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Semantic, Factual, and Social Language Comprehension in Adolescents with Autism: An FMRI Study

Language in high-functioning autism is characterized by pragmatic and semantic deficits, and people with autism have a reduced tendency to integrate information. Because the left and right inferior frontal (LIF and RIF) regions are implicated with integration of speaker information, world knowledge, and semantic knowledge, we hypothesized that abnormal functioning of the LIF and RIF regions might contribute to pragmatic and semantic language deficits in autism. Brain activation of sixteen 12- to 18-year-old, high-functioning autistic participants was measured with functional magnetic resonance imaging during sentence comprehension and compared with that of twenty-six matched controls. The content of the pragmatic sentence was congruent or incongruent with respect to the speaker characteristics (male/female, child/adult, and upper class/lower class). The semantic- and world-knowledge sentences were congruent or incongruent with respect to semantic expectancies and factual expectancies about the world, respectively. In the semantic-knowledge and world-knowledge condition, activation of the LIF region did not differ between groups. In sentences that required integration of speaker information, the autism group showed abnormally reduced activation of the LIF region. The results suggest that people with autism may recruit the LIF region in a different manner in tasks that demand integration of social information.

Keywords: autism, brain, Broca's area, integration, pragmatics

Introduction

Autistic disorder (or autism) is characterized by impairments of verbal and nonverbal communication, along with impairments in reciprocal social interaction, and restricted behaviors and interests (American Psychiatric Association 1994). Autistic individuals tend to use language instrumentally in a nonreciprocal fashion rather than for social and communicative purposes, and they have difficulties with the implicit social rules that govern the use of language (i.e., pragmatics). Some people with autism never develop language (Rapin 1991), and in all individuals with autism, even the most highly functioning, linguistic deficits are present. The linguistic impairments include syntactic (Eigsti et al. 2007), semantic (Kjelgaard and Tager-Flusberg 2001), and to some extent phonologic deficits (Rapin and Dunn 2003). However, pragmatics is typically the most severely affected domain of language in autism (Boucher 2003).

Despite the well-researched clinical manifestations of the language impairments in autism, little is known about their neural basis (Groen et al. 2008). Linguistic stimuli led to greater right than left-hemisphere evoked response potentials in children with autism than in controls (Dawson et al. 1986). A positron emission tomography study also suggested reversed

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hemispheric language dominance in autism and found reduced cerebellar activation during auditory perception in autism (Müller et al. 1999). Recent functional magnetic resonance imaging (FMRI) studies have suggested that activation of the posterior-superior temporal region is increased, whereas activation of the left inferior frontal (LIF) region is decreased in sentence reading (Just et al. 2004) and single-word semantic decision tasks (Harris et al. 2006; Gaffrey et al. 2007). These findings are consistent with the hypothesis that the LIF region is affected by abnormal neurodevelopment in autism and that this is linked to the observed characteristic language deficits. Furthermore, greater occipital activation during visually presented language processing has been observed in participants with autism in 2 studies (Kana et al. 2006; Gaffrey et al. 2007). An FMRI study found robust occipital activation in participants with autism, but not in controls, that correlated with the number of errors in a semantic word categorization task (Gaffrey et al. 2007). Another FMRI study contrasted low-imagery sentences with high-imagery sentences and also found greater occipital participation (Kana et al. 2006). Additionally, decreased functional connectivity was observed (a lower degree of correlation of activation time series) between language and spatial processing regions in the autism group. Decreased functional connectivity among various cortical regions was also found in an earlier language FMRI study in autism (Just et al. 2004), giving rise to the hypothesis that autism entails an abnormal degree of integration of neural information across cortical regions.

Cognitive tests do not always accurately predict real-life behavior and capabilities in autism. People with autism may succeed in certain tasks in the laboratory or in clinical settings, whereas in real life, they fail to respond adequately in situations that appear to require the same abilities (Channon et al. 2001). This reflects an important problem that applies to studies that require explicit judgment or processing in autism. When instructed to explicitly process a set of stimuli, the neural correlates of the explicit task and the neural correlates of the implicit cognitive process under investigation may become confounded. For example, 2 studies on irony perception in autism differed mainly in tasks instruction but yielded opposite results (Wang et al. 2006, 2007). Although in both studies children actively judged whether speakers were being sincere or ironic, the authors found increased activation in of the right superior temporal regions in the first study (Wang et al. 2006) and decreased activation in left and right temporal regions in the second study (Wang et al. 2007). Of note, the first study only required implicit attention to prosodic clues, whereas in the second study, participants were explicitly instructed to attend to tone of voice and facial expression. These results thus

illustrate how task context is critical for real-life performance. To be able to generalize findings to real-life situations, we designed a study that assessed the ability to integrate linguistic contextual information that required implicit online processing only. Our goal was to investigate language function in autism based on a language model that focuses on the integrative capacities of the left IF gyrus (LIFG) centered on Broca's complex (Hagoort 2005).

According to the theory of decreased functional connectivity in autism, key cortical components involved in integrating neural input from lower sensory areas will show reduced activation during tasks that require integration (Belmonte, Allen, et al. 2004). In healthy subjects, one such key area is the LIFG that is involved in semantic unification (Hagoort et al. 2004, Hagoort 2005). In a series of experiments, Hagoort and colleagues (for a review see Hagoort and van Berkum 2007) found that language comprehension involves rapid incorporation of information conceptualized as taking place in parallel and with the recruitment of LIFG as a unification domain (Vosse and Kempen 2000; Jackendoff 2008). In this framework, information includes semantic knowledge (word meanings are integrated into a meaningful sentence), world knowledge (sentence meaning is combined with stored knowledge about the world; Hagoort et al. 2004), speaker information (sentence meaning is combined with knowledge about the speaker; Van Berkum et al. 2007), and information from other modalities (sentence meaning is combined with gestures; Willems et al. 2007). Specifically, fMRI experiments in healthy subjects showed that the LIFG is more activated when sentences are presented in which a critical word does not fit the context semantically (e.g., "Dutch trains are 'sour'"), reflecting a greater difficulty or greater unification load for combining the individual words into a meaningful whole. Similarly, sentences at odds with voice-based inferences of gender, age, and social class increased LIFG activation (for coordinates of the center of activation, see the Materials and Methods section) (Tesink et al. 2009b) and triggered an N400 effect (Van Berkum et al. 2007). Most important for the study at hand, however, are our results in adults with autism and controls. We found an increase in the right hemisphere IFG homologue in the autism group during sentences at odds with speaker identity (Tesink et al. 2009a). We interpreted the increased RIFG activation in high-functioning adults with autism as a compensation strategy to resolve social challenges, resulting from spillover processing from the language dominant left hemisphere due to higher task demands for the autism group. Of note, our previous study (Tesink et al. 2009a) used the same implicit auditory stimulus paradigm (i.e., 4 classes of sentences: correct sentences; sentences with a semantic anomaly; sentences with a world-knowledge anomaly; and sentences with a speaker inference anomaly) but rather than adolescents, high-functioning autistic adults and controls with an average age of 26 years participated. There was no pseudo-word target condition in the adult trial.

In the current study, 4 classes of sentences (correct sentences; sentences with a semantic anomaly; sentences with a world-knowledge anomaly; and sentences with a speaker inference anomaly) were presented to high-functioning adolescents with autism (12–18 years old) and matched controls (matched for age, gender, handedness, and IQ). We hypothesized that the LIFG in participants with autism would show reduced activity in speaker-incongruent, semantic-incongruent, and world-knowledge-incongruent sentences. The reduced

activity of the autism group might be more pronounced in the socially incongruent condition. This hypothesis is based on evidence of a reduced tendency to integrate information into a composite whole in autism. In healthy subjects, words that are incongruent with sentence meaning increase the neural processing load needed to integrate the separate words into a meaningful whole. Because we had previously found a difference between adults with autism and controls in the RIFG for the speaker-incongruent condition (Tesink et al. 2009a), we were also interested in the auxiliary role of the RIFG in children and adolescents. As autism is a developmental disorder by definition, we aimed to investigate to what extent this right-sided compensation strategy had evolved in children and adolescents with autism. Importantly, we did not ask participants to make explicit sentence judgments as then the processing would be implicit and thus reflect real-life situations more closely.

Materials and Methods

Participants

Two groups participated in the study: 30 adolescents with high-functioning autism and 31 matched, typically developing (TD) adolescents. All participants were Caucasian adolescents aged between 12 and 18 years. Exclusion criteria were left handedness, IQ (total, verbal, or performance) lower than 85, any general medical condition affecting brain function, neurologic disorders, and substance abuse. The study was approved by the local medical ethics committee. Informed consent was obtained from all participants and their parents. Due to excessive head movements during MRI data acquisition, defined as a translation of more than one voxel in either direction, 5 sessions from the control group and 14 sessions from the autism group were excluded from further analysis so that 16 participants with autism and 26 TD participants were entered in the final analysis.

The participants with autism were recruited from referrals to Karakter Child and Adolescent Psychiatry University Center in Nijmegen. Diagnostic assignment followed DSM-IV criteria for autistic disorder (American Psychiatric Association 1994). Diagnostic characterization included the Autism Diagnostic Interview—Revised (Lord et al. 1994) as assessed by a trained professional and a series of clinical assessments that included a detailed developmental history, clinical interview and observation, medical workup, and cognitive testing. The participants with autism were tested with the full Wechsler Intelligence Scale for Children III to assess their IQ (Wechsler 1991). Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield 1971).

Control participants were recruited through local schools. To exclude psychiatric disorders or learning problems, CBCL questionnaires (Child Behavior Check List) (Achenbach 1991a) were completed by the parents/guardians and TRF questionnaires (Teacher Report Form) (Achenbach 1991b) were completed by a teacher at school. None of the control participants had problem scores for the narrow-band or broadband scales on the CBCL or TRF in the clinical range. To obtain an estimate of the IQ, a short form of the Wechsler Intelligence Scale for Children III including Vocabulary, Similarities, Block Design and Picture Completion (Psychological Corporation 1999) was administered. The control group was matched to the autism group for age, gender, handedness, head circumference (maximal occipital-frontal head circumference), total IQ, performance IQ, and verbal IQ. None of the participants used psychotropic medication (see Table 1).

Data Acquisition

The fMRI data were acquired at the Donders Center for Cognitive Neuroimaging, Nijmegen, the Netherlands, on a 1.5-T Siemens Sonata whole-body scanner (Erlangen, Germany). The auditory stimuli were presented through headphones, and the visual stimuli were projected onto a translucent screen that participants could view through a mirror

Table 1

Demographics

	Mean (SD)		<i>P</i> value
	Autism group (<i>N</i> = 16)	Control group (<i>N</i> = 26)	
Age	15.3 (1.6)	15.7 (1.7)	0.594
Handedness	83.2 (16.7)	81.7 (18.0)	0.905
Total IQ	100.4 (20.6)	105.3 (8.7)	0.263
Verbal IQ	101.9 (18.9)	105.1 (9.8)	0.396
Performance IQ	98.8 (20.0)	105.7 (11.9)	0.160
Gender (m/f)	12/4	21/5	0.742
ADI Social (10)	17.9 (5.6)	—	—
ADI Verbal (8)	13.7 (5.1)	—	—
ADI Stereotypy (3)	4.1 (3.1)	—	—
ADI Onset (1)	1.8 (1.0)	—	—

Note: ADI, Autism Diagnostic Interview—Revised (The ADI-R is a clinical diagnostic instrument for assessing autism in children and adults. The instrument focuses on behavior in 3 main areas: qualities of reciprocal social interaction; communication and language; and restricted and repetitive, stereotyped interests and behaviors.). SD, standard deviation; and ADI-R thresholds are shown in parentheses.

mounted on the head coil. Functional images were acquired using a gradient echo planar imaging sequence (time repetition 2440 ms, time echo 40 ms, flip angle 90 deg, 31 adjacent oblique-axial slice in interleaved sequence, field of view 224 mm, matrix 64 × 64, in-plane resolution 3.5 × 3.5 mm with a 0.5-mm slice gap). In order to include the entire cerebellum, a small part of the superior parietal cortex was not scanned in a number of participants. For anatomical localization, a 3D Magnetization Prepared Rapid Acquisition GRE pulse sequence with 1-mm resolution was used.

FMRI Stimuli Paradigm

In a separate session prior to the MRI scanning procedure, all participants practiced the experimental paradigm in a dummy scanner to get adjusted to the scanner environment. To make sure that the participants focused their attention on the auditory stimuli without enforcing explicit processing of the sentence meaning, participants were asked to perform a task that was orthogonal to the experimental conditions of interest. That is, the task entailed pushing a button upon hearing the target condition, that is, sentences that only contained pseudowords. All participants were able to master the experimental task in the practice session without mistakes. The sentences used in the practice session were different from those in the actual experiment.

The MRI scanning was done in 2 30-min runs with a 30-min break in between. Spoken sentences were presented in a pseudorandomized event-related design, with an interstimulus interval jittered in 0.5-s steps from 8.2 to 9.7 s after each sentence during which an asterisk was shown. The participants were asked to attentively listen to all sentences and to press a button whenever they heard a sentence that contained pseudowords.

Apart from the target condition, 80 pairs of sentences that differed only with respect to the speaker voice (male/female, child/adult, upper class/lower class; referred to as speaker-identity condition), 36 triplets of sentences that differed only with respect to one critical word (no anomaly; semantic anomaly; and world-knowledge anomaly) and 36 speech-like noise fragments matched on spectral and temporal properties with an average duration of 3.0 s (Dreschler et al. 2001) were used (referred to as noise condition). The critical words were matched on word frequency, average length, and word class. The sentences were recorded in a sound studio by a total of 26 actors, 2 of whom were children.

The speaker-identity sentences were utterances in which sentence meaning did or did not match voice-based expectations about speaker's age, gender, or social background. Examples were: "I have a very large tattoo on my back" spoken in an upper class and a lower-class accent; "Every morning, I drink a cup of coffee at breakfast" spoken by a child and an adult; and "If only I looked like Britney Spears in her latest video" spoken by a male and a female. For this condition, there were 40 sentences that were congruent and 40 sentences that were in-

congruent with the speaker's gender; 20 sentences that were congruent, and 20 sentences that were incongruent with speaker's age; 20 sentences that were congruent and 20 sentences that were incongruent with speaker's social status. We counterbalanced the sentences pairs over the participants so that only one sentence of each pair was played per participant.

The world knowledge and semantic-knowledge sentences were piloted among 90 12-year-old, high-school children to ensure that they knew the world knowledge and semantic knowledge referred to in the sentences. Only those sentences that could be understood and explained correctly (for the semantic-knowledge condition) or appreciated for their veridicality (in the world-knowledge condition) were used in the experiment. Examples were "Dutch trains are sour" (semantic anomaly) and "Dutch trains are white." The last sentence comprises a world-knowledge anomaly because it is a well-known fact among Dutch people that Dutch trains are yellow. In the example, the third sentence of the triplet was "Dutch trains are yellow" containing no anomaly. In the current experiment, 36 triplets (world-knowledge anomaly, semantic-knowledge anomaly and no anomaly) of sentences were used. These sentences were also counterbalanced over participants.

Data Analysis

The data were preprocessed and statistically analyzed with SPM5 (Wellcome Department of Cognitive Neurology, London). The first 5 volumes of every functional run were discarded from the analysis to minimize transient T1 saturation effects. Preprocessing included motion correction, slice-time correction, and spatial normalization to the MNI305 stereotactic space using linear affine registration, followed by nonlinear registration using cosine basis functions, resampling to 2-mm-cubic voxels, and finally smoothing with an isotropic 3D Gaussian kernel (full width at half maximum 10 mm). The event-related design was convolved with a canonical hemodynamic response function provided by SPM5. Statistical analysis was performed on individual and group data by using the general linear model, and group analyses were performed using a random effects model. In the individual and group analysis, the sentences consistent with the speaker's gender, social status, or age were collectively contrasted with the sentences that were inconsistent with speaker's gender, social status, or age. Also, the sentences with world-knowledge and semantic anomalies were contrasted with the normal control sentences. The speech-like noise fragments were also contrasted with normal sentences. To account for signal changes due to head motion, the 6 realignment parameters were entered as regressors for each participant.

Region of Interest (ROI) Analysis

Because we had specific hypotheses about the integrating role of the IFG, we performed ROI analysis in this region (see Introduction). In our previous 2 experiments, brain regions that are involved with the integration of speaker characteristics and sentence meaning were identified in the LIFG and RIFG (Tesink et al. 2009a, 2009b). Specifically, Tesink et al. found the center of activation at $-54, 26, 14$ (*x, y, z*, mm, MNI coordinates) in the LIFG and $50, 34, 12$ in the RIFG in healthy adult controls (these ROIs were also used in our study of adults with autism (Tesink et al. 2009a). In our meta-analysis of the linguistic involvement of the prefrontal cortex (Pettersson et al. 2004), we found that the pars opercularis ($-46, 12, 26$ in MNI space) is activated during phonologic integration. Thus, this region corresponds with the integration of the acoustic elements that carry the information about speaker identity, so that voice-based inferences on speaker's gender, age, and social status can be made. Therefore, in these 3 areas, we defined ROIs with a radius of 15 mm centered at the abovementioned coordinates (see Fig. 1). ROIs were thresholded at $P = 0.001$ uncorrected. Activation within the ROIs was considered significant at a voxel, cluster or set-level threshold of $P = 0.05$ corrected for multiple comparisons.

Whole-Brain Analysis

For all contrasts, a second-level random effects analysis of the whole brain was performed. Images were thresholded at $P < 0.001$; the cluster size was used as the test statistic; and only clusters significant at $P < 0.05$ and corrected for multiple nonindependent comparisons are reported. All local maxima are reported as MNI coordinates.

Results

The ROI results are shown in Table 2. The 3 ROIs were analyzed for every condition. The location and extent of significant clusters is the whole-brain analysis in the control and autism group are shown in Tables 3 and 4 and Figure 2. Activation differences derived from the random effects group comparison are depicted in Figure 3 and Table 5. Only results with $P < 0.05$ corrected for multiple nonindependent comparisons are reported.

ROI Results

To test our hypotheses about integration of speaker identity, we firstly tested the speaker-incongruent greater than speaker-congruent contrast in the control group. As we had hypothesized, both the LIFG ($-54, 26, 14$) and the RIFG ($50, 34, 12$) were significantly activated. The autism group, however, failed to activate those ROIs in the speaker-identity contrast. In the inverse contrast (congruent greater than incongruent), neither



Figure 1. ROIs: Figure 1 shows the location of the 3 predefined ROIs. Left brain: RIFG, pars triangularis ($50, 34, 12$) and middle: LIFG, pars triangularis ($-54, 26, 14$). These coordinates represent the center of activation for integrating speaker identity and sentence meaning as observed in healthy adults (Tesink et al. 2009b). Left: LIFG, pars opercularis ($-46, 12, 26$). These coordinates reflect the phonologic integration area (needed for voice-based inferences of speaker's identity) found in a meta-analysis of the linguistic involvement of the prefrontal cortex (Pettersson et al. 2004).

Table 2
Activations in ROIs

Region	BA	X	Y	Z	Contrast	Z	P
Control > autism							
LIFG, pars triangularis	45	-54	26	14	Speaker incongruent > speaker congruent	3.15	0.01 ^a
LIFG, pars opercularis	44	-46	12	26	Speaker incongruent > speaker congruent	3.15	0.01 ^a
Autism > control							
RIFG, pars triangularis	45	50	34	12	World-knowledge anomaly > no anomaly	3.78	0.02 ^b
Controls							
LIFG, pars triangularis	45	-54	26	14	Speaker incongruent > speaker congruent	3.19	0.05 ^b
					World-knowledge anomaly > no anomaly	4.01	<0.01 ^b
					Semantic-knowledge anomaly > no anomaly	4.78	<0.01 ^b
					Normal sentence > noise	3.85	<0.01 ^b
RIFG, pars triangularis	45	50	34	12	Speaker incongruent > speaker congruent	3.27	0.01 ^a
					Semantic-knowledge anomaly > no anomaly	3.60	<0.01 ^a
Autism							
LIFG, pars triangularis	45	-54	26	14	World-knowledge anomaly > no anomaly	4.04	<0.01 ^b
					Semantic-knowledge anomaly > no anomaly	4.87	
					Normal sentence > noise	4.53	<0.01 ^b
RIFG, pars triangularis	45	50	34	12	World-knowledge anomaly > no anomaly	3.72	0.03 ^b

^aSet level corrected (set-level refers to the inference that the number of clusters comprising an observed activation profile is highly unlikely to have occurred by chance).

^bVoxel level corrected and BA = Brodmann area.

group activated any ROI. In the direct group comparison, the LIFG ($-54, 26, 14$) was significantly more activated in the control group, whereas the RIFG did not yield significant differences. Secondly, we tested the world knowledge greater than correct sentence contrast. In the control group, the random effects analysis produced significant activation in the LIFG ($-54, 26, 14$) but not in RIFG. In the autism group, however, the world-knowledge contrast yielded significant activation in both the RIFG and LIFG ($-54, 26, 14; 50, 34, 12$). This difference was also seen in the direct group comparison, in which the autism group showed greater activation of the RIFG ($50, 34, 12$). Interestingly, there was no group difference in the LIFG in this condition. Again, the inverse contrasts did not produce significant results. Thirdly, we tested the semantic-knowledge condition. In the control group, we found significant activation in the LIFG and RIFG ($-54, 26, 14; 50, 34, 12$). In the autism group, we found significant activation only in the LIFG ($-54, 26, 14$). Yet, these differences were not found in the direct group comparison for random effects. Fourthly, we tested the speech versus noise contrasts. In the control group, correct sentences produced greater activation than speech-like noise in the LIFG ($-54, 26, 14$). In the autism group, only the ROI located at the coordinates $-54, 26, 14$ was significantly activated. Thus, in the control group, the area of main interest, the left pars triangularis of the IFG ($-54, 26, 14$), was activated in all contrasts. The autism group, however, failed to activate this region for the social-speaker-identity contrast, whereas it activated this region for all other contrasts.

Whole-Brain Results

For the whole-brain analysis, we tested the same contrasts as for the ROI analyses. Firstly, we tested the speaker-identity condition. In this condition, speaker-incongruent and speaker-congruent sentences were contrasted. Greater activation for speaker-incongruent than speaker-congruent sentences was observed in the control group in the left and right precuneus and cuneus. Conversely, speaker-congruent versus speaker-incongruent sentences showed greater activation in the right supramarginal, right superior, middle and inferior temporal gyrus, the right superior-frontal gyrus, as well as in the right anterior cingulate cortex and the superior orbital gyrus in controls (see Fig. 2). Interestingly, there were no significant clusters in the autism group in the social condition, suggesting that the autism group does not recruit cortical resources so extensively as the control group during integration of the speaker's identity and message. However, the group comparison did not reveal any significant differences.

Secondly, we tested the world-knowledge condition. In this condition, sentences at odds with well-known facts were contrasted with factually correct sentences. The control group showed distinct activation of language association areas, including the left middle and superior temporal gyrus, the LIFG, and the contralateral cerebellum. In the autism group, the LIF and RIF regions were activated but the temporal regions and the cerebellum were not. Interestingly, direct comparison of the subject groups revealed an area in the left middle occipital gyrus that showed significantly greater activation in the control group.

Thirdly, we tested the semantic-knowledge condition. In the control group, the activation pattern for sentences that contained semantic anomalies contrasted against correct sentences, mirrored the activation pattern for the world-knowledge

Table 3

Significant clusters in the control group

Location of peak activation	BA	<i>P</i>	Cluster size	<i>Z</i>	<i>X</i>	<i>y</i>	<i>z</i>
Speaker incongruent > speaker congruent							
Left/right precuneus/cuneus	7/31	0.013	198	4.07	-6	-82	24
Speaker congruent > speaker incongruent							
Right supramarginal gyrus	40	<0.001	522	4.97	52	-34	42
Right superior/middle/inferior temporal gyrus	20/21/22	<0.001	371	4.74	52	-14	-12
Right superior-frontal gyrus	10	0.001	344	4.71	18	50	10
Right precentral gyrus	4/6	<0.001	333	4.60	32	-18	42
Right rectal gyrus/anterior cingulate cortex/right superior orbital gyrus	11/25/32	<0.001	848	4.59	12	22	-14
World-knowledge anomaly > no anomaly							
Right cerebellum (crus 1/crus 2)		<0.001	826	4.36	32	-70	-40
Left middle/superior temporal gyrus	21/22	<0.001	638	4.35	-56	-42	-2
LIFG/pars triangularis	45/47	<0.001	687	4.14	-52	26	-6
Semantic-knowledge anomaly > no anomaly							
Left superior/middle temporal gyrus	21/22	<0.001	2932	5.02	-54	-2	-14
LIFG	45/47	<0.001	2932	4.91	-42	24	-4
Right cerebellum (crus 1/crus 2)		0.002	301	4.47	16	-82	-32
Normal sentence > speech-like noise							
Left superior/middle temporal gyrus/fusiform gyrus	21/22 19/37	<0.001	5992	6.22	-62	-6	-6
Left fusiform gyrus	37/19	<0.001	744	5.52	-36	-40	-22
Left middle cingulate cortex	32	<0.001	1284	5.41	-8	8	42
Right superior temporal gyrus	22	<0.001	2393	5.36	62	2	-10
Right fusiform gyrus	37/19	0.020	199	4.83	26	-4	-42
Left middle occipital gyrus	18/19	<0.001	407	4.36	-16	-96	4
Right cerebellum (crus 1)		0.004	274	4.19	26	-82	-36

Note: BA, putative Brodmann area. *P*, *P* value corrected for multiple comparisons at cluster level. *Z*, highest *Z*-score within a region. *x*, *y*, *z*, stereotactic coordinates in MNI space.

anomalies: distinct activation of the language association regions (left superior and middle temporal gyrus and LIFG) and the contralateral cerebellum. In the autism group, the LIFG was activated, but the temporal areas were not. In contrast to the world-knowledge condition, the RIFG was not activated. However, direct group comparison did not reveal significant differences.

Fourthly, we tested the speech versus noise condition. When sentences were contrasted against noise that resembled the temporal and spectral characteristics of speech, a large number of voxels were significant both in the autism and the control group. These activations included temporal, frontal, and occipital regions. Additionally, in the control group, the left middle cingulate and the right cerebellum were activated. Direct group comparison revealed significantly greater activation in the left middle occipital gyrus in the autism group, the same region that showed greater activation in the control group in the world-knowledge condition. It would therefore appear that during auditory presented sentences, activation of the occipital cortex can be either increased or decreased in autism.

Behavioral Results

After the scanning sessions, all participants underwent an extensive exit interview in which they were asked to state whether they had heard odd sentences. All participants were able to describe the experimental manipulation for world knowledge, semantic knowledge, and speaker inferences and mentioned all three types of incongruencies spontaneously (e.g., world knowledge, semantic knowledge, and speaker inference). Specifically, all participants in both groups could give at least one example of an utterance with a world-knowledge incongruency and a semantic-knowledge incongruency. Speaker inference sentences: All participants in both groups could give at least one example of an utterance in which the speaker's gender was incongruent with the speakers utterance. This was also the case for speaker's age. Finally, 18 of

Table 4

Significant clusters in autism group

Location of peak activation	BA	<i>P</i>	Cluster size	<i>Z</i>	<i>X</i>	<i>y</i>	<i>z</i>
World-knowledge anomaly > no anomaly							
LIFG	47	<0.001	1378	4.72	-42	18	-10
RIFG	45/47	0.002	243	4.17	50	22	2
Semantic-knowledge anomaly > no anomaly							
LIFG	44/45	0.011	199	4.87	-48	22	14
Normal sentence > speech-like noise							
Left middle temporal gyrus	21	<0.001	2664	5.65	-60	-12	2
Right superior/middle temporal gyrus/right rolandic operculum	5/21/22	<0.001	925	5.32	62	0	-6
LIFG	44/45	<0.001	410	4.82	-58	12	26
Left middle occipital gyrus	18/19/37	0.002	271	4.13	-36	-74	6

Note: Only significant clusters are reported. Note that social anomaly contrasts did not yield significantly activated voxels in the autism group. BA, putative Brodmann area. *P*, *P* value corrected for multiple comparisons at cluster level. *Z*, highest *Z*-score within a region. *x*, *y*, *z*, stereotactic coordinates in MNI space.

26 (69%) controls versus 10 of 16 (63%) participants with autism could give at least one example of an utterance in which the sentence meaning did not match voice-based expectations about speaker's social status (*P* = 0.66). Thus, for both groups, the social status anomalies were least salient and to a similar extent in both groups. The behavioral data therefore suggest that the autism group was as able to identify world knowledge, semantic knowledge, and speaker inference incongruencies as the control group and that observed fMRI differences cannot be attributed to behavioral differences.

Discussion

In the current study, we compared brain activation patterns in high-functioning adolescents with autism and well-matched control subjects during sentence processing. For the social contrasts, only the speaker differed so that the content of the

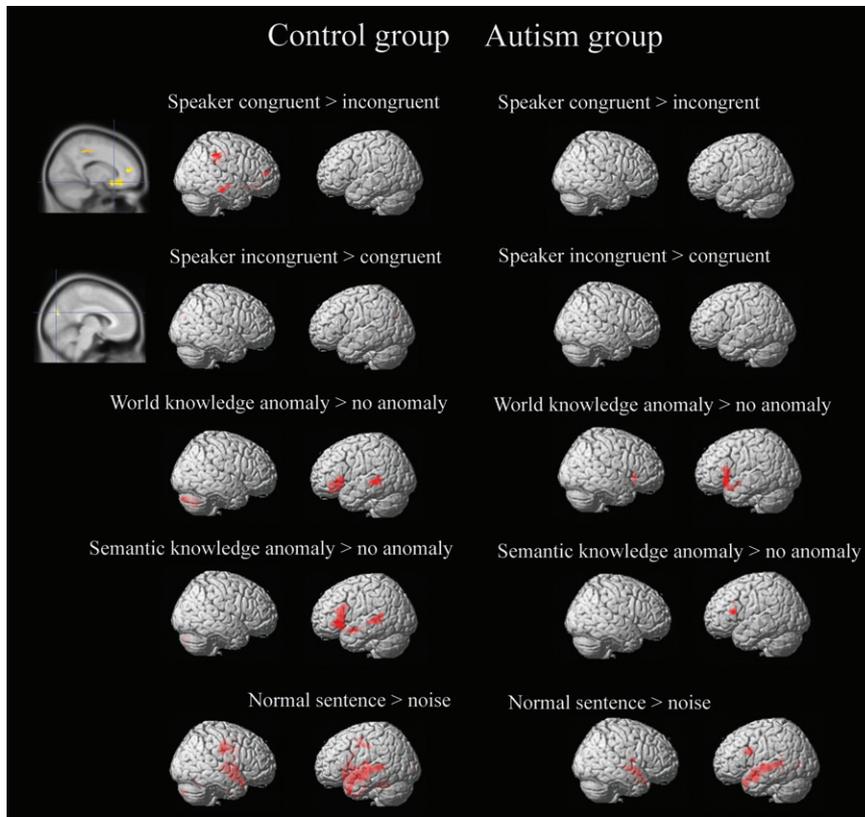


Figure 2. Activation patterns in the control and autism group: Figure 2 shows the random effects analysis of the fMRI activations in 16 autistic participants and 26 control participants. The sagittal slices show activations that are not on the surface of the cortex. In the control group, the social contrasts (speaker congruent and speaker incongruent) gave rise to right-sided activation, whereas there was no significant activation in the autism group. The world-knowledge and semantic-knowledge contrasts gave rise to distinct LIF and posterior-superior temporal region and contralateral cerebellar activation in the control group and to the LIF region activation in the autism group. In the autism group, there was additional right-sided activation in the LIF region homologue in the RIFG. The normal sentence contrasted to speech-like noise resulted in extensive temporal and frontal activation in both groups.

sentence was in line (speaker congruent) or at odds (speaker incongruent) with voice-based inferences of the speaker's age, gender, or social class. For the semantic-knowledge and world-knowledge contrasts, sentences differed only for one critical word that was at odds or in line with knowledge about language or the world. With this paradigm, we could manipulate the unification load, that is, we could manipulate the neural demands of integrating the critical words into the sentence context.

The first main finding was that although the autism group showed activation of the LIF region and the posterior-superior temporal region during world knowledge, semantic knowledge, and noise contrasts, the LIF region showed reduced activation in the autism group during the social contrasts compared with the control group. Thus, the integrative demand imposed by the socially incongruent sentences led to an increased activation of the LIF region in the control group only. The second main finding was that left extrastriate visual regions were involved during auditory language comprehension in the autism group. During the world-knowledge anomaly condition, the autism group showed a reduced activation of the extrastriate area, whereas during a different condition (sentence vs. speech-like noise), the same region was activated. This activation pattern has also been observed during single-word processing, in which autistic participants had to make semantic judgments (Gaffrey et al. 2007). In the following paragraphs, we discuss the implications of the selective social processing deficit and the

putative causes of the atypical extrastriate involvement in language processing in autism.

Because the LIF region subserves integration processes that extend beyond semantic-knowledge and world-knowledge categories (Hagoort and Van Berkum 2007), we hypothesized that individuals with autism would show a reduced activation in the LIF region in the social condition. This was indeed what we found. In addition, we found no activation in the autism group in the social condition, either in the ROI or in the whole-brain analysis. Apparently, in the autism group, speaker-congruent versus speaker-incongruent sentences do not lead to differential activation. In the control group, we found RIFG and LIFG activation for the speaker-incongruent greater than speaker-congruent contrast. For the opposite contrast, large, mainly right-sided areas became active in the control group, including the medial frontal cortex (MFC), temporal areas and the precuneus. The MFC and especially the anterior region of the rostral MFC (BA 10) have been associated with self-knowledge, person perception, and mentalizing (Amodio and Frith 2006). Self-knowledge involves the ability to differentiate the self from others and to recognize subjective preferences related to oneself. One might argue that listening to people who make stereotypical statements that involve their preferences (such as in the social condition) promotes contrasting those preferences with one's own. However, self-reflective thought is not necessarily involved since the MFC is also associated with person perception (Mitchell et al. 2002). Mentalizing refers to

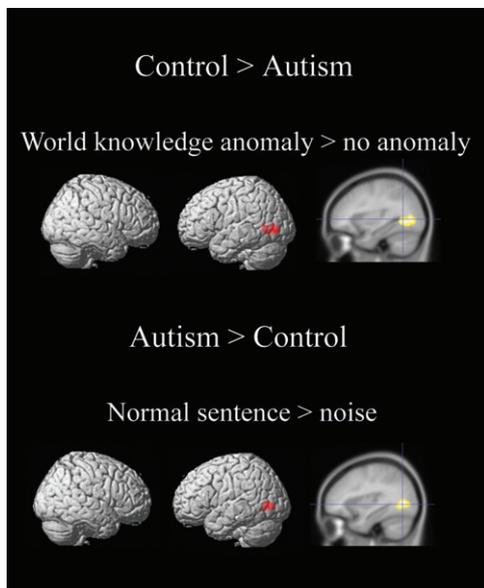


Figure 3. Activation patterns difference between the control and autism group: Figure 3 shows the group comparison of random effects; only contrasts that yielded significant clusters are shown. The middle occipital gyrus was more activated in controls during world-knowledge-incongruent sentences contrasted with world-knowledge congruent sentences. In contrast, the middle occipital was more activated in the autism group during sentences contrasted with speech-like noise.

Table 5

Activation differences between subject groups

Location of peak activation	BA	<i>P</i>	Cluster size	<i>Z</i>	<i>x</i>	<i>y</i>	<i>z</i>
Control > autism							
World-knowledge anomaly > no anomaly							
Left middle occipital gyrus	19/37	<0.001	566	4.33	-32	-60	2
Autism > controls							
Normal sentence > speech-like noise							
Left middle occipital gyrus	19/37	0.004	337	4.51	-34	-70	0

Note: BA, putative Brodmann area. *P*, *P* value corrected for multiple comparisons at cluster level. *Z*, highest *Z*-score within a region. *x,y,z*, stereotactic coordinates in MNI space.

the ability to represent another person's psychologic perspective. The ability to form a theory of mind will facilitate, to some extent, the ability to appreciate the difference between a child and an adult saying that they love a large cup of coffee in the morning. An extensive amount of research has shown that people with autism have a deficit in theory of mind (Baron-Cohen 1995), which may, in part, explain the absence of activation in the social condition in the autism group. Other regions involved in theory of mind are the superior temporal region and the temporoparietal junction (Gallagher and Frith 2003). In controls, we indeed found activation in the right superior temporal area (BA 22) and temporoparietal region (BA 40). Yet, we also found activation in the cuneus and precuneus (this region showed greater activation for speaker-incongruent than speaker-congruent regions instead of the other way around). The precuneus, located at the posteromedial part of the parietal lobe, is increasingly recognized for its central role in highly integrated tasks, including mental imagery and social cognition (Farrow et al. 2001; Lou et al. 2004; Cavanna and Trimble 2006). One might speculate that sentence content at odds with the speaker's identity may give rise to more extensive

mental imagery. Likewise, social cognition may be more involved with sentences at odds with speaker's identity than sentences in line with speaker's identity. In our study paradigm, incongruent trials require a greater integrative effort than congruent trials, which is reflected by the LIFG activation. At the same time, however, the current paradigm may prompt processing components that are not specific to trial types, such as error detection. The activation of the cingulate area in 2 contrasts (speaker congruent > speaker incongruent; normal sentence > speech-like noise) may reflect this.

As we hypothesized, the semantic and world-knowledge anomaly condition did not show any differential activation in the LIFG between the groups. Both the autism and control group showed robust LIFG activation, suggesting that integration of incongruent words (semantic) and integration of "facts" at odds with the current state of the world (e.g., false statements) increased activation in the LIFG in both groups in equal amounts. It would therefore appear that the activation of the LIFG and the RIFG is only reduced under certain circumstances in autism. The activation pattern in autism, in which one cortical area may show reduced or normal/increased activation depending on the task, has been observed before. An elegant example, as described previously, comes from 2 studies by the same group that accessed the neural basis of irony comprehension in autism. In one study "hypo"activation of prefrontal and temporal regions was found during judgment of scenarios that involved irony (Wang et al. 2007), whereas in another study that involved irony, "greater" activation of prefrontal and temporal regions (Wang et al. 2006) was observed. This time, though, the study demanded explicit attention to socially relevant clues. Thus, with support from contextual clues, participants with autism may have had increased activation since adequate support was provided to process the irony with greater effort, whereas this did not occur without the support.

Using the world-knowledge and semantic-knowledge paradigm in healthy adults (Hagoort et al. 2004), activations have been found that are in line with our current findings: activation of the LIFG during world-knowledge and semantic-knowledge anomalies. In our subsequent study on the integration of speaker characteristics in healthy adults, we found activation for speaker-incongruent sentences in both the LIFG and the RIFG. The current replication of these results in children and adolescents provides evidence for the validity of the unification model and suggests that the integration role of the LIFG and RIFG is already fully developed in early adolescence. Interestingly, the speaker-identity paradigm has also been applied to adults with autism (Tesink et al. 2009a) Activation of the RIFG was stronger for the autism group than for the control group, while no difference was found in the LIFG. We interpreted the RIFG findings as a compensation mechanism for solving complex social tasks due to higher task demands in the autism group. A highly speculative inference from combining our current findings in adolescents and the previous results in adults would be that this compensatory mechanism has not yet evolved in the still developing brain of children and adolescents with autism. Another explanation may be that adults with autism, who were diagnosed at an older age, represent a different subtype on the autism spectrum with better compensation skills that were already present during adolescence. Further fMRI studies are needed to

replicate and extend our findings by focusing on the development of social skills in relation to activation of the LIFG and RIFG over time.

Direct comparison between both groups did reveal a region situated in the extrastriate cortex with greater activation in the control group during the world-knowledge anomaly condition. During the noise condition that contrasted normal sentences with speech-like noise, the same region showed greater activation in the autism group. Similar findings have been reported in an auditory event-related brain potential paradigm (Kemner et al. 1995). Specifically, Kemner and colleagues used an auditory oddball task in which only the autism group showed a larger occipital P3 for deviant stimuli, thus providing independent evidence for the notion that the visual cortex may be involved in nonvisual tasks in autism (in either direction). Hyperactivation of the extrastriate areas in autism has been previously observed in a visually presented, single-word processing (Gaffrey et al. 2007) and sentence-processing study (Kana et al. 2006). In the latter fMRI study, participants with autism processed high-imagery (e.g., “The number eight when rotated 90 degrees looks like a pair of eyeglasses”) and low-imagery sentences. Not only the high-imagery but also the low-imagery sentences activated parietal and occipital areas in the autism group. In the control group, these areas were only activated in the high-imagery condition. These results are in line with anecdotal evidence of an increased tendency to visually process information about the world in autism (Sacks 1995). It might be argued that increased mental imagery may yield cognitive advantages, as is the case for the autistic associate professor that Sacks describes, because her movie-like memory and realistic mental imagery helped her to design livestock facilities to the last detail. On the other hand, one might hypothesize that increased mental imagery may also give rise to cognitive disadvantages such as a decrease in mental flexibility, which is one symptom of the triad of symptoms in autism. In the present study, we found an increase of occipital activation in the autism group for correct sentences (compared with noise). However, we found a decrease in the same area when incorrect sentences were processed (compared with correct sentences). It might well be possible that this effect is caused by an inability in the autism group to visualize factually incorrect situations. The appreciation of certain types of humor and metaphoric meaning (rather than the literal meaning), requires a flexible cognitive apparatus rather than an increased ability to visualize. Thus, mental imagery and mental flexibility may be related in autism. It may also be the case that the current findings reflect the end result of the complex cascade of neural processes that underlie language perception, in which the current occipital findings reflect a neural “overspill.” One possibility of such an atypical process involves the putative insufficient pruning of inefficient synapses in autism (Barnea-Goraly et al. 2004). The early brain overgrowth in autism (Courchesne et al. 2001) has been related to atypical connectivity between brain regions that may result in either hyperconnected or hypoconnected systems (Belmonte, Cook, et al. 2004). Although speculative, retained connections between the temporal and occipital cortex may account for the atypical activation of the occipital lobe during auditory sentence perception. Of note, the hypothesis of hypoconnected systems in autism may also be related to the current findings of hypoactivation of the LIFG.

Decreased functional connectivity of lower order areas may lead to a situation in which information does not reach the LIFG. The hypoactivation of the LIFG would then be an epiphenomenon of decreased functional connectivity rather than that a malfunctioning LIFG causes integrative problems in autism. Finally, analysis of language function in patients with brain lesions may be of interest in the context of the theory of underconnectivity as well as in the context of the unification framework that suggests that language comprehension can be conceptualized as taking place in parallel and with the recruitment of LIFG as a unification domain.

In conclusion, using semantic-knowledge, world-knowledge, and social contrasts, we observed significant differences in the involvement of the LIFG during social contrasts and an atypical activation during world-knowledge contrasts in autism. Uncovering the causal processes that underlie these brain activation patterns is a pressing research target for the future.

Notes

Conflict of Interest: None declared.

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