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ABNORMAL VENTRAL TEMPORAL CORTICAL ACTIVITY AMONG INDIVIDUALS WITH AUTISM AND ASPERGER SYNDROME DURING FACE DISCRIMINATION

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Background: Recognition of individual faces is an integral part of interpersonal interactions and successful functioning within a social group. It is, therefore, of considerable interest that individuals with autism and related conditions have selective deficits in face recognition (sparing nonface object recognition). ***Method:*** We used functional magnetic resonance imaging (fMRI) to study face and subordinate-level object perception in 14 high functioning individuals with autism or Asperger syndrome (the "Autism group"), in comparison to two groups of matched normal controls (NC1 and NC2; n=14 in each). Regions of interest (ROIs) were defined in NC1 and then applied in comparisons between NC2 and the Autism group. ROIs were also defined in NC2 and then applied to comparisons between NC1 and the Autism group as a replication study. ***Results*:** In the first set of comparisons, we found significant task by group interactions for the size of activation in the right fusiform gyrus (FG), and right inferior temporal gyri (ITG). Post hoc analyses showed that during face (but not object) discrimination the Autism group had significantly greater activation than controls in the right ITG and less activation of the right FG. The replication study showed again that the Autism group used the ITG significantly more for processing faces than the controls, but for these analyses the side of the effect was now on the left. Greater ITG activation was the pattern found in both control groups during object processing. ***Conclusions:*** Individuals with autism spectrum disorders demonstrate a pattern of brain activity during face discrimination that is consistent with feature-based strategies that are more typical of nonface object perception.

INTRODUCTION

The symptoms of autism spectrum disorders such as a preference for inanimate objects, and lack of interest in the human face, are evident as early as the first year of life[1-3]. Abnormalities in face recognition skills are of particular interest, for they may provide clues about the developmental mechanisms involved in the pathobiology of autism and Asperger syndrome (AS). Recognition of individual faces is necessary for successful interpersonal relationships.

It has been argued that faces are a special class of object[4,5], and some evidence suggests an innate preference for faces over other objects. For example, newborns preferentially respond to the human face, though this rudimentary skill or looking preference must be practiced to develop further[6,7].

A growing body of literature suggests that individuals with autism and AS have abnormalities in

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face perception[8-14]. For example, Tantam and colleagues[12] found that autistic children were less able to discriminate pictures of faces in an "odd person out" task compared to age and nonverbal IQ matched controls. Hauck and colleagues[13] found relative deficits in face *vs*. object perception and memory in boys with autism. In addition, difficulty with face perception has been found in Asperger syndrome[9] and pervasive developmental disorder[13], suggesting that face perception abnormalities may be a core feature of the social disabilities.

The effect size for this deficit, however, may be modest, and at least one study failed to find overall performance differences between groups[15]. Depending on the methods and the nature of the stimuli employed, there are a variety of compensatory perceptual encoding mechanisms that might be used by individuals with autism during face perception, some of which are more typical of object perception. Face perception is normally a holistic process, relying on the spatial configuration of the major features of the face – the eyes, nose and mouth[5,16-19]. In contrast, nonface object recognition is typically reliant on the detection of individual features and not the overall configuration[5,16-20]. One way to disturb holistic processing and to force segmental strategies is to invert the face, thereby changing the accustomed configuration of the main features and making perception more difficult (a phenomenon known as the "inversion effect")[16]. Since object processing is more reliant on the analysis of discrete features, it follows that object recognition shows less marked inversion effects [5,16-19]. An exception can be found, however, among individuals with special expertise for a given class of visual stimuli (e.g., ornithologists, car enthusiasts)[16-19]. The development of expertise is associated with a transition from feature-based to configural processing and an increase in the magnitude of the inversion effect[17-19].

In light of these differences between face and object perception, one of the most interesting findings in the autism literature is that patients with social disabilities rely more on individual pieces of the face for identification (e.g., the lower face and mouth area) than the overall configuration[10,11]. Consistent with this, numerous studies have found that individuals with autism spectrum disorders show less of an inversion effect for faces and better object perception than expected based on their ability with faces[8-13]. These results suggest that individuals with autism are performing perceptual processes on faces as if they were objects, perhaps because of a lack of expertise for faces and/or specific perceptual difficulties with configural processing.

The current study used functional MRI (fMRI) to examine brain activation patterns while subjects with autism or AS made perceptual judgments on pairs of faces or objects. It is well documented that the fusiform gyrus (FG) responds preferentially to faces[4,18,21,23,24,27]. Object specific brain processes are less well understood, owing in part to the diversity of their physical properties. Nevertheless, brain regions straddling the FG such as the posterior inferior temporal gyri (ITG), the lateral occipital gyri (LOG), and parahippocampal gyri (PHG) appear to be involved in common object perception[4,18,21,22,28-33]. Anatomical specializations, however, appear relative rather than absolute[34], as object and face tasks typically activate some tissue in common, and each varies somewhat between subjects in its precise location[4,18,21,23,24,30,32]. This makes *a priori* definition of object and face regions of interest (ROIs) a challenge, and between-group comparisons difficult, because differences that are part of normal variation might be found between any two groups of ostensibly healthy subjects. Thus, in the current study we first defined our face and object ROIs within one sample of normal control subjects, and then applied these definitions in our comparison of patients and a new sample of controls.

METHODS

Subjects

Right handed male subjects with a clinical diagnosis of autism or AS were recruited from the Yale Child Study Center Autism Clinic and from queries to our research web page. Prior to participation all subjects or their legal guardian gave informed written consent. The study was approved by the Human Investigations Committee of the Yale University School of Medicine. Diagnoses were assigned on the basis of parental interview (Autism Diagnostic Interview-Revised; ADI-R)[35], and proband assessment (Autism Diagnostic Observation Schedule; ADOS)[36]. Eight of the 14 subjects met ADI-R and ICD-10[37] criteria for autism, while six satisfied ICD-10 criteria for AS. All 14 patients were severely impaired in their social functioning, the core feature of both autism and AS (Vineland[38] Socialization scores averaged 4 SDs below prorated Wechsler Full Scale IQs[39-41]). All 14 met ADI-R social, motor and stereotypy criteria for autism, with the main difference being that the AS subjects did not meet age of onset criteria for autism (see Table 1) and had more impaired motor functioning (Vineland Motor scores; (t[1, 9]=2.39, p=.04). There were no significant differences between the patient subgroups on FSIQ, VIQ or PIQ (p's > .2), but for the combined patient sample VIQ was significantly higher than PIQ (paired t [13]=4.27, p <.001). This pattern is typical of AS[42] and of persons with autism when FSIQ is > 100 (Klin et al., unpublished data). Initial analyses of fMRI data employed both

subgroups, but because there were no significant subgroup differences on any fMRI measure (*p's* all > .5) subjects were collapsed into one patient group for all subsequent analyses (hereafter referred to simply as the Autism group). Four of the 14 patients were taking a medication at the time of fMRI (an SSRI-3 or Haldol-1). There were no significant differences for any fMRI activation variable between the patients on *vs*. off medications (*p's* > .85).

For the comparison group, twenty-eight right-handed male subjects, screened for history of traumatic loss of consciousness, major psychiatric illness and neurological problems, were recruited from the community. They were divided into 2 control groups (randomly labeled NC1 and NC2), group matched on age and FSIQ to each other and to the Autism group. Initially, 29 controls 29 controls and 23 patients participated in the fMRI procedure but 9 patients and 1 control were later dropped because of motion artifacts. The final control and patient groups did not differ significantly (*p's* all > .50) from each other on age, IQ scores, or movement during the fMRI procedure (see Table 2).

Tasks

Changes in blood oxygen level dependent (BOLD) contrast were measured as subjects performed perceptual discrimination tasks, indicating by a button press whether side-by-side images of faces, objects or patterns were the "same" or "different" (see Figure 1). Each of the 4 runs was composed of three blocks (41s each, with an 8s rest in between blocks) in an ABA design, with 7 image pairs per block. Pilot data on 15 controls and 4 patients outside the magnet was used to set the stimulus duration at 4 s and the ISI at 2 s (faster presentation rates provoked anxiety in patients and younger subjects), and to select image pairs that were of equal difficulty across the three tasks. The tasks were not optimized to document object > face perceptual accuracy in autism, e.g., total item number was low, and the response interval was long enough for subjects to succeed on most items.

Runs 1 and 2 compared patterns with familiar objects (pairs of cars, boats, birds, planes, bottles or chairs). Each object discrimination was at the same subordinate level of categorization (e.g., chair *vs*.

Table 1

Mean Scores (± SD, range) for the ADI-R and the Vineland Adaptive Behavior Scale

	Autism Spectrum Groups		
	Combined Group (n=14)	Autism Subgroup (n=8)	Asperger Syndrome Subgroup (n=6)
ADI-R Social Domain (cut off for diagnosis of autism=10)	17.7 (4.7, 11 - 25)	19.0 (4.0, 11 - 22)	15.6 (5.6, 11 - 25)
ADI-R Communication Domain (cut off for autism=8)	12.9 (4.4, 6 - 21)	13.9 (3.8, 10 - 21)	11.4 (5.3, 6 - 17)
ADI-R Stereotypy Domain (cut off for autism=3)	6.7 (2.6, 3 - 11)	7.3 (2.6, 3 - 11)	5.8 (2.6, 3 - 10)
ADI-R Onset (cut off for autism=1)	1.8 (1.8, 0 - 5)	2.9 (1.4, 1 - 5)	0
Vineland Composite SS	62.9 (17.2, 25 - 100)	64.9 (9.0, 48 - 76)	60.3 (25.3, 25 - 100)
Vineland Communication SS	81.1 (20.5, 38 - 109)	82.0 (17.0, 55 - 104)	80.0 (26.1, 38 - 109)
Vineland Daily Living Skills SS	73.7 (12.1, 20 - 106)	79.6 (19.2, 54 - 106)	65.8 (32.6, 20 - 74)
Vineland Motor SS	100.1 (18.9, 52 - 113)	108.6 (5.7, 97 - 113)	85.3 (25.8, 52 - 108)
Vineland Social SS	48.8 (25.7, 27-119)	49.6 (3.9, 46 – 58)	47.7 (19.0, 27-119)

Table 2
Subject Characterization (Mean ± SD).

	Normal Control Group 1 (NC1) n=14	Normal Control Group 2 (NC2) n=14	Autism group n=14
Age	21.7 (7.2)	21.5 (10.6)	23.8 (12.4)
FSIQ[1]	110.4 (17.2)	108.7 (16.3)	109.1 (19.5)
VIQ	111.2 (18.4)	112.4 (15.4)	117.1 (19.7)
PIQ	103.9 (13.2)	102.5 (16.5)	97.6 (19.0)
Movement (pixels) Object-Pattern Runs	.21 (.09)	.17 (.09)	.20 (.09)
Movement (pixels) Face-Pattern Runs	.22 (.11)	.20 (.11)	.20 (.09)

1 Full Scale IQ was prorated from an abbreviated form of the Wechsler (Block Design, Picture Completion, Vocabulary & Information subtests) that correlates >.90 with the full form (Sattler, 1988)

chair, but never chair *vs*. bottle) in order to control for the possibility that patients with autism differ from normal in their ability to make any within-object category discrimination. Runs 3 and 4 compared pattern and face identity discrimination. The identity task employed same-gender pairs of neutral/non expressive face pictures[43,44] that were edited to remove hair, ears and shirt collars, so as to force subjects to focus on features of the face with central relevance to nonverbal social communication, i.e., the eyes, nose and mouth. Nonsense patterns used in all runs were created by grossly distorting the object pictures to form unnamable images similar in appearance to the control stimuli used in prior studies[30,31] that showed FG activity during face perception. Edge features were occluded on each object and pattern to make them as difficult as the face pairs. Images were back-projected onto a translucent screen mounted near the end of the MRI gantry, and viewed through a periscopic prism system on the head coil.

Image Acquisition.

Imaging was performed with a 1.5T GE Signa MRI scanner with a standard quadrature head coil, equipped for echo planar imaging (Advanced NMR, Wilmington, MA). The subject's head was positioned along the canthomeatal line and immobilized using a bead-filled vacuum cushion, foam wedges, and tape across the forehead. T1-weighted sagittal scout images were used to place an oblique axial image along the longitudinal extent of the FG, so that one slice maximally captured the posterior two thirds of the ventral surface of the temporal lobes (see Figure 2). Functional images were acquired using a gradient echo, single shot echo planar sequence (TR=1500 ms, TE=60, flip angle=60, 92 images per slice, NEX=1, voxel size=3.125 x 3.125 x 9.0 mm). Susceptibility artifacts were routinely present in the lateral and mesial anterior temporal lobe (stemming from the ear canals and paranasal sinuses). Signal drop out and spatial distortions were severe enough that data rostral to the posterior commissure were not analyzed and were masked in the composite maps (see Figure 3) because they are likely inaccurate and misleading. Data analyses, therefore, focused on posterior temporoccipital areas during each primary task (face or object discrimination) were compared to pixel intensities in the baseline task (pattern discrimination) to calculate a *t* statistic at each voxel. These *t*-values were then averaged across both runs of each task comparison, and filtered using a minimum cluster size of 5 to remove isolated voxels that likely represented noise. The averaged *t*-values for each pixel were not used to test statistical significance, but rather they were used as an outcome variable which quantified the relative amount of task specific activity. Next, voxel locations that survived the first set of comparisons were subtracted from each other to yield face and object specific activation maps - a "double subtraction". We called these new values the "DS" data, in order to distinguish them from the original *t*-values. The DS data were used in determining the size of activation within ROIs for each subject. Composite activation maps were created with the DS data overlaid on composite anatomic images (Figure 3), thresheld at a value (.15) which subjectively seemed to best illustrate the significant findings from

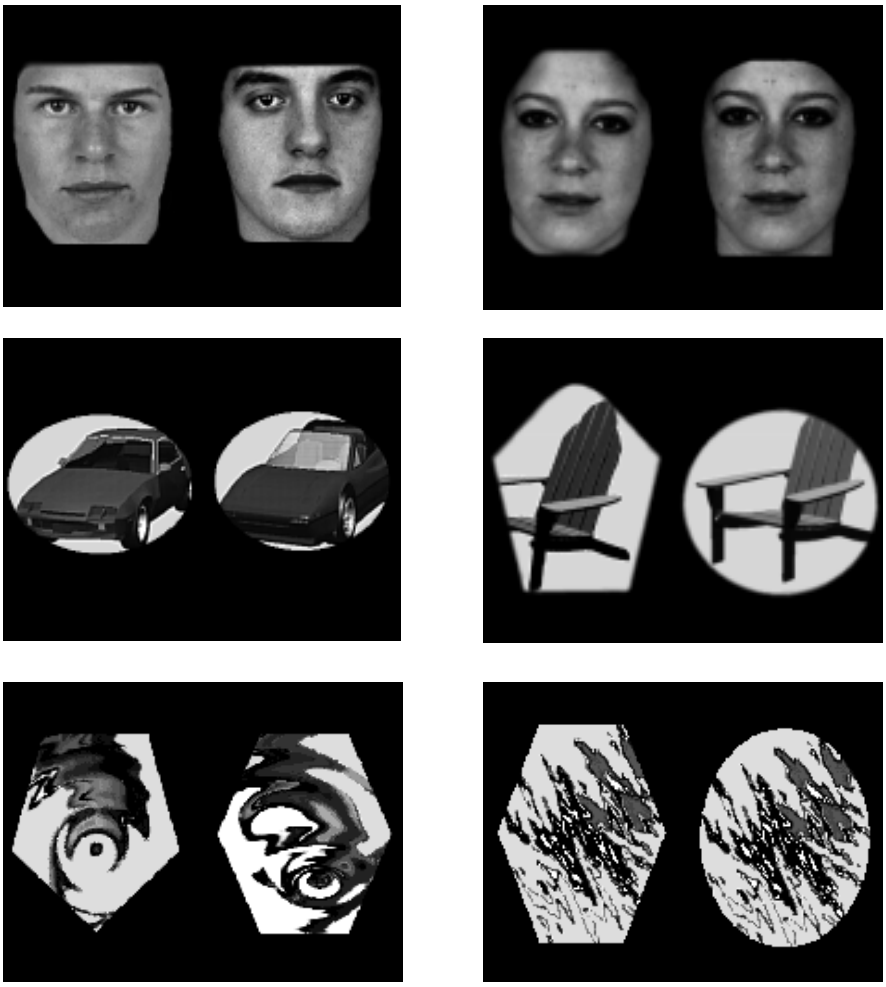

Figure 1
Examples of stimulus pairs used in the Face, Object and Pattern tasks. For each stimulus type, the pair on the left is "different" while the one on the right is the "same".

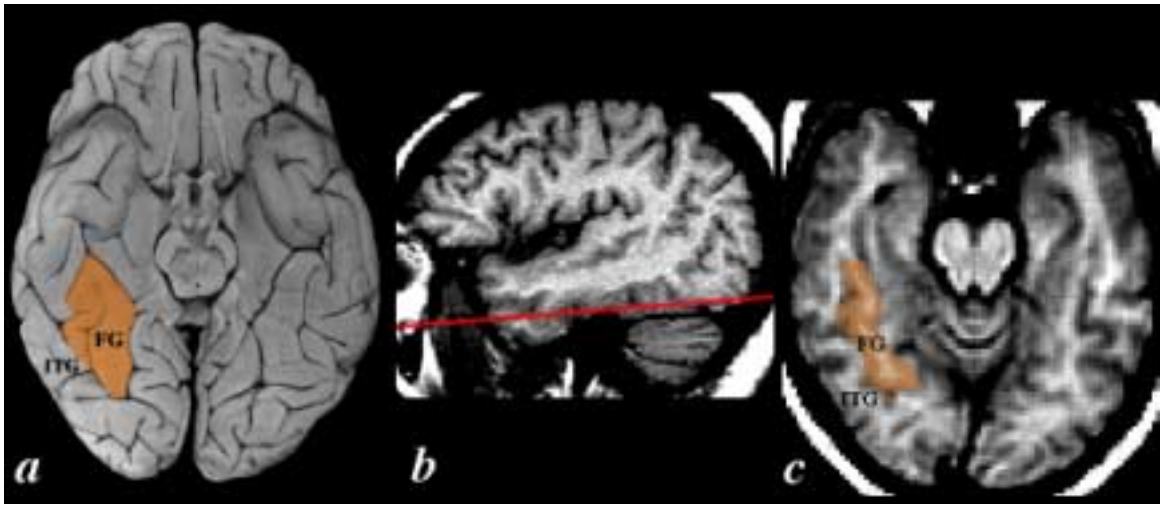

Figure 2
Ventral Temporal-Occipital Neuroanatomy. (a) Illustration of the Fusiform and Inferior Temporal gyri (FG, ITG) in a postmortem brain. (b) Demonstration of the MRI slice selection used to maximally capture the FG. (c) An example an oblique axial MRI through the ventral temporal-occipital cortex.

the ANCOVAs presented below. ROIs were formed by superimposing a proportional grid system of the same resolution as the Talairach system (approximately 8 by 8 mm grid boxes) onto the activation maps. ROI definitions were established in NC1 by combining grid boxes to enclose the strongest areas of activation (see Figure 3a, b). This process focused on *a priori* areas of interest and it resulted in a right FG ROI for faces and a right ITG ROI for objects. In order to limit the number of comparisons, other activations were not analyzed because they were either smaller or in locations that we had not predicted beforehand.

Most fMRI studies are concerned solely with defining significant areas of activation specific to a certain task contrast within healthy subjects.

Comparison of the pattern of activation between groups must address different concerns. Outcome indices (e.g., number of pixels above threshold) usually will not be distributed normally in a group of subjects if thresholds are set relatively high, because some subjects will show no activation at such cutoffs. This causes a variety of statistical concerns, and it creates a poor metric for between group comparisons because the data are not continuously distributed. Constable and colleagues[46] have demonstrated that the number of pixels (size of activation) is most sensitive for detecting group and task differences when the threshold of activation is set just above zero. Thus, the number of pixels with DS values above 0.1 was calculated within each ROI and used as the measure of the size of activation for all between-group statistical analyses.

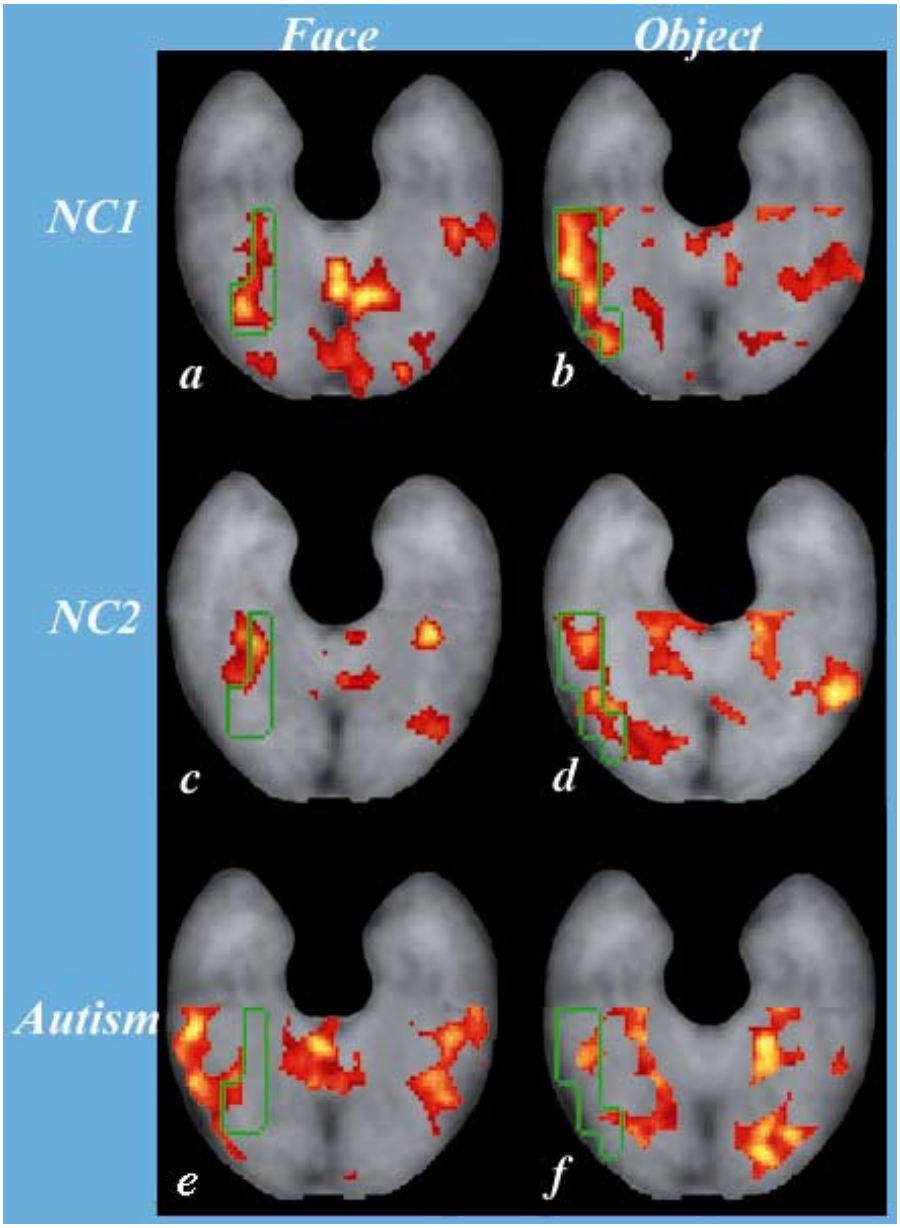

Figure 3
Composite Activation maps superimposed on averaged anatomical images by group and task using. ROIs defined in NC1 are outlined in green on each map. Right and left are reversed by radiologic convention. Note in *e* the ITG activation during face processing in the Autism group.

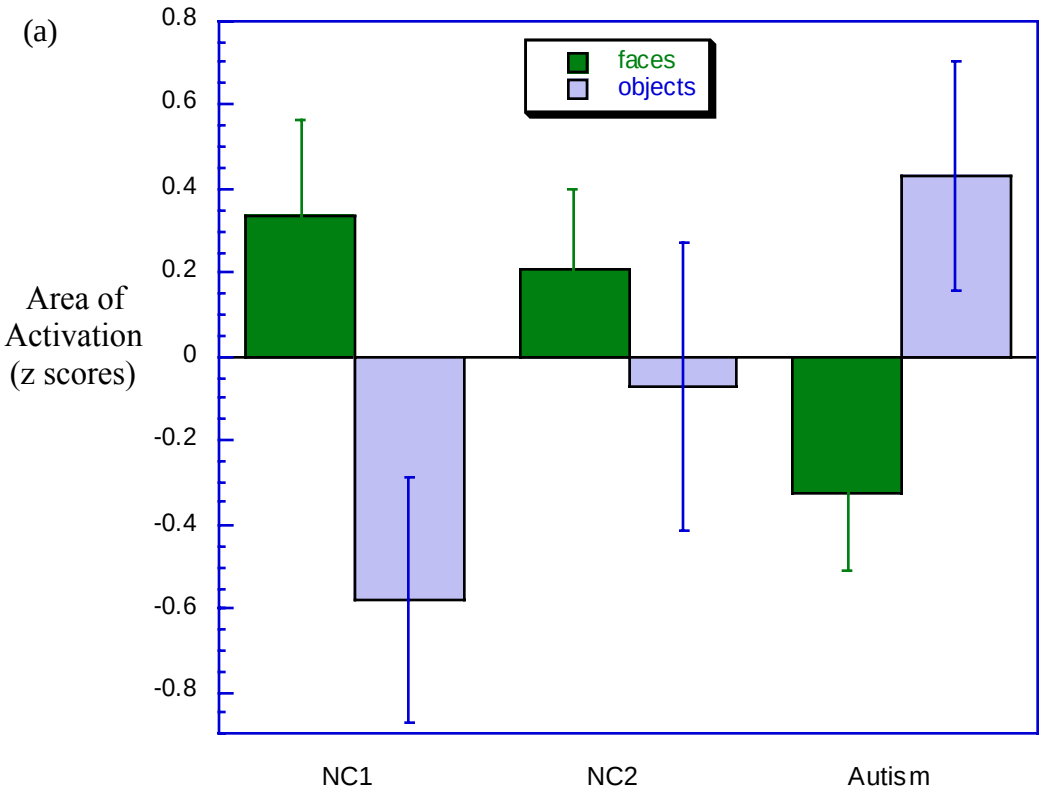

Figure 4
Area of activation (standardized residual scores, after partialling out global activation, ± SE) by group (n =14 in each) and task. (a) FG and (b) ITG. ANCOVA revealed significant task by group interactions (see text).

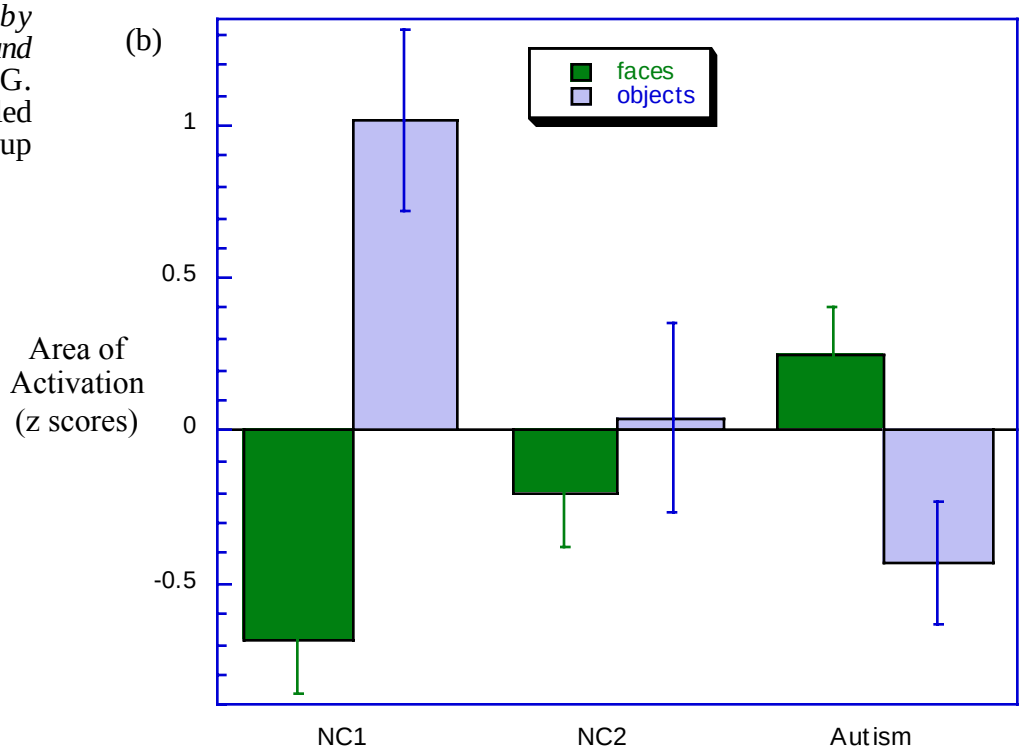

Table 3
fMRI Task Performance (Mean ± SD).

	NC1 n=14	NC2 n=14	Autism Group n=14	ANOVAs and Planned Comparisons (t tests)*
% Pattern Correct	96.2 (3.0)	95.5 (4.6)	92.0 (7.0)	$F = 2.72$, $p = .078$ $t_{NC1\ vs.\ NC2} = 0.47$, $p = .64$ $t_{NC1\ vs.\ AUT} = 2.06$, $p = .05$ $t_{NC2\ vs.\ AUT} = 1.58$, $p = .12$
% Object Correct	100 (0.0)	97.1 (3.4)	95.9 (5.4)	$F = 4.55$, $p = .017$ $t_{NC1\ vs.\ NC2} = 3.20$, $p = .004$ $t_{NC1\ vs.\ AUT} = 2.83$, $p = .009$ $t_{NC2\ vs.\ AUT} = 0.69$, $p = .50$
% Face Correct	83.7 (14.4)	86.7 (9.2)	76.0 (13.6)	$F = 2.66$, $p = .083$ $t_{NC1\ vs.\ NC2} = -0.66$, $p = .51$ $t_{NC1\ vs.\ AUT} = 1.45$, $p = .16$ $t_{NC2\ vs.\ AUT} = 2.43$, $p = .02$

* NOTE: For all ANOVAs, df = 2, 41. For all t-tests, df = 1, 26

Statistical Analyses

Analyses of covariance (ANCOVA) were used to test for main effects of task (object *vs*. face), group (Autism *vs*. control), and task by group interactions, covarying both overall activation and task performance. Task performance, however, was dropped from the final model in every instance because it did not contribute significantly to any analysis (*p's* > .50). Figure 4 shows the relative amount of activation in FG and ITG ROIs by task in z scores (standardized residuals from regressing the size of activation within each ROI onto global activation within the slice). Similarly, Pearson correlations were computed with these z scores. In all analyses the alpha level for significance was set at .05.

RESULTS

Planned comparisons revealed no significant differences between the groups in accuracy on the pattern task (see Table 3 for test statistics and performance data by group and task). Object task performance was significantly greater in NC1 compared to the other 2 groups (*p's* < .05), but this result is of questionable practical significance since each group averaged > 95% correct. There were no significant face task performance differences between the control groups or between NC1 and the Autism group, but NC2 performed significantly better than the Autism group.

Analyses with ROIs defined in NC1

ANCOVA was used to test the main hypothesis that NC2 and the Autism group would differ in the be predicted by the size of brain activations. These analyses are limited by the restricted range of the pattern of brain activation during object *vs*. face perception. These analyses revealed significant task by group interactions for the right ITG (F[1, 51]=4.78, p=.033) and for the right FG (F[1, 51]=4.43, p=.04); there were no main effects. Post hoc ANCOVAs by task showed that the interactions were driven by between group differences on the face task; there were no group differences in object activations. The Autism group showed significantly more right ITG activation than NC2 on the face task (F[1,51]=3.75, p=.038) but not on the object task (F[1,51]=0.67, p=.43). NC2 showed significantly more right FG activation than the Autism group on the face task (F[1,51]=5.14, p=.014) but not on the object task (F[1,51]=0.67, p=. 52).

The pattern of activations in Figure 3 confirms these ROI analyses (e.g., compare right ITG and FG activations in Fig. 3a and 3e). Talairach coordinates for the center of the face selective activation in the right FG of NC1 (+38x, -58y, -10z) and of NC2 (+36x, -50y, -10z) are consistent with prior normative studies[18]. In contrast, the center of the face selective activation for the Autism group (+48x, -48y, -14z) was most similar to the center of activation in the ITG during object perception for NC1 (+48x, -52y –14z). Although a scattering of other activity in response to faces can be seen in Figure 3 (e.g., cerebellar vermis in NC1 and the Autism group), there is no lesion or imaging evidence that these areas are critical to face perception, and they likely represent normal individual differences[21] or epiphenomena.

Correlational analyses explored whether individual differences in face and object task performance could performance data, but they are nonetheless consistent with the group comparisons. The correlation

between amount of right FG and performance on the face task was positive but failed to reach statistical significance among the controls (r=.35, p=.069), and among the patients (r=.15, *ns*). In contrast, right FG activation was significantly correlated with object perception among the patients (r=.73, p=.003) but not among the controls (r=.04). Right ITG activation was not significantly correlated to task performance inside the magnet in either group, but in patients it correlated with a test of face perception administered outside the magnet (Benton Face Recognition Test; r=.68, p=.01).

ANCOVA tested the reproducibility of the activations in NC1 and NC2. There was no significant effect of Group (NC1 *vs*. NC2) for the right FG ($F[1,51]=0.43$, p =. 51) or the right ITG ($F[1,51]=1.02$, p =. 32). There was a significant Task by Group interaction for the right ITG ($F[1,51]=8.38$, p =.006), but not for the right FG ($F[1,51]=1.23$, p=.27). A post hoc ANCOVA showed that the right ITG was more activated in NC1 than NC2 during the object task (F[1, 26]=6.18, p=.02) (Cf. Figures 3c, d), but there were no differences during the face task.

Analyses with ROIs defined in NC2

The robustness of the main finding was tested by reversing the process, and defining the ROIs in NC2 and then applying those definitions to a comparison between NC1 and the Autism group (using one-tailed tests for the directional hypotheses involving the right FG and right ITG). These new analyses also employed a left FG, a left ITG, and left and right PHG ROIs.

The comparison between NC1 and the Autism group revealed a significant task by group interaction for the right ITG (F[1, 51]=4.62, p =.018). Post hoc analyses indicated that NC1 used the right ITG more during the object task than did the Autism group (F[1, 25]=3.55, p=.035), as had been found in the NC1 vs. NC2 comparison just described. While the Autism group showed higher mean levels of right ITG activation than NC1 during the face task, this result did not reach statistical significance (F[1, 25]=2.19, p=.076). There was, however, a significant task by group interaction for the left ITG (F[1, 51]=9.31, p=.004). Post hoc analyses showed that the Autism group used the left ITG significantly more than NC1 during face perception (F[1, 25]=7.37, p=.012), but not during the object task. Thus, this part of the replication study confirmed that the Autism group used the ITG more perceptual processing of objects in persons free from social disability.

Consistent with all prior studies on face perception, each control group showed focal areas of activation in the right FG during face discrimination, while the Autism group did not. Although there were no significant differences in the right FG activation between NC1 and NC2, the composite maps show that it was relatively more focal and anterior in NC2 than the controls for face perception, but the effect switched from the right to left hemisphere (NB:, the left ITG was not examined in the first set of analyses because the composite maps for NC1 were strongly lateralized to the right ITG for object processing).

Although NC1 also showed greater right FG activation during the face task and less during the object task compared to the Autism group, the interaction addressing this comparison failed to reach statistical significance (F[1, 51]=2.52, p=.059). Examination of the activation maps (Figure 3a, c, and e) indicates that while both NC1 and NC2 strongly activated the right FG, the center of the activation was more anterior in NC2. Thus, even though there is clear right ITG and little or not right FG in the Autism group during face discrimination, when the right FG ROI was defined as more anterior by reference to NC2, there were no statistically significant results comparing NC1 and Autism.

In addition, there were no significant main or interaction effects for the left FG (p's > .10), the right PHG (p's > .25). Although there was not a significant main effect for the left PHG (p's ≥ .09), there was a significant task by group interaction (F[1, 51]=4.58, p=.037); post hoc analyses showed significantly greater left PHG activation for the Autism group vs. NC1 during object discrimination (F[1, 25]=5.47, p=.028), but not during face discrimination.

COMMENT

We found significant differences in the pattern of brain activations during face discrimination among individuals with autism and AS compared to two different control groups. The primary difference involved increased activity in the ITG during the discrimination of faces in the Autism group compared to two separate control groups; however, in one comparison the effect was significant for the left ITG, while for the other it was significant for the right ITG. Although the issue of laterality will need to be clarified by future studies, the important discovery is that persons with autism or AS used their ITG more than controls when they processed faces. Among the controls, the ITG was the area most strongly associated with object-specific perceptual discriminations. These results, therefore, suggest that the perceptual processing of faces in autism spectrum conditions is more like the

than NC1 (see Figure 3a and c). This difference may account for the fact that the Autism group showed significantly less right FG activation to faces when this ROI was defined in NC1 but not when defined in NC2. Moreover, the probability value in the latter analyses just missed criteria for significance. One possibility is that with a slightly larger sample both sets of analyses might have found significantly reduced right FG activation during face perception in the Autism group.

Several explanations might account for these results. First, it is likely that individuals with an autism spectrum disorder process faces in a different manner than normal subjects, relying more on feature-based than configural analyses[10,11]. The reduced FG and increased ITG activation may relate to such a difference since the FG appears specialized for configural processing[4,5,18]. Feature level processing, on the other hand, is observed with nonface objects and activation of regions that flank the FG[4,18,21,22,28-33]. Such differences in perceptual style among persons with autism would be consistent with a selective lack of expertise for faces. This hypothesis is strengthened by the recent results of Gauthier and colleagues[18] who showed that development of expertise for a class of novel objects is associated with an increase in FG related activity in the same area engaged by faces. A critical test of this hypothesis in persons with autism might be a pre- and post-imaging study with a training program that increases perceptual expertise for faces.

Second, there may be a more general cognitive-perceptual disturbance affecting face and object perception, as has been hypothesized by Uta Frith[47,48] (see also Mottron et al.[49,50]). Frith proposes that abnormal cognitive function in autism is due to "weak central coherence", a cognitive processing style that favors piecemeal analysis over configural processing. In fact, a deficit beyond face perception is suggested by the current DSM[51] which lists "persistent preoccupation with parts of objects" as one symptom of both AS and autism. However, the autism research literature suggests that deficits are probably confined to faces and do not generalize to nonface objects[8-13]. Future studies could test face-specific and more general perceptual hypotheses by, for example, tracking eye movements and analyzing the manner and path by which pictures of faces and other stimuli are scanned. Eye tracking is also now discrimination across time. It is known that the ventral temporal visual areas are quite plastic and can be shaped by early experiences[34,52,53,67,68]. In fact, these areas have dense reciprocal connections with the amygdala[56]. Inadequate attention to faces during critical periods of cortical development might effect the maturation of these areas. A developmental hypothesis involving an interaction between limbic possible during fMRI; this would allow correlation of configural *vs*. segmental strategies with activation in the FG *vs.* neighboring regions.

With our data, it is not possible to know whether the differences in brain activations reflect differences in perceptual "strategy" in the context of biologically intact perceptual systems, or whether the differences are an emergent property of perturbed neurobiology. These findings could be due to fundamental problems in the FG and associated structures, necessitating compensatory processing by neighboring regions. Current models suggest that columns of neurons with similar selectivities for higher visual dimensions (e.g., shape) cluster together in patches[52]. Patches that respond to canonical features of faces and nonface objects form interconnected ensembles for recognition[34,53]. It is possible that autism and AS involve a congenital abnormality in face ensembles within the FG region. However, examination of structural MRI scans of the patients and controls in this study conducted independently by two experienced neuroradiologists blind to participant diagnosis failed to find any abnormalities in the morphology, symmetry or gray scale intensity of the FG. This being so, it is still possible that more subtle morphometric differences exist that can only be revealed with careful quantitative measurement from MRI or postmortem tissue.

It is also possible that the primary pathology lies outside the ventral cortices, in regions that connect to and influence the function of the FG. Although less parsimonious, this hypothesis gains support from an intriguing body of data on medial temporal lobe structures, particularly the amygdala. The amygdala is implicated in a variety of inter-related functions, each with relevance to face perception and autism, including: visual-reward association ("emotional") learning[54,55], signaling the emotional salience of events[55,56], social behavior[57-60] and the perception of faces and facial expressions[60-62]. Moreover, postmortem studies have found that the amygdala and related limbic system structures are structurally abnormal in autism (AS has not been studied)[63], and most theoretical models of autism postulate a key role for the amygdala[56,63-66]. The amygdala's role in the development of face recognition skills may be in signaling the emotional salience of a face, thereby motivating the development of expertise in face and cortical regions might also explain why nonhuman primates with lesions to the amygdalae shortly after birth don't show social-emotional changes reminiscent of autism for many months[66]. Moreover, neonatal lesions to the medial temporal lobe of monkeys have been shown to produce distal changes in the frontal cortex in adulthood[69,70], suggesting that similar effects could be found in

other areas with especially strong connectivity, such as temporal visual areas.

While the current study showed diminished face-related right FG activation and increased ITG activation in the Autism group, there were no consistent or replicable differences between patients and controls during object processing (save the stronger right ITG activation in NC1 *vs.* both Autism and NC2). The variability in object activation seen in this study is not atypical[25,30-32,71,72], and it may be related to the heterogeneous set of objects employed. Objects with different physical properties and functional attributes may engage different ensembles of neurons for higher level perception, leading to more widely scattered activations[21,71,72]. More systematic study of the properties and attributes of objects are needed to delineate the contributions of different ventral temporal lobe regions in healthy subjects. This would set the stage for studies designed to test the specificity of perceptual differences in autism.

The current study had several limitations. First, although three-quarters of all individuals with autism are mentally retarded[1], our sample had an average IQ of 109 (lower IQ subjects moved during scanning). We do not know if these results will extend to lower IQ subjects. Second, the patient group was comprised of participants with autism and AS. Although we found no differences in brain activation between the groups, further work with larger samples will need to explore this issue in depth. Third, there may be neuroanatomical abnormalities in autism spectrum conditions that impact the accuracy of the brain warping procedures used to create the composite activation maps. Future studies should consider defining areas of activation individually, by hand tracing the relevant anatomy, perhaps in combination with approaches that first localize face and object selective ROIs through independent measurement[4,18]. Fourth, the task design and imaging sequence that we employed could be improved. Because of concerns that patients would have difficulty with task switches (a potential executive function problem), we chose to separate object and face tasks into different runs. In hindsight, movement between runs is probably more of a concern (because it contributed noise to our measurements) than multiple task switches within a run, especially since the patients who had most difficulty with task switches failed the procedure anyway because of movement. Finally, the inferior temporal cortex is a challenging area to obtain strong fMRI signal, especially in anterior lateral and anterior mesial regions where susceptibility problems are prevalent, but even in posterior areas, as evidenced by the fairly large standard errors of the mean for our ROIs (see Figure 4). While T2* averages about 60 ms in more superior brain areas, it can be as much as 70% shorter in inferior temporal regions (Gatenby & Schultz, unpublished) resulting in weaker BOLD effects and spatial distortions[73]. This is especially true in the amygdala, and thus we were not able to test its role in our results. Potential solutions include use of a shorter TE or an asymmetrical spin echo pulse sequence, more signal averaging (i.e., more images/run and more runs) to boost the signal to noise ratio, gradient coil shimming tailored to individual subjects, and a coronal orientation for studies with anisotropic voxels[73].

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