Neural mechanisms of social-emotional dysfunction in autism spectrum disorder and conduct disorder

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3 Altered white matter architecture in autism versus conduct disorder

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Klapwijk, E.T., Aghajani, M., Popma, A., van Lang, N.D.J., van der Wee, N.J.A., Vermeiren, R.R.J.M., Colins, O.F. (2017) Altered white matter architecture in autism spectrum disorders versus conduct disorder and callous-unemotional traits.

Abstract

Problems in social interaction are observed in individuals with autism spectrum disorders (ASD) and in individuals with conduct disorder and co-occurring callous-unemotional traits (CD/CU+). Studies that directly compared ASD versus CD/CU+ directly suggest group differences in social-emotional reactivity and associated brain functioning. Since white matter connectivity of several tracts associated with social functioning is also altered in both conditions, for the first time we compared ASD versus CD/CU+ using diffusion tensor imaging (DTI). Tract-based spatial statistics (TBSS) was used to assess white matter microstructure in ASD (N = 22), CD/CU+ (N = 24), and typically developing (TD) male adolescents (N = 32), aged 15–19 years. Using TBSS, we examined fractional anisotropy (FA), and subsequently axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD). TBSS revealed increased FA coupled with decreased MD and RD in the cingulum and corpus callosum (splenium and body) among CD/CU+ youths relative to ASD with the TD group being intermediate. These findings show disorder-specific alterations in white matter connectivity among ASD and CD/CU+ youths that may relate to social and executive dysfunctioning.

Introduction

Autism spectrum disorder (ASD) and conduct disorder (CD) are distinct mental disorders both characterized by social dysfunction. Difficulties in social interactions in these disorders, however, are likely underpinned by different neurocognitive deficits (Bird & Viding, 2014; Blair, 2008). Many studies have reported difficulties in mentalizing, or the ability to represent other people's mental states, in ASD (Baron-Cohen et al., 1985; Frith, 2001) and problems in experiencing affective reactions to other's emotions in CD, particularly in individuals with CD who display high levels of callous-unemotional traits (CU+; i.e., lack of guilt and empathy, callous use of others for one's own gain) (Jones et al., 2009; Marsh et al., 2013). In addition, neuroimaging studies show that participants with ASD have altered

hemodynamic responses in brain regions involved in mentalizing, such as the medial prefrontal cortex (MPFC) and temporoparietal junction (TPJ) ((Castelli et al., 2002; Pelphrey et al., 2011) whereas abnormal activation in the amygdala, insula and anterior cingulate cortex (ACC) accompanies diminished affective reactions to other's emotions in CD/CU+ (Blair et al., 2016; Jones et al., 2009; Lockwood et al., 2013b; Marsh et al., 2013; Marsh et al., 2008). Some studies have also directly compared groups with ASD and CD/CU+, showing mainly problems in cognitive aspects of social tasks such as mentalizing in ASD versus selective impairments in affective domains in CD/CU+ (Jones et al., 2010; Schwenck et al., 2012).

Two recent neuroimaging studies directly comparing individuals with ASD and those with CD/CU+ additionally report disorder-specific brain abnormalities during cognitive and affective emotion processing (Klapwijk et al., 2016a; O'Nions et al., 2014). We compared ASD, CD/CU+, and typically developing (TD) youths during neural processing of facial emotions (Klapwijk et al., 2016a). When participants had to cognitively label the presented emotions, the ASD group showed reduced responses compared to the other groups in the ventral MPFC. When participants had to judge their own emotional response to the presented emotions, both the CD/CU+ and ASD groups showed reduced amygdala responses compared to TD. In addition, the ASD group showed hypoactivation compared to the other groups in bilateral hippocampus and the CD/CU+ boys in the inferior frontal gyrus (IFG) and anterior insula in this condition. Along the same line, O'Nions et al. (2014) showed that ASD youths display diminished MPFC reactivity during cognitive mentalizing compared to CD/CU+ and TD groups that did not differ in this task. These studies collectivity suggest disorder-specific alterations in brain functioning in ASD and CD/CU+ during social-emotional processing, indicative of cognitive social deficits in ASD versus affective in CD/CU+.

The handful of comparative studies between ASD and CD/CU+ have thus far focused on differences in behavior and brain functioning (Jones et al., 2010; Klapwijk et al., 2016a; O'Nions et al., 2014; Schwenck et al., 2012), while overlooking possible differences in brain structure and connectivity. The current study hence addressed this important topic by comparing white matter connectivity in ASD, CD/CU+, and TD youths. White matter connections are deemed crucial

for linking distributed brain regions involved in social-emotional processes into integrated neural circuits critical to adaptive social behavior and functioning (Ameis & Catani, 2015; Kennedy & Adolphs, 2012). Especially limbic white matter tracts, as well as long-range associative and interhemispheric tracts, are thought to play an important role in processing social-emotional information (Herbet et al., 2014; Parkinson & Wheatley, 2014; Philippi et al., 2009). Several of these tracts are altered in both ASD and CD (with and without CU+) compared to TD controls (e.g., Breeden et al., 2015; Haney-Caron et al., 2014; Kumar et al., 2010; Pugliese et al., 2009), but disorder-specific alterations for ASD and CD/CU+ have yet to be elucidated.

One prominent limbic white matter tract that is implicated in both ASD and CD/CU+ is the uncinate fasciculus (UF); a tract that connects the orbitofrontal cortex to the anterior temporal lobes (including the amygdala) through a direct, bidirectional monosynaptic pathway (Von Der Heide et al., 2013). Although the exact function of the UF is still unclear, this tract has been associated with social-emotional functioning (Oishi et al., 2015; Parkinson & Wheatley, 2014) and is thought to be a likely candidate for disruption in disorders characterized by social and emotional deficits, such as ASD and CD/CU+ (Olson et al., 2015). Reduced FA of the UF has indeed been reported in children, adolescents and adults with ASD (Kumar et al., 2010; Lee et al., 2007; Pugliese et al., 2009) and a meta-analysis in which data from 14 DTI studies were pooled consistently showed reduced FA (among other tracts) in the UF in ASD (Aoki et al., 2013). In CD (regardless of CU traits), studies have reported abnormalities in the UF that was reflected in both increased (Passamonti et al., 2012; Sarkar et al., 2012) and decreased (Haney-Caron et al., 2014) FA values in the UF. Importantly, a recent study showed reduced white matter integrity in the UF in relation to CU traits in youth with conduct problems (Breeden et al., 2015), echoing previous findings of reductions in the UF in adult psychopathy (Craig et al., 2009). Previous studies have found white matter abnormalities in both ASD and CD in various other tracts that are thought to be important for social-emotional functioning such as the cingulum (Ameis & Catani, 2015; Aoki et al., 2013; Haney-Caron et al., 2014; Waller et al., 2017). This limbic white matter tract has been linked to social functioning and mentalizing (Hadland et al.,

2003; Herbet et al., 2014) and is affected in both ASD and CD/CU+ (Ameis et al., 2013; Haney-Caron et al., 2014; Pape et al., 2015; Travers et al., 2012). Despite these exciting findings, disorder-specific perturbations in white matter connectivity for ASD and CD/CU+ have yet to be elucidated. This is especially critical when searching for brain measures as potential biomarkers to aid diagnosis and treatment, as any useful biomarker should not only differentiate a specific disorder from healthy controls but must also differentiate the specific disorder from any other psychiatric disorder (Boksa, 2013).

We employed diffusion tensor imaging (DTI), to assess disorder-specific profiles of white matter integrity in ASD versus CD/CU+. We compared ASD, CD/CU+, and TD boys on white matter integrity in the UF and cingulum, using tract-based spatial statistics (TBSS; Smith et al., 2006). Additionally, whole brain analysis was performed to establish whether any other tracts might exhibit between-groups differences. We first focused on fractional anisotropy (FA) as an overall measure of white matter integrity, which measures the degree to which water molecules diffuse in a given direction and is affected by axon diameter, myelination and axonal organization (Beaulieu, 2002; Mori & Zhang, 2006). To aid interpretation of FA differences, we additionally evaluated axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) as more specific measures of white matter microstructural integrity (Aghajani et al., 2014; Alexander et al., 2007b).

Methods

Participants

Data of 22 participants with ASD, 24 with CD/CU+, and 32 TD controls were included in the current study (see Table 1 for group characteristics). All participants were males aged 15-19 years. Participants and their parents (for minors under 18 years) gave their written informed consent to participate in the study. The ethics committee of the Leiden University Medical Center approved the study protocol. Exclusion criteria for all participants were neurological abnormalities, a history of epilepsy or seizures, head trauma, left-handedness, and IQ less than 75. To obtain

an estimate of intelligence, participants completed the Wechsler Adult Intelligence Scale – third edition (WAIS-III) or Wechsler Intelligence Scale for Children – third edition (WISC-III) subscales Vocabulary and Block Design.

Table 1. *Group characteristics*

	Autism spectrum disorders (ASD) (N = 22)		Conduct disorder and CU traits (CD/CU+) (N = 24)		Typically developing (TD) (N = 32)		Difference
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	17.0	1.3	16.6	1.0	17.1	1.2	
IQ *	107.3	10.6	94.0	4.9	96.7	8.7	ASD > CD/CU+,TD
Minority [N / %]	0	0.0	21	87.5	11	34.3	
Autistic traits [a] *	67.9	21.2	39.4	11.3	35.1	13.6	ASD > CD/CU+,TD
Callous-unemotional traits *	28.1	7.0	36.7	6.4	19.7	5.9	CD/CU+ > ASD > TD
Empathy [b]							
Cognitive empathy	34.3	4.2	34.0	6.8	36.5	5.0	
Affective empathy *	35.8	8.0	25.5	6.1	36.1	5.8	ASD,TD > CD/CU+
Aggression [c]							
Reactive aggression*	7.9	4.5	13.1	4.5	6.3	3.1	CD/CU+ > ASD,TD
Proactive aggression*	2.1	2.3	8.7	6.2	1.5	1.7	CD/CU+ > ASD,TD

** Significantly different at p < 0.001.*
[a] ASD symptomology was assessed in participants from all three groups using the Social Responsiveness Scale (SRS) self-report version (Constantino & Gruber, 2002).
[b] Self-report of affective and cognitive empathy was measured using the Basic Empathy Scale (BES; Jolliffe & Farrington, 2006).
[c] Reactive and proactive aggression was assessed using the Reactive-Proactive Aggression Questionnaire (RPQ; Raine et al., 2006)

Twenty-three participants with ASD were recruited from specialized child psychiatric centers providing both inpatient and outpatient care for persons with ASD. Data from one ASD participant was excluded due to image artifacts in the DTI data, resulting in a final sample of 22 participants with ASD. Clinical ASD diagnoses according to DSM-IV-TR criteria were autistic disorder for three participants, Asperger's syndrome for ten participants, and pervasive developmental disorder not otherwise specified (PDD-NOS) for nine participants. Three participants also

met DSM-IV-TR criteria for ADHD, two for dysthymia, and one for major depression. In addition to clinical diagnoses, we administered the Autism Diagnostic Observational Schedule-Generic (ADOS-G; Lord et al., 2000) and autism diagnostic interview-revised (ADI-R; Lord et al., 1994). Twenty participants met the criteria for autism or ASD on the Social Interaction and Communication domains of the ADOS-G, and two scored above the cut-off point only in one of these domains. However, these two participants fulfilled the ADI-R criteria for autism. We were able to administer the ADI-R for 19 participants and all 19 fulfilled the autism criteria on the ADI-R Social Interaction and Communications domains. Review of the medical charts of the other three indicated that autistic features were already present from an early age. Eleven participants with ASD took medication at the time of testing (N = 3 atypical antipsychotics, N = 3 psychostimulants, N = 3 selective serotonin re-uptake inhibitors, N = 2 multiple medications).

Participants with CD/CU+ were recruited from a juvenile detention centre and a forensic psychiatric unit, since relatively high amounts of boys with CD are present at forensic settings (Colins et al., 2010). CD diagnoses were determined using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) Behavioral Disorders screening (Kaufman et al., 1997). First, boys that fulfilled DSM-IV-TR criteria for CD with at least one aggressive symptom (e.g., used a weapon, has been physically cruel to people, has stolen while confronting a victim) were included in the study (N = 54). Next, participants with CD/CU+ were selected from this larger pool of boys with CD based on scores on the self-report Inventory of Callous-Unemotional traits (ICU; Kimonis et al., 2008). Echoing prior work (e.g., Jones et al., 2010; Klapwijk et al., 2016a; Schwenck et al., 2012), participants (N = 26) scoring above the median ICU score of the full CD sample (median score = 27.0) were included in the CD/CU+ group. Data from two CD/CU+ participants were excluded due to image artifacts in the DTI data, resulting in a final sample of 24 participants with CD/CU+. Eight participants with CD/CU+ also met DSM-IV-TR criteria for ADHD. None of the participants with CD/CU+ took medication at the time of testing.

Thirty-two TD control boys were recruited through local advertisement. They were screened using the K-SADS-PL behavioral disorders module in order

to exclude participants with behavioral disorders. The Youth Self Report (YSR; Achenbach, 1991) was used to assess general psychopathology; none of the TD boys scored in the clinical range on the YSR externalizing and internalizing scales.

DTI data acquisition

DTI data were collected at the Leiden University Medical Center using a 3T Philips Achieva MRI scanner. Prior to scanning, participants were familiarized with the scanner environment using a mock scanner. For DTI data collection, a single-shot echo–planar imaging (EPI) sequence was used with the following scan parameters: repetition time = 6600 ms, echo time = 60 ms, flip angle = 90°, b factor =1000 s/mm2, voxel dimensions = 2.3 mm isotropic, number of slices = 60, and no slice gap. DTI data were acquired along 32 directions, together with a baseline image having no diffusion weighting (b=0). The DTI sequence was repeated two times and averaged to obtain stable diffusion parameters; scanning time was ~10 min.

DTI data analysis

DTI data were preprocessed and analyzed using FSL version 5.0.8 (www.fmrib.ox.ac.uk/fsl). Diffusion-weighted images were registered to the non-diffusion weighted (b = 0) image by affine transformations to minimize distortions due to eddy currents and simple head motion. Non-brain tissue and background noise was removed using the Brain Extraction Tool. The diffusion tensor model was then fitted to each voxel using the FSL Diffusion Toolbox to generate individual FA, AD, RD and MD maps for each participant. AD was defined as the largest eigenvalue ($\lambda 1$), RD was calculated as the average of the two small eigenvalues ($\lambda 2$ and $\lambda 3$), and MD was calculated as the average of the three eigenvalues ($\lambda 1$, $\lambda 2$ and $\lambda 3$). Tract-based spatial statistics (TBSS) version 1.2 was used for voxelwise analysis of the preprocessed FA data. First, all FA images were non-linearly registered to the FMRIB58_FA standard-space image using FMRIB's Non-linear Registration Tool (FNIRT). The mean FA image was calculated to create a mean FA skeleton, a representation of the centers of all tracts common to the entire group. The mean FA skeleton was then thresholded at a FA value of ≥0.35 to exclude peripheral tracts and minimize partial voluming. In a similar manner, AD, RD and MD data were

projected onto the skeleton using the FA registration and skeleton projection parameters. Finally, each participant's aligned FA, AD, RD, and MD images were projected onto the mean FA skeleton, and the resulting data were fed into voxel-wise permutation-based analysis.

To test FA alterations in specific tracts we used regions of interest (ROI) analysis in TBSS, as described previously (Aghajani et al., 2014; Westlye et al., 2011). Binary masks of the UF and cingulum (subjacent to the cingulate gyrus) were created using the Johns Hopkins University (JHU) white matter atlases provided by FSL (Mori et al., 2005). Next, the masks were applied to the mean FA skeleton in order to include only voxels comprised in the mean FA skeleton. This confines the statistical analysis exclusively to voxels from the center of the tract, thereby minimizing anatomic inter-subject variability, registration errors, and partial voluming.

Voxelwise statistical analysis of individual skeleton images of all subjects was performed between ASD, CD/CU+, and TD groups using FSL's permutation-based Randomise tool with threshold-free cluster enhancement (TFCE; Smith & Nichols, 2009) and family-wise error (FWE) correction. Based on prior work we tested both for direct group comparisons (two-sample t-tests), as well as linear effects that cut across groups. Echoing data on *decreased* FA in the UF and cingulum in ASD vs. TD (Ameis et al., 2013) and *increased* FA in these tracts in CD youth with and without CU traits vs TD (Pape et al., 2015; Passamonti et al., 2012; Sarkar et al., 2012), we tested the following linear effect: CD/CU+ > TD > ASD (1, 0, -1). Exploratory whole-brain analysis was also performed testing both two-sample t-tests and linear effects. FA was examined in both ROIs and in the whole-brain analysis whereas AD, RD and MD were only subsequently examined in regions showing significant group differences in FA. Reverse linear effects (ASD > TD > CD/CU+; 1, 0, -1) for RD and MD were tested given that increased FA is generally coupled with decreased RD and MD and vice versa. Statistics were built up over 5000 random permutations and the statistical threshold was set to $p < 0.05$ FWE-corrected for multiple comparisons. To account for possible effects of age and IQ, these variables were included (mean-centered across groups) as covariate of no interest. We explored whether additional clinical factors, such as medication exposure or comorbidity, might have influenced the results. These analyses were

conducted with the FA values from the regions showing significant group differences in SPSS to compare participants with ASD and CD/CU+ (excluding either those with a comorbid disorder or those using medication) to TD controls.

Results

ROI analysis of the cingulum (subjacent to the cingulate gyrus) revealed a significant linear group effect, in which CD/CU+ youths exhibited increased FA relative to the ASD youths, with TD youths being intermediate (CD/CU+ > TD > ASD; see Figure 1 and Table 2). This was additionally coupled with decreased MD and RD (but no differences in AD) among CD/CU+ compared to ASD, with TD being intermediate. No group differences in AD values were found. We did not find significant FA differences between the groups for the UF.

Whole-brain TBSS analysis similarly revealed group differences in clusters in the cingulum (in its retrospenial subdivision, see Jones et al., 2013a) extending to the body of the corpus callosum, in the splenium of the corpus callosum and in the cingulum (hippocampus) (see Table 2). These group differences were found for the linear effects analysis and showed increasing FA values from ASD to TD to CD/CU+ in these tracts. We also found decreased MD and RD (but no differences in AD) in the CD/CU+ compared to the ASD group with the TD group being intermediate in these clusters. Voxelwise regression analyses did not yield any significant relationships between clinical measures of autistic (SRS) or CU traits (ICU) and mean FA, MD, or RD within affected tracts in the ASD and CD/CU+ groups. Post-hoc analyses revealed that linear trends remained significant while excluding ASD boys with a comorbid disorder or ASD boys using medication, and also while excluding CD/CU+ boys with a comorbid disorder (all $ps < .05$).

Table 2. *MNI coordinates and cluster size for tracts showing significant different FA values between groups.*

White matter tract	MNI peak coords			Size in voxels
	x	y	z	
CD/CU+ > TD > ASD				
Cingulum ROI				
L cingulum (cingulate)	-15	-35	34	344
Whole-brain				
L cingulum (cingulate) extending to the body of the corpus callosum	-14	-34	33	118
L splenium of the corpus callosum	-21	-52	25	45
L cingulum (hippocampus)	-22	-57	21	16

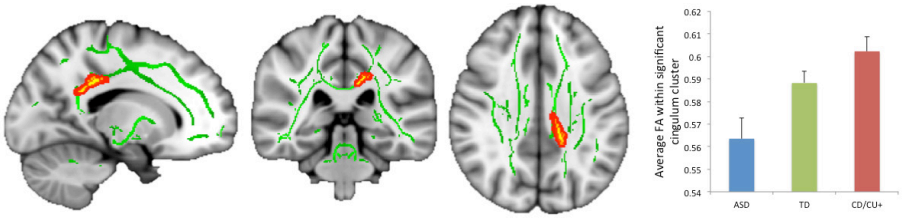

Figure 1. *Tract-based spatial statistics (TBSS) results for cingulum region of interest (ROI). Sagittal, coronal and axial sections of the white matter skeleton (in green), showing significant linear group effect (CD/CU+ > TD > ASD) of fractional anisotropy (FA) (thickened red/yellow), p < 0.05, threshold-free cluster enhancement (TFCE) and family-wise error (FWE) corrected (yellow/orange).*

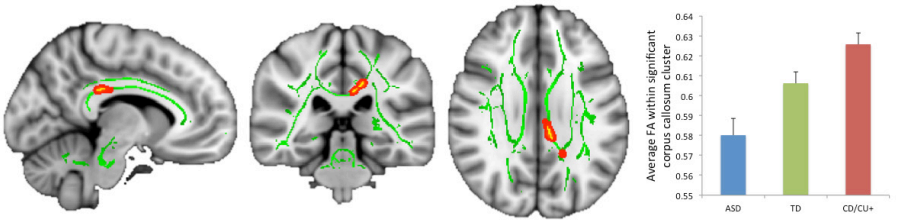

Figure 2. *Whole-brain tract-based spatial statistics (TBSS) results. Sagittal, coronal and axial sections of the white matter skeleton (in green), showing significant linear group effect (CD/CU+ > TD > ASD) of fractional anisotropy (FA) in the corpus callosum (thickened red/yellow), p < 0.05, threshold-free cluster enhancement (TFCE) and family-wise error (FWE) corrected (yellow/orange).*

Discussion

This study is the first to compare white matter microstructure between ASD and CD/CU+; two conditions characterized by social dysfunction. Our analysis revealed increased FA values coupled with decreased MD and RD values in the cingulum and the splenium and body of the corpus callosum in the CD/CU+ group compared to the ASD group with the TD group being intermediate. Contrary to our expectations, no group differences were found in the UF.

Previous studies have reported alterations in the cingulum in both ASD and CD/CU+ (e.g., Ameis et al., 2013; Kumar et al., 2010; Pape et al., 2015). In the current study, we found that the CD/CU+ group compared to the ASD group had increased FA values coupled with decreased MD and RD values in this tract with the TD group showing intermediate FA, MD and RD values. Decreased MD and RD in the CD/CU+ group suggest the increased FA results from a higher degree of myelination, whereas the opposite pattern of increased MD and RD seen in ASD suggests demyelination (Song et al., 2002). The cingulum bundle is a medial limbic tract that connects the cingulate gyrus with medial frontal, parietal, occipital and temporal lobes (Catani & Thiebaut de Schotten, 2008). This tract also seems crucial for connecting the MPFC and precuneus as part of the brain's default mode network (van den Heuvel et al., 2008), a network largely overlapping with the brain regions involved in mentalizing (Schilbach et al., 2012). Indeed, the importance of this tract for social-emotional processing was highlighted by two recent studies showing that damage to the cingulum is associated with decreased cognitive empathy and impaired mentalizing accuracy (Herbet et al., 2014; Herbet et al., 2015). Thus, decreased FA in the cingulum in the ASD group may contribute to the mentalizing deficits observed in ASD. Previously, alterations in the cingulum were also reported in ASD, such as decreased FA in the cingulum in children and adolescents with ASD (Ameis et al., 2013; Jou et al., 2011; Kumar et al., 2010; Shukla et al., 2011) and an increased number of streamlines (i.e., the lines that depict the fibers in a tract) in adults with ASD (Pugliese et al., 2009). Furthermore, density of the cingulum tract in ASD has been associated with brain activation during processing of social information, suggesting cingulum alterations may underlie impaired social behavior in ASD (Just et al., 2014).

In line with our current findings, CU traits have recently been associated with increased FA in the cingulum in at-risk antisocial youth (Pape et al., 2015). However, alterations in the cingulum in adult psychopathic offenders show the opposite effect, that is decreased FA compared to controls (Sethi et al., 2015). Such differences in the direction of FA alterations might be due to the relatively late developmental trajectory of the cingulum (Lebel et al., 2012), and may reflect accelerated maturation of white matter in the cingulum in CD/CU+ followed by marked reductions in adulthood (Fairchild et al., 2013; Passamonti et al., 2012). Interestingly, Sethi et al. (2015) discuss their finding in relation to the default mode network and conclude that abnormal cingular white matter underlying this network might contribute to social-emotional abnormalities in psychopathy (of which CU traits form the affective component). They argue that in ASD, a similar relation between the default mode network and social-emotional deficits might exist (Assaf et al., 2010; Sethi et al., 2015). The current finding of significant differences in the cingulum in a direct comparison of those with ASD with CD/CU+ do not support this suggestion. Alterations in the cingulum and the default mode network may indeed contribute to social difficulties in both disorders, while the current group differences suggest that either the pathways leading to these difficulties or their specific manifestations may be different. Additionally, decreased FA in the cingulum has also been associated with abnormal executive functioning and increased repetitive behavior in ASD (Ikuta et al., 2014; Thakkar et al., 2008), suggesting that cingulum alterations in ASD may not be restricted to social dysfunction. However, functional MRI investigations of the default mode network in ASD suggest that atypical integration of information about the self and others in this network underlies social deficits in ASD (Assaf et al., 2010; Lombardo et al., 2010; Padmanabhan et al., 2017). More speculatively, increased FA in the CD/CU+ group might be related to preserved or even enhanced mentalizing abilities in this group (Dolan & Fullam, 2004; Schwenck et al., 2012), as some data suggest that individuals with high levels of psychopathic traits have good mentalizing skills that they can use to manipulate others (Wheeler et al., 2009). However, increased FA does not necessarily have to reflect enhanced cognitive functioning, as several factors such as increased myelination, decreases in axonal diameter or reduced

neural branches may contribute to higher FA values that may also relate to poorer cognitive functioning (Beaulieu, 2002; Hoeft et al., 2007).

Our study further demonstrated increased FA values together with decreased MD and RD values in the body and splenium of the corpus callosum in the CD/CU+ versus ASD group with intermediate values in the TD group. The corpus callosum is the largest white matter bundle of the brain and crucial for interhemispheric communication, since it connects the two cerebral hemispheres. Deviating FA values of the corpus callosum might therefore impact cognitive, social, and emotional processing that is reliant on the integration of lateralized functions (Aboitiz & Montiel, 2003; Paul et al., 2007). Studies of participants with agenesis of the corpus callosum have linked callosal abnormalities to difficulties in social cognition (Symington et al., 2010). Indeed, such congenital abnormalities of the corpus callosum can yield elevated autistic symptoms comparable with those with ASD in the social and communication domains (Badaruddin et al., 2007; Paul et al., 2014). Subdivisions of the corpus callosum suggest that especially the genu and body are implicated in social processing, as the genu connects the prefrontal cortices and the body mainly connects motor, temporal and insular cortices (Hofer & Frahm, 2006; Raybaud, 2010). The splenium is the most posterior part of the corpus callosum and connects both occipital and inferior temporal areas (Catani & Thiebaut de Schotten, 2008; Hofer & Frahm, 2006), suggesting a role mainly in visual processing but probably also in social-emotional functions supported by temporal areas (Hein & Knight, 2008; Olson et al., 2007; Park et al., 2008; Pelphrey et al., 2004). Thus, the current findings of altered white matter in the body and splenium of the corpus callosum in ASD and CD/CU+ might contribute to social difficulties observed in both disorders.

Our findings are in line with previous studies showing reduced FA in the corpus callosum in ASD (Alexander et al., 2007a; Aoki et al., 2013; Jou et al., 2011; Kumar et al., 2010; Shukla et al., 2011) and elevated FA in CD (with and without CU+) (Menks et al., 2017; Pape et al., 2015; Zhang et al., 2014). Along with altered white matter microstructure, decreased size of the corpus callosum in ASD has also been reported frequently (Frazier & Hardan, 2009; but see Lefebvre et al., 2015 for a notable null finding of size differences in a large multicentre study).

Subsequently, theories of underconnectivity in ASD, which propose that decreased connectivity between cortical areas underlie the diverse set of symptoms that characterize ASD, have pointed to interhemispheric connections through the corpus callosum as one of the key underconnected components (Geschwind & Levitt, 2007; Just et al., 2012). Especially higher order cognitive functions such as language, social cognition and executive functioning that are affected in ASD could be disturbed by decreased interhemispheric communication among cortical areas (Just et al., 2007). The current findings of decreased FA in the corpus callosum in ASD converge with these previous findings and additionally suggest that these FA reductions are specific for ASD compared to CD/CU+. Previous DTI studies have found increased FA values in the body and genu of the corpus callosum to be linked with impulsivity in boys with CD (Zhang et al., 2014) and associations between higher CU traits and increased FA values in the corpus callosum in at-risk youth (Pape et al., 2015). Moreover, a DTI study in girls with CD found that compared to controls they had increased FA values coupled with decreased MD in the body of the corpus callosum (Menks et al., 2017). In addition to a broader role for the corpus callosum in higher order cognition, theoretical and empirical work suggests altered interhemispheric connectivity plays a role in aggressive behavior (Hoppenbrouwers et al., 2014; Raine et al., 2003; Schutter & Harmon-Jones, 2013). Hence, given the elevated levels of aggression in the current CD/CU+ sample, our findings of increased FA values in the corpus callosum might also be related to their impulsive and aggressive behavior.

Contrary to expectations, we did not observe significant group differences in the UF between the ASD, CD/CU+, or TD groups. Given the anatomical location of the UF, as it connects the amygdala and prefrontal cortex, many studies in ASD and CD/CU+ have focused on the UF for its alleged role in social-emotional functioning. Various studies indeed reported altered UF connectivity in ASD (Jou et al., 2011; Kumar et al., 2010; Lee et al., 2007; for meta-analysis see Aoki et al., 2013) and in CD/CU+ (Breeden et al., 2015; Haney-Caron et al., 2014; Pape et al., 2015; Sarkar et al., 2012). However, previous research both in ASD and CD/CU+ has shown inconsistencies in UF connectivity (Olson et al., 2015; Travers et al., 2012; Waller et al., 2017), suggesting alterations in the UF might not be universal to either of

these conditions. These inconsistent results may be due to differences in sample characteristics and DTI methodologies, and to relatively small sample sizes. The current study adds that no differences were found in FA values in the UF between ASD and TD (cf., Shukla et al., 2011), between CD/CU+ and TD (cf., Finger et al., 2012), but also not between both clinical groups of ASD and CD/CU+ boys.

Limitations of the current study include the cross-sectional design of the study, which prevents firm conclusions about the hypothesized developmental trajectories of white matter maturation in the cingulum and corpus callosum in both ASD and CD/CU+. Relatedly, the current adolescent sample limits the generalizability of the results to children and adults with ASD and CD/CU+. Since this sample contained boys only, we also do not know whether our results are generalizable to girls with ASD and CD/CU+. On the contrary, by selecting adolescent boys only within a limited age range, we have reduced sex- and age-related variability that might have influenced our results.

In sum, previous studies have shown differences in social-emotional task performance and associated brain functions in ASD and CD/CU+. By directly comparing white matter microstructure between ASD and CD/CU+, we add that adolescents with these disorders also differ in brain structural connectivity. The CD/CU+ group had increased FA values compared to the ASD group (with the TD group being intermediate) in the cingulum and the corpus callosum. Emerging evidence suggests that many mental disorders might share a common neural substrate (Goodkind et al., 2015; Sprooten et al., 2017), However, the observed group differences between ASD and CD/CU+ suggest that these distinctive disorders, although with superficial overlap in social dysfunction, seemingly exhibit disorder-specific alterations in white matter connectivity.