Data Supplement for Ameis et al., A Diffusion Tensor Imaging Study in Children with ADHD, ASD, OCD and Matched Controls: Distinct and Non-distinct White Matter Disruption and Dimensional Brain-Behavior Relationships

Contents:

I. Additional information regarding continuous behavior measures used for brain-behavior analyses

For the Attention Problem Subscale from the Child Behavior Checklist for 6-18 year-olds, higher scores signify increased attention problems: a T score of 65-70 indicates borderline pathology and >70 indicates scores in the pathological range (1).

The Toronto Obsessive-Compulsive Scale was chosen for the present study over other self-report measures of obsessive-compulsive symptoms as it allows the measurement of a wide distribution of obsessive compulsive traits; it's items cover a comprehensive, multidimensional range of obsessive compulsive traits; and it is designed as a parent-report measure. Negative scores on this meaasure signify presence of few obsessive-compulsive symptoms, scores >0=clinically significant symptoms)(Park et al, in preparation).

The Social Communication Questionnaire is a 40-item scale adapted from the Autism Diagnostic Interview-Revised(2), scores ≥15 reflect clinically significant deficits in social communication.

The Adaptive Behavior Assessment System-II is a measure of adaptive behavior that has been validated in a number of child psychiatric populations and has been used to assess functioning in childhood disorders, including autism spectrum disorder (ASD) (3), and attention-deficit/hyperactivity disorder (ADHD) (4). For the General Adaptive Composite of the Adaptive Behavior Assessment System-II, lower scores represent lower functional ability: 80-89=below average, 71-79=borderline, ≤70=extremely low(5).

II. Table S1. Detailed Information Regarding Documented Psychiatric Comorbidities and Psychotropic Medications Taken for the Analyzed Sample

	ASD (n=71)	ADHD (n=31)	OCD (n=36)
Confirmed Comorbidity	3 Yes	23 Yes	13 Yes
Comorbid Diagnoses	1 ADHD + Anxiety + ID 1 ADHD 1 Anxiety	1 ASD + LD 1 ASD + Tic + LD 1 OCD + DBD 3 DBD + LD 4 DBD 2 Anxiety + LD 2 Anxiety 9 LD	1 ADHD + Tic 1 ADHD + Anxiety 4 ADHD 4 Anxiety 1 Anxiety + Tic 2 Tic
Any Psychotropic Medication	29 Yes	13 Yes	13 Yes
Specific Psychotropic Medications Used	10 stimulant 4 SSRI/SNRI 1 Atomoxetine 2 AAP 1 Omega 3 1 melatonin 4 SSRI + stimulant 1 SSRI + Atomoxetine 1 AAP + tryptophan 1 AAP + SSRI 1 AAP + SSRI + melatonin 2 stimulant + clonidine	11 stimulant 1 stimulant + AAP 1 stimulant + Atomoxetine	6 SSRI 3 SSRI + stimulant 3 SSRI + AAP 1 SSRI + stimulant + AAP

ADHD=attention/deficit-hyperactivity disorder, OCD=obsessive compulsive disorder, ASD=autism spectrum disorder, ID=intellectual disability, LD=learning disorder, DBD=discruptive behavior disorder (oppositional defiant disorder or conduct disorder, Anxiety=any anxiety disorder (excludes OCD), AAP=atypical antipsychotic, SSRI=selective serotonin reuptake inhibitor, SNRI=selective norepinephrine reuptake inhibitor

III. Table S2. Number of NDD Cases with Clinically Significant Psychiatric Symptoms Based on DSM-Oriented Subscale T Scores from the Child Behavior Checklist/6-18

	ASD (n=62)	ADHD (n=30)	OCD (n=24)
Affective Problems	17(27%)	9(30%)	4(16%)
Anxiety Problems	30(48%)	6(20%)	8(33%)
Somatic Problems	8(13%)	2(7%)	2(8%)
Attention-Deficit/Hyperactivity Disorder Problems	13(21%)	13(43%)	3(13%)
Oppositional Defiant Disorder Problems	11(18%)	10(33%)	5(21%)
Conduct Disorder Problems	8(13%)	10(33%)	1(4%)
Obsessive Compulsive Disorder Problems	28 (45%)	7(23%)	16(67%)
Post-Traumatic Stress Disorder Problems	18(29%)	9(30%)	8(33%

Number of cases (and percentage of group) with T scores in the clinically significant range (≥70) are presented for each clinical group.

IV. Additional information regarding diffusion imaging acquisition procedure

Acquisition of diffusion scans for the present study was split into three separate acquisitions consisting of 19, 20, and 21 direction acquisition sequences. Three b=0 reference scans were acquired at the beginning, middle, and end of each acquisition. Separate acquisitions and interleaved b=0 scans were used to maintain shorter scan times and facilitate acquisition of high quality scans. Prior to diffusion tensor fitting, the 6 degree-of-freedom rigid body transformations between 1) all b=0 reference images and the very first b=0 image, and 2) any given diffusion weighted image and the 'closest' b=0 reference image were determined. A single transformation matrix per volume was calculated and applied to bring all 69 volumes(60 b=1000 + 9 b=0) into a single 60-direction dataset per participant.

V. Multi-group comparison of additional diffusion tensor imaging (DTI) measures

Multi-group comparison of additional diffusion tensor imaging measures, including mean, radial and axial diffusivity were run using separate univariate tests comparing each DTI index across ASD, ADHD, obsessive-compulsive disorder (OCD) and control groups at the same time. To control for potentially confounding variables, all analyses were run while controlling for: age, age^2, sex, and medication status.

Although, no significant differences were found for mean or radial diffusivity, axial diffusivity was found to be significantly different amongst our 4 groups. Differences found for axial diffusivity localized to voxels corresponding to the left thalamus and extending into the internal capsule ($F_{3,196}$=18.9, $p<0.001$). Post-hoc t-test comparisons between groups indicated that axial diffusivity values within this region were lower in each NDD group compared to controls, but were no different between NDDs (See Figure S1). Of note, the location of axial diffusivity

results did not overlap with our fractional anisotropy (FA) findings reported in our main manuscript.

VI. Post-hoc univariate test comparing FA in males only across ASD, ADHD, OCD and control groups.

In the present study, the presence of significant group differences in gender-ratio in our ASD and ADHD groups, compared to controls, had the potential to influence our multi-group comparison FA results. Therefore, we repeated our multi-group comparison test in males only (excluding all females across our NDD and control groups). Multi-group analysis run in males only continued to show FA differences amongst all 4 groups that were localized to voxels within the splenium of the corpus callosum, as found when all participants were included in multi-group analysis.

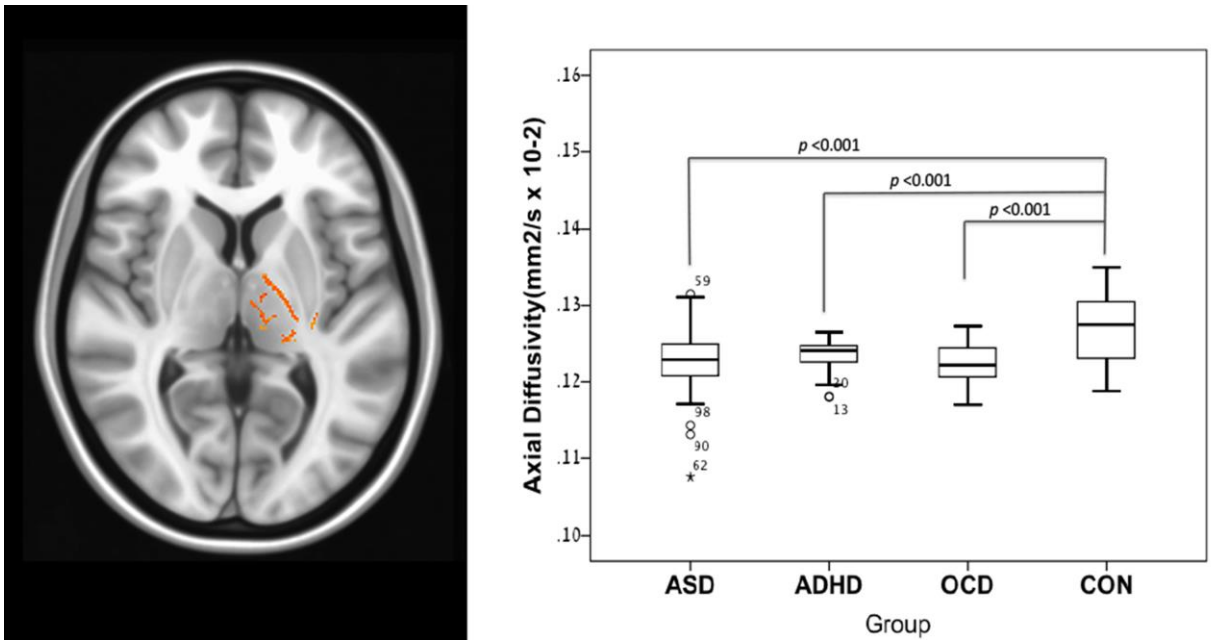
VII. Post-hoc analyses examining relations between clinical symptoms and findings on voxel-wise pair-wise comparison of FA in ADHD versus OCD.

To better understand the behavioral correlates of FA differences in fronto-cortical white matter connections in ADHD versus OCD, we conducted post-hoc analyses to examine whether white matter within this circuitry was related to dimensional measures of symptoms characteristic of either disorder. FA values for voxels that differed between ADHD and OCD were extracted. Using R 2.15.2 software(http://www.R-project.org)(6), obsessive-compulsive symptom and ADHD symptom scores, as measured by the Toronto Obsessive-Compulsive Scale and Child Behavior Checklist Attention Problem Subscale, respectively, were linearly regressed against extracted FA values for each participant. Linear regression analyses showed that fronto-cortical white matter FA was positively associated with obsessive-compulsive scores ($F_{1,48}$=11.02, p=0.0017) and negatively associated with attention problem scores ($F_{1,43}$=14.55, p=0.0043) across children with ADHD and OCD (see Figure S3).

Supplemental References

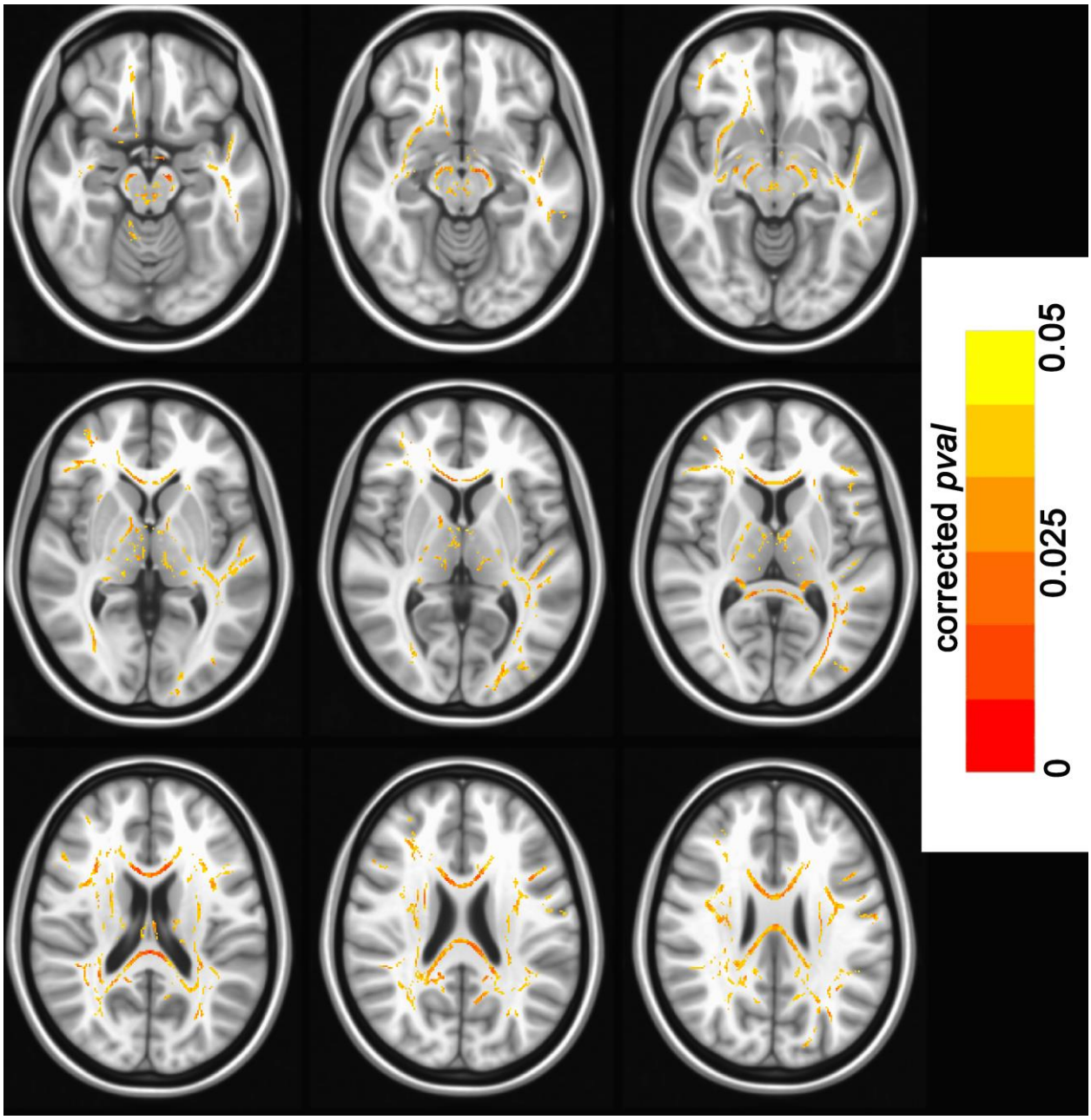
1. Achenbach TM. Child Behavior Checklist (CBCL 6-18). Burlington, Vermont: University Associates in Psychiatry; 2001.
2. Berument SK, Rutter M, Lord C, Pickles A, Bailey A. Autism screening questionnaire: diagnostic validity. Br J Psychiatry. 1999;175:444-51.
3. Kenworthy L, Case L, Harms MB, Martin A, Wallace GL. Adaptive behavior ratings correlate with symptomatology and IQ among individuals with high-functioning autism spectrum disorders. J Autism Dev Disord. 2010;40(4):416-23.
4. Lindblad I, Svensson L, Landgren M, Nasic S, Tideman E, Gillberg C, et al. Mild intellectual disability and ADHD; a comparative study of school age children's adaptive abilities. Acta Paediatr. 2013;102(10):1027-31.
5. Waisbren SE, He J, McCarter R. Assessing Psychological Functioning in Metabolic Disorders: Validation of the Adaptive Behavior Assessment System, Second Edition (ABAS-II), and the Behavior Rating Inventory of Executive Function (BRIEF) for Identification of Individuals at Risk. JIMD Rep. 2015;21:35-43.
6. Team RC. R: A Language and Environment for Statistical Computing. Computing RFfS, editor. Vienna, Austria2012.

VIII. Figure S1. Differences in Axial Diffusivity on Multi-Group Comparison across ASD, ADHD, OCD and Controls



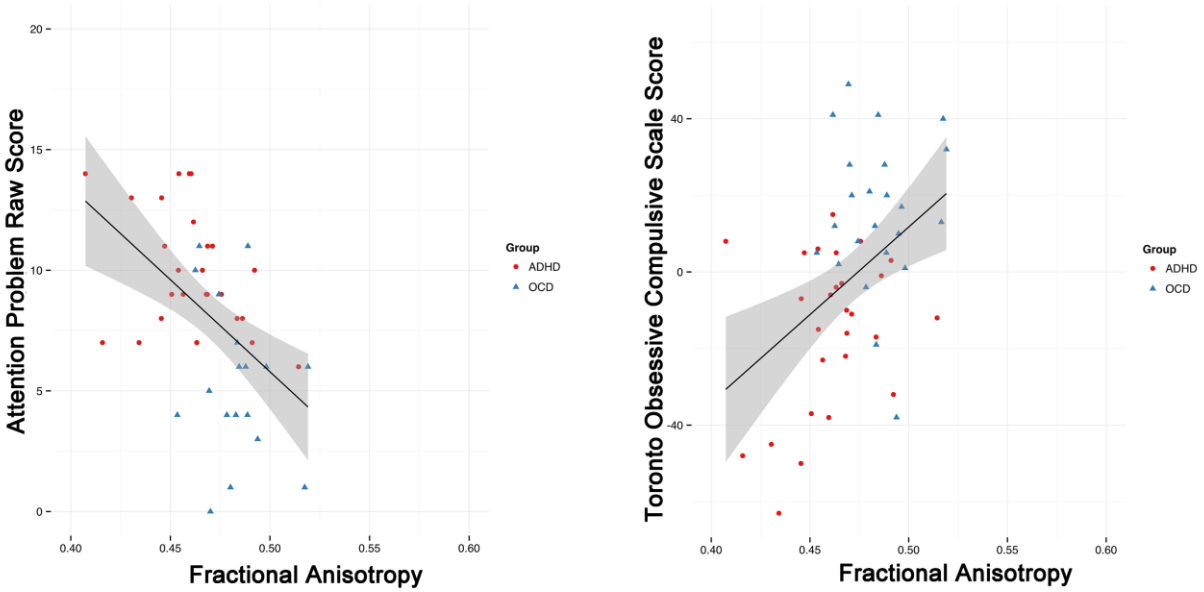
Voxels within the left thalamus and internal capsule where white matter axial diffusivity differed between groups on multi-group comparison of ASD, ADHD, OCD and control groups is presented on left side of image ($F=18.9$, $df=3,196$, $p<0.001$). All voxels displayed in red/yellow are significant at p value ≤ 0.05, fully corrected for multiple comparisons across space using family-wise error. Boxplot on the right of image presents results of post-hoc pair-wise comparisons indicating that axial diffusivity values that differed on multi-group analysis were lower in each NDD group, compared to controls, but were not different between NDDs.

IX. Figure S2. Lower white matter fractional anisotropy in neurodevelopmental (NDD) disorder group versus controls



Voxels within the white matter skeleton where fractional anisotropy(FA) was lower in an NDD group versus controls (groups matched for age, sex and excluding participants with below average IQ). All voxels displayed in red/yellow are significant at p value ≤ 0.05, fully corrected for multiple comparisons across space using family-wise error.

X. Figure S3. Reduced white matter fractional anisotropy in ADHD versus OCD and relation with attention problems and obsessive-compulsive symptoms



Left: linear regression illustrating a significant negative association between average white matter FA across white matter voxels that differed in ADHD versus OCD and raw score for Child Behavior Checklist Attention Problem Subscale scores across children and adolescents with ADHD and OCD ($F_{1,43}$=14.55, p=0.0043). Right: linear regression illustrating a significant positive association between average white matter FA across white matter voxels that differed in ADHD versus OCD and Toronto Obsessive Compulsive Scale scores across children and adolescents with ADHD and OCD ($F_{1,48}$=11.02, p=0.0017). Note: For visualization, a scaled range of fractional anisotropy (FA) values including all mean values found for our sample has been used, the full range of potential FA scores for the present study was >0.2-1.