White matter correlates of sensory processing in autism spectrum disorders

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ABSTRACT

Autism spectrum disorder (ASD) has been characterized by atypical socio-communicative behavior, sensorimotor impairment and abnormal neurodevelopmental trajectories. Diffusion tensor imaging (DTI) has been used to describe both typical and aberrant white matter microstructure. DTI 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).

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, is used to characterize white matter microstructure. DTI studies have shown that the development of white matter is a complex process that involves the coordination of cellular and molecular events, which are influenced by genetic, environmental and social factors. The development of white matter is both a dynamic and a highly regulated process, 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).
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., Cepioni 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 ± 0.72; 17 males) and 22 children with TD (7.10 years ± 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; Burmell 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 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 ± 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: 6.47 ± 1.59, TD: 9.00 ± 1.98, t(41) = −2.81, p = 0.008), which was driven by verbal mental age (ASD: 2.94 ± 2.27, TD: 3.0–3.10, 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 hand wave) distractor 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 domain. Scores from four sensory measures of interest were included in this study: two general sensory orientation measures from the SPA domain. Scores from four sensory measures of interest were included in this study: two general sensory orientation measures from the SPA domain.

Table 1

| Group          | Age (Mean ± SD) | % Male | Mental age (Mean ± SD) | Sensory score (mean rank) |
|----------------|-----------------|--------|------------------------|--------------------------|
|                |                 |        | Average | Nonverbal | Verbal | Social Orienting | Non-social Orienting | Tactile Defensiveness |
| ASD (N = 19)   |                 |        | 7.34 ± 0.72 | 5.9–8.4 | 89.47% | 6.96 ± 2.22 | 3.0–13.0 | 9.10 ± 19.2 | 9.14 ± 19.2 |
| Range          |                 |        |          |          |       | 7.49 ± 3.40 | 3.17–18.5 | 9.06 ± 2.98 | 9.14 ± 19.2 |
| TD (N = 22)    |                 |        | 7.1 ± 1.11 | 5.3–8.9 | 81.81% | 6.43 ± 1.68 | 2.63–9.5 | 9.14 ± 19.2 | 9.14 ± 19.2 |
| Range          |                 |        |          |          |       | 7.43 ± 1.5 | 5.0–16.0 | 8.53±13.0 | 8.53±13.0 |
| Test statistic | t = 0.843       | p-value| 0.040   | 0.489    | 0.065  | t = −2.38  | 0.127    | t = −4.69  | 0.001    |
|                |                 |        |          |          |       |           |          |            |          |

* Statistically significant between-group difference in sensory score.

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 (Laouz et al., 2013). A QTA 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 then 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 mm²), “Minimum Z-value” = 3 (standard deviations from global mean signal), and “Minimum B0-value” = 100 (intensity threshold to remove floor noise). The proportion of rejected pixels did not differ significantly between groups (t(39) = 1.06, p = 0.299; 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 weight) as the dependent variable. weighted data were acquired using a high angular-resolution diffusion imaging (HARDI) sequence (2.5 mm² isotropic voxels, 50 axial slices, 14 min 34 s). We collected 92 diffusion directions (b = 1600 s/mm²) and one T2-weighted volume (b = 0 s/mm²).

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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 covariates were mental age, ASD group, and post-hoc analyses are summarized in Table 2.

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, and 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 (F(3,346) = 5.36, p = 0.026, η² = .12) and ILF (F(1,36) = 6.14, p = 0.018, η² = .17). There was also a nonsignificant trend for lower FA in the CS (F(1,38) = 3.66, p = 0.063, η² = .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,
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, 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.

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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; Noodoost 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
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.

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