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## Neuroimaging of the Functional and Structural Networks Underlying Visuospatial versus Linguistic Reasoning in High-Functioning Autism

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### Abstract

**High-functioning individuals with autism** have been found to favor visuospatial processing in the face of typically poor language abilities. We aimed to examine the neurobiological basis of this difference using functional magnetic resonance imaging and diffusion tensor imaging. We compared 12 children with high functioning autism (HFA) to 12 age- and IQ-matched typically developing controls (CTRL) on a pictorial reasoning paradigm under three conditions: V, requiring visuospatial processing, S, requiring language (i.e. semantic) processing, and V+S, a hybrid condition in which language use could facilitate visuospatial transformations. Activated areas in the brain were chosen as endpoints for probabilistic diffusion tractography to examine tract integrity (FA) within the structural network underlying the activation patterns. The two groups showed similar networks, with linguistic processing activating inferior frontal, superior and middle temporal, ventral visual, and temporo-parietal areas, whereas visuospatial processing activated occipital and inferior parietal cortices. However, HFA appeared to activate occipito-parietal and ventral temporal areas, whereas CTRL relied more on frontal and temporal language regions. The increased reliance on visuospatial abilities in HFA was supported by intact connections between the inferior parietal and the ventral temporal ROIs. In contrast, the inferior frontal region showed reduced connectivity to ventral temporal and middle temporal areas in this group, reflecting impaired activation of frontal language areas in autism. The HFA group's engagement of posterior brain regions along with its weak connections to frontal language areas suggest support for a **reliance on** visual mediation in autism, even in tasks of higher cognition.

### Introduction

Individuals with autism spectrum disorders (ASD) are known to have difficulties with certain aspects of language, most evident in pragmatics, verbal memory, and in taking advantage of

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semantic context cues (Harris et al., 2006; Kamio, Robins, Kelley, Swainson, & Fein, 2007; Perkins, Dobbins, Boucher, Bol, & Bloom, 2006; Rapin & Dunn, 2003; Tager-Flusberg, Lindgren, & Mody, 2008). However, access to semantics via pictures, as well as picture naming, appear less affected in autism, particularly at the higher-functioning end of the spectrum (Kamio & Toichi, 2000; Walenski, Mostofsky, Gidley-Larson, & Ullman, 2008), such that non-social cognitive difficulties in autism may arise primarily when the use of verbal strategies is required (Joseph, Steele, Meyer, & Tager-Flusberg, 2005; Whitehouse, Maybery, & Derkin, 2006). In contrast to linguistic difficulties, visuospatial abilities have been reported as intact or superior in autism, in tasks such as the Block Design subtest of the Wechsler Intelligence Scale, low-level visual discrimination, or Raven's Progressive Matrices (Caron, Mottron, Berthiaume, & Dawson, 2006; Dakin & Frith, 2005; Dawson, Soulières, Gernsbacher, & Mottron, 2007; de Jonge et al., 2007; Edgin & Pennington, 2005). To the extent that high-functioning autism (HFA) has been associated with a cognitive bias towards visuospatial mediation (Sahyoun, Soulières, Belliveau, Mottron, & Mody, 2009; Toichi & Kamio, 2001), there appears to be a dichotomy between visuospatial and linguistic abilities in autism (Behrmann, Thomas, & Humphreys, 2006; Tager-Flusberg & Joseph, 2003). We propose to examine the neurobiological basis of this difference with functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), using a pictorial reasoning task that differentially manipulates visuospatial and linguistic (semantic and/or verbal) demands across three conditions (semantic, visuospatial, and a hybrid visuospatial+semantic condition).

Verbal stimuli are likely to bias brain activation toward language centers; pictures, on the other hand, may be processed and manipulated "as a referent" (i.e. visually) or as a representation of a referent (i.e. semantically) (Schwartz, 1995). Pictorial tasks, thus, provide opportunities to study both visuospatial and linguistic abilities, which have been shown to rely on different but overlapping functional networks (Luo et al., 2003). Visual tasks that entail structural coding and perceptual matching of stimuli have been found to activate bilateral parietal, occipital, posterior temporal, as well as premotor and prefrontal regions (Brambilla et al., 2004; Ecker, Brammer, & Williams, 2008; Fangmeier, Knauff, Ruff, & Sloutsky, 2006; Goel, 2007; Zacks, 2008). In comparison, picture-based semantic coding and conceptual reasoning processes appear to be associated with increased activation within left inferior frontal as well as inferior/ventral temporal and occipital cortices (Ricci et al., 1999; Rossion et al. 2000; Simons, Koutstaal, Prince, Wagner, & Schacter, 2003; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). Interestingly, visuospatial tasks where verbal strategies are facilitative have been shown to activate language areas (Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997); conversely, visuospatial activation has been found in verbal tasks involving visual/spatial relations (Goel, Gold, Kapur, & Houle, 1998; Knauff, Fangmeier, Ruff, & Johnson-Laird, 2003). Thus, reasoning-related activation may be modulated by visuospatial and linguistic task demands, as well as by working memory capacity and differences in individual cognitive profiles (Casasanto, 2003; Goswami, Leavers, Pressley, & Wheelwright, 1998; Richland, Morrison, & Holyoak, 2006; Waltz, Lau, Grewal, & Holyoak, 2000). In a sentence-verification task, Reichle et al. (Reichle, Carpenter, & Just, 2000) found that verbal and visuospatial mediation recruited different cortical regions, such that activation within each network was correlated with the linguistic vs. visuospatial abilities of their typically developing participants. Taken together, the results from these studies point to a functional network of overlapping areas involved in **tasks like** pictorial reasoning, which may be differentially modulated depending on visuospatial vs. linguistic demands of the task or individual cognitive processing differences.

Functional imaging findings in autism have been consistent with a **cognitive style favoring the use of** visuospatial coding strategies, evident in increased reliance on extrastriate and parietal regions (Koshino et al., 2005; Manjaly et al., 2007). This has been argued to reflect a disruption in fronto-striatal and fronto-parietal functional connectivity (Just, Cherkassky,

Keller, Kana, & Minshew, 2007), such that activation in prefrontal but not parieto-striatal regions is decreased in autism (Silk et al., 2006), even when using low-imageability verbal stimuli (Kana, Keller, Cherkassky, Minshew, & Just, 2006). In yet other studies, increased functional synchronization within posterior regions but decreased synchronization within frontal regions has been observed compared with controls (Koshino et al., 2005). Individuals with autism also show atypical processing along the ventral visual stream. In visuospatial tasks such as the Embedded Figures Test, or Raven's Progressive Matrices, these individuals showed increased activation compared with neurotypical control subjects in a ventral occipital and striate network (Belmonte & Yurgelun-Todd, 2003; Soulières et al., **in press**), whereas frontal activation was larger in controls (Ring et al., 1999). Stronger reliance on a ventral occipito-temporal network and a functional imbalance between frontal and posterior regions have, in fact, been argued to play a role in the strong visuospatial abilities of individuals with autism (Boddaert & Zilbovicius, 2002); in turn, abnormal activation within frontal and temporal regions has been related to the linguistic difficulties in this population (Groen, Zwiers, van der Gaag, & Buitelaar, 2008).

In a sentence comprehension task, participants with autism showed decreased activation within the left inferior frontal gyrus but increased activation in the left superior caudal temporal region (Just, Cherkassky, Keller, & Minshew, 2004; Muller et al., 1998), whereas other studies have suggested bilateral hypoperfusion or underconnectivity of the temporal lobe in autism (Boddaert & Zilbovicius, 2002; Castelli, Frith, Happe, & Frith, 2002). In a separate study, the inferior frontal gyrus showed reduced activation differences between semantic and perceptual (letter case judgement) processing of words in autism compared with controls (Harris et al., 2006). In summary, individuals with autism present a neurocognitive profile of increased reliance on visuospatial skills and ventral stream processing, and decreased use of language functions within frontal areas. In fact, these patterns of activation are consistent with a recent model of altered brain growth dynamics in autism (Courchesne et al., 2007; Just et al., 2004; Kana et al., 2006; Kennedy and Courchesne, 2008; Schmitz, Daly, & Murphy, 2007).

Mechanistically, early brain overgrowth followed by decreased growth rate in autism is thought to result in overconnectivity within primary areas, whereas white matter tracts involving regions of slow maturation, such as the frontal lobe, would be underdeveloped (Courchesne & Pierce, 2005). In keeping with this general picture of reduced long-distance connections and local overconnectivity, morphometric MRI studies have found relative increases in gray matter and decreases in white matter volume in autism compared with control participants (Bonilha et al., 2008; Brambilla et al., 2003; Eigsti & Shapiro, 2003; Herbert et al., 2004), particularly evident in the corpus callosum (Alexander et al., 2007; Egaas, Courchesne, & Saitoh, 1995; Vidal et al., 2006; Waiter et al., 2005). Other autism studies have used functional connectivity measures to infer anterior-posterior underconnectivity between the occipital or parietal cortices and frontal regions, and not between occipital and parietal areas (Just et al., 2004, 2007; Kana et al., 2006; Villalobos, Mizuno, Dahl, Kemmotsu, & Muller, 2005). Diffusion tensor imaging (DTI), which allows one to assess white matter integrity *in vivo*, has helped provide additional insight into structural connectivity patterns in autism. These studies have found lower fractional anisotropy (FA) in individuals with autism, compared with controls, in the anterior cingulate, ventromedial and subgenual prefrontal areas, temporoparietal junction, corpus callosum, and in the STG white matter and temporal stem (Barnea-Goraly et al., 2004; Lee et al., 2007). Contrary to expectations, Sundaram and colleagues (2008) found decreased tract integrity in both long-range fibers of the frontal lobe and in short-range fibers throughout the autistic brain. The mixed results reflect the need for carefully designed structure-function relationship studies to better understand the role of connectivity in autism.

In the present study, we used a combination of fMRI and DTI to examine the neurobiological basis of the difference in visuospatial and linguistic processing in autistic cognition. We used

a pictorial problem-solving paradigm involving three conditions designed to vary in the extent to which linguistic vs. visuospatial mediation may be necessary **or available** to solve each problem. This task, used previously in a behavioral study, established that individuals with HFA were less efficient in a reasoning condition that involved linguistic (i.e. semantic) rather than visuospatial abilities, whereas control and Asperger syndrome participants showed similar cognitive profiles and benefited from the availability of both visuospatial and linguistic processing routes (Sahyoun et al., 2009). Here we used fMRI to investigate the **neural** signature of this difference between the groups in **cognitive** strategies. We used DTI to examine the white matter integrity of a priori pathways of interest connecting functionally implicated nodes to understand the structural basis of potentially impaired brain mechanisms. Based on our previous findings, we hypothesized that a reliance on visuospatial processing in high-functioning children with autism would be evident in increased activation of posterior occipito-parietal and ventral temporal regions, supported by greater fractional anisotropy in the white matter connections between these regions. Conversely, we predicted that the typically developing group would rely more on frontal language nodes in reasoning, supported by greater FA, compared with HFA, in pathways involving these regions.

## Materials and Methods

### Participants

Participants consisted of 12 typically developing children (CTRL; 3 females; 10-17 years old; mean = 13.3, std dev = 2.45), and 12 high-functioning children with autism (HFA; 2 females; 11-18 years old; mean = 13.3, std dev = 2.07). Participants had no history of frank neurological or psychological damage, and 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 ( $p = .94$ ) or IQ ( Full-Scale IQ,  $p = .24$ , Performance IQ,  $p = .48$ ), despite a trend for lower Verbal IQ in HFA ( $p = .08$ ) (Table 1) and were matched for handedness (Annett, 1970). All subjects had normal hearing and 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, Rutter & Le Couteur, 1994; CARS, Schopler, Reichler & Renner, 1988). They also had delayed and/or atypical spoken language development, evident in histories of speech delay, echolalia and pronoun reversals. None of the children had previously participated in our earlier behavioral study using the same task (Sahyoun et al., 2009). 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.

### Stimuli

The experimental paradigm consisted of a pictorial problem solving task (Sahyoun et al., 2009). Participants were presented plates in the form of a matrix of items (individual items ©2009 Jupiter Images Corporation) related by visuospatial or semantic relationships. 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 layout of the problem “plates” was 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. The experiment consisted of 3 conditions, VISUOSPATIAL (V), SEMANTIC (S), and VISUOSPATIAL + SEMANTIC (V+S), varying in the extent to which linguistic skills were needed **or available** to solve the plates. 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 **semantic** 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 (V) condition. The semantic information carried by the stimuli was not needed, but their labels were accessible for verbal mediation, and potentially served a facilitative role. As such, the V+S condition provided an opportunity to examine the use of different cognitive strategies drawing on linguistic or visuospatial mediation to assist in a visuospatial task. Example plates from each condition are shown in Figure 1A.

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 etc.), and number of dimensions manipulated (e.g. shape, orientation, size, semantic category [animals, foods, sports...]). 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, Holyoak, & Cannon, 2007; Halford, 2005). For a more detailed description of the relational complexity framework used, see Sahyoun et al. (2009).

### MRI Protocols

Data were acquired on a 3-tesla Siemens Trio scanner using a 12-channel standard head coil. High-resolution (sagittal) structural MRI scans were obtained using a T1-weighted MPRAGE protocol (176 slices, matrix =  $256 \times 256$ , voxel size =  $1.3 \times 1 \times 1.3 \text{mm}^3$ , TR = 2530 ms, TE = 3.48ms, Flip angle =  $7^\circ$ ). Functional scans were divided into six runs of 5 minutes to allow for short in-scanner breaks (EPI sequence, matrix =  $64 \times 64$ , voxel size =  $3.1 \times 3.1 \times 5 \text{mm}^3$ , TR = 2760 ms, TE = 28 ms, Flip Angle =  $90^\circ$ , 150 volumes). Diffusion-weighted images were acquired with 60 gradient directions, with a *b*-value of  $700 \text{s/mm}^2$ , in addition to 10 non-weighted (*b* =  $0 \text{s/mm}^2$ ) volumes (64 slices, matrix =  $256 \times 256$ , voxel size =  $2 \times 2 \times 2 \text{mm}^3$ , TR = 7980ms, TE = 84ms).

### Experimental Procedure

All participants were given supervised practice on the task outside of the MRI scanner, using 12-24 additional plates (not used during functional MRI scanning), to ensure adequate performance and understanding of the procedure. During scanner acquisition, stimuli were projected onto a screen at the back of the scanner bore, which participants could see using a mirror mounted on the head coil. A total of 144 plates (3 conditions  $\times$  48 plates/condition) were presented in six 5-minute runs on a PC laptop running the Presentation software (Neurobehavioral Systems, Inc., CA, USA), synchronized to scanner acquisition. Within each run, the plates were presented using a pseudo-randomized event-related paradigm, with equiprobable conditions (i.e., 8 plates/condition) 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, and no more than three plates of the same condition were shown consecutively. The paradigm was self-paced, with each plate presentation lasting between 1 and 10s, as the plate disappeared upon subject response or timed out after 10 seconds. A fixation cross was shown between plates, with a randomly varied inter-stimulus interval ranging from 1500 to 3500ms. A longer rest period was inserted after every six plates in order to equate the length of each run. Figure 1B illustrates a typical sequence of stimulus presentation. Participants were instructed to respond using a nonmagnetic button box as fast and accurately as possible, and to fixate on the cross that appeared in the middle of the screen

between plates. Short in-scanner breaks were offered between each run for comfort, after which head position was measured again to ensure correct localization.

### Behavioral Analysis

Accuracy and response times (RT) were computed by the Presentation software and 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 analysis. Trial outliers were defined as any trial more than 2 standard deviations from the mean response time **for each individual** for that condition, and represented 5.27% of all trials in the comparison group, and 5.73% of all trials in the HFA group (n.s. for group differences,  $p = 0.27$ ). Repeated measures 2 (CTRL, HFA)  $\times$  3 (V, S, V+S) ANOVAs were carried out for accuracy and RT separately, with group as between-subject factor, condition as 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  $p < 0.05$ .

### Functional MRI processing

Functional BOLD analysis and structural processing were undertaken using FS-FAST and Freesurfer tools, respectively (<https://surfer.nmr.mgh.harvard.edu>). Structural processing, surface reconstruction, and cortical parcellation were carried out to generate inflated surface brain maps, registered to an average template via spherical morphing (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999). Automated segmentation of structural scans generated surface-based labels, including cortical ribbons for each hemisphere (Fischl & Dale, 2000; Fischl et al., 2002, 2004).

EPI pre-processing involved motion correction (using AFNI, [afni.nimh.nih.gov](http://afni.nimh.nih.gov)), smoothing with a 5mm FWHM Gaussian kernel, intensity normalization (to correct for intensity changes and temporal drifts across runs), and brain mask creation (using FSL's BET, [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). Signal intensity was averaged for each condition across runs, excluding incorrect behavioral responses. A whitening filter was applied to account for autocorrelation in the data for each participant (Burock & Dale, 2000). Voxelwise general linear modeling was performed both assuming a hemodynamic response gamma function (onset time 2.25, dispersion 1.25) and using a finite impulse response model for region-of-interest timecourse analysis. Trials were modeled between stimulus onsets and correct button presses for each condition. Incorrect and missed trials were also modeled as a separate explanatory variable. Although no subject presented excessive motion during functional acquisition, motion correction parameters were used as external regressors to model out the effects of head motion.

The mean and variance volumes of each subject were resampled in surface space and group statistics were computed using a random effects model, correcting for multiple comparisons using simulation testing (10000 permutations). Both within-group contrasts between conditions and between-group contrasts for each condition were generated. Within-group contrasts were of particular interest as the task was specifically designed to capture response differences to the varying conditions as a function of the availability of linguistic and visuospatial mediation, especially in the V+S condition. In fact, our earlier behavioral study (Sahyoun et al., 2009) revealed differences in cognitive profiles across conditions for the groups, whereas there were no between-group differences within each condition. In addition, within-group contrasts would help shed light on the loci of differences in activation between groups within each condition. Statistical results were displayed on the average inflated cortical surface ( $p < 0.05$ , corrected). It should be noted that in pediatric populations, and in clinically heterogeneous disorders like autism in particular, high variability in both brain anatomy and activation patterns may result in non-significant group differences when using modest sample

sizes, even when true effects exist. Our stringent analyses will, therefore, likely reflect only the most reliable differences between the groups.

### DTI Analysis

Diffusion data were processed using the FMRIB Diffusion Toolbox (FDT, <http://www.fmrib.ox.ac.uk/fsl/fdt/index.html>). Pre-processing involved correction for eddy current distortions by affine registration to a non-diffusion weighted volume, and brain masking using the same volume. Diffusion tensors were fitted at each voxel (Basser, Mattiello, & LeBihan, 1994) and fractional anisotropy (FA) and mean diffusivity (MD) maps were created. A probability distribution function was calculated using Markov Chain Monte-Carlo sampling, to support probabilistic tractography (Behrens et al., 2003a; 2003b, Smith et al., 2004). In order to directly examine structure-function relationships in our subjects, regions of interest (ROI) based on functional activation in our reasoning task were used in the tractography algorithm as endpoints of pathways potentially implicated in autism. Findings of reduced activation in the inferior frontal language region (Harris et al., 2006), decreased fronto-parietal functional connectivity (Just et al., 2007; Kana et al., 2006; Koshino et al., 2006), and lower FA in the temporal stem in autism (Lee et al., 2007), motivated the investigation of specific pathways connecting the frontal (inferior frontal area, IF) to posterior (superior/middle temporal areas, STS/MTG, and inferior parietal sulcus, IPS), and ventral temporal (fusiform/lingual area, FG) regions of interest. These ROIs (IF, STS/MTG, IPS, and FG) were defined and manually drawn on an omnibus map of functional activation of all three condition contrasts across all subjects, on the template inflated surface (Kuperberg et al., 2000, 2003) (see Figure 2A). They were then spherically morphed to each participant's structural scan, by aligning with individual cortical folding patterns (Fischl et al., 1999) and projected 2.5mm from the grey-white surface into the underlying white matter. This projection maximized our ability to perform tractography between endpoints that may otherwise lie in regions of high uncertainty within grey matter. Finally, the ROIs were resampled to native DTI space by linear registration (FLIRT) to serve as seed and target masks for tractography. Given the impaired function of frontal language regions in autism (Groen et al., 2008), we hypothesized lower FA in the pathways between frontal and posterior brain areas. However, in light of evidence for intact access to pictorial semantics (Kamio & Toichi, 2000) and increased reliance on the ventral temporal and parietal cortices in higher cognition in autism (Belmonte & Yurgelun-Todd, 2003; Boddaert & Zilbovicius, 2002; Just et al., 2007; Manjaly et al., 2007), we hypothesized that FG-STS/MTG and FG-IPS pathways would be intact in the HFA group. The tractography algorithm used drew 5000 samples from each seed voxel on the principal diffusion directions, which stopped upon encountering a target voxel, and progressed with a step length of 0.5mm, a curvature threshold of 0.01, and a maximum of 2000 steps. Only samples reaching the target region without looping on themselves were kept in the corresponding pathway map. For each pair of ROIs used, tracking was performed in both directions, and the probabilistic union of the pathways was calculated. The values at each voxel, representing the number of samples passing through it, were converted to percentages of the maximum number of samples passing through any voxel, and thresholded at 0.2, to exclude voxels with low probability of lying on the pathway of interest (Ciccarelli et al., 2006). These thresholded pathways were binarized and used as masks to extract mean FA along the path for each subject. Independent samples t-tests ( $p < 0.05$ ) were conducted between groups using these extracted values, to evaluate differences in white matter integrity along the hypothesized pathways involved in pictorial reasoning.

## Results

### Behavioral

All participants were able to perform the task as shown by their performance on the three conditions (see Table 2). Group (HFA, CTRL)  $\times$  Condition (V, S, V+S) ANOVA with both accuracy and response times, using age as a covariate, did not yield any main effects (Accuracy: group  $F = 1.7, p = .205$ , condition  $F = .7, p = .5$ ; RT: group  $F = .855, p = .366$ , condition  $F = .11, p = .89$ ), or significant interactions (Accuracy:  $F = .72, p = .49$ ; RT:  $F = .346, p = .7$ ).

### Functional MRI

Both groups revealed a similar pattern of bilateral activation on the pictorial reasoning task, regardless of condition (Figure 2B). The network comprised the extrastriate cortex, intraparietal sulcus (IPS), ventral temporal cortex (including the fusiform and lingual cortices, FG), superior precentral and inferior frontal (IF) areas, as well as the insula and postcentral gyrus. In addition, there were areas of decreased activation compared to the fixation condition within the temporo-parietal junction (TPJ), supramarginal gyrus, cingulate cortex, superior frontal sulcus, and medial frontal cortex, as well as in the left hemisphere superior temporal sulcus (STS) and right hemisphere middle temporal gyrus (MTG) in both groups. It is likely that task-related deactivation in these regions may be inversely related to their recruitment (Raichle, 1998), and may therefore be reflective of differential involvement of the regions in the three task conditions.

Direct group contrasts, however, yielded a number of activation differences between the groups (Figure 3). CTRL relative to HFA showed increased activation in all three conditions within the left hemisphere in MTG, lingual gyrus and precentral sulcus; HFA, on the other hand, showed increased activation in the lateral occipito-temporal sulcus, pre- and post-central sulcus, and in the posterior segment of the lateral fissure in the left hemisphere, regardless of condition. There were also differences between the groups as a function of condition (Table 3). Of note, CTRL activated left STS/MTG and RH supramarginal gyrus, most noticeable in the S condition. They also showed greater activation than HFA in the angular gyrus, STS and IF in the right hemisphere for V+S. The HFA group, in comparison, showed greater activation than controls within the left hemisphere IPS and right hemisphere STS/MTG, most noticeably in the V+S condition.

Finally, within-group comparisons between the three conditions revealed different patterns across the two groups in response to the manipulation of visuospatial and linguistic (semantic or verbal) demands. These may be seen in Figure 4 and are summarized in Table 3.

A few of these differences were particularly worth noting: there was significantly greater activation in S and V+S than in V in both groups in ventral temporal areas, bilaterally. Additionally, in both groups, activation in S and V+S was greater than in V in the left hemisphere (LH) occipito-temporal area, whereas this difference was much smaller in S vs. V+S. Although both groups showed greater activation in S compared to either V or V+S within the LH STS, the location of this activation appeared to extend more anteriorly (close to the temporal pole) in CTRL than HFA. In addition, the right anterior STS showed greater activation in S compared to V or V+S in CTRL but not in HFA. In the typically developing group, the left inferior frontal area was more strongly activated for S and V+S compared to the V condition. These differences were noticeably reduced in the HFA group. Similarly, the right hemisphere IF area was also activated in the CTRL group, but absent in HFA in V+S compared to V. Both groups, however, showed greater activation in bilateral IPS in V and V+S compared to S.

## Diffusion tractography

We examined mean fractional anisotropy (FA) in probabilistic pathways defined a priori, between functionally defined ROIs (Figure 2A). Three HFA participants were excluded from the analysis due to excessive motion during DTI acquisition. In order to illustrate the tractography results, the pathway distributions between the left IPS and left IF of all subjects were resampled to a common template, binarized, and added for each group. The resulting group maps therefore represented the overlap in location of the IPS-IF pathway for each group, confirming the consistency of the tracking algorithm across subjects (Rilling et al., 2008). Group maps were thresholded to only keep voxels through which at least three subjects had pathways to confirm that all subjects produced similar pathway distributions (Figure 5A).

The pathways investigated and their mean FA, calculated after thresholding out low probability voxels, are listed in Table 4. The results revealed pathways where the HFA group showed lower FA compared with the CTRL group, whereas no pathway showed greater FA in HFA (Figure 5B). The HFA group had lower FA in pathways between the IF and FG in the left hemisphere ( $p < 0.02$ ), as well as in the right hemisphere (trend,  $p = 0.07$ ). In the right hemisphere, the pathway between the IF and MTG also showed reduced FA in HFA ( $p < 0.02$ ), but not the pathway between IF and STS in the left hemisphere. We also found no differences between the groups in pathways connecting the IF and IPS regions in either hemisphere. Finally, there were no group differences in FA between FG and either IPS or STS/MTG, in both left and right hemispheres..

## Discussion

The current study aimed at examining the neurocognitive basis of visuospatial vs. linguistic processing differences between high-functioning children with autism and typically developing controls. Our findings revealed that despite similar behavioral performances of the two groups, the underlying structural and functional neuroanatomy were significantly different between HFA and CTRL.

The two groups did not differ in accuracy or response times on the task, supporting the view that HFA have intact visuospatial processing skills (Dakin & Frith, 2005; Edgin & Pennington, 2005), and intact pictorial access to semantics (Kamio & Toichi, 2000). Although non-significant, we noted a qualitatively lower accuracy of the HFA group in the S than in the V and V+S conditions, consistent with a trend for a difference in verbal IQ between the groups. As children with autism typically do worse under language processing conditions (Rapin & Dunn, 2005; Sahyoun et al, 2009; Tager-Flusberg, Lindgren & Mody, 2008), this may help in the interpretation of some of the brain activation differences found in our HFA participants.

We found that regardless of the differing linguistic versus visuospatial demands of the task, pictorial reasoning engaged a similar, largely overlapping network of cortical regions in both groups. This core network comprised of areas related to language processing (TPJ, supramarginal gyrus, STS, MTG, IF), visuospatial manipulations (IPS, superior precentral sulcus), and visual processing and picture identification (occipital cortex, ventral temporal stream). Regions known to be involved in visuospatial processing were more active during V and V+S than in S (Ecker et al., 2008; Klingberg, 2006; Zacks, 2008), and language-processing areas were more active and often, more anterior (suggesting more conceptual coding) (Gold & Buckner, 2002) in S and V+S than in V.

The two groups, however, clearly differed in their activation profiles. Whereas CTRL appeared to engage fronto-temporal areas when verbal mediation was available and/or necessary, as in the V+S and S conditions, HFA relied more on posterior, occipito-temporal and ventral temporal, brain areas, evident in the within-group fMRI comparisons. Compared to the control

group, HFA's poorer frontal activation in S and V+S than in V (Fig. 4), and greater activation of IPS, especially in V+S (Fig 3), together with its reduced structural connectivity between frontal and ventral temporal areas (Fig 5), suggest an impaired frontal language system and greater reliance on visual mediation via inferior parietal and ventral temporal areas to do the task. This could account for the absence of significant difference between the groups in behavioral performance, reflecting an intact visually-mediated access to semantics in a pictorial reasoning task like the one used in the present study.

That both CTRL and HFA participants showed greater activation of the occipito-temporal and ventral temporal areas in the S and V+S conditions than in V, implies more of a conceptual than structural coding of pictorial stimuli by both groups; however, the CTRL group also showed greater activation in language areas, STS and IF, for S and V+S than V. A direct contrast between CTRL and HFA in the S condition revealed greater activation in CTRL in the left STS/MTG and right supramarginal gyrus, as well as in right angular gyrus in the V+S condition in keeping with their tendency to use semantic and visuospatial information, when both processing routes are available (Sahyoun et al., 2009). These results also suggest that control subjects may engage an extended network of language areas, including right hemisphere homologues, during tasks that involve linguistic (**semantic and/or verbal**) mediation (Harris et al., 2006).

In striking contrast to the increased activation in the CTRL group within the language network in S and V+S, the HFA group showed increased activation in these conditions in left IPS and occipital cortex. This pattern of increased reliance on posterior processing areas has been associated with "structural" coding of information (Kellenbach, Hovius, & Patterson, 2005) and **with a cognitive use of** visual strategies in problem-solving in autism (Manjaly et al., 2007; Soulières et al., **in press**). The HFA group also showed increased activation in all three conditions in the left hemisphere lateral occipito-temporal sulcus, and pre- and post-central sulci, which have been implicated in visuospatial transformations (Ecker et al., 2008); in contrast, the CTRL group showed greater activation in all conditions in left hemisphere MTG and lingual gyrus which may reflect greater processing of semantic attributes of the stimuli in CTRL. The superior precentral sulcus was also consistently activated in this group. Given its location in what might be functionally defined as the frontal eye field, the activation in the superior precentral sulcus warrants a closer investigation of eye movements and potential differences in visual search strategies between HFA and CTRL.

The results of our tractography analysis provide a window into the structural basis for the activation differences in pictorial reasoning between HFA and CTRL. Connections between the FG and IPS and FG and STS/MTG were intact in both hemispheres in the HFA group (Figure 5, Table 4), consistent with accounts of a reliance on visuospatial processing abilities and intact pictorial access to language in autism. These results also highlight an important mediating role for the FG in higher-level cognition in autism. The HFA group, however, showed reduced FA compared to CTRL in the IF-FG pathways in both hemispheres (Koshino et al., 2008; Lee et al., 2007), consistent with lower functional activation of the IF in semantic processing observed in this group, relative to CTRL, and in keeping with accounts of decreased use of covert speech strategies in autism (Kana et al., 2006). In addition, HFA participants showed lower FA compared to CTRL in the right hemisphere IF-MTG pathway, consistent with our finding that CTRL but not HFA may engage the right frontal areas as part on an extended language network. Surprisingly, we did not find reduced fronto-parietal connectivity, or left hemisphere IF-STS underconnectivity, seen in some studies (Just et al., 2004; Kennedy & Courchesne, 2008). These studies used functional correlations between activated areas, and assess connectivity using a different (i.e., indirect) approach (Hughes, 2007), making it difficult to compare results across the studies. Insofar as functional underconnectivity may be associated with altered grey matter, white matter, or both, with little information about potential

cytoarchitectural underpinnings (Kleinmans et al., 2008), recent methods, including DTI, could allow one to examine the potential correspondence between functional and anatomical connectivity (Just et al., 2006). It is worth noting that the present tractography approach averages FA over large pathways, such that some localized differences in white matter integrity may not be detected, as these may lie primarily within the tails of the FA distributions (Ciccarelli et al., 2006). Further developments in quantitative tractography, such as point-by-point comparisons along pathways (Salat et al., 2008), may provide better sensitivity to localized differences and help reconcile differences between functional and structural connectivity findings.

In conclusion, the neuroimaging results from the present study on pictorial reasoning suggest that individuals with autism may favor the use of visual mediation strategies in tasks of higher cognition. The HFA recruited posterior brain regions particularly the occipital and ventral temporal areas and the intraparietal sulcus, related to visuospatial processing. The typically developing group, in contrast, relied more on a fronto-temporal language network for reasoning. This pattern was consistent with differences in white matter integrity: HFA showed intact connections between ventral temporal areas and posterior language and visuospatial processing regions, but reduced connectivity with inferior frontal areas.

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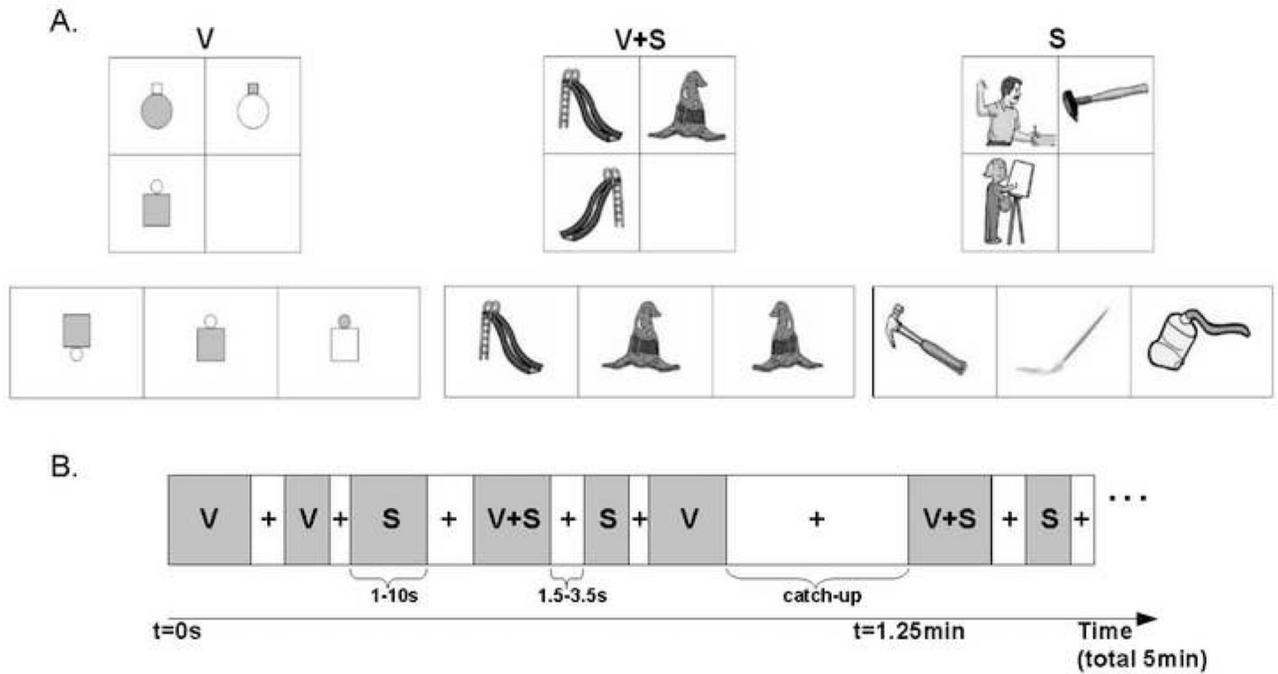
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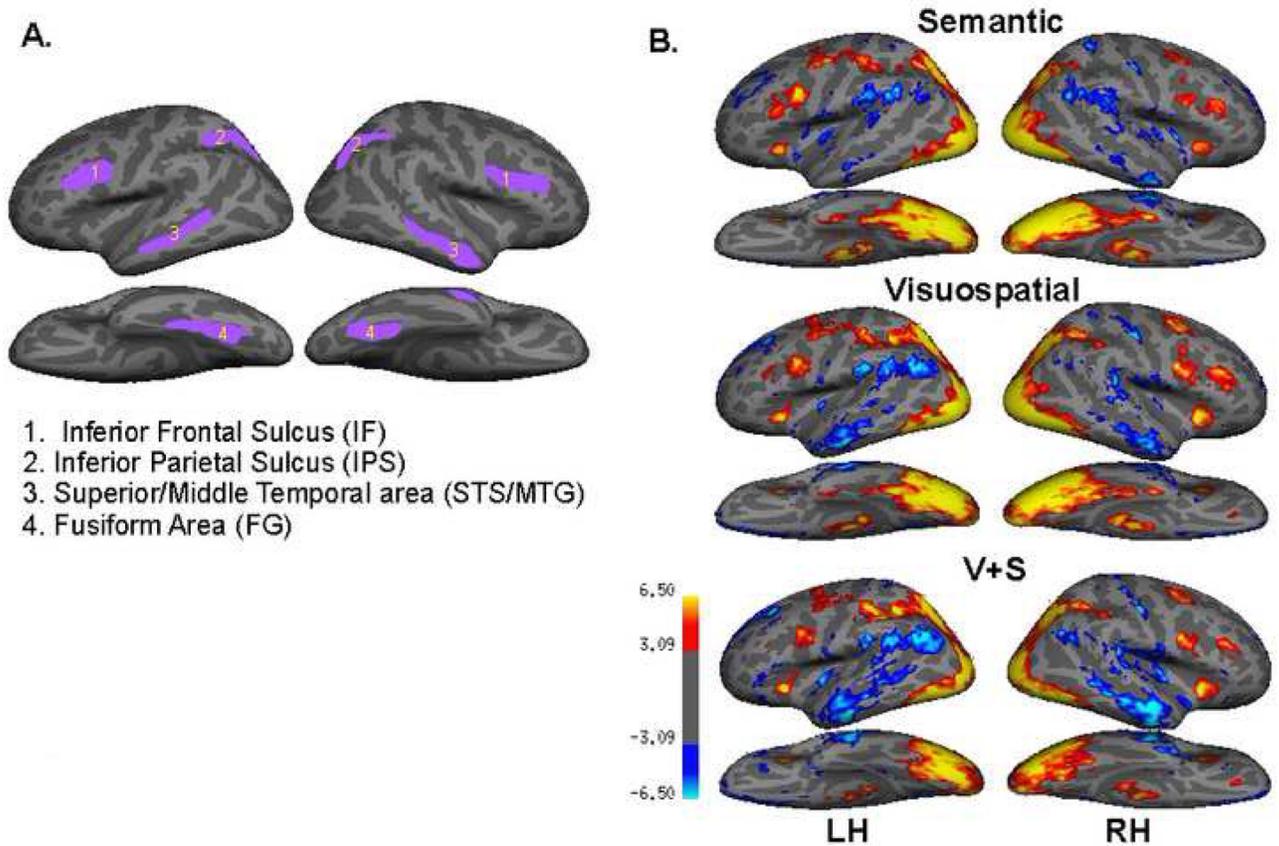
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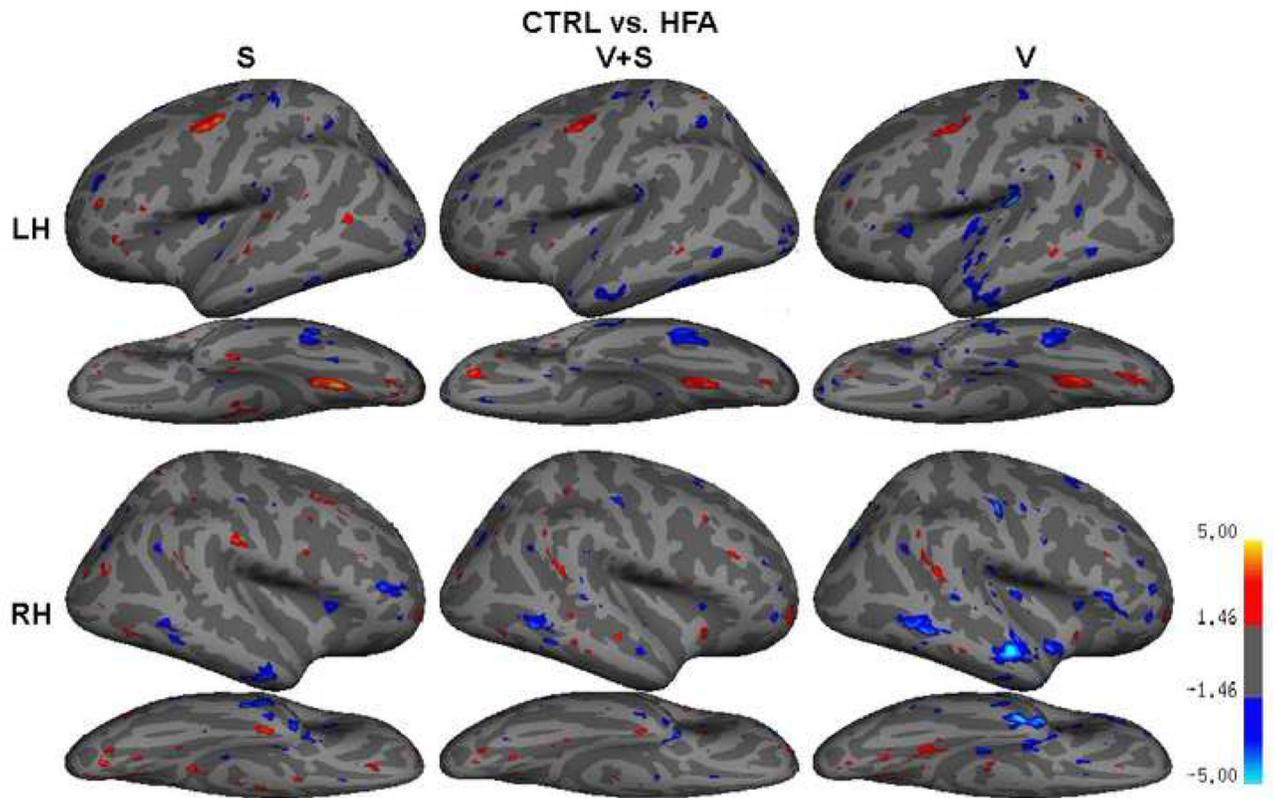
**Figure 1.**

A. Example Stimuli for each condition: left: VISUOSPATIAL (V); middle: VISUOSPATIAL + SEMANTIC (V+S), 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 potential facilitating strategy. B. Schematic of a typical stimulus presentation sequence for the beginning of a run. The catch-up times (4 per run) represent fixation periods of varying durations, adjusted for equating the total duration of each run to 5 minutes.



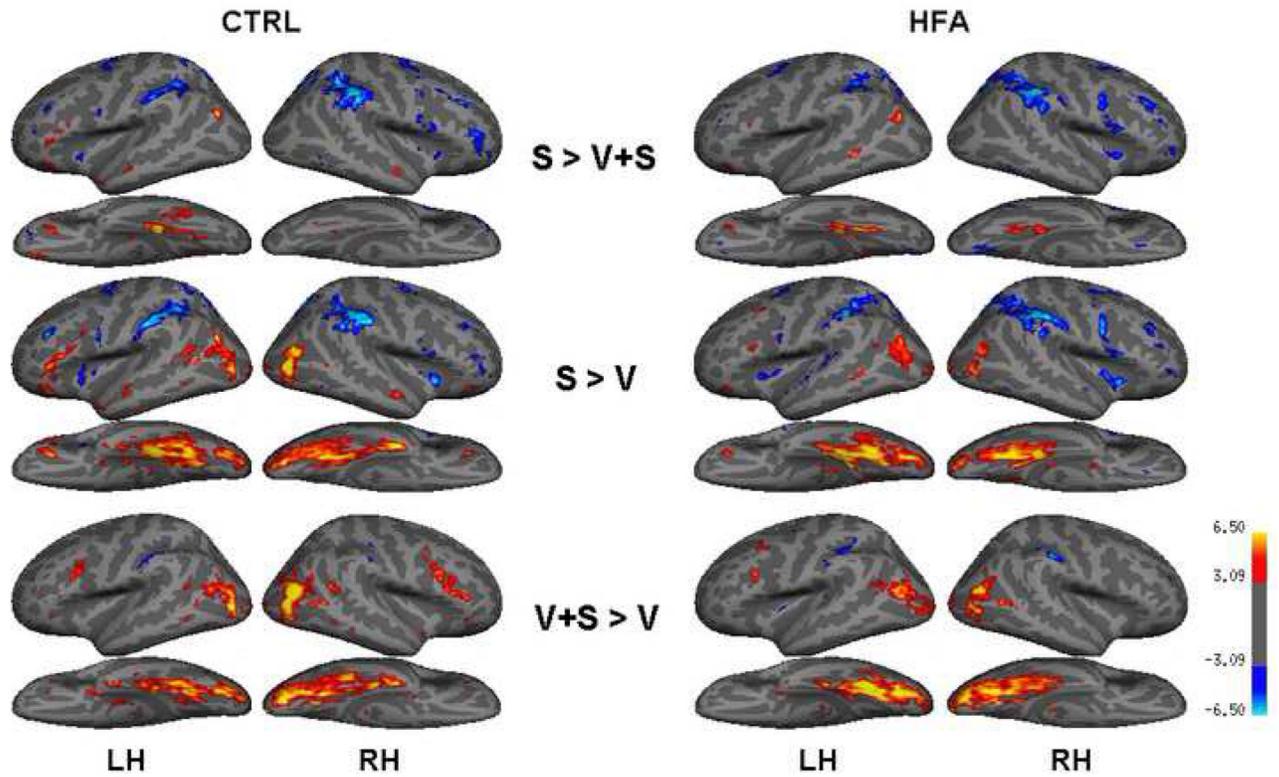
**Figure 2.**

A. Regions of interest obtained from omnibus activation maps, used in tractography analysis. LH: left hemisphere; RH: right hemisphere. B. Statistical z-maps of fMRI activation for each condition vs. fixation (shown here for the CTRL group). Lateral (top) and ventral (bottom) views are shown for each condition. The maps are displayed on an inflated cortical surface template, where sulci and gyri are represented in dark and light gray, respectively.



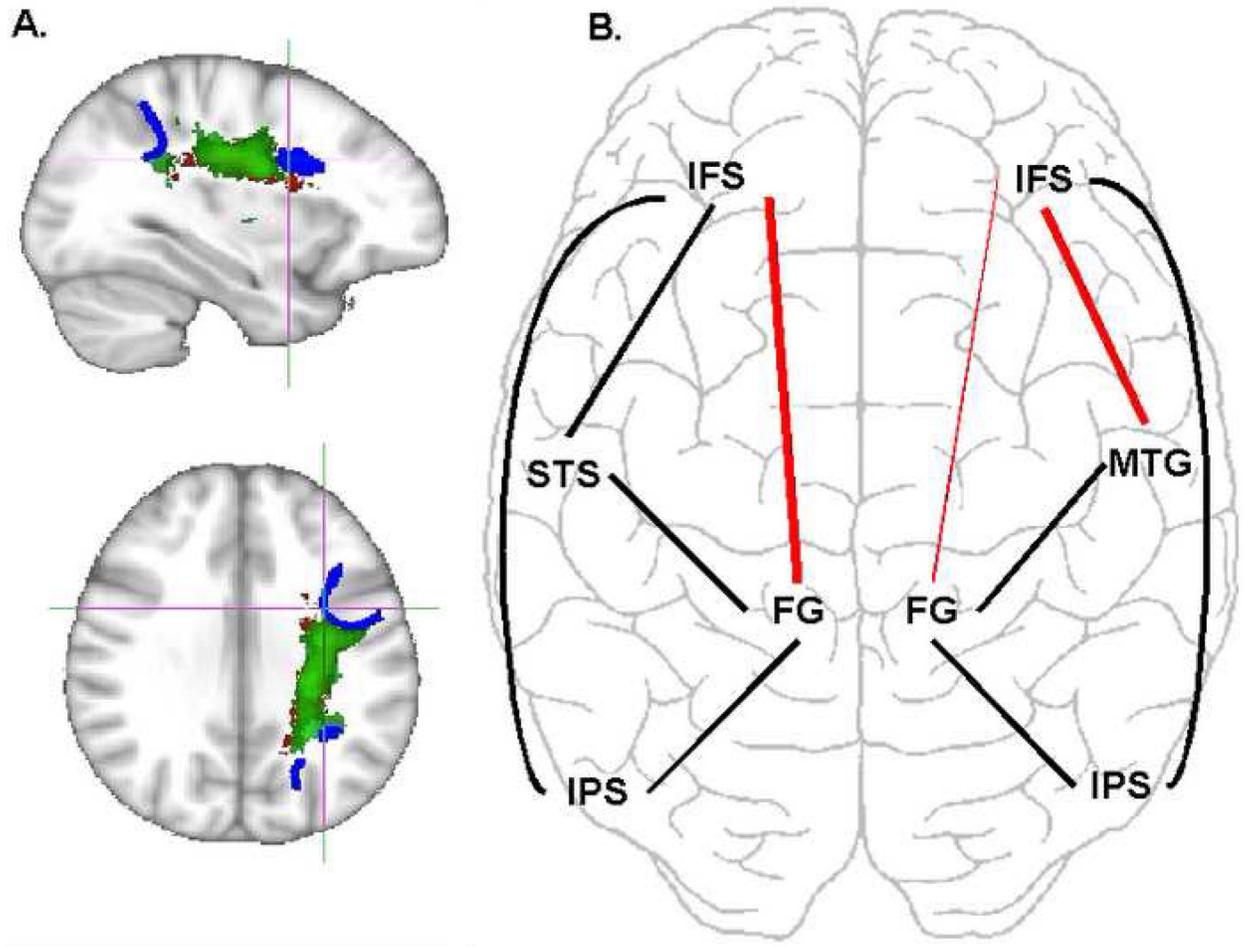
**Figure 3.**

Group comparison of fMRI activation (z-map): CTRL > HFA (red/yellow) and HFA > CTRL (blue/light blue) for each condition (S, left; V+S, middle; C, right). The maps are displayed on an inflated cortical surface template, where sulci and gyri are represented in dark and light gray, respectively. The top and bottom rows represent left (LH) and right (RH) hemisphere differences between the two groups, respectively.



**Figure 4.**

Within-group subtraction z-maps of fMRI activation ( $S$  vs.  $V+S$ ,  $S$  vs.  $V$ ,  $V$  vs.  $V+S$ ) between condition pairs in CTRL (left) and HFA (right) groups. The maps are displayed on an inflated cortical surface template, where sulci and gyri are represented in dark and light gray, respectively. The direction of subtractions was chosen such that increased language demands are shown in red/yellow, vs. blue/light blue for visuospatial demands. LH: left hemisphere; RH: right hemisphere.



**Figure 5.**

A. Example output of tractography, overlaid on MNI template; Blue: endpoints of tractography (left hemisphere IPS and IF), Green: CTRL group pathway, Red: HFA group pathway. As shown in this example, pathways generally overlap almost perfectly in HFA and CTRL. B. Summary schematic of FA differences: Black lines represent pathways investigated where no differences in FA were found between HFA and CTRL. Red Lines represent pathways showing significantly decreased FA in HFA compared with CTRL; thinner red lines represent pathways showing a trend for decreased FA in HFA compared with CTRL. IPS: Inferior parietal sulcus; FG: Fusiform gyrus; STS: Superior temporal sulcus; MTG: Middle temporal gyrus; IF: Inferior frontal area.

**Table 1**

High-functioning autism (HFA) and typically developing (CTRL) group descriptions. VIQ: Verbal IQ; PIQ: Performance IQ; FSIQ: Full-scale IQ; F: female participants.

	CTRL (N = 12, 3F)		HFA (N = 12, 2F)		P (2-tailed t-test)
	Mean	StDev	Mean	StDev	
AGE	13.3	2.5	13.3	2.1	0.94
VIQ	108.4	9.3	98.9	15.4	0.08
PIQ	104.9	10.1	101.8	10.9	0.48
FSIQ	106.1	8.6	100.8	12.3	0.24

**Table 2**

Behavioral performance (means and standard deviations) of CTRL and HFA on V, S, and V+S conditions. Acc: Accuracy (percent correct); RT: Response time (ms).

	CTRL		HFA	
	Mean	StDev	Mean	StDev
<b>V Acc</b>	84.9	7.4	81.8	10.8
<b>S Acc</b>	85.1	6.8	78.6	11.8
<b>V+S Acc</b>	85.6	7.1	83.3	7.6
<b>V RT</b>	4250.6	586.7	4472.2	748.3
<b>S RT</b>	4116.7	759.0	4366.7	615.0
<b>V+S RT</b>	4085.5	647.4	4161.4	693.6

**Table 3**

Summary of results for each **between-group** contrast (left) and **within-group** contrast (right). S; Semantic; V+S: Visuospatial+Semantic; V: Visuospatial; LH: left hemisphere; RH: right hemisphere; Bil. Bilateral; STS: Superior Temporal Sulcus; IF: Inferior Frontal area; IPS: Inferior Parietal Sulcus; MTG: Middle Temporal Gyrus; TPJ: Temporo-Parietal Junction; ant.: anterior; post.: posterior

	CTRL > HFA	HFA > CTRL	CTRL	HFA
<b>S</b>	LH: MTG, lingual gyrus, superior precentral sulcus RH: supramarginal gyrus, occipito-temporal cortex	LH: lateral occipito-temporal sulcus, posterior lateral fissure, RH: insula, MTG (ant.), ITS, IF (ant.)	S > V  S > V+S	Bil.: Ventral stream, Occipito-temporal cortex LH: STS RH: STS  LH: STS
<b>V+S</b>	LH: MTG, lingual gyrus, superior precentral sulcus RH: angular gyrus, IF, STS	Bil.: MTG (ant), ITS LH: lateral occipito-temporal sulcus, posterior lateral fissure, IPS, occipital cortex RH: postcentral gyrus	V > S  V > V+S	Bil.: IPS, insula, superior precentral sulcus RH: IF (post.)  Bil.: IPS
<b>V</b>	LH: MTG, lingual gyrus, superior precentral sulcus RH: angular gyrus	Bil.: MTG (ant.) ITS LH: lateral occipito-temporal sulcus, pre/post-central sulcus, posterior lateral fissure RH: IF (ant.), postcentral gyrus	V+S > V  V+S > S	Bil.: Ventral stream, Occipito-temporal cortex LH: IF RH: IF (ant.)  Bil.: IPS, insula, superior precentral sulcus RH: IF (post.)

**Table 4**

Mean FA within probabilistic pathways between ROIs involved in pictorial reasoning. Significant differences in FA between HFA and CTRL are highlighted. IPS: Inferior parietal sulcus; FG: Fusiform gyrus; STS: Superior temporal sulcus; MTG: Middle temporal gyrus; IF: Inferior frontal area.

LH	CTRL		HFA		p	RH	CTRL		HFA		p
	Mean	FA	Mean	FA			Mean	FA	Mean	FA	
IPS-IF	0.44	0.44	0.44	0.43	1	IPS-IF	0.44	0.43	0.43	0.2	
FG-IF	0.46	0.42	0.47	0.38	<b>0.02</b>	FG-IF	0.47	0.38	0.38	<b>0.07</b>	
IPS-FG	0.49	0.48	0.5	0.47	0.6	IPS-FG	0.5	0.47	0.47	0.14	
FG-STG	0.53	0.52	0.5	0.48	0.75	FG-MTG	0.5	0.48	0.48	0.19	
STS-IF	0.49	0.48	0.48	0.45	0.43	MTG-IF	0.48	0.45	0.45	<b>0.02</b>	