ORIGINAL ARTICLE

Abnormal Ventral Temporal Cortical Activity During Face Discrimination Among Individuals With Autism and Asperger Syndrome

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Background: Recognition of individual faces is an integral part of both interpersonal interactions and successful functioning within a social group. Therefore, it is 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 with 2 groups of matched normal controls (normal control group 1 [NC1] and normal control group 2 [NC2]) (n = 14 for each). Regions of interest (ROIs) were defined in NC1 and then applied in comparisons between NC2 and the autism group. Regions of interest 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 × 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 control groups, but for these analyses, the effect was now on the left side. 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.

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

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However, the effect size for this deficit may be modest, and at least one study failed to find overall performance differences between groups.[15] Depending on the methods used 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 per-

SUBJECTS AND METHODS

SUBJECTS

Right-handed male subjects with a clinical diagnosis of autism or AS were recruited from the Yale Child Study Center Autism Clinic, New Haven, Conn, 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]) (C. Lord, PhD, M. Rutter, MD, and P.C. Dilavore, PhD, Autism Diagnostic Observation Schedule [unpublished version], 1996).[36] Eight of the 14 subjects met the ADI-R and *International Classification of Diseases, 10th Revision (ICD-10)*,[37] criteria for autism, while 6 satisfied the *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 IQ [FSIQ][39-41]). All 14 met the ADI-R social, motor, and stereotypy criteria for autism, with the main difference being that the AS subjects did not meet the age-of-onset criteria for autism (**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, verbal IQ (VIQ), or performance IQ (PIQ) (P>.20 for all 3), 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 less than 100 (A.K., unpublished data, 1997-1999). Initial analyses of fMRI data employed both subgroups, but because there were no significant subgroup differences on any fMRI measure (P>.50 for all comparisons) subjects were collapsed into 1 patient group for all subsequent analyses (hereafter referred to as the autism group). Four of the 14 patients were taking a daily medication at the time of fMRI (selective serotonin reuptake inhibitors [n = 3] or haloperidol [n = 1]). There were no significant differences for any fMRI activation variable between the patients taking vs not taking medications (P>.85 for all).

For the comparison group, 28 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 (hereafter referred to as NC1 and NC2), which were group-matched on age and FSIQ to each other and to the autism group. Initially, 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>.50 for all) from each other on age, IQ scores, or movement during the fMRI procedure (**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" (**Figure 1**). Each of the 4 runs was composed of 3 blocks (41 seconds each, with an 8-second rest between blocks) in an ABA design, with 7 image pairs per block. Pilot data on 15 controls and 4 patients outside the magnet were used to set the stimulus duration at 4 seconds and the interstimulus interval at 2 seconds (faster presentation rates provoked anxiety in patients and younger subjects), and to select image pairs that were of equal difficulty across the 3 tasks. The tasks were not optimized to document object vs face perceptual accuracy in autism (eg, the total item number was low, and the response interval was long enough for subjects to succeed on most items). Rather, task parameters were selected to drive the perceptual systems engaged during successful face and object discrimination.

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 (eg, chair vs chair but never chair vs bottle) to control for the possibility that patients with autism differ from normal controls 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-sex pairs of neutral/nonexpressive 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 (ie, 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.

ception 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*).[16,21] 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 (eg, 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 (eg, the lower face and mouth area) than the overall configuration.[10,11] Consistent with this, numer-

IMAGE ACQUISITION

Imaging was performed with GE Signa 1.5-T MRI scanner with a standard quadrature head coil equipped for echo-planar imaging (Advanced NMR, Wilmington, Mass). 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. The 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 (**Figure 2**). Functional images were acquired using a gradient-echo, single-shot echo-planar sequence (repetition time, 1500 milliseconds; echo time, 60 milliseconds; flip angle, 60°; 92 images per slice; number of excitations, 1; voxel size, 3.125 × 3.125 × 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 dropout and spatial distortions were severe enough that data rostral to the posterior commissure were not analyzed and were masked in the composite maps (**Figure 3**) because they are likely inaccurate and misleading. Data analyses therefore focused on posterior temporoccipital areas only, which seems sensible, since this is where activations have been consistently reported in prior studies.[4,21-33]

IMAGE PROCESSING AND MEASUREMENT OF ROI ACTIVITY

Motion correction software, SPM 96 (Statistical Parametric Mapping 96),[45] was used to reregister images within a run and to decorrelate each pixel's time course with estimated motion parameters. Data were smoothed with a gaussian filter (full width half maximum, 6.25 mm), and images were transformed into a common space using a piecewise linear warping of 6 brain subvolumes for between-subject averaging. Pixel intensities during each primary task (face or object discrimination) were compared with 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 significance, but rather they were used as an outcome variable that 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* 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 anatomical images (Figure 3), with the threshold at a value (0.15) that subjectively seemed to best illustrate the significant findings from the analyses of covariance (ANCOVAs) presented below. Regions of interest were formed by superimposing a proportional grid system of the same resolution as the Talairach system (approximately 8 × 8-mm grid boxes) onto the activation maps. Region of interest definitions were established in the NC1 group by combining grid boxes to enclose the strongest areas of activation (Figure 3, A and 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. 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 (eg, 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 0. 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.

STATISTICAL ANALYSES

Analyses of covariance were used to test for main effects of task (object vs face), group (autism vs control), and task × group interactions, covarying both overall activation and task performance. However, task performance was dropped from the final model in every instance because it did not contribute significantly to any analysis ($P>.50$ for all). **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 level for significance was set at $\alpha = .05$.

ous 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.

We used functional magnetic resonance imaging (fMRI) to examine brain-activation patterns while subjects with autism or AS were making perceptual judgments on pairs of faces or objects. It is well documented that the fusiform gyrus (FG) responds preferentially to faces.[4,18,21-27] 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 the parahippocampal gyri (PHG), seem to be involved in common object perception.[4,18,21,22,28-33] However, anatomical specializations seem 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

Table 1. Scores for the ADI-R and the Vineland Adaptive Behavior Scale

	Autism Spectrum Groups, Mean (SD) [Range]		
	Combined Group (n = 14)	Autism Subgroup (n = 8)	Asperger Syndrome Subgroup (n = 6)
ADI-R Social Domain (cutoff 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 (cutoff 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 (cutoff for autism, 3)	6.7 (2.6) [3-11]	7.3 (2.6) [3-11]	5.8 (2.6) [3-10]
ADI-R Onset (cutoff 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]

**ADI-R indicates Autism Diagnostic Interview–Revised; SS, standard score.*

Table 2. Subject Characterization

	Normal Control Group 1 (n = 14)	Normal Control Group 2 (n = 14)	Autism Group (n = 14)
Age, y	21.7 (7.2)	21.5 (10.6)	23.8 (12.4)
FSIQ score	110.4 (17.2)	108.7 (16.3)	109.1 (19.5)
VIQ score	111.2 (18.4)	112.4 (15.4)	117.1 (19.7)
PIQ score	103.9 (13.2)	102.5 (16.5)	97.6 (19.0)
Movement, pixels			
During object pattern runs	0.21 (0.09)	0.17 (0.09)	0.20 (0.09)
During face pattern runs	0.22 (0.11)	0.20 (0.11)	0.20 (0.09)

**Values are presented as mean (SD). FSIQ indicates full-scale IQ; VIQ, verbal IQ; and PIQ, performance IQ. The FSIQ was prorated from abbreviated forms of the Wechsler Intelligence Scale for Children and the Wechsler Adult Intelligence Scale–Revised (Block Design, Picture Completion, Vocabulary, and Information subtests) that correlate with the full form at* $r \geq 0.90$ *(Sattler[41]).*

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 2 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.

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 the NC1 group compared with the other 2 groups ($P<.05$ for all), but this result is of questionable practical significance since each group averaged more than 95% correct. There were no significant face task performance differences between the control groups or between the NC1 group and the autism group, but the NC2 group performed significantly better than the autism group.

ANALYSES WITH ROIs DEFINED IN THE NC1 GROUP

Analysis of covariance was used to test the main hypothesis that the NC2 group and the autism group would differ in the pattern of brain activation during object vs face perception. These analyses revealed significant task × group interactions for the right ITG ($F_{1,51} = 4.78$; $P = .03$) 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 the NC2 group on the face task ($F_{1,51} = 3.75$; $P = .04$), but not on the object task ($F_{1,51} = 0.67$; $P = .43$). The NC2 group showed significantly more right FG activation than the autism group on the face task ($F_{1,51} = 5.14$; $P = .01$), but not on the object task ($F_{1,51} = 0.67$; $P = .52$).

The pattern of activations in Figure 3 confirms these ROI analyses (eg, compare the right ITG and FG activations in Figure 3, A and E). Talairach coordinates for the center of the face selective activation in the right FG of the NC1 group (+38*x*, –58*y*, –10*z*) and of the NC2 group (+36*x*, –50*y*, –10*z*) are consistent with those in prior normative studies.[18] In contrast, the center of activation during the selection for the autism group (+48*x*, –48*y*, –14*z*) was most similar to the center of activation in the ITG during object perception for the NC1 group (+48*x*, –52*y*, –14*z*). Although a scattering of other activity in response to faces can be seen in Figure 3 (eg, cerebellar vermis in the NC1 group 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 be predicted by the size of brain activations. These analyses are limited by the restricted range of the performance data, but they are nonetheless consistent with the group comparisons. The correlation between amount of right FG activation and performance on the face task was positive but failed to reach significance among the controls ($r = 0.35$, $P = .07$) and among the patients ($r = 0.15$, $P = .62$). In contrast, right FG activation was

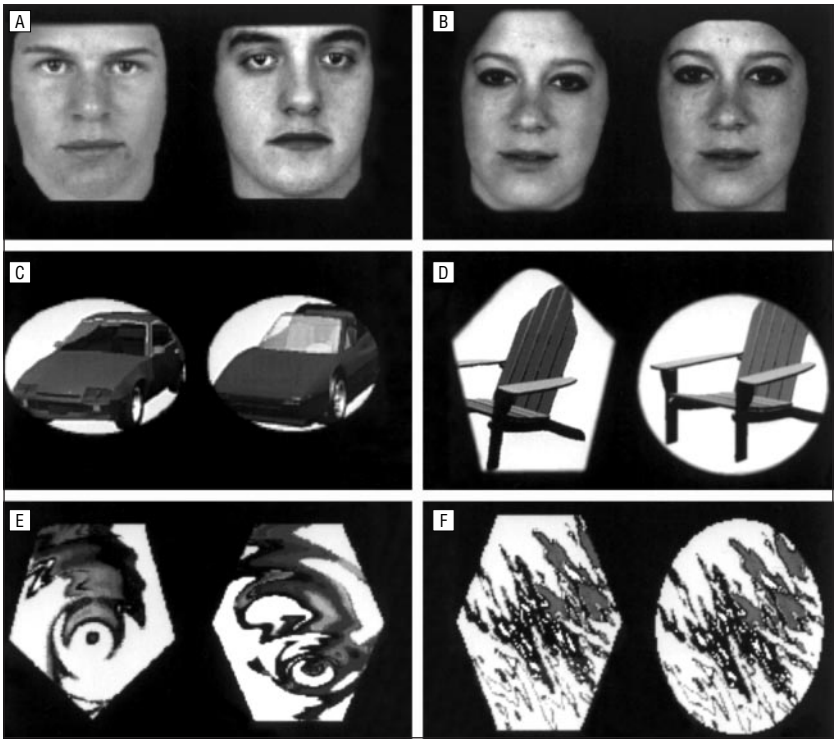

Figure 1. *Examples of stimulus pairs used in the face, object, and pattern tasks. For each stimulus type, the pair on the left is "different" while the one on the right is the "same."*

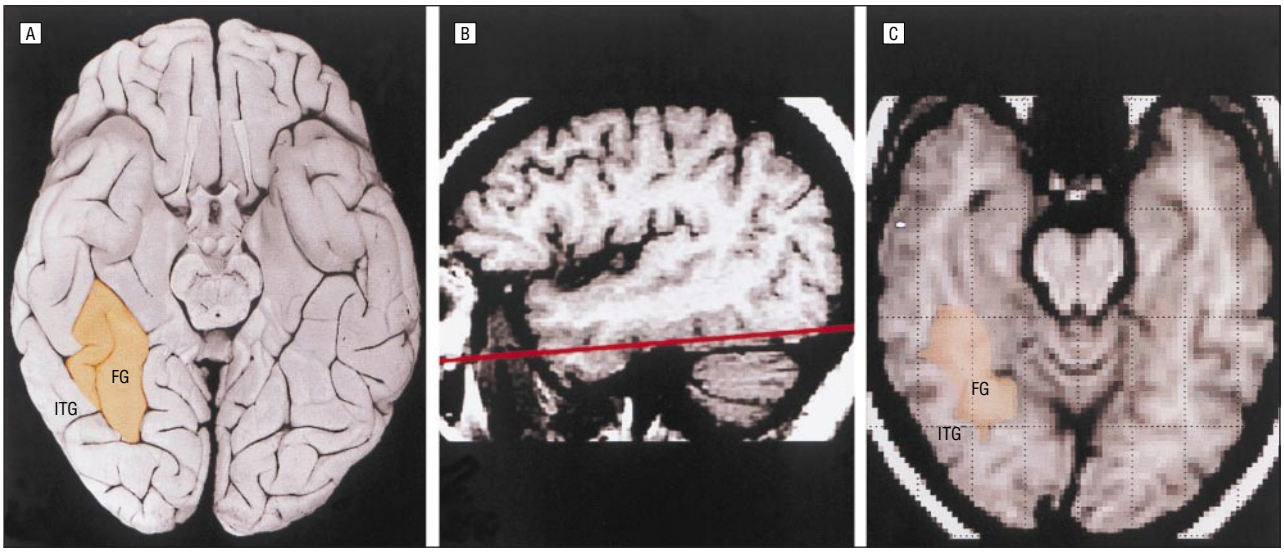

Figure 2. *Ventral temporal-occipital neuroanatomy. A, Illustration of the fusiform gyrus (FG) and inferior temporal gyrus (ITG) in a brain examined postmortem. B, Demonstration of the magnetic resonance imaging slice selection used to maximally capture the FG. C, An example of an oblique axial magnetic resonance imaging scan through the ventral temporal-occipital cortex.*

significantly correlated with object perception among the patients ($r = 0.74$, $P = .002$), but not among the controls ($r = 0.04$, $P = .84$). Right ITG activation was not significantly correlated with task performance inside the magnet in either group, but in patients it was correlated with a test of face perception administered outside the magnet (Benton Face Recognition Test) ($r = 0.68$, $P = .01$).

Analysis of covariance tested the reproducibility of the activations in the NC1 and NC2 groups. 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 × 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 the NC1 group than the NC2 group during the object task ($F_{1,26} = 6.18$, $P = .02$) (Figure 3, C and D), but there were no differences during the face task.

ANALYSES WITH ROIs DEFINED IN THE NC2 GROUP

The robustness of the main finding was tested by reversing the process and defining the ROIs in the NC2 group, and applying those definitions to a comparison

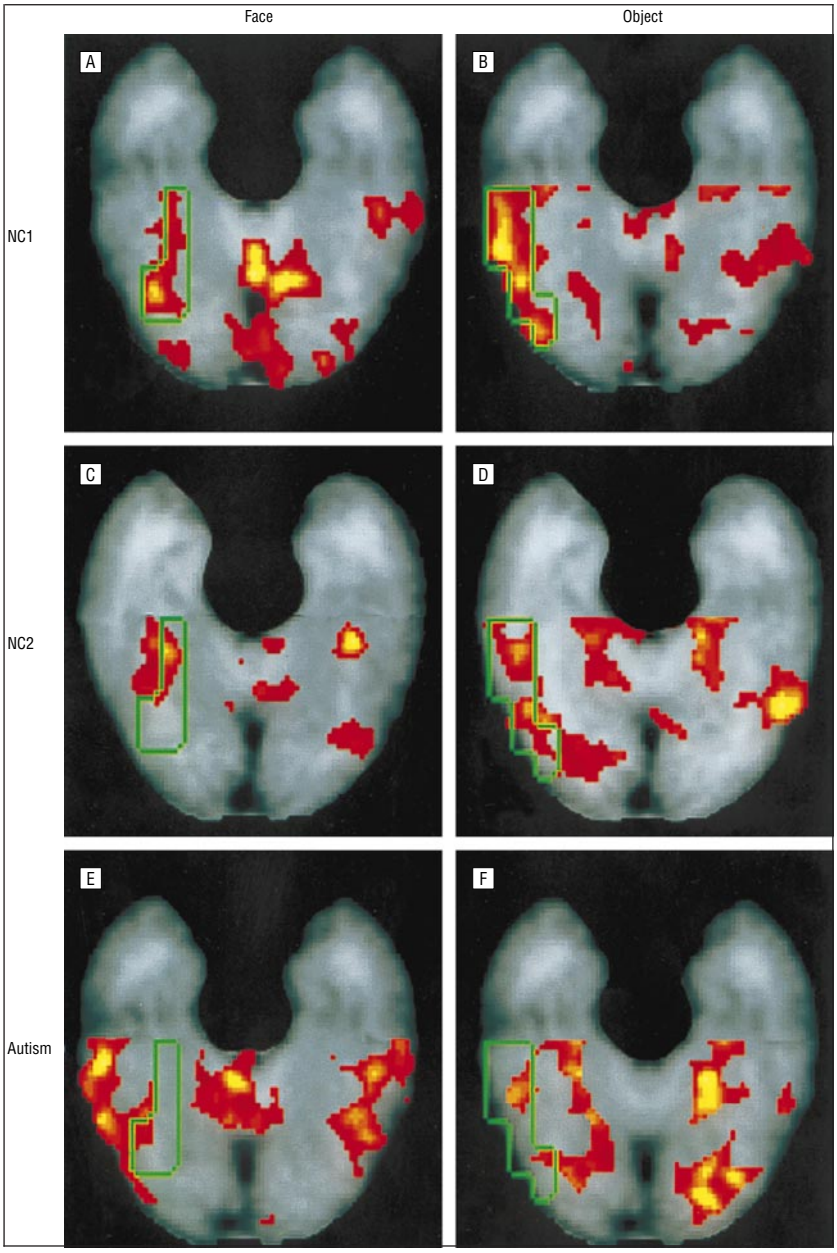

Figure 3. *Composite activation maps superimposed on averaged anatomical images by group and task using regions of interest defined in normal control group 1 (NC1) (A, B) are outlined in green on each map. Activations in normal control group 2 (NC2) (C, D) are not significantly different from those in NC1. Right and left are reversed by radiologic convention. Note the inferior temporal gyrus activity during face processing in the autism group (E, F).*

between the NC1 group and the autism group (using 1-tailed tests for the directional hypotheses involving the right FG and right ITG). These new analyses also employed left FG, left ITG, and left and right PHG ROIs, because these were areas of strong activation in the NC2 group.

The comparison between the NC1 group and the autism group revealed a significant task × group interaction for the right ITG ($F_{1,51} = 4.62$, $P = .02$). Post hoc analyses indicated that those in the NC1 group used the right ITG more during the object task than did those in the autism group ($F_{1,25} = 3.55$, $P = .04$), as in the NC1 vs NC2 comparison just described. While the autism group showed higher mean levels of right ITG activation than the NC1 group during the face task, this result did not reach significance ($F_{1,25} = 2.19$, $P = .08$). However, there was a significant task × 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 the NC1 group during face perception ($F_{1,25} = 7.37$, $P = .01$), but not during the object task. Thus, this part of the replication study confirmed that the autism group used the ITG more than the controls for face perception, but the effect switched from the right to the left hemisphere (the left ITG was not examined in the first set of analyses because the composite maps for the NC1 group were strongly lateralized to the right ITG for object processing).

Although the NC1 group also showed greater right FG activation during the face task and less during the object task compared with the autism group, the interaction addressing this comparison failed to reach significance ($F_{1,51} = 2.52$, $P = .06$). Examination of the activation maps (Figure 3, A, C, and E) indicates that while the right FG was strongly activated in both the NC1 and NC2 groups, the center of the activation was more anterior in the NC2

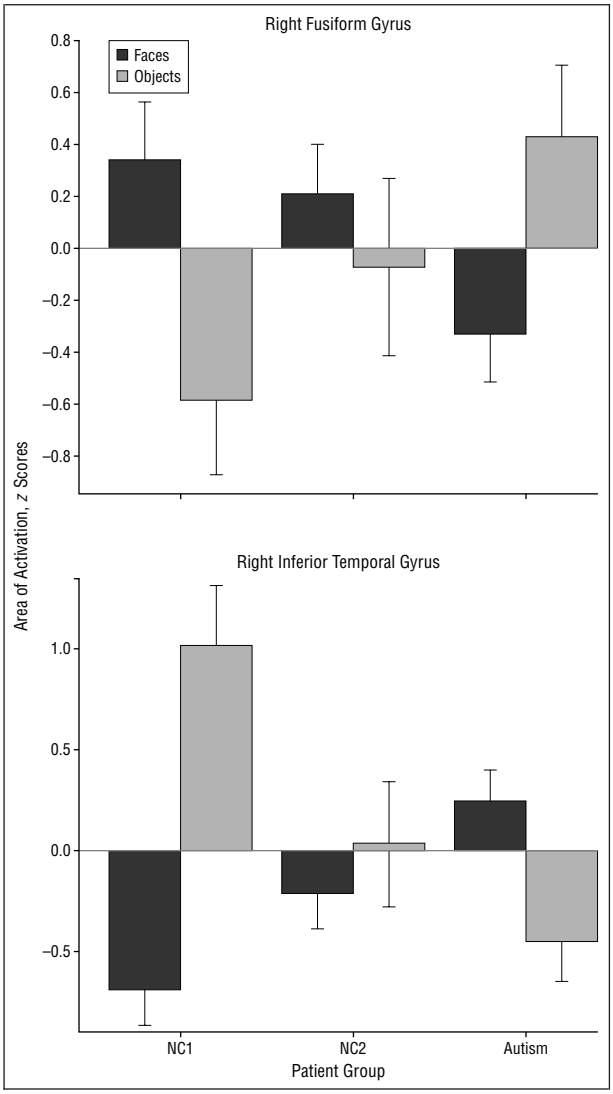

Figure 4. *Area of activation (standardized residual scores after partialling out global activation, mean ± SE) by group (n = 14 in each) and task. Analysis of covariance revealed significant task × group interactions (see the "Statistical Analyses" subsection of the "Subjects and Methods" section). NC1 indicates normal control group 1; NC2, normal control group 2.*

group. Thus, even though there is clear right ITG activation and little or no right FG activation in the autism group during face discrimination, when the right FG ROI was defined as more anterior, there were no significant results comparing the NC1 and autism groups.

In addition, there were no significant main or interaction effects for the left FG ($P>.10$ for all) or the right PHG ($P>.25$ for all). Although there was not a significant main effect for the left PHG ($P\geq.09$), there was a significant task × group interaction ($F_{1,51} = 4.58$, $P = .04$); post hoc analyses showed significantly greater left PHG activation for the autism group vs the NC1 group during object discrimination ($F_{1,25} = 5.47$, $P = .03$), but not during face discrimination.

COMMENT

We found significant differences in the pattern of brain activation during face discrimination among individuals with autism and AS compared with 2 different control groups. The primary difference involved increased activity in the ITG during the discrimination of faces in the autism group compared with 2 separate control groups; however, in one comparison the effect was significant for the left ITG, while in 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 did when they processed faces. Among the controls, the ITG was the area most strongly associated with object-specific perceptual discriminations. Therefore, these results suggest that the perceptual processing of faces in autism spectrum conditions is more like the 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 right FG activation between the NC1 and NC2 groups, the composite maps show that it was relatively more focal and anterior in the NC2 group than the NC1 group (Figure 3, A and C). This difference may account for the fact that the autism group showed significantly less right FG activation during face discrimination when this ROI was defined in the NC1 group but not when defined in the NC2 group. Moreover, the probability value in the latter analyses just missed the 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

Table 3. Functional Magnetic Resonance Imaging Task Performance*

	Normal Control Group 1 (n = 14)	Normal Control Group 2 (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* = .08 *t* = 0.47, *P* = .64§ *t* = 2.06, *P* = .05‖ *t* = 1.58, *P* = .12¶
Object correct, %	100.0 (0.0)	97.1 (3.4)	95.9 (5.4)	F = 4.55, *P* = .02 *t* = 3.20, *P* = .004§ *t* = 2.83, *P* = .009‖ *t* = 0.69, *P* = .50¶
Face correct, %	83.7 (14.4)	86.7 (9.2)	76.0 (13.6)	F = 2.66, *P* = .08 *t* = −0.66, *P* = .51§ *t* = 1.45, *P* = .16‖ *t* = 2.43, *P* = .02¶

**Values are presented as mean (SD) unless otherwise indicated. ANOVAs indicates analyses of variance.*
†*For all ANOVAs, the degrees of freedom were 2, 41.*
‡*For all* t *tests, the degrees of freedom were 1, 26.*
§*For normal control group 1 vs normal control group 2.*
‖*For normal control group 1 vs the autism group.*
¶*For normal control group 2 vs the autism group.*

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 seems 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 them having 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 might be an imaging study before and after a training program that increases perceptual expertise for faces in persons with autism.

Second, there may be a more general cognitive-perceptual disturbance affecting face and object perception, as hypothesized by Uta Frith[47,48] (see also Mottron et al[49,50]). Frith proposed that abnormal cognitive function in autism was caused by "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 *DSM-IV*,[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 cannot be generalized 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 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 activation 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 caused by 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 (eg, 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 2 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 interrelated functions, each with relevance to face perception and autism, including visual reward association ("emotional") learning,[54,55] signaling of 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 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 affect the maturation of these areas. A developmental hypothesis involving an interaction between limbic and cortical regions might also explain why nonhuman primates with lesions in the amygdala shortly after birth do not show social-emotional changes reminiscent of autism for many months.[66] Moreover, neonatal lesions in the medial temporal lobe of monkeys have been shown to produce distal changes in the frontal cortex in adulthood,[69,70] suggesting that similar distal effects could be found in other areas with especially strong connectivity to the amygdala, 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 (except for the stronger right ITG activation in the NC1 group vs both the autism and NC2 groups). 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 activation.[21,71,72] More systematic study of the properties and attributes of objects is 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 (subjects with lower IQs moved during scanning). We do not know if these results will extend to subjects with lower IQs. Second, the patient group was composed 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 affect 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 in which to obtain strong fMRI signal, especially in the anterior lateral and anterior mesial regions, where susceptibility problems are prevalent, but even in posterior areas, as evidenced by the fairly large SEMs for our ROIs (Figure 4). While T2* averages about 60 milliseconds in more superior brain areas, it can be as much as 70% shorter in inferior-temporal regions (C. Gatenby, PhD, and Robert T. Schultz, PhD, unpublished data, May 1998) 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 echo time or an asymmetrical spin-echo pulse sequence, more signal averaging (ie, more images per 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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