were collected via Conners Parent Rating Scale, and W3 scores were collected via the Conners’ Adult ADHD Rating Scale. Symptom scores in W1 and W2 were collected via Conners Parent Rating Scale, and W3 scores were collected via the Conners’ Adult ADHD Rating Scale. Symptom scores in W1 and W2 were collected via Conners Parent Rating Scale, and W3 scores were collected via the Conners’ Adult ADHD Rating Scale.

Table 1

Demographic and clinical characteristics of participants at Wave 1 (W1), Wave 2 (W2), and Wave 3 (W3) with mean and standard deviation (or numerical count and percentage). W3 included only those who fulfilled full ADHD diagnostic criteria in at least one previous wave. Values reported here are for all participants in the final sample after all quality control (N = 139).

<table>
<thead>
<tr>
<th>Wave 1</th>
<th>Wave 2</th>
<th>Wave 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 119</td>
<td>N = 135</td>
<td>N = 55</td>
</tr>
<tr>
<td>Age, years</td>
<td>16.98 (3.47)</td>
<td>20.22 (3.48)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>N = 48 46%</td>
<td>N = 53 39%</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>98.41 (14.81)</td>
<td>105 (16.82)</td>
</tr>
<tr>
<td>Head motion, framewise displacement</td>
<td>0.47 (0.17)</td>
<td>0.53 (0.42)</td>
</tr>
<tr>
<td>Handedness, right</td>
<td>N = 96 81%</td>
<td>N = 111 82%</td>
</tr>
<tr>
<td>Medication ever used, yes</td>
<td>N = 66 56%</td>
<td>N = 45 33%</td>
</tr>
</tbody>
</table>

Symptom raw score by diagnostic group

<table>
<thead>
<tr>
<th>Combined score</th>
<th>Hyperactivity-impulsivity score</th>
<th>Inattention score</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.03 (12.33)</td>
<td>4.94 (5.73)</td>
<td>8.05 (7.51)</td>
</tr>
<tr>
<td>12.96 (13.05)</td>
<td>4.71 (5.68)</td>
<td>7.55 (7.45)</td>
</tr>
<tr>
<td>20.53 (9.34)</td>
<td>10.85 (5.38)</td>
<td>9.67 (4.85)</td>
</tr>
</tbody>
</table>

Comorbidity diagnosis

| Anxiety disorder | N = 2 2% | N = 2 1% | N = 1 2% |
| Avoidant personality disorder | N = 1 1% | N = 2 1% | N = 0 0% |
| Conduct disorder | N = 2 2% | N = 2 1% | NA NA |
| Major depression | N = 1 1% | N = 1 1% | N = 4 7% |
| Oppositional defiant disorder | N = 15 13% | N = 16 12% | NA NA |
| Panic disorder | N = 0 0% | N = 1 1% | N = 0 0% |

Substance use

| Alcohol | N = 19 16% | N = 21 16% | N = 7 13% |
| Tobacco | N = 43 36% | N = 45 33% | N = 12 22% |
| Cannabis or hash | N = 22 18% | N = 23 17% | N = 6 11% |
| Other drugs | N = 7 5% | N = 6 4% | N = 2 4% |

For continuous measures of symptom dimension severity and in accordance with our previous report, we used randomised Conners’ Parent Rating Scale (CPRS) scores from W1 and W2, and Conners’ Adult ADHD Rating Scale (CAARS) scores from W3 for hyperactivity-impulsivity (HI) and inattention (IA) (Conners et al., 1999, 1998; Leenders et al., 2021). Here, we define symptom change (Δ) as the Conners’ score difference: Δscore = score follow-up − score baseline.

Baseline scores follow-up were always positively correlated with each other (Figure S2). A more positive Δ value indicates the worsening of symptoms, while a more negative Δ value indicates the improvement of symptoms over time. In this report, we refer to “symptom remission” dimensionally and not diagnostically, i.e. a decrease or improvement in symptom severity over time.

At W1 and W2, we assessed history of comorbid disorders with the Kiddie Schedule for Affective Disorder and Schizophrenia Present and Lifetime Version (K-SADS-PL) semi-structured interview (Donker et al., 2010; Kaufman et al., 1997). For children aged <12 years, the child’s parents or the researchers assisted in completing the self-report questionnaires. Participants with elevated scores on ≥ 1 of the K-SADS-PL screening questions had to complete a full supplement for each disorder. At W3 (all participants were aged ≥18 years), we recorded history of comorbidity using the Structured Clinical Interview for DSM-5 Disorders (SCID-V) (First et al., 2018). IQ was estimated using the vocabulary and block design subtests of the Wechsler Intelligence Scale for Children (WISC-III) or Wechsler Adult Intelligence Scale. We excluded one whole dataset from a participant who had an estimated IQ < 70. Our final sample’s demographic characteristics are summarized in Table 1.

2.3. Diffusion-weighted imaging acquisition, pre-processing, and quality control

At W2, single-shell DWI data were acquired with a 1.5-Tesla AVANTO scanner (Siemens, Erlangen, Germany) equipped with an 8-channel receive-only phased-array head coil using the following parameters: echo time/repetition time (TE/TR) = 97/8500 ms; GRAPPA-acceleration factor 2; voxel size = 2 × 2 × 2.2 mm; b-values = 0 (5 volumes, interleaved) and 1000 (60 directions) s/mm²; twice refocused pulsed-gradient spin-echo EPI; no partial Fourier. More details of this MRI data acquisition have been described previously (Damatac et al., 2020; Leenders et al., 2021). Because our models only included follow-up neuroimaging data as a further investigation of the aforementioned analyses, we did not include W1 DWI.

At W3, multi-shell DWI data were acquired with a 3-Tesla Prisma scanner (Siemens, Erlangen, Germany) equipped with a 32-channel receive-only phased-array head coil using the following parameters: TE/TR = 75/2940 ms; multi-band acceleration factor = 3; voxel size = 1.94 mm³; b-values = 0 (11 volumes, interleaved), 1250 (86 directions), and 2500 (85 directions) s/mm².

W2 and W3 images were pre-processed with MRtrix3 (version 3.0.1, https://www.mrtrix.org/) according to recommended quality-control and FBA protocols for multi-shell data (Rafelt et al., 2017b; Tournier et al., 2019). Pre-processing included denoising and unringing, motion and distortion correction, and bias field correction (Smith et al., 2004;
Fig. 2. Change in participant characteristics from Wave 1, to Wave 2, to Wave 3. Longitudinal data points are connected by a line. Note that participants at W3 were selected on the basis of their history of ADHD diagnosis, so W3 tends to differ quite markedly from the other two waves, which also include never-affected controls. This conceals the typical pattern of average symptom remission that would be expected in a follow-up study without this selection criterion.
Following pre-processing, we computed two unique group average tissue response functions for W2: WM and cerebrospinal fluid (CSF) (Dhollander et al., 2016). B0 images can be utilized like a second shell to estimate a CSF-specific response function for each participant (Dhollander et al., 2016). By modeling distinct response functions for WM and CSF, we were able to enhance the signal from WM relative to CSF and include our single shell data in the multi-shell FBA pipeline.

For W3, we calculated three response functions: WM, gray matter, and CSF (Dhollander et al., 2016). We upsampled to 1.25 mm$^3$ and performed multi-shell multi-tissue constrained spherical deconvolution on all images, resulting in a WM fiber orientation distribution (FOD) within each voxel (Jeurissen et al., 2014; Tournier et al., 2007). Afterwards, we performed joint bias field correction and global intensity normalization for each of the multi-tissue compartment parameters (Raffelt et al., 2017a). We then separately generated two study-specific FOD population templates for W2 and W3 using 40 unrelated participants from each wave per template. Symptom scores did not differ between the individuals included in the population templates versus those of the overall samples (P > 0.06).

For each population template, we calculated the FD, log(FC), and FDC (FDC = FD · FC) for each participant across all fixels. Instead of FC, we chose to calculate log(FC) so data would be centered around zero and normally distributed. The derivation of these fixel metrics, which are based on FOD lobe segmentation and subject-to-template registration warps, are described in detail elsewhere (Raffelt et al., 2015). For each FOD template, we performed whole-brain probabilistic tractography (iFOD2) seeded from a whole-brain white matter mask to generate a tractogram of 20 million streamlines and a fixed-fixel connectivity matrix (Tournier et al., 2019, Tournier et al., 2010). To reduce tractography biases in each whole-brain tractogram, we selected a subset of 2 million streamlines that best fit the diffusion signal using the SIFT algorithm (Smith et al., 2013).

To obtain each region-of-interest (left corticospinal tract: lCST; left superior longitudinal fasciculus: ISLFI, ISLFI2, ISLFI3), we extracted the spherical harmonic peaks from each voxel of both FOD population templates. We then applied TractSeg, which is an automated convolutional neural network-based approach that directly segments tracts in fields of FOD peaks, circumventing any biases that may result from user-defined or atlas-based delineation (Wasserthal et al., 2018). To maintain consistency with our previous study and hypothesis, we concatenated the ISLFI, ISLFI2, and ISLFI3 track files into one ISL tractogram. Finally, we converted the resultant tractograms to fixed maps used as masks to constrain our search space during connectivity-based fixed enhancement (Raffelt et al., 2015) (Fig. 3 and Figure S5).

2.5. Statistical analyses

To control for the lack of independence in our sample due to siblings, we designed multi-level exchangeability blocks per wave and used FSL PALM to generate a set of 5000 permutations per wave (Winkler et al., 2015, Winkler et al., 2014). Our blocks did not allow permutation between all individuals; instead, we constrained permutations at both the whole-block level (i.e. permute within families of the same size) and within-block level (i.e. permute within families) (Figure S4). We used each set as an input for its respective wave to define permutations in data shuffling during nonparametric testing.

We demeaned our design matrices using Jmisc in R (version 4.0.2) and applied connectivity-based fixed enhancement to the fixed-fixel connectivity matrices using smoothed fixed data (Raffelt et al., 2015). Using only models in which we previously found significant effects (i.e. not IA, but only HI and combined scores), for each fixed metric and each tract region-of-interest, we constructed general linear models (GLMs) to separately test whether combined ADHD or HI symptom score change (Δscore as independent variables) are associated with fixel metrics at follow-up (as dependent variables) (Leenders et al., 2021). Our covariates were: symptom score (either combined or HI) at baseline, change in age (Δage = age follow-up – age baseline), age at baseline, sex, and head motion (framewise displacement) at follow-up. For the W2 FBA, follow-up was W2 and baseline was W1, while for the W3 FBA, follow-up was W3 and baseline was W2.
W3 and baseline was W2: fixel metric follow-up − Δscore + score baseline + Δage + age baseline + sex + head motion follow-up.

We performed statistical analyses using connectivity-based fixel enhancement, which exploits local connectivity information (derived from probabilistic fiber tractography) to enhance the test-statistic of each fixel based on the support lent to it by other structurally connected fixels (Raffelt et al., 2015). Local connectivity thus acts as a neighborhood definition for threshold-free enhancement of locally clustered statistic values. Fixels were considered statistically significant at family-wise error-corrected \( p < 0.05 \) (\( P_{\text{FWE}} < 0.05 \)).

3. Results

3.1. Association between white matter at Wave 2 and the change in symptoms from Wave 1 to Wave 2

W2 fiber density (FD) in the ICST was significantly negatively associated with ΔHI score (\( t_{\text{max}} = 1.092, \text{standardized effect(SE)} = 0.044, P_{\text{FWE}} = 0.016; \text{Fig. 4} \)). There were no other significant associations between WM microstructure in the ISL at follow-up and Δcombined or ΔHI score (all \( P_{\text{FWE}} > 0.12; \text{Table S1} \)). Compared to HI symptom persistence, HI symptom remission over time was correlated with more FD in the ICST at follow-up (Figure S5, top).

3.2. Association between white matter at Wave 3 and the change in symptoms from Wave 2 to Wave 3

W3 log of fiber cross-section (log(FC)) in the ICST was significantly negatively associated with Δcombined symptom score (\( t_{\text{max}} = 3.775, \text{SE} = 0.051, P_{\text{FWE}} = 0.019; \text{Fig. 4} \)). There were no other significant associations between WM microstructure in the ISL at follow-up and Δcombined or ΔHI symptom score (all \( P_{\text{FWE}} > 0.25; \text{Table S2} \)). Compared to HI symptom persistence, HI symptom remission over time was correlated with more FC at follow-up (Figure S5, bottom).

4. Discussion

We conducted a unique study of WM microstructure and longitudinal ADHD symptom development between ages 9 and 34 years. Using the FBA framework, we discovered two findings in the ICST: (1) HI symptom improvement was associated with axonal expansion at follow-up, and (2) combined ADHD symptom improvement was associated with a larger total cross-sectional area at follow-up at a slightly later age-range. Initially, a previous voxel-wise analysis in an overlapping sample found that improved HI symptoms were associated with lower follow-up FA (W1, aged 9 – 26 years) (Franx et al., 2015). Subsequently, we extended this sample by adding a second DWI time-point (W2, aged 12 – 29 years), and systematically applied and excluded specific models—ultimately replicating the same effects on follow-up FA in the same WM region (Leenders et al., 2021). Given the counterintuitive nature of these previous highly consistent results, the present analysis aimed to further understand the physiological origins and its dynamic nature in relation to maturation. Thus here, in the exact same sample (W1-W2) and including yet a third DWI acquisition (W3, aged 18 – 34 years), using the more advanced FBA method, and employing the same GLMs in which we previously found significant voxel-wise effects, we have found increased FD in relation to HI remission, and increased FC in relation to combined symptom remission, in only the ICST and not the ISL. In contrast to our previous finding using DTI-based methods, our current finding using FBA is more intuitive in the direction of its effect: Indices that are generally indicative of “stronger” fibers were associated with clinical improvements over time.

The fixel metrics we used for quantifying WM microstructure contain complementary information. FD is thought to be related to the microstructural properties of WM, whereas FC pertains to the macrostructural properties (cross-sectional area). In our W1-to-W2 analysis, greater ICST axonal density in individuals who became less hyperactive-impulsive over time suggests plasticity, or a greater ability to relay information, after symptom improvement. FD is an estimate of the intracellular volume of fibers oriented in a particular direction. Higher FD at follow-up...
could result from developmental processes like axon diameter growth, or more axons occupying a given space. Because FD is proportional to the total intra-cellular volume of axons along a fixel, we cannot distinguish between effects specific to axon count or axon diameter. Another explanation is a reduced exchange rate between intra- and extra-axonal spaces because of increased myelination, causing an apparent increase in the intra-axonal compartment and hence an increase in FD (Cohen and Assaf, 2012). However, FD is largely not sensitive to myelin, as myelin-associated water has a very short T2 relaxation time and therefore contributes little to the diffusion signal (D‘ hobbies et al., 2021; Raffelt et al., 2012). Our second analysis found associations with FC, which measures the morphological macroscopic change in the cross-sectional area perpendicular to a fiber bundle (calculated during registration to the template image). In W2-to-W3, higher follow-up ICST cross-sectional area in individuals whose combined symptom score improved, again, suggests plasticity, greater myelination, or fiber bundle organization after symptom remission (Raffelt et al., 2017b). Although the direction of effects in our FBA analyses are opposite to that of our aforementioned FA analyses, they are not incompatible. In some cases, crossing fiber complexity can have an inverse correlation with FA, wherein greater complexity occurs when more fixels in a voxel have the same fiber density (Grazioplene et al., 2019). An analogous inverse association exists in our previous W1-to-W2 voxel-wise analysis, wherein less follow-up FA was associated with improved HI symptom score. Notably, our results were in the approximate location of where the ISL and ICST cross, while our present fixel-wise results in the ICST seem to be absent from where the ISL crosses this tract. Therefore, as we previously suggested, our tract-based spatial statistics results may have been due to the neuroanatomical location of the effects, which, when labeled with an atlas, were in an area where these tracts cross. Compared to our voxel-wise study, we presently accounted for crossing fibers better through FBA, as well as the specific, FOD-based segmentation of these tracts as separate regions-of-interest. Accordingly, symptom improvement over time can conceivably be associated with increased CST fiber maturation, which by our previous DTI methods may have the same fiber density (Grazioplene et al., 2018). An analogous mechanism to improve motor control, followed by more myelination of those fibers. Then, as our participants became slightly older, improvement in both dimensions may have led to greater ICST WM macrostructure and improved motor control (Figure S6). We speculate that improved IA (and related executive control) could help suppress HI, leading to greater motor control evinced as larger FC at a later age. In our remitters, higher measures of ICST WM might also result from reorganization in other brain areas outside of the tracts we studied. Like our previous study, we have again found that alterations in WM microstructure appear to follow symptom improvement, suggesting that WM micro- and macrostructural changes may be a downstream effect of ADHD symptom remission.

A strength of the current study is its large sample size over three clinical and two DWI time-points. Our approach using two separate follow-up analyses lent further characterization to the temporal dynamics of ADHD-WM microstructure interplay. Of particular concern given this disorder, we mitigated potential confounding effects of head motion through careful data screening, correction during preprocessing, and inclusion as a covariate in our models. Using multi-shell FBA, we demonstrated that WM-associated differences are fiber-specific even within regions of crossing fibers, and we were able to further characterize WM micro- and macrostructural properties. However, the age ranges of our W2 sample overlaps with that of W3 (Fig. 2, top left), and the acquisition methods differed between waves. Therefore, we refrain from drawing conclusions about the specificity of the relevance of micro- and macrostructural elements in specific waves or age-intervals. Because we used cluster-based inference, effects were observed consistently across a large number of connected fixels; thus, maximum effect sizes at any specific fixel within a cluster can be much smaller than in standard statistical tests. Similar small effect sizes have been found in other MRI studies on the neurobiological correlates of ADHD (Hoogman et al., 2017; Zhang-James et al., 2021). It is more likely that small effects across many different regions and imaging modalities each slightly contribute to explaining individual differences in ADHD symptom trajectories. We can expect that the current rapid increase in neuroimaging sample sizes will yield meaningful results, not by identifying single brain traits of direct clinical utility but by describing the true effects of many traits across the brain with increasing accuracy, which could collectively describe individual differences even if individual effects are small. Our study adds to this scientific development, especially given that our effects replicate those in our previous studies. Nonetheless, a limitation of this study is the quality of our Wave 2 imaging data. The first follow-up analysis included DWI data acquired with a single relatively low b-value at 1.5 T with anisotropic voxel dimensions, which may have precluded us from discovering effects in other tracts and/or symptom dimensions. Higher diffusion weighting has been shown to improve correspondence between FD estimates and intra-axonal signal fraction simulations by increasing extra-axonal signal suppression (Genc et al., 2020). While diffusion-weighting was negatively associated with FD estimates, it was not a confounder for our
effect of interest; the effect was balanced across both waves and b-values (Figure S7). Despite upampling and tractogram filtering, anisotropic voxel dimensions may have still affected our tractography results (Neher et al., 2013). Second, our follow-up samples were prone to selection bias from attrition and our explicit selection criteria in W3, where we also used different instruments (CRPS vs. CAARS) and raters. Returning participants were different from those who participated only once. Finally, even in a longitudinal study, we cannot prove causality. ADHD symptom persistence is likely associated with many other factors in daily life, or medication, or comorbid symptomatology—and any combination of these could also contribute to neurological differences at follow-up. Given our small sample size, we used a priori regions-of-interest and models, but a larger, systematic and data-driven whole-brain analysis would be a more sufficient test for mechanisms of remission.

Our findings contribute to the growing body of evidence describing the progression of symptoms in relation to WM development. Defining the correlates and predictors of remission may eventually lead to an improved allocation of treatment resources for persistent or complicated ADHD. A better understanding of the underlying neural mechanisms of these changes in time can contribute to the promotion of favorable perspectives for children and adolescents with this disorder.

5. Funding, acknowledgments, and financial disclosures

The authors would like to thank all of the families who participated in this study and all of the researchers who collected the data. This study sample is from the DELTA and NeuroIMAGE projects. NeuroIMAGE was the longitudinal follow-up study of the Dutch part of the International Multisite ADHD Genetics (IMAGE) project, which was a multi-site, international effort. NeuroIMAGE was supported by a Dutch Research Council (NWO) Large Investment Grant (no. 1750102007010) and NWO Brain & Cognition as an Integrative Approach Grant (no. 433-09-242 to J.K.B.), and grants from Radboud University Medical Center, University Medical Center Groningen and Accare, and VU University Amsterdam. DELTA was funded by a Hypatia Tenure Track Grant from Radboud University Medical Center (to E.S.). Funding agencies had no role in study design, data collection, interpretation or influence on writing. J.N. is supported by an NWO Veni grant (no. VI.Veni.194.032). B.F. has received educational speaking fees from Medice. J.K.B. has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda/Shire, Roche, Medice, Angelini, Janssen, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties, E.S. is supported by a Hypatia Tenure Track Grant (Radboudumc), Christine Mohrman Fellowship (Radboud University), and a NARSAD Young Investigator Grant (Brain and Behavior Research Foundation, Grant No. 25034). All other authors report no biomedical financial interests or potential conflicts of interest.

CRediT authorship contribution statement


Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jlinc.2022.103057.

References


