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Atypical participation of visual cortex during word processing in autism: an fMRI study of semantic decision

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Abstract

Language delay and impairment are salient features of autism. More specifically, there is evidence of atypical semantic organization in autism, but the functional brain correlates are not well understood. The current study used functional MRI to examine activation associated with semantic category decision. Ten high-functioning men with autism spectrum disorder and 10 healthy control subjects matched for gender, handedness, age, and nonverbal IQ were studied. Participants indicated via button press response whether visually presented words belonged to a target category (tools, colors, feelings). The control condition required target letter detection in unpronounceable letter strings. Significant activation for semantic decision in the left inferior frontal gyrus (Brodmann areas 44 and 45) was found in the control group. Corresponding activation in the autism group was more limited, with smaller clusters in left inferior frontal areas 45 and 47. Autistic participants, however, showed significantly greater activation compared to controls in extrastriate visual cortex bilaterally (areas 18 and 19), which correlated with greater number of errors on the semantic task. Our findings suggest an important role of perceptual components (possibly visual imagery) during semantic decision, consistent with previous evidence of atypical lexicosemantic performance in autism. In the context of similar findings from younger typically developing children, our results suggest an immature pattern associated with inefficient processing, presumably due to atypical experiential embedding of word acquisition in autism.

Keywords

Autism; Language delay; Functional MRI; Lexical; Semantic categorization; Visual perception

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1. Introduction

Autism is a neurodevelopmental disorder characterized by lifelong socio-communicative impairments and a restricted range of behaviors. Individuals without clinically significant language delay before age 3 years usually receive a diagnosis of Asperger's Disorder, which is considered part of Autism Spectrum Disorders (ASD; Volkmar et al., 2004).

Despite some recent evidence for partial overlap between ASD and specific language impairment (Tager-Flusberg, 2004), the current evidence overwhelmingly suggests that pragmatic functions are the most consistently impaired language domain in ASD, whereas syntax and phonology are less consistently impaired (Boucher, 2003). Experiential effects in language acquisition are likely to play an important role with regard to lexicosemantic development. Children with ASD do not interact with their environment in typical ways. Indeed, autistic children's atypical patterns of interaction with people and with objects (Pierce & Courchesne, 2001) imply by necessity that their range of experience relevant to language acquisition is grossly abnormal.

In typically developing children, language acquisition proceeds through interaction of child and other with the opportunity for constant application of the child's growing body of linguistic knowledge (Locke, 1995;Papousek & Papousek, 1986). Pragmatic impairments characteristic of ASD reduce interactive learning experiences (Charman, 2003;Hobson & Lee, 1998;Loveland & Tunali, 1991;Ozonoff & Miller, 1996). Consequently, normal interactive mechanisms of language acquisition are likely compromised in ASD in at least two ways. First, joint attention – an important predictor of language acquisition (Markus et al., 2000;Morales et al., 2000) – is impaired in ASD (Bruinsma et al., 2004;Dawson et al., 2004;Trepagnier et al., 2002) and there is a strong correlation between joint attention deficits and delays in language acquisition (Bono et al., 2004;Mundy et al., 1990). Secondly, children with ASD speak much less frequently than expected for their chronological age – if at all – which limits opportunities for interactive language acquisition.

Reviewing language studies of autism, Tager-Flusberg (1981) concluded that autistic children showed no consistent phonological or syntactic deficits, whereas semantics and pragmatics were prominently impaired. For example, children with autism tend to violate semantic constraints and do not use semantically based strategies for lexical tasks. More recently, Toichi and Kamio (2001) examined semantic associations in autism. Although they observed typical semantic priming effects, unusual correlations were found between task performance and nonverbal cognitive ability. This suggests that factors beyond verbal intelligence are involved in semantic performance in autism, possibly implying different strategies or cognitive component processes. Furthermore, using a related semantic priming paradigm, Kamio and Toichi (2000) found priming effects in autism to be moderated by primer modality. A significant gain in performance for picture versus word primes was found in the autism group suggesting a possible advantage for perceptually-based stimuli in accessing semantic information.

Abnormal organization for semantic information in autism has also been found in studies examining verbal long-term memory. In one study examining levels of processing, ASD subjects failed to show the expected recall advantage for semantically encoded words (Toichi & Kamio, 2002). Again, a relation between task performance and nonverbal cognitive ability was found only for the autism group. Another study by this group examined word meaningfulness (concrete vs. abstract) on recall in autism and also demonstrated a lack of advantage for semantically richer words (Toichi & Kamio, 2003).

The above results suggest atypical semantic organization in ASD. Surprisingly few neuroimaging and electrophysiological studies are currently available to address this question. Studying sentence comprehension, Just and colleagues (2004a) found consistently lower levels of functional connectivity between cortical areas in their autism group, suggesting reduced neurofunctional integration during complex language processing. Harris and others (2006) observed diminished left inferior frontal activation for semantic (compared to perceptual) processing of words in autistic adults. In earlier electrophysiological work, Dunn and colleagues (1999) found that autistic children failed to show an increased N400 response for semantic violations, suggesting impaired lexicosemantic processing. As a result, children with ASD may not utilize deep semantic strategies in lexical tasks and instead rely upon perceptual information.

The present study examined the neurofunctional correlates of semantic decision in ASD. Lesion and functional imaging studies have demonstrated the importance of left frontal and temporal lobes in lexicosemantic processing (Petersen et al., 1988;Silveri et al., 1997). Further, organization of the semantic system appears to rely on experience and interaction with the environment during lexical learning (Grabowski et al., 1998;Martin & Chao, 2001). Recognizing diminished experiential effects (as discussed above), we hypothesized that individuals with ASD would present atypical patterns of neural activation in response to a semantic decision task when compared to healthy controls. Specifically, we predicted that reduced experience in ASD would be associated with a less mature pattern of lexicosemantic organization and with greater reliance on perceptual components (cf. Brown et al., 2005).

2. Methods and materials

Twelve ASD participants were recruited, but due to excessive movement during image acquisition two were removed from further analyses. The remaining 10 individuals with an ASD diagnosis (mean age 26.1 years ± 10.5) were individually matched with 10 healthy control subjects (mean age 25.3 years ± 9.8) for age, gender, and handedness. The ASD group was composed of 8 participants diagnosed with autism and two with a diagnosis of Asperger's Disorder, as determined by an experienced neuropsychologist (co-author N.A.). Each participant with autism met diagnostic criteria for Autistic Disorder according to the DSM-IV (APA, 1994), the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), and the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000). A diagnosis of Asperger's Disorder was given if a participant met the criteria for Autistic Disorder or ASD on the ADI-R and Autism Diagnostic Observation Schedule (ADOS) and DSM-IV criteria for Asperger's Disorder. The DSM-IV differentiates Asperger's Disorder from Autistic Disorder by requiring an absence of a clinically significant history of delay in language, cognitive functioning, or adaptive skills. Potential participants who had another diagnosable medical condition that might affect brain development, a visual, auditory, or motor impairment, or who were born preterm, were excluded from the study. For one ASD participant, diagnosis was based on ADOS and DSM-IV criteria only. Each ASD participant's full scale IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI; TPC, 1999). All participants scored above the cutoff for mental retardation (IQ > 70). One control subject did not undergo IQ testing. Groups were matched for performance IQ (see Table 1) and handedness (eight right, two left per group). No attempt at matching groups for VIQ was made given that intellectual impairment is considered to be an inherent characteristic of ASD (Bailey et al., 1996) and correlates positively with symptom severity (Rapin, 1997). Hand preference was ascertained by participant self-report (see Table 2 for individual participant information in the ASD group).

The experimental protocol was approved by the Institutional Review Boards of San Diego State University, San Diego Children's Hospital Research Center, and the University of California, San Diego. After the study was explained, written consent was obtained from each

participant. Written parent consent, in addition to participant verbal and written assent, was obtained for participants under the age of 18.

2.1 Experimental Procedures and Task conditions

In the experimental condition, participants were asked to indicate category membership for visually presented words via a yes/no button response. Each experimental block started with a category word and a question mark (e.g., TOOL?), which alerted participants to the target category and was presented for 3.7 seconds. This was followed by 11 trials of words (2.5 seconds each) for category decision. Total block length was 31.2 sec (12 image repetition times [TRs]; see below). In each block, eight words were targets (e.g., HAMMER) requiring a "Yes" response and three were non-targets (e.g., SOCCER; Figure 1A). Three target categories were used: Tool, Color, and Feeling. Each category was presented twice per run, alternating with a Perceptual control task described below (block sequence in the two runs: CPTPFPFPTPC; FPCPTPTPCPF). Every participant completed two runs. No word was repeated within the experiment.

In the perceptual control task, participants decided whether a target letter was present in an unpronounceable consonants string. Presentation of stimuli and response collection were identical with the semantic decision condition, except for a slight difference in the timing of the instruction prompt (Figure 1B). The target letter prompt (LETTER K?) was presented for 3.3 seconds. Total block length was 20.8 sec (8 TRs). There were 7 trials (2.5 seconds each) per block, with 5 targets (letter present) and 2 non-targets (letter not present) presented in pseudorandomized order. The control task was designed to match the semantic decision condition with regard to (a) the perceptual aspects of stimulus material and (b) task difficulty.

For the semantic decision condition, target words were taken from the 'Category Norms as a Function of Culture and Age' database (Yoon, 2003), which includes normative data for 105 verbal categories acquired from 100 young American adults. For each category, the most frequent items were selected, including only words ranging from three to eleven letters. Mean word length was balanced across categories, with an average of five letters. Control letter strings were analogously balanced and matched for length with the semantic decision condition. Word stimuli are presented in Appendix 1.

Throughout the experiment participants held a response device. Responses were relayed to a laptop computer for digital recording of Yes/No responses and reaction time, used to assess task compliance and participant performance. Stimuli were presented and responses and reaction times logged using Presentation® (nbs.neuro-bs.com). All target/non-target sequences were pseudorandomized. Button assignment (left vs. right) was counterbalanced for Yes/No responses across participants within each group.

2.2 MR Data Acquisition

Participants lay supine in the MR scanner, with their heads secured within the head coil using foam padding. Stimuli were presented on a rear-projection screen at the foot of the scanner gurney using a projector located in the control room. A mirror attached to the head coil allowed the participants to view the presented stimuli.

Imaging data were collected on a 1.5T Siemens Symphony MR scanner (Erlangen, Germany). In each subject, 228 whole-brain T2*-weighted volumes were acquired using a single-shot gradient-recalled echo-planar imaging sequence, each containing 28 contiguous axial slices (4 mm slab; TR 2500 ms; TE 36 ms; flip angle 90°; field of view [FOV] 256 mm; matrix 64x64; in-plane resolution 4 mm^2). For anatomical localization, a high-resolution structural scan was

acquired for each participant during the same session (TR 11.08 ms; TE 4.3 ms; flip angle 45°; FOV 256 mm; matrix 256 × 256; 180 slices; resolution 1 mm^3).

2.3 Data Analyses

Image preprocessing and statistical analyses were performed using Analysis of Functional NeuroImages (http://afni.nimh.nih.gov/afni/; Cox & Hyde, 1997). The first two time points in each run, characterized by signal instability, were discarded. Functional images were motion-corrected using a three-dimensional volume registration algorithm, which co-registered each volume in the time series to a reference volume (time point 77 of each run) using an iterative least squares algorithm (Cox & Jesmanowicz, 1999). Functional time series were then smoothed with a Gaussian filter (full-width at half-maximum = 5 mm). Each participant's structural and functional data sets were normalized to Talairach space (Talairach & Tournoux, 1988). The two functional runs for each participant were concatenated and again motion corrected using the above procedure. Time series were then correlated with four hemodynamic response function (HRF) models, each based on a boxcar wave with slightly varying delays and slopes to accommodate hemodynamic latency. Based on the best fitting HRF, a fit coefficient score was produced for each voxel.

Fit coefficients were entered into 1-sample *t* tests for within group analyses and paired 2-sample *t* tests for group comparison. To adjust for multiple comparisons, cluster significance was determined by Monte Carlo alpha simulations (Forman et al., 1995) for a corrected significance threshold of $p < .01$ (within-group comparisons) and of $p < .05$ (between-group comparisons).

3. Results

3.1 Behavioral Data

Due to equipment failure, response data for three control and one ASD participant were unavailable. Behavioral data from the remaining participants (ASD $n = 9$; control $n = 7$) were analyzed using a 2 factor mixed design ANOVA with group (ASD, control) and condition (color, tool, feeling, perceptual control) as the factors. The mean accuracy for each condition is shown in Table 3.

There was a significant main effect of condition ($F_{(3,42)} = 6.96$, $p<.001$) as well as a significant interaction of group and condition ($F_{(3,42)} = 4.33$, $p<.009$). After controlling for multiple comparisons the simple effects for group and condition were explored. The ASD group performed significantly better on the Perceptual control condition than for Feelings (mean difference = 11.32, $p<.002$). No difference in accuracy across conditions was found for the control group. A significant between-group difference for task accuracy was found as well ($F_{(1,14)} = 11.35$, $p<.005$). Group difference was further examined using MANOVA with accuracy for each condition as dependent variables. The control group was significantly more accurate than the ASD group for Colors and Feelings (See Table 3). However, overall ASD performance was significantly greater than what would be expected for random responding (i.e. 50% correct; $F(1,16) = 19.72$, $p<.001$). Group differences in reaction times (in milliseconds) for semantic decision did not reach significance (ASD mean = 825.9, $SD = 66.7$; control mean = 797.2, $SD = 62.9$; $F_{(1,14)} = 2.39$, $p = 0.14$).

Comparisons for the Perceptual control task showed a different pattern. Both groups were equally accurate at detecting the target letter (ASD mean = 93.2, $SD = 5.4$; control mean = 93.5, $SD = 5.5$; $F_{(1,14)} = .016$, $p = .89$), but the ASD group had significantly longer reaction times (mean = 899.3, $SD = 94.3$) than the control group (mean = 797.6, $SD = 50.6$; $F_{(1,14)} = 7.87$, $p < .014$; see Table 3).

No significant correlations were found between accuracy and age or reaction time and age in either group (all: $p>.6$).

3.2 Imaging Data: Within-Group Analyses

Significant clusters of activation and negative effects for semantic decision are listed in Table 4 and illustrated in Figure 2. Anatomical identifications are based on the atlas by Talairach and Tournoux (1988) and statistical overlays on mean anatomical images for each group.

Activations—Significant activation in left inferior frontal areas was observed for both groups. In the control group, an extensive cluster was found in Brodmann areas 44 and 45 of the left hemisphere (Figure 2A). Corresponding activation in the ASD group was more limited (Figure 2C), with clusters in left inferior and middle frontal gyri (areas 45, 46, 47). The control group further showed activation clusters in the left superior and medial frontal gyri (areas 6, 8). In the ASD group, two medial frontal clusters were seen in area 6. The ASD group showed several additional activation clusters in visual areas, including striate cortex (area 17) in the left hemisphere and a large bilateral cluster in extrastriate cortex (areas 18, 19; Figure 2D). Only a small cluster of activation in the right cuneus (area 18) was observed in the control group. Both groups also exhibited subcortical activations. The control group showed clusters in the left thalamus and caudate nucleus as well as in the right insula. For the ASD group, activity was found in the left amygdala and in the right cerebellum.

Inverse effects—The control group showed extensive clusters of negative effects (higher BOLD signal for the control task compared to semantic decision) in posterior cortices that extended from superior parietal area 7 to the posterior cingulate gyrus (Figure 2B). Further clusters of inverse effects occurred in superior and middle occipital gyri (areas 19/37), mostly in the left hemisphere. Inverse effects were also found in the lateral and medial frontal regions (areas 9, 10, 24) and inferior parietal area 40 bilaterally. The ASD group showed no significant clusters of inverse effects.

3.3 Imaging Data: Direct Group Comparisons

Figure 2E–F illustrates clusters of significant group differences (for complete listing, see Table 4). Such differences were predominantly found in extrastriate visual cortex. The ASD group showed significantly greater activation in area 18 bilaterally and in area 19 of the left hemisphere. Additional clusters were found in left medial frontal gyrus (area 6), right postcentral gyrus (area 2), right posterior cingulate gyrus (area 23), and in temporal cortex (areas 21, 22). No clusters of significantly greater activation for control compared to ASD participants were identified.

Post hoc analyses—In order to better describe the nature of atypical extrastriate activity associated with semantic decision in autistic participants, we performed two post hoc analyses examining (a) the cognitive-behavioral relevance of the finding, and (b) whether the observed hemodynamic effects were driven by a particular semantic category (see Discussion for a detailed rationale).

Relation between extrastriate activity and performance

This analysis used occipital activation clusters identified in the autism group as a region of interest (see asterisks in Table 4), for which the number of activated voxels ($p< .05$; uncorr.) was determined in each subject as a measure of activation extent. We expected negative correlations between number of activated voxels and level of behavior (i.e., positive correlations with RT and number of errors). When including all 16 subjects with available behavioral data, Pearson correlation analyses showed significant correlations in the expected

direction of activated voxel count with the number of errors (r = .51, p = .02) and with RT (r = .47, p = .03). For the nine ASD participants only, we found concordant trends that did, however, not reach significance (voxels by errors: r = .19, p = .31; voxels × RT: r = .21, p = .29). One subject was a clear outlier with highest number of errors (43), but lowest number of activated voxels within the ROI (16; Figure 3A). Inspection of this subject's data revealed extensive extrastriate activation (489 voxels) in the immediate vicinity of this ROI. Excluding this outlier from the sample, the remaining ASD sample showed a marginally significant correlation between activation extent and number of errors (r = .53, p = .089). RT and number of errors were also positively correlated with extrastriate activation extent in the control group (voxels by errors: r = .79, p = .017; voxels × RT: r = .61, p = .074; Figure 3B and 3D), despite the absence of significant activation in this ROI for the control group overall (see Discussion). We also examined the relation between IQ scores and extrastriate activity, expecting inverse correlations (Figure 3E–H). In the ASD group, correlations reached significance only for performance IQs (r = −.66, p = .019), but not for verbal IQs (r = −.14, p = .35), whereas they were non-significant in the control group (voxels by VIQ: r = −.36, p = .17; voxels by PIQ: r = −.04, p = .46).

Correlations between age and active voxel count showed trends in the expected direction, but did not reach significance in either group (controls r = −.30, p = .20; ASD r = −.42, p = .12; see Discussion for rationale).

Analyses for individual semantic categories

Since one of our semantic decision categories (colors) was exclusively visual, we examined whether atypical extrastriate activity in the autism group was solely driven by this category. We tested effects by category, examining only BOLD changes for a single category of interest compared to the perceptual control condition (and discarding time points associated with semantic decision for the other two categories). These analyses focused solely on posterior cortex in the vicinity of the occipital activation found in the autism group for semantic decision overall (see asterisks in Table 4 and Figure 2D). Although activation for single categories, which was examined at a relaxed threshold (p<.05, uncorr.) given reduced power and limited region of interest, was slightly larger for color, a similar pattern of activity was identified for the other two categories (Figure 2E and Discussion).

4. Discussion

Our finding of increased errors on the semantic category decision task in the ASD group (compared to controls) is consistent with previous studies suggesting impaired lexicosemantic accuracy in autism (Dunn et al., 1999;Tager-Flusberg, 1981;Toichi & Kamio, 2001). Nonetheless, ASD participants were clearly cooperative, performing at levels far greater than chance.

On the perceptual control task, both groups were equally accurate, consistent with studies suggesting that visual search is a spared ability in ASD (O'Riordan, 2004). Unexpectedly, reaction times were significantly longer for the ASD group, which may be related to impaired attention shifting. Townsend et al. (1996) found slowed visual orienting in autism when participants had to shift attention from a central fixation point to stimuli presented more peripherally. In our control task, each letter string was preceded by a central fixation cross (Figure 1B). Target letter location was randomized within consonant strings and required spatial attention shifts, potentially explaining longer RTs in ASD participants.

Our imaging results showed that semantic category decision was associated with extensive left inferior frontal activation in the control group, consistent with numerous lexicosemantic studies in healthy adults (Damasio et al., 1996;Martin & Chao, 2001;Petersen et al., 1988;Tyler et al.,

2003;Wiggs et al., 1999). In the ASD group, inferior frontal activation clusters in areas 45 and 47 were comparatively small, possibly consistent with evidence of left-hemisphere dysfunction and rightward asymmetry of frontal language areas in autism (Bruneau et al., 2003;Herbert et al., 2002;Rojas et al., 2002;Sussman & Lewandowski, 1990). However, we did not observe right frontal activation for semantic decision in the ASD group, nor did direct group comparisons yield significant differences in left prefrontal cortex. Absence of group differences in inferior frontal cortex could be related to heterogeneity within the autism population. De Fosse and colleagues (2004) reported atypical volumetric asymmetries in inferior frontal lobes only in autistic boys with language impairment, but not in autistic boys with normal language, whose mean VIQ (97.7) was close to mean VIQ in our ASD sample (91.6).

Large areas of inverse effects (reduced activation for semantic decision compared to the perceptual control condition) were found for the normal control group in middle occipital, temporoparietal, and bilateral frontal regions. These effects may be related to our control task. Manjaly et al. (2003) found similar activation patterns for visual search in an embedded figures test compared to a visual match condition. As in our perceptual control condition, participants had to identify a stimulus in a more complex visual pattern. Our control task was relatively hard compared to easy baseline conditions often applied in functional imaging studies, since it had been calibrated to match the semantic decision condition on RTs and accuracy in a pilot sample of healthy adults. This explains why BOLD effects for the two conditions were overall balanced in our control group (with approximately equally extensive “activation” and “inverse” effects).

In the ASD group, a large additional area of activation was found in extrastriate visual cortex bilaterally, which was not seen in the control group (see Figure 2). This finding is significant in the context of previous studies suggesting qualitatively different lexicosemantic strategies in autism (Dunn et al., 1999;Kamio & Toichi, 2000;Toichi & Kamio, 2001,2002,2003). As hypothesized, this strategy may involve increased visualization of target items. The areas of activation found in extrastriate visual cortex correspond to activations seen for mental imagery (Just et al., 2004a;Mellet et al., 2000), even when exclusively auditory stimuli were used as prompts for visual imagery (Just et al., 2004b;Lambert et al., 2004). In a recent study of verbal working memory, Koshino and colleagues (2005) reported unusually high levels of extrastriate activity in autistic adults, consistent with the present findings.

Direct statistical comparison between the ASD and control groups revealed significant differences in extrastriate visual cortex bilaterally. These effects are unlikely to be explained by the inverse effects in the control group described above, as they occurred in different loci (cf. Figure 2B versus 2F). Our finding suggests that lexical representations in ASD may be more perceptually based, possibly because they are anchored in reduced experience (as described in the Introduction). As a result, adolescents and adults with ASD appear to process lexicosemantic stimuli in an immature fashion, continuing to rely heavily on perceptual components and visual imagery. Furthermore, reliance on such perceptual components may be associated with performance slightly below normal (see below).

Lexical organization is considered to be affected by the sensory modalities involved in the acquisition of word meanings (Martin & Chao, 2001). However, little direct neuroimaging evidence is available to demonstrate an initial dependence of lexicosemantic organization on sensorimotor representations in children. Potentially consistent, Mills and colleagues (1994) found that ERP components (N200 and N350) distinguishing known from unknown words were distributed across bilateral frontal, temporal and parietal lobes in 13–17 month old infants, whereas they were more localized to left temporo-parietal areas in 20 month olds. In a recent fMRI study on lexical association in children and young adults, Brown and colleagues

(2005) observed age-related activity increases in left frontal cortex, whereas age-related decreases were seen in extrastriate cortex bilaterally. These findings may reflect initial dependence of lexical representation on perceptual (especially visual) systems. This view is also supported by behavioral studies showing that perceptual information is a guide to word learning from early stages on (Smith et al., 1996). In particular, children's early word learning is largely based on visual information about object shape (Gershkoff-Stowe & Smith, 2004;Samuelson & Smith, 1999). This normal developmental profile would be consistent with our interpretation of visual cortical activation in older autistic participants during semantic decision as reflecting an 'immature' pattern of lexicosemantic processing.

We further tested this hypothesis in post hoc analyses examining the relation between atypical posterior activity and performance. We found that in the entire sample (both groups), this posterior activity was positively correlated with errors and RT. This suggests that indeed extrastriate activity was associated with a relatively inefficient mode of processing. However, this correlation between performance and extrastriate activation was more robust in the control group than in our ASD sample, for which it did not reach significance. This is surprising since the control group did not show significant activation in extrastriate cortex. It suggests that activity in visual cortex occurs in the typically developing brain during lexical processing in children, but then decreases with age (as discussed above, and consistent with the findings by Brown et al., 2005). However, residual activity identified even in typically developing adolescents and adults in our study (several of whom showed ≥10 activated voxels in these regions) was still correlated with relatively low performance on semantic decision. These control participants could be characterized as displaying a subtly immature pattern of lexicosemantic activation (cf. Brown et al., 2005). Most – but not all – individuals with ASD in our sample showed a corresponding association between extrastriate activity and performance, albeit at the lower end of the performance spectrum. Note, however, that in a block design – as in our study – performance effects cannot be analyzed on a trial-by-trial basis. Event-related fMRI studies will be necessary for a more detailed examination of the links between performance and activation profiles in posterior cortex.

With regard to general level of functioning, extrastriate activity showed a significant negative correlation with nonverbal performance IQs – but not with verbal IQs – in the ASD group, potentially suggesting association with low level of functioning in nonverbal domains. No such correlation was seen in the control group.

Taken together, the findings suggest that posterior activity during lexicosemantic processing reflects an initial perception-based strategy in young children that is gradually substituted by top-down frontal control in older typically developing children. Individuals with ASD tend to rely on a processing mode similar to the initial perception-based strategy even in adolescence and adulthood. Some typically developing adolescents and adults show residual traces of a perception-based processing mode as well. Although these are subtle (i.e., associated with minimal activity), they result in less efficient processing and therefore slightly lower performance accuracy.

A further post hoc analysis examining effects for individual categories showed that our finding in the autism group was not solely driven by a single category (Figure 2E), which suggests that visual imagery may play a general role in semantic processing and lexical retrieval in autism, rather than an exclusive role only in visually based representations. This is consistent with the recent finding by Kana and colleagues (2006) of atypically strong extrastriate activity in ASD during sentence comprehension in particular for a low-imagery condition, for which only small effects of visual imagery would be expected.

Our above interpretation may appear more obvious for the categories “color” and “tool” (which can also be visualized) than for “feeling”. However, it is known that facial expressions associated with different emotions are characterized by specific visual features (Ekman, 1993,1999). Processing of these features is associated in neurotypical adults with activation in occipital cortex, besides medial prefrontal cortex, amygdala, cingulate gyrus, and insula (Ishai et al., 2000;Phan et al., 2002). Similar sites of activation including occipital cortex have been recently identified for the processing of emotional words (Kensinger & Schacter, 2006). Finally, activation associated with visual imagery has been demonstrated not only in extrastriate, but also in primary visual cortex (Chen et al., 1998), which appears to be involved specifically when imagery relates to high resolution detail or physical shape (Kosslyn & Thompson, 2003). Our finding of activation in area 17 in the ASD sample could therefore suggest such local-level imagery during semantic decision.

Our results are more broadly consistent with atypical reliance on extrastriate activity in autism during a variety of tasks. In one study on face perception in autism, unusually robust occipital activity was found in medial occipital area 19 (Hubl et al., 2003). In a study on visually prompted finger movement, significantly greater activation was seen in autistic individuals compared to controls in lateral portions of area 19 (Müller et al., 2001). During visually prompted sequence learning autistic individuals showed atypically strong activation in visual cortices during later learning stages, despite mild behavioral improvements (Müller et al., 2003). Together with the convergent results by Koshino et al. (2005) on verbal working memory described above, these findings suggest that individuals with ASD may rely on perception-based processing modes even after prolonged exposure to a given task, whereas control subjects tend to use such modes only initially, either in childhood or at later ages before practice becomes effective (depending on the type of task).

Just and colleagues (Just et al., 2004a) recently reported atypical neurofunctional profiles for sentence comprehension in high functioning autism. As in our study, inferior frontal activation clusters were smaller in their autism group compared to controls, but no direct statistical group comparison was presented. Further, BOLD signal cross-correlations between a number of cortical areas, considered measures of functional connectivity, were consistently lower for the autism group, suggesting deficient integration of individual components into more complex meaning in the autistic brain.

Although our study provides neurofunctional evidence that is consistent with an ‘immature’ lexicosemantic strategy involving visual imagery in ASD, a number of questions remain. Current literature suggests areas activated in our ASD group are involved in visual imagery regardless of input modality (Just et al., 2004b;Lambert et al., 2004). However, the effects of different input modalities (i.e., visual, auditory) remain to be explored. To our knowledge, only one functional imaging study to date has examined semantic functions using auditory stimulation in autism. In this study (Müller et al., 1999), a small sample of autistic adults showed atypical absence of leftward asymmetry of perisylvian activations during passive listening to meaningful speech, but normal levels of left inferior frontal activity for sentence generation based on an auditory word prompt. Neither of the conditions was associated with significant activity in extrastriate cortex.

It is likely that atypical functional organization, as demonstrated in our study, relates to recent anatomical findings of brain overgrowth during the first two years of life in autism (Courchesne et al., 2001). Neurofunctional abnormality may thus result in part from aberrant neuronal growth in the absence of environmental influence. Specifically, it has been proposed that the reduction of long-distance, reciprocal cortical connectivity leads to defects in the processing of complex information (Courchesne & Pierce, 2005). Although our study was not designed to address this issue directly, our findings suggest that in ASD perceptual brain regions play a

relatively strong role during lexicosemantic processing, whereas in healthy controls top-down functions of supramodal frontal regions are more predominant. One may also note that the visual areas active in our task are considered relatively preserved in ASD, possibly due to their early course of maturation (Carper et al., 2002). Atypical reliance on posterior brain regions for language tasks may result from this relative integrity of visual cortices.

In conclusion, our study is consistent with previous findings suggesting atypical organization of the lexicosemantic system in autism. Such atypical organization may relate to lack of interpersonal experience, which is the primary basis of word learning in typically developing children. Reduced interpersonal language experience is likely to result in greater reliance on nonverbal information. This is supported by the results of the current study showing that individuals with ASD exhibit atypical activity in extrastriate visual regions during semantic category decisions.

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Appendix 1

Stimuli in Category Decision Task

Tool	Color	Feeling
Hammer	Red	Anger
Drill	Pink	Love
Screw	Magenta	Anxiety
Knife	Indigo	Jealousy
Chisel	White	Melancholy
Bolt	Chartreuse	Envy
Razor	Orchid	Fury
Tacks	Tan	Disgust
Nail	Blue	Happiness
Wrench	Black	Grief
Pliers	Brown	Shame
Axe	Silver	Surprise
Ladder	Blonde	Sorrow
Scissors	Burgundy	Ecstasy
Handsaw	Beige	Lust
Shovel	Puce	Regret
Saw	Yellow	Sadness
Ruler	Orange	Hate

Tool	Color	Feeling
Sandpaper	Violet	Joy
Wood	Cyan	Frustration
Glue	Aquamarine	Calm
Nut	Mauve	Despair
Bench	Rouge	Loneliness
Rake	Rust	Rage
Screwdriver	Green	Depression
Tape	Purple	Excitement
Sander	Gold	Gladness
Pencil	Gray	Fear
File	Maize	Cheer
Socket	Maroon	Contentment
Clamp	Amber	Nervousness
Belt	Sanguine	Pride
Nontarget	Nontarget	Nontarget
Football	Octagon	Thought
Volleyball	Trapezoid	Dream
Lacrosse	Circle	Lunacy
Basketball	Square	Idea
Golf	Oval	Motive
Track	Diamond	Concept
Soccer	Triangle	Conscience
Tennis	Hexagon	Intent
Rugby	Sphere	Resolve
Baseball	Rectangle	Guess
Hockey	Pentagon	Fanaticism
Karate	Star	Plan

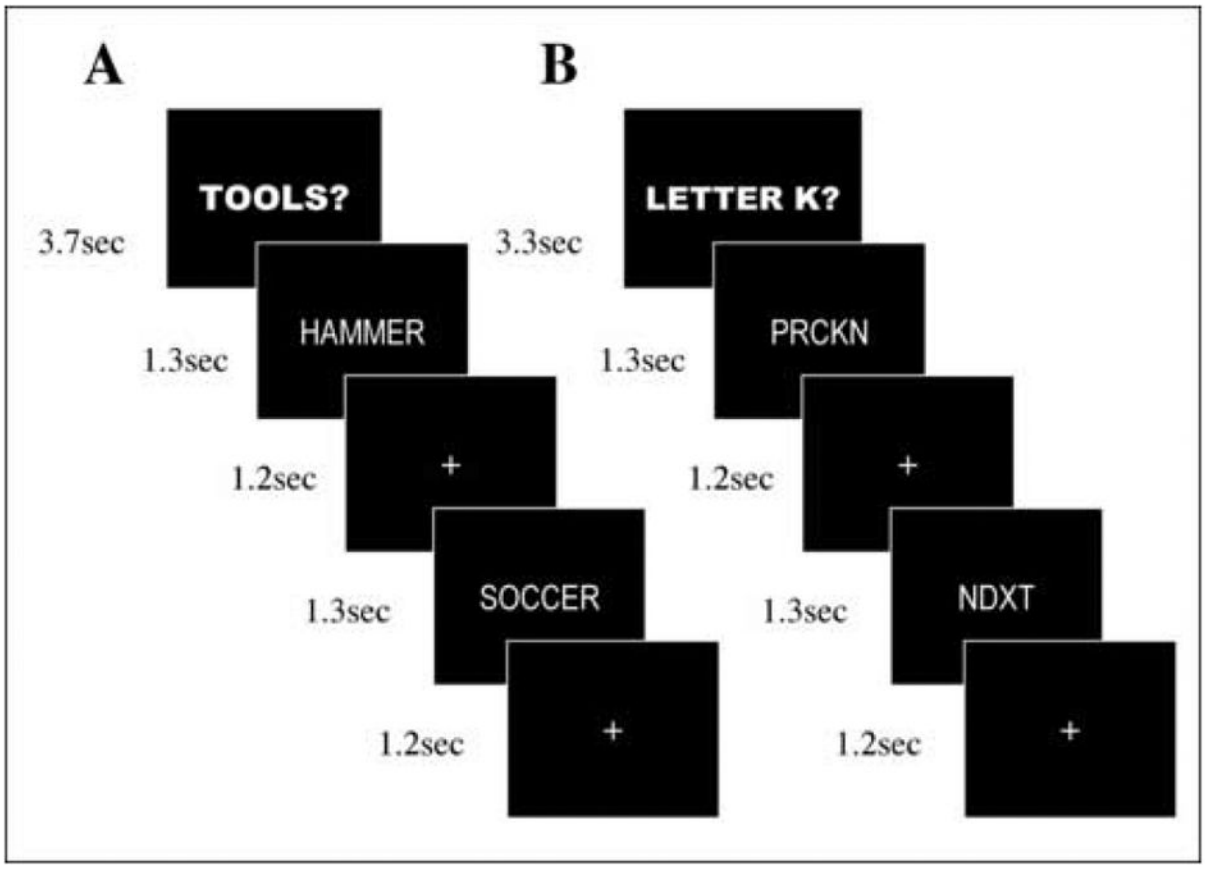

Fig 1.
Stimulus sequence and timing for (A) experimental and (B) control conditions.

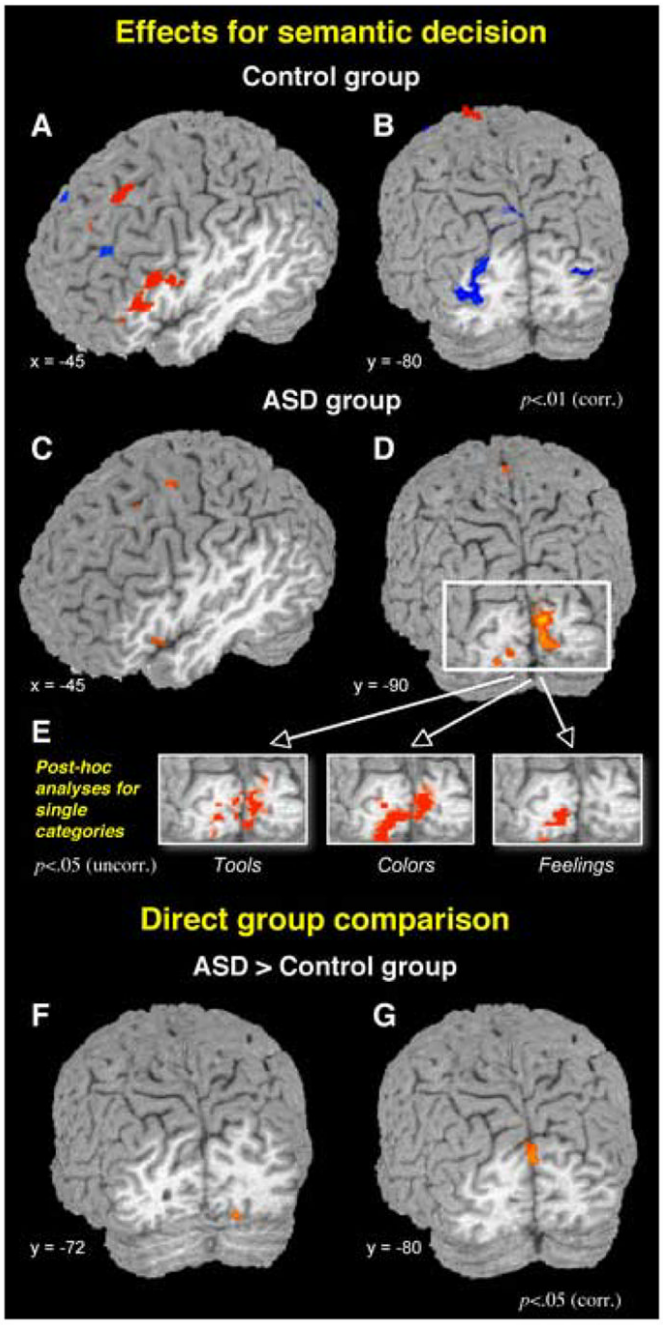

Fig 2.

Significant clusters of effects for semantic decision in control (A–B) and ASD groups (C–D). Red scale in (A–D) represents activation and blue scale represents inverse effects. Occipital effects for each individual semantic category in the ASD group are shown in (E). Clusters of group differences from direct comparison are shown in (F–G). Red scale here represents significantly greater ASD group activation in direct group comparison. No significant inverse effects (Control > ASD group) were identified.

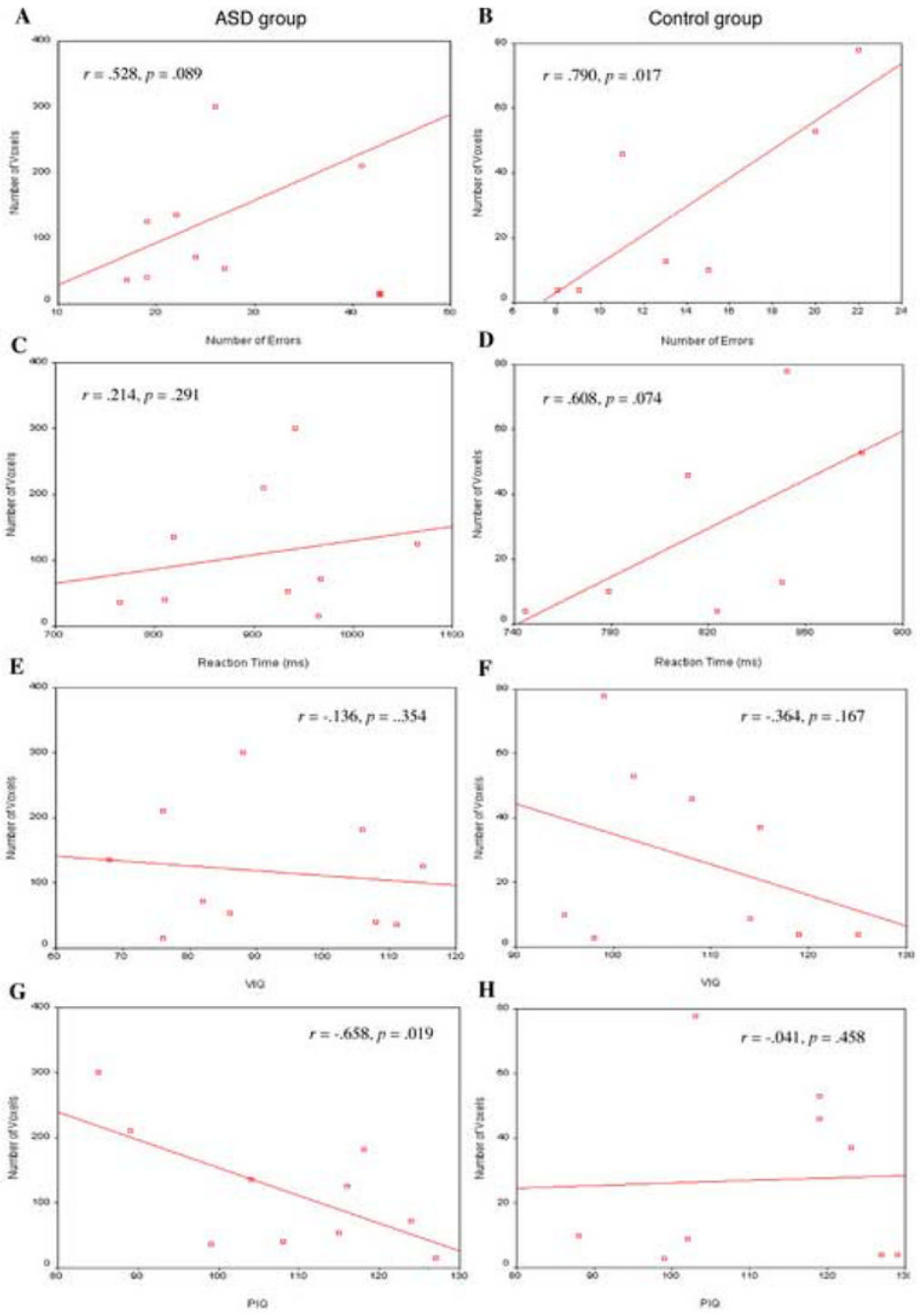

Fig 3.

Post-hoc correlation analyses examining the relation between activity in extrastriate ROI and behavioral performance (errors, reaction time) as well as IQ scores in each group. All correlations with behavioral measures are positive, indicating association of extrastriate activity with low level of performance in both groups. In (A), an outlier excluded from the analysis is indicated by the filled square (see Results for details). Correlations with IQ scores (E–H) are negative, indicating association of extrastriate activity with lower level of functioning. Interestingly, this trend is significant only for nonverbal performance IQs in the ASD group (G).

Table 1

Group comparisons for age, verbal IQ (VIQ), performance IQ (PIQ), and full scale IQ (FSIQ).

Group Characterization Data

	ASD Group	CONTROL Group	*t* value	*p* value
Age, y	26.1 (10.5)	25.3 (9.8)	.17	.43
VIQ†	91.6 (16.93)	108.3 (10.48)	−2.55	.01
PIQ†	111.2 (11.7)	113.8 (10.8)	−.43	.67
FSIQ†	101.5 (11.9)	112.6 (12.6)	−1.9	.07

Note. Data are given as mean (*SD*).

† Wechsler Abbreviated Scale of Intelligence (WASI).

Table 2

Individual ASD group member scores on ADI-R social, verbal, and repetitive interests and behaviors subscales and IQ profiles.

Participant[a]	HFA1	HFA2	HFA3	HFA4	HFA5	HFA6	HFA7	HFA8	ASP1	ASP2
Age (years)	**14**	**15**	**16**	**23**	**27**	**37**	**39**	**44**	**21**	**22**
ADI-R[b]										
Social (cutoff = 10; max = 30)	N	26	27	18	30	26	21	22	21	22
Verbal (cutoff = 8; max = 26)	N	19	19	21	16	20	22	19	20	16
Restricted interests and repetitive behavior (cutoff = 3; max = 12	N	6	7	10	11	6	10	6	7	8
Wechsler Abbreviated Scale of Intelligence										
Verbal IQ	88	108	76	115	76	68	82	86	111	106
Performance IQ	85	108	89	116	127	104	124	115	99	118
Full Scale IQ	85	108	80	117	99	83	101	100	106	112

Note. N = not available.

[a] HFA = High Functioning Autism; ASP = AspergerÕs Disorder.

[b] Autism Diagnostic Interview Š Revised

Table 3

Comparison of group scores on percentage correct and reaction time for semantic decision and control tasks.

Task Performance				
	ASD Group	**CONTROL Group**	**$F_{(1,14)}$ value**	***p* value**
		Semantic Decision		
		% Correct		
Color	81.9 (9.1)	93.6 (3.6)	10.21	.006
Tool	84.4 (9.2)	88.0 (9.8)	.587	.456
Feeling	73.8 (9.9)	93.5 (5.5)	15.95	.001
Reaction Time, ms	825.9 (66.7)	797.2 (62.9)	2.39	.144
		Control Task		
% Correct	93.2 (5.4)	93.5 (5.5)	.016	.899
Reaction Time, ms	899.3 (94.3)	797.6 (50.6)	7.87	.014

Note. Data are given as mean (*SD*).

Table 4

Significant clusters of within-group and between-group effects.

Control Group						Autism Group					
		Talairach coordinates						Talairach coordinates			
Volume (μl)	Peak *t*	x	y	z	Peak Localization (Brodmann area)	Volume (μl)	Peak *t*	x	y	z	Peak Localizat (Brodma area)
Activations						**Activations**					
Frontal											
2786	13.5	−45	25	12	L Inferior Frontal (44/45)	208	6.4	−45	20	−4	L Inferior Fr (47)
						152	6.6	−50	21	19	L Inferior Fr (45)
						80	6.1	−46	19	10	L Inferior Fr (45)
						48	5.9	−46	40	4	L Inferior Fr Sulcus (45
						80	5.5	−40	24	22	L Middle Fr (46)
224	9.7	−6	24	54	L Superior Frontal (6)	176	7.3	−5	10	52	L Superi Frontal (
64	8.9	−20	5	−18	L Superior Frontal (6)						
40	6.3	−11	36	46	L Superior Frontal (8)						
216	10.3	−4	19	44	L Medial Frontal (8)	200	6.8	−1	−10	58	L Medial Fr (6)
152	12.3	−8	44	35	L Medial Frontal (8)						
160	7.4	−44	−2	34	L Precentral (6)						
64	7.3	33	33	1	R Inferior Frontal (47)						
48	6.5	1	27	45	R Medial Frontal (8)						
144	8.2	57	−9	26	R Precentral (4)						
Temporal											
Occipital											
						280*	8.5	−10	−94	1	L Lingual (
						288*	9.1	−15	−84	−8	L Lingual (
						144*	7.1	−20	−93	15	L Middl Occipital (
						2448*	12.5	7	−88	12	B Cuneus (1
64	12.5	11	−90	18	R Cuneus (18)						
Parietal											
Subcortical											
						88	5.7	−21	−11	−9	L Amygd
376	8.9	−12	−1	11	L Thalamus						
96	9.5	−9	9	10	L Caudate						
72	6.4	29	−8	17	R Insula						
Cerebellar											
						48	5.5	10	−72	−13	R Decliv
Inverse effects						**Inverse effects**					
						No significant effects					
Frontal											
136	−9.2	−25	41	33	L Superior Frontal (9)						
72	−6.4	−1	24	20	L Anterior Cingulate (24)						
896	−10.0	28	30	30	R Middle Frontal (9)						
128	−6.9	25	45	35	R Superior Frontal (9)						
104	−8.0	9	47	12	R Medial Frontal (10)						
88	−8.1	6	51	6	R Medial Frontal (10)						
Temporal											
136	−9.2	−59	−30	−5	L Middle Temporal (21)						
104	−7.7	−27	−64	−7	L Fusiform (19)						
56	−7.5	49	−62	−1	R Inferior Temporal (19)						

Control Group						Autism Group					
		Talairach coordinates						Talairach coordinates			
Volume (μl)	Peak *t*	x	y	z	Peak Localization (Brodmann area)	Volume (μl)	Peak *t*	x	y	z	Peak Localizat (Brodma area)
Occipital											
1592	−10.1	−31	−81	17	L Middle Occipital (19)						
216	−7.3	−39	−73	−6	L Inferior Occipital (19)						
88	−9.8	−38	−67	10	L Middle Occipital (19)						
56	−6.5	−49	−68	5	L Middle Occipital (37)						
696	−8.3	33	−76	15	R Middle Occipital (19)						
Parietal											
4856	−24.0	−6	−48	40	L Precuneus (7)						
120	−6.9	−51	−44	31	L Supramarginal (40)						
720	−8.9	42	−46	36	R Supramarginal (40)						
440	−10.8	54	−35	36	R Inferior Parietal (40)						

* Clusters combined to region of interest in post hoc analyses (see Results)