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White Matter Integrity and Pictorial Reasoning in High-Functioning Children with Autism

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Abstract

The current study investigated the neurobiological role of white matter in visuospatial versus linguistic processing abilities in autism using diffusion tensor imaging. We examined differences in white matter integrity between high-functioning children with autism (HFA) and typically developing controls (CTRL), in relation to the groups' response times (RT) on a pictorial reasoning task under three conditions: visuospatial, V, semantic, S, and V+S, a hybrid condition allowing language use to facilitate visuospatial transformations.

Diffusion-weighted images were collected from HFA and CTRL participants, matched on age and IQ, and significance maps were computed for group differences in fractional anisotropy (FA) and in RT-FA association for each condition.

Typically developing children showed increased FA within frontal white matter and the superior longitudinal fasciculus (SLF). HFA showed increased FA within peripheral white matter, including the ventral temporal lobe. Additionally, RT-FA relationships in the semantic condition (S) implicated white matter near the STG and in the SLF within the temporal and frontal lobes to a greater extent in CTRL. Performance in visuospatial reasoning (V, V+S), in comparison, was related to peripheral parietal and superior precentral white matter in HFA, but to the SLF, callosal, and frontal white matter in CTRL.

Our results appear to support a preferential use of linguistically-mediated pathways in reasoning by typically-developing children, whereas autistic cognition may rely more on visuospatial processing networks.

Keywords

High-functioning autism; pictorial reasoning; language; white matter

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1. Introduction

A characteristic feature of individuals with autism is their difficulty with certain aspects of language, most evident in pragmatics, verbal memory, and in taking advantage of semantic context (Harris et al., 2006; Kamio et al., 2007; Perkins et al., 2006; Rapin and Dunn, 2003; Tager-Flusberg et al., 2008). However, access to semantic information via pictures, as well as picture naming, appear relatively spared in autism (Kamio and Toichi, 2000; Walenski et al., 2008), suggesting that non-social cognitive difficulties in autism may arise primarily when the use of verbal strategies is required (Joseph et al., 2005; Whitehouse et al., 2006). In contrast to linguistic difficulties, visuospatial abilities have been reported to be intact or superior in autism, using tasks such as the Block Design subtest of the Wechsler Intelligence Scale, low-level visual discrimination, or Raven's Progressive Matrices (Caron et al., 2006; Dakin and Frith, 2005; Edgin and Pennington, 2005; de Jonge et al., 2007). We investigated this dichotomy between visuospatial and linguistic processing in autism both behaviorally and with functional neuroimaging (Sahyoun et al., 2009a, 2009b), using a pictorial reasoning task involving three conditions that varied in the extent to which they engaged verbal versus visuospatial processes. We found that high-functioning individuals with autism (HFA) were slowest on the condition that required the use of semantic information, but were fastest when visuospatial strategies were available to solve the problem. Furthermore, the HFA showed decreased activation in frontal lobe language regions mediating the use of verbal strategies in reasoning, while relying more extensively on ventral temporal and parietal regions involved in visuospatial processing. The aim of the present study was to further explore these findings by examining the integrity of white matter pathways involved in visuospatial and linguistic reasoning in high-functioning children with autism and age- and IQ-matched controls, for a more complete understanding of the neurobiology of autistic cognition. Of specific interest was whether white matter differences between the groups support a visuospatial vs. linguistic dichotomy in terms of processing strategy preferences in high functioning autism.

To date, neuroimaging studies of structural-functional impairments in autism, have yielded patterns of underconnectivity in the form of decreased coherence of EEG/MEG oscillations, reduced fMRI correlations across areas, and anatomical differences in brain volume, cortical folding, or white matter integrity (Hughes, 2007; McAlonan et al., 2005). In the present study, we focus on using diffusion tensor imaging (DTI) to examine white matter integrity in children with autism, and its relation to performance on a task of higher level cognition involving visuospatial and linguistic abilities. Diffusion tensor imaging allows one to examine connections in the brain by measuring directional hindrance to the movement of water molecules in white matter. It has become a tool of choice for assessing disorders of connectivity such as multiple sclerosis and autism (Beaulieu, 2002; Ciccarelli et al., 2008; Jones, 2008). Of particular interest is fractional anisotropy (FA), a measure of directional cohesiveness of water movement in the brain, such that increased FA is thought to reflect greater integrity of white matter tracts. DTI studies of autism have found increased fractional anisotropy prior to three years of age, mainly in the corpus callosum (CC) and left frontal cortex (Ben Bashat et al., 2007). However, older children and adults with autism present with decreased white matter integrity (Barnea-Goraly et al., 2004; Keller et al., 2007; Alexander et al., 2007; Sundaram et al., 2008), predominantly in the body and genu of the corpus callosum, as well as in the white matter adjacent to the anterior cingulate and prefrontal cortices, temporo-parietal junction (TPJ), superior temporal sulcus, and optic radiations extending towards the amygdala and fusiform regions (Barnea-Goraly et al., 2004). FA has also been shown to be significantly reduced in the temporal lobe and temporal stem in autism (Lee et al., 2007). These patterns are thought to reflect the social, communicative, and behavioral deficits of the disorder. However, the relationship between patterns of white matter integrity and specific aspects of cognition in autism remains elusive.

Functional connectivity studies, while not pointing to specific white matter tracts, allow one to identify connections in the brain, based on correlated activity of different brain areas under specific task conditions. Reduced functional connectivity has been found in individuals with autism (Courchesne and Pierce, 2005; Horwitz et al., 1988; Kennedy and Courchesne, 2008; McAlonan et al., 2005; Müller et al., 1998) in fronto-temporal, fronto-parietal (Just et al., 2004, 2007) and fronto-striatal (Silk et al., 2006) networks, in tasks of executive function, working memory, as well as mental rotation and sentence comprehension (Kana et al., 2006). However, parieto-occipital connections appear to be intact (Villalobos et al., 2005), with posterior brain areas, including occipital and ventral temporal regions, playing an important role in visuospatial cognition in autism (Ring et al., 1999; Soulières et al., 2009). This pattern has been argued to reflect increased reliance on visual codes and pictorial processing along the ventral stream in autism (Kana et al., 2006), consistent with reports of reduced use of inner speech and verbal codes (Joseph et al., 2005; Koshino et al., 2005; Whitehouse et al., 2006), and our own functional MRI findings (Sahyoun et al., 2009b).

It is important to note that a particular tract with decreased white matter integrity may be involved in a number of functional networks or symptoms; similarly, functional neuroimaging may reveal disrupted functional connections between specific cortical processing nodes, but provides no details about the white matter underlying these connections. Thus, there remain questions regarding the relationship between white matter findings in autism and characteristic behaviors of the disorder (Klingberg et al., 2000; Moseley et al., 2002).

Attempts to relate structural brain abnormalities to cognitive measures in autism have focused largely on volumetric studies or region-of-interest (ROI) approaches. In one study, Hadjikhani et al. (2006) found scores on the Autism Diagnostic Interview–Revised (ADI-R) to correlate with cortical thinning in inferior frontal (IF), parietal, superior temporal, inferior occipital, and supramarginal cortices. In a volumetric study of the superior temporal gyrus (STG), Bigler et al. (2007) demonstrated that although there were no absolute differences between groups in gray, white, or total STG volume, performance on the Clinical Evaluation of Language Fundamentals-3 (CELF-3), a measure of language ability, was correlated with STG volume in typically developing children, but not in the autism group. Using diffusion tractography, Kumar et al. (2009) found that Gilliam Autism Rating Scales (GARS) scores were associated with fiber volume and density in the uncinate and arcuate fasciculi. Alexander et al. (2007) found correlations between FA in the corpus callosum and a measure of performance IQ (PIQ) in autism but not in normal controls; and Conturo et al. (2008) found that a reduction in across-fiber diffusivity in autism within the right hippocampo-fusiform pathway was associated with performance IQ. In summary, only few studies have attempted to relate specific cognitive behaviors in autism with measures of white matter diffusion and observed connectivity patterns.

In the current study, we explicitly tested for differences in white matter anisotropy (FA) between children with HFA and typically developing controls in relationship to their performance on a pictorial reasoning task (Sahyoun et al., 2009a). Despite behavioral variability in children, we expected that the relationship between tract integrity and response times as a function of processing condition (viz., V, S, V+S) would reflect differences in the groups' cognitive preferences, related to the processing bias in autism. We used a tract-based statistical approach to relate differences in white matter integrity of the two groups, to their response times under the three pictorial reasoning conditions (visuospatial (V), semantic (S), and a hybrid condition (V+S), which allows language use to facilitate visuospatial transformations). Our aim was to investigate the potential role of white matter in autistic cognition, motivated by the neurocognitive profile observed in our previous studies.

2. Methods

2.1. Participants

Written informed consent was obtained from all participants in accordance with the Human Subjects Committee at Massachusetts General Hospital. Subjects consisted of 12 typically developing children (CTRL), and 12 high-functioning children with autism (HFA), who were also participants in a functional neuroimaging study (Sahyoun et al, 2009b). However, three of the HFA participants were excluded from the final analysis in the present study due to excessive motion during DTI acquisition. Thus, data from 12 typically developing controls (3 females; mean = 13.3 yrs, s.d. 2.45), and 9 HFA children (2 females; mean = 12.8 yrs, s.d. 1.5) were used here. All subjects were right-handed (except for one control subject), and without any history of frank neurological or psychological damage. They scored in the normal range (80-125) on FSIQ, as measured by the Wechsler Intelligence Scales (WISC-III or WASI, Wechsler, 1991, 1999). The two groups did not differ on age ($p = .6$) or IQ (Verbal IQ, CTRL: 108.4 (s.d. 9.34), HFA: 100.3 (s.d. 14.36), $p = .13$; Performance IQ, CTRL: 104.9 (s.d. 10.06), HFA: 102.4 (s.d. 12.49), $p = .62$; Full-Scale IQ, CTRL: 106.1 (s.d. 8.56), HFA: 101.4 (s.d. 12.48), $p = .32$). Additionally, all subjects had normal hearing, normal or corrected-to-normal vision, with no evidence of color blindness. Children with autism were diagnosed by experienced clinicians and met DSM-IV criteria, based on standardized test instruments (ADI-R, Lord et al., 1994; CARS, Schopler et al., 1988). They also had delayed and/or atypical spoken language development, evident in histories of speech delay, echolalia and pronoun reversals. Subjects were also screened for comorbid neurodevelopmental conditions and medication history based on their medical record. In addition, first-degree relatives of participants in the CTRL group were without neurological or major psychiatric disorders, based on a screening questionnaire. None of these children participated in an earlier behavioral study using the same task (Sahyoun et al., 2009a).

2.2. Stimuli

The experimental paradigm consisted of a pictorial problem solving task. Participants were presented plates in the form of a matrix of picture stimuli (individual items ©2009 Jupiter Images Corporation) related by visuospatial or semantic relationships. The problem plates were presented in the form of a grid of 2×2 to 3×3 images with an empty cell, to be filled using one of 3 choices given below the grid. Subjects were instructed to select the most appropriate item from among three choices to fill a blank in the matrix, as fast and accurately as possible. The task thus consisted of 3 conditions, VISUOSPATIAL (V), SEMANTIC (S), and VISUOSPATIAL + SEMANTIC (V+S), varying in the extent to which linguistic vs. visuospatial skills were needed to solve the problems. Example plates from each condition are shown in Figure 1. In the nonlinguistic, V condition, reasoning was based on visuospatial transformations of geometric patterns similar to those in the standard Test of Nonverbal Intelligence (Brown, 1997). In the S condition, clipart drawings readily identifiable and easy to label were used in problems where selection of the correct answer necessitated the ability to draw thematic or associative relationships between the presented items. In this condition, a successful strategy would require linguistic mediation, that is, extracting meaning from individual clipart pictures, recognizing semantic relationships between them, and inferring a logical solution consistent with these relationships. In the V+S condition, pictorial stimuli, similar to those in the semantic case, were to be manipulated visuospatially, with reasoning operations similar to those in the visuospatial condition. In this case, the semantic information carried by the pictures was not needed, but their verbal labels were available for use, and potentially served a facilitative role. As such, the V+S condition provided an opportunity to examine cognitive strategy preferences for the use of verbal mediation to assist in a visuospatial task.

Plates were matched across the three conditions in terms of manipulations of interest (e.g., analogy, series completion, group formation, or addition/subtraction/intersection), number of transformations or relationships (e.g., part-whole, sequential transformation, identity matching, spatial inclusion.), and number of dimensions manipulated (e.g., shape, orientation, size, semantic category [animals, foods, sports, etc]). This matching was operationalized in keeping with the relational complexity theory of reasoning, whereby task difficulty is measured by the number of relations available and necessary for successful solving (Cho et al., 2007; Halford, 2005). For a more detailed description of the task and relational complexity framework used, see Sahyoun et al. (2009a).

2.3. DTI Protocols

Data were collected on a 3-tesla Siemens Trio scanner using a 12-channel standard head coil, as part of a longer structural and functional imaging session with same subjects (Sahyoun et al., 2009b). Participants were given a choice to sleep/relax or watch a movie during the 10-minute DTI protocol. Diffusion-weighted images were acquired with 60 gradient directions, with a b-value of 700 s/mm², in addition to 10 non-weighted (b = 0 s/mm²) volumes (64 slices, matrix = 256 × 256, voxel size = 2×2×2 mm³, TR = 7980 msec, TE = 84 msec).

2.4. Experimental Procedure

The task consisted of a total of 144 stimulus plates (3 conditions X 48 plates/condition) presented in six 5-minute runs on a PC laptop using Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA.). The stimuli were presented in a pseudo-randomized event-related paradigm, with equiprobable conditions (i.e., 8 plates/condition/run) and correct button assignments (no more than three consecutive repetitions of the same correct button). The order of presentation of the plates was identical for each participant, with no more than three consecutive plates from the same condition. Each plate was presented for a maximum duration of 10s, disappearing upon subject response or after timing out. A randomly varying inter-stimulus interval, made up of a fixation cross ranging in duration from 1500 to 3500 msec was inserted between plates. A longer rest period was inserted after every six plates in order to equate the length of the runs. Participants were instructed to respond as fast and accurately as possible, using a nonmagnetic button box, and to fixate on the cross that appeared in the middle of the screen between plates. The behavioral data were collected during the functional scanning protocol (Sahyoun et al, 2009b) within an extended imaging session which also incorporated the DTI acquisition for this study. Short in-scanner breaks were offered between each run for subject comfort, after which the participant's head position was measured again to ensure correct localization.

2.5. Behavioral Analysis

Accuracy and response times (RT) were computed by the Presentation software and only correct responses were submitted to statistical analysis in SPSS v.15.0 (SPSS Inc., IL, USA). Incorrect responses and trial outliers, including timed-out trials, were discarded from the analysis. Trial outliers were defined as any trial more than 2 standard deviations from the mean response time for that condition, and represented 5.3% of all trials in the comparison group, and 5.7% of all trials in the HFA group (n.s. for group differences, $p = .27$). A Group (CTRL, HFA) × Condition (V, S, V+S) repeated measures MANCOVA was carried out for accuracy and response time separately, with group as a between-subject factor, condition as a within-subject factor, and age as a covariate to control for developmental effects. Post-hoc t-tests included Bonferroni correction for multiple comparisons, and results were considered significant at $p < .05$.

2.6. MRI processing

Diffusion data were processed using the FMRIB Diffusion Toolbox (FDT, <http://www.fmrib.ox.ac.uk/fsl/fdt/index.html>). Voxelwise statistical analysis of the FA data was carried out using Tract-Based Spatial Statistics (TBSS; Smith et al., 2006), part of the FMRIB Software Library (FSL, Smith et al., 2004). Pre-processing involved correction for eddy current distortions by affine registration to a non-diffusion weighted volume, and brain masking using the same volume. Fractional Anisotropy (FA) images were created by fitting a tensor model to the raw diffusion data (Basser et al., 1994) using FDT, and then brain-extracted using FSL's Brain Extraction Tool (BET, Smith, 2002). All subjects' FA data were then aligned to a common standard template for group comparison (MNI152, Montreal Neurological Institute, McGill, USA) using the nonlinear Image Registration Tool Kit (IRTK, Rueckert et al., 1999; www.doc.ic.ac.uk/~dr/software). Next, a mean FA skeleton representing the centers of all tracts was used for group comparisons to minimize partial voluming effects seen with voxel-based methods (Smith et al., 2006). Each subject's maximum local FA was orthogonally projected onto this skeleton for voxelwise cross-subject statistics.

A general linear model was applied using explanatory variables for each group, and demeaned response times for each condition and group. Correction for multiple comparisons was carried out using 5,000 permutations testing, and effects were considered significant for a corrected $p < .05$. Statistical maps were obtained for FA, and response time-FA relationship in each condition for each group, as well as for differences in these relationships between the groups. Results identifying white matter regions where increased FA was associated with decreased RT, will be referred to in this paper as areas of significant (negative) RT-FA correlation. Regions of significant FA difference within the skeleton frame were thickened for visualization purposes and identified with reference to tracts from the Johns Hopkins University probabilistic white matter atlas (Hua et al., 2008; Mori et al., 2005; Wakana et al., 2007). The relevant pathways implicated are shown schematically for reference (Figure 2). For purposes of interpretation, differences in radiate white matter regions were associated with short-distance U-fibers (Herbert et al., 2004), and hence, taken to reflect the function of nearby gray matter, whereas findings within large tracts (i.e., "deeper" within white matter) were assumed to be functionally related to known anatomical end-points of the corresponding major pathways. Thus, a significant correlation between FA and response time was interpreted in terms of the relevance of the pathway involved to the specific reasoning condition. Mean FA values within significant clusters were extracted for each subject for plotting representative relationships between FA and response time in each group, and to illustrate group differences.

3. Results

3.1. Behavioral

All participants were able to perform the task, as shown by their performance on the three conditions (see Table 1). Group (HFA, CTRL) $\times$ Condition (V, S, V+S) MANCOVA, with age as a covariate, did not yield any main effects or significant interactions for accuracy or reaction times.

3.2. Diffusion Tensor Imaging

FA—Group differences in fractional anisotropy between the HFA and CTRL groups were evident in many areas on the skeletonized tracts (Figure 3). These were localized relative to major pathways identified using the Johns Hopkins University probabilistic atlas of white matter. The locations were further refined using adjacent gray matter structures (in parentheses in Tables 2, and 3 and in Figure 4).

Specifically, the typically developing group showed increased FA, compared to HFA, of white matter tracts connecting with the frontal lobe: bilaterally within the forceps minor, in the left inferior fronto-occipital fasciculus (IFOF) adjacent to the middle and inferior frontal gyri, the left superior longitudinal fasciculus (SLF), and the right posterior IFOF. In contrast, the HFA group had increased FA, relative to CTRL, bilaterally within the uncinate fasciculus in the temporal lobe, as well as in the right SLF peripherally near the middle frontal gyrus (MFG). Mean FA for each group within all significant clusters are shown in Table 2.

FA and reaction times—An analysis of the relationship between tract anisotropy and reaction times for each experimental condition revealed distinct white matter networks in HFA and CTRL (Table 3). A direct comparison of the groups yielded differences in RT-FA correlations in specific areas of white matter, implicated in each condition. These areas are highlighted in Figure 4, along with representative plots to illustrate the correlation for each group in these regions. As mentioned earlier (see Methods), the analysis focused on negative RT-FA correlations to allow us to meaningfully relate performance to white matter integrity.

In the V+S condition, shorter response times were associated with increased FA in the left hemisphere uncinate fasciculus near the frontal pole and IFG for CTRL, but in the left hemisphere ILF near the superior division of the lateral occipital cortex, and in white matter near the fusiform cortex for HFA. A comparison between the groups revealed significantly greater correlation in HFA than in CTRL in the left ILF (near the inferior /middle temporal gyri), as well as in the superior parietal lobule, (Figure 4a, Table 3). The CTRL group, however, did not show significantly greater correlation than HFA in this condition in any region.

The V condition, similarly, yielded a number of correlations between FA and response time, most notably within the body of the corpus callosum in CTRL, but within the left hemisphere SLF near the superior parietal lobule in HFA (Table 3). A comparison between the groups revealed a significantly greater correlation in CTRL, compared to HFA, in the body of the corpus callosum and left forceps minor for the V condition. In the right hemisphere cingulum (near the precuneus), however, RT and FA were more strongly correlated in HFA than in CTRL in this condition (Figure 4b).

In the S condition, the HFA group did not show any significant association between reaction time and FA (Table 3). A comparison of the two groups showed that there was a significantly greater correlation between increased FA and decreased response time in CTRL than HFA, within the genu of the corpus callosum, the left hemisphere ILF near the STG, and along the right SLF near the middle temporal gyrus (Figure 4c).

4. Discussion

The current study examined differences in white matter integrity between high-functioning children with autism and age- and IQ-matched typically developing controls in relation to their performance on a pictorial reasoning task with varying degrees of linguistic vs. visuospatial processing demands. We found differences in the pattern of relationships of tract integrity (FA) to reaction times in the different conditions (V, S, V+S) within as well as between groups, supporting our earlier findings in functional neuroimaging with the same participants, of a potential visual processing bias in children with autism at the neurobiological level (Sahyoun et al., 2009b).

White Matter Integrity in HFA versus CTRL

White matter comparisons between the HFA and control groups revealed differences in FA, consistent with models of long-distance disconnection to the frontal lobe and increased local peripheral connectivity in autism. The HFA group showed decreased FA compared to controls

in the left SLF. As the SLF forms the main connection between frontal and parietal regions, we may infer decreased fronto-parietal connectivity in HFA. This is consistent with previous reports of decreased functional correlation in ASD in fronto-parietal networks (Just et al., 2007; Kana et al., 2006; Keller et al., 2007). Similarly, the IFOF showed reduced FA in HFA bilaterally (though anteriorly in the left hemisphere and posteriorly in the right hemisphere), consistent with reports of decreased fronto-occipital and fronto-striatal connectivity in autism (Silk et al., 2006; Villalobos et al., 2005). In addition, there was a decrease in FA bilaterally within the forceps minor near the frontal pole in HFA compared to CTRL. The forceps minor radiates from the genu of the corpus callosum towards the frontal pole, and the anterior part of the corpus callosum has consistently been implicated in autism (Keller et al., 2007; Müller, 2007). Taken together, these differences suggest that connections involving the frontal cortex are affected in autism, consistent with long-distance underconnectivity models and with decreased use of frontal brain areas in higher cognition (Kana et al., 2006; Sahyoun et al., 2009b; Soulières et al., 2009).

Compared to the typically developing children, the HFA group showed increased FA in ventral temporal white matter, possibly supporting greater reliance on visualization strategies associated with this region (Manjaly et al., 2007; Mottron et al., 2006; Sahyoun et al., 2009b). The HFA group also showed increased FA peripherally close to the middle frontal gyrus in the right hemisphere, in keeping with radial overconnectivity within frontal regions and a bias toward short peripheral fibers that has been reported in connectivity studies of autism (Kana et al., 2006; Koshino et al., 2008; Minshew et al., 2007).

White Matter Tracts Underlying Visuospatial and Linguistic Processing in HFA versus CTRL

A comparison of HFA and CTRL yielded differences in RT-FA correlations in specific areas of white matter consistent with inherent differences in processing biases favoring the use of visuospatial strategies over linguistic ones in high-functioning autism. Thus, despite the similar behavioral performance of the two groups, the DTI findings here, together with our earlier functional imaging results with the same participants (Sahyoun et al., 2009b), suggest differences between the groups' underlying neurobiological organization.

In the HFA group, fractional anisotropy correlated with reaction times on the V+S condition within the ILF posteriorly near the lateral occipital cortex, as well as in white matter near the fusiform area. A similar pattern was evident within the left ILF near the inferior /middle temporal gyri, and within white matter near the left superior parietal lobule, consistent with the group's negative RT-FA correlation in the V condition in posterior SLF within the parietal lobe. Both V and V+S conditions, thus, appeared to rely on parietal visuospatial and ventral visual pathways, in support of an apparent preference for visual strategies in posterior brain regions in autism (Sahyoun et al. 2009b). It has been proposed that parieto-occipital and ventral visual stream networks are preserved in autism, possibly underlying increased reliance on visuospatial strategies in autistic cognition (Belmonte and Yurgelun-Todd, 2003; Boddaert and Zilbovicius, 2002; Koshino et al., 2008; Manjaly et al., 2007; Ring et al., 1999).

In the CTRL group, FA correlated with reaction times on the V+S condition within the uncinate fasciculus near the IFG, possibly reflecting the use of frontal language processes. It would therefore appear from the white matter networks involved that typically developing children use verbal mediation strategies in solving the V+ S condition. In addition, CTRL showed a higher correlation than HFA between fractional anisotropy and reaction time in the V condition within the anterior body of the corpus callosum and forceps minor, suggesting an involvement of both hemispheres for solving the V condition in CTRL, especially in the frontal lobe. This finding appears to be consistent with reports of decreased FA within the corpus callosum in autism compared to neurotypical participants (Alexander et al., 2007; Keller et al., 2007).

It appears, then, that visuospatial reasoning in the presence of available verbal mediation, may rely on intact frontal interhemispheric fibers in typically developing children, but on parietal and ventral temporal connections in HFA.

In the Semantic condition (S), the CTRL group showed a negative correlation between FA and response time in the SLF within the frontal lobe; importantly, the HFA group did not show any significant correlation between white matter integrity and performance in this condition, possibly reflecting inadequately developed language pathways, in keeping with their diagnostic early language difficulties. However, this result warrants further investigation with a larger cohort of children followed longitudinally in order to conclusively link it to language processing abilities in autism. Significant differences in RT-FA correlations between the groups in the S condition were found in the corpus callosum, SLF near the middle temporal gyrus, and in the left ILF near the superior temporal gyrus, suggesting an increased use of pathways connecting temporal and frontal language areas, as well as an increased reliance on bilateral processing networks, in typically developing children. The HFA participants, however, showed less involvement of language pathways, structurally and functionally, in keeping with a lack of correlation between STG volume and language ability in autism (Bigler et al., 2007). Additionally, decreased FA has also been found in areas along the SLF in individuals with autism (Lee et al., 2007; Barnea-Goraly et al., 2004; Keller et al., 2007), consistent with decreased functional connectivity between STG and IFG (Groen et al., 2008; Just et al., 2004; Müller et al., 1998). Finally, the difference in RT-FA correlation between HFA and CTRL in the S condition, within the ILF, reveals a pattern of spared vs. impaired white matter connections in autism in keeping with observations in other studies (Koshino et al., 2008; Sahyoun et al., 2009b).

Interestingly, the emerging pattern of increased reliance on parieto-occipital and ventral temporal networks in autism, together with decreased involvement of the SLF and superior temporal tracts, parallels the distinction between the dorsal and ventral pathways of the dual stream model of language processing (Saur et al., 2008; Hickok & Poeppel, 2007). In the V+S condition, typically developing children showed reliance on dorsal networks (near the IFG), whereas children with autism relied on ventral white matter. Similarly, the autistic group showed reduced dorsal stream involvement in solving the S condition. Insofar as the dorsal stream has been found to be activated in covert speech production (Okada & Hickok, 2006), this is in agreement with reduced use of verbalization strategies in autism.

Unlike the findings in our earlier behavioral study with children and adults, (Sahyoun et al., 2009a), the high-functioning children with autism and typically developing controls here did not differ in their performance on the same task. This was not completely surprising given the variability in children's behavioral performance. Regardless, it would be important to replicate these results with a larger number of subjects to reduce the effects of behavioral variance observed in young participants, as well as increase statistical power of the neuroimaging analyses.

In summary, the current study aimed at examining white matter integrity in children with autism, in relation to their performance under visuospatial vs. linguistic processing demands. We found decreased FA in autism within long-reaching white matter tracts, especially those connected to the frontal lobe, as well as within frontal callosal fibers. In contrast, children with HFA showed increased FA in radiate and ventral temporal white matter. Additionally, we found differences in the networks implicated in pictorial reasoning, with CTRL relying more extensively on fronto-temporal language connections and bilateral frontal networks, and HFA on peripheral U-fibers and ventral processing networks. While the results should be viewed with caution due to the small number of participants, the white matter findings in this study

appear to provide neurobiological support for an inherent difference in cognitive processing styles between children with high-functioning autism and neurotypical controls.

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Figure 1.

An example of a stimulus plate for each condition: left: VISUOSPATIAL+SEMANTIC (V +S); middle: VISUOSPATIAL (V), right: SEMANTIC (S). Subjects were asked to fill in the blank in the matrix with one of the three proposed choices. In the V+S condition, visuospatial manipulations are necessary for successful solving, but language mediation is available as a potentially facilitative strategy.

Figure 2. Summary schematic of major white matter pathways found to be differentially implicated in HFA versus CTRL. Pathways were traced to reflect known anatomy in order to serve as a reference in interpreting results.

Figure 3.

Group differences in fractional anisotropy (FA), overlaid on white matter skeletonized template (green). Regions of significance were thickened and color-coded for visualization. The top panel shows regions where typically developing children presented increased FA compared to HFA participants (Purple). The bottom panel shows the opposite contrast, where FA was higher in HFA than in the CTRL group (Orange). Crosshairs indicate the orthogonal slices, in radiological view, chosen to capture a maximum number of regions of significant difference. All statistics were significant at a fully-corrected level of $p < 0.05$.

Figure 4.

Group differences in correlation between fractional anisotropy (FA) and response time on the V+S (a), V (b) and S (c) conditions, overlaid on white matter skeletonized template (green), and thickened and color-coded for visualization. Purple: increased RT-FA correlation in CTRL compared to HFA; Orange: increased RT-FA correlation in HFA compared to CTRL. Inserts show representative plot of FA versus response time within areas of interest in each group, to illustrate the direction of the effect. All statistics were significant at a fully-corrected level of $p < 0.05$.

Table 1

Behavioral performance (means and standard deviations) of typically developing (CTRL) and high-functioning autism (HFA) groups on visuospatial (V), semantics (S) and a combination of visuospatial and semantic (V+S) conditions. Acc: Accuracy (percent correct); RT: Response time (msec).

	CTRL		HFA	
	Mean	StDev	Mean	StDev
V+S Acc	85.6	7.1	83.3	7.6
V Acc	84.9	7.4	81.8	10.8
S Acc	85.1	6.8	78.6	11.8
V+S RT	4085	647	4161	694
V RT	4251	587	4472	748
S RT	4117	759	4367	615

Table 2

Regions of significant difference in fractional anisotropy (FA) between HFA and CTRL. Closest gray matter structures are indicated in parentheses. LH: left hemisphere, RH: right hemisphere, CC: corpus callosum, SLF: superior longitudinal fasciculus, IFOF: inferior fronto-occipital fasciculus, WM: white matter, MFG: middle frontal gyrus.

CTRL>HFA	CTRL		HFA		p
	Mean	StDev	Mean	StDev	
LH forceps minor (frontal pole)	0.531	0.03	0.451	0.03	0.0000
LH forceps minor (frontal pole)	0.414	0.06	0.342	0.03	0.0027
LH forceps minor (frontal pole)	0.600	0.07	0.509	0.03	0.0020
LH SLF (parietal operculum / splenium of CC)	0.571	0.05	0.479	0.03	0.0001
LH SLF (supramarginal gyrus)	0.607	0.05	0.519	0.05	0.0011
LH anterior IFOF (IFG/MFG)	0.529	0.03	0.454	0.03	0.0000
RH forceps minor (frontal pole)	0.614	0.06	0.505	0.06	0.0004
RH posterior IFOF	0.411	0.02	0.348	0.02	0.0000
RH SLF (precentral gyrus)	0.453	0.15	0.270	0.06	0.0022
RH IFOF (superior occipital cortex)	0.555	0.04	0.479	0.05	0.0008
RH cerebellar WM	0.603	0.05	0.490	0.05	0.0001
HFA > CTRL					
RH uncinate fasciculus (temporal pole)	0.255	0.06	0.417	0.12	0.00066
LH uncinate fasciculus (temporal pole)	0.323	0.05	0.424	0.08	0.00240
RH SLF (MFG)	0.410	0.02	0.490	0.04	0.00001

Table 3

Locations of significant correlations between fractional anisotropy (FA) and response time for each condition (V+S, V, S) in each group, as well as of differences in these correlations between the two groups. Localization was based on a white matter probabilistic atlas of main pathways, and further defined by proximity to gray matter cortical regions, shown here in parentheses. LH: left hemisphere; RH: right hemisphere; Bil.: bilateral; WM: white matter; G: gyrus; CC: corpus callosum; IFOF: inferior fronto-occipital fasciculus; SLF: superior longitudinal fasciculus; ILF: inferior longitudinal fasciculus; UF: uncinate fasciculus; CST: cortico-spinal tract; SFG: superior frontal gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; STG: superior temporal gyrus; MTG: middle temporal gyrus; ITG: inferior temporal gyrus.

	CTRL	HFA	CTRL>HFA	HFA>CTRL
Visuospatial +Semantic RT	LH cingulum (parahippocampus)	CC (genu)		CC (genu)
	LH anterior thalamic radiation	LH ILF (superior lateral occipital cortex)		LH superior parietal lobule WM
	LH UF (frontal pole, IFG)	LH UF (frontal orbital cortex)		
	LH cerebellar WM	LH fusiform WM		LH ILF (ITG/MTG)
	RH SLF (precentral G)	LH insula WM		
		RH SLF (MTG, precentral G) RH planum temporale WM		
Visuospatial RT	CC (body)	LH cingulum (parahippocampus)	CC (body)	RH SFG WM
	anterior corona radiata	LH SLF (superior parietal lobule)	LH forceps minor	RH cingulum (precuneus)
		LH IFOF (operculum/IFG)		
Semantic RT	LH SLF (SFG)		CC (genu)	
	Bil. SFG WM		LH ILF (STG)	
	Bil. CST		RH SLF (MTG, precentral G)	
			Bil. SLF (postcentral G)	