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Brain activation during semantic processing in autism spectrum disorders via functional magnetic resonance imaging

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Abstract

Language and communication deficits are core features of autism spectrum disorders (ASD), even in high-functioning adults with ASD. This study investigated brain activation patterns using functional magnetic resonance imaging in right-handed adult males with ASD and a control group, matched on age, handedness, and verbal IQ. Semantic processing in the controls produced robust activation in Broca's area (left inferior frontal gyrus) and in superior medial frontal gyrus and right cerebellum. The ASD group had substantially reduced Broca's activation, but increased left temporal (Wernicke's) activation. Furthermore, the ASD group showed diminished activation differences between concrete and abstract words, consistent with behavioral studies. The current study suggests Broca's area is a region of abnormal neurodevelopment in ASD, which may be linked with semantic and related language deficits frequently observed in ASD.

Keywords: Autism; Asperger syndrome; Autism spectrum disorders; Functional magnetic resonance imaging; Language; Semantic processing

1. Introduction

Impairments in language and communication skills are among the core clinical features of autism (APA, 1994). Across all individuals with autism spectrum disorders (ASD), including people with Asperger syndrome, deficits in pragmatic functioning, use of language, and aspects of semantic processing, especially interpreting language in context, are universal (Howlin, 2003; Lord & Paul, 1997; Tager-Flusberg, 2003, 2004). In contrast, there is significant variability in linguistic ability ranging from the absence of functional speech, to language impairment, to normal or even superior language skills, as measured on standardized tests of vocabulary and language processing (Tager-Flusberg & Joseph, 2003). However, subtle abnormalities in semantic processing are found in ASD, even among high-functional individuals. These abnormalities include difficulties with non-literal language including comprehension of idioms (Kerbel & Grunwell, 1998), and impairments in the understanding of language in context. The consistent presence of language deficits in ASD have led researchers to investigate structural and functional brain markers in areas of the brain classically defined as language areas, i.e., Broca's (inferior frontal gyrus) and Wernicke's (posterior superior temporal) areas.

Neuroanatomical studies using structural magnetic resonance imaging (MRI) in children with ASD have found morphometric differences in key language regions, particularly Broca's area and Wernicke's area (De Fosse et al., 2004; Herbert et al., 2002). Specifically, these studies found reversed asymmetry (i.e., larger in the right-hemisphere) in inferior lateral frontal areas, corresponding to Broca's area, among boys with ASD, especially in boys with ASD and language impairment (De Fosse et al., 2004), and an

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exaggerated left-hemisphere asymmetry in posterior superior temporal regions, corresponding to the planum temporale in Wernicke's area.

There have been few studies using functional brain imaging methodologies investigating language processing in ASD. Muller and his colleagues (Muller et al., 1998) used Positron Emission Tomography (PET) to investigate sentence processing in a pilot study of four adult males with high-functioning autism and five controls. The men with autism showed reduced activation in left frontal areas compared to controls, specifically Brodmann area (BA) 46. In a larger scale study, Just and his colleagues used functional MRI (fMRI) to investigate brain activation patterns during sentence comprehension in 17 high-functioning men with autism, and 17 well-matched controls (Just, Cherkassky, Keller, & Minshew, 2004). They too reported reduced activation in Broca's area with corresponding increased activation in Wernicke's area (BA21, 22) in the autism group. Just and colleagues also found less synchronization among the cortical areas involved in sentence comprehension, suggesting lower functional connectivity in the brains of adults with autism (Just et al., 2004).

The goal of our study was to investigate brain activation patterns in adults with autism, using a *lexical semantic* processing task with individual word stimuli, in combination with assessment of ASD processing of abstract vs. concrete word classes. Thus, our work extends distinctly and expands upon prior functional imaging studies on sentence processing in ASD. Functional brain imaging studies in language-normal control subjects have demonstrated that semantic processing tasks activate regions of Broca's area (especially BAs 45 and 47) in the left inferior prefrontal cortex (LIPC), as well as Wernicke's area (especially BA21) in the posterior superior temporal region (see Bookheimer, 2002 for a review). However, within each of these broad language regions there are differences in which specific areas are activated during semantic, syntactic, and phonological processing tasks (Bookheimer, 2002; Chee, O'Craven, Bergida, Rosen, & Savoy, 1999; Muller, Kleinhans, & Courchesne, 2003; Newman, Just, Keller, Roth, & Carpenter, 2003; Poldrack et al., 1999). Peterson et al. were the first to demonstrate activation during semantic word processing in BA47 in Broca's area using PET (Petersen, Fox, Posner, Mintun, & Raichle, 1988). Their findings have been confirmed in many studies using a number of different tasks (Bookheimer, 2002). One task frequently used to stimulate Broca's area activation in normal control subjects involves contrasting "deep" semantic processing tasks (e.g., asking the subject to respond based on the meaning of a presented word; for example, whether the word is positive vs. negative, or abstract vs. concrete) with "shallow" perceptual processing tasks (e.g., asking the subject to respond based on the perceptual quality of a word; for example, whether the word is presented in UPPER vs. lower case, or in color vs. black/white) (Chee et al., 1999; Demb et al., 1995; Kapur et al., 1994; Poldrack et al., 1999). This effect corresponds behaviorally with the "levels-of-processing" memory effect, whereby words processed during "deep" semantic tasks are recalled better from long-term memory than words processed during "shallow" perceptual tasks. Semantic processing leads to greater activation in LIPC compared to perceptual processing (Demb et al., 1995). Bookheimer (2002) suggests that Broca's area is specifically involved in the comparison of semantic concepts in working memory. The functional role of BA45/47 and BA21 in semantic processing is independent of modality of stimulus presentation (Booth et al., 2002).

Other functional brain imaging studies on semantic processing have explored whether there are regional activation patterns associated with content specific lexical categories, including concrete versus abstract nouns (Beauregard et al., 1997; Grossman et al., 2002; Jessen et al., 2000; Kiehl et al., 1999; Perani et al., 1999), although the findings in this area have been less consistent because category effects may be more sensitive to task differences. Bookheimer (2002) suggests that tasks that do not require an explicit judgment distinguishing between different lexical/semantic categories will not yield many contrasting patterns of activation.

Our imaging study design was based on three behavioral abnormalities previously reported in ASD. First, Toichi and Kamio found that, in contrast to matched controls, high-functioning adolescents and adults with autism did not recall words that had been semantically encoded better than perceptually encoded words indicating that they do not show a "levels-of-processing" effect (Toichi & Kamio, 2002). Second, in another study, participants with ASD did not recall concrete words better than abstract words, again, in contrast to matched controls (Toichi & Kamio, 2003). Third, people with autism have deficits in understanding mental states (Baron-Cohen, Tager-Flusberg, & Cohen, 1993, 2000) and use mental state terms significantly less frequently than controls (Tager-Flusberg, 1992). Together, these behavioral findings suggest atypical semantic processing in autism.

Therefore, we followed up these behavioral findings in the current study, using fMRI to explore activation patterns during a semantic processing task, in high-functioning adults with ASD and matched normal control subjects. Our fMRI investigation was designed to test these three semantic domains: (1) comparing Semantic vs. Perceptual tasks for "levels-of-processing" effects, (2) comparing Concrete vs. Abstract words, and (3) comparing Mental State abstract words to other abstract word classes. We tested the hypothesis that impaired semantic processing of words in ASD is associated with abnormal functional organization in cortical language processing areas, especially in the left inferior prefrontal regions involved in semantic processing, by using a task that compared semantic to perceptual processing of single words. Furthermore, in light of suggestions that abstract and concrete words are processed differentially in normal controls compared with subjects with ASD, we modified the traditional semantic encoding task to group words into blocks of concrete and abstract words. Given the atypical processing of mental state words in individuals with ASD (Baron-Cohen, Leslie, & Firth, 1986; Tager-Flusberg, 1992) we included both Mental State and Metaphysical abstract word classes, predicting that individuals with ASD would differ in their pattern of activation in comparison to controls. One imaging study (Baron-Cohen et al., 1994) with normal controls using SPECT compared activation patterns to mental state (e.g., think) and action (e.g., jump) verbs. They found that mental state verbs differentially activated the right orbito-frontal cortex, relative to the left frontal region. Therefore, we divided our Abstract words into Metaphysical and Mental State terms to explore whether our participants with ASD would show reduced right orbito-frontal activation to the Mental State abstract words compared to the controls. Furthermore, based on prior behavioral studies showing reduced semantic vs. perceptual, and concrete vs. abstract differences in ASD, we hypothesized that ASD subjects would show reduced fMRI activation differences for these contrasts in our functional brain imaging study.

2. Methods

2.1. Participants

Subjects included 14 adult males who met criteria for a clinical diagnosis of an autism spectrum disorder, ASD (autism, Asperger syndrome, or PDD-NOS), on the basis of current clinical presentation and developmental history, and 22 normal control males matched on age, Verbal IQ, and vocabulary (see Table 1). ASD diagnoses were confirmed using the Autism Diagnostic Interview-Revised (ADI-R; (Lord, Rutter, & Le Couteur, 1994)) and the Autism Diagnostic Observation Schedule (ADOS; (Lord et al., 2000)), which were administered by personnel trained to the standards of research reliability on both instruments. Participants were classified according to DSM-IV (APA, 1994) diagnoses, based on criteria developed by the NICHD/NIDCD Collaborative Programs for Excellence in Autism (Lord & Risi, 2003), using scores on the ADI-R and ADOS. Seven participants met criteria for autism (two of these participants only had ADOS scores available), five met criteria for Asperger syndrome, and two met criteria for PDD-NOS.

Table 1
Participant characteristics

	Autism spectrum disorders ($n = 14$) mean ± *SD* (range)	Control subjects ($n = 22$) mean ± *SD* (range)
Age (years)	36 ± 12 (18–52)	31 ± 9 (19–50)
Full-scale IQ	116 ± 8 (95–128)	122 ± 9 (101–138)
Non-verbal IQ	112 ± 11 (95–126)	119 ± 10 (98–134)
Verbal IQ	117 ± 13 (80–134)	119 ± 9 (104–133)
PPVT	118 ± 15 (89–140)	122 ± 11 (106–147)
EVT	116 ± 18 (63–134)	115 ± 13 (81–145)
ADOS	10.2 ± 4.2 (6–20)	N/A

PPVT, Peabody Picture Vocabulary Test-III (Dunn & Dunn, 1997); EVT, Expressive Vocabulary Test (Williams, 1997); ADOS, Autism Diagnostic Observation Schedule (Lord et al., 2000), total score.
N/A, not applicable.
Note. IQ and language (PPVT, EVT) scores have a population mean of 100 and *SD* of 15.

All participants were native English speakers, and were right-handed as measured by a modified version of the Dean Laterality Preference Schedule (Dean, 1988), with the exception of one participant with ASD who showed no hand preference. All participants had verbal and non-verbal IQ standard scores over 80 as measured using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Receptive and expressive vocabulary were assessed using the Peabody Picture Vocabulary Test-III (Dunn & Dunn, 1997) and Expressive Vocabulary Test (Williams, 1997), respectively. The groups were well matched on verbal IQ and vocabulary scores (all p values >.40), however there was a trend for the participants with ASD to be older ($p = .10$) and have lower non-verbal ($p = .053$) and full-scale ($p = .07$) IQ scores.

Exclusion criteria included: head injury leading to unconsciousness greater than one hour or ferromagnetic metal implants for subjects in either group, as well as a history of DSM Axis I psychiatric disorder in control subjects. An additional six participants with ASD and 10 controls were scanned but excluded from the fMRI analyses for the following reasons: scanning issues, e.g., gross structural abnormality (2 controls), excessive motion (1 ASD), or incomplete/technical problems (3 ASD, 2 controls); tasks during scan not performed correctly as indicated by accompanying behavioral data (1 ASD, 3 controls); or for group-matching based on descriptive data, or counterbalancing across conditions (1 ASD, 3 controls; selected for exclusion solely based on demographic or experimental conditions, blinded to the scan results).

2.2. Functional imaging protocol

Participants were scanned on a Siemens 1.5T Sonata System at Massachusetts General Hospital, after signing written informed consent forms approved by the institutional human studies Investigational Review Board. After subjects were checked for all metal objects, they lay flat on the scanner bed, with their head snugly fit into the head coil. A soft pillow and foam padding minimized head movements. Subjects were fitted with earplugs (29 dB rating) to reduce their exposure to scanner noise. Those who needed vision correction were fitted with scanner-compatible lenses. Subjects were given a squeeze ball for communicating with the experimenter and for emergencies.

Functional imaging included an automated shim procedure to improve B0 magnetic field homogeneity, and T2*-weighted echo-planar pulse sequences sensitive to BOLD contrast. Four functional scan series were collected using a gradient-echo echo-planar pulse sequence with a quadrature transmit/receive head coil (TR = 3000 ms, TE = 30, 64 × 64 matrix, 200 mm FOV, 20 slices, 6 mm thick, 0 mm skip, parallel to AC/PC line and extending from the top of the cortex into the cerebellum) lasting 273 s. The first four images in each series were acquired and discarded to allow longitudinal magnetization to reach equilibrium. A set of T1-weighted structural images (TR = 6.5 ms, TE = 2.9 ms, 256 × 192 matrix, 256 mm FOV, 128 contiguous slices, 1.32 mm thick) were obtained for aligning the structural and functional images. Each participant's images were examined for motion in each activation acquisition series, and motion-corrected (see fMRI image analysis below).

2.3. *fMRI stimuli and response paradigms*

Word stimuli were presented during MR scanning using a Macintosh G4 computer with PsyScope software (Macwhinney, Cohen, & Provost, 1997), and back-projected via an LCD projector and a mirror attached to the head coil. The words were presented in black lettering on a white background. Button press responses were collected using an MR-compatible button box connected to the Macintosh via a custom USB interface, providing both response choice and reaction time data. The stimulus delivery system generated markers that indicate the timing of the stimulus presentations with respect to the MRI acquisitions.

The four functional scans included two successive runs of each of the following conditions: (1) *Semantic processing*, (2) *Perceptual processing*, counterbalanced for order across subjects, within each group. Thus, there were two runs presenting the Semantic task and two runs of the Perceptual task, with task order counterbalanced. Identical word lists were used for Semantic and Perceptual conditions (see word list details below and in Appendix A). In the Semantic condition, subjects were asked to press one of two response keys indicating whether they evaluated the words as positive or negative. The Perceptual condition required subjects to indicate whether a word was presented in UPPER or lower case. At the beginning of each run, instructions were presented indicating which type of response was required, Semantic (positive vs. negative) or Perceptual (UPPER vs. lower case). Three sets of words were constructed for three categories: Concrete (e.g., *piano*), Mental State abstract (e.g., *happy*), and Metaphysical abstract (e.g., *freedom*). Words were classified as abstract or concrete (Clark & Paivio, 2004; Paivio, Yuille, & Madigan, 1968) based on Paivio, Colerado, and Gilhooly-Logie "concreteness" norms (Coltheart, 1981). "Concreteness" values of our Concrete word list had no overlap with the two Abstract word lists. The two abstract categories were similar in "concreteness" and were substantially lower than the Concrete words (see Table 2 for details). Each run consisted of 91 image acquisitions with three blocks of words, and each block consisted of three sub-groupings from these three categories: Concrete ("cc"), Mental State ("ms") abstract, and Metaphysical ("mp") abstract, with a shorter block of fixation (a plus sign) between each word block. The presentation order of word category blocks was varied so that each of the three possible category orders within a 21-word block occurred once during each task, to counter potential ordering or desensitization effects (i.e., the block sequence for the two runs within each task was: run 1:FABCFACBFBACF – run 2:FBCAFCABFCBAF, where F stands for 7 trials of fixation, and A, B, and C each stand for 7 trials of one of the three word categories). Each fixation block consisted of 7 scan time points (21 s), and each word block consisted of 21 words (3 subgroups of 7 words from each word category per word block) synchronized with 21 scan time points (63 s), with each word displayed for 2500 ms with 500 ms fixation between words. Thus, there were 63 words per run and two runs of each type, for a total of 126 words used (see Appendix A for word lists— the same word lists were used for Semantic and Perceptual conditions). Words in each list were evenly divided between lengths of 1, 2, and 3 syllables, with half presented in UPPER case and half in lower case (stimuli were the same, half UPPER, half lower case, for both Semantic and Perceptual conditions; only the required response varied). As shown in Table 2, each category list was matched on length and mean word frequency (Francis & Kucera, 1982; Kucera, 1967), since frequency has been demonstrated to impact the LIPC semantic activation effect (Chee, Hon, Caplan, Lee, & Goh, 2002). All words were present in reading material used by third-graders according to a standard corpus (Carroll, Davies, & Richman, 1971).

2.4. *fMRI image analysis*

Preprocessing and statistical analysis of the data were performed using SPM99 software (Wellcome Department of Cognitive Neurology, London). Preprocessing with SPM99 included slice time correction, motion correction, and spatial normalization to the MNI305 stereotactic space (using linear affine registration followed by nonlinear registration using cosine basis functions, resampling to 3 mm cubic voxels), and spatial smoothing with an 8 mm Gaussian kernel. Statistical analysis was first performed for each individual subject using a general linear model in SPM99. The block design is modeled as a boxcar reference function

Table 2
Measures of "concreteness" (Coltheart, 1981), frequency, and length (Francis & Kucera, 1982) for Concrete, Mental State abstract, and Metaphysical abstract word lists

	"Concreteness" mean ± *SD* (range)	Frequency mean ± *SD* (range)	Length mean ± *SD* (range)
Concrete	586 ± 25 (532–634)	98 ± 116 (6–591)	6.1 ± 1.9 (3–10)
Mental State abstract	304 ± 51 (247–509)	106 ± 136 (9–683)	6.5 ± 2.0 (3–11)
Metaphysical abstract	300 ± 33 (223–365)	112 ± 107 (9–611)	6.6 ± 2.2 (4–11)

Note. "Concreteness" values are integer, in the range of 100–700 (min 158, max 670, mean 438, and *SD* 120), with 700 being the highest possible score for concreteness.

convolved with a canonical hemodynamic response function (HRF), with low-frequency (66 s cutoff) components of the fMRI signal modeled as nuisance covariates. The model-fit was performed individually for each subject, and contrast images were generated to compare each of the three types of words and each of the two conditions, as well as comparisons against the explicitly un-modeled baseline/fixation. The baseline fixation for each run was used as a reference to normalize the activations so that comparisons could be made by concatenating runs to analyze relative activation across runs. Following statistical analysis at the individual level, group analyses were performed for each contrast using a one-sample t test to compare the value of the contrast images against zero. This analysis treats subjects as a random effect and ensures valid inference to the sampled population. These results were further characterized according to the theory of Gaussian random fields, to obtain SPMs identifying regions of activation with a map-wise corrected alpha level, with a pixel-level threshold at $p < .001$ and a cluster-extent threshold of 5 voxels. Activation regions meeting these criteria were reported in the results and tables if the regional, cluster-level p value threshold (corrected for multiple comparisons) met $p < .05$ criteria with cluster size of at least 20 voxels. In addition, region-of-interest (ROI) analyses of time course data were performed based on an 8 mm diameter spherical region centered on the coordinates of maximum activation in semantic activated language-regions: left-hemisphere BAs 45, 47, and 21, and contralateral right-hemisphere corresponding homologous regions, using Freesurfer fMRI analysis software (http://surfer.nmr.mgh.harvard.edu), developed at Massachusetts General Hospital. The first two time points in each stimulus block were discarded from the ROI analyses to allow for 6-s hemodynamic transitions at the start of each block. ROI statistical analyses were performed with two-tailed t tests to detect activations within and between groups in language-related regions.

Although motion correction techniques can realign the images in a scanning run, they do not fully protect from artifacts related to head motion. We performed statistical comparisons of the contrast mentioned above using motion as a covariate and determined that no significant amount of activation was accounted for by motion.

3. Results

3.1. Behavioral testing

In the Semantic condition, participants evaluated the words as positive or negative. Response choices were analyzed with a repeated measures general linear model by group for the three word classes: Concrete (cc), Metaphysical abstract (mp), and Mental State abstract (ms). Behaviorally, both subject groups demonstrated similar response patterns for each word class (see Fig. 1), with no group or interaction effects. The percentage of positive responses was similar between groups ($p > .30$) for each word class. The percentages of words scored as 'positive' differed among word classes: ms words (68.6% positive) were less frequently judged positive by both subject groups compared with mp (84.9% positive) and cc (87.6% positive) word classes ($p < .001$). Thus, while there was an effect of word category, there were no subject group effects and no interaction effects. The similarity in attributing valence to the words between subject groups supports the hypothesis that both groups were performing the task appropriately, and understood the instructions and the word lists. In the Perceptual condition, participants evaluated words as UPPER or lower case, and both groups' responses were over 98% correct for all word classes, with no group, word class, or interaction effects.

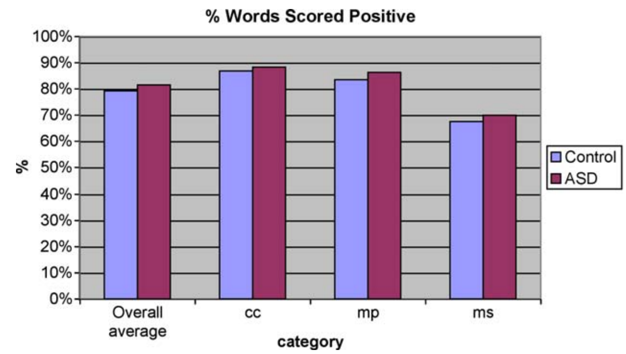

Fig. 1. Percent of words scored as positive across categories for the Semantic word task.

Reaction times were also assessed with a repeated measures general linear model, analyzed by subject group (ASD vs. Control), task (Semantic vs. Perceptual), and word class (cc, mp, ms). Groups performed similarly on reaction times ($p > .35$), and there were no significant interaction effects. There was a large task effect ($p < .001$), with longer reaction times for Semantic processing (1032 ms) compared with Perceptual processing (647 ms), as expected given the greater depth of processing required in the Semantic task. There was a trend toward a condition effect, with Mental State abstract words having shorter reaction times than the other two word classes ($p = .07$), but again, there were no subject group effects or interactions.

Thus, for both reaction times and response classifications, both subject groups performed the tasks similarly behaviorally, and no group behavioral effects were observed. These results confirm that the ASD subjects understood the tasks and the word lists, and behaved during these tasks in the same manner as the controls. Any observed group differences in neural activity observed with fMRI during the tasks, then, cannot be attributed to performance differences between the groups.

3.2. fMRI of Semantic vs. Perceptual word processing

Table 3 presents details of the regions with significant activations contrasting the Semantic > Perceptual tasks for both groups. In the analysis of the Semantic vs. Perceptual

Table 3
Regions that displayed significant activation for Semantic > Perceptual word processing tasks

MNI Coordinates (x, y, z, in mm)	Cluster size	Cluster-level p value	Anatomical region (Brodmann area number)
Control subjects			
−48, 27, −6			Ventral L. Frontal (47)
−54, 21, 9	722 voxels	$p < .0001$	Broca's Area LIPC (45)
−3, 33, 45			
−3, 18, 54	139	$p < .0001$	Medial Sup. Fr. Gyrus (8)
27, −69, −42			
18, −75, −36	46	$p < .03$	R. Cerebellum[a]
42, 24, −12	39	$p < .07$	Ventral R. Frontal (47)
ASD subjects			
−30, 15, −9			
−51, 24, −9	69	$p < .001$	Ventral L. Frontal (47)
−54, −42, 0	40	$p < .02$	L. Mid. Temp. Gyrus (21)

L, Left; R, Right; Fr., Frontal; Sup, Superior; Mid, Middle; Temp, Temporal; LIPC, Left Inferior Prefrontal Cortex.
[a] Cerebellum analyses included 15 Control and 10 ASD subjects whose scans included the cerebellum. Seven control subjects and four ASD subjects did not have complete cerebellum scan coverage.

task epochs (for the Semantic > Perceptual activation contrast), the control subjects robustly and specifically activated the left inferior prefrontal cortex (LIPC) in Broca's area. For the controls, the activation included a large cluster of 722 voxels with local maxima in lateral inferior frontal gyrus (anterior Broca's area), in BA45 superiorly, continuing inferiorly with local maxima in BA47 ventrally. Another strongly activating region (139 voxels) in control subjects was superior medial frontal gyrus (BA8), a region that runs along the superior medial frontal lobes adjacent to the interhemispheric fissure. There was a trend toward activation ($p = .07$) in a 39-voxel cluster in right BA47, contralateral to the ventral frontal activation local maxima observed on the left side.

The participants with ASD had weaker frontal activation for Semantic relative to Perceptual task conditions, as shown in Fig. 2, even though they were right-handed and behaved during the task similarly compared with the control subjects. There was an area of left ventral frontal activation in BA47 that included a 69-voxel cluster. However, the robust activation seen in control subjects in Broca's area (BA45) was not observed among participants with ASD. There was a significantly activated cluster in subjects with ASD including 40 voxels in middle temporal gyrus (BA21), a region also involved in semantic processing. For the participants with ASD, temporal lobe and frontal language activations were balanced, of similar size and magnitude, whereas the controls demonstrated a large and robust frontal language regional activation with minimal temporal lobe activation.

The slice prescription for our functional MRI scans did not cover the entire cerebellum for 4 ASD and 7 control subjects. In the remaining 15 controls with cerebellum coverage, there was significant activation in the Semantic > Perceptual contrast in the right cerebellar hemisphere, contralateral to the left inferior frontal Broca's area activation. The 10 subjects with ASD who had complete cerebellum scan coverage did not display significant activation in the cerebellum.

As further confirmation that the group difference in Broca's area activation in Brodmann area 45 was not a result of differences in group sizes, the 15 controls in the cerebellum analysis subgroup also showed significant activations in BA45, 8, as well as activation in BA47 on the left and a trend in BA47 on the right. Thus, even in similar sized groups (15 control vs. 14 ASD), the Broca's area activation in BA45, as well as the medial superior frontal activation in BA8, were present in the control group but not in the ASD group for Semantic relative to Perceptual word processing.

Regions of interest (ROI) were defined in left-hemisphere BAs 45, 47, and 21, based on the coordinates of the frontal and temporal lobe Semantic > Perceptual group activations, and in corresponding contralateral regions in right-hemisphere. While both groups showed significant activation for the Semantic relative to the Perceptual task condition in the ventral frontal BA47 ROI ($p < .05$ in both groups), only the control group displayed significant ROI activation in Broca's area in BA45 ($t(21) = 3.5$; $p < .002$ in controls, $t(13) = 1.4$; $p = .19$ in ASD). However, comparing Semantic activation to fixation and Perceptual activation to fixation, it appears that the control group had strong activation in response to the Semantic task ($t(21) = 6.8$; $p < .0001$), but not in response to the Perceptual task ($t(21) = 1.3$; $p > .20$). In contrast, the ASD group had similar activation in both Semantic and Perceptual tasks (for both tasks: $t(13) = 3.6$; $p < .005$), which were intermediate between the control group's responses. As a result of the similarity of activation between tasks in ASD, no significant difference in activation between Semantic and Perceptual tasks was observed in ASD in this Broca's Area region (BA45) (see Fig. 3). Thus, it was not that the ASD group failed to activate Broca's area in response to words altogether, but rather that there was not a differential activation between the two conditions in ASD subjects.

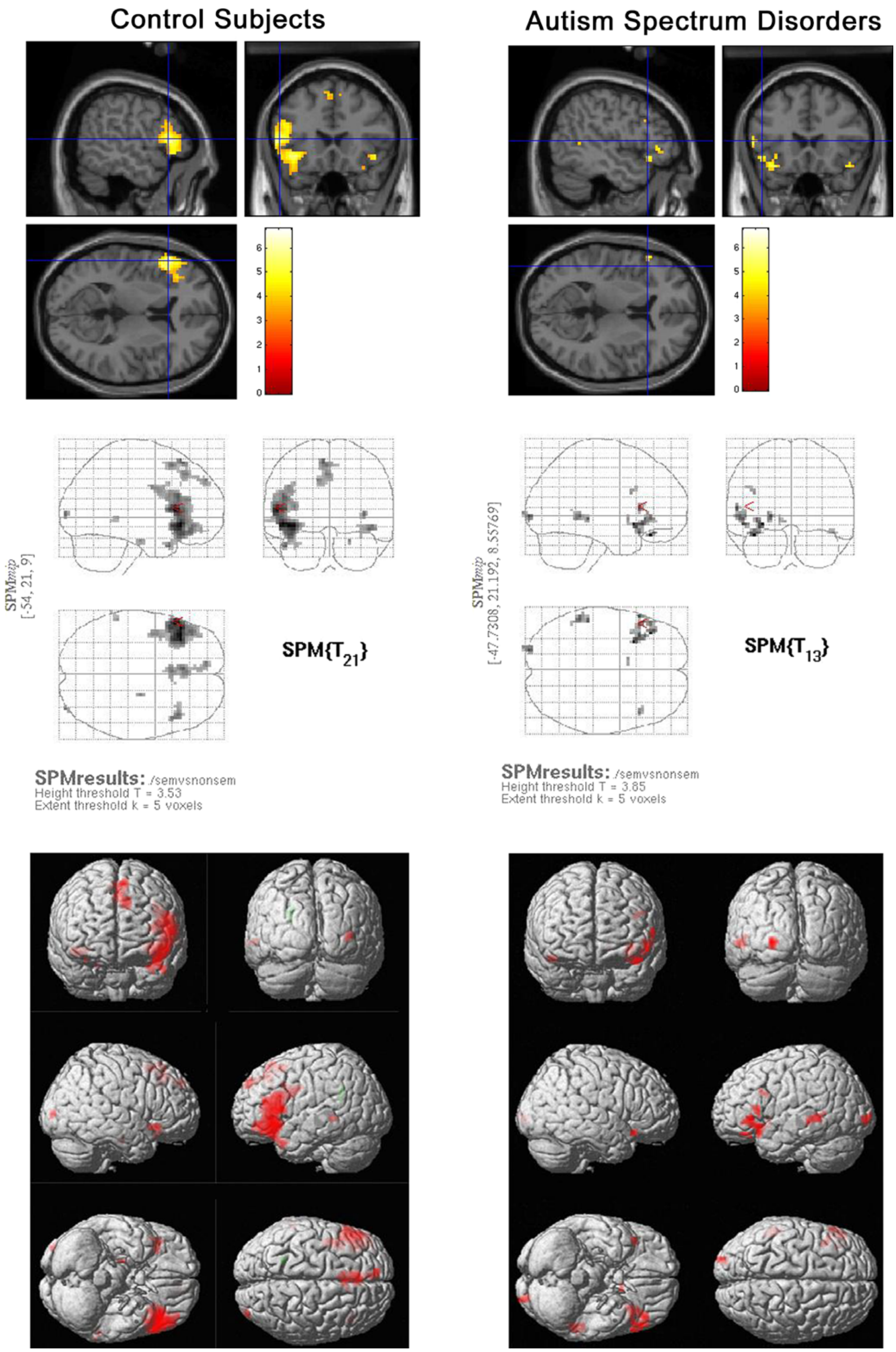

Fig. 2. Functional MRI (fMRI) activation patterns for Semantic > Perceptual word processing tasks in 14 autism spectrum disorders (ASD) subjects (right) and 22 normal controls (left). Activation local maxima in Broca's area (Brodmann area 45) in left inferior prefrontal cortex (LIPC) shown at cross-hairs in multiplanar view (top images) corresponds to functional activation in normal subjects during Semantic contrasted to Perceptual word task, while ASD subjects had aberrant activation in this region. Middle images represent SPM "glass brain" orthogonal display views. Bottom images represent surface rendered views demonstrating fMRI regions of activation (red).

The left middle temporal gyrus (BA21) region that presented a significant SPM activation in the ASD group had a Semantic > Perceptual ROI significance at the one-tailed level of $p < .05$ in ASD subjects, but the control group did not show significant activation in this region. Compared with the fixation condition, both groups showed significant BA21 ROI activation for both the Semantic and Perceptual conditions (for each condition vs. fixation in each group,

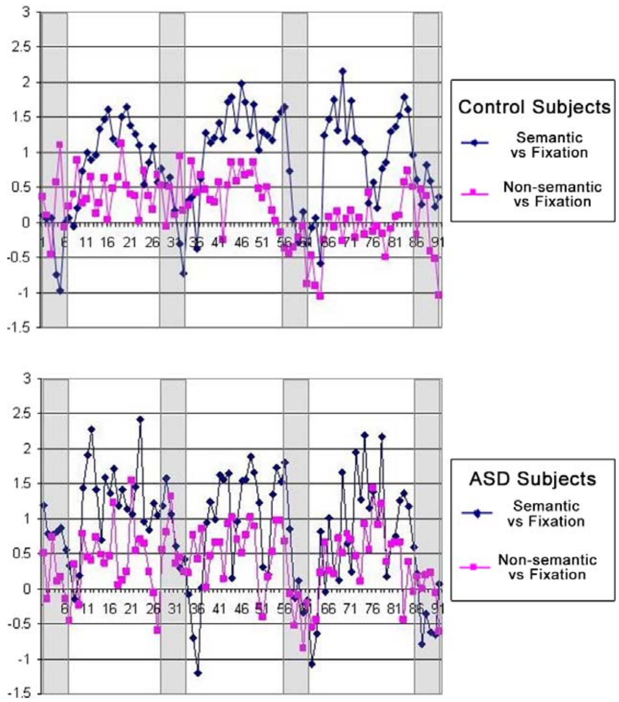

Fig. 3. Time course data in left inferior frontal gyrus (Broca's area, Brodmann 45), for Semantic and Perceptual ("Non-semantic") word tasks vs. fixation baselines in normal control (top) and ASD subjects (bottom). Gray bands indicate periods of fixation (y-axis represents percent signal change from baseline; x-axis represents scan number, 1–91, with each scan lasting 3 s: total scan time, 273 s). The control subjects had significant activation for Semantic vs. Fixation ($t(21) = 6.8$; $p < .0001$) but not for Perceptual vs. Fixation ($t(21) = 1.3$; $p > .20$) tasks, and the Semantic > Perceptual comparison was significant ($t(21) = 3.5$; $p < .002$). For ASD subjects, both Semantic vs. Fixation ($t(13) = 3.6$; $p < .005$) and Perceptual vs. Fixation ($t(13) = 3.6$; $p < .005$) tasks had similar activations, resulting in non-significant Semantic > Perceptual Broca's area contrast in ASD ($t(13) = 1.4$; $p = .19$).

$p < .007$). However, the ASD group had a larger mean activation difference (Semantic mean activation, 0.9%; Perceptual mean activation, 0.3%) than did the control group (Semantic mean activation, 0.6%; Perceptual mean activation, 0.4%), leading to the significant Semantic > Perceptual contrast in the ASD group. Right-sided ROIs did not show significant Semantic vs. Perceptual differences.

There were no significant activation clusters in either group in response to the reverse fMRI analysis contrast comparing Perceptual > Semantic processing.

3.3. fMRI of Concrete vs. Abstract words, and Mental State vs. Metaphysical abstract words

Within the Semantic task, the Mental State vs. Metaphysical abstract word class contrasts displayed no significant clusters in either group in either contrast direction at $p < .05$ with cluster threshold of 20 voxels. Next, we compared Concrete Words vs. Abstract Words (combining the two Abstract Word classes to simplify results and improve power, since no differences were observed between Abstract Word class comparisons; we checked the validity of this assumption by comparing contrasts of Concrete vs. each Abstract class separately—see below). Within the Semantic processing task, when contrasts were compared between Concrete and Abstract (Mental State and Metaphysical abstract combined) word classes, both subject groups showed activation for Concrete relative to Abstract words in posterior cingulate bilaterally, in left posterior parahippocampal gyrus, and in left middle occipital gyrus (BA19), however the activations in these regions were all much larger and stronger in the control group (see Table 4 and Fig. 4). As a check of combining the two Abstract word classes as a contrast to Concrete words, we compared the above results of the combined-Abstract/Concrete contrast with the contrasts of Concrete words to each of the Abstract word classes (Concrete vs. Mental State and Concrete vs. Metaphysical separately). The same three regions described above were activated for each contrast for each Concrete vs. Abstract word class. Therefore, for simplicity, we only report the

Table 4
Regions that displayed significant activation for Concret > Abstract word processing tasks

MNI coordinates (x, y, z, in mm)	Cluster size	Cluster-level p value	Anatomical region (Brodmann area number)
Control subjects			
−6, −54, 12	279	$p < .0001$	L. Posterior Cingulate (23)
6, −54, 12			R. Posterior Cingulate (23)
−36, −81, 39	179	$p < .0001$	L. Mid. Occip. Gyrus (19)
−48, −72, 12			
−21, −27, −21	102 voxels	$p < .0001$	L. Parahippoc. Gyrus (36)
−21, −42, −9			
−3, 42, −15	31	$p < .06$	Medial frontal Gyrus (11)
21, −18, −21	28	$p < .08$	R. Parahippoc. Gyrus (36)
ASD subjects			
−3, −54, 6	130	$p < .0001$	L. Posterior Cingulate (23)
6, −54, 9			R. Posterior Cingulate (23)
−30, −33, −24	39	$p < .01$	L. Parahippoc. Gyrus (36)
−45, −72, 15	25	$p < .07$	L. Mid. Occip. Gyrus (19)

L, Left; R, Right; Mid, Middle; Occip, Occipital; Parahippoc, Parahippocampal.

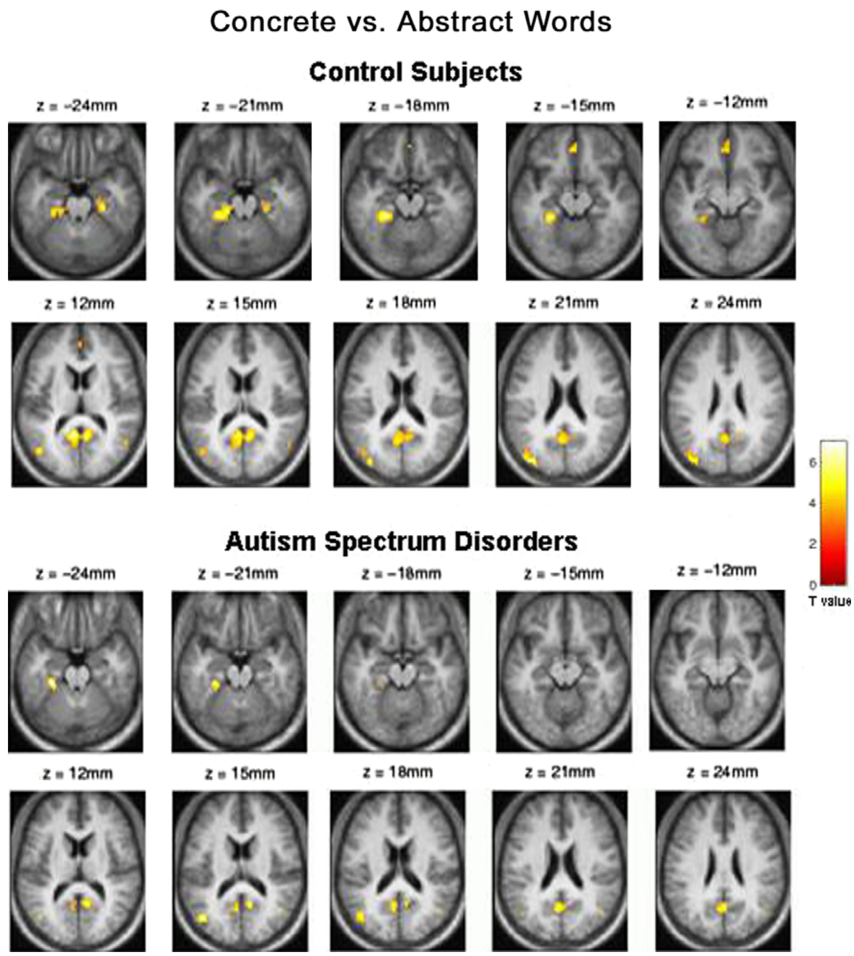

Fig. 4. Limbic (parahippocampal gyrus), posterior cingulate, parieto-occipital, and inferior medial frontal activation in control subjects performing Semantic processing for the contrast of Concrete > Abstract words (top). ASD subjects had less pronounced activation for Concrete vs. Abstract words (bottom).

contrasts for Concrete vs. combined-Abstract word classes. The control group also had a region of activation in inferior medial frontal gyrus, with a cluster of 31 voxels with voxel-level $p < .001$, although the cluster-level showed a trend at $p < .06$ corrected for multiple comparisons. No medial frontal cluster of activation was observed in the ASD group. Although the groups had activation patterns in several similar regions, the Concrete > Abstract word activation differences were far less pronounced in the ASD group.

The reverse contrast of Abstract > Concrete words produced two significant activation clusters in the control group, but no significant activation clusters in the ASD group. The control group had a significant activation cluster (60 voxels, $p < .002$) in left middle temporal gyrus (BA21), in a location (x, y, z: −45, −42, −3) similar to that of the ASD group in the Semantic > Perceptual contrast. The control group also had a significant activation cluster (32 voxels, $p < .05$) in right caudate/putamen (x, y, z: 15, 15, 0).

4. Discussion

This was the first study to compare brain activation patterns in high-functioning adults with ASD and well-matched control subjects during a single-word lexical semantic processing task: our study design included both a "levels of processing" Semantic vs. Perceptual design, combined with comparisons of Concrete vs. Abstract word classes, including a set of Mental State abstract word stimuli. The main findings were that, in comparison to the control subjects, during Semantic vs. Perceptual processing, the ASD group showed: (1) relatively less activation in Broca's area, especially BA45, with similar fMRI responses in this region during both tasks, while control subjects specifically activated this region during Semantic processing only; (2) relatively increased activation in middle temporal gyrus; and (3) no activation in either medial superior frontal gyrus or right cerebellum. The ASD group also showed diminished differential activation to the Concrete relative to Abstract words during Semantic processing.

Our brain imaging findings comparing Semantic vs. Perceptual processing are consistent with behavioral evidence for semantic deficits in ASD. Adolescents and adults with autism show impairments in the traditional "levels-of-processing" effect in memory encoding and retrieval for "deep" semantic vs. "shallow" perceptual tasks (Toichi & Kamio, 2002), even when compared to controls matched for cognitive ability who displayed the expected depth effect. In a sample of high-functioning ASD individuals and matched controls, semantically processed words displayed a memory benefit compared with phonologically processed words in both groups, but the control group showed enhanced recall when presented with semantic cues compared with phonological cues, while the ASD group did not show improved recall with semantic cueing (Mottron, Morasse, & Belleville, 2001). A particular form of deep encoding, deciding whether the word presented describes oneself, was more effective for facilitating recall in normal subjects than was standard semantic encoding, but had no benefit for autistic subjects (Toichi et al., 2002). These behavioral findings are consistent with our imaging observation that BA45 in Broca's area was activated to similar levels in ASD subjects for both the Semantic and Perceptual tasks, while controls activated this region specifically for the Semantic, but not the Perceptual, task. In contrast, normal semantic priming effects were observed in autistic adolescents (Toichi & Kamio, 2001). In semantic priming paradigms, however, explicit attention to semantic aspects of the stimuli is not required, and the implicit activation of semantic information is revealed by the priming effect. These behavioral findings suggest that individuals with ASD may have difficulty with, or perhaps avoid, explicitly encoding semantic aspects of verbal material. Furthermore, subjects with ASD may be performing more semantic and phonological processing during perceptual tasks, i.e., they may be less able to suppress semantic, and particularly phonological and/or syntactic processing, which would be consistent with the lack of semantic "levels-of-processing" effects in ASD observed in the above prior behavioral studies as well as in the current fMRI results. Thus, behavioral studies using a variety of paradigms demonstrated evidence for an impairment of the usual encoding benefit from semantic processing in ASD.

Our results demonstrating Broca's area activation in control subjects in response to a Semantic vs. Perceptual word processing task (Semantic > Perceptual activations) are consistent with numerous studies pointing to semantic processing functions localizing to this region of left inferior prefrontal cortex (LIPC). Several PET and fMRI studies (Bookheimer, 2002; Chee et al., 1999; Demb et al., 1995; Kapur et al., 1994; Muller et al., 2003; Newman et al., 2003; Poldrack et al., 1999) have been consistent in identifying a lateral portion of LIPC as a site activated by the processing of verbal stimuli at semantic compared to perceptual levels in healthy individuals. Our robust activations in BA45 and BA47 in normal control subjects closely match the Talairach coordinates reported in prior studies (Poldrack et al., 1999; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001). It has been hypothesized that this area may subserve semantic processes that are active when normal individuals encode verbal information for meaning.

For a review of the role in semantic processing of Broca's area, and its subdivisions in LIPC, particularly the left inferior frontal gyrus (IFG), and a summary of studies demonstrating centers of activation for semantic, syntactic, and phonological processing in the left IFG, see (Bookheimer, 2002). Semantic areas tend to cluster around the anterior, ventral IFG (pars orbitalis, Brodmann area 47), while more posterior, superior portions of IFG (pars opercularis and pars triangularis, Brodmann areas 44 and 45) are more responsive to phonological and syntactic processing. Functional neuroimaging has demonstrated that ventral inferior frontal gyrus, BA47, is involved in semantic processing per se in normal control subjects (Poldrack et al., 1999). Activation of this region (BA47) is not related to phonological and syntactic processing that takes place in more superior and posterior portions of the inferior prefrontal cortex, in BA44 and BA45. The role of BA47 during semantic processing appears more involved with response selection and the implementation of task parameters or with guiding the retrieval of information in posterior semantic areas. In fact, activation in this region is modulated by task parameters like the difficulty of the selection process (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Thompson-Schill, D'Esposito, & Kan, 1999; Wagner et al., 2001).

In the present study, as expected, control subjects demonstrated significant peaks of activation for the contrast between the Semantic and the Perceptual tasks both in BA47 related to semantic processing and BA45 related to phonological processing. Activation in BA45 is expected because our experiment did not control for the automatic activation of phonological representations during the Semantic task. While the most robust activation for control subjects for the Semantic vs. Perceptual task contrast was in BA45 and BA47, this contrast only showed differential task activation in BA47 alone in ASD.

The ASD subjects achieved the same level of behavioral performance as the control subjects, suggesting that any difference between groups in the pattern of neuronal activation is irrelevant in terms of performance to this Semantic task. Furthermore, the absence of Semantic vs. Perceptual activation in BA45 in the group of ASD patients appears to be at least partly the result of increased activation in this region during the Perceptual control task. Thus, in the current study, the ASD subjects appeared to be doing relatively more semantic work during the Perceptual judgment task, which may partially explain the overall reduction in differential Semantic vs. Perceptual task activation in Broca's area BA45 in ASD. These results suggest that ASD patients were more likely to access the phonological and syntactic representation of the items during the Perceptual task than control participants.

Alternatively, the ASD subjects may rely less on Broca's area for linguistic processing. For example, in the current study, the ASD group displayed increased activation for the Semantic > Perceptual task contrast in BA21 in middle temporal gyrus, a temporal lobe region involved in semantic processing, but a region that did not display significant activation for this contrast in the control subjects. Thus, adults with ASD in this study demonstrated not only reduced frontal language regional activation, but also increased temporal lobe language-related regional activation for semantic processing, consistent with the findings reported by Just et al. (2004) for sentence comprehension. While Just et al. (2004) assessed activation in response to sentence processing, our paper is the first to investigate lexical semantic processing for single words in ASD, and in particular, for words of varying abstract and concrete classes. While the Semantic and Perceptual mean activations in the left middle temporal gyrus (BA21) region were comparable between tasks in the control subjects in the current study, resulting in no activation difference between tasks, the ASD subjects had a larger difference between tasks in this region, leading to significant Semantic > Perceptual contrast in ASD subjects, even though each group activated this region for each task when contrasted with fixation baseline. Taken together, the activation pattern differences between ASD and control subject groups in Broca's area (BA45) and left middle temporal gyrus (BA21) during Semantic and Perceptual word processing indicate that alternative networks are enrolled and activated in ASD during language processing tasks compared with control subjects.

Several functional and structural imaging studies have identified irregularities in language-related regions in ASD. In the functional imaging literature, as discussed above, a recent fMRI study by Just et al. (2004) focused on a sentence comprehension task in high-functioning adults with autism, and consistent with the current study, found reduced Broca's area activation in the autism group. Furthermore, PET and SPECT studies reported abnormal language-related asymmetry in autism. High-functioning adults with autism demonstrated reversed hemispheric dominance during verbal auditory stimulation observed with PET (Muller et al., 1999). Consistent with these observations, a SPECT study reported reversal of rCBF asymmetry in frontal language regions in children with autism compared with controls (Chiron et al., 1995), and another SPECT study reported decreased left inferior frontal rCBF in children with autism (Ohnishi et al., 2000). Studies using evoked potentials (Dawson, Finley, Phillips, & Lewy, 1989; Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1995) or fMRI (Takeuchi, Harada, Matsuzaki, Nishitani, & Mori, 2004) suggest that children with autism are more likely than normal children to show right-hemisphere lateralization for language.

Abnormalities in LIPC/IFG (Broca's area) have also been reported in structural imaging studies of ASD. For example, in a study using voxel-based morphometry, left inferior frontal gray matter was decreased in autism (Abell et al., 1999). Furthermore, boys with ASD demonstrated abnormal cortical volume asymmetry of Broca's area (De Fosse et al., 2004; Herbert et al., 2002). MRI studies of handedness and language-dominance have reported larger left-hemisphere cortical language regions in right-handed, left-hemisphere language dominant normal subjects (Foundas, Leonard, Gilmore, Fennell, & Heilman, 1994; Foundas, Leonard, Gilmore, Fennell, & Heilman, 1996; Foundas, Leonard, & Heilman, 1995; Steinmetz, Volkmann, Jancke, & Freund, 1991). A portion of Broca's area was specifically correlated with handedness in normal subjects, larger on the right in left-handed subjects and larger on the left in right-handers (Foundas, Eure, Luevano, & Weinberger, 1998). In quantitative volumetric MRI studies of right-handed, language-impaired boys with autism, as well as in right-handed boys with specific language impairment (SLI), this typical pattern of Broca's area asymmetry was reversed, i.e., larger right-sided volumes, whereas the typical asymmetry pattern of larger left-sided volume in Broca's area was observed in normal control boys (De Fosse et al., 2004; Herbert et al., 2002). However, right-handed *language-normal* boys with autism had the typical left-sided asymmetry pattern in Broca's area similar to the language-normal control boys, in contrast to the reversed pattern in the *language-impaired* groups with autism or SLI (De Fosse et al., 2004). Based on studies to date, it is difficult to determine whether this reversal of Broca's asymmetry in language-impaired boys with ASD, also observed in boys with specific language impairment, is a predisposing factor toward language-impairment or a compensatory neurodevelopmental response to language dysfunction in the left-hemisphere. One possible explanation is that language-impaired children with ASD or SLI do not acquire language normally during toddler and preschool years, and in response, the structural and functional organization of language areas does not follow typical patterns as a result of differences in language experience. Alternatively, genetic transcription factors may lead to atypical asymmetry patterns that emerge very early in fetal development. Sun et al. recently identified a significant number of genes that were differentially expressed in the left and right perisylvian regions in cortices from 14-week-old fetuses (Sun et al., 2005). These important findings suggest that genetic factors may contribute to the normal development of cerebral asymmetry, and may influence the atypical asymmetry patterns reported in autism and SLI. However, in the current study with language-normal, high-functioning right-handed subjects with ASD, we would not expect structural asymmetry reversal in Broca's area, nor did we observe a reversal of fMRI activation in Broca's area, but rather a lack of differential activation between semantic and perceptual word tasks in this left-hemisphere region in ASD.

Control subjects also activated an extensive area of medial superior frontal gyrus (BA8). This is an area associated with eye movements (Talairach & Tournoux, 1988), which has also been identified as a region activated in normal control subjects during Theory of Mind tasks (Fletcher et al., 1995; Gallagher & Frith, 2003). Perhaps this area was significantly activated during semantic processing because we included mental state words and we asked participants to make an evaluation of the words as positive or negative. A third region that was significantly activated during semantic processing in the control group was the right cerebellum. The cerebellum has direct, contralateral connections to Broca's area, which enable the cerebellum to facilitate verbal abilities (Leiner, Leiner, & Dow, 1989). Thus, in normal subjects, semantically processed words activated both Broca's area in LIPC, and a contralateral region in right cerebellar hemisphere.

In contrast to the controls, the ASD group did not show activation in either medial superior frontal gyrus (BA8) or right cerebellum. The absence of activation in ASD subjects in BA8, a region associated with theory of mind processing, is consistent with other imaging studies in ASD that reported an absence of activation in this area during a theory of mind task (Happe et al., 1996). The absence of activation in right cerebellum may reflect reduced neural connectivity for language processing, as reported in Just et al. (2004) who found lower integration across cortical networks involved in sentence processing.

Extending from the behavioral studies discussed above that identified abnormal semantic versus perceptual processing, further behavioral research indicated that control subjects demonstrated an encoding memory benefit effect for concrete relative to abstract words, but ASD subjects did not (Toichi & Kamio, 2003). In that report, control subjects showed better memory for concrete than abstract words, an effect that correlated with the number of associations the subjects were able to make to the words. In contrast, autistic subjects showed no difference between concrete and abstract words in the context of overall performance equal to that of the control group.

Therefore, in addition to comparing Semantic to Perceptual activation patterns, we compared activation patterns in response to Abstract and Concrete words during the Semantic processing task. The control group displayed much stronger differential fMRI activation patterns than the ASD subjects when contrasting Concrete and Abstract word stimuli on the Semantic task in a variety of brain regions (see Table 3), a finding consistent with the concrete vs. abstract behavioral observations in ASD discussed above. The greater activation in parahippocampal gyrus for Concrete relative to Abstract words may be related to a greater activation of tangible memories for concrete objects relative to abstract terms. We note however, that the brain regions activated in this study in the control participants are not consistent with other imaging findings that compared abstract and concrete word categories (Jessen et al., 2000; Kiehl et al., 1999; Mellet, Tzourio, Denis, & Mazoyer, 1998). Even though ASD subjects responded behaviorally similarly to the controls based on the task responses and reaction times for each word class, the fMRI activation results suggest that the cognitive and mental constructs for representing and processing concrete and abstract words are relatively similar for these word classes in ASD, whereas cognitive processing of these word classes is more distinct in control subjects.

In the current study, performance difficulty could impact our Abstract/Concrete contrasts in the Semantic task, since the proportion of positive Semantic responses was significantly lower for Mental State abstract words, and response latencies tended to be shorter than for the two other categories, suggesting that semantic judgments about the Mental State abstract words were made more easily. The difficulty of the task could impact the comparison between Mental State abstract words and other kinds of concepts (as well as the Semantic comparison between Abstract and Concrete stimuli since Mental State words were considered abstract). However, the groups performed these tasks similarly, and no group differences were observed for Mental State vs. Metaphysical abstract behavioral performance or fMRI activation, indicating that the groups did not differ behaviorally in performance difficulty, and thus, this effect may not be differential between groups.

Finally, based on prior behavioral studies indicating that ASD subjects have atypical processing of mental state words (Baron-Cohen et al., 1986; Tager-Flusberg, 1992), have deficits in understanding mental states (Baron-Cohen et al., 1993, Baron-Cohen, Tager-Flusberg, & Cohen, 2000) and use mental state terms significantly less frequently than controls (Tager-Flusberg, 1992), we included both Mental State and Metaphysical abstract word classes, predicting that individuals with ASD would differ in their pattern of activation in comparison to controls. A prior SPECT study in cognitively normal adults reported activation in right orbito-frontal cortex during a mental state word task (Baron-Cohen et al., 1994). However, we were not able to identify differential activation between these two types of abstract words in the current study. The orbito-frontal region is subject to susceptibility artifacts in fMRI, limiting signal from this region and making fMRI analysis problematic. To confirm this, we created SPM maps of each subject's activation pattern, displaying all voxels that had adequate echo-planar signal to create the analysis. For most subjects in both groups, there was an absence of fMRI signal for SPM analysis in orbito-frontal regions due to susceptibility artifacts associated with its close proximity to the sinus cavities. This resulted in orbito-frontal regions being excluded from the SPM analyses. Therefore, we cannot draw direct comparisons with this earlier SPECT study.

In conclusion, the current study identified abnormal language-related regional fMRI response in Broca's area (left inferior prefrontal cortex, BA45) and left middle temporal gyrus (BA21) during "deep" (Semantic) vs. "shallow" (Perceptual) processing of visually presented words in adults with ASD. Thus, even in high-functioning adults with ASD who performed the task well, semantic processing activation viewed by fMRI does not demonstrate the normal robust activation pattern in Broca's area seen in matched controls. Subjects with ASD also showed diminished differential fMRI activation to Concrete vs. Abstract words. These fMRI findings are consistent with other behavioral studies showing reduced "levels-of-processing" recall benefit for "deep" semantically processed words relative to "shallow" perceptually processed words (Toichi & Kamio, 2002), and for concrete relative to abstract words (Toichi & Kamio, 2003). Prior imaging reports in ASD have also identified Broca's area as having abnormal structural asymmetry or language function (De Fosse et al., 2004; Herbert et al., 2002; Just et al., 2004). Taken together, these structural and functional imaging studies suggest a neurodevelopmental, neuroanatomical, and neurophysiological basis for the language deficits often present in individuals with ASD, even high-functioning individuals without pervasive language impairment.

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Appendix A. Word Stimuli

Syllable length	Concrete	Mental State abstract	Metaphysical abstract
1	tongue	guilt	fate
	crowd	trust	risk
	fruit	hate	hint
	bag	doubt	fail
	plane	fear	soul
	iron	mad	lack
	heart	dream	cause
	stick	hope	luck
	hat	guess	deal
	plant	glad	worth
	hand	wish	chance
	sun	want	gone
	saw	think	take
	house	know	find
2	missile	regret	justice
	ankle	assume	promise
	doorway	concern	attempt
	motor	ashamed	challenge
	shoulder	aware	account
	doctor	expect	duty
	dollar	worry	effort
	forest	forget	purpose
	cattle	reason	culture
	machine	decide	freedom
	lady	wonder	safety
	garden	believe	describe
	table	suppose	common
	mother	surprise	famous
3	avenue	intention	essential
	professor	fantasize	distinction
	vehicle	suspicion	genuine
	magazine	concentrate	advantage
	microphone	desire	agreement
	ambulance	amazement	description
	restaurant	sympathy	tradition
	photograph	embarrassed	excellent
	camera	confusion	condition
	uniform	consider	influence
	hospital	recognize	liberty
	telephone	imagine	evidence
	library	understand	importance
	radio	remember	quality

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