

## A typical participation of visual cortex during word processing in autism: An fMRI study of semantic decision

Michael S. Gaffrey<sup>a,b</sup>, Natalia M. Kleinhaus<sup>c,d</sup>, Frank Haist<sup>e</sup>, Natacha Akshoomoff<sup>e</sup>,  
Ashley Campbell<sup>a</sup>, Eric Courchesne<sup>f</sup>, Ralph-Axel Müller<sup>a,g,\*</sup>

<sup>a</sup> Brain Development Imaging Laboratory, Department of Psychology, San Diego State University, San Diego, CA 92120, United States

<sup>b</sup> Department of Psychology, University of Wisconsin, Milwaukee, WI 53211, United States

<sup>c</sup> Joint Doctoral Program in Clinical Psychology, San Diego State University and University of California, San Diego, United States

<sup>d</sup> Department of Radiology, University of Washington, Seattle, WA 98195, United States

<sup>e</sup> Department of Psychiatry, University of California, San Diego, CA 92093, United States

<sup>f</sup> Department of Neuroscience, University of California, San Diego, CA 92093, United States

<sup>g</sup> Department of Cognitive Science, University of California, San Diego, CA 92093, United States

Received 5 June 2006; received in revised form 26 December 2006; accepted 7 January 2007

Available online 16 January 2007

### 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.

© 2007 Elsevier Ltd. All rights reserved.

**Keywords:** Autism; Language delay; Functional MRI; Lexical; Semantic categorization; Visual perception

### 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 Spec-

trum Disorders (ASD; Volkmar, Lord, Bailey, Schultz, & Klin, 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

\* Corresponding author at: Department of Psychology, San Diego State University, 6363 Alvarado Ct., #225 E, San Diego, CA 92120-1863, United States. Tel.: +1 619 594 5276; fax: +1 619 594 8707.

E-mail address: amueller@sciences.sdsu.edu (R.-A. Müller).

URL: <http://www.sci.sdsu.edu/~amueller> (R.-A. Müller).

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, Mundy, Morales, Delgado, & Yale, 2000; Morales et al., 2000) – is impaired in ASD (Bruinsma, Koegel, & Koegel, 2004; Trepagnier, Sebrechts, & Peterson, 2002) and there is a strong correlation between joint attention deficits and delays in language acquisition (Bono, Daley, & Sigman, 2004; Mundy, Sigman, & Kasari, 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 versus 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, Cherkassky, Keller, and Minshew (2004) found consistently lower levels of functional connectivity between cortical areas in their autism group, suggesting reduced neurofunctional integration during complex language processing. Harris et al. (2006) observed diminished left infe-

rior frontal activation for semantic (compared to perceptual) processing of words in autistic adults. In earlier electrophysiological work, Dunn, Vaughan, Kreuzer, and Kurtzberg (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, Fox, Posner, Mintun, & Raichle, 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, Damasio, & Damasio, 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  $\pm$  10.5) were individually matched with 10 healthy control subjects (mean age 25.3 years  $\pm$  9.8) for age, gender, and handedness. The ASD group was composed of eight 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, Rutter, & Le Couteur, 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, Phillips, & Rutter, 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.

Table 1

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

|                             | ASD group    | Control group | <i>t</i> Value | <i>p</i> Value |
|-----------------------------|--------------|---------------|----------------|----------------|
| Group characterization data |              |               |                |                |
| Age (years)                 | 26.1 (10.5)  | 25.3 (9.8)    | 0.17           | 0.43           |
| VIQ <sup>a</sup>            | 91.6 (16.93) | 108.3 (10.48) | −2.55          | 0.01           |
| PIQ <sup>a</sup>            | 111.2 (11.7) | 113.8 (10.8)  | −0.43          | 0.67           |
| FSIQ <sup>a</sup>           | 101.5 (11.9) | 112.6 (12.6)  | −1.9           | 0.07           |

Note: Data are given as mean (S.D.).

<sup>a</sup> Wechsler Abbreviated Scale of Intelligence (WASI).

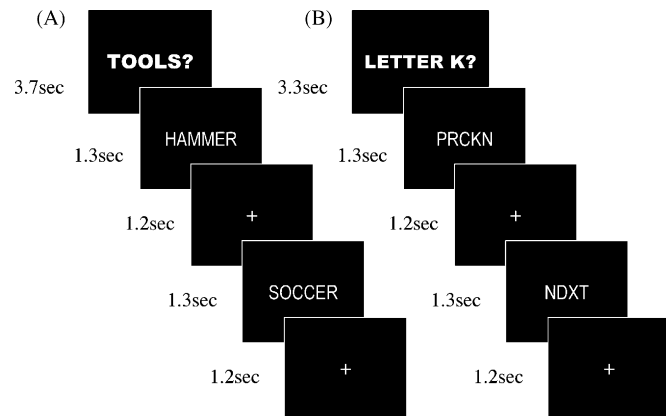


Fig. 1. Stimulus sequence and timing for (A) experimental and (B) control conditions.

### 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 s. This was followed by 11 trials of words (2.5 s each) for category decision. Total block length was 31.2 s (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; Fig. 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: CPTPFPTPC; FPCPTPTPCPF). Every participant completed two runs. No word was repeated within the experiment.

Table 2

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

| Participant <sup>a</sup>  | HFA1 | HFA2 | HFA3 | HFA4 | HFA5 | HFA6 | HFA7 | HFA8 | ASP1 | ASP2 |
|---|------|------|------|------|------|------|------|------|------|------|
| Age (years)   | 14   | 15   | 16   | 23   | 27   | 37   | 39   | 44   | 21   | 22   |
| ADI-R <sup>b</sup>  |      |      |      |      |      |      |      |      |      |      |
| 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.

<sup>a</sup> HFA: high functioning autism; ASP: Asperger's Disorder.

<sup>b</sup> Autism Diagnostic Interview-Revised.

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 (Fig. 1B). The target letter prompt (LETTER K?) was presented for 3.3 s. Total block length was 20.8 s (8 TRs). There were seven trials (2.5 s each) per block, with five targets (letter present) and two 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 et al., 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 A.

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 versus 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 64 × 64; in-plane resolution 4 mm<sup>2</sup>). 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<sup>3</sup>).

### 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

Table 3

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

|                    | ASD          | Control      | $F_{(1,14)}$<br>value | $p$ Value |
|--------------------|--------------|--------------|-----------------------|-----------|
| Task performance   |              |              |                       |           |
| Semantic decision  |              |              |                       |           |
| Correct (%)        |              |              |                       |           |
| Color              | 81.9 (9.1)   | 93.6 (3.6)   | 10.21                 | 0.006     |
| Tool               | 84.4 (9.2)   | 88.0 (9.8)   | 0.587                 | 0.456     |
| Feeling            | 73.8 (9.9)   | 93.5 (5.5)   | 15.95                 | 0.001     |
| Reaction time (ms) | 825.9 (66.7) | 797.2 (62.9) | 2.39                  | 0.144     |
| Control task       |              |              |                       |           |
| Correct (%)        | 93.2 (5.4)   | 93.5 (5.5)   | 0.016                 | 0.899     |
| Reaction time (ms) | 899.3 (94.3) | 797.6 (50.6) | 7.87                  | 0.014     |

Note. Data are given as mean (S.D.).

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  $p < 0.01$  (within-group comparisons) and of  $p < 0.05$  (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 ( $F_{(3,42)} = 6.96$ ,  $p < 0.001$ ) as well as a significant interaction of group and condition ( $F_{(3,42)} = 4.33$ ,  $p < 0.009$ ). 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,  $p < 0.002$ ). No difference in accuracy across conditions was found for the control group. A significant between-group difference for task accuracy was found as well ( $F_{(1,14)} = 11.35$ ,  $p < 0.005$ ). Group difference was further examined using MANOVA with accuracy for each condition as dependent variables. The control group was sig-

nificantly 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;  $F_{(1,16)} = 19.72$ ,  $p < 0.001$ ). Group differences in reaction times (in milliseconds) for semantic decision did not reach significance (ASD mean = 825.9, S.D. = 66.7; control mean = 797.2, S.D. = 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, S.D. = 5.4; control mean = 93.5, S.D. = 5.5;  $F_{(1,14)} = 0.016$ ,  $p = 0.89$ ), but the ASD group had significantly longer reaction times (mean = 899.3, S.D. = 94.3) than the control group (mean = 797.6, S.D. = 50.6;  $F_{(1,14)} = 7.87$ ,  $p < 0.014$ ; see Table 3).

No significant correlations were found between accuracy and age or reaction time and age in either group (all:  $p > 0.6$ ).

#### 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 Fig. 2. Anatomical identifications are based on the atlas by Talairach and Tournoux (1988) and statistical overlays on mean anatomical images for each group.

##### 3.2.1. 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 (Fig. 2A). Corresponding activation in the ASD group was more limited (Fig. 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; Fig. 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.

##### 3.2.2. 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 (Fig. 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.

Table 4  
Significant clusters of within-group and between-group effects

| Control group (activations) |        |                       |     |     |                                   | Autism group (activations) |        |                       |     |     |                                   | Group differences (autism > control) |        |                       |     |     |                                   |
|-----------------------------|--------|-----------------------|-----|-----|-----------------------------------|----------------------------|--------|-----------------------|-----|-----|-----------------------------------|--------------------------------------|--------|-----------------------|-----|-----|-----------------------------------|
| Volume (μl)                 | Peak t | Talairach coordinates |     |     | Peak localization (Brodmann area) | Volume (μl)                | Peak t | Talairach coordinates |     |     | Peak localization (Brodmann area) | Volume (μl)                          | Peak t | Talairach coordinates |     |     | Peak localization (Brodmann area) |
|                             |        | x                     | y   | z   |                                   |                            |        | x                     | y   | z   |                                   |                                      |        | x                     | y   | z   |                                   |
| Frontal                     |        |                       |     |     |                                   |                            |        |                       |     |     |                                   |                                      |        |                       |     |     |                                   |
| 2786                        | 13.5   | −45                   | 25  | 12  | L inferior frontal (44/45)        | 208                        | 6.4    | −45                   | 20  | −4  | L inferior frontal (47)           |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   | 152                        | 6.6    | −50                   | 21  | 19  | L inferior frontal (45)           |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   | 80                         | 6.1    | −46                   | 19  | 10  | L inferior frontal (45)           |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   | 48                         | 5.9    | −46                   | 40  | 4   | L inferior frontal sulcus (45/46) |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   | 80                         | 5.5    | −40                   | 24  | 22  | L middle frontal (46)             |                                      |        |                       |     |     |                                   |
| 224                         | 9.7    | −6                    | 24  | 54  | L superior frontal (6)            | 176                        | 7.3    | −5                    | 10  | 52  | L superior frontal (6)            |                                      |        |                       |     |     |                                   |
| 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 frontal (6)              | 48                                   | 7.5    | −18                   | 2   | 53  | L medial frontal (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                    |        |                       |     |     |                                   |                            |        |                       |     |     |                                   |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   |                            |        |                       |     |     |                                   | 48                                   | 10.7   | −56                   | 1   | −18 | L middle temporal (21)            |
|                             |        |                       |     |     |                                   |                            |        |                       |     |     |                                   | 72                                   | 9.5    | 51                    | 9   | −3  | R superior temporal (22)          |
| Occipital                   |        |                       |     |     |                                   |                            |        |                       |     |     |                                   |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   | 280*                       | 8.5    | −10                   | −94 | 1   | L lingual (17)                    |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   | 288*                       | 9.1    | −15                   | −84 | −8  | L lingual (18)                    | 48                                   | 6.6    | −17                   | −80 | −10 | L lingual (18)                    |
|                             |        |                       |     |     |                                   | 144*                       | 7.1    | −20                   | −93 | 15  | L middle occipital (18)           | 56                                   | 5.8    | −24                   | −79 | 13  | L cuneus (18)                     |
| 64                          | 12.5   | 11                    | −90 | 18  | R cuneus (18)                     | 2448*                      | 12.5   | 7                     | −88 | 12  | B cuneus (18/19)                  | 192                                  | 9.5    | −1                    | −78 | 35  | B cuneus (19)                     |
|                             |        |                       |     |     |                                   |                            |        |                       |     |     |                                   |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   |                            |        |                       |     |     |                                   |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   |                            |        |                       |     |     |                                   | 336                                  | 7.5    | 20                    | −72 | −9  | R lingual (18)                    |
|                             |        |                       |     |     |                                   |                            |        |                       |     |     |                                   | 120                                  | 7.0    | 27                    | −85 | 3   | R middle occipital (18)           |
| Parietal                    |        |                       |     |     |                                   |                            |        |                       |     |     |                                   |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   |                            |        |                       |     |     |                                   | 72                                   | 6.6    | 49                    | −20 | 45  | R postcentral (2)                 |
|                             |        |                       |     |     |                                   |                            |        |                       |     |     |                                   | 72                                   | 5.9    | 2                     | −51 | 11  | R posterior cingulate (23)        |
|                             |        |                       |     |     |                                   |                            |        |                       |     |     |                                   | 48                                   | 6.0    | 7                     | −79 | 40  | R precuneus (7/19)                |
| Subcortical                 |        |                       |     |     |                                   |                            |        |                       |     |     |                                   |                                      |        |                       |     |     |                                   |
|                             |        |                       |     |     |                                   | 88                         | 5.7    | −21                   | −11 | −9  | L amygdala                        |                                      |        |                       |     |     |                                   |
| 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 declive                         |                                      |        |                       |     |     |                                   |



Table 4 (Continued)

| Control group (inverse effects) |        |                       |     |    |                                      | Autism group (inverse effects—no significant effects) |        |                       |   | Group differences (control > autism—no significant effects) |                                      |                |        |                       |   |   |                                      |
|---------------------------------|--------|-----------------------|-----|----|--------------------------------------|---|--------|-----------------------|---|---|--------------------------------------|----------------|--------|-----------------------|---|---|--------------------------------------|
| Volume<br>(μl)                  | Peak t | Talairach coordinates |     |    | Peak localization<br>(Brodmann area) | Volume<br>(μl)  | Peak t | Talairach coordinates |   |   | Peak localization<br>(Brodmann area) | Volume<br>(μl) | Peak t | Talairach coordinates |   |   | Peak localization<br>(Brodmann area) |
|                                 |        | x                     | y   | z  |                                      |   |        | x                     | y | z   |                                      |                |        | x                     | y | z |                                      |
| 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)             |   |        |                       |   |   |                                      |                |        |                       |   |   |                                      |
| 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 Section 3).

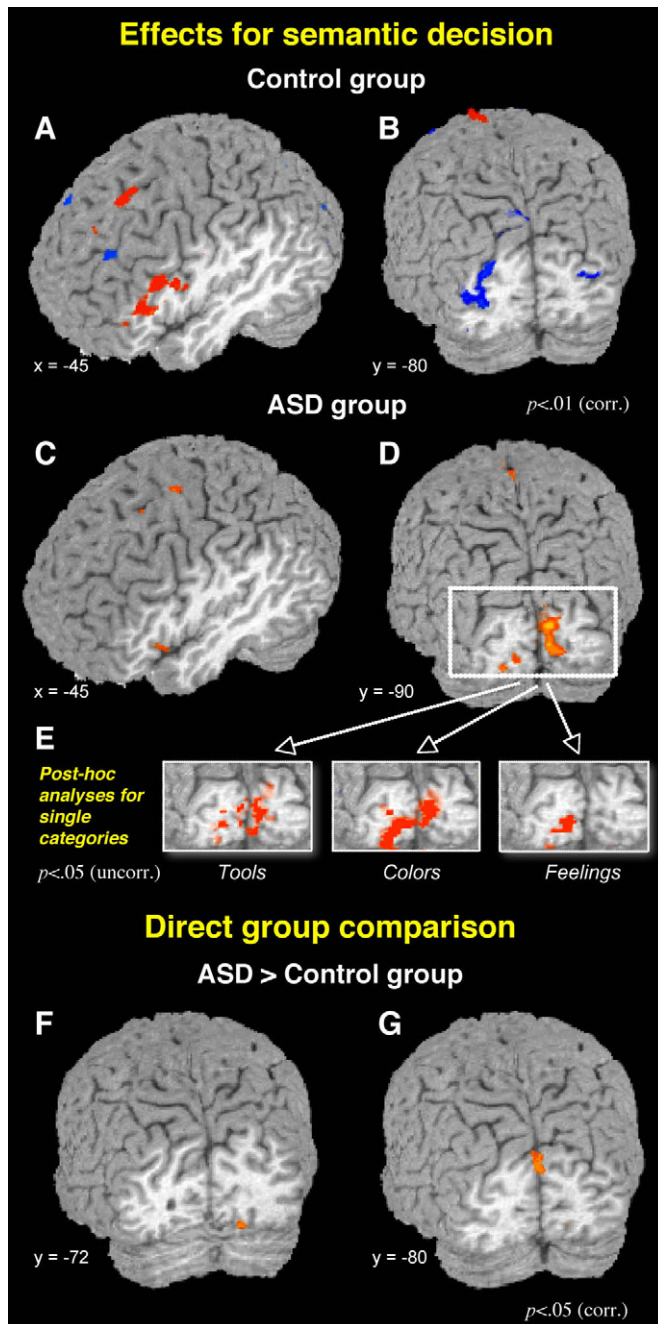


Fig. 2. Significant clusters of effects for semantic decision in control (A and B) and ASD groups (C and D). Red scale in (A–D) represents activation and blue scale represents inverse effects. Occipital effects for each individual semantic category in the ASD group are shown in (E). Clusters of group differences from direct comparison are shown in (F and G). Red scale here represents significantly greater ASD group activation in direct group comparison. No significant inverse effects (control > ASD group) were identified.

### 3.3. Imaging data: direct group comparisons

Fig. 2F–G 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.

### 3.4. 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 Section 4 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 ( $p < 0.05$ ; 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 ( $r = 0.51$ ,  $p = 0.02$ ) and with RT ( $r = 0.47$ ,  $p = 0.03$ ). For the nine ASD participants only, we found concordant trends that did, however, not reach significance (voxels by errors:  $r = 0.19$ ,  $p = 0.31$ ; voxels  $\times$  RT:  $r = 0.21$ ,  $p = 0.29$ ). One subject was a clear outlier with highest number of errors (43), but lowest number of activated voxels within the ROI (16; Fig. 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 ( $r = 0.53$ ,  $p = 0.089$ ). RT and number of errors were also positively correlated with extrastriate activation extent in the control group (voxels by errors:  $r = 0.79$ ,  $p = 0.017$ ; voxels  $\times$  RT:  $r = 0.61$ ,  $p = 0.074$ ; Fig. 3B and D), despite the absence of significant activation in this ROI for the control group overall (see Section 4). We also examined the relation between IQ scores and extrastriate activity, expecting inverse correlations (Fig. 3E–H). In the ASD group, correlations reached significance only for performance IQs ( $r = -0.66$ ,  $p = 0.019$ ), but not for verbal IQs ( $r = -0.14$ ,  $p = 0.35$ ), whereas they were non-significant in the control group (voxels by VIQ:  $r = -0.36$ ,  $p = 0.17$ ; voxels by PIQ:  $r = 0.04$ ,  $p = 0.46$ ).

Correlations between age and active voxel count showed trends in the expected direction, but did not reach significance in either group (controls  $r = -0.30$ ,  $p = 0.20$ ; ASD  $r = -0.42$ ,  $p = 0.12$ ; see Section 4 for rationale).

#### 3.4.1. Analyses for individual semantic categories

Since one of our semantic decision categories (colors) was exclusively visual, we examined whether atypical extrastriate

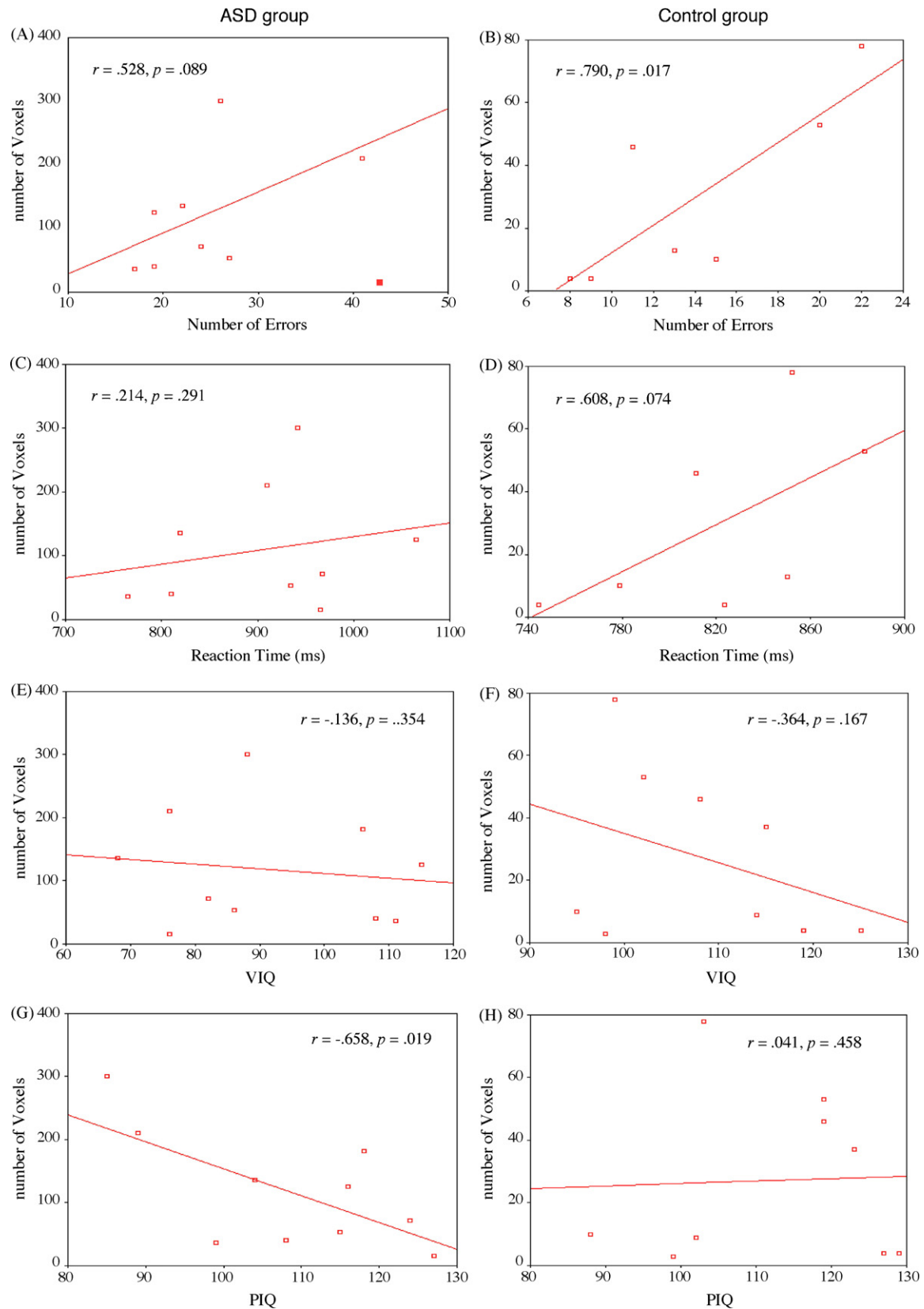


Fig. 3. Post hoc correlation analyses examining the relation between activity in extrastriate ROI and behavioral performance (errors, reaction time) as well as IQ scores in each group. All correlations with behavioral measures are positive, indicating association of extrastriate activity with low level of performance in both groups. In (A), an outlier excluded from the analysis is indicated by the filled square (see Section 3 for details). Correlations with IQ scores (E–H) are mostly 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).



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 Fig. 2D). Although activation for single categories, which was examined at a relaxed threshold ( $p < 0.05$ , 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 (Fig. 2E and Section 4).

#### 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, Harris, & Courchesne (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 (Fig. 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, Grabowski, Tranel, Hichwa, & Damasio, 1996; Martin & Chao, 2001; Wiggs, Weisberg, & Martin, 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, Bonnet-Brilhault, Gomot, Adrien, & Barthelemy, 2003; Rojas, Bawn, Benkers, Reite, & Rogers, 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 et al. (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 Fig. 2). This finding is significant in the context of previous studies suggesting qualitatively different lexicosemantic strategies in autism (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, Cherkassky, et al., 2004; Mellet et al., 2000), even when exclusively auditory stimuli were used as prompts for visual imagery (Just, Newman, Keller, McEleney, Carpenter, 2004; Lambert, Sampaio, Mauss, & Scheiber, 2004). In a recent study of verbal working memory, Koshino et al. (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. Fig. 2B versus F). 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, Coffey-Corina, & Neville (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 months old infants, whereas they were more localized to left temporoparietal areas in 20 months old. In a recent fMRI study on lexical association in children and young adults, Brown et al. (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, Jones, & Landau, 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  $\geq 10$  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 (Fig. 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, Keller, Cherkassky, Minshew, & Just (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, Ungerleider, & Haxby, 2000; Phan, Wager, Taylor, & Liberzon, 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, Pierce, Ambrose, Allen, & Courchesne, 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., 2004). 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, Cherkassky, et al., 2004) 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, Newman, et al., 2004; 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 2 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, Moses, Tigue, & Courchesne, 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.

## Acknowledgments

This study was supported by the National Institutes of Health, grants R01-DC006155 (M.S.G., F.H., N.A., A.C, R.-A.M) and R01-MH36840 (N.K., E.C.). Thanks to Drs. Beverly Wulfeck and John J. Spinetta for insightful comments, and to Akiko Mizuno for technical assistance.

## Appendix A. 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     |
| Hand saw    | Beige      | Lust        |
| Shovel      | Puce       | Regret      |
| Saw         | Yellow     | Sadness     |
| Ruler       | Orange     | Hate        |
| 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    | Pentangle  | Guess       |
| Hockey      | Pentagon   | Fanaticism  |
| Karate      | Star       | Plan        |

## References

- APA. (1994). *Diagnostic and statistical manual of mental disorders*. Washington, DC: American Psychiatric Association.
- Bailey, A., Phillips, W., & Rutter, M. (1996). Autism: Towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. *Journal of Child Psychology and Psychiatry*, 37(1), 89–126.
- Bono, M. A., Daley, T., & Sigman, M. (2004). Relations among joint attention, amount of intervention and language gain in autism. *Journal of Autism & Developmental Disorders*, 34(5), 495–505.
- Boucher, J. (2003). Language development in autism. *International Journal of Pediatric Otorhinolaryngology*, 67(Suppl. 1), S159–S163.
- Brown, T. T., Lugar, H. M., Coalson, R. S., Miezin, F. M., Petersen, S. E., & Schlaggar, B. L. (2005). Developmental changes in human cerebral functional organization for word generation. *Cerebral Cortex*, 15(3), 275–290.

- Bruinsma, Y., Koegel, R. L., & Koegel, L. K. (2004). Joint attention and children with autism: A review of the literature. *Mental Retardation and Developmental Disabilities Research Reviews*, 10(3), 169–175.
- Bruneau, N., Bonnet-Brilhault, F., Gomot, M., Adrien, J. L., & Barthelemy, C. (2003). Cortical auditory processing and communication in children with autism: Electrophysiological/behavioral relations. *International Journal of Psychophysiology*, 51(1), 17–25.
- Carper, R. A., Moses, P., Tigue, Z. D., & Courchesne, E. (2002). Cerebral lobes in autism: Early hyperplasia and abnormal age effects. *Neuroimage*, 16(4), 1038–1051.
- Charman, T. (2003). Why is joint attention a pivotal skill in autism? *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 358(1430), 315–324.
- Chen, W., Kato, T., Zhu, X. H., Ogawa, S., Tank, D. W., & Ugurbil, K. (1998). Human primary visual cortex and lateral geniculate nucleus activation during visual imagery. *Neuroreport*, 9(16), 3669–3674.
- Courchesne, E., Karns, C. M., Davis, H. R., Ziccardi, R., Carper, R. A., Tigue, Z. D., et al. (2001). Unusual brain growth patterns in early life in patients with autistic disorder: An MRI study. *Neurology*, 57(2), 245–254.
- Courchesne, E., & Pierce, K. (2005). Brain overgrowth in autism during a critical time in development: Implications for frontal pyramidal neuron and interneuron development and connectivity. *International Journal of Developmental Neuroscience*, 23(2–3), 153–170.
- Cox, R. W., & Hyde, J. S. (1997). Software tools for analysis and visualization of fMRI data. *NMR in Biomedicine*, 10(4–5), 171–178.
- Cox, R. W., & Jesmanowicz, A. (1999). Real-time 3D image registration for functional MRI. *Magnetic Resonance in Medicine*, 42(6), 1014–1018.
- Damasio, H., Grabowski, T. J., Tranel, D., Hichwa, R. D., & Damasio, A. R. (1996). A neural basis for lexical retrieval. *Nature*, 380(6574), 499–505.
- Dawson, G., Toth, K., Abbott, R., Osterling, J., Munson, J., Estes, A., et al. (2004). Early social attention impairments in autism: Social orienting, joint attention, and attention to distress. *Developmental Psychology*, 40(2), 271–283.
- De Fosse, L., Hodge, S. M., Makris, N., Kennedy, D. N., Caviness, V. S., Jr., McGrath, L., et al. (2004). Language-association cortex asymmetry in autism and specific language impairment. *Annals of Neurology*, 56(6), 757–766.
- Dunn, M., Vaughan, H., Jr., Kreuzer, J., & Kurtzberg, D. (1999). Electrophysiologic correlates of semantic classification in autistic and normal children. *Developmental Neuropsychology*, 16(1), 79–99.
- Ekman, P. (1993). Facial expression and emotion. *The American Psychologist*, 48(4), 384–392.
- Ekman, P. (1999). Facial expressions. In T. Dalgleish & T. Power (Eds.), *The handbook of cognition and emotion* (pp. 301–320). Sussex (UK): John Wiley.
- Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magnetic Resonance in Medicine*, 33(5), 636–647.
- Gershkoff-Stowe, L., & Smith, L. B. (2004). Shape and the first hundred nouns. *Child Development*, 75(4), 1098–1114.
- Grabowski, T. J., Damasio, H., & Damasio, A. R. (1998). Premotor and prefrontal correlates of category-related lexical retrieval. *Neuroimage*, 7(3), 232–243.
- Harris, G. J., Chabris, C. F., Clark, J., Urban, T., Aharon, I., Steele, S., et al. (2006). Brain activation during semantic processing in autism spectrum disorders via functional magnetic resonance imaging. *Brain and Cognition*, 61(1), 54–68.
- Herbert, M. R., Harris, G. J., Adrien, K. T., Ziegler, D. A., Makris, N., Kennedy, D. N., et al. (2002). Abnormal asymmetry in language association cortex in autism. *Annals of Neurology*, 52(5), 588–596.
- Hobson, R. P., & Lee, A. (1998). Hello and goodbye: A study of social engagement in autism. *Journal of Autism and Developmental Disorders*, 28(2), 117–127.
- Hubl, D., Bolte, S., Feineis-Matthews, S., Lanfermann, H., Federspiel, A., Strik, W., et al. (2003). Functional imbalance of visual pathways indicates alternative face processing strategies in autism. *Neurology*, 61(9), 1232–1237.
- Ishai, A., Ungerleider, L. G., & Haxby, J. V. (2000). Distributed neural systems for the generation of visual images. *Neuron*, 28(3), 979–990.
- Just, M. A., Cherkassky, V. L., Keller, T. A., & Minshew, N. J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain*, 127(Pt 8), 1811–1821.
- Just, M. A., Newman, S. D., Keller, T. A., McEleney, A., & Carpenter, P. A. (2004). Imagery in sentence comprehension: An fMRI study. *Neuroimage*, 21(1), 112–124.
- Kamio, Y., & Toichi, M. (2000). Dual access to semantics in autism: Is pictorial access superior to verbal access? *Journal of Child Psychology and Psychiatry*, 41(7), 859–867.
- Kana, R. K., Keller, T. A., Cherkassky, V. L., Minshew, N. J., & Just, M. A. (2006). Sentence comprehension in autism: Thinking in pictures with decreased functional connectivity. *Brain*, 129(Pt 9), 2484–2493.
- Kensinger, E. A., & Schacter, D. L. (2006). Processing emotional pictures and words: Effects of valence and arousal. *Cognitive, Affective & Behavioral Neuroscience*, 6(2), 110–126.
- Koshino, H., Carpenter, P. A., Minshew, N. J., Cherkassky, V. L., Keller, T. A., & Just, M. A. (2005). Functional connectivity in an fMRI working memory task in high-functioning autism. *Neuroimage*, 24(3), 810–821.
- Kosslyn, S. M., & Thompson, W. L. (2003). When is early visual cortex activated during visual mental imagery? *Psychological Bulletin*, 129(5), 723–746.
- Lambert, S., Sampaio, E., Mauss, Y., & Scheiber, C. (2004). Blindness and brain plasticity: Contribution of mental imagery? An fMRI study. *Brain Research. Cognitive Brain Research*, 20(1), 1–11.
- Locke, J. L. (1995). Development of the capacity for spoken language. In P. Fletcher & B. MacWhinney (Eds.), *Handbook of child language* (pp. 278–302). Oxford: Basil Blackwell.
- Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Jr., Leventhal, B. L., DiLavore, P. C., et al. (2000). The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders*, 30(3), 205–223.
- Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, 24(5), 659–685.
- Loveland, K. A., & Tunali, B. (1991). Social scripts for conversational interactions in autism and Down syndrome. *Journal of Autism and Developmental Disorders*, 21(2), 177–186.
- Manjaly, Z. M., Marshall, J. C., Stephan, K. E., Gurd, J. M., Zilles, K., & Fink, G. R. (2003). In search of the hidden: An fMRI study with implications for the study of patients with autism and with acquired brain injury. *Neuroimage*, 19(3), 674–683.
- Markus, J., Mundy, P., Morales, M., Delgado, C. E., & Yale, M. (2000). Individual differences in infant skills as predictors of child-caregiver joint attention and language. *Social Development*, 9(3), 302–315.
- Martin, A., & Chao, L. L. (2001). Semantic memory and the brain: Structure and processes. *Current Opinion in Neurobiology*, 11, 194–201.
- Mellet, E., Tzourio-Mazoyer, N., Bricogne, S., Mazoyer, B., Kosslyn, S. M., & Denis, M. (2000). Functional anatomy of high-resolution visual mental imagery. *Journal of Cognitive Neuroscience*, 12(1), 98–109.
- Mills, D. L., Coffey-Corina, S. A., & Neville, H. J. (1994). Variability in cerebral organization during primary language acquisition. In G. Dawson & K. W. Fischer (Eds.), *Human behavior and the developing brain* (pp. 427–455). New York: Guilford.
- Morales, M., Mundy, P., Delgado, C. E., Yale, M., Messinger, D., Neal, R., et al. (2000). Responding to joint attention across the 6- through 24-month age period and early language acquisition. *Journal of Applied Developmental Psychology*, 21(3), 283–298.
- Müller, R.-A., Behen, M. E., Rothermel, R. D., Chugani, D. C., Muzik, O., Mangner, T. J., et al. (1999). Brain mapping of language and auditory perception in high-functioning autistic adults: A PET study. *Journal of Autism and Developmental Disorders*, 29, 19–31.
- Müller, R.-A., Pierce, K., Ambrose, J. B., Allen, G., & Courchesne, E. (2001). Atypical patterns of cerebral motor activation in autism: A functional magnetic resonance study. *Biological Psychiatry*, 49, 665–676.

- Müller, R.-A., Cauich, C., Rubio, M. A., Mizuno, A., & Courchesne, E. (2004). Abnormal activity patterns in premotor cortex during sequence learning in autistic patients. *Biol Psychiatry*, 56(5), 323–332.
- Mundy, P., Sigman, M., & Kasari, C. (1990). A longitudinal study of joint attention and language development in autistic children. *Journal of Autism and Developmental Disorders*, 20(1), 115–128.
- O'Riordan, M. A. (2004). Superior visual search in adults with autism. *Autism*, 8(3), 229–248.
- Ozonoff, S., & Miller, J. N. (1996). An exploration of right-hemisphere contributions to the pragmatic impairments of autism. *Brain & Language*, 52(3), 411–434.
- Papousek, H., & Papousek, M. (1986). Structure and dynamics of human communication at the beginning of life. *European Archives of Psychiatry and Neurological Sciences*, 236(1), 21–25.
- Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., & Raichle, M. E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature*, 331(6157), 585–589.
- Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*, 16(2), 331–348.
- Pierce, K., & Courchesne, E. (2001). Evidence for a cerebellar role in reduced exploration and stereotyped behavior in autism. *Biological Psychiatry*, 49, 655–664.
- Rapin, I. (1997). Autism. *New England Journal of Medicine*, 337, 97–104.
- Rojas, D. C., Bawn, S. D., Benkers, T. L., Reite, M. L., & Rogers, S. J. (2002). Smaller left hemisphere planum temporale in adults with autistic disorder. *Neuroscience Letters*, 328(3), 237–240.
- Samuelson, L. K., & Smith, L. B. (1999). Early noun vocabularies: Do ontology, category structure and syntax correspond? *Cognition*, 73(1), 1–33.
- Silveri, M. C., Gainotti, G., Perani, D., Cappelletti, J. Y., Carbone, G., & Fazio, F. (1997). Naming deficit for non-living items: Neuropsychological and PET study. *Neuropsychologia*, 35(3), 359–367.
- Smith, L. B., Jones, S. S., & Landau, B. (1996). Naming in young children: A dumb attentional mechanism? *Cognition*, 60(2), 143–171.
- Sussman, K., & Lewandowski, L. (1990). Left-hemisphere dysfunction in autism: What are we measuring? *Archives of Clinical Neuropsychology*, 5(2), 137–146.
- Tager-Flusberg, H. (1981). On the nature of linguistic functioning in early infantile autism. *Journal of Autism and Developmental Disorders*, 11(1), 45–56.
- Tager-Flusberg, H. (2004). Do autism and specific language impairment represent overlapping language disorders? In M. Rice & S. Warren (Eds.), *Developmental language disorders: From phenotypes to etiologies* (pp. 31–52). Erlbaum.
- Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. Stuttgart, Germany: Thieme.
- Toichi, M., & Kamio, Y. (2001). Verbal association for simple common words in high-functioning autism. *Journal of Autism and Developmental Disorders*, 31(5), 483–490.
- Toichi, M., & Kamio, Y. (2002). Long-term memory and levels-of-processing in autism. *Neuropsychologia*, 40(7), 964–969.
- Toichi, M., & Kamio, Y. (2003). Long-term memory in high-functioning autism: Controversy on episodic memory in autism reconsidered. *Journal of Autism and Developmental Disorders*, 33(2), 151–161.
- Townsend, J., Harris, N. H., & Courchesne, E. (1996). Visual attention abnormalities in autism: Delayed orienting to location. *Journal of the International Neuropsychological Society*, 2, 541–550.
- TPC. (1999). *Wechsler abbreviated scale of intelligence*. San Antonio, TX: Author.
- Trepagnier, C., Sebrechts, M. M., & Peterson, R. (2002). Atypical face gaze in autism. *Cyberpsychology & Behavior*, 5(3), 213–217.
- Tyler, L. K., Stamatakis, E. A., Dick, E., Bright, P., Fletcher, P., & Moss, H. (2003). Objects and their actions: Evidence for a neurally distributed semantic system. *Neuroimage*, 18(2), 542–557.
- Volkmar, F. R., Lord, C., Bailey, A., Schultz, R. T., & Klin, A. (2004). Autism and pervasive developmental disorders. *Journal of Child Psychology and Psychiatry*, 45(1), 135–170.
- Wiggs, C. L., Weisberg, J., & Martin, A. (1999). Neural correlates of semantic and episodic memory retrieval. *Neuropsychologia*, 37(1), 103–118.
- Yoon, C., Feinberg, F., Hu, P., Gutchess, A. H., Hedden, T., Chen, H. Y., et al. (2003). *Category norms as a function of culture and age: Comparisons of item responses to 105 categories by American and Chinese adults*. University of Michigan., unpublished manuscript