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ORIGINAL RESEARCH

Differences in attentional control and white matter microstructure in adolescents with attentional, affective, and behavioral disorders

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Abstract

Adolescence is a critical time of physiological, cognitive, and social development. It is also a time of increased risk-taking and vulnerability for psychopathology. White matter (WM) changes during adolescence have been better elucidated in the last decade, but how WM is impacted by psychopathology during this time remains unclear. Here, we examined the link between WM microstructure and psychopathology during adolescence. Twenty youth diagnosed with affective, attentional, and behavioral disorders (clinical sample), and 20 age-matched controls were recruited to examine group differences in WM microstructure, attentional control, and the link between them. The main results showed that clinical sample had relatively lower attentional control and fractional anisotropy (FA) in WM throughout the brain: two association tracts were identified, and many differences were found in areas rich in callosal and projection fibers. Moreover, increased FA was positively associated with attention performance in the clinical sample in structures supporting ventral WM pathways, whereas a similar link was identified in controls in dorsal WM association fibers. Overall, these results support a model of general impairment in WM microstructure combined with reliance on altered, perhaps less efficient, pathways for attentional control in youth with affective, attentional, and behavioral disorders.

Keywords DTI · Imaging · ADHD · Emotion · Adolescent · Cognition · Mental health

Introduction

Adolescence is a major transitional development period from childhood to young adulthood, characterized by structural and functional brain maturation and pubertal changes, as well as cognitive and emotional development (Spear 2000; Paus 2005). This period represents a transition from a state of dependency to that of a more independent young adult, and is marked by increases in cognitive control, social awareness, and emotional regulatory skills. However, it is also associated

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with vulnerability to psychopathology and increases in risk-taking behaviors (Luna et al. 2004; Luna and Sweeney 2004; Rosso et al. 2004; Steinberg 2004; Asato et al. 2010). Although large individual differences are observed with social-cognitive development during adolescence (Fuhrmann et al. 2015), including varied levels of risk-taking and behavioral problems (Maggs et al. 1995), adolescent risky behavior is exacerbated by psychopathology (Zhou et al. 2012; Kaess et al. 2014). For example, during adolescence suicide is the third leading cause of death in the United States (Heron 2013) and the second leading cause of death in Canada (Statistics Canada, https://www.statcan.gc.ca/), with psychiatric disorders including anxiety and depression identified as major risk factors (Moscicki 2001; Dirks 2017). It is of paramount importance to better understand the adolescent brain and how it relates to behavior, especially in adolescent populations vulnerable to increased risky behavior. The present investigation examined behavioral and neural changes linked to psychopathology during adolescence by investigating differences in attentional control and white matter (WM) microstructure in adolescents with and without affective, attentional, and behavioral disorders.

White matter (WM) tracts and microstructure (i.e., orientation and diffusivity) may be identified with diffusion tensor imaging (DTI), a non-invasive magnetic resonance imaging (MRI) technique. DTI relies on the principle that water diffusion along healthy WM tracts is anisotropic (favoring a specific direction), because it moves more easily parallel (rather than perpendicular) to the axonal membrane. Properties of diffusion within a voxel: axial diffusivity (AD)–diffusion along the long axis, radial diffusivity (RD)–diffusion perpendicular to the long axis, and mean diffusivity (MD)–average diffusion can be measured to provide information about WM microstructure in a brain region (Beaulieu 2013; Jones et al. 2013). The eigenvalues of the diffusion tensor that constitute these parameters can also be combined to produce fractional anisotropy (FA) (Basser and Pierpaoli 1996), which offers a simple way of comparing the anisotropy of an area of tissue, as FA values range from 0 (totally isotropic) to 1 (totally anisotropic). FA offers a good index of overall anisotropy, sensitive to tissue characteristics that result in changes in anisotropy in a voxel of WM (e.g., the degree of myelination, fiber coherence, fiber density, axon diameter, tract geometry, presence of crossing fibers) (Beaulieu 2002, 2013). It should be noted that, whereas FA is the primary imaging metric of choice for many in examining differences in WM, interpreting FA in the context of other diffusivity parameters can allow for more informed inferences to be made about the characteristics of the tissue microstructure (Pierpaoli et al. 2001; Song et al. 2002, 2003, 2005; Oh et al. 2004; Alexander et al. 2007a, b; Lebel and Deoni 2018).

Over the last 10 years, longitudinal DTI studies have shown linear and non-linear regionally dependent increases in FA during adolescence (see Lebel et al. 2017 for review). Increased FA during this period is often accompanied by decreases in MD and RD and, less frequently, by increases in AD (see Lebel et al. 2017 for review). Although controversy surrounds what underlying microstructural changes best correspond to diffusion parameters, findings from other types of MRI (i.e., T1-, T2-, and T2-weighted fluid attenuation inversion recovery) and post-mortem studies suggest that in development, myelination, which occurs rapidly during infancy, slows down during adolescence. Furthermore, data converge to suggest that the majority of microstructural changes taking place during adolescence are comprised of neurite density, axonal packing, and reduced tortuosity (Deoni et al. 2012; Mah et al. 2017; Lebel and Deoni 2018). Regarding WM maturity, some tracts reach their maximum FA during the teen years and others not until the mid-twenties or early thirties (Mukherjee et al. 2001; Schmithorst et al. 2002; Barnea-Goraly et al. 2005; Ben Bashat et al. 2005; Bonekamp et al. 2007; Giorgio et al. 2008; Lebel et al. 2008; Bava et al. 2010). Overall, although we have been gaining insight into WM development during adolescence, we are far from understanding how these microstructural changes are impacted by psychopathology.

There is an undeniable link between psychiatric disorders and WM structure, as evidenced through WM disorders and post-mortem studies looking at gene expression in the cortex in populations with psychiatric disorders (Filley 2005a, b, 2011; Fields 2008). In adults, extant DTI research shows aberrant neural connectivity associated with psychiatric disorders (Alexopoulos et al. 2002; Adler et al. 2004; Beyer et al. 2005; Szeszko et al. 2005; Abe et al. 2006; Bae et al. 2006; Kim et al. 2006; Cannistraro et al. 2007; Rusch et al. 2007; Taylor et al. 2007). However, findings to date show that there is large spatial heterogeneity in the location of WM abnormalities in various psychiatric disorders (see Fields 2008 for a review). During adolescence, the paucity of studies investigating the relationship between WM and psychopathology has produced conflicting results with no clear consensus. This is partly due to the challenges of grasping a concrete understanding of psychopathology during such a unique time period. In fact, adolescent psychopathology may be best described as a constellation of co-occurring disorders (Price and Zwolinski 2010). The typically high degree of co-morbidity in adolescent psychopathology (Jensen et al. 2006) may be reduced as the individual "ages out" of psychopathology or moves into a predominant symptom cluster. Consequently, during adolescence there may be overarching similarities in the neural and cognitive processes linked to the co-occurring disorders or clusters of psychiatric symptoms (Sauder et al. 2012;

Singhal et al. 2012). For example, attentional control is one process that may be affected by several affective psychiatric disorders (Wang et al. 2005, 2008).

Attentional control (executive/endogenous attention) is operationally defined here as the ability to maximize sustained top-down, goal-directed attention resulting in the minimization of interference from task-irrelevant distracter items (Hopfinger et al. 2000). Continuous performance tests offer one way to measure sustained attention and one's ability to inhibit responding to distractor items. Therefore, performance on such tests offer a good representation of the attentional control construct that is reliable and easy to implement. A dorsal neural circuitry (including dorsolateral prefontal, superior parietal, dorsal anterior cingulate cortices) has been identified as important for attentional control (Corbetta and Shulman 2002; Petersen and Posner 2012) and its impairment may result in a hyper-active emotional response or the inability to ignore task-irrelevant emotional information (Shafer and Dolcos 2010; Shafer et al. 2012). The processing of emotional information is reliant on ventral neural circuity (including amygdala, ventrolateral prefrontal, lateral temporo-occipital, and ventral anterior cingulate cortices) (Phillips et al. 2003; Dolcos and McCarthy 2006). Previous research has shown that these two neural circuitries (in many, but not all scenarios) operate in opposition to one another (Yamasaki et al. 2002; Dolcos et al. 2011). Although the nature of their interactions is not fully understood, evidence suggests that resources utilized by one system, impairs the functioning of the other system (Dolcos et al. 2008; Iordan et al. 2013),

Investigations of the relationship between FA and individual differences in cognitive control have revealed increased FA associated with both increases and decreases in cognitive control scores during childhood and early adolescence (Treit et al. 2014). Increased FA in anterior frontal and orbitofrontal corpus callosum was associated with increased inhibition errors. Conversely, increased FA in the splenium, occipital blade, and posterior limb of the internal capsule was linked to a reduction in inhibition errors. This shows that enhanced connectivity in networks during childhood and adolescence supports certain maladaptive behavior and is consistent with functional studies identifying a ventral-to-dorsal developmental shift in the functional network of medial prefrontal cortex (Gee et al. 2013; Gabard-Durnam et al. 2014). Therefore, while it is necessary to identify general WM differences between clinical and non-clinical individuals, it is also important to see how the relationships between structure and function (specifically in behavior linked to cognitive processes known to be impacted by psychopathology) are also different.

This study investigated three main aspects of potential changes in WM microstructure associated with clinical psychopathology during adolescence. First, we examined basic differences in attentional control and FA between a group of adolescents with affective, attentional, and behavioral disorders and a group of healthy control participants. Second, we investigated similarities and differences between these groups in the link between attentional control and FA. Third, we examined individual diffusion properties to better characterize the observed differences in FA. Based on the literature, we tested two main hypotheses. First, we expected to replicate previous research showing impaired attentional control and WM microstructure in individuals with attention and affective-based psychiatric disorders. Second, we also predicted group differences in the relationship between WM microstructure and attentional control.

Methods

Participants Forty adolescents (20 clinical, 20 control) participated in this study. The control adolescents were matched to the clinical sample on age (within 1 year of scanning), sex (8 males), and handedness (1 left-handed). A two-sample t-test was performed to confirm that there was no significant age difference between groups [$t(38) = 0.041$, $p = 0.968$, 95% CI (−0.936, 0.975); Healthy Mean (SD) = 14.959 (1.519), Clinical Mean (SD) = 14.978 (1.467)]. The clinical sample adolescents were recruited from a residential mental-health treatment facility in the City of Edmonton, Alberta, Canada and were previously diagnosed with affective, attentional, and behavioral disorders using the *Diagnostic and Statistical Manual of Mental Health Disorders* 4th edition (DSM-IV). Due to the large comorbidity and heterogeneity in our sample's diagnoses, we grouped depressive disorders (major depression and dysthymia) and anxiety disorders (generalized anxiety, post-traumatic stress disorder, social phobia) together into one "distress disorders" category. We also grouped all sub-types of ADHD (combined, predominantly inattentive type, predominantly hyperactive/impulsivity type) together into one "ADHD" category. Clinical characteristics are summarized in Table 1, and further information about this population is described by Singhal et al. (2012) and Van Vliet et al. (2017). Healthy controls, recruited from the City of Edmonton, were screened for psychiatric illness and drug/alcohol use with the mini-international neuropsychiatric interview for kids (M.I.N.I-Kid) (Sheehan et al. 1998, 2010). All participants had normal or corrected-to-normal vision. Informed consent and assent were obtained from parental guardians and adolescents, respectively, before participating. The experimental protocol was approved for the ethical treatment of human participants by the Health Research Ethics Board at the University of Alberta.

Test of variables of attention Participants completed the Test of Variables of Attention (TOVA) (Greenberg 2011). The TOVA is a computerized continuous performance test that measures sustained attention (assessed during a target-

Table 1 Diagnostic and medication information for the 20 clinical adolescents

Diagnosis	Sex	Medication (number of patients)				
	(M/F)	Unknown/ None	Stimulants	Anti-depressants	Anti- psychotics	Other
Distress disorders *(MDD, Dysthymia, SP, GAD, PTSD)* co-morbid with one or more following disorders						
Distress disorders and ADHD, PCRP	(2/4)	1/–	4	5 - SSRI	2	–
ADHD, CD, ODD, PCRP, RAD	(4/3)	–/–	2	4 – SSRI	4	1 - BZD
ADHD co-morbid with one or more following disorders						
CD, ODD, PCRP, RAD	(2/2)	–/–	4	2 – SSRI 1 - NDRI	6	–
Others: one or more following disorders						
ODD, PCRP, AD	3 (0/3)	–/2	–	1-SSRI	1	–
Total	20 (8/12)	1/2	10	12 – SSRI 1 - NDRI	13	1 - BZD

AD Attachment Disorder, *ADHD* attention-deficit/Hyperactivity disorder, *CD* Conduct Disorder, *GAD* Generalized Anxiety Disorder, *MDD* Major Depressive Disorder, *PTSD* Post Traumatic Stress Disorder, *ODD* Oppositional Defiant Disorder, *PCRP* Parent-Child Relational Problem, *RAD* Reactive Attachment Disorder, *SP* Social Phobia, *SSRI* selective serotonin reuptake inhibitor, *NDRI* norepinephrine-dopamine reuptake inhibitor, *BZD* benzodiazepine

infrequent block) and inhibitory control (assessed during a target-frequent block). In both blocks, each stimulus was presented for 100 ms and the inter-stimulus interval was 2000 ms. In the target-infrequent block, one target appeared for every 3.5 non-targets (22.5%, $n = 72$), whereas in the target-frequent block, 3.5 targets appeared for every one non-target (77.5%, $n = 252$). Test-retest reliability (one-week interval) of the TOVA as measured by Pearson product coefficients range between 0.74 and 0.87, depending on the outcome variable of interest (Leark et al. 2004). Response times within 150 ms of stimulus onset were automatically categorized as an anticipatory response and excluded from analyses. Participants were instructed to respond to the target as quickly as possible. The total test time was 21.6 min (10.8 min per block). Data from one control participant was lost due to computer error.

Imaging protocol

Data acquisition DTI data were acquired on a 1.5 T Siemens Sonata MRI scanner using a dual spin-echo, single shot echo-planar imaging sequence with the following parameters: 50, 2.2-mm thick slices with no inter-slice gap, TR = 7700 ms, TE = 94 ms; 30 diffusion sensitizing gradient directions with $b = 1000$ s/mm^2; 5 non-diffusion-weighted, T2 images ($b = 0$ s/mm^2), field of view 212 × 212 mm^2. Total DTI acquisition time was 4:39 min. DTI data were obtained as the last sequence of an imaging protocol that also contained sequences for MPRAGE, 5 task-fMRI runs, and resting state fMRI. The total scanning protocol lasted approximately 44 min.

DTI image processing DTI data were processed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB, FSL 5.0.6) Diffusion Toolbox (FDT). First, raw data were screened for artifacts and volumes with slice artifacts and/or signal dropout were removed. No more than two diffusion weighted volumes were removed for a single subject. A two-sided Fisher's Exact Test showed that the number of volumes removed did not significantly differ between groups ($p = 0.13$). Second, all non-diffusion-weighted (b0) images were motion- and eddy current-corrected using FMRIB's linear registration tool (FLIRT) (Jenkinson and Smith 2001; Jenkinson et al. 2002) and then averaged. This corrected, non-diffusion average was then used as the template for motion and eddy current correction of the non-diffusion and diffusion-weighted images. These corrected images were then used for brain extraction (BET) (Smith 2002), creating a mask to be used for tensor fitting. The fractional intensity threshold was set at 0.3 to provide the best extraction results across subjects. The diffusion tensor model was fit at each voxel using DTIFIT with weighted least-squares regression (Abdi 2003; Jones et al. 2013). A diagram summarizing the image processing pipeline can be found in Supplementary Material.

Data analysis

Behavioral data analysis Attention performance index (API) scores were analyzed using a univariate analysis of variance (ANOVA), with age as a covariate. Confidence intervals were calculated using bootstrapping (5000 samples). The API is a composite score automatically generated by the TOVA software. The API score results from the following equation, [reaction time (block 1) + d-prime (block 2) + total variability + calibration constant] and provides information about overall

performance (across blocks 1 and 2) on the TOVA, compared to the TOVA ADHD population, and is an index of likely impairment (Leark et al. 2007).

Whole brain FA analysis FMRIB's tract-based spatial statistics (TBSS) toolbox was used to prepare the FA images for statistical analysis. Every individual FA image was aligned to every other FA image to identify the most representative image (the image that requires the least amount of warping) using the nonlinear registration tool FNIRT (Andersson et al. 2007a, b), which uses a b-spline representation of the registration warp field (Rueckert et al. 1999). The most representative FA image was then affine-aligned to 1 mm^3 MNI152 standard space. All other individual FA images were transformed into 1 mm^3 MNI152 standard space by combining the affine transform of the most representative FA image to MNI152 space with the non-linear (FNIRT) transform to the most representative FA image. These transformations were combined before being applied. Aligning individual FA images to the most representative FA image within our sample, rather than to an FA template, was done as a result of working with adolescents, where the adult-derived FA template was inappropriate. A sample-specific mask was then created to eliminate cross-subject variability and ensure only FA values associated with WM were included in the analysis, thus eliminating voxels associated with grey matter and cerebral spinal fluid. To create the sample-specific mask, an FA threshold of 0.2 (Taoka et al. 2009) was applied to each individual standardized FA image and then binarized such that voxels with an FA value greater than 0.2 were assigned a value of 1 and those not meeting the FA threshold were given a value of 0. All binary images were then multiplied to create the sample-specific mask. Thus, any voxel not meeting the FA threshold across participants was dropped from analysis.

To examine group differences, standardized FA images were entered into a non-parametric voxel-wise two-sample permutation test using FMRIB's Randomise (Winkler et al. 2014) with 5000 permutations and variance smoothing kernel of 2 mm^3. Analysis was restricted to voxels included in the sample-specific WM mask. Although subjects were age-matched within 1 year of age at the time of scanning, adolescence is a time of large WM maturation (Lebel et al. 2008) and 1 year may be too large of a difference to adequately control for these effects. Therefore, any potential effects due to age were removed from all analyses by entering age as a nuisance covariate. Furthermore, with head motion being a significant predictor of some adolescent disorders (Couvy-Duchesne et al. 2016; Pardoe et al. 2016) and one of the main artifacts in DTI voxel-wise analyses (Le Bihan et al. 2006; Soares et al. 2013), 7 motion parameters (3 translation, 3 rotation and the absolute displacement) were extracted for each subject and entered as nuisance covariates in all statistical models. Moreover, to ensure that there were no group differences in motion, an independent samples t-test (bootstrapped using 5000 samples) was performed on the amount of absolute displacement. The maximum absolute displacement value was taken for each subject and inverse transformed to meet the assumption of normality. Results showed no significant difference in absolute displacement between groups [$t(38) = 1.15$, $p = 0.26$, $M_{diff} = .04$, 95% CI (−.03, .11)].

Correction for multiple comparison was performed using Monte Carlo simulation implemented in 3dClustSim (3dClustSim, compile date November 23, 2016; http://afni.nimh.nih.gov) (Forman et al. 1995; Xiong et al. 1995) using 20,000 iterations on the sample-specific WM mask and incorporated the size of the variance smoothing kernel implemented in Randomise (2 mm^3). Clusters larger than or equal to 32 voxels at a threshold of $p \leq 0.005$ (corresponding to a corrected $\alpha = 0.05$) were considered significant. The JHU-ICBM-DTI-81 White-Matter Labels Atlas and *MRI Atlas of Human WM* were used to identify the anatomical location of significant clusters (Wakana et al. 2007; Hua et al. 2008; Mori et al. 2008; Oishi et al. 2008).

To explore the patterns of diffusivity parameters associated with overall differences in FA, we obtained non-FA images from the DTIFIT output (i.e., AD, MD) for each participant and then calculated RD images, [$RD = (\lambda_2 + \lambda_3)/2$]. Preparation for analysis was as follows: the non-linear and linear transformations from the FA image standardization were applied to the AD, MD, and RD images resulting in all images being standardized in MNI152 1 mm^3 space. To better characterize group differences in FA, each diffusion parameter was subjected to the same statistical analysis with reduced thresholding ($p \leq .05$, uncorrected) and overlaid with the statistical maps showing FA differences. This allowed us to better identify which if any of the diffusion parameters were driving the differences in FA.

The relationship between FA and attention performance To investigate similarities and differences in the relationship between attention performance (API score) and FA for clinical and control adolescents, two sets of voxel-wise correlations were performed on the standardized FA images. One set (positive and negative correlations) was performed between API scores and FA using only data for the control adolescents. The other set was performed between API scores and FA on the clinical adolescents' data. Within-group correlations were performed by implementing non-parametric permutation tests using Randomise with 5000 permutations and a variance

smoothing kernel of 2 mm^3. The within-group models had 9 regressors (API score was the regressor of interest, and age and the 7 motion parameters where entered as nuisance covariates). Analyses were restricted to voxels included in the sample-specific WM mask. Similarities between groups in the relationship between attention performance and FA were identified by performing two conjunction analyses on the correlation *t* maps from each group (i.e., one using positive correlation *t* maps and the other negative). For the conjunction analyses, the statistical threshold was determined as the product of the two independent *p*-values from the maps from which the conjunction was created (i.e., $0.05 \times 0.05 = 0.0025$). Correction for multiple comparison was performed using Monte Carlo simulation implemented in AFNI on the sample-specific WM mask and incorporated the size of the variance smoothing kernel. Clusters larger or equal to 23 voxels at a threshold of $p \leq 0.0025$ (corresponding to a FWE $\alpha = 0.05$) were considered significant.

Differences between groups in the relationship between API score and FA were examined by implementing non-parametric permutation tests in combination with conjunction analyses. Permutation tests were carried out using Randomise with 5000 permutations and a variance smoothing kernel of 2 mm^3. The model had 10 regressors, these included one between-subjects factor (group), two interaction terms for group by API score, and 8 nuisance covariates (age and 7 motion parameters). The conjunction analyses involved the interaction terms and the appropriate within-group correlation. This approach identified WM structures where both the interaction term and within-group correlation between API score and FA were significant. A significant interaction term showing the slope for one group to be different from the other group could be driven by either an increase in slope for one group, or a decrease in slope for the other group. To that end, two conjunction analyses were performed per interaction term: one that used the interaction term with the *t* map showing positive correlation between API score and FA, and the other using the *t* map showing negative correlation. For example, r(FA, API) for the control group greater than r(FA, API) for the clinical group intersected with r(FA, API) for the control group. Correlation maps were corrected for multiple comparisons using Monte Carlo simulation implemented in AFNI on the sample-specific WM mask and incorporated the size of the variance smoothing kernel. Clusters larger than 23 voxels at a threshold of $p \leq 0.05$ for each independent *t* map (joint $p = .0025$, corrected $\alpha = 0.05$) were considered significant. For display purposes, averaged FA values were extracted from significant clusters and partial correlations were performed between the averaged FA and API score, controlling for age. All correlations where bootstrapped using 5000 samples.

Results

Decreased attention performance in clinical adolescents As can be seen in Fig. 1, the clinical group had significantly reduced API scores compared to controls, [$F(1, 36) = 6.36$, $p = .016$, $\eta^2 = .15$].

Decreased FA in clinical adolescents Results from the model testing general group differences in FA identified 29 clusters where FA was significantly reduced for the clinical group compared to healthy controls. These 29 clusters spanned 10 WM structures (see Table 2). Association fibers affected were bilateral superior longitudinal fasciculus (SLF) and right uncinated fasciculus (UF). Inter-hemispheric/commissural fibers showing reductions in FA were identified in the genu, body, and splenium of the corpus callosum (see Fig. 2). Furthermore, subcortical-cortical connections were also impacted, with areas rich in projection fibers showing reduced FA. These included bilateral anterior corona radiata (ACR), superior coronal radiata (SCR), posterior limb of the internal capsule (PLIC), left anterior limb of the internal capsule (ALIC), and the right cerebral peduncle (CP). There were no areas with increased FA for clinical compared to controls.

To better characterize the significant differences in FA found between groups, we overlaid the *t* maps for AD, RD, and MD on the FA *t* maps. We categorized the significant FA clusters according to the patterns of overlap exhibited with the other diffusion maps (see Table 2). Each pattern identified represents a unique combination of directionality in diffusivity parameters that accompany the differences in FA. This qualitative assessment shows what diffusion parameters (if any) are driving differences in FA. Directionality of changes in the diffusion parameters are discussed according to how clinical adolescents differed from controls. This assessment revealed that 17 of the 29 clusters showing reduced FA in the clinical group also had decreased AD and increased RD (pattern 1). Six of the 29 clusters had decreased AD, and increased RD and MD (pattern 2). Four of the 29 clusters had increased RD and MD, but no change in AD (pattern 3). Of the two remaining clusters, one showed decreased AD and MD (pattern 4) and the other showed increased RD (pattern 5).

Differential relationship between FA and attention performance in clinical vs. healthy adolescents There were no WM regions that showed a similar relationship between FA and attention performance for both groups. The existence of such similarities was investigated using two conjunction

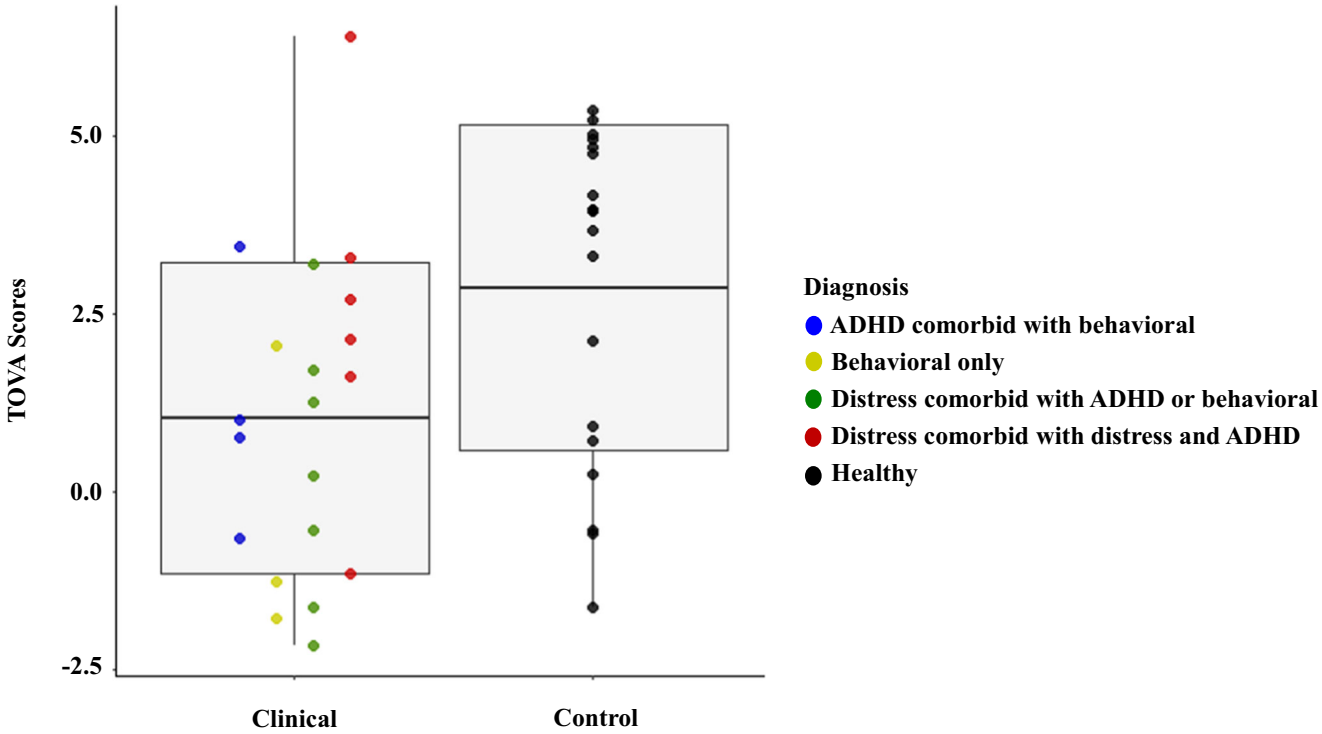

Fig. 1 Reduced attention performance in clinical adolescents. Figure shows TOVA performance for both clinical and control groups. The vertical line represents the range. The thick horizontal line represents the mean, and the top and bottom of the box plots represent the 95% confidence interval. For the clinical group, performance is shown as a function of diagnosis grouping. Blue, ADHD comorbid with a behavioral disorder; yellow, behavioral disorders only; green, distress disorder comorbid with ADHD or a behavioral disorder; red, distress disorder comorbid with another distress disorder and ADHD. Abbreviations: TOVA, test of variables of attention

analyses (one for positive and one for negative correlations maps that were created for the clinical and control groups separately, see Table 3).

Examining differences in the relationship between FA and attention performance identified three WM structures where the slope for FA and API score was greater for clinical compared to controls. These included the right ventral external capsule [$r(18) = .8$, $p < .001$, 95% CI (.62, .91) for clinical vs. $r(17) = -.11$, $p = .65$, 95% CI (−.56, .26) for control], a cluster that spanned both the right PLIC and retrolenticular part of the internal capsule (RLIC) [$r(18) = .65$, $p = .002$, 95% CI (.23, .89) for clinical vs. $r(17) = -.17$, $p = .49$, 95% CI (−.54, .24) for control], and a cluster that spanned both the right PCR and RLIC [$r(18) = .68$, $p = .001$, 95% CI (.32, .87) for clinical vs. $r(17) = -.18$, $p = .46$, 95% CI (−.55, .19) for control, see Table 3 and Fig. 3]. One WM structure, the right SLF, was identified showing greater slope for controls compared to clinical [$r(17) = 0.74$, $p < .001$, 95% CI (.5 .89) for control vs. $r(18) = -.42$, $p = .63$, 95% CI (−.68, −.15) for clinical]. No regions were driven by negative correlations between FA and attention performance (see Table 3 and Fig. 3).

When examining overlap between FA and the other diffusion maps, the right external capsule (which had a positive relationship between FA and API for clinical) also showed decreased RD for the clinical group. Additionally, the cluster that spanned both the right PCR and RLIC (and showed positive relationship between FA and API for the clinical group) also showed decreased MD for the clinical group (see Table 3).

Discussion

The current study investigated general and attention-related differences associated with WM microstructure in adolescents with and without affective, attentional, and behavioral disorders. Overall, this study had three main findings which supported our main hypotheses. First, the clinical group had significantly lower attentional control (as measured by performance on the TOVA). Second, clinical participants also had lower FA in 29 clusters, spanning 10 WM structures (see Table 2). These structures were comprised of association fibers (bilateral SLF, right UF), inter-hemispheric fibers

Table 2 White matter structures with decreased FA for clinical adolescents

White matter structure	Hemi.	MNI coordinates			Cluster size	Diffusivity pattern
		x	y	z		
Clinical < Control FA						
Callosal fibers						
Genu of the CC	L	−16	29	21	64	1 - ↓ FA, ↓ AD, ↑ RD
		−7	21	11	39	3 - ↓ FA, ↑ RD, ↑ MD
	R	11	32	6	115	1 - ↓ FA, ↓ AD, ↑ RD
		8	12	−4	39	2 - ↓ FA, ↓ AD, ↑ RD, ↑ MD
Body of the CC	M	0	2	20	1244	2 - ↓ FA, ↓ AD, ↑ RD, ↑ MD
	L	−10	14	18	44	3 - ↓ FA, ↑ RD, ↑ MD
	R	4	18	19	48	1 - ↓ FA, ↓ AD, ↑ RD
Splenium of the CC	L	−9	−44	20	57	1 - ↓ FA, ↓ AD, ↑ RD
		−5	−34	11	36	3 - ↓ FA, ↑ RD, ↑ MD
	R	2	−41	18	363	2 - ↓ FA, ↓ AD, ↑ RD, ↑ MD
		9	−39	9	167	1 - ↓ FA, ↓ AD, ↑ RD
Association fibers						
SLF	L	−38	−23	32	62	5 - ↓ FA, ↑ RD
	R	42	−17	32	65	1 - ↓ FA, ↓ AD, ↑ RD
UF	R	39	−1	−18	33	1 - ↓ FA, ↓ AD, ↑ RD
Projection fibers						
ACR	L	−18	34	0	591	1 - ↓ FA, ↓ AD, ↑ RD
		−24	33	−4	231	1 - ↓ FA, ↓ AD, ↑ RD
	R	15	24	−12	115	1 - ↓ FA, ↓ AD, ↑ RD
		29	31	−2	45	4 - ↓ FA, ↓ AD, ↓ MD
		22	33	2	32	1 - ↓ FA, ↓ AD, ↑ RD
SCR	L	−17	−7	37	72	1 - ↓ FA, ↓ AD, ↑ RD
	R	28	−22	28	34	1 - ↓ FA, ↓ AD, ↑ RD
ALIC	L	−16	4	8	121	2 - ↓ FA, ↓ AD, ↑ RD, ↑ MD
		−20	1	16	95	2 - ↓ FA, ↓ AD, ↑ RD, ↑ MD
PLIC	L	−20	−23	9	39	1 - ↓ FA, ↓ AD, ↑ RD
		−10	−5	5	69	1 - ↓ FA, ↓ AD, ↑ RD
	R	14	−1	3	354	2 - ↓ FA, ↓ AD, ↑ RD, ↑ MD
		23	−15	1	63	1 - ↓ FA, ↓ AD, ↑ RD
CP	R	12	−17	−5	334	1 - ↓ FA, ↓ AD, ↑ RD
		6	−9	−10	39	3 - ↓ FA, ↑ RD, ↑ MD

Coordinates are reported for the peak voxel from the contrast assessing group differences in FA. The diffusivity pattern represents changes in clinical relative to non-clinical adolescents

Abbreviations: *SLF* superior longitudinal fasciculus, *UF* uncinated fasciculus, *ACR* anterior corona radiata, *SCR* superior corona radiata, *ALIC* anterior limb of the internal capsule, *PLIC* posterior limb of the internal capsule, *CC* corpus callosum, *CP* cerebral peduncle, *L* left, *R* right, *M* midline, *FA* fractional anisotropy, *AD* axial diffusivity, *RD* radial diffusivity, *MD* mean diffusivity

of the corpus callosum (genu, body, and splenium), and sub-cortical projection fibers (ACR, SCR, PLIC, ALIC, and right CP). Exploratory analyses also identified five patterns of diffusivity parameters that allowed us to better characterize the observed differences in FA. Third, different WM structures were also linked to attentional control in each group. Below we discuss, these findings in detail with an emphasis on the DTI results.

Decreased FA in clinical adolescents

Our results showing a reduction of FA values for the clinical vs. control group are consistent with a number of studies examining WM microstructure in specific psychiatric disorders during adolescence. Decreased FA in bilateral SLF fits well with literature arguing that these fasciculi are important for human-specific functions underlying basic cognition and

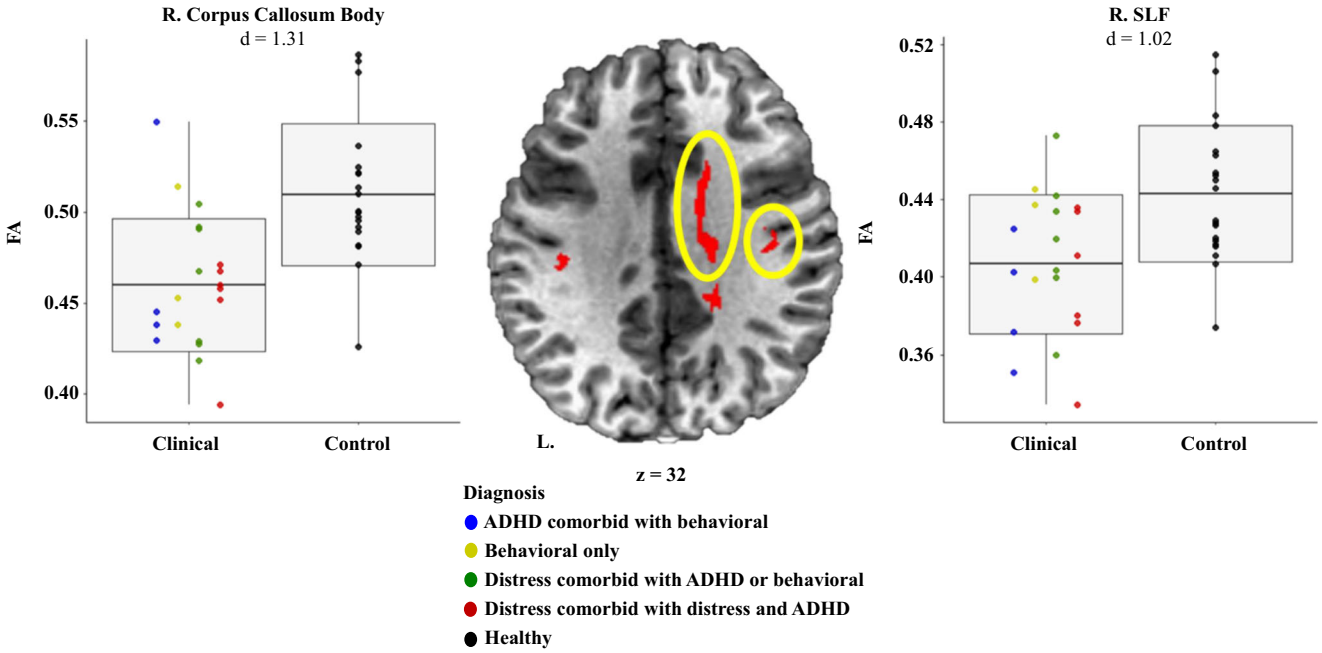

Fig. 2 Decreased FA for clinical adolescents. Decreased FA was found in callosal, projection, and association tracts. Figure shows differences in R. CC body and R. SLF. For visualization FA values were extracted from these clusters and plotted. The vertical line represents the range. The thick horizontal line represents the mean and the top and bottom of the box plots represent the 95% confidence interval. For the clinical group, FA is shown as a function of diagnosis grouping. Blue, ADHD comorbid with a behavioral disorder; yellow, behavioral disorders only; green, distress disorder comorbid with ADHD or a behavioral disorder; red, distress disorder comorbid with another distress disorder and ADHD. Abbreviations: FA, fractional anisotropy; CC, corpus callosum; SLF, superior longitudinal fasciculus

language (Bernal and Altman 2010). Anatomically, the SLF is a major bi-directional set of connections between the occipital, parietal, temporal, and frontal lobes (Petrides and Pandya 1984; Martino et al. 2013), including connections from Broca's to Wernicke's area (Powell et al. 2006), with many identified subcomponents (Paus 2005; Kamali et al. 2014a, b; Wang et al. 2016). Despite work showing a critical role for the developing SLF in childhood (Zhang et al. 2007), the relationship between FA in the SLF and cognitive function in adolescence is not well understood. The SLF is one of the slowest developing WM tracts in childhood and adolescence and has been implicated in language development (Paus et al. 1999), with elevated MD in SLF being associated with more profound language impairments in children with autism (Nagae et al. 2012). The SLF is also important for visuospatial attention (Hoeft et al. 2007; Shinoura et al. 2009; Thiebaut de Schotten et al. 2011) and working memory operations (Karlsgodt et al. 2008). Indeed, results from healthy children aged 7–14, Vestergaard et al. (2011) showed that when controlling for age, high FA in SLF was linked to better performance on a short-term working memory task. FA reductions in the SLF have also been observed in ADHD in youths and adults (Chiang et al. 2015). Moreover, this reduction was associated with poor scores on a continuous performance task, as well as clinical symptoms of inattention. In a follow-up study, Chiang et al. (2016) replicated their earlier results and further showed that low FA in left hemisphere SLF is associated with a wide range of cognitive deficits including poorer performance in set-shifting, sustained attention, visuospatial processes, and inhibitory control. These authors argued that abnormal SLF development plays a critical role in ADHD and executive dysfunction. Our findings extend the available evidence showing compromised SLF WM in adolescents with affective, attentional, and behavioral disorders.

Our finding of reduced FA values for clinical compared to control groups in the right hemisphere UF is interesting because it is the largest of the frontotemporal pathways in the brain connecting ventral limbic cortex with ventral, medial, and orbitofrontal cortex (Price et al. 2008). The UF is one of the last WM tracts to reach maturation, typically developing from adolescence into early adulthood and peaking after the age of 30. The UF has been implicated in many psychiatric and developmental disorders including anxiety, schizophrenia, psychopathy and antisocial personality disorder (Von Der Heide et al. 2013), autism, conduct disorder, ADHD, and post-traumatic stress disorder (Olson et al. 2015). It has been argued that developmental disorders characterized by impulsive decision making may have alterations in WM microstructure in the UF (Olson et al. 2015).

In addition to the association fiber regions that were impacted, our current findings show FA deficits throughout the corpus callosum linked to adolescent psychopathology. The corpus callosum is the main commissural fiber in the human brain, responsible for the majority of inter-hemispheric communication. The anterior part of the corpus callosum (i.e., the genu) has connections with the prefrontal cortex. The midline

Table 3 White matter structures showing increased FA as a function of attention performance

White matter structure	Hemi.	MNI coordinates			Cluster size	Pearson r, p-val [95% CI]	Diffusivity pattern
		x	y	z			
Clinical adolescents							
Callosal fibers							
Body of the CC	R	5	−25	25	278	.5, .03 [.25, .75]	–
Association fibers							
External Capsule[a]	R	28	4	−10	486 (*244)	.61, .005 [.42, .79]	↓ RD
Projection fibers							
SCR	L	−23	−33	23	299	.78, <.001 [.44, .91]	–
PCR/RLIC[a]	R	30	−33	21	222 (*108)	.68, .001 [.49, .84]	↓ MD
PLIC/RLIC[a]	R	25	−29	−1	270 (*54)	.8, <.001 [.48, .93]	None
CP	L	−13	−15	−9	233	.65, .002 [.23, .85]	–
Healthy adolescents							
Association fibers							
SLF[a]	R	28	−40	34	224 (*189)	.69, .001 [.4, .87]	None

Coordinates are reported for the peak voxel from clusters identified from the *t* maps created for each group separately that examined the positive correlation between API score and FA. There were no regions showing decreased FA as a function of Attention Performance. The (*) in the cluster size column denotes the cluster size of the interaction. Pearson r-values and their corresponding *p*-values are based FA values averaged across the entire cluster. Diffusivity patterns represent the overlap of group differences in the diffusion parameters with clusters showing a significant interaction between FA and behavior

Abbreviations: *CI* Confidence Interval, *Hemi.* hemisphere, *SLF* superior longitudinal fasciculus, *SCR* superior corona radiata, *PCR* posterior corona radiate, *RLIC* retrolenticular part of the internal capsule, *PLIC* posterior limb of the internal capsule, *CC* corpus callosum, *CP* cerebral peduncle, *L* left, *R* right, *FA* fractional anisotropy, *RD* radial diffusivity, *MD* mean diffusivity

[a] denotes a significant difference in slope for FA and API between groups

section connects pre- supplementary, and motor cortices. The posterior portion (i.e., the splenium) connects parietal, temporal and occipital areas (Hofer and Frahm 2006; Putnam et al. 2010). The relationship between corpus callosum integrity and mental health has been established through research looking at agenesis of the corpus callosum (see Paul et al. 2007 for review) as well as volumetric and inter-hemispheric information transfer studies (Diwadkar et al. 2006; Hiatt and Newman 2007; Gilliam et al. 2011; Lopez et al. 2013). Hynd et al. (1991) and Giedd et al. (1994) were among the first MRI studies to link abnormalities in corpus callosum development with ADHD symptoms. DTI revealed reductions in FA in anterior corpus callosum as a function of behaviorally measured impulsivity (Moeller et al. 2005). In autism, the genu, body, and splenium FA values are reduced compared to controls, particularly in the individuals performing poorly on IQ tests (Alexander et al. 2007a, b), and youth with or at risk for bipolar disorder also show decreased FA values in the corpus callosum (Frazier et al. 2007). Decreases in FA for each major division of the corpus callosum (genu, body, and splenium) in our clinical group support the general idea that inter-hemispheric communication is critically necessary for healthy higher-order functioning (Paul et al. 2007) and, more importantly, is a key component in understanding the nature of adolescent psychiatric illnesses.

Finally, we also observed decreased FA in areas rich in sub-cortical projection fibers. This is not surprising given the idea that WM development follows a central-to-peripheral trajectory in the developing brain (Asato et al. 2010; Rose et al. 2014). In other words, if the normal developmental pattern of WM is from evolutionarily primitive sub-cortical structures to more advanced peripheral-cortical structures that support higher-level cognition, it stands to reason that WM abnormalities throughout association and callosal fibers, as we have clearly observed in our data, would be associated with abnormalities in the lower-level regions. Moreover, this also suggests that the lower-level differences from early childhood likely persist into adolescence and may be critically related to the resulting WM abnormalities at higher levels.

Regarding the findings exploring diffusivity patterns in regions showing lowered FA in clinical adolescents, differences in FA may be related to other tissue characteristics, such as the amount of myelination, the degree of fiber coherence and density, the axon diameter, tract geometry (tortuosity), and the presence of crossing fibers (Rose et al. 2014). WM microstructure is determined by some combination of these characteristics, and in clinical, developing, and aging populations differences in FA may be further informed by examining differences in other diffusion parameters. In our clinical group we identified sets of regions with unique diffusivity patterns

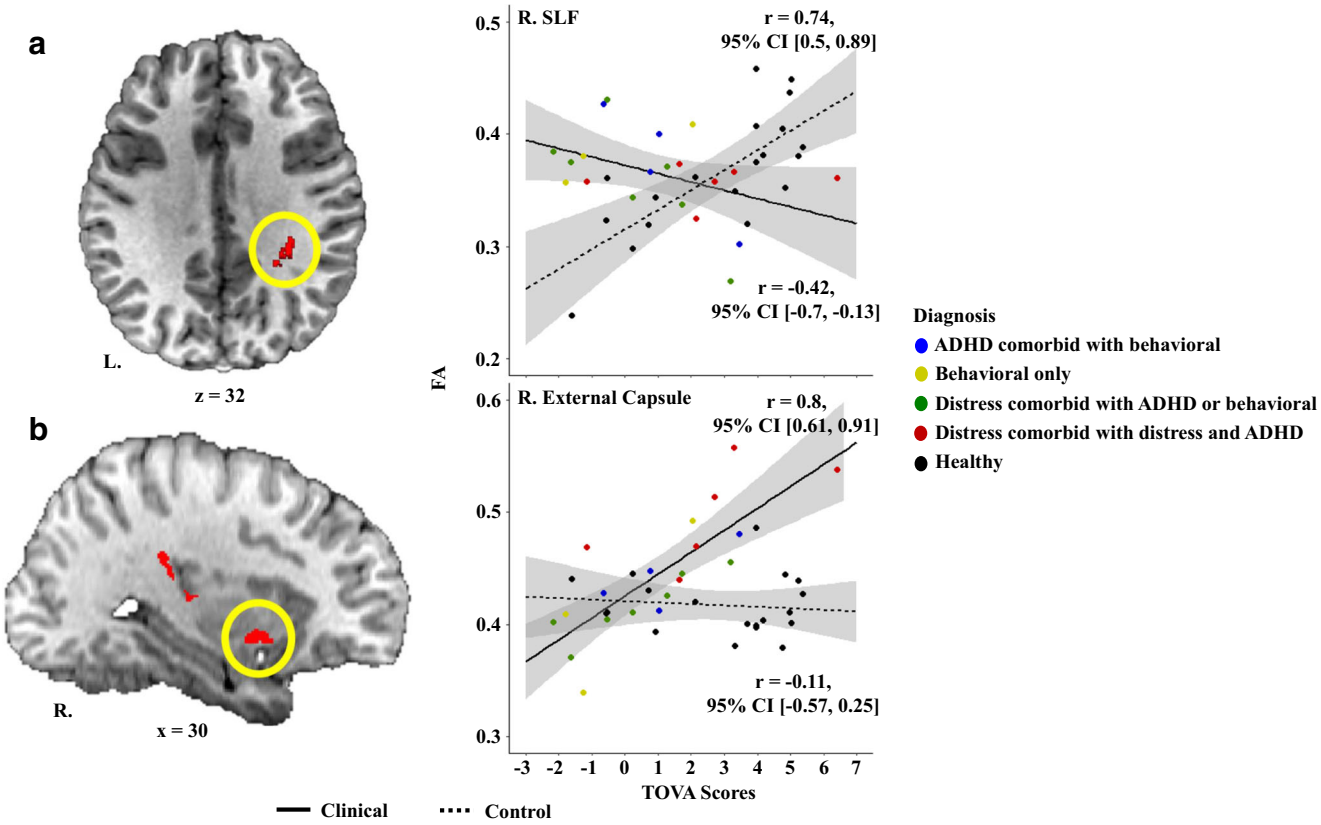

Fig. 3 Different FA-Behavior relationships for clinical vs. control adolescents. Areas show where the slope for FA and attention is significantly different between groups. **a** Greater FA was associated with better TOVA scores in the R. SLF for the control group. **b** Greater FA was associated with higher TOVA scores in the R. external capsule for the clinical group. For the clinical group FA is shown as a function of diagnosis grouping. Blue, ADHD comorbid with a behavioral disorder; yellow, behavioral disorders only; green, distress disorder comorbid with ADHD or a behavioral disorder; red, distress disorder comorbid with another distress disorder and ADHD. Abbreviations: TOVA, test of variables of attention; FA, fractional anisotropy; SLF, superior longitudinal fasciculus

associated with lower FA. Pattern 1 showed decreased FA, decreased AD, and increased RD in the SLF, right UF, throughout the corpus callosum, and in the ACR, SCR, PLIC, and CP projection fibers. During this period of development, this pattern may suggest that these areas have reduced neurite density and increased tortuosity. In our study, 17 clusters spanning 10 structures showed this pattern, which strongly suggests that our clinical group has widespread WM impairment in fibers throughout the brain that support general cognition, executive function, and motor control. The second pattern associated with lower FA in the clinical group was lower AD with increased RD and MD. We observed this in the corpus callosum, ALIC, and PLIC. Unlike pattern 1, the change in MD in pattern 2 suggests that the radial diffusivity changed enough to increase the overall amount of diffusivity in voxels comprising these clusters in clinical adolescents. The reduction in AD indicates altered fiber geometry, but increased RD and MD together suggest greater impairment in perpendicular diffusivity due perhaps due to fiber density. This is an exacerbated pattern 1. It has also been suggested that concurrent increases in RD and MD are related to a decrease in the organization of fibers rather than a straight decrease in WM volume (Fletcher et al. 2010). Pattern 3 was increased RD and MD. This was found throughout the corpus callosum and the right CP projection fibers. Pattern 4 had decreased AD and MD, suggesting that tract geometry may be the primary cause of decreased anisotropy in this part of the right anterior corona radiata (the only area to display pattern 4). Finally, for pattern 5, observed in the left SLF, only increased RD accompanied the differences in FA. Changes in RD were once thought to be a proxy for myelination, but this interpretation may not be accurate (Arshad et al. 2016) or could be age-dependent. That is, during periods of development, the primary driver of perpendicular diffusion could, in part, reflect the continued myelination that is occurring, whereas in aging increases in RD may be less reflective of demyelination.

Differential relationship between FA and attention performance in clinical vs. healthy adolescents

In our study, when comparing the pattern of data between groups we did not identify any regions showing similarities between FA and attention performance. This is

important and further confirms the clear difference in our two populations regarding WM and attentional control. However, our secondary conjunction analyses showed that the right SLF was associated with increased FA as a function of attention score only in the healthy group (see Fig. 3a), and the FA values in the right hemisphere external capsule showed increased FA values as a function of attention score only in the clinical group (Fig. 3b). On the face of it, these results support the general idea that dorsal brain circuitry plays an important role in top-down attentional control (Corbetta and Shulman 2002; Petersen and Posner 2012). This assumption relies on the point of view that emotion regulation and attentional control processes are associated with increased blood-oxygenated-level-dependent (BOLD) response in dorsal-lateral, medial pre-frontal, and lateral parietal cortices (Yamasaki et al. 2002; Urry et al. 2006; Dolcos et al. 2011). That is, our healthy control sample had greater FA values in an important dorsal frontoparietal connection (SLF). This difference was found in general and as a function of attention performance, with higher FA resulting in better performance. Thus healthy, typically developing WM in that pathway is a critical component for top-down attentional control in normally maturing adolescents (Zhang et al. 2007). On the other hand, the clinical group was not without a range of performance on the attention task, and high attention scores were associated with increased FA in the right external capsule. This is interesting because the external capsule contains association fibers connecting ventral limbic structures to ventral frontal regions (Petrides and Pandya 1988; Wakana et al. 2004), suggesting that the clinical group of adolescents in our study may require access to different pathways to accomplish the attention task and perhaps reflects a delay in the shift from a ventral to dorsal functional network Gee et al. 2013).

Limitations

A major difference of our study from previous studies is the large heterogeneity of attention and affective-based diagnoses in our clinical population. Although such heterogeneity is not unusual in clinical samples, it makes it more difficult to directly compare our results with those of previous studies showing WM differences related to more specific psychiatric disorders during adolescence. Nevertheless, we observed widespread decreases in FA in the clinical group and, as seen by the distribution of data points in Fig. 2, the reduction in FA was evenly distributed across all diagnostic categories. The small sample size is also limitation of the current study. To alleviate type I errors, we implemented non-parametric permutation-based statistics that make no assumptions about the null distribution, yielding reliable results for the sample under investigation. Replication in a different and ideally larger sample of adolescents with significant mental health challenges will be required to validate these findings.

Another limitation of the current study, as with many studies investigating psychiatric disorders, is the inability to fully control for the type, dose, or duration of medication (Schrantee et al. 2016). The question of how pediatric psychopharmacology affects structural brain imaging metrics has only recently been explored due to the complexity of investigating this issue. Marrus et al. (2014) reviewed literature examining psychotropic medications and brain volume in children and adolescents for five disorders and identified mostly decreases in volume for regions-of-interest implicated in each disorder. In adults, the use of antipsychotics aripiprazole and risperidone has been associated with decreased FA (Szeszko et al. 2014). Although we do not know how psychotropics are influencing white matter in the developing brain we can make a reasonable assumption that they are, and the current results are undoubtedly confounded by these effects. Hopefully future investigations will be able to examine these effects more systematically as datasets with the necessary sample size become available. Finally, attempting to co-vary the effects of age is another limitation, especially since age and pathology are likely to have synergistic or interacting effects, because it most likely removed variance that was shared between age and our effects of interest.

Summary and conclusion

This study aimed to shed light on the nature of WM microstructure associated with affective, attentional, and behavioral disorders in adolescence. To that end, our results show widespread differences in FA throughout the brain; increases and decreases in FA were found as a function of behavior and were modified by group. Our results support the existing literature on developmental disorders and brain function by showing a reduction in both. Moreover, they add to the literature by showing that cognitive performance-WM relationships in domains susceptible to the pathology under investigation can highlight important differences of the associated neural circuitry due to the pathology. Despite the heterogeneity in the modest size sample of our clinical sample, the clear differences in DTI measurements relative to age-matched controls indicate very robust differences in WM characteristics associated with psychopathology in adolescence.

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Authors' contributions FD, AS, SV, and KJVV designed the study; ATS collected the data; ATS and JRB constructed the preprocessing pipeline; ATS, AS, and FD contributed to the analytical approach, with input from JRB; ATS performed the analyses; ATS, AS, and FD wrote the manuscript. All authors provided feedback and approved the content of the article.

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Compliance and ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent Informed consent was obtained from the parents of all individual adolescent participants included in the study, and informed assent was obtained from all adolescents included in the study.

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