NeuroImage: Clinical 6 (2014) 379–387

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

White matter correlates of sensory processing in autism spectrum disorders

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ARTICLE INFO

Article history:
Received 4 May 2014
Received in revised form 24 September 2014
Accepted 26 September 2014
Available online 13 October 2014

ABSTRACT

Autism spectrum disorder (ASD) has been characterized by atypical socio-communicative behavior, sensorimotor impairment and abnormal neurodevelopmental trajectories. DTI has been used to determine the presence and nature of abnormality in white matter integrity that may contribute to the behavioral phenomena that characterize ASD. Although atypical patterns of sensory responding in ASD are well documented in the behavioral literature, much less is known about the neural networks associated with aberrant sensory processing. To address the roles of basic sensory, sensory association and early attentional processes in sensory responsiveness in ASD, our investigation focused on five white matter fiber tracts known to be involved in these various stages of sensory processing: superior corona radiata, centrum semiovale, inferior longitudinal fasciculus, posterior limb of the internal capsule, and splenium. We acquired high angular resolution diffusion images from 32 children with ASD and 26 typically developing children between the ages of 5 and 8. We also administered sensory assessments to examine brain-behavior relationships between white matter integrity and sensory variables. Our findings suggest a modulatory role of the inferior longitudinal fasciculus and splenium in atypical sensorimotor and early attention processes in ASD. Increased tactile defensiveness was found to be related to reduced fractional anisotropy in the inferior longitudinal fasciculus, which may reflect an aberrant connection between limbic structures in the temporal lobe and the inferior parietal cortex. Our findings also corroborate the modulatory role of the splenium in attentional orienting, but suggest the possibility of a more diffuse or separable network for social orienting in ASD. Future investigation should consider the use of whole brain analyses for a more robust assessment of white matter microstructure.

1. Introduction

1.1. DTI studies of typical white matter development and abnormalities in ASD

Autism spectrum disorder (ASD) has been characterized by atypical socio-communicative behavior, sensorimotor impairment and abnormal neurodevelopmental trajectories. Diffusion tensor imaging (DTI), which measures the displacement of water molecules in the brain (Basser et al., 1994; Le Bihan et al., 2001) and is used to characterize white matter microstructure, has been used to describe both typical and aberrant white matter development. White matter volume increases with typical development in all four major lobes of the brain, with the most rapid increases occurring before age 10 (Giedd et al., 1999; Giedd, 2004; Iwasaki et al., 1997; Pfefferbaum et al., 1994; Rivkin, 2000) and progressing in parallel with regional maturation of function. Higher fractional anisotropy (FA, a measure that reflects the orientational coherence of fiber tracts) and a lower apparent diffusion coefficient (ADC, an intravoxel measure of diffusion magnitude) tend to reflect more developed tracts with higher signal transmission speeds (Basser & Pierpaoli, 2011; Bonekamp et al., 2007; Cascio et al., 2007).

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http://dx.doi.org/10.1016/j.nicl.2014.09.018

DTI has been used to determine the presence and nature of white matter abnormalities that may contribute to the behavioral phenomena that characterize ASD. This literature has been reviewed recently (Aoki et al., 2013; Travers et al., 2012), and suggests that although widespread differences in white matter integrity have been reported (Cheng et al., 2010; Shukla et al., 2011), the most commonly replicated findings involve the corpus callosum, cingulum bundle, superior longitudinal fasciculus, and temporal white matter tracts. A lack of a clear consensus likely reflects methodological differences, including means of addressing data quality, choice of comparison groups, and inclusion criteria such as age and developmental level. One large scale study suggested that when groups were carefully matched on degree of motion, the only apparent FA differences were in the inferior longitudinal fasciculus (Koldewyn et al., 2014). In addition to controlling for motion, another important way to clarify white matter differences specific to ASD is to control for age and development. While this is best accomplished with large scale longitudinal studies, another approach is to use cross-sectional studies with a focus on narrow age ranges. This approach ameliorates the masking of differences that could occur through averaging a range of developmental white matter profiles into a single sample.

1.2. Sensory symptoms of ASD and putative neural correlates

Sensory processing abnormalities have been reported in ASD since the earliest clinical and autobiographical accounts (Cesaroni & Garber, 1991; Grandin & Scariano, 1986; Kanner, 1943), and have been added to the diagnostic criteria for ASD in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013). Among the specific sensory symptoms featured in the DSM-5 are sensory hyper-responsiveness (an oversensitivity to sensory stimuli that often include a defensive reaction such as covering one's ears to an innocuous sound) and sensory hypo-responsiveness (a depressed sensitivity that includes failure to orient to salient stimuli, e.g., pain; Baranek et al., 2006; Ben-Sasson et al., 2009). These sensory patterns relate to both the social communication impairments (Brock et al., 2012; Foss-Feig et al., 2012; Watson et al., 2011) and restricted and repetitive behaviors that characterize ASD (Baranek et al., 1997; Boyd et al., 2010; Foss-Feig et al., 2012; Wiggins et al., 2009). A third pattern of sensory responding in ASD – sensory seeking (unusual interest in sensory properties of environmental stimuli) – is less understood, but has been theorized to serve as a compensatory mechanism for both hypo-responsiveness (e.g., seeking to increase sensory input to overcome high thresholds; Dunn, 1997) and hyper-responsiveness (e.g., seeking limited, repetitive sensory stimuli to soothe over-arousal; Liss et al., 2006).

Although these patterns of sensory responding in ASD are well documented in the behavioral literature, much less is known about the neural networks associated with processing basic sensory stimuli in ASD. A recent fMRI study using simple auditory and visual stimuli showed increased activation in the primary sensory cortices, as well as in limbic areas related to emotion processing and regulation in children with ASD, relative to controls. These findings suggest atypical lower (i.e., at the level of primary or association sensory cortex) and higher (i.e., at the level of attentional or limbic cortices) order processing of sensory stimuli in ASD (Green et al., 2013). On the contrary, previous fMRI studies investigating both visual (Hadjikhani et al., 2004) and auditory (Gomot et al., 2008) stimuli report intact processing in primary sensory regions. Similarly, ERP studies routinely note higher order processing abnormalities (e.g., Ceponiene et al., 2003), with a subset also showing early (lower order) sensory differences (Donkers et al., 2013). The complexity of the sensory stimulus (Bertone & Faubert, 2003; Bertone et al., 2005) and the degree of social relevance (Greene et al., 2011) also play important roles in neural processing, and behavioral data further suggest a potentially important distinction between social and nonsocial sensory orienting in ASD (Baranek et al., 2013).

1.3. White matter tracts for sensory processing and orienting

In this study, our goal was to focus on white matter tracts with known roles in sensorimotor processing, and in early attentional processes, including alerting and orienting, which are relevant to aberrant sensory behaviors seen in ASD. The superior corona radiata (SCR) and centrum semiovale (CS) contain both motor and sensory fibers projecting to and from the anterior parietal and posterior frontal lobes. The integrity of the fibers contained in these pathways may modulate the transmission of cortical sensory signals and subsequently impact reactivity patterns in ASD, such as hypo- or hyper-responsiveness, implicating primary involvement of early sensory processing, rather than attention or limbic processes. The inferior longitudinal fasciculus (ILF) carries fibers between the occipital, temporal, and parietal sensory association cortex (Martino & De Lucas, 2014; Schmahmann et al., 2007) and may be important for linking integrated sensory input with limbic structures for the evaluation of affective significance, thus its integrity in ASD might reflect the degree to which higher order processing drives sensory abnormalities.

Each of three component functional processes in attention – alerting, orienting and executive function – have been linked to a unique neural network (Fan et al., 2009; Posner & Petersen, 1990; Posner & Rothbart, 2007; Posner et al., 2006; Raz & Buhle, 2006). Fibers carried by the posterior limb of the internal capsule (PLIC) are associated with the function and modulation of attentional alerting (Callejas et al., 2005; Fan et al., 2009; Fan et al., 2005; Fimm et al., 2001; Rueda et al., 2004; Sturm & Willmes, 2001; Yin et al., 2012), while the splenium of the corpus callosum (SPLEN) is heavily linked to orienting (Luders et al., 2009; Noudoost et al., 2006; Weber et al., 2005). Niogi et al. (2010) found correlations between FA in the SPLEN and orienting, and between FA in the PLIC and alerting. Thus, we focused our investigation on these five tracts (SCR, CS, ILF, PLIC, SPLEN) in order to address the roles of basic sensory (SCR, CS), sensory association (ILF), and early attentional processes (PLIC, SPLEN) in sensory hyper- and hypo-responsiveness in ASD.

2. Methods

2.1. Participant characterization

Thirty-two children with ASD and 26 typically developing (TD) children between the ages of 5 and 8 years completed this study. After excluding participants with poor image quality resulting from excessive motion ($n = 13$) and scanner/acquisition errors($n = 4$), the final sample resulted in 19 children with ASD (7.34 years $\pm$ 0.72; 17 males) and 22 children with TD (7.10 years $\pm$ 1.11; 18 males). Within each group, included and excluded participants did not differ in chronological age, mental age, or autism severity as measured by the ADOS (all $ps > .1$). Participants in the ASD group were recruited from the university medical center and surrounding community, and a diagnosis of ASD was confirmed with research-reliable administration of the Autism Diagnostic Observation Schedule (ADOS; Gotham et al., 2007) and the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), as well as the judgment of a licensed clinical psychologist based on DSM (4th ed.; DSM-IV; American Psychiatric Association (2000)) criteria. Participants in the TD control group were excluded if they had a diagnosed psychiatric or learning disorder or had a first-degree relative with ASD. Additionally, control participants were screened using the Social Communication Questionnaire (SCQ; Berument et al., 1999; Rutter et al., 2003) and the Child Behavior Checklist (CBCL; Achenbach et al., 2001) to confirm that ASD and other psychiatric symptomatology did not reach an at-risk level for diagnosis. All participants were screened and excluded for any genetic and neurological problems, had not experienced head injuries, and were free of all MRI contraindications.

2.2. Cognitive and sensory assessments

Participants' cognitive ability was assessed by trained research assistants using the *Kaufman Brief Intelligence Test, Second Edition* (KBIT-2; Kaufman & Kaufman, 2004) or Mullen Scales of Early Learning (MSEL; Mullen, 1995), dependent on the language level of the participant. Nonverbal and verbal mental age scores were calculated using mental age equivalents provided in the KBIT-2 and MSEL manuals. Although the groups did not differ on chronological age, mental age was significantly higher in the TD group (ASD: 7.01 ± 2.11, TD: 8.94 ± 2.37, $t(41) = -2.81$, $p = 0.008$), which was driven by verbal mental age (ASD: 6.47 ± 1.59, TD: 9.00 ± 1.98, $t(41) = -4.5$, $p < 0.001$). Nonverbal mental age, however, did not differ significantly between groups (ASD: 7.55 ± 3.22, TD: 8.87 ± 3.04, $t(41) = -1.38$, $p = 0.17$). See Table 1 for a summary of participant characteristics.

Participants completed two structured sensory assessments — the Sensory Processing Assessment (SPA; Baranek, 1999) and the Tactile Defensiveness and Discrimination Test-Revised (TDDT-R; Baranek, 2010), administered by trained personnel and consensus coded by blind raters under the supervision of a team member who had achieved reliability with the author of the instruments. Both assessments are play-based and involve toys and activities that have specific sensory features. The SPA measures response to sensory stimuli across multiple sensory domains, with novel toys presented to measure both sensory avoidance and sensory fascination/repetitive engagement, while simultaneously presenting both social (name call, tapping of shoulder, and hand wave) and nonsocial (sound stick, air puff to the back of the neck, and a light flash) distracter items to observe orientation and habituation patterns to such salient stimuli. The TDDT-R includes self-directed activities and experimenter-administered items to assess sensory defensiveness and seeking, specifically limited to the tactile domain. Scores from four sensory measures of interest were included in this study: two general sensory orientation measures from the SPA ('social orienting' and 'non-social orienting') and two tactile-specific measures from the TDDT-R ('tactile seeking' and 'tactile defensiveness'). High scores on each measure are associated with more atypical sensory processing patterns.

2.3. Image processing

All images were acquired during a single scan session on a 3 Tesla Philips Achieva MRI scanner (Philips Healthcare, Inc., Best, Netherlands), located at the Vanderbilt University Institute of Imaging Science. During scanning procedures, participants wore foam earplugs in both ears and Philips headphones to attenuate noise, and watched a video of their choice for the duration of the scan. A high-resolution T1-weighted anatomical volume (TR = 9 ms, TE = 4.6 ms, FOV = 256 mm^2, 1 mm isotropic voxels, 170 sagittal slices, 6 min 30 s duration) was collected to provide a template for image registration. Diffusion weighted data were acquired using a high angular-resolution diffusion imaging (HARDI) sequence (2.5 mm^2 isotropic voxels, 50 axial slices, 14 min 34 s). We collected 92 diffusion directions ($b = 1600$ s/mm^2) and one T2-weighted volume($b = 0$ s/mm^2).

A novel image processing pipeline was developed to measure FA and ADC in the SCR, CS, ILF, PLIC and SPLEN of individual brains (Fig. 1). All images were visually inspected for common artifacts such as fat shift and ghosting and underwent standard preprocessing and quality assurance procedures that incorporated head motion, artifact propensity, variance, and bias of estimated measures (Lauzon et al., 2013). A QA rating between 1 and 5 was assigned based on these measures and only scans with ratings above 3 were included in the analysis. HARDI data were eddy current and motion corrected, and skull stripped in FMRIB Software Library (FSL; Jenkinson et al., 2012; Smith et al., 2004). Raw T1-weighted images were re-oriented along the anterior commissure–posterior commissure (ACPC) line in Brain Voyager (Formisano et al., 2005; Goebel et al., 2006), then skull stripped in FSL. Each subject's brain-extracted HARDI and T1W/3D images were coregistered, and a tensor fit was performed for each ACPC-oriented HARDI image in DTI Studio (Jiang et al., 2006). Pixel-based outlier rejection was used to eliminate noisy pixels by the following threshold criteria: "Minimum bad area" = 80 (based on recommended value of 30 pixels per 1 mm^2), "Minimum Z-value" = 3 (standard deviations from global mean signal), and "Minimum B_0-value" = 100 (intensity threshold to remove floor noise). The proportion of rejected pixels did not differ significantly between groups ($t(39) = 1.06$, $p = .299$; see also Supplementary Table S1). Tensor fit output files were used as input in Reproducible Objective Quantification Scheme (ROQS), a software-based tool to obtain regional white matter measurements of diffusion tensor imaging parameters (Niogi et al., 2007).

ROQS exploits fiber information from the diffusion tensor to semi-automatically segment anatomically distinct WM fiber tracts for quantitative DTI analysis. ROQS is able to segment WM fiber tracts faster than manual delineation and with better reproducibility and accuracy. For each brain, nine WM fiber tracts were delineated on a best-fit 2D slice: SPLEN, and bilaterally CS, SCR, PLIC, and ILF (Fig. 2, Supplementary Fig. S1). Bilateral fiber tracts were delineated separately for each side. We obtained measures of FA and ADC (mean diffusivity) from each tract, for each individual, calculated in native space. For the TD group and the ASD group separately, within each tract, individual outliers (having an individual FA or ADC value greater or less than 3 standard deviations from the group mean) were excluded for quality assurance.

2.4. Statistical analyses

Group differences in sensory behavior were analyzed using a multivariate analysis of covariance (MANCOVA) test, with group as the independent variable and each of the four sensory behavior scores (nonsocial orienting, social orienting, tactile seeking, tactile

Table 1
Participant characterization and sensory scores for ASD and TD groups. For each group (ASD = autism spectrum disorder; TD = typically developing), means and standard deviations are reported for participant characteristics, including chronological age, sex and mental age (calculated using the KBIT-2 or the MSEL). Ranges are also reported for chronological and mental age. Group mean sensory scores (calculated using the SPA and TDDT-R) are also reported. For each variable, between-group comparison values (t- or χ^2 tests) are reported with corresponding *p* values.

Group	Age	% Male	Mental age (Mean ± SD)			Sensory score (mean rank)		
			Average	Nonverbal	Verbal	Social Orienting	Nonsocial Orienting	Tactile Defesnsive
ASD (N = 19)	7.34 (±0.72)	89.47%	6.96 (±2.22)	7.49 (±3.40)	6.43 (±1.68)	25.03	21.97	26.37
Range	5.9–8.4		3.0–13.0	3.17–18.5	2.63–9.5			
TD (N = 22)	7.1 (±1.11)	81.81%	9.10 (±1.92)	9.06 (±2.98)	9.14 (±1.92)	17.52	20.16	16.36
Range	5.3–8.9		5.0–14.0	5.0–16.0	5.83–13.0			
Test statistic	t = 0.843	$\chi^2 = 0.478$	t = −2.98	t = −1.56	t = −4.69	U = 132.5	U = 190.5	U = 107
p-value	0.404	0.489	0.005	0.127	<0.001	0.033[a]	0.622	0.008[a]

[a] Statistically significant between-group difference in sensory score.

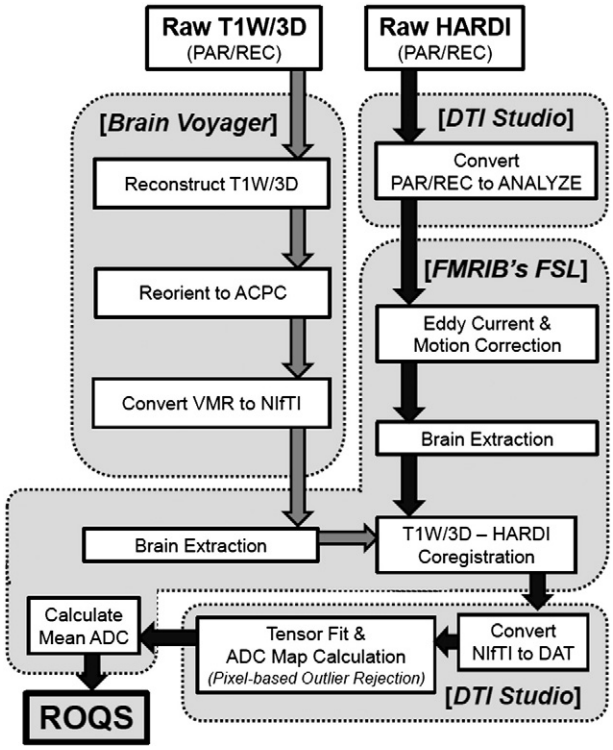

Fig. 1. Image processing pipeline. Raw T1W/3D (3D T1-weighted image; PAR/REC = Philips image file format) image was reconstructed and reoriented to ACPC (anterior commissure–posterior commissure orientation) using Brain Voyager software (VMR = file format inherent to Brain Voyager software); following, the T1W/3D image was brain extracted in FMRIB's FSL software program. HARDI (high angular-resolution diffusion image) data were converted to Analyze format in DTI Studio and motion corrected, eddy current corrected and brain extracted in FSL. Preprocessed T1W/3D images were coregistered with preprocessed HARDI data using FSL. Coregistered images were subsequently converted to DAT file format in DTI Studio where tensor fit and ADC calculation was then performed, incorporating pixel-based outlier rejection. The mean ADC map, calculated using FSL, and other files resulting from the tensor fit were used as input files to perform image analysis in Reproducible Objective Quantification Scheme (ROQS) software.

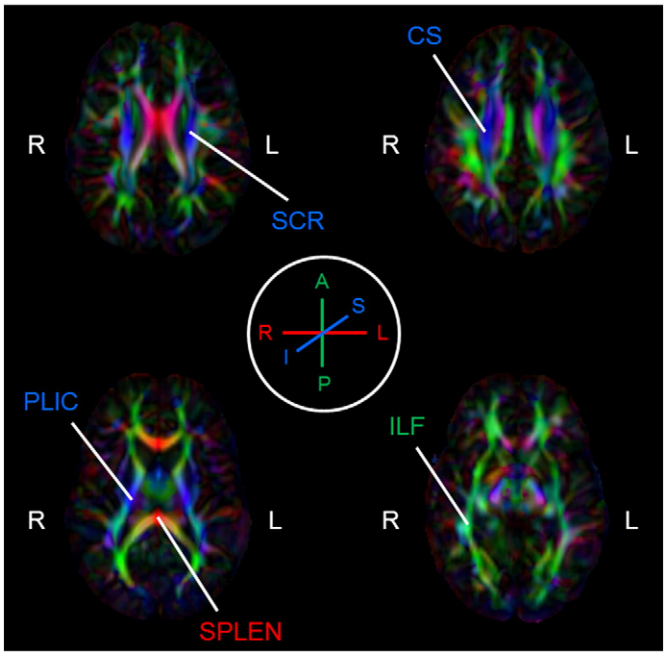

Fig. 2. White matter fiber tracts identified in representative participant. White matter fiber tracts include superior corona radiata (SCR), centrum semiovale (CS), posterior limb of the internal capsule (PLIC), splenium (SPLEN) and inferior longitudinal fasciculus (ILF). Tracts are shown on an FA color map of a representative participant, giving fiber orientation – red (right–left), green (anterior–posterior), blue (superior–inferior) – indicated by legend (encircled in middle of figure). Brain is in radiological orientation, as indicated by right (R) and left (L) hemispheric labels.

defensiveness), as dependent variables. Mental age was used as a covariate because it has been shown to influence sensory responses (Baranek et al., 2006, 2013) and differed between groups. For the DTI data, FA and ADC were analyzed as separate dependent variables, using analysis of covariance (ANCOVA) tests. Laterality (left, right, commissural) and tract (SPLEN, CS, SCR, PLIC, ILF) were within-subject variables while group was the between-subjects variable. Because there was a trend for a group difference ($p = 0.0549$, see Supplementary Table S1 for details) in image quality rating even after our rigorous QA procedure, the QA rating was included as a covariate. Post hoc, independent samples two-tailed t-tests or Mann–Whitney U tests (for variables where data were not normally distributed, given by a Shapiro–Wilk test) were used to assess between-group differences for each of the four sensory behavior scores and both FA and ADC in each white matter fiber tract.

A Spearman rank correlation test was used to evaluate correlations between significant DTI parameters and sensory behavior scores in the ASD group. Spearman rank was chosen for correlation testing to address the non-normal distribution of most of the sensory variables.

3. Results

3.1. Sensory assessment

There was an overall significant effect of group ($F(4,34) = 7.27$, $p < 0.001$), but no effect of mental age ($F(4,34) = 1.074$, $p = 0.384$) on sensory scores. ASD group mean scores were higher across all four variables, consistent with more aberrant sensory responsiveness. Follow-up tests revealed significant effects of group for three of the four sensory scores (social orienting: $F(1,40) = 4.26$, $p = 0.046$; tactile seeking $F(1,40) = 23.93$, $p < 0.001$; and tactile defensiveness: $F(1,40) = 4.51$, $p = 0.041$). There was no significant effect of group on nonsocial orienting ($F(1,40) = 0.438$, $p = 0.512$).

3.2. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) in white matter fiber tracts

An ANCOVA, with laterality (left, right, or commissural fiber) and individual tract (SPLEN, CS, ILF, SCR, and PLIC) as within-subject variables, group as a between-subjects variable, QA rating as a covariate, and FA as the dependent variable, revealed main effects of group ($F(1, 346) = 8.75$, $p = 0.003$) and tract ($F(3,346) = 225.5$, $p < 0.001$) as well as a group by tract interaction ($F(3,346) = 3.96$, $p = 0.008$). There was not a significant main effect of laterality, or the QA rating covariate ($F(1,346) = 1.48$, $p > .1$) nor any other significant interactions. These results indicate tract-specific differences in FA in children with ASD.

Because there was no effect of laterality, right and left FA values for the four bilateral tracts (CS, ILF, SCR, PLIC) were then collapsed into average bilateral values to reduce the number of post-hoc comparisons. A Shapiro–Wilk test for normality revealed normal distributions of FA values within each tract, within each group, with the exceptions of CS in the ASD group ($p = 0.041$) and PLIC in the TD group ($p = 0.049$). An analysis of group means with QA rating included as a covariate revealed that FA was significantly lower for the ASD group than the TD group in two tracts (Fig. 3): SPLEN ($F(1,38) = 5.36$, $p = 0.026$, $\eta_p^2 = .12$) and ILF ($F(1,36) = 6.14$, $p = 0.018$, $\eta_p^2 = .17$). There was also a nonsignificant trend for lower FA in the CS ($F(1,38) = 3.66$, $p = 0.063$, $\eta_p^2 = .14$). There was no significant effect of QA rating on any of these tests (all $ps > .1$). Mean FA values for each collapsed tract in each group and post-hoc analyses are summarized in Table 2.

A separate ANCOVA with ADC as the dependent variable revealed similar main effects. There were significant main effects of group (ASD > TD; $F(1, 349) = 4.67$, $p = 0.031$), tract ($F(3, 349) = 188.6$,

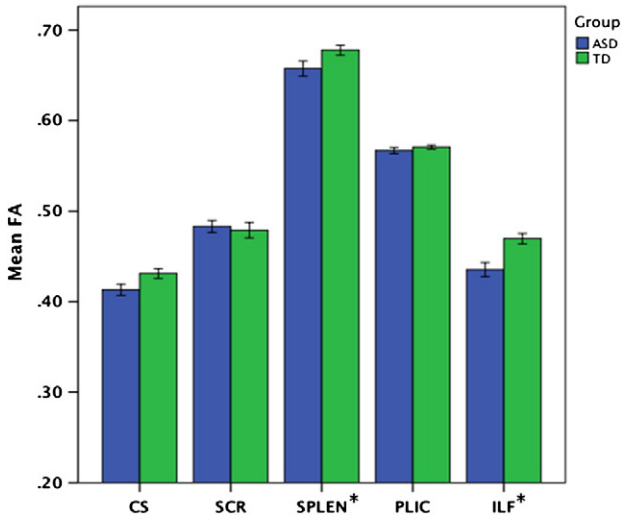

Fig. 3. Mean FA by group and tract. Mean fractional anisotropy (FA) for the ASD (blue, N = 19) and TD (green, N = 22) groups for the centrum semiovale (CS), superior corona radiata (SCR), splenium (SPLEN), posterior limb of the internal capsule (PLIC), and inferior longitudinal fasciculus (ILF). Error bars: ±1 SE. * = Statistically significant between-group difference in tract-specific FA.

$p < 0.001$), and laterality ($F(1, 349) = 20.4$, $p < 0.001$). There was no effect of QA rating and no significant interactions, suggesting generalized increases in ADC in children with ASD. Mean ADC values for each tract in each group are summarized in Table 3.

3.3. Sensory assessment correlations with WM integrity

We used the Spearman Rank correlations (ρ = correlation coefficient) within groups to test for relationships between the four sensory scores obtained from behavioral observations and FA in three tracts: SPLEN and ILF (the two regions that showed significant differences in post-hoc tests), and CS (considered exploratory as the effect of group did not reach statistical significance). In the ASD group, nonsocial orienting was found to significantly correlate with FA in the SPLEN ($\rho = -0.49$; $p = 0.03$) and tactile defensiveness significantly correlated with FA in the ILF ($\rho = -0.57$; $p = 0.01$), such that lower FA was associated with more abnormal scores (less orienting and more tactile defensiveness, respectively). These relations between sensory response and FA are depicted in Fig. 4. No significant ASD group correlations were found for FA in the CS. No significant correlations were found within the TD group for any measure.

4. Discussion

Consistent with the growing literature supporting pervasive sensory processing impairments in ASD (Marco et al., 2011; Rogers & Ozonoff, 2005), the ASD group scored higher on all sensory variables measured by behavioral observation, suggesting impairments related to tactile processing and sensory orienting across modalities. Failure to orient to salient stimuli is commonly observed in individuals with ASD and has been shown to predict deficits in social-communication abilities (Dawson et al., 2004). In the current study, although social orienting was significantly decreased in the ASD group, nonsocial orienting did not show a difference between groups. This finding suggests some degree of specificity to these commonly observed behavioral deficits, in agreement with previous work (Baranek et al., 2013). It will be important for future studies to examine social and nonsocial orienting separately in order to better understand the scope of orienting deficits in ASD.

A lack of tract-specific differences in ADC suggests a global increase in intravoxel diffusion in the ASD group, consistent with current evidence describing global white matter abnormality in ASD (Alexander et al., 2007; Barnea-Goraly et al., 2004; Brito et al., 2009; Keller et al., 2007; Lee et al., 2007; Shukla et al., 2010; Sundaram et al., 2008). The measurement of ADC is influenced by the complexity of fiber architecture, where higher values indicate simpler configurations such as a single dominant fiber orientation or multiple fibers that cross at a smaller angle (Vos et al., 2012). Under this assumption, globally increased ADC may reflect an aberrantly simple neuroarchitecture in ASD. This supports the idea that, rather than being limited to socio-communicative networks, impairments in ASD affect a range of sensorimotor, socio-communicative and cognitive domains.

There was also a main effect of group for FA whereby FA was decreased in the ASD group. A reduction in FA reflects a loss of white matter integrity caused by underlying microstructural abnormalities that may be influenced by decreased fiber density and/or reduced directional coherence of fiber bundles related to demyelination and/or compromised axonal integrity (Basser & Pierpaoli, 2011; Pierpaoli & Basser, 1996). In contrast to ADC findings, the group by tract interaction for FA and particular brain–behavior relationships suggest tract-specific differences in FA among children with ASD.

Reduced FA in the SPLEN is consistent with previous findings in ASD (Egaas et al., 1995; Frazier & Hardan, 2009; Hardan et al., 2009; Piven et al., 1997; Shukla et al., 2010), and a disruption in SPLEN myelination would support the neurophysiologic profile of ASD as a late information processing disorder (Minshew et al., 1997; Novick et al., 1980). In the ASD group, decreased FA in the SPLEN was related to decreased nonsocial orienting, consistent with a modulatory role for the splenium in orienting patterns (Luders et al., 2009; Noudoost et al., 2006; Weber et al., 2005), although a similar relation was not seen in the TD group. The association between SPLEN FA and nonsocial orienting in ASD corroborates recent evidence that inefficient visual orienting and associated SPLEN white matter integrity reduction may be early markers of risk for ASD (Elison et al., 2013). Decreased FA in this region has also been associated with sensory inattention in a sample of children with sensory processing disorder (Owen et al., 2013), which may relate to the current

Table 2
Mean FA values for ASD and TD groups. For each of the five target tracts, the mean fractional anisotropy (FA) is shown for each group (ASD = autism spectrum disorder; TD = typically developing; F = between-group F-test value with QA rating covaried out; p = *p*-value). Bilateral tracts have been collapsed due to no main effect of laterality.

Tract	Fractional anisotropy		F	p
	ASD	TD		
SPLEN	.658 (±.04)	.678 (±.03)	5.358	0.026[a]
CS	.413 (±.03)	.431 (±.03)	3.663	0.063
SCR	.483 (±.03)	.479 (±.05)	0.28	0.599
PLIC	.567 (±.02)	.572 (±.01)	0.042	0.839
ILF	.434 (±.04)	.467 (±.04)	6.138	0.018[a]

[a] Statistically significant between-group difference in tract-specific FA.

Table 3
Mean ADC values for ASD and TD groups. For each of the five target tracts, the mean apparent diffusion coefficient (ADC) is shown for each group (ASD = autism spectrum disorder; TD = typically developing). Bilateral tracts showed a significant main effect of laterality and are therefore displayed individually (R = right; L = left).

Tract	Apparent diffusion coefficient	
	ASD	TD
SPLEN	8.65E−04 (±6.20E−05)	8.48E−04 (±5.19E−05)
R CS	6.68E−04 (±2.35E−05)	6.70E−04 (±2.26E−05)
L CS	6.84E−04 (±2.80E−05)	6.79E−04 (±2.39E−05)
R SCR	6.44E−04 (±2.57E−05)	6.42E−04 (±1.68E−05)
L SCR	6.57E-04 (±1.79E−05)	6.49E−04 (±1.75E−05)
R PLIC	6.50E−04 (±1.43E−05)	6.40E−04 (±1.26E−05)
L PLIC	6.60E−04 (±2.00E−05)	6.47E−04 (±1.62E−05)
R ILF	7.32E−04 (±3.95E−05)	7.26E−04 (±3.30E−05)
L ILF	7.59E−04 (±2.99E−05)	7.52E−04 (±4.32E−05)

finding of reduced SPLEN FA and orienting in ASD. Although the association between sensory orienting behaviors and the SPLEN (Niogi et al., 2010) and its relevance for ASD (Elison et al., 2013) have been reported previously, the specific relationship to nonsocial (and not to social) orienting was surprising. In particular, even though behavioral evidence suggested specificity related to social orienting deficits in ASD, the brain–behavior relationship revealed a pattern specific to nonsocial orienting in ASD. Imaging studies have shown a number of brain regions that are preferentially involved in social orienting, including the extrastriate cortex (Engell et al., 2010; Greene et al., 2009; Hietanen et al., 2006; Tipper et al., 2008), inferior frontal gyrus (Engell et al., 2010), medial frontal cortex (Tipper et al., 2008), and superior temporal sulcus (Kingstone et al., 2004). Therefore, it is possible that a more diffuse network is involved in orientation to social stimuli and relies less on the specific modulatory role of the SPLEN.

Reduced white matter integrity in the ILF is consistent with previous studies (Jou et al., 2011; Koldewyn et al., 2014; Shukla et al., 2011). The ILF primarily comprises association fibers that connect ventral temporal and occipital regions (Schmahmann et al., 2007). It has been heavily associated with social functions (Peters et al., 2011) that are affected in ASD, such as face processing (Philippi et al., 2009; Tavor et al., 2014). Reduced ILF FA in the ASD group may reflect decreased myelination or diminished microstructural integrity of these white matter fibers, suggesting differences at the level of sensory association and limbic processing. Although reduced FA in the ILF in ASD replicated previous studies, the correlation between FA in the ILF and tactile defensiveness in the ASD group was a novel finding. The vertical branch of the ILF connects temporal limbic structures with the inferior parietal lobule (Schmahmann et al., 2007; Seltzer & Pandya, 1986), which is a multimodal sensory association region (Banat et al., 2000) that integrates input from the somatosensory association cortex and is important for bodily perception and agency (Hargreaves et al., 2012; Yang et al., 2011). Thus, the relation between FA in this pathway and negative emotional reaction to touch in the ASD group may reflect an aberrant connection between the inferior parietal cortex and limbic structures deep within the temporal lobe. As with orienting, the variability of defensiveness scores in the TD group was restricted, which may have limited our ability to detect a similar relation in this group.

The current study has several strengths. Our use of validated observational sensory measures with blind raters, rather than parent report, was a unique strength, eliminating some of the drawbacks of parent report such as response bias and variability in interpretation of questionnaire items. The integration of this rich sensory data with neuroimaging data is also a strength of the study. Our data are gathered from younger children than many neuroimaging studies, allowing a snapshot of the brain at a time when sensory features are more prominent than later in life. The narrow age range of our sample also minimizes the "blurring" that comes with obtaining cross-sectional behavioral and neuroimaging measures across many developmental stages. A 92-direction acquisition provides high signal to noise ratio.

Regarding limitations of the current study, ROQS uses semi-automated tract selection for anatomically reliable definition; using TBSS or tractography in a whole-brain analysis may provide a more robust assessment of white matter microstructure and the opportunity for additional metrics such as tract volume and fiber density. Further, to investigate the potential of aberrant connections, such as that between the inferior parietal cortex and temporal limbic structures, tractography would provide a means for the identification of innervated cortical regions. Finally, a potential limitation was that our processing pipeline did not allow for re-orientation of the b matrix, which may have introduced bias in our results (Leemans and Jones, 2009).

5. Conclusion

We used high angular-resolution diffusion imaging in children with and without ASD to investigate a brain–behavior relationship in white matter tracts with known roles in sensorimotor and early attentional processing. We targeted the centrum semiovale (CS), superior corona radiata (SCR), inferior longitudinal fasciculus (ILF), splenium of the corpus callosum (SPLEN) and posterior limb of the internal capsule (PLIC), which we predicted all might be relevant to aberrant sensory behaviors seen in young children with ASD. At the time of publication, this is the first known study of ASD to link sensory variables in directly observed behaviors to white matter integrity. The relationship between increased tactile defensiveness and reduced FA may reflect an aberrant connection between limbic structures in the temporal lobe and the inferior parietal cortex. Our findings also corroborate the modulatory role of the SPLEN in orienting deficits in ASD, but suggest the possibility that a more diffuse or separable network may underlie the social orienting deficits that are more specific to ASD. Future investigation should consider the use of whole brain analyses, including tractography, for a more robust assessment of white matter microstructure. In summary, our findings suggest a modulatory role of ILF and SPLEN in atypical sensorimotor and early attention processes in ASD.

Acknowledgments

This work was supported by the National Institute of Mental Health (K01 MH090232 awarded to C.J.C.), the Landreth Family Discovery Grant, and the Nicholas Hobbs Society of the Vanderbilt Kennedy Center. The National Center for Advancing Translational Sciences (UL1 TR000445) provided database support and supplemental funding for image acquisition (VR 2719 awarded to C.J.C.). The laboratory of Dr. Grace Baranek (University of North Carolina, Chapel Hill) provided access to sensory assessments and training in their administration and scoring. The authors thank Dr. Bruce McCandliss for providing software

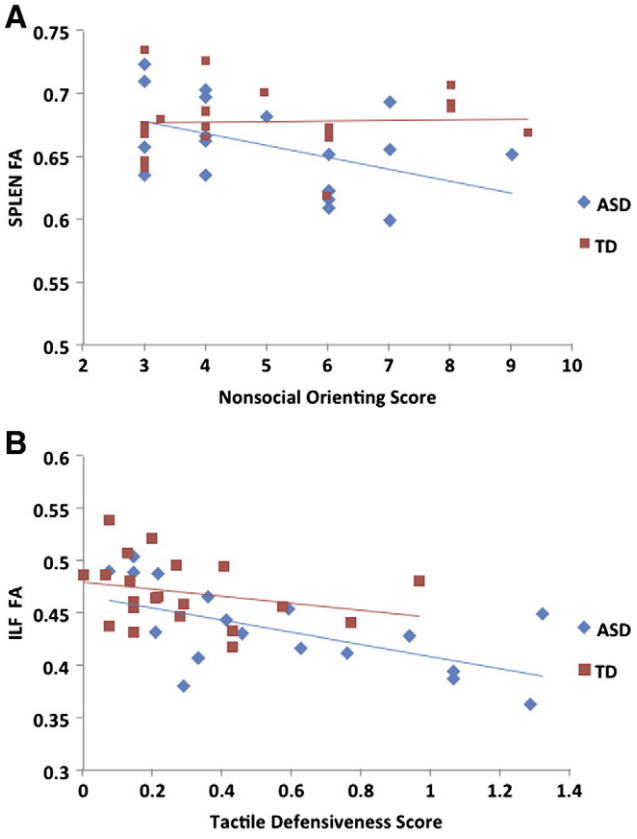

Fig. 4. Mean FA by group and tract. Scatter plots depicting relation of (A) nonsocial sensory orienting score and FA value in the SPLEN, and (B) tactile defensiveness and FA value in the ILF. Higher scores on sensory measures indicate more atypical behavior and values were calculated according to the SPA and TDDT-R manuals.

and training for the ROQS analysis, and Micheal Gmaz Sandbank for behavioral training assistance for the scanner in a subset of participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2014.09.018.

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