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Neural correlates of pragmatic language comprehension in autism spectrum disorders

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Difficulties with pragmatic aspects of communication are universal across individuals with autism spectrum disorders (ASDs). Here we focused on an aspect of pragmatic language comprehension that is relevant to social interaction in daily life: the integration of speaker characteristics inferred from the voice with the content of a message. Using functional magnetic resonance imaging (fMRI), we examined the neural correlates of the integration of voice-based inferences about the speaker's age, gender or social background, and sentence content in adults with ASD and matched control participants. Relative to the control group, the ASD group showed increased activation in right inferior frontal gyrus (RIFG; Brodmann area 47) for speaker-incongruent sentences compared to speaker-congruent sentences. Given that both groups performed behaviourally at a similar level on a debriefing interview outside the scanner, the increased activation in RIFG for the ASD group was interpreted as being compensatory in nature. It presumably reflects spill-over processing from the language dominant left hemisphere due to higher task demands faced by the participants with ASD when integrating speaker characteristics and the content of a spoken sentence. Furthermore, only the control group showed decreased activation for speaker-incongruent relative to speaker-congruent sentences in right ventral medial prefrontal cortex (vMPFC; Brodmann area 10), including right anterior cingulate cortex (ACC; Brodmann area 24/32). Since vMPFC is involved in self-referential processing related to judgments and inferences about self and others, the absence of such a modulation in vMPFC activation in the ASD group possibly points to atypical default self-referential mental activity in ASD. Our results show that in ASD compensatory mechanisms are necessary in implicit, low-level inferential processes in spoken language understanding. This indicates that pragmatic language problems in ASD are not restricted to high-level inferential processes, but encompass the most basic aspects of pragmatic language processing.

Keywords: autism; functional MRI; pragmatics; language comprehension; voice processing

Abbreviations: ASDs = autism spectrum disorders; HFA = high-functioning autism; LIFG = left inferior frontal gyrus

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Introduction

Impairments in language and communication are among the defining characteristics of autism spectrum disorders (ASDs; American Psychiatric Association, 1994). Although evidence is mixed, semantic language processing (i.e. constructing the content of a sentence based on just the meaning of the words) seems to be relatively spared in high-functioning individuals with ASD (Tager-Flusberg and Joseph, 2003; Noens and van Berckelaer-Onnes, 2005). The most striking language difficulties concern pragmatic language aspects (i.e. the ability to use and comprehend language in context) and these are universal across individuals with ASD, irrespective of their level of functioning (Tager-Flusberg *et al*., 2005). Language comprehension in (verbal) social communication calls upon pragmatic language skills, since the listener is often required to work out the non-literal meaning of the speaker's message by using the context and his own knowledge of the world. One of the most salient features of the impaired pragmatic language comprehension in ASD is an overly literal interpretation of utterances which causes problems in understanding humour, irony and metaphors, as well as in making inferences and comprehending indirect requests (Happe, 1993; Ozonoff and Miller, 1996).

In the past years, neuroimaging studies have sought to elucidate the neural underpinnings of language comprehension in healthy participants. This research has revealed that during language comprehension our brains integrate different sources of incoming information immediately and in parallel to interpret the ongoing sentence or discourse (Hagoort and van Berkum, 2007). The left inferior frontal gyrus (LIFG) plays a key role in this integration process by unifying a broad range of information, such as knowledge about the context and the world, as well as co-speech gestures (Hagoort *et al*., 2004; Willems *et al*., 2007). Functional magnetic resonance imaging (fMRI) studies have shown that, next to the inferior frontal gyrus, the temporal cortex plays an important role in (spoken) language comprehension (Bookheimer, 2002). Within the temporal cortex, there seems to exist a subdivision with the inferior and middle temporal cortex being involved in storage and retrieval of lexical-semantic information and the superior temporal cortex supporting sound-based processes (Hickok and Poeppel, 2000, 2007). Although the left hemisphere is seen as the language dominant one, an increasing number of fMRI studies, including our own (Tesink *et al*., 2009), report additional activation in right hemispheric brain regions during language comprehension. This seems especially to be the case when task demands are increased and higher-level language processing is needed, for example in the comprehension of semantically ambiguous sentences or discourse (St George *et al*., 1999; Robertson *et al*., 2000; Rodd *et al*., 2005; Xu *et al*., 2005; Zempleni *et al*., 2007).

Given that the language difficulties observed in ASD can cause serious problems in social interaction and persist into adulthood, it is important to clarify their neural basis. These problems manifest themselves most prominently at the sentence and discourse level, i.e. at the higher levels of language processing. An fMRI study on semantic processing at the sentence level (Just *et al*., 2004) revealed decreased activation in the LIFG (BA 45/47) for adults with ASD relative to control participants. Next to reduced activation in the LIFG, there was increased activation for the ASD group in the left middle/superior temporal gyrus (BA 21/22). Comparable results have been reported for semantic processing at the word level (Harris *et al*., 2006; Gaffrey *et al*., 2007). These findings are taken to imply that, during semantic processing, the brains of individuals with ASD engage less in integrative processing (as takes place in LIFG), but focus more on lower level lexical processing (Just *et al*., 2004; Harris *et al*., 2006).

Difficulties with language comprehension displayed in daily life by adults with ASD are more evident at the pragmatic than at the semantic level: they show impairments in comprehending language in context, but not in constructing a context-independent meaning of an utterance. Nevertheless, very few fMRI studies have examined neural correlates of pragmatic language comprehension. Two studies that did investigate pragmatics in children and adults with ASD found that making inferences from discourse and comprehending irony elicited increased activation in RIFG for the ASD group relative to the control group (Wang *et al*., 2006; Mason *et al*., 2008). In LIFG, there was no difference in activation between the two groups. In both studies on pragmatics, increased activity in the ASD groups fell within networks that were activated for the control groups. Since making inferences and comprehending irony seem to be more difficult for individuals with ASD, increased activation in right hemispheric regions possibly reflects the higher task demands that the ASD group faces when interpreting discourse in context (Wang *et al*., 2006; Mason *et al*., 2008).

Given the pragmatic language impairments observed in adults with ASD, we tackled an aspect of pragmatic language comprehension that is relevant to social interaction in daily life: the integration of speaker characteristics (age, gender, social background) derived from the voice with the content of a message. During verbal communication the voice is an important source of pragmatic information as it implicitly reveals a lot about a speaker. To make sense of what a speaker is saying, we use this speaker information inferred from the voice and integrate it with the literal meaning of the utterance. For instance, 'every evening I drink some wine before I go to sleep' sounds odd when spoken by a young child. To look into the integration of speaker and message, we presented a control and ASD group with spoken sentences whose meaning did (speaker-congruent) or did not (speaker-incongruent) match voice-based inferences about the speaker's age, gender or social background. In contrast to the earlier studies on pragmatic language processing in individuals with ASD, in our study no explicit inferences were required during online language processing. Therefore, all effects are a consequence of an automatic process of matching inferences about the speaker from low-level acoustic features with the content of the message. In line with earlier findings, we hypothesize that both groups recruit overlapping brain regions for processing speaker-incongruent and speaker-congruent sentences. Our previous study in control participants showed significantly stronger bilateral activation in inferior frontal gyrus for speaker-incongruent sentences relative to speaker-congruent sentences (Tesink *et al*., 2009). The integrative aspect of pragmatic language comprehension required by the speaker inference sentences is more difficult for adults with ASD than for control participants. Therefore, we expect to find compensatory activation in the ASD group in regions in inferior frontal gyrus that were found to be involved in processing speaker-incongruent sentences.

Materials and Methods

Participants

The ASD group comprised 24 right-handed adults (eight females; mean age ± SD = 26.3 ± 6.3 years; age range 18–40 years) diagnosed with high-functioning autism (HFA) or Asperger syndrome (AS). The diagnosis of HFA or Asperger syndrome was established by expert clinical opinion following DSM-IV criteria (American Psychiatric Association, 1994) supplemented by the Autism Diagnostic Interview-Revised (ADI-R; Lord *et al*., 1994). Subjects were included in the ASD group if they fulfilled the DSM-IV criteria for autistic disorder or Asperger syndrome (10 participants with HFA, 14 with AS). Table 1 displays the diagnosis and ADI-R scores per participant. Three participants did not meet one of the specified cut-off points of the ADI-R. This could be attributed to the fact that several participants only received a diagnosis in adolescence or adulthood and parents were consequently unable to report the relevant developmental information. For four participants no parents or caretakers were available and hence the ADI-R was not administered. In all cases, participants were only included if the clinical diagnosis of HFA or AS was undisputed. Participants had no reported history of neurological disorders, head trauma or psychiatric disorders other than autism. The control group included 24 medically healthy adults (mean age ± SD = 26.2 ± 6.0 years; age range 18–39 years) recruited through advertisements in the local community. The control participants were matched with the ASD participants for age, gender and verbal IQ [assessed by the Wechsler Adult Intelligence Scale-Revised, WAIS-R (Wechsler, 1981); or Wechsler Adult Intelligence Scale, third edition, WAIS-III (Wechsler, 1997)]. Prior to inclusion, control subjects were screened to exclude those with psychiatric, neurological or developmental disorders.

All participants were right-handed native speakers of Dutch and had normal or corrected-to-normal vision and normal hearing. Furthermore, all had full-scale IQ scores of 85 or above based on the WAIS-R or WAIS-III. The ASD and control groups did not differ significantly in chronological age, verbal IQ or full-scale IQ (for all comparisons $P > 0.1$), although the mean performance IQ was higher in the control group ($P = 0.008$). Participant characteristics, including age, sex, verbal, performance and full-scale IQ are presented in Table 2. The study was approved by the local Medical Ethical Committee. All participants gave written informed consent according to the Declaration of Helsinki.

Table 1 **Diagnosis and score on the domains social interaction, communication and behaviour of the ADI-R per participant of the ASD group**

Participant	Diagnosis	Diagnostic algorithm ADI-R		
		Social interaction Cut-off = 10 (max = 30)	Communication Cut-off = 8 (max = 26)	Behaviour Cut-off = 3 (max = 12)
p01	HFA	12	11	5
p02	AS	12	9	4
p03	AS	19	8	5
p04	HFA	20	16	8
p05	HFA	27	20	3
p06	HFA	16	13	**2**
p07	AS	**6**	11	3
p08	HFA	24	17	7
p09	HFA	23	17	5
p10	AS	20	10	6
p11	HFA	13	12	3
p12	HFA	22	13	3
p13	AS	20	18	7
p14	AS	NA	NA	NA
p15	AS	11	10	4
p16	AS	16	18	4
p17	HFA	NA	NA	NA
p18	HFA	22	14	**2**
p19	AS	12	12	5
p20	AS	NA	NA	NA
p21	AS	12	16	5
p22	AS	12	10	3
p23	AS	10	12	7
p24	AS	NA	NA	NA

Note that the ADI-R is a semi-structured diagnostic interview that is administered to the parents or caregivers (Lord, 1994). The scores displayed here are from the diagnostic algorithm and represent behaviour of the participant at the age of 4- or 5-years old. Scores above cut-off points on all domains are thought to be indicative for ASD. Three participants (p06, p07 and p18) did not meet one of specified cut-off points of the ADI-R (see scores in bold). This could be attributed to the fact that these participants received a diagnosis relatively late in life and consequently parents were unable to report the relevant developmental information. One subject participated in another study and the ADI-R was already administered then. Exact scores could not be recalled but scores were above cut-off on all domains. For four participants no parents or caretakers were available and hence the ADI-R was not administered (NA; p14, p17, p20 and p24). In all cases, the clinical diagnosis of HFA or AS was undisputed.

Stimulus material

The stimulus materials consisted of two sets of sentences: a set of speaker-inference sentences and a set of sentences with lexical semantic or world knowledge anomalies (Hagoort *et al*., 2004). The stimulus materials used in this study were identical to those of the fMRI study by Tesink *et al*. (2009) and to the ERP study by Van Berkum *et al*. (2008). For the set of speaker-inference sentences, we constructed 160 sentences with a lexical content that was congruent with voice-based inferences about a particular speaker, but incongruent with inferences about another speaker. To increase variability and to cover a broad range of information captured in the voice, sentence meaning could be incongruent with three different dimensions: the speaker's age, gender or social background. The speaker-incongruity always emerged at a single critical word, which was never sentence-final. Furthermore, the fragment before the critical word was compatible with either speaker ('Yesterday I went to . . .', 'I have a large . . .'). An example of each sentence type is provided in Table 3.

Next to the speaker-inference sentences, we included sentences with a semantic anomaly, a world knowledge anomaly or without an anomaly (Hagoort *et al*., 2004). This set of sentences is not relevant for the research question at hand and will therefore not be discussed here. Forty-two items consisting of reversed speech were used as a baseline and inserted as filler sentences. These items were created by reversing a selection of the speaker-inference and world knowledge sentences (two sentences per speaker) and were matched

Table 2 Demographic characteristics of participants

	ASD group (mean ± SD)	Control group (mean ± SD)
Sex (male:female)	16:8	16:8
Age (years)	26.3 ± 6.3	26.2 ± 6.0
Verbal IQ	113.2 ± 13.9	113.5 ± 12.1
Performance IQ	113.0 ± 15.2	124.8 ± 14.0
Full-scale IQ	114.3 ± 14.1	119.9 ± 11.7

Table 3 Speaker-inference dimensions

- **Age: child versus adult (40 sentences in total)**
    - I cannot sleep without my *teddy bear* in my arms (child congruent/adult incongruent).
    - Every evening I drink a glass of *wine* before going to bed (adult congruent/child incongruent).
- **Gender: male versus female (80 sentences in total)**
    - If only I looked like *Britney Spears* in her latest video (female congruent/male incongruent).
    - I broke my ankle playing *football* with my friends (male congruent/female incongruent).
- **Social background: upper-class accent versus lower-class accent (40 sentences in total)**
    - In my free time, I prefer to listen to *piano music* of Chopin (upper class accent congruent/lower class accent incongruent).
    - I have a big *tattoo* on my back (lower class accent congruent/upper class accent incongruent).

on sentence length with the sentence duration in the other experimental conditions. Overall, the experimental sentences varied in length from 1638 to 5648 ms, with the average sentence length being 3247 ms (SD = 597 ms). The critical words had an average duration of 480 ms (SD = 136 ms).

To distribute all versions of speaker-inference and world knowledge items equally, we created six different stimulus lists. These pseudo-randomized trial lists all contained 80 exemplars for each of the two speaker-inference conditions, 36 sentences for each of the three world knowledge conditions, 42 reversed speech items and 4 neutral filler sentences. The lists were created in such a way that none of the participants heard more than one version of a sentence.

Experimental design and procedure

Each participant listened to a total of 314 sentences (i.e. 160 speaker-inference sentences, 108 world knowledge sentences, 42 reversed speech items and 4 neutral sentences that served as filler items) that were presented in an event-related design. During image acquisition, subjects lay in a supine position in the MR scanner and head movements were minimized by an adjustable padded head holder. The spoken sentences were presented via headphones while a fixation cross was presented via an LCD projector standing outside the scanner room, projecting the computer display onto a semi-transparent screen, which the subject viewed through a mirror device attached to the head coil. Stimulus presentation was controlled by a PC running the Presentation software (nbs.neuro-bs.com/Neurobehavioral Systems, San Francisco, CA, USA).

Participants were instructed to process each sentence attentively for comprehension. To ensure attentive listening, they were told that afterwards questions would be asked about the presented sentences. Before the beginning of the experiment, each participant received a practice block consisting of 10 sentences. These items were also used to adjust the volume level for sentence presentation. The functional data acquired during the practice run were not used in the analysis. The experiment was divided into two blocks of 157 sentences each. Following the first block of sentences, there was a short break. At the start of each experimental block we inserted two filler items (neutral sentences) to minimize loss of data due to saturation transients at the beginning of each block.

At the end of the scanning session, participants were extensively debriefed to check whether they were capable of identifying speaker-incongruities. Participants were asked if they noted something strange about the sentences and, if so, to report speakers that pronounced sentences that did not match with voice-based inferences about their characteristics. There were six speaker-incongruities to be identified (adult-incongruent, child-incongruent, male-incongruent, female-incongruent, upper-class-incongruent and lower-class-incongruent).

MRI data acquisition

During the listening task, we acquired whole head T_2*-weighted EPI-BOLD fMRI data with a SIEMENS 1.5 T MR-scanner using an ascending slice acquisition sequence (volume TR = 2440 ms, TE = 40 ms, 90° flip angle, 31 axial slices, slice-matrix size = 64 × 64, slice thickness = 3 mm, slice gap = 0.5 mm, field of view = 224 mm, isotropic voxel size = $3.5 \times 3.5 \times 3.5\ \text{mm}^3$). Following the experimental session, a high-resolution structural MR image was acquired for each participant, using a T_1-weighted MP-RAGE sequence (volume TR = 2250 ms, TE = 3.93 ms, 15° flip angle, 176 sagittal slices, slice-matrix size = 256 × 256, slice thickness = 1 mm, no slice gap, field of view = 256 mm).

MRI data analysis

Image pre-processing and statistical analyses were performed using SPM5 (www.fil.ion.ucl.ac.uk/spm). The first five volumes of each participant's dataset were discarded to allow for T1 equilibration. The functional EPI-BOLD images were realigned, and the subject-mean functional MR images were co-registered with the corresponding structural MR images. These images were subsequently slice-time corrected, spatially normalized (i.e. the normalized transformations were generated from the structural MR images and applied to the functional MR images) and transformed into a common space, as defined by the SPM Montreal Neurological Institute (MNI) T1 template. The functional EPI-BOLD images were then spatially filtered by convolving the functional images with an isotropic 3D Gaussian kernel (10 mm FWHM).

The fMRI data were then statistically analysed using the general linear model and statistical parametric mapping (Friston *et al*., 1995). At the first level, single-subject fixed effect analyses were conducted. A model with the experimental conditions (speaker-incongruent, speaker-congruent) was tested in each participant's data separately. In this linear model, mini-block regressors were included to model events as the duration of the sentence presentation from the onset of the critical word to the end of the trial. We then temporally convolved the explanatory variables with the canonical hemodynamic response function provided by SPM. To remove any artefactual signal changes due to head motion, we included six realignment parameters describing the head movements as confounds in the model. The data were high-pass filtered to account for various low-frequency effects. Temporal autocorrelation was modelled as a first-order autoregressive AR(1) + noise process. For the second-level analysis, the generated single-subject contrast images for the main effects (speaker-incongruent and speaker-congruent) were entered in a random effects analysis. As we were interested in group × task interaction effects, between-group differences were examined using a full factorial model with group as between-subject factor and condition as within-subject factor (two levels: speaker-incongruent, speaker-congruent). In addition, effects for each group separately were assessed by conducting one-sample t-tests for the contrasts speaker-incongruent > speaker-congruent and speaker-congruent > speaker-incongruent. As in the previous study, the three speaker dimensions (i.e. gender, age and social background) were collapsed and combined into the more general categories speaker-incongruent and speaker-congruent sentences to increase statistical power.

Region of interest analyses

In our previous fMRI study in control participants (Tesink *et al*., 2009), we identified brain regions involved in integrating speaker characteristics and sentence meaning that were located in left and right inferior frontal gyrus. Given these results and our *a priori* hypothesis concerning the role of the inferior frontal cortex in language processing in ASD as derived from existing literature (see Introduction), we defined two regions of interest (ROI) for the present study in LIFG and RIFG. Accordingly, we applied small volume correction using two spherical ROIs with a radius of 15 mm around (−54, 26, 14) in LIFG and (50, 34, −12) in RIFG, thresholded at $P < 0.005$ (uncorrected). Clusters of activation were considered significant at a voxel- or cluster-level threshold of $P < 0.05$ (corrected for multiple comparisons). From the resulting clusters of activation, average beta-values were extracted with MarsBar (Brett *et al*., 2002) and these values were then used to perform repeated-measures GLM's and *post hoc* paired t-tests in SPSS (version 14.0.0).

Whole-brain analysis

In addition to testing condition effects in the ROIs, we also tested for the presence of other regions that were differentially activated by the experimental conditions. In this explorative whole brain search, the results of the random effects analyses were thresholded at $P < 0.005$ (uncorrected). We employed cluster-size as the test-statistic for our whole-brain analysis and only considered activation clusters significant at a threshold of $P < 0.05$ (corrected for multiple non-independent comparisons). All local maxima are reported as MNI coordinates. Relevant anatomical landmarks and Brodmann areas were identified using the atlas of the human brain (Mai *et al*., 2004), the Anatomy Toolbox (Amunts *et al*., 2000; Eickhoff *et al*., 2005) and the Talairach Daemon (Lancaster *et al*., 2000).

Results

Behavioural results

At the end of the scanning session, all participants were extensively debriefed by means of a questionnaire. Both the ASD and control participants were able to describe the experimental manipulation in the stimulus material and could provide examples of specific trials. On average, the control group mentioned 4.1 out of six speaker-incongruities and the average for the ASD group was 3.7 speaker-incongruities. The two groups did not differ significantly in the number of identified speaker-incongruities ($P > 0.17$) and there were no speaker-incongruities that were more often identified by one of the groups (all $P > 0.22$). This confirms that, outside the scanner, the ASD group was able to perform the task at the same behavioural level as the control group and indicates that any observed group differences on the fMRI task cannot be attributed to between-group differences in detecting speaker-incongruities (Price and Friston, 2002).

fMRI results

ROI analyses

We had specific *a priori* hypotheses regarding the role of inferior frontal regions in processing speaker-incongruent and speaker-congruent sentences in the ASD and the control group. Therefore, we first explored interaction effects of group (autism versus control participants) × condition (speaker-incongruent versus speaker-congruent) in our regions of interest (ROIs; see Methods) in LIFG and RIFG. While the ROI analysis revealed no significant clusters in the LIFG, the response of the ASD and control group to the speaker-inference conditions differed significantly in the RIFG [$t(92) = 3.58$; $P < 0.05$, FWE corrected]. *Post hoc* tests showed that this significant interaction was due to the effect displayed by the ASD group (see also Fig. 1). In this group, RIFG (BA 47) was significantly more activated for the speaker-incongruent sentences than for speaker-congruent sentences [$t(23) = 2.843$; $P = 0.009$], while the control group did not show this activation pattern [$t(23) = -1.172$; $P > 0.25$]. As is also evident from Table 4 and Fig. 2, the within-group analyses showed that both groups activated LIFG significantly more strongly for speaker-incongruent than for speaker-congruent sentences. In addition to activation of the RIFG and LIFG, the ASD group displayed significantly stronger activation for speaker-incongruent than for speaker-congruent sentences in the right medial transverse frontopolar region (BA 10) extending into the medial part of right superior frontal regions (BA 6/9). The control group showed, next to activation in LIFG, significantly stronger activation for speaker-incongruent sentences in the medial part of left middle and superior frontal gyrus (BA 8–10). However, activation in middle and superior frontal regions found in the within-group analyses did not survive the statistical threshold when both groups were compared directly. These results are in line with our previous fMRI study (Tesink *et al*., 2009) in which the inferior frontal gyrus was bilaterally involved in the integration of speaker characteristics and sentence meaning. In the current study, the previously reported bilateral effect in inferior frontal gyrus was present in both groups, but the increased activation in RIFG was only significant in the ASD group.

Whole-brain analysis

In addition, in the whole-brain analysis we found a significant interaction effect of group × condition in right anterior cingulate cortex [ACC; BA 24/32; $t(92) = 3.91$; $P < 0.05$, FWE corrected] that extended into the medial prefrontal cortex (MPFC; BA 10; Fig. 3). *Post hoc* tests revealed that this interaction was driven by the effect for the control participants. In the control group,

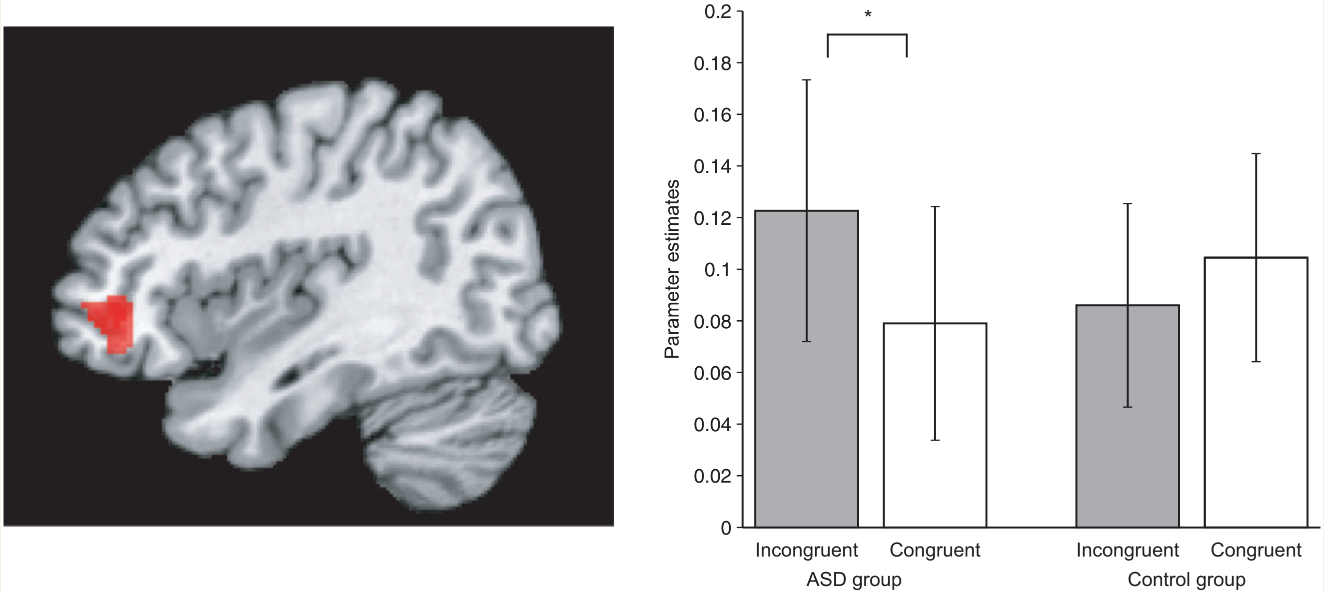

Figure 1 The left panel displays a sagittal slice showing the significant cluster of activation in RIFG for speaker-incongruent sentences in the ASD group as resulting from the ROI analysis. The right panel presents the mean response (mean ± SEM) in the cluster of activation in RIFG to speaker-incongruent and speaker-congruent sentences for the ASD and the control group. As indicated by the asterisk, the difference in response to speaker-incongruent and speaker-congruent sentences in RIFG was only significant for the ASD group.

Table 4 **Significant clusters of activation per group for the contrast speaker-incongruent > speaker-congruent sentences**[a]

Anatomical region	Brodmann area	Cluster size	Voxel *T*-value	MNI coordinates		
				x	*y*	*z*
ASD group						
R. medial transverse frontopolar gyrus	10	971	5.80	2	62	6
R. medial superior frontal gyrus	9		4.59	12	50	36
R. medial superior frontal gyrus	6		4.53	2	30	54
L. inferior frontal gyrus	47	605	5.61	−44	28	−14
L. planum polare	38		5.47	−34	22	−24
L. inferior frontal gyrus	47		5.35	−34	20	−16
R. inferior frontal gyrus	47	456	4.85	40	26	−18
R. inferior frontal gyrus	11/47		4.44	40	42	−16
R. inferior frontal gyrus	45		3.79	56	24	0
Control group						
L. medial middle/superior frontal gyrus	10	1005	5.03	−4	62	18
L. medial superior frontal gyrus	8/9		4.42	−2	46	36
L. medial superior frontal gyrus	8		3.77	−6	38	52
L. inferior frontal gyrus	45	697	5.68	−54	26	14
L. inferior frontal gyrus	47		4.59	−50	22	−6
L. superior temporal gyrus	38		4.27	−52	16	−12

[a] Tables show all clusters at a significance level of $P < 0.05$ corrected at cluster-level (first thresholded at $P < 0.005$ uncorrected). All local maxima are reported as MNI coordinates. Significant activation peaks >8 mm apart.

the activation in right ACC and ventral MPFC was significantly stronger for speaker-congruent sentences relative to speaker-incongruent sentences [$t(23) = -3.873$; $P = 0.001$]. There was no such difference in activation for both conditions in the ASD participants [$t(23) = 0.434$; $P = 0.669$].

Finally, for completeness, we investigated for each group separately which regions were activated stronger for speaker-congruent than for speaker-incongruent sentences. This within-group contrast revealed that both groups significantly activated left superior temporal gyrus (BA 22/42/41). In addition, the ASD group showed significant activation for speaker-congruent sentences in right superior temporal gyrus (BA 22/41) as well as in left pre- and post-central gyrus. For the control group, speaker-congruent sentences elicited significantly stronger activation than speaker-incongruent sentences in regions that were, except for the left superior temporal gyrus, all right hemispheric and included the anterior transverse temporal gyrus (BA 41), the pre- (BA 4/6) and post-central gyrus (BA 2), the precuneus (BA 31), inferior temporal regions (BA 37), as well as anterior cingulate cortex and medial orbital gyrus (BA 24/32). An overview of the significant clusters for this contrast per group is given in Table 5. The clusters of activation for speaker-congruent relative to speaker-incongruent sentences in the current study largely overlap with those in our previous study in healthy participants (see Tesink *et al*., 2009 for a more detailed overview).

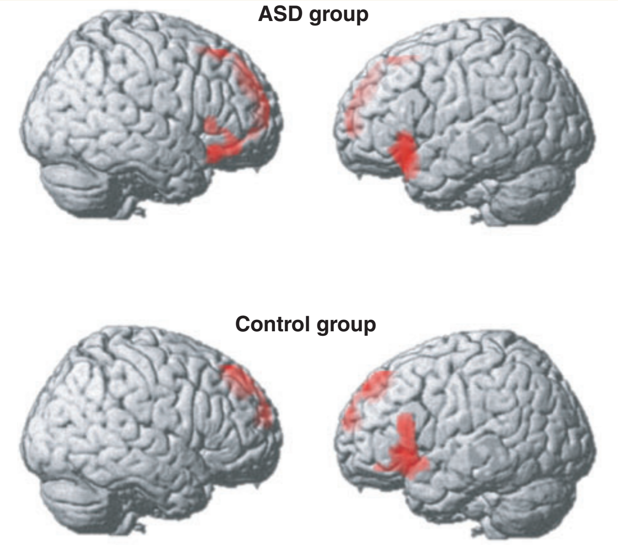

Figure 2 Significant clusters of activation for speaker-incongruent sentences relative to speaker-congruent sentences for the ASD group (top panel) and the control group (bottom panel).

As mentioned in the Methods section, the ASD and control group differed significantly on performance IQ (PIQ), with mean PIQ being higher in the control group ($P = 0.008$). To exclude the possibility that our results were influenced by this difference in PIQ, we conducted additional whole brain analyses with PIQ as covariate. Including PIQ as a covariate did not change our results.

Discussion

In this fMRI study, we elucidated the neural correlates of the integration of speaker characteristics inferred from the voice and the content of a spoken sentence in adults with ASD. This integration encompasses an aspect of pragmatic language comprehension that is crucial for social interaction in daily life and possibly partly accounts for the communication problems seen in ASD. Relative to the control group, the ASD group showed significantly stronger activation in RIFG (BA 47) for speaker-incongruent sentences than for speaker-congruent sentences, while there were no significant differences in behavioural performance between the groups on a debriefing interview outside the scanner. Furthermore, manipulating the congruency of voice-based inferences about the speaker's age, gender or

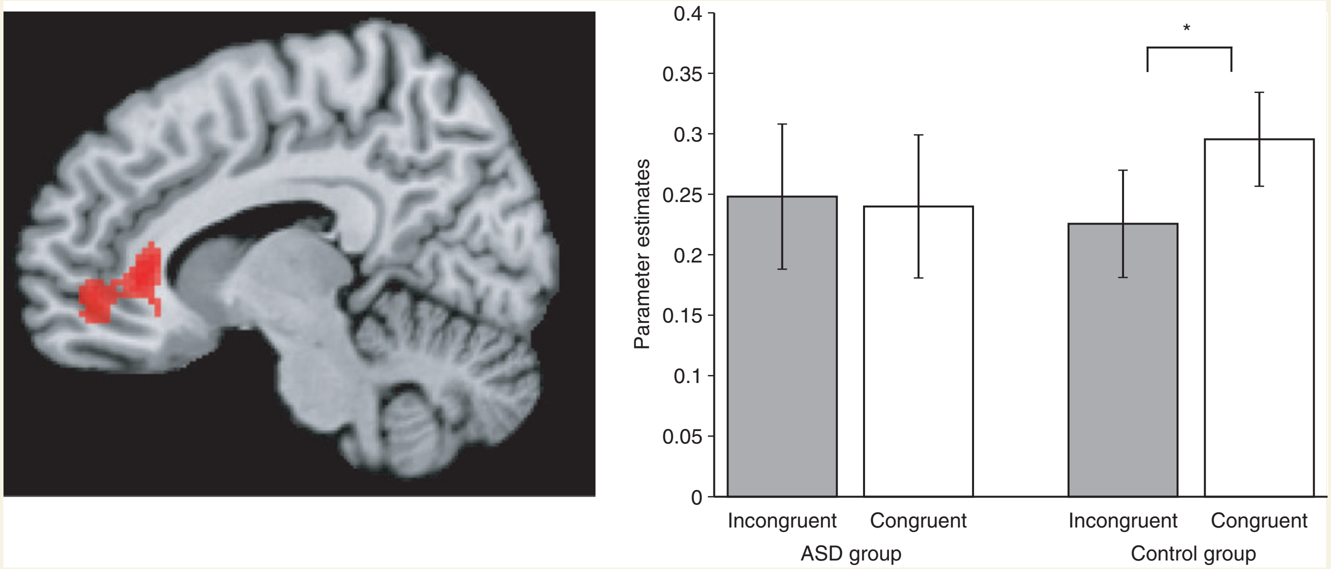

Figure 3 The left panel displays a sagittal slice showing the significant cluster of activation in the whole-brain random effects analysis. The significant cluster is located in right vMPFC and right ACC and represents increased activation for speaker-congruent sentences relative to speaker-incongruent sentences in the control group. The right panel presents the mean response (mean ± SEM) in the cluster of activation in vMPFC and ACC to speaker-incongruent and speaker-congruent sentences for the ASD and the control group. As indicated by the asterisk, the difference in response to speaker-incongruent and speaker-congruent sentences in right vMPFC and ACC was only significant for the control group.

Table 5 Significant clusters of activation per group for the contrast speaker-congruent > speaker-incongruent sentences[a]

Anatomical region	Brodmann area	Cluster size	Voxel *T*-value	MNI coordinates		
				x	*y*	*z*
ASD group						
L. superior temporal gyrus	22/42	981	5.48	−62	−24	8
L. posterior transverse temporal gyrus	42		5.12	−56	−32	20
L. anterior transverse temporal gyrus	41		4.07	−42	−28	14
L. precentral gyrus	4	438	4.44	−38	−18	54
L. postcentral gyrus	2		4.32	−46	−28	54
L. postcentral gyrus	2		4.05	−56	−26	48
R. superior temporal gyrus	41	394	4.15	56	−22	8
R. superior temporal gyrus	22		3.94	66	−12	4
R. superior temporal gyrus	22		3.67	66	−32	12
Control group						
L. superior temporal gyrus	41	1735	4.89	−36	−38	10
L. precentral gyrus	6		4.80	−46	0	28
L. superior temporal gyrus	41		4.66	−42	−28	6
R. anterior transverse temporal gyrus	41	1553	5.16	34	−26	14
R. precentral gyrus	4/6		4.18	46	−14	26
R. postcentral gyrus	2		4.04	42	−22	30
R. precuneus	31	1548	5.42	8	−66	26
R. fusiform gyrus	37		4.89	36	−50	−10
R. inferior temporal gyrus	37		4.87	46	−42	−16
R. anterior cingulate gyrus	24/32	1165	4.75	2	26	4
R. medial orbital gyrus	24/32		4.47	16	28	−10
R. anterior cingulate gyrus	32		4.45	14	46	−2
R. brain stem		379	5.82	4	−30	−6
R. thalamus			3.87	6	−20	4

a Tables show all clusters at a significance level of $P<0.05$ corrected at cluster-level (first thresholded at $P<0.005$ uncorrected). All local maxima are reported as MNI coordinates. Significant activation peaks >8 mm apart.

social background and sentence content modulated activity in right ventral MPFC (BA 10), including anterior cingulate cortex (ACC; BA 24/32), in the control group, but not in the ASD group.

Increased activation in RIFG for the ASD group during pragmatic language comprehension is in line with previous findings on discourse and irony comprehension in adults and children with ASD (Wang *et al*., 2006; Mason *et al*., 2008). In these studies, increased right hemisphere activity for the ASD group was interpreted as reflecting more effortful processing. One crucial difference between previous studies and ours is that we examined fully automatic low-level inferential processes during language comprehension. Speaker characteristics captured in the voice are inherent to speech signal and are not part of the communicative intention (e.g. in contrast higher-level aspects as irony). Our study is the first to investigate the integration of very basic speaker information revealed by the voice and sentence content in individuals with ASD. In the present study, a debriefing interview outside the scanner showed that there were no significant differences between the groups in detecting speaker-incongruities, suggesting that differences in neural activation patterns are unlikely to be explained by differences in behavioural performance. Hence, the increase in neural activation in the ASD group can be regarded as compensatory in nature and is possibly related to the following underlying language mechanisms. First, although the left hemisphere is usually the primary site of language comprehension, processing may spill over to right homotopic regions if demands on the language processing system are increased and become too high to handle for the language-dominant left hemisphere regions. This effect has been observed in sentence and discourse comprehension in control subjects (Just *et al*., 1996; Rodd *et al*., 2005; Xu *et al*., 2005; Zempleni *et al*., 2007) and might also account for the increased activity in RIFG present in the ASD group. Second, fMRI research in healthy participants has suggested that RIFG is involved in forming and updating a situation model, i.e. a mental representation of the situation described in the sentence or discourse that is connected to incoming information and to general world knowledge (Van Dijk and Kintsch, 1983; Zwaan and Radvansky, 1998; Ferstl *et al*., 2005; Menenti *et al*., 2009). When encountering information that is implausible or unexpected given the current situation model and general world knowledge, a listener will attempt to revise the situation model by integrating the unexpected information into the ongoing representation. In our speaker-incongruent sentences, the integration of inconsistent information and on-line revision of the situation model were needed to overcome unexpected inferences about the speaker and sentence content as represented in the situation model. The stronger activation in the ASD group in RIFG for speaker-incongruent sentences possibly points to greater effort in constructing and/or updating the situation model.

Although research on semantic language processing in ASD and control participants (Just *et al*., 2004; Harris *et al*., 2006) has reported decreased activation in LIFG for the ASD group, no such difference was present in our study. The suggestion has been put forward that the decreased activation in LIFG in ASD is related to a reduction in integrative processing. Our results, however, do not support this idea. In our study, both groups displayed stronger activation in LIFG for speaker-incongruent sentences than for speaker-congruent sentences. The increased activation for speaker-incongruent sentences in LIFG is in line with the suggested role for this region in sentence and discourse comprehension (Dapretto and Bookheimer, 1999; Robertson *et al*., 2000; Hagoort *et al*., 2004; Rodd *et al*., 2005; Kuperberg *et al*., 2006; Zempleni *et al*., 2007). It is also consistent with a view of language comprehension in which LIFG is a crucial region for unification (Hagoort, 2005) in which a wide range of incoming information is continuously integrated and combined into an unfolding representation of a multiword utterance, such as a sentence. When incoming information is conflicting, as in the case of a mismatch between voice-based inferences about the speaker and sentence content, unification load is increased and this is reflected in stronger activation in LIFG. A recent fMRI study has shown that during discourse comprehension LIFG and RIFG are both recruited in on-line semantic unification of incoming information with previously stored knowledge in long-term memory (Menenti *et al*., 2009). However, RIFG was more sensitive to discourse anomalies and might be relatively more involved than LIFG in forming a general representation (a situation model) of ongoing discourse (Menenti *et al*., 2009). Applying these findings to our results suggests that the ASD and control group are equally able to recruit LIFG for unification purposes, since both groups activated LIFG to the same extent for speaker-incongruent sentences. The additional activation in RIFG for the ASD group might be related to increased difficulty with forming and revising a situation model.

Besides a difference between the groups in RIFG, we found a region in right ventral MPFC (BA 10), including the ACC (BA 24/32), to be modulated by speaker-congruity in the control group, but not in the ASD group. While the control group showed decreased activation in right ventral MPFC for speaker-incongruent sentences relative to speaker-congruent sentences, there was no such effect in the ASD group. In general, it has been suggested that the MPFC (including ACC) contributes to fundamental aspects of social cognitive functioning, such as mentalizing and theory of mind (ToM) reasoning, person perception and self-referencing (see for a review Vogeley *et al*., 2001; Vogeley and Fink, 2003; Amodio and Frith, 2006; Buckner *et al*., 2008). Especially the ventral part of MPFC, including ACC, seems to be implicated in both self-referential judgments and inferences about others that are perceived as similar to oneself (Vogeley *et al*., 2001; Kelley *et al*., 2002; Mitchell *et al*., 2006). This finding points to a tight link between thinking about oneself and thinking about other people. Moreover, it suggests that people automatically refer to their own mental states when considering those of similar others and use self-reflection as a strategy for understanding the minds of other people (Mitchell *et al*., 2005; Jenkins *et al*., 2008).

This self-referential mechanism might explain the activation in right ventral MPFC (vMPFC) and ACC observed in our study. The presented sentences always contained self-referential pronouns, such as ‘I’, ‘my’, ‘we’ or ‘our’, to assure that the voice-based inferences made by the listeners were related to the speaker at hand. This construction prompted the listener to make inferences about the speaker’s characteristics, (mental) state and beliefs, which might have triggered self-referential processing as mediated by vMPFC.

It is important to note that the response in vMPFC displayed by the control group was stronger for the speaker-congruent than for the speaker-incongruent sentences. Given that the speaker-congruent condition can be seen as a baseline condition, it seems more appropriate to describe this modulation in vMPFC as a relative decrease. This interpretation seems to fit with reports from other neuroimaging studies suggesting that responses in vMPFC during self-referential processing frequently occur as decreases in activation (see Kelley *et al*., 2002; Mitchell *et al*., 2005). Furthermore, the activation pattern in vMPFC is in line with its suggested role in the so-called default mode network, which shows higher activity in more passive task conditions compared to more attention demanding cognitive tasks (Shulman *et al*., 1997; Gusnard and Raichle, 2001; Raichle *et al*., 2001; Greicius and Menon, 2004; Buckner *et al*., 2008).

The decrease in activation in vMPFC for speaker-incongruent sentences was only present in the control group and not in the ASD group. This result is in line with an fMRI study using the Stroop task and reporting that, while both groups had a similar behavioural performance, the ASD group did not show a deactivation effect from resting baseline in MPFC as present in the control group (Kennedy *et al*., 2006). The comparison between these and our findings must be treated with caution given the absence of a true deactivation and resting state baseline in our study. Although the exact functions supported by the default mode regions are far from clear, it has been suggested that self-referential mental activity is one aspect of MPFC’s contribution to the default network (Gusnard *et al*., 2001; Gusnard and Raichle, 2001; Kennedy *et al*., 2006). Speculatively, the absence of a reduction in activity in vMPFC in the ASD group might point to a failure to engage in self-referential processes mediated by this default mode region during rest or baseline (i.e. speaker-congruent sentences) (see Iacoboni, 2006; Kennedy *et al*., 2006; Buckner *et al*., 2008).

We chose to investigate pragmatic language comprehension in the auditory domain, since this is the most common modality for communication in daily life. However, little research has been done on auditory language processing in adults with ASD and findings are not unequivocal. Earlier studies on perception of speech and speech-like sounds in ASD have reported reversed asymmetry, i.e. more right than left hemisphere activation during auditory (language) processing (Muller *et al*., 1999; Boddaert *et al*., 2003). Since we contrasted two conditions of sentence processing that differed only with respect to speaker-incongruity, it is unlikely that the increased activation in RIFG in our study can be attributed to a reversed hemispheric dominance for speech processing. Another neuroimaging study on voice processing revealed that, relative to control participants, adults with ASD failed to activate voice-selective areas in superior temporal sulcus, whereas they displayed a normal activation pattern in response to non-vocal sounds (Gervais *et al*., 2004). According to the authors, these results indicated abnormal cortical processing of socially relevant auditory information in ASD. Although voice processing plays an important role in our experiment, our results cannot be explained by such a difference since our study involved higher-level language processing and not perception of single sounds.

The intact behavioural performance of the ASD group on our pragmatic language task contrasts markedly with the obvious difficulties with pragmatic aspects of verbal communication displayed by adults with ASD in daily life. The behavioural performance of the ASD group on its own is in accordance with earlier findings that adults and children with ASD have access to knowledge of social stereotypes and an intact ability to use them (White *et al*., 2006; Hirschfeld *et al*., 2007). The discrepancy between the pragmatic difficulties of individuals with ASD in daily life and intact behavioural performance on our debriefing interview outside the scanner might be clarified by drawing a parallel to patients with a lesion in vMPFC (a brain region revealing between-group differences in activation in our study). In daily life, these patients often demonstrate social conduct problems that overlap with those in ASD, such as an inability to respond appropriately to social cues or to obey conventional social rules (e.g. Dimitrov *et al*., 1999). Milne and Grafman (2001) examined the intactness of social knowledge in patients with a lesion in vMPFC by asking them for implicit and explicit judgments of gender stereotypes. The patients showed impaired performance for the implicit condition only, suggesting intact (stereotypical) social knowledge, but a deficit in automatic access of this knowledge that can be compensated for if asked for an explicit conscious judgment (Milne and Grafman, 2001). Given our results and the existing literature, we suggest that, like patients with lesions in vMPFC, high-functioning individuals with ASD do possess and can access the social knowledge that they appear not to use in daily life. However, access to this knowledge might occur less automatically and requires more effort or explicit processing. While our task was designed to investigate implicit pragmatic language processes (related to social stereotypes), the experimental setting has possibly triggered a more explicit judgment or recognition of (stereotypical) social knowledge that might have resulted in the intact behavioural performance by the ASD group on our debriefing interview.

In conclusion, investigating pragmatic language comprehension in adults with ASD and a matched control group revealed an overlap in recruited brain regions, but also activation differences between the groups in RIFG and vMPFC. The ASD group was able to detect incongruities between voice-based inferences about speaker characteristics and sentence meaning at a similar level as the control group, but showed increased activation in RIFG for sentences containing a speaker-incongruity. We suggest that the additional activation in RIFG for speaker-incongruent sentences is compensatory in nature. It possibly reflects spill over processing from the language dominant left hemisphere due to higher task demands for the ASD group during pragmatic language comprehension. Speculatively, the increased RIFG activation might be due to greater effort in constructing and revising a situation model. In addition, unlike the control group, the ASD group did not display a decrease in activation for speaker-incongruent relative to speaker-congruent sentences in vMPFC. Since vMPFC is involved in self-referential processing related to judgments and inferences about self and others, the absence of a decrease in activation in the ASD group possibly points to atypical self-referential mental activity in ASD. Our study is the first to show that in ASD compensatory mechanisms are necessary in implicit, low-level inferential processes in spoken language understanding. In a way, this indicates that the language problems of individuals with ASD are not restricted to high-level inferential processes, relevant for the subtleties such as irony and bridging inferences in complex discourse, but are pervasive all the way down to the most basic aspects of pragmatic language processing. Further studies should unravel whether problems with pragmatic language comprehension in ASD can be attributed to atypical pragmatic language processing per se or to deviant self-referential and mentalizing processes, since this will have consequences for training of communication skills in individuals with ASD.

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