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Cortical Patterns of Category-Selective Activation for Faces, Places and Objects in Adults with Autism

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Abstract

Autism is associated with widespread atypicalities in perception, cognition and social behavior. A crucial question concerns how these atypicalities are reflected in the underlying brain activation. One way to examine possible perturbations of cortical organization in autism is to analyze the activation of category-selective ventral visual cortex, already clearly delineated in typical populations. We mapped out the neural correlates of face, place and common object processing, using functional magnetic resonance imaging (fMRI), in a group of high-functioning adults with autism and a typical comparison group, under both controlled and more naturalistic, viewing conditions. There were no consistent group differences in place-related regions. Although there were no significant differences in the extent of the object-related regions, there was more variability for these regions in the autism group. The most marked group differences were in face-selective cortex, with individuals with autism evincing reduced activation, not only in fusiform face area but also in superior temporal sulcus and occipital face area. Ventral visual cortex appears to be organized differently in high-functioning adults with autism, at least for face-selective regions, although subtle differences may also exist for other categories. We propose that cascading developmental effects of low-level differences in neuronal connectivity result in a much more pronounced effect on later developing cortical systems, such as that for face-processing, than earlier maturing systems (those for objects and places).

Keywords

high-functioning autism; fMRI; object perception; occipito-temporal cortex; visual system

Introduction

Although the behavioral profile associated with autism is becoming increasingly well characterized, the extent to which it can be attributed to alterations in cortical organization remains unknown. There have been few attempts at large-scale mapping of the organization of the cortex [although see Just et al., 2004]. Here, in two experiments, we chart the category-related organization of ventral visual cortex in autism. Rather little is known about the topography of this region in autism, with the exception of face-related cortex. Even studies of face-selective cortex have yielded conflicting results. Many [e.g. Dalton et al., 2005; Deeley et al., 2007; Hubl et al., 2003; Pierce et al., 2001; Schultz et al., 2000] have found reduced BOLD activation in the fusiform face area [FFA; Kanwisher et al., 1997], but five studies have

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failed to replicate this finding [Bird et al., 2006; Hadjikhani et al., 2004, 2007; Kleinhans et al., 2008; Pierce et al., 2004]. Furthermore, it has been proposed that FFA activation is normalized when people with autism look at the face stimuli [Hadjikhani et al., 2004], specifically the eye region [Dalton et al., 2005, 2007].

Less attention has been paid to other face-selective regions such as the superior temporal sulcus (STS) and the "occipital face area" (OFA) [Haxby et al., 2000]. Increased activation in individuals with autism has been reported in the right inferotemporal gyrus (ITG) [Schultz et al., 2000, study 1] as well as in the left ITG [Schultz et al., 2000, study 2]. Reduced activation in the ITG, STS and amygdala, simultaneous with aberrant sites of activation to faces in regions such as the frontal cortex and primary visual cortex has also been reported [Pierce et al., 2001], as has hypoactivation of a network of brain areas including the right amygdala, inferior frontal cortex, STS and face-related somatosensory and premotor cortex, alongside normal FFA and inferior occipital gyrus activation [Hadjikhani et al., 2007]. Finally, the lateral occipital cortex (LO) object-related region apparently responds to both face and pattern processing in individuals with autism, and the superior parietal lobule, usually associated with visuospatial processing [Gitelman et al., 2000, 2002], is also more active.

Inconsistency between findings also applies to cortical responses to other visual object classes, although few studies have been conducted in this domain and results are mixed. One study found no consistent differences in cortical object activation in individuals with autism [Schultz et al., 2000], whereas others found no differences in activation for houses [Bird et al., 2006; Kleinhans et al., 2008]. However, in a magnetoencephalography (MEG) study, the sources of object-related signals were more variable in the autism than the typical group [Bailey et al., 2005].

Here, for the first time, we examined systematically, using functional magnetic resonance imaging (fMRI), whether atypicalities in high-level visual cortex in autism are evident for faces and other stimulus categories.

Materials and Methods

Participants

Participants were 13 high-functioning male adults (age range 18–53 years, mean=27, s.d.=10) with autism and 15 typical male adults (age range 18–44 years, mean=29, s.d.=10). Twelve participants in each group were included in Experiment 1, and ten participants in each group in Experiment 2 (nine autism and seven comparison participants took part in both). Data from an additional five participants (two with autism) from Experiment 1 and seven participants (three with autism) fromExperiment 2 were excluded because of head motion (jerky movement >1mm or 1°) during scanning. The sample size is comparable to similar studies [e.g. Deeley et al., 2007; Hadjikhani et al., 2007; Pierce et al., 2001]. Written informed consent was obtained using procedures approved by the Institutional Review Boards (IRBs) of the University of Pittsburgh Medical Center (UPMC) and Carnegie Mellon University (CMU).

All participants with autism had IQ (intelligence quotient) scores of 75 or above (Table I). The group mean IQ was in the average range (VIQ=103, PIQ=106). Diagnosis of autism was established using the Autism Diagnostic Interview Revised [Lord et al., 1994], the Autism Diagnostic Observation Schedule [Lord et al., 2000] and expert clinical diagnosis. Potential participants were excluded if they had an associated neuropsychiatric disorder or a history of birth asphyxia, head injury or seizure disorder. Exclusions were based on neurological history and examination, chromosomal analysis and, if indicated, metabolic testing. All had normal or corrected-to-normal vision.

Comparison participants were volunteers, screened for a history of developmental, psychiatric or neurological conditions, matched to the participants with autism on age and gender. *T*-tests confirmed that the ages of the two groups did not differ (both experiments, $P>0.05$). As IQ data were not available for five comparison participants, we do not know whether the groups were exactly matched on IQ. However, no link has been found between IQ and performance on non-speeded visual perceptual tasks in either neurotypical [Deary et al., 1997] or autism [Behrmann et al., 2006] groups.

Magnetic Resonance Imaging

Images were acquired on a Siemens 3T Allegra scanner (Erlangen, Germany) in a single session. BOLD contrast was acquired using gradient-echo echo-planar imaging sequence (TR=3,000 ms, TE=35 ms, flip angle=90°, FOV=210 × 210mm^2, matrix size=64 × 64, 35 axial slices, 3mm thickness, no gap). High-resolution anatomical scans (T1-weighted 3-D MPRAGE, sagittal slices) were also acquired.

Experiment 1: Conventional Face and Object Mapping Experiment

Static line drawings of faces, buildings, common objects and patterns (Fig. 1a) were presented in a short block design [for details, see Levy et al., 2001]. A block, as opposed to event-related, design, was employed to provide a paradigm that had already provided robust results with typical populations [Avidan et al., 2005;Hasson et al., 2003]. It also yields stronger signals with better statistical power. Each block contained nine stimuli from the same category (eight different images and one immediate repetition of one of the stimuli). Participants fixated on a red central fixation dot and pressed a key on a response glove when immediate repetition of the previous image was detected.

Each stimulus was presented for 800 ms, followed by 200ms blank inter-stimulus interval (ISI). Blocks were each repeated seven times in a pseudo-randomized order (6 s blank between blocks). The experiment started and ended with blank epochs of 27 and 9 s, respectively (450 s total length).

Experiment 2: Motion Pictures Experiment

Participants viewed naturalistic, real-time movies of unfamiliar faces, buildings, navigation through open fields and objects in a blocked fMRI paradigm (Fig. 3a). Clips were organized into 32 blocks of 15 s duration, each containing a single stimulus category, and the experiment started with a 29 s blank period followed by 9 s of pattern stimuli and ended with 21 s of blank screen (9 min total). This task has been used successfully to map category-selective activation in the ventral visual cortex [Avidan et al., 2005;Hasson et al., 2004;Scherf et al., 2007]. There are no specific task demands, and so potential differences in performance between the autism and comparison groups cannot account for different levels of functional activation.

Data Analysis

Data were preprocessed and analyzed using BrainVoyager 2000 (Brain Innovation, Maastricht, The Netherlands). 3D motion correction was applied, with filtering of low frequencies up to ten cycles per experiment. Each condition was defined as a separate predictor. To obtain the group flattened cortical maps, time series images of brain volumes for each subject were converted into Talairach space. Although individuals with autism and typical individuals may differ in brain size [Herbert, 2005], Talairach transformation is still widely used [e.g. Deeley et al., 2007]. There was no spatial smoothing.

A within-group random effects analysis was applied to the BOLD signal within and between groups as a function of experimental condition. Statistical maps were computed by comparing

the mean fit coefficients for each condition. A minimum cluster size of eight voxels (chosen after a Monte Carlo simulation) was adopted to correct for multiple comparisons, yielding a false-positive probability of $P<0.05$ (Experiment 1) and $P<0.01$ [Experiment 2; Ward, 2000]. Because activation was stronger and more widespread in Experiment 2, different thresholds were adopted for producing the visual representation of the activated areas on the flattened cortical maps for the two experiments. Thresholds for statistical analyses were identical across experiments.

Definition of Regions of Interest (ROIs) for Experiments 1 and 2—Although both whole-brain analyses and regions of interest (ROIs) approaches have advantages and disadvantages, we employed an ROI-based approach because of our a priori interest in particular regions of cortex (those known to be selective for faces, places and objects), and also to reduce the risk of type 2 errors. A critical issue, then, is how to identify ROIs in the autism maps given that the activation patterns are inconsistent or even, in some individuals' cases, absent entirely, at least for face-related regions. Also, it is circular to define ROIs based on data from the same experiment, and defining ROIs based on the data from the control subjects would bias findings in favor of the typical individuals. As a solution, we defined ROIs independently, based on data acquired on eight typical individuals who completed the identical experiments as part of a different study [Avidan et al., 2005; Table II for Talairach-based coordinates for these ROIs]. ROIs include bilateral FFA [Kanwisher et al., 1997], defined using the contrast "faces vs. objects and buildings", collateral sulcus [CoS; Aguirre et al., 1998; Experiment 1: "buildings vs. faces and objects"; Experiment 2: "buildings and natural scenes vs. faces and objects"] and object-related LO [Malach et al., 1995; "objects vs. faces and buildings"]. ROIs were created by selecting all contiguous responsive voxels from these specific contrasts that met statistical threshold within a location (e.g. fusiform gyrus). The coordinates of these regions are similar to other studies (Table II).

We computed group differences in these ROIs using the activation profiles extracted for each participant. Raw activation level at each time point was *z*-normalized and then averaged across all participants in each group.

Results

Experiment 1: Behavioral Data

Accuracy and reaction time data were recorded for all participants (a technical error resulted in data loss for two individuals, one from each group). Analysis of variance (ANOVA; on the data from those included in the fMRI data only) showed no main effects or any significant interaction involving group (autism vs. typical comparison, all $P>0.1$). This is unsurprising as the task was simple. Thus, group differences in BOLD are not attributable to performance differences per se.

Experiment 1

The average face-, object- and house-related activation maps are shown projected onto the flattened cortex of a single individual. (See Fig. 1b for derivation of flattened cortex.)

Figure 2a shows activation maps for the two groups. In the typical comparison group, faces activated the FFA, OFA and STS-face-related regions to a greater degree in the right than left hemisphere [e.g. Hasson et al., 2003; Kanwisher et al., 1997], whereas images of houses activated the CoS [Aguirre et al., 1998] and common objects activated the LO-object-related region [Malach et al., 1995]. In the participants with autism, face areas (in red) appear relatively under-activated, particularly in the STS and FFA, with only OFA remaining in the right hemisphere. In contrast, house-related activation (in green) appears strong, with the CoS well

activated in both hemispheres. At this threshold, there is no object-related activation (in blue) in the right hemisphere; however, in the left hemisphere, object-related activation appears enhanced, relative to the typical group, with, notably, an increased region of LO activation.

To evaluate these patterns, we extracted activation relating to faces, objects, houses and patterns from three bilateral ROIs (FFA, CoS, LO—Table II) and conducted ANOVAs separately on the average and peak activation in each ROI with group as the between-subjects variable, and hemisphere and stimulus category (faces, objects, houses and patterns) as within-subjects variables. For peak percentage signal change in FFA, relative to the blank baseline, see Figure 2b. The peak was defined as the activation at TR=3 after the onset of each block (visual inspection showed that this corresponded to the greatest activation). Results are reported for each ROI in turn. For brevity, we only discuss significant main effects and interactions.

FFA—The ANOVA on the peak activation data revealed a main effect of stimulus category, $F(3,66) = 20.75$, $P < 0.001$, with activation strongest, not surprisingly, for faces and a significant category by group interaction, $F(3,66) = 3.24$, $P = 0.028$. Follow-up tests showed that activation to faces was stronger for the typical than autism group bilaterally (right, $t(22) = 2.01$, $P = 0.028$, left $t(22) = 1.91$, $P = 0.035$, both one-tailed given the prediction of reduced FFA activation in autism). Surprisingly, activation to objects was also weaker in the R-FFA for the autism than the typical group ($t(22) = 2.48$, $P = 0.021$). Within the comparison group, selectivity for faces was high in both hemispheres (all $P < 0.01$, except L-FFA faces–objects; $P = 0.028$). The autism group, too, showed some (albeit weaker) evidence of selectivity in the R-FFA (faces–houses, $t(11) = 2.14$, $P = 0.055$; faces–objects, $t(11) = 2.22$, $P = 0.049$; faces–patterns, $t(11) = 2.75$, $P = 0.019$) but, in the L-FFA, faces only differed fromhouses (faces–houses, $t(11) = 2.51$, $P = 0.029$; faces–objects, $t(11) = 0.61$, $P = 0.552$; faces– patterns, $t(11) = 1.10$, $P = 0.296$). Analysis of average activation showed no significant main effects or interactions involving group.

CoS—ANOVA on the peak activation data revealed stronger peak activation in the R-CoS than L-CoS, $F(1,22) = 24.93$, $P < 0.001$, and strongest activation for houses of all categories, $F(3,66) = 10.04$, $P < 0.001$. Increased house activation was greater in the R-CoS (all $P = <0.001$) than the L-CoS (left, houses-objects $P > 0.05$), $F(3,66) = 12.20$, $P < 0.001$. Importantly, there were no significant main effects or interactions involving group. Analysis of average activation also showed no significant main effects or interactions involving group.

Object-related LO—The ANOVA on the peak activation data revealed a stronger peak in the R-LO than L-LO, $F(1,22) = 7.45$, $P = 0.12$, and higher peak activation for objects than houses and patterns, but not faces, $F(3,66) = 9.42$, $P < 0.001$. The stronger overall selectivity was more apparent in the L-LO (all $P = <0.01$) than the R-LO (right, objects-faces $P > 0.05$), $F(3,66) = 3.27$, $P = 0.027$. There were no significant main effects or interactions involving group. The analysis of average activation showed no significant main effects or interactions involving group.

In summary, the results are fairly straightforward. There were differences in the degree to which equivalent face-related regions were selectively activated at peak. All face-related regions except right OFA showed hypoactivation in the autism group and the FFA showed less selectivity to faces. This was despite the fact that the task was simple and behavior for the two groups was equivalent. No differences were apparent in the magnitude (average or peak) of house-related activation. There were also no differences in object-related cortex, although activity to objects was reduced in the right FFA in the autism group, and there was a trend to greater object-related activity on the left in this group, too.

Experiment 2

To confirm initial findings and uncover any further group differences, we employed rich, moving stimuli from multiple categories (see Fig. 3a), given that previous studies showing that these movie stimuli induce stronger activation in ventral cortex than do static, black and white images [see Avidan et al., 2005;Hasson et al., 2004]. The movement was naturalistic so that, for example, the faces were talking and egg-beaters whisked eggs. There was no soundtrack.

Figure 3b shows average activation maps for the autism and typical groups. We group together the building- and scene-related activation, as both typically activate CoS [Scherf et al., 2007].

Findings from the typical group largely replicate the maps for Experiment 1, except that the activation is perhaps more extensive for faces (red) and objects (blue) than in the previous experiment, and building/scene-related activation (green) in CoS appears somewhat reduced, especially in the left hemisphere. As in Experiment 1, the most marked feature is clear reduction in face-related activity in the autism group and the only face-related activity at this threshold for the autism group is in the right OFA. In contrast, object-related activity in object-related LO appears more extensive for the autism than comparison group, this time in both hemispheres.

Figure 4 shows activation maps for each individual participant; because there is usually some heterogeneity, even within a group of well-selected and clearly characterized individuals with autism; we show the data for each individual separately, and the increased variability in the autism group is evident on these maps.

Unlike Experiment 1, where activation is compared with a blank, fixation spot, there is no obvious baseline condition in this experiment. Thus, to quantify the comparison between the typical and autism groups, we extracted and *z*-normalized the raw time courses from the three bilateral ROIs (FFA, LO, CoS), using the independently acquired ROI coordinates (Table II). Separate ANOVAs were performed on this activation in the three ROIs with group as the between-subjects variable, and hemisphere and stimulus category (faces, objects, buildings, scenes) as the within-subjects variables (although we averaged buildings and scenes for the cortical maps, here we analyze them separately to explore the data fully).

FFA—ANOVA revealed higher activation in the R-FFA than L-FFA, $F(1,18) = 7.78$, $P = 0.012$, and higher activation for faces than any other category, $F(3,54) = 18.65$, $P < 0.001$. There was a significant stimulus category by group interaction, $F(3,54) = 6.12$, $P = 0.001$, with activation to faces stronger for the typical than autism group bilaterally (right, $t(18) = 2.35$, $P = 0.030$, left $t(18) = 2.45$, $P = 0.025$; Fig. 3c). Interestingly, activation to scenes in face-selective cortex was stronger bilaterally for the autism than typical group (right, $t(18) = 3.77$, $P = 0.001$, left, $t(18) = 3.06$, $P = 0.007$) reflecting reduced selectivity in this region. Within-group comparisons showed excellent selectivity for faces in both hemispheres in the comparison group (all $P < 0.01$, except L-FFA faces–objects $P = 0.017$). The autism group, in contrast, showed little evidence of selectivity in either the R-FFA (with just a slight advantage for faces over houses but not over other categories: faces–buildings, $t(9) = 2.36$, $P = 0.043$ but faces–scenes, $t(9) = 0.379$, $P = 0.714$; faces–objects, $t(9) = 1.33$, $P = 0.217$) or L-FFA (faces–buildings, $t(9) = 2.62$, $P = 0.028$ but faces–scenes, $t(9) = 0.906$, $P = 0.389$; faces–objects, $t(9) = 0.616$, $P = 0.553$).

CoS—ANOVA revealed stronger activation for buildings and scenes than faces (but not objects, $P > 0.05$), $F(3,54) = 25.99$, $P < 0.001$, and this was so to a great extent in the R-CoS than L-CoS, $F(3,54) = 3.87$, $P = 0.014$, ($t(19) = 3.32$, $P = 0.004$). There were no significant main effects or interactions involving group.

Object-related LO—ANOVA revealed that overall activation was significantly higher for objects than buildings, scenes and faces, $F(3,54) = 17.79$, $P < 0.001$. There were no significant main effects or interactions and, in particular, none involving group.

To investigate individual variability within groups, we performed pairwise comparisons between all members of each group within each hemisphere then, for each participant, averaged the correlation coefficients obtained to produce a "similarity index" reflecting how similar the individual's time course was to that of the other members of their group (e.g. we correlated comparison participant 1s data with that of comparison participant 2, then comparison participant 3, etc. and then averaged the set of correlation coefficients to give the similarity index for comparison participant 1). Similarity indices for the autism and comparison individuals were then compared to reveal whether the within-group variability differed between groups. All analyses are reported by ROI.

FFA—A comparison of the individual similarity indices between the groups showed significantly more variability within the group with autism than the typical comparison group for both hemispheres (L-FFA, mean similarity index autism = 0.047, typical = 0.22, $t(18) = 3.89$, $P = 0.001$; R-FFA, mean similarity index autism = 0.002, typical = 0.15, $t(18) = 6.07$, $P < 0.001$).

CoS—Within-group variability did not differ significantly between the groups (L-CoS, mean similarity index autism = 0.077, typical = 0.095, $t(18) = 0.79$, $P = 0.44$; R-CoS, mean similarity index autism = 0.10, typical = 0.13, $t(18) = 1.22$, $P = 0.24$).

Object-related LO—Comparison of the individual similarity indices between groups showed significantly more variability within the group with autism than for the typical comparison group for both hemispheres (L-LO, mean similarity index autism = 0.041, typical = 0.12, $t(18) = 3.66$, $P = 0.002$; R-LO, mean similarity index autism = 0.065, typical = 0.27, $t(18) = 6.56$, $P < 0.001$).

In summary, reduced activation to faces in autism was apparent, both on the flattened cortical maps and the sampled time course from the group-defined ROIs. Additionally, there was an aberrant increase in scene-related activity in FFA for the group with autism. No significant group differences were found in activation of object- or building- and scene-related ventral visual cortex. When group activation time courses were examined as a whole, the group with autism showed significantly more variability in the time-course signals than the typical group in FFA and LO, but not CoS.

Discussion

Our aim was to map out, in detail, activation in visual ventral cortex in high-functioning adults with autism in response to three visual categories—faces, houses (including buildings and scenes) and common objects. The topography of this region is well demarcated in typical individuals and, thus, serves as a useful standard against which to examine category selectivity of this region in autism. We employed both a highly constrained, experimental paradigm, with static images and a behavioral task and a more naturalistic experiment, using moving photographic images under free viewing. Although previous studies have found differences in face-related activation in autism, this represents the first study to systematically compare cortical activation in response to *multiple* high-level visual categories simultaneously. Findings were broadly consistent across both experiments, and different dependent measures, lending support to the robustness of the data.

Activation of the Face-Processing Network

Group differences were most marked for face-related cortex, with (a) decreased specificity to faces in FFA and (b) reduction of activation in response to faces in autism within the whole face network including the FFA, STS and OFA (with the possible exception of right OFA). These results replicate and extend existing findings that suggest alteration in the neural correlates associated with face representation not only in FFA but in a more distributed face-processing network [also see Bailey et al., 2005; Hadjikhani et al., 2007]. Of note, there was also increased FFA activity in the autism individuals in response to objects and scenes, suggesting that FFA is less specialized for faces in autism, activating to a wider range of stimuli.

Can Differences in Fixation Account for the Differences in FFA Activity?

In common with many studies (see Introduction), we found a reduction in FFA activity in response to faces in autism. An immediate question concerns the source of this FFA reduction in our study. One possibility is that the reduced BOLD pattern arises because individuals with autism are simply not looking at the faces. Some have suggested that if these individuals are forced to look at the face stimuli, especially the eyes, by means of a central fixation dot, then the FFA is activated to the same extent as in typical individuals [Dalton et al., 2005; Hadjikhani et al., 2004]. Although this may account for our data, in part, it cannot fully explain the results or the reduced selectivity of this region.

Indeed, in Experiment 1, participants fixated a central dot, overlaid on the center of the input, and present on the screen at all times, as in Hadjikhani et al. [2004], and had been trained to do so before entering the scanner. As is also true for most other fMRI studies of visual processing in ASD [e.g. Deeley et al., 2007; Hadjikhani et al., 2007], we visually monitored the eyes of the individual participants in the scanner, using a camera, to ensure that they were looking at fixation at all times. Also, given that both groups showed equivalent accuracy and reaction times for a concurrent one-back task, it seems that the reduced amplitude in FFA activation in autism cannot be easily explained as the failure to look at the faces. Without eye-tracking data, in the movie experiment, we cannot be definitively sure that the group differences for faces were not owing to differences in the gaze patterns [Klin et al., 2002; Morris et al., 2007]. However, the similarity in the pattern of results obtained in the free-viewing and fixation point studies is noteworthy.

Whether there are differences in locus of fixation between individuals with autism and typical controls at all remains controversial in and of itself [see Boraston and Blakemore, 2007]. For example, one study reported no typical/autism group differences in the amount of time spent fixating on face and eye regions [Dapretto et al., 2006] and still revealed group differences in cortical activation patterns. Clearly, further studies are necessary to elucidate the relationship between eye-movement trajectories and BOLD activation.

Object- and Building-Related Activation

In contrast to the group differences in face-related regions, there were no consistent BOLD differences between the groups in house- (and building- and scene-) related CoS, in either experiment. This replicates the absence of a group difference for activation to house stimuli [Bird et al., 2006; Kleinhans et al., 2008]. Selective activity in house-related cortex was fairly low for both groups relative to other regions sampled; hence, it is possible that this result represents a floor effect. If any atypicalities exist for houses in autism, they are much more subtle than those affecting faces.

It does not, however, seem that differences in autism high-level ventral cortical are limited to face-related regions, as there was evidence of, albeit subtle, differences affecting the representation of common objects. Within object-related LO, there was increased within-group

variability in the time course for the group with autism, relative to the comparison group but no group differences in themagnitude or extent of the object activation. Unlike the face and house stimuli, the object stimuli formed a more heterogeneous group; hence, it seems unsurprising that there was a high degree of variability in the size of the object-related cortex identified within both groups, particularly in Experiment 1. Also note that behavioral difficulties with objects in autism are subtle, when they are found, and manifest under taxing perceptual conditions [Behrmann et al., 2006].

Finally, the individual cortical maps were more variable within the autism than comparison group. There was also more within-group variability in the time course of activation in both FFA and object-related LO for this group. High within-group variability has been noted in autism in other contexts [e.g. Muller et al., 2003], and may be a feature of atypical development.

Different Developmental Trajectories for Face-, Place- and Object-Selective Cortex in Autism?

How should we interpret the broad pattern of results, of markedly reduced activation and selectivity in face-related cortex in the group with autism, but with activation in object and place areas, which is broadly similar (albeit with a few subtle differences) to that of controls? Notably, studies with typically developing children have shown that activation in place and object areas is adult-like even in early childhood, whereas the development of the FFA is much more protracted, becoming more selective and responsive to faces with age, but not reaching adult-like activation until adolescence [Golarai et al., 2007; Scherf et al., 2007]. This finding is mirrored in behavioral studies of face processing, in which face-processing abilities continued to improve through late childhood [e.g. Diamond and Carey, 1977; Mondloch et al., 2004], thought to be related to the acquisition of expertise in processing faces “configurally” [Diamond and Carey, 1986].

One, rather obvious, possibility, then, is that visual category-selective cortex in autism reflects a delay in development, rather than deviance, with the category selectivity resembling that of younger children. Studies comparing individuals with autism with typically developing children of different ages would be useful to see whether and where the results from those with autism fall on the typical developmental trajectory. However, we are inclined to think that the explanation of delay is not sufficient, as some subtle differences, such as increased variability in the time courses of activation, were found even in the object-related cortex of the autism group in our study [see also Kylliainen et al., 2006]. A number of authors propose abnormalities of neural connectivity in autism [Belmonte et al., 2004a,b; Frith, 2003; Courchesne and Pierce, 2005a,b; Rippon et al., 2007], specifically under-connectivity between different functions (long-range) and possible over-connectivity within at a more local level (short-range) and this is true even intrinsically when the brain is at rest [Kennedy and Courchesne, 2008]. Along with previous authors [e.g. Johnson et al., 2002], we speculate that, the longer a particular function takes to mature, the greater the cascading effects of differences in the development of neurons and synapses in the condition, such that differences in face-related cortex are much more pronounced than those in the earlier maturing place or object-related cortex. The refinement in selectivity of later-developing cortex may be impeded in autism as a result of over-connectivity at a local level giving rise to a face-processing system prone to crosstalk and noise, with resulting reduced selectivity [see Rippon et al., 2007]. If correct, a further prediction is that greater typical/autism group differences would be evident in other, later developing brain functions, as opposed to earlier developing functions. For example, we would predict greater differences on tasks that engage secondary and tertiary cortex than primary cortices [Hasson et al., in preparation]. Additionally, we might expect greater divergence between the groups on tasks tapping frontal functions. Recent work on cognitive control upholds this prediction [Solomon et al., 2008; Takarae et al., 2007].

Limitations

Naturally, this study suffers from a number of limitations. Determining the neurobiological basis of atypical selectivity of ventral cortex remains elusive and lack of eye-tracking data further complicates this issue. We do not know whether the autism and comparison groups were perfectly IQ matched. Of particular note is that the sample size was relatively small (although not greatly discrepant from many similar studies and of sufficient power to reveal group differences) and was limited to high-functioning male participants. Whether the findings are generalizable to more severely affected individuals is an open question, but presumably if these differences are apparent in the high-functioning individuals, they might be even more apparent in individuals with autism who are more severely affected.

Implications for Theories of Autism

This study uncovers atypical functional topography in ventral cortex in autism and, as such, suggests that other areas may also be organized differently in these same individuals. Although the strongest deficits were in face-processing networks, there were also some differences in the non-face networks. That ventral visual cortex in autism atypicalities extends beyond face-related cortex, albeit subtly, is not obviously predicted by theories that cast autism as a purely social disorder [e.g. Schultz, 2005] and calls for a broader neurobiological explanation. We posit that a more compelling explanation be cast at the level of cascading developmental effects of low-level differences in neuronal connectivity, which result in a much more pronounced effect on later developing cortical systems, such as that for face processing, than earlier maturing systems (objects and places). Clearly, further empirical support is needed to substantiate this speculation.

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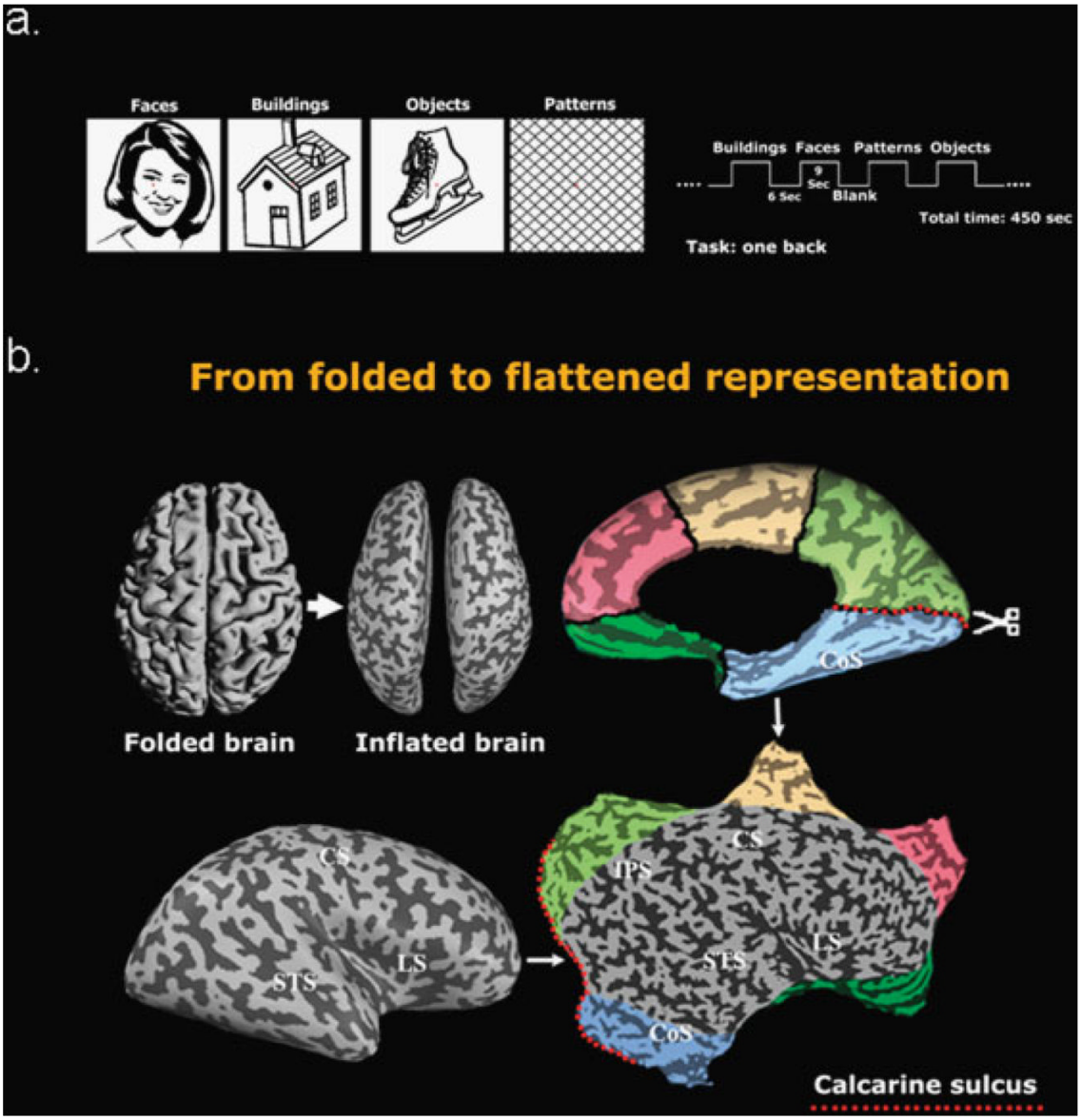

Figure 1.
Experiment 1 (conventional face, house and object mapping): (**a**) examples of the stimuli and the experimental design and (**b**) explanation of how the flattened cortical maps were created (courtesy of R. Malach, used with permission).

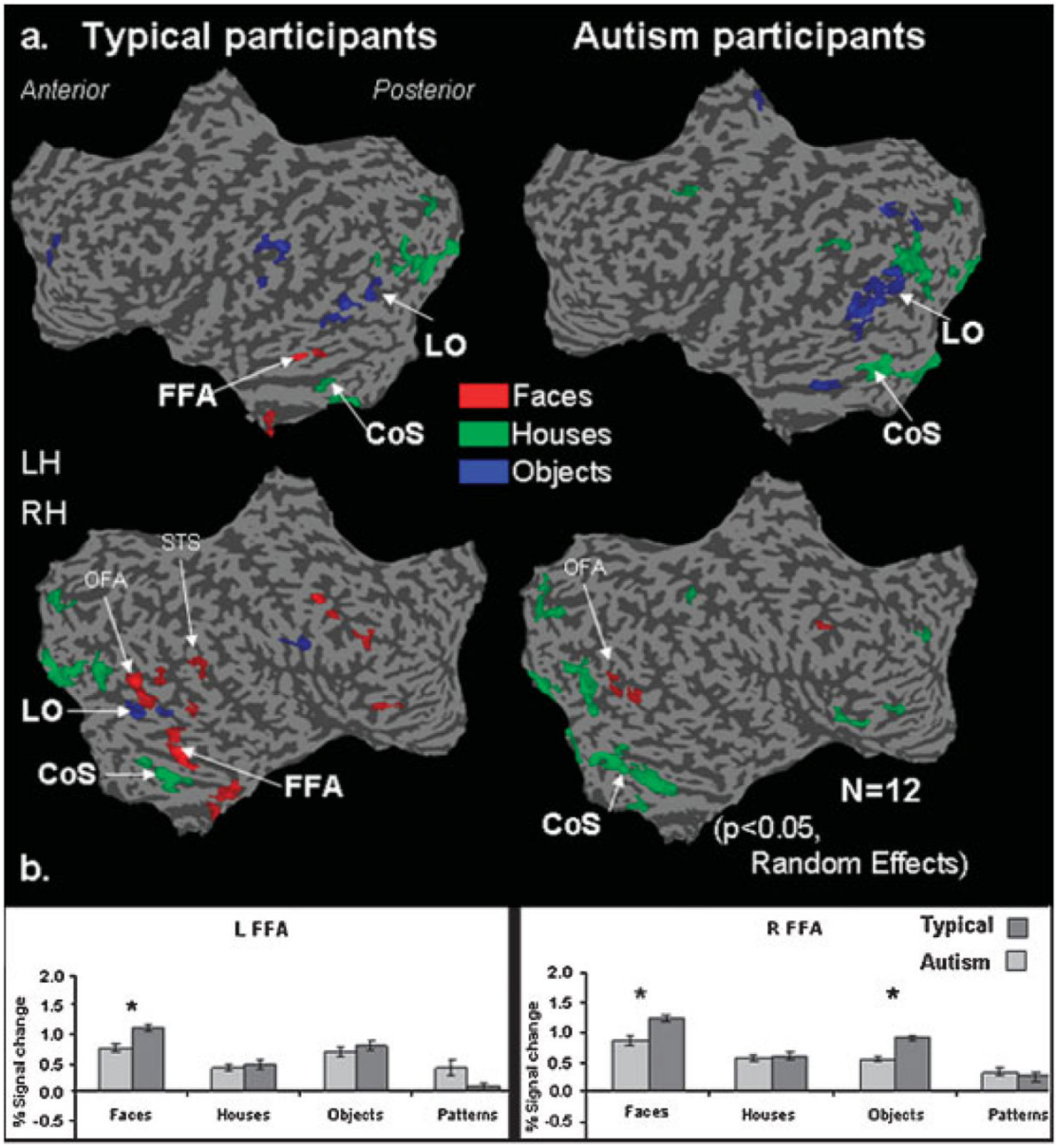

Figure 2.

Experiment 1 (conventional face, house and object mapping): (**a**) flattened group cortical maps from the typical and autism individuals showing activation in response to faces, houses and objects. The first map shows the average activation map for typical individuals ($P < 0.05$) and the second for individuals with autism ($P < 0.05$) and (**b**) average peak activation in the right and left fusiform face area to faces, houses, objects and patterns for the typical and autism groups (error bars, standard error mean; significant differences marked with an asterisk).

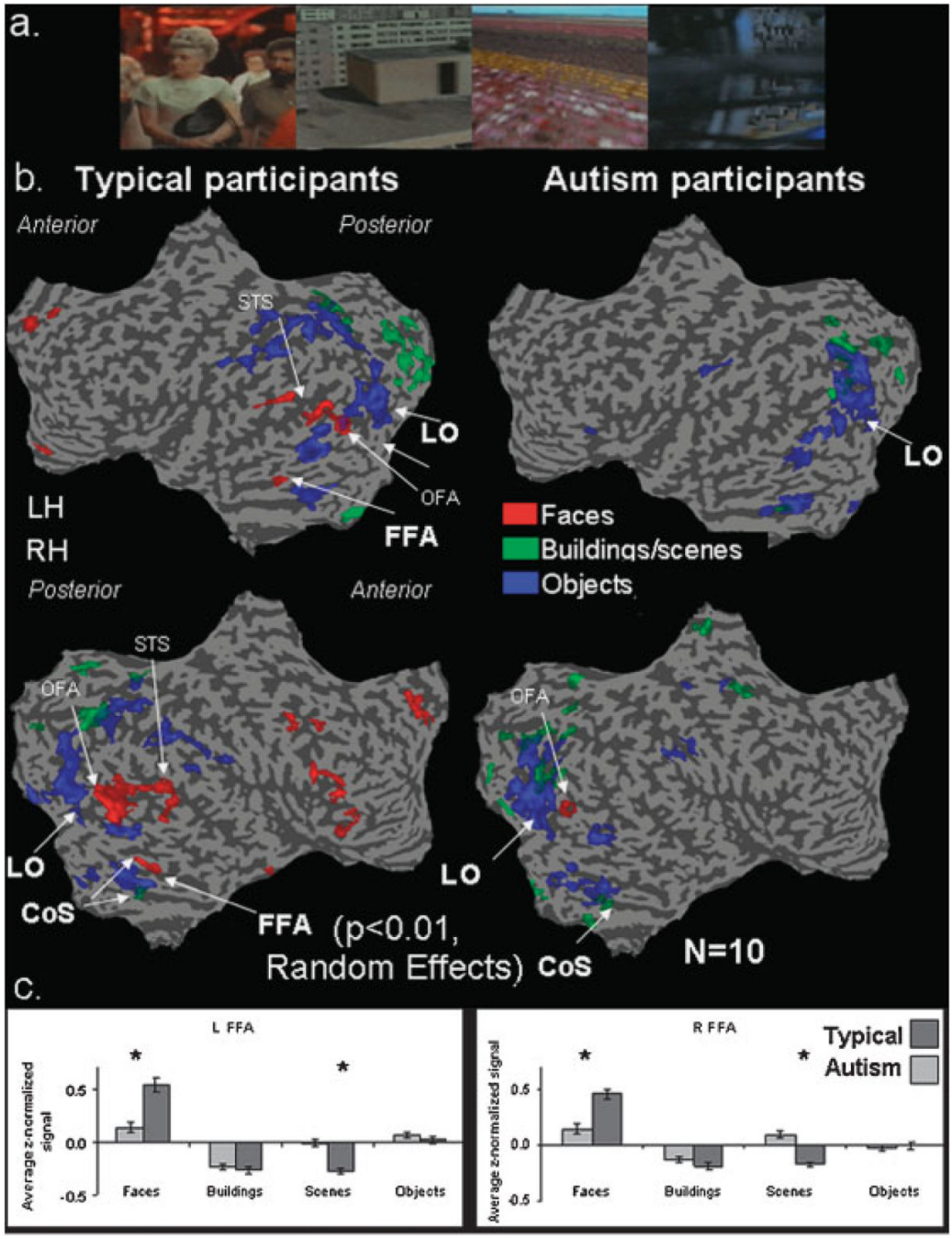

Figure 3.

Experiment 2 (moving pictures of faces, buildings, scenes and objects): (**a**) examples of the stimuli and (**b**) flattened cortical maps from the typical and autism groups showing activation in response to faces, buildings and landscapes and objects. The first map shows the average activation map for typical individuals ($P < 0.01$) and the second for individuals with autism ($P < 0.01$); (c) average ***z***-normalized activation in the right and left fusiform face area to faces, buildings, scenes and objects for the neurotypical and autism groups (error bars, standard error mean; significant differences marked with an asterisk).

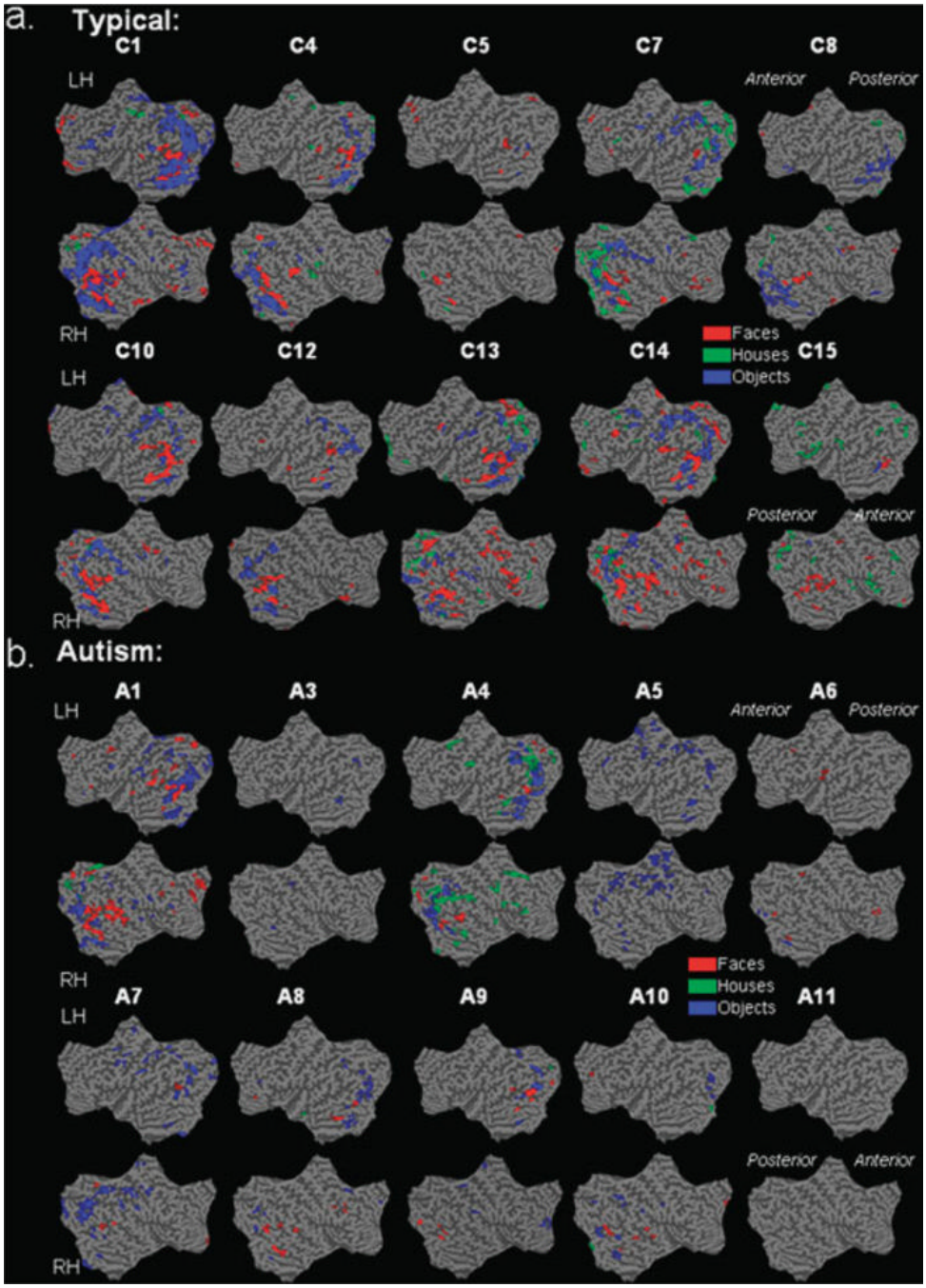

Figure 4.

Experiment 2 (moving pictures of faces, buildings, scenes and objects): individual flattened cortical activation maps (projected onto the same brain) for the ten typical comparison individuals and ten participants with autism, all $P < 0.05$.

Table I

Background Information for Participants with Autism (A1–13) and Comparison Individuals

ID	Age	Sex	Exp.	PIQ	VIQ	ADOScom	ADOSsoc	ADOSstbeh	ADIsoc	ADIcomm	ADIstebeh
A1	18	M	1,2	88	109	7	10	0	27	22	5
A2	18	M	1	121	111	5	13	3	20	13	3
A3	18	M	1,2	116	108	4	8	2	37	21	11
A4	20	M	1,2	119	97	4	8	0	22	10	3
A5	21	M	1,2	108	107	4	11	0	28	22	5
A6	21	M	1,2	101	88	6	13	4	11	8	2
A7	21	M	2	75	96	6	10	0	25	13	4
A8	25	M	1,2	116	116	5	8	1	36	17	9
A9	28	M	1,2	100	113	5	10	3	23	19	4
A10	32	M	1,2	116	104	5	7	3	21	16	8
A11	35	M	1,2	95	95	4	6	2	20	11	3
A12	35	M	1	110	83	4	10	5	15	8	10
A13	53	M	1	103	88	6	11	6	27	20	8
C1	18	M	1,2	123	116						
C2	19	M	1	[a]							
C3	21	M	1	115	90						
C4	22	M	1,2	96	106						
C5	22	M	2	109	105						
C6	22	M	1	[a]							
C7	23	M	1,2	124	114						
C8	23	M	2	120	110						
C9	23	M	1	[a]							
C10	33	M	1,2	100	99						
C11	39	M	1	115	102						
C12	40	M	1,2	118	107						
C13	41	M	1,2	[a]							
C14	44	M	1,2	[a]							
C15	44	M	2	[a]							

[a] IQ data not available.

Exp., Experiment; PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient; ADOS, autism diagnostic observation schedule.

Table II

Size (voxels) and Location (*x*, *y*, *z* Talairach Coordinates) of the Regions of Interest (FFA, COS, Object- Related LO) for Experiments 1 and 2 Defined, Based on Data From an External Group of Neurotypical Individuals

	Experiment 1				Experiment 2			
	Voxels	***x***	***y***	***z***	**Voxels**	***x***	***y***	***z***
L-FFA	828	42	−44	−24	379	38	−43	−15
R-FFA	2,406	−38	−41	−19	247	−37	−48	−18
L-COS	3,603	23	−42	−8	816	23	−40	−7
R-COS	2,949	−22	−38	−9	288	−21	−40	−7
L-LO	2,647	46	−67	−1	1507	40	−70	−1
R-LO	1,610	−43	−61	−9	626	−40	−64	−4

FFA, fusiform face area; COS, collateral sulcus; LO, lateral occipital cortex.