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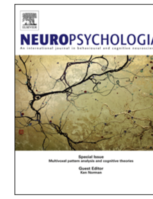

White matter microstructure correlates of narrative production in typically developing children and children with high functioning autism

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A B S T R A C T

This study investigated the relationship between white matter microstructure and the development of morphosyntax in a spoken narrative in typically developing children (TD) and in children with high functioning autism (HFA). Autism is characterized by language and communication impairments, yet the relationship between morphosyntactic development in spontaneous discourse contexts and neural development is not well understood in either this population or typical development. Diffusion tensor imaging (DTI) was used to assess multiple parameters of diffusivity as indicators of white matter tract integrity in language-related tracts in children between 6 and 13 years of age. Children were asked to spontaneously tell a story about at time when someone made them sad, mad, or angry. The story was evaluated for morphological accuracy and syntactic complexity. Analysis of the relationship between white matter microstructure and language performance in TD children showed that diffusivity correlated with morphosyntax production in the superior longitudinal fasciculus (SLF), a fiber tract traditionally associated with language. At the anatomical level, the HFA group showed abnormal diffusivity in the right inferior longitudinal fasciculus (ILF) relative to the TD group. Within the HFA group, children with greater white matter integrity in the right ILF displayed greater morphological accuracy during their spoken narrative. Overall, the current study shows an association between white matter structure in a traditional language pathway and narrative performance in TD children. In the autism group, associations were only found in the ILF, suggesting that during real world language use, children with HFA rely less on typical pathways and more on alternative ventral pathways that possibly mediate visual elements of language.

1. Introduction

Autism is a neurodevelopmental disorder characterized by language and communication impairments. Although autism is widely recognized as having genetic and neurological origins (Bailey et al., 1995), the relationship between abnormalities in language acquisition and neural development is not well understood. Studies of language development have often used standardized tests to measure these abilities; however, some children with high functioning autism (HFA) will perform within the normal range on these tests (Tager-Flusberg, Paul, & Lord, 2005). A more consistent finding is that children with HFA show language deficits in naturalistic contexts (Condouris, Meyer, & Tager-Flusberg, 2003; Loveland & Tunali-Kotoski, 2005). To date, investigations of children's use of language in discourse genres have evaluated children's unstructured conversational language or their narration of picture books, rather than more complex, elaborative tasks such as a child's production of an autobiographical narrative. Accordingly, studies that have begun to examine the relationship between language and brain development in children with HFA have focused on standardized tasks and have not yet investigated possible correspondences between naturalistic language performance and neural development.

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The act of telling an autobiographical narrative challenges a child to spontaneously recall events and engage his or her knowledge of morphology and syntax in real time to organize and convey the elements of the story in a coherent manner. In typically developing children, this ability begins to emerge at four to five years of age, when children can produce the major grammatical structures of their native language (Berman & Slobin, 1994). In the school-age period, between 6 and 13 years of age, children become more skilled in expressing the relationships between local and thematic elements by combining multiple propositions with greater syntactic complexity. Thus, the narratives that school-age children produce provide an opportunity to examine children's dynamic use of morphology and syntax in a naturalistic context.

In a recent study, Lai (2011) examined language use in children with HFA with an autobiographical narrative task. Children produced a story about an instance in which they had a conflict with another person. The group's use of language differed from their typically developing (TD) peers in multiple ways. Children with HFA produced shorter narratives with more morphological errors and fewer instances and types of complex syntax than controls. Importantly however, their use of emotional terms was comparable to the TD group. In addition, the children with HFA produced fewer mental state terms and narrative components (i.e., setting in time and place, statement of the problem, internal response, resolution, and conclusion) during their stories than the TD group. In order to understand whether or not these behavioral deficits are linked to features of neuroanatomical development, the current study builds on this recent narrative study by investigating white matter development in these same children.

MRI-based studies show white matter abnormalities in infants and children with autism. A well-established finding is an early, enlargement of brain volume (Anagnostou & Taylor, 2011; Stanfield et al., 2008), largely driven by increases in white matter volume (Herbert et al., 2004). Recently, diffusion tensor imaging (DTI) studies of autism show developmental abnormalities in fractional anisotropy (FA), an index of the structural integrity of fiber tracts. Up to roughly three years of age, children with HFA show elevated FA values (Ben Bashat et al., 2007; Weinstein et al., 2011) followed by lower FA and an overall greater motility of water within white matter tissue in early childhood and adolescence compared to TD children (Brown et al., 2012; Cheng et al., 2010; Keller, Kana, & Just, 2006; Noriuchi et al., 2010). Fiber pathways showing reductions in FA include the superior longitudinal fasciculus (SLF) (Noriuchi et al., 2010), which connects fronto-temporal language networks (Broca's and Wernicke's areas), and the arcuate fasciculus, a subsection of the SLF (Fletcher et al., 2010; Kumar et al., 2010). Studies have also revealed lower FA in the inferior fronto-occipital fasciculus (IFO) (Bode et al., 2011; Jou, Jackowski et al., 2011; Jou, Mateljevic et al., 2011; Shukla, Keehn, & Müller, 2011) and the inferior longitudinal fasciculus (ILF) (Jou, Jackowski et al., 2011; Shukla et al., 2011), which are tracts that appear to play a role in language (Saur et al., 2008). However, not all studies have found differences in FA. After taking IQ and age into account, one study found an absence of FA differences, but increases in apparent diffusion coefficient (ADC) in individuals with autism (Groen, Buitelaar, Van Der Gaag, & Zwiers, 2011). Whether or not there is an association between abnormal white matter development and real world language deficits in children with HFA is unknown.

Few studies have directly examined the relationship between these two domains. One study of FA asymmetry between the left and right arcuate fasciculi (Lainhart et al., 2010) found that the HFA group lacked this tract's typical leftward asymmetry of FA. However, the abnormalities in lateralization did not correlate with performance on the Clinical Evaluation of Language Fundamentals (CELF). Another study of linguistic reasoning found that performance was related to FA in the SLF in typical children; however, in children with HFA, correlations were found in non-traditional language pathways such as the ILF. These findings suggest that the ILF, rather than traditional language tracts, may be importance for children with HFA and may reflect different cognitive strategies utilized for mediating language (Sahyoun, Belliveau, & Mody, 2010).

The current understanding of the typical development of language and white matter relationships is also limited. The few studies that have examined these associations have shown mixed findings with regard to the direction of correlations. Some studies have found positive relationships between reading performance and FA (Deutsch et al., 2005; Nagy, Westerberg, & Klingberg, 2004). Conversely, others found that better performance on a standardized word reading task was related to lower FA (Frye et al., 2011). Similarly, investigators have found that better phonological performance is associated with lower FA (Dougherty et al., 2007; Yeatman et al., 2011).

To our knowledge, the present study is the first to investigate the relationship between children's morphosyntactic production in the context of naturalistic discourse and white matter microstructure. This study will assess white matter tract integrity in children with HFA and determine whether the tracts' microstructure is associated with profiles of spontaneous language use. Since relationships between language development and white matter microstructure are not well understood in any population, another important aim of this study is to assess these relationships in typical children. To examine naturalistic language ability, morphological proficiency and syntactic complexity will be assessed in the context of an autobiographical narrative. To assess white matter microstructure, this examination will focus on three diffusivity measurements, FA, which measures the degree of water movement in the principle direction, ADC, which measures the overall magnitude of water diffusion across three orthogonal directions, and the transverse diffusion coefficient (TDC), which measures the degree of water diffusion perpendicular to the principle direction of water movement. FA values are highest in tracts composed of uniformly oriented, well myelinated, and closely packed axon fibers. In contrast, ADC and TDC values are lowest in coherent, myelinated tracts and highest in tissue with greater interstitial space (Basser & Pierpaoli, 1996). While some studies report FA alone, taken together these diffusion measurements can more fully characterize the structural constitution of white matter tracts. This investigation will target fiber tracts traditionally linked to language processing, the SLF and two of its subregions, the arcuate fasciculus that connects the posterior temporoparietal cortex with the inferior frontal cortex, and the parietal subdivision that projects from the inferior parietal lobe to the inferior frontal cortex. We also evaluate two ventral, posterior–anterior pathways that constitute the “semantic ventral stream” (Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007; Parker et al., 2005). A direct pathway, the inferior fronto-occipital fasciculus (IFO), which projects from the occipital lobe to frontal cortex, and an indirect route comprised of both the ILF, which projects from the occipital to the anterior temporal lobe, and the uncinate fasciculus (UNC), which interconnects anterior temporal and inferior frontal cortices (Catani, Jones, & Donato, 2003; Mandonnet et al., 2007). Based on previous findings, we hypothesize that children with HFA will have abnormalities and show lower FA and higher ADC and TDC values in language pathways, the SLF (and its subcomponents), as well as the IFO, ILF, and UNC. In these pathways, it is expected that children with HFA who have less compromise in white matter integrity will have better language performance during their spoken narrative. In TD children, we predict that language use in the narrative will be most strongly associated with fiber structure in the central language tract, the SLF and its subdivisions.

2. Material and methods

2.1. Participants

Participants consisted of 17 TD children (8 males) and 10 children with HFA (8 males) ranging from 6 to 13 years of age. All children had normal or corrected-to-normal auditory and visual acuity, and were from an English-speaking background. Table 1 shows each group's mean age and standard deviation, standardized IQ scores, as well as p values from Welch's tests of group differences of age, verbal, performance, and full scale IQ measurements.

Children in the TD group were recruited through community fairs, flyers placed in the community, and advertisements in local parent and news magazines. They were screened to meet the following criteria: performance within normal limits on standardized tests of language (i.e., Clinical Evaluation of Language Fundamentals Screener) (Semel, Wigg, & Secord, 2003) and intelligence (i.e., Wechsler Intelligence Scale for Children) (Weschsler, 2000), average-range academic functioning and neurological exams without a history of developmental or language delay. Children must also have been free from chronic use of a medication that might have minimized performance (e.g., decongestants that cause drowsiness). Children with a potential diagnosis of HFA were identified from a pediatric neurology clinic population, as well as through referrals from other clinicians and health care professionals and from recruitment at autism events in the community. Children in the HFA group met the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV), the Autism Diagnostic Interview-Revised (ADI-R) and/or the Autism Diagnostic Observation Schedule (ADOS), and had full scale IQ scores of 70 or above. Table 2 shows group means, standard deviations, and ranges for the ADOS and ADI-R. Children were excluded if diagnosed with a specific underlying genetic or metabolic diagnosis (e.g., Fragile X syndrome). All children in the HFA group had received past speech and language services.

2.2. Spoken narrative elicitation task

This task was selected to prompt school-age children to produce a narrative. Since narratives inherently involve a problem, a task that asks a child to produce a narrative about a personal conflict is consistent with that structure. Further it cues a child to generate a story with certain components such as a presentation of the problem, a possible resolution to the conflict, and the outcome. This task is well established for use with typically developing children in this age range (Berman & Verhoeven, 2002; Reilly, Zamora, & McGivern, 2005) and with children with neurodevelopmental disorders (Reilly, Wasserman, & Appelbaum, 2013). The participants were asked to tell a personal story about a conflict. The experimenter's verbal instructions were, “People disagree and they get into fights or arguments all the time. I'm sure there has been a time when you had an argument or a disagreement or when someone hurt your feelings. I'd like you to tell me about a time when someone made you sad or mad or angry, maybe it was a friend or someone at school. Tell me how it started, what happened, and how it ended. Take your time and think about it. When you're ready, go ahead and start.” After the instructions were given, each participant produced a spoken narrative. If the narrative was too general in nature, they were prompted to describe a specific instance (e.g., Can you tell me about a particular time?). Children were recorded with both audio and video equipment.

Narrative coding procedures and criteria: Audio files were used to transcribe spoken language using CHAT from the Child Language Data Exchange System (CHILDES) (MacWhinney, 2000). To ensure coding reliability a second coder blind to the group status coded 25% of the spoken narratives. Inter-rater reliability for all measures was greater than 85%. Coding criteria for micro-structural measures were adapted from Reilly, Losh, Bellugi, and Wulfeck's (2004) coding schema. See Appendix A for more information. Measures of interest included length, proportion of morphological errors, and the proportion of complex syntax within the spoken narrative.

Spoken narrative length: The total number of propositions produced during the Narrative Elicitation Task was tallied to quantify the length of each narrative. A proposition was defined as a verb and its arguments. The total number of propositions was used as a denominator for computing the proportion of morphological errors and complex syntax to control for the variability of story lengths.

Morphological performance: Morphology refers to the rules that govern how morphemes are combined to form words. Total instances of morphological errors in each narrative were tallied. These errors included omission, substitution, or overgeneralization in the following subcategories: errors in pronouns, verb auxiliaries, determiners, noun plurals, verb tense, verb agreement for number, and prepositions (see Appendix A). Colloquial syntactic structures (e.g., “Me and Jessica”) or hypercorrections (e.g., “Between Jessica and I”) were not considered morphological errors in this study. The proportion of morphological errors was the ratio of total morphological errors to the total number of propositions. This measure was reverse coded (1 minus the number of errors) so that higher values represented smaller proportion of morphological errors and better morphological performance.

Frequency of complex syntax: This measure was used to assess linguistic complexity. Complex sentences included multiple propositions that fell within a sentence intonational contour. Subcategories included sentences with coordinate conjunctions combining simple clauses (e.g., and, or, then), subordinate adverbial clauses (e.g., when, because), verb complements (e.g., try+verb, keep+verb, that, and infinitival complements), relative clauses, and passive sentence structures (see Appendix A). The proportion of complex syntax was the ratio of total instances of complex sentences to the total number of propositions.

2.3. MRI methods

2.3.1. Image acquisition

All MRI data were obtained on a 1.5 T GE Signa HDx 14.0M5 Twin Speed scanner (GE Healthcare, Waukesha, WI) using an eight-channel phased array head coil. A high resolution anatomical data set was acquired with a single 3D inversion recovery spoiled gradient echo (IR-SPGR) T1-weighted volume was acquired with pulse sequence parameters optimized for maximum gray/white matter contrast (TE = 3.9 ms, TR = 8.7 ms, TI = 270 ms, flip angle = 8°, TD = 750 ms, bandwidth = ± 15.63 kHz, FOV = 24 cm, matrix = 192 × 192, voxel size = 1.25 × 1.25 × 1.2 mm^3). Diffusion tensor imaging sets for white matter quantification were acquired using single-shot echo planar imaging with isotropic 2.5 mm voxels (matrix size = 96 × 96, field of view = 24 cm, 47 axial slices), covering the entire cerebrum and brainstem without gaps. Three volume series were acquired with 51 diffusion gradient directions using b-values of 600, 800, and 1000 mm^2/s, each with an additional $b=0$ volume. For use in nonlinear B0 distortion correction, two additional volume series were acquired with one $b=0$ volume and a single diffusion direction ($b=800$ mm^2/s), with either forward or reverse phase-encode polarity.

2.3.2. Image preprocessing, reconstruction, and segmentation

Image files in DICOM format were transferred to a Linux workstation for viewing, rating, and automated cortical reconstruction. The T1-weighted volume was rigid-body registered and realigned into a common stereotactic space. Heterogeneities in image intensity were corrected online using GE's calibration normalization procedure as well as off-line using the FreeSurfer software suite (version 3.0.5; http://surfer.nmr.mgh.harvard.edu). Preprocessing of the diffusion-weighted images was performed according to previously described procedures (Hagler et al., 2009). In brief, preprocessing of DTI images involved the correction of subject motion, correction for image distortion in the diffusion weighted volumes due to eddy currents created by the gradient coils (Jovicich et al., 2006), magnetic susceptibility artifacts, and differences in intensity scaling. Images were resampled to a higher resolution using linear interpolation (1.875 mm^3 isotropic voxels).

White matter tracts of interest were identified and segmented from surrounding white matter based on a probabilistic atlas with information about the location and orientation of a comprehensive set of cerebral fiber tracts. An illustration of the substages is presented in the Supplementary material. The fiber atlas was previously constructed by manually generating a full set of tracts in 21 subjects

Table 1
Demographic and IQ data by group

	TD $n=17$, 8 Males		HFA $n=10$, 8 Males		p Value
	M	*SD*	*M*	*SD*	
Age in years	9.2	1.8	9.8	1.4	0.45
Verbal IQ	121	12.3	97.2	20.5	< 0.05
Non-verbal IQ	105	12.2	93.5	19	0.09
Full scale IQ	114.5	11.9	94.2	16	< 0.05

Table 2
ADOS and ADI-R test scores for the HFA group

Diagnositc test	Average (*SD*)	Range
ADOS communication total	3 (0)	3–3
ADOS social affect+restricted and repetitive behavior total-revised	15.6 (2.4)	12–19
ADI-R social	22.5 (1.9)	19–24
ADI-R communication	19.3 (3.5)	14–24
ADI-R repetitive behaviors	8.4 (2.1)	6–12
ADI-R early development	4.1 (1.2)	2–5

individually. In each subject, diffusion tensors were derived from the DTI dataset and three eigenvectors and corresponding eigenvalues were calculated from the tensor matrix. FA, ADC, and TDC were each calculated based on these eigenvalues. With the use of DTI Studio software (Laboratory of Brain Anatomical MRI, Johns Hopkins Medical Institute) and eigenvector maps, a deterministic fiber tracking method generated streamlines from each voxel. Manually drawn ROIs identified streamlines that connected known anatomical sites and formed known tracts. For each subject, the T1-weighted dataset were registered to a common space and the transformation matrix was applied to the fiber streamline maps for coregistration and to produce an average fiber streamline map. The average fiber streamline maps indicate the relative probability that a fiber tract is positioned in a given space.

For each participant, the eigenvector maps were rotated, aligned and resampled to coregister to the atlas. The fiber orientation probability distribution at each voxel was then assessed for the likelihood that a voxel was part of a particular fiber path given the diffusion values. This automated probabilistic method has previously been described in detail (Hagler et al., 2009).

2.4. White matter tracts

In each fiber tract, the mean FA, ADC and TDC over the extent of the white matter pathway were calculated individually for each subject. White matter fibers measured in this study are association fibers that have previously been implicated in language functioning. Tracts include the SLF as a whole, the temporal subsection of the SLF (tSLF, i.e., the arcuate fasciculus), the parietal subsection of the SLF (pSLF), the IFO, the ILF and the UNC. Fig. 1 displays a 3D reconstruction of each tract.

For all participants, T1-weighted structural volumes, individual DTI frames, FA volumes, DTI to T1-weighted volume registrations, and automatically generated DTI ROIs were visually inspected for artifacts and processing errors. Participants included in analyses had no more than ten DTI frames with any motion artifacts and did not have significant artifacts at any other level of visual inspection.

2.5. Statistical analysis

The behavioral measures of language performance (morphology and complex syntax), and diffusivity measurements (FA, ADC, and TDC) were each compared between the TD and HFA groups with Welch's tests ($p \leq 0.05$). For each of the diffusivity measures, FA, ADC and TDC, a set of tests assessed the partial correlation between diffusivity and language performance (morphology and syntax) in the fiber tracts of interest while controlling for age. In each of the three sets, the p value threshold was adjusted for comparisons in six tracts with a Bonferroni correction ($p \leq 0.008$). These analyses were performed separately for the TD and HFA groups. In addition, the majority of findings are also significant with an approach of correcting for 18 comparisons ($p \leq 0.003$).

3. Results

3.1. Group comparisons of language performance

Syntactic complexity and morphological errors in the spoken narrative were each compared between the TD and HFA groups with Welch's tests to account for differences in sample sizes. A significant group difference was found in the amount of complex syntax used within the narrative ($t(26)=4.29$, $p=0.0004$). After adjusting for the total number of propositions, TD children had a greater proportion of complex sentences ($M=0.91$, $SD=0.15$) than did children with HFA ($M=0.65$, $SD=0.15$). No group difference were found in morphological error rate ($t(26)=1.39$, TD=0.04, HFA=0.10, $p=0.15$). Each child in the TD and HFA groups was able to identify and produce a narrative about an appropriate instance of personal conflict.

3.2. Group comparisons of white matter diffusivity

In order to test for group differences in white matter structure, Welch's tests compared TD and HFA groups on each of the diffusivity measures, FA, ADC, and TDC, in each fiber tract listed above. Analyses revealed that the HFA group had higher ADC ($M=2.6$, $SD=0.08$) than the TD group ($M=2.50$, $SD=0.07$) in the right ILF ($t(25)=2.1$, $p=0.049$). The HFA group also had higher TDC ($M=0.99$, $SD=0.03$) than the TD group ($M=0.98$, $SD=0.03$) in the right ILF ($t(25)=2.1$, $p=0.037$). No group differences in FA were found.

3.3. Correlations between language performance and FA

In the TD group, analysis of the relationship between language performance and FA revealed that children who used more complex syntax within their spoken narrative also had lower FA in the right arcuate fasciculus ($F(1, 15)=4.9$, $p=0.046$, partial $r=-0.505$). This relationship was a trend after correction for multiple comparisons and is displayed in Fig. 2.

In the HFA group, analysis of the relationship between language and FA revealed that children with better morphological performance had higher FA in the ILF within the right hemisphere ($F(1,8)=45.9$, $p=0.0003$, partial $r=0.931$). Morphological performance also showed

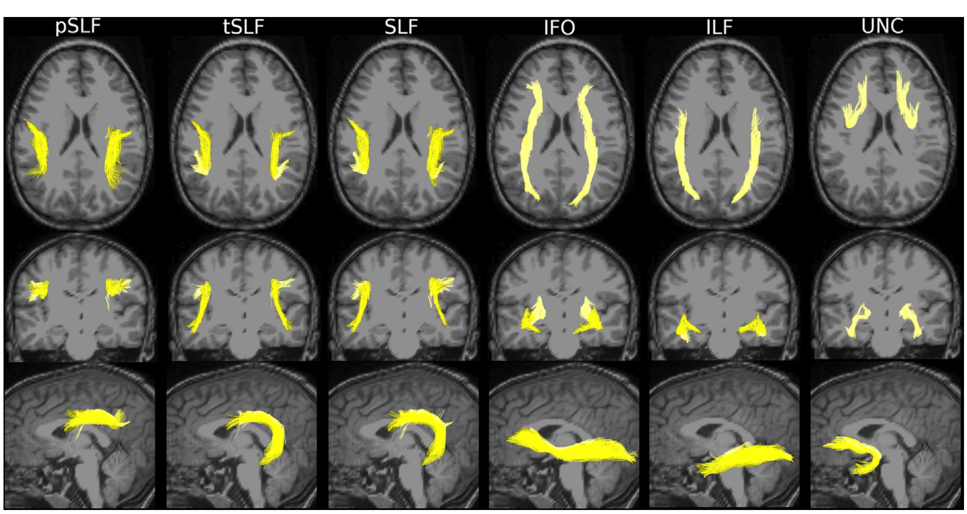

Fig. 1. 3D reconstructions of the white matter tracts of interest (from left to right): the parietal aspect of the superior longitudinal fasciculus (pSLF), the arcuate fasciculus or temporal aspect of the superior longitudinal fasciculus (tSLF), the total superior longitudinal fasciculus (SLF), the inferior fronto-occipital fasciculus (IFO), the inferior longitudinal fasciculus (ILF), and the uncinate fasciculus (UNC). The 3D tracts are shown against T1-weighted anatomical slices in the axial (top row), coronal (middle row) and sagittal (bottom row) views.

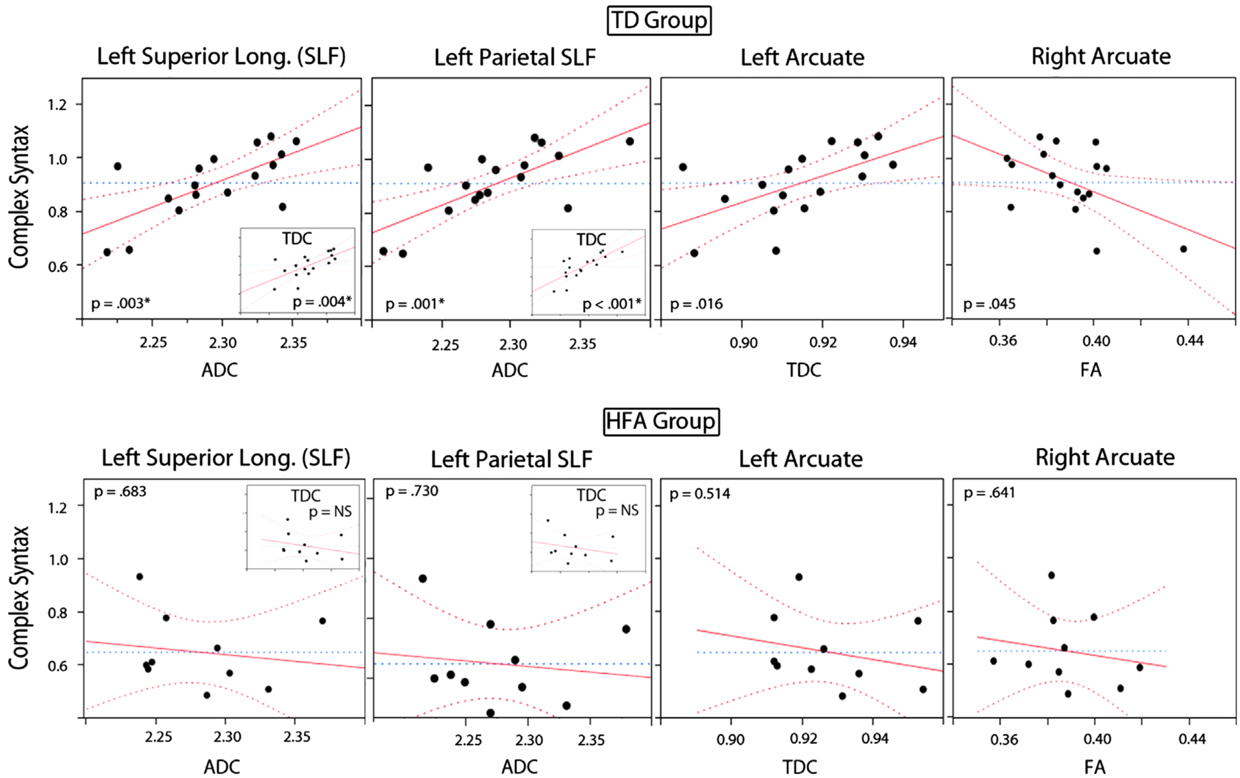

Fig. 2. The relationship between complex syntax and diffusivity in the SLF. In the TD group, systematic associations are found between complex syntax and diffusivity in the central language pathway, the SLF. Graphs represent the significant correlations in the TD group and the absence of corresponding relationships in the HFA group, after controlling for age. Diffusivity measurements (ADC, TDC, and FA) are shown on the *x*-axes of graphs from left to right, respectively, and an index of complex syntax during a child's spoken narrative is shown on the *y*-axes. The two dotted lines represent the 95% confidence interval and the horizontal dotted line represents the average complex syntax score. *Partial correlations are significant after Bonferroni correction for multiple comparisons ($p<0.008$).

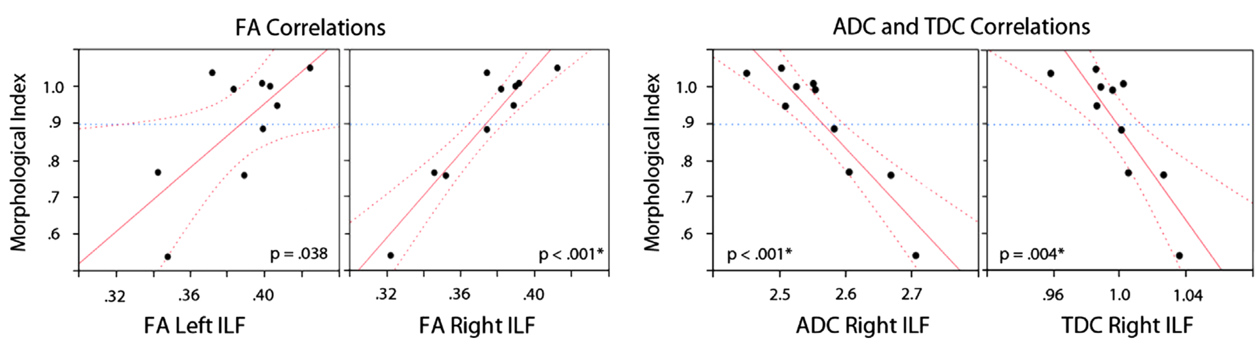

Fig. 3. HFA group relationships between morphological performance and diffusivity in the ILF. Correlations between morphological accuracy and diffusivity measures are specific to the ILF in the HFA group. Graphs show partial correlations, after controlling for age, between diffusivity measures (FA, ADC and TDC, from left to right) on the *x*-axes, and the proportion of morphological errors, adjusted for narrative length, on the *y*-axis. The two dotted lines represent the 95% confidence interval and the horizontal dotted line represents average morphological performance. *Partial correlations are significant after Bonferroni correction for multiple comparisons ($p<0.008$).

a trend toward an association with FA in the left ILF ($F(1,8)=6.4$, $p=0.038$, partial $r=0.692$). These relationships are illustrated in Fig. 3. No additional associations were found between FA and morphology or FA and complex syntax in the HFA group.

3.4. Correlations between language performance and ADC

TD children who used more complex syntax within their spoken narrative had higher ADC values in the left SLF ($F(1,\ 15)=11.9$, $p=0.003$, partial $r=0.678$), left pSLF ($F(1,\ 15)=14.7$, $p=0.001$, partial $r=0.716$), and left arcuate fasciculus ($F(1,\ 15)=8.7$, $p=0.010$, partial $r=0.619$). All three associations are shown in Fig. 2. In addition, the TD group showed a trend between more complex syntax and higher ADC in the right pSLF ($F(1,\ 15)=5.2$, $p=0.038$, partial $r=0.522$), and the right ($F(1,\ 15)=9.2$, $p=0.009$, partial $r=0.629$) and left UNC ($F(1,\ 15)=8.2$, $p=0.012$, partial $r=0.607$).

In the HFA group, children with better morphological performance had lower ADC in the right ILF ($F(1,8)=36.7$, $p=0.0005$, partial $r=-0.916$), as shown in Fig. 3. No additional associations were found between ADC and morphology or complex syntax in the HFA group.

3.5. Correlations between language performance and TDC

TD children who used more complex syntax within their spoken narrative had higher TDC measurements in the left SLF ($F(1,15)=11.2$, $p=0.005$, partial $r=0.666$), left pSLF ($F(1,15)=18.6$, $p=0.0007$, partial $r=0.755$) (see Fig. 2). A trend was found between more complex syntax and higher TDC values in the left arcuate fasciculus ($F(1,15)=7.4$, $p=0.016$, partial $r=0.130$), the left ($F(1,15)=7.0$, $p=0.0192$, partial

$r=0.577$) and right UNC ($F(1, 15)=6.07$, $p=0.027$, partial $r=0.550$). A trend was also found between better morphological performance and higher TDC in the right arcuate fasciculus ($F(1, 15)=4.9$, $p=0.043$, partial $r=0.509$).

In the HFA group, children with better morphological performance had lower TDC in the right ILF ($F(1,8)=17.4$, $p=0.004$, partial $r=-0.844$), as shown in Fig. 3. No additional associations were found between TDC and morphology or complex syntax in the HFA group.

3.6. *Examination of additional factors*

Since the subject groups differed in size and in the proportion of females, we conducted the same correlation analyses with a subset of the TD group matched to the number of males and females in the HFA group. In this TD sample, after controlling for age, similar to the full sample, correlations between syntactic complexity and FA in the right arcuate fasciculus, and ADC and TDC within the pSLF and SLF more broadly were found with each association remaining below $p<0.05$.

In order to determine whether or not the associations between morphosyntax and white matter structure seen in children with HFA reflect compromise in general cognitive function not specific to morphosyntax, separate partial correlation analyses controlled for performance IQ, as well as age, in the HFA and TD groups individually. In the HFA group, the three main associations remained significant when performance IQ was accounted for; morphological performance was significantly correlated with FA ($p=0.0007$), ADC ($p=0.001$), and TDC ($p=0.0079$) in the right ILF. Additionally, consistent with the previous trending correlation, morphological performance remained marginally associated with FA in left ILF, $p<0.05$. Further, to confirm that these associations were not attributable to the two subjects with the lowest full scale IQ scores, the data was then analyzed after removal of the two HFA subjects with scores of 70 and 74. In this smaller subset, in concert with the previous analyses, morphological performance was significantly correlated with FA ($p=0.002$), ADC ($p=0.002$), and TDC ($p=0.007$) in the right ILF, while the relationship between FA in the left ILF and morphological performance was no longer significant ($p=0.08$). In the TD group, when covarying for age and performance IQ in the full sample, the results also resembled the original findings. In the left pSLF, complex syntax remained significantly correlated with ADC ($p=0.006$) and TDC ($p=0.003$). Similarly, in the left SLF more broadly, these correspondences were also present without correction for multiple comparisons ($p<0.05$), as was the previous trend between complex syntax and FA in the right arcuate fasciculus.

4. Discussion

The purpose of the current study is to assess white matter microstructure in children with HFA in order to understand how white matter development relates to naturalistic language production abilities. Since relationships between white matter microstructure and spontaneous language are not well understood in any population, an important contribution of this study is also to assess these relationships in typical children. To assess white matter microstructure in children, a probabilistic atlas-based approach identified and delimited language-related fiber tracts and measured three properties of diffusion, FA, ADC, and TDC. In our analysis of correspondences between white matter structure and language in TD children, we found that diffusion in the SLF, a tract commonly implicated in language functions, corresponds with syntactic complexity during the spoken narrative. Relative to TD children, children with HFA had compromised white matter integrity in the right ILF. In the HFA group, correspondences between diffusivity and morphosyntax were not found in the SLF, but were instead found between diffusivity and narrative performance in the left and right ILF.

At the anatomical level, analysis of group differences in white matter fiber diffusivity shows that the autism group had increased ADC and TDC in the ILF relative to controls. The ILF is a major fiber pathway running through the inferior temporal lobe connecting the visual association cortex to the temporal pole. The ILF is a visual association pathway that constitutes the indirect route in the ventral semantic stream and is typically thought to play a non-essential, but supporting role in language production by mediating visual information used during language processing, naming, and semantic access (Mandonnet et al., 2007). The current findings are based on a modest sample size, yet they coincide with previous studies. A recent review of 48 DTI autism studies concluded that individuals with autism tend to have increased ADC and TDC measurements in multiple regions, but are consistently reported to have abnormalities in the temporal lobe (Travers et al., 2012) as well as the ILF more specifically (Groen et al., 2011; Jou, Jackowski et al., 2011; Shukla et al., 2011). Counter to our hypothesis, children with HFA showed differences in ADC and TDC, but not FA. The literature contains mixed reports with regards to the white matter microstructure in autism. While some studies find differences in FA, others have found no group differences in FA, but significant group differences in other measurements such as ADC (Groen et al., 2011). The diffusivity measures yield complimentary information about the microstructural properties of the white matter. By examining these additional measurements we detected changes in white matter properties that may be overlooked by a reliance on FA. Although research on the nature of the anatomical differences between these diffusivity measurements is in its infancy, evidence suggests that FA may more readily detect differences in axon membrane circumference and axonal packing (Concha, Livy, Beaulieu, Wheatley, & Gross, 2010); whereas, TDC may be slightly more sensitive to the degree of myelination (Song et al., 2002). Therefore, given the increased TDC and ADC values in the HFA group, we speculate with caution that in children with HFA, white matter abnormalities in the ILF may be due to compromised axonal myelination.

In the typical profile of development represented by the TD group, examination of the relationship between the structure of a child's white matter and language proficiency revealed an association between diffusion properties in the traditional language-related fiber pathway, the SLF, and performance during the autobiographical narrative. Specifically, TD children with a trend toward lower FA and significantly higher ADC and TDC values within the left SLF used more complex syntax during their spoken narratives. The direction of these correlations are counter-intuitive with regard to the developmental trends typically observed in large-scale studies, where FA generally increases and ADC generally decreases with age from early childhood into adolescence (Brown et al., 2012). However, existing studies looking at the relationship between diffusion and language ability in typical children have reported both positive and negative correlations, often in studies of similar age ranges. Some studies have found that higher FA corresponds to better performance on tasks involving reading and word identification (Deutsch et al., 2005; Nagy et al., 2004) and visual and semantic reasoning (Sahyoun et al., 2010). However, others have found that FA is negatively related to language skills. Frye et al. (2011) found that FA was negatively related to reading skills (Frye et al., 2011) and Dougherty et al. (2007) found that in TD children between 7 and 12 years of age, better phonological scores related to lower FA and higher ADC and TDC values. Furthermore, in accordance with our observation of a trend in which better morphosyntactic production relates to lower FA in the arcuate fasciculus, Yeatman et al. (2011) similarly found that those with lower FA in the arcuate fasciculus have better performance on a standardized test of phonology. Different factors could be at play. The combination of lower FA and higher ADC and TCD in the SLF structure may reflect larger axon fibers or greater elaboration of connections with axonal branching or crossing within a tract. Our findings point to the possibility that children with more complex white matter connections are also better at spontaneously integrating multiple elements of a sentence to produce an autobiographical narrative with fewer morphological errors.

One factor contributing to the inconsistencies seen in the direction of correlations between FA and language reported in previous studies may involve the method used to sample white matter. Diffusivity measures in white matter are often sampled within discrete regions of interest (ROIs) within a tract or across the entirety of a fiber pathway. Since water diffusion properties can vary throughout a tract as its fibers bend or fan out into the cortex, more bending and fanning would be captured by whole tract averaging rather than discrete sampling. Consequently, these two different approaches may reflect and emphasize different aspects of a tract's structural composition. ROI methods that select distinct sites or cross sections within a tract often assess white matter in well-defined and easily identifiable sections of the pathway with high FA. In contrast, an approach of assessing a full tract often incorporates tractography algorithms that can reconstruct portions of a tract with low FA that would otherwise be difficult to distinguish or define such as portions of the tract that fan, comingle with, or cross other fibers. Therefore, measurements of diffusivity properties across a whole tract likely include parts of the tract with more complex fiber patterns and lower FA. Thus, ROI approaches may result in higher FA values and lower ADC and TDC, while methods of averaging FA across an entire tract may result in the inverse pattern of diffusivity measures and affect correlations with behavioral measures. Accordingly, Deutsch et al. (2005) sampled white matter diffusivity in a predetermined ROI and found a positive correlation between FA and language performance. In contrast, Doughtery et al. (2007), Frye et al. (2011), and Yeatman et al. (2011) all sample average diffusivity across a large volume or the entirety of a fiber tract. Strikingly, these studies all show negative correlations between FA and language performance. Yeatman et al. subsequently conducted an ROI analysis as well and found attenuation in the negative correlation, which demonstrates an effect of methodological differences. The current study uses a fully automated probabilistic fiber tract atlas method to delimit tracts and average diffusivity across the full extent of each pathway and similarly finds negative FA language relationships in typical children. One speculative interpretation of the latter findings is that enriched and supportive connections surrounding language cortices increase the matrix of axonal fibers or number of crossing fibers, which attenuate FA values, but supports better online language production.

The HFA group does not show correlations linking language with the SLF; rather, associations are found between diffusivity and morphological performance in the left and right ILF, a language pathway involved less directly in speech production, but which supports visual object representations through the inferior temporal lobe. Our study found that children with HFA who show higher FA and lower ADC and TDC values in the ILF produced more morphologically accurate language. These associations remain evident when analyses accounted for performance IQ. Therefore, these findings do not seem to be attributable to general cognitive functioning. Previous research shows that children with HFA rely less on semantic and abstract information when processing language; instead, they rely more on concrete visual elements (Kamio & Toichi, 2000). Some have suggested that individuals with autism use visual modalities as a compensatory mechanism for their language deficits (Hermelin & O'Connor, 1990; O'Connor & Hermelin, 1987). FMRI studies have further supported these ideas by showing that individuals with autism recruit more cortical areas responsible for visual analysis than TD controls during sentence comprehension (Kana, 2006) and word processing (Gaffrey et al., 2007). Furthermore, in an FMRI study in which children had to reason using either visual or semantic information, children with HFA relied more on visual than semantic information. Additionally, during tasks in which both visual and semantic information was available, children with HFA showed more activation in the ventral temporal cortex, a region supported by the ILF. In contrast, TD children relied more on frontal and temporal language regions for this task (Sahyoun, Belliveau, Soulières, Schwartz, & Mody, 2010). Sahyoun et al. (2010) also examined correspondences between performance on this task and FA. Consistent with the results in the current study, in typical children, FA in the SLF corresponded with performance, but in children with HFA, performance was positively related to FA in the ILF. However, this previous study measured response times during a decision making task, rather than a naturalistic language task. Our data suggest that in children with HFA, tracts involved in mediating visual information are also important for mediating language use during naturalistic speech. These alternative patterns may reflect a compensatory reliance on visual modalities for processing language in real world contexts.

In summary, the current study is the first to examine associations between white matter development and naturalistic language use in either TD children or children with HFA. Although future studies of this nature would benefit from larger samples sizes, the current research highlights a number of novel contributions. We show that between six and 13 years of age, when the structural state of the brain is developing and language abilities are rapidly being refined, microstructural properties within white matter correspond with a child's ability to produce a morphosyntactically proficient autobiographical narrative. In the TD group, language is associated with diffusivity properties in the SLF. This finding suggests that in TD children, fiber structure in pathways that connect Broca's area to temporal and parietal cortical regions are important for productive morphosyntax. Relative to controls, the HFA group shows white matter compromise, as seen by increased ADC and TDC, in the right ILF. Furthermore, children with less white matter compromise also produce fewer morphological errors. Interestingly, children with HFA do not show associations between language and diffusivity in traditional lan-

Table A1
Spoken narrative coding sheet (adapted from Reilly et al. (2004)).

Narrative length	
Total number of propositions	Total ______
Morphological errors	Total ______
a. Pronoun errors (e.g., me and my mom)	______
b. Verb auxiliaries (e.g., it was like make0 me sick)	______
c. Determiners (e.g., my favorite is a geese)	______
d. Noun plurals: (e.g., four cat0)	______
e. Verb tense errors (e.g., I was so scared because it's Ghost Galaxy)	______
f. Verb agreement for number (e.g., he have his horns stickin' up)	______
g. Prepositional errors (e.g., come along in his plan)	______
Complex syntax/syntactic diversity	Total ______
1. Coordinate sentences (and, or, but)	______
2. Subordinate adverbial clauses (when, how, because, so)	______
3. Verb complements (say(that)+S; try+V; keep+V; want+V/S)	______
4. Relative clauses (the boy was calling for the frog that was lost)	______
5. Passives, both full (the dog's bein' chased by bees)	______
"got" passives (he got throwed in the water)	______

guage fibers, but only show correspondences in the ILF. The ILF transmits visual information from the occipital lobe through the ventral temporal lobe. These correspondences suggest that children with HFA who produce better narratives may do so by relying on visuoperceptual elements to support language production. This study highlights a primary association between the integrity of fibers in the SLF and TD children's ability to organize and link components of a story with more complex syntax in the course of typical development. It also suggests a role of increased coherence of ventral visual association fiber structure in a more accurate use of morphology in children with HFA. This initial investigation of higher order language use in a naturalistic task provides a platform for further investigation by showing that correspondences are evident between a child's language production proficiency and neurobiological development of white matter during the normal course of development and in the case of atypical development in autism.

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Appendix A

See Table A1.

Appendix B. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2013.06.012.

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