

fMRI activation of the fusiform gyrus and amygdala to cartoon characters but not to faces in a boy with autism

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Abstract

Abnormal hypoactivation in the amygdala and fusiform gyrus, brain areas that participate in face processing and social cognition, has consistently been demonstrated in persons with autism. We investigated activity in these areas in a boy with autism, DD, who had a special interest in “Digimon” cartoon characters. DD individuates Digimon faster than familiar faces and objects, but he individuates familiar faces no faster than objects. In contrast, a typically developing boy with an interest in “Pokémon” cartoon characters is equally fast at individuating faces and Pokémon and faster at individuating faces and Pokémon than objects and Digimon. In addition, using functional magnetic resonance imaging (fMRI), we show that DD activates his amygdala and fusiform gyrus for perceptual discriminations involving Digimon but not for those involving familiar or unfamiliar faces. This pattern of activation is not seen in the typically developing control with an interest in Pokémon or in a second comparison case who has autism but no interest in Digimon. These results have important implications for our understanding of autism, cortical face specialization, and the possible role of the amygdala in the development of perceptual expertise.

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1. Introduction and case history

Autism is a Pervasive Developmental Disorder (PDD) characterized by social impairments, deficits in the development of language, and the presence of stereotypic or repetitive behaviors (American Psychiatric Association, 1994). Individuals with autism also have significant deficits in face perception (reviewed in Grelotti, Gauthier, & Schultz, 2002). These deficits seem to be related to the social impairments at the core of autism (Klin, Sparrow, de Bildt, Cicchetti, Cohen,

Volkmar, 1999; Schultz, Gauthier, Klin, Fulbright, Anderson, Volkmar, et al., 2000a; Schultz, Romanski, & Tsatsanis, 2000b). The kinds of face recognition errors made by persons with autism suggest that they do not employ a normal configural or holistic face processing strategy (Hobson, Ouston, & Lee, 1988b; Joseph & Tanaka, 2002; Langdell, 1978).

Accompanying their deficits in face perception, persons with autism and related disorders show hypoactivation of the fusiform face area “FFA” in fMRI studies of face perception (Critchley et al., 2000; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Schultz et al., 2000a; Schultz et al., 2001; Hubl et al., 2003; Piggot et al., 2004; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004). In neuroimaging studies of typically developing individuals, no class of visual stimuli has been shown to activate the lateral aspect of the middle fusiform gyrus (FG), an occipito-temporal visual cortical

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area, more than the human face (Kanwisher, 2000), and it has come to be known as the FFA (Haxby et al., 1999; Kanwisher, McDermott, & Chun, 1997; Malach et al., 1995; Puce, Allison, Gore, & McCarthy, 1995). Face-selectivity is often taken as evidence for a neural module specific for face processing (Farah, Rabinowitz, Quinn, & Liu, 2000; Kanwisher et al., 1997; Kanwisher, 2000). The FFA roughly corresponds with the location of brain injury in some persons who have a face recognition defect known as prosopagnosia (e.g., Damasio, Tranel, & Damasio, 1990; Farah, Levinson, & Klein, 1995; Whiteley & Warrington, 1977). It is not known whether hypoactivation to faces in the FG of persons with autism is the result of a defect in the cortex or whether the underlying cortex is normal and an FFA fails to develop for some other reason.

Amygdala dysfunction is thought to be an important component of the neuropathology of autism (Bachevalier, 1994; Baron-Cohen et al., 1999; Adolphs, Sears, & Piven 2001; Bauman & Kemper, 1994; Schultz et al., 2000b). Perhaps the best evidence for this comes from postmortem studies which demonstrate that the neurons of the amygdala in persons with autism are smaller and more densely packed than normal and have stunted neuronal arborization (Bauman, 1996; Kemper & Bauman, 1998). Three published fMRI studies on the amygdala in autism seem to demonstrate the functional consequence of these pathological findings. Each has shown hypoactivation of the left amygdala during perceptual judgment tasks involving the face and/or facial expressions (Baron-Cohen et al., 1999; Critchley et al., 2000; Pierce et al., 2001). These findings appear to be related to known deficits in emotion perception among persons with autism and other pervasive developmental disorders (Adolphs & Tranel, 1999; Celani, Battacchi, & Arcidiacono, 1999; Fein, Lucci, Braverman, & Waterhouse, 1992; Hobson & Lee, 1989; Hobson, Ouston, & Lee, 1988a,b; Hobson et al., 1986a,b; Macdonald et al., 1989; Ozonoff, Pennington, & Rogers, 1990). Whether amygdala dysfunction in persons with autism extends to objects of a non-social nature has not been investigated.

It has been argued that because of developmental abnormalities in the acquisition of social cognition, persons with autism fail to find salience in social stimuli and instead find salience in physical stimuli such as objects (Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Klin, Jones, Schultz, & Volkmar, 2003). While social motivations and cognition fail, a person with autism may grow to value objects or other socially irrelevant aspects of the environment instead of interaction with other people (Klin et al., 2003). Accordingly, some persons with autism develop a special interest for objects of a restricted domain such as coins, stamps, etc. (Lord, Rutter, & Le Couteur, 1994; Mercier, Mottron, & Belleville, 2000).

It has been suggested that the FG (Pierce & Courchesne, 2000; Grelotti et al., 2002) and amygdala of individuals with autism might respond to their special interests despite a lack of activation to faces. Some fMRI studies suggest that cate-

gorical specialization in ventral temporal cortex is related to our experience with faces and the use of a subordinate level of categorization, i.e., individuation (Gauthier, Anderson, Tarr, Skudlarski, & Gore, 1997; Gauthier et al., 2000b; Tarr & Gauthier, 2000). For example, car experts, bird experts, and individuals trained to be experts at discriminating novel objects called “Greebles” all show enhanced FFA activation for the nonface objects for which they have visual expertise (Gauthier, Skudlarski, Gore, & Anderson, 2000a; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999b). Indeed, the lack of a normal configural processing strategy for faces in persons with autism suggests that they are face novices (Grelotti et al., 2002) and this lack of face expertise underlies observed neurofunctional abnormalities in the FFA (Schultz et al., 2000a).

We investigated these hypotheses in a boy with autism (DD, for “*DigiDestined*”) who is very interested in the animated “digital monsters” known as Digimon, cartoon characters of Japanese origin. Despite a lack of interest in other people, DD had a strong interest and preoccupation with Digimon. Given the salient nature of the cartoon characters to DD and his vast experience with them, we used images of Digimon as a probe to test for activity in DD’s FG and amygdala that might be greater than activity for other objects and faces.

This case study involved behavioral and fMRI studies of familiar and unfamiliar faces, common objects, and Digimon. In behavioral testing, we evaluated DD’s proficiency at individuating familiar faces, common objects, and Digimon. By comparing the relative speed at which DD could correctly characterize images of familiar faces, Digimon, and common objects at the subordinate level of categorization, we evaluated his perceptual expertise for faces and Digimon. DD’s behavioral response to Digimon, familiar faces, and common objects was juxtaposed with the neuroimaging results of two fMRI studies. These experiments provide insight into the nature of domain specificity in the FFA and the neuropathology of autism.

2. Methods

2.1. Participants

Three subjects participated in some or all of the experiments described herein. DD watched the Digimon television show daily for 2 years, knew most of the characters’ names, spoke of good, bad, and lucky Digimon, and wished to become a “*DigiDestined*” like the cartoon children who train Digimon on the television show. He was 11 years old at the time of initial testing, and 12 years old at follow-up. DD’s behavioral performance and fMRI activity was compared to two other boys matched to DD in different ways. CC, a 17-year-old boy with autism who did not have any interest in or experience with Digimon, was recruited to test whether the results would be common to persons with autism or more specific to DD because of his experience with Digimon. TDC,

Table 1
Patient characterization

	DD	CC	TDC	Cutoff criterion for the diagnosis of autism
ADI-R social domain	22	21		10
ADI-R communication domain	23	22		8
ADI-R stereotypy domain	7	4		3
ADI-R onset	5	3		1
ADOS communication algorithm	7	7		3
ADOS social interaction algorithm	14	14		6
ADOS combined algorithm	21	21		10
Vineland composite standard score	45	45		
WISC-III full scale IQ	69	65		
WISC-III verbal IQ	67	64		
WISC-III Performance IQ	74	71		
Benton test of face discrimination	33	27	39	
Age	11	17	10	

a 10-year-old typically developing male Pokémon enthusiast with above average intelligence who occasionally watched Digimon, was recruited as a comparison to test how his own expertise in Pokémon (a related but distinct group of cartoon characters) would compare to his expertise for faces in behavioral testing and to test how his response to Digimon would compare to his response to faces in imaging experiments. We started this research in the waning days of the Digimon popularity, and despite an active effort to recruit additional subjects, we found no other Digimon enthusiasts and no children other than TDC who knew the names of eight recurring Digimon characters required to complete behavioral testing.

The subjects were assessed with the Benton Test of Facial Recognition (Benton, Sivan, Hamsher, Varney, & Spreen, 1983) and, for the patients with autism, standard diagnostic instruments (see Table 1). A forced-choice verification test assessed perceptual expertise, and because it required knowledge of the names of Digimon characters, only DD and TDC were tested. DD underwent fMRI testing using two different protocols (one at his initial visit and one at follow-up), whereas CC was scanned in the first fMRI experiment, and because of special hypotheses regarding Digimon faces, TDC was scanned in the second fMRI experiment. Parents of the participants gave written, informed consent and all three participants gave written, informed assent for the procedures in accordance with protocols approved by the Human Investigations Committee at Yale University School of Medicine.

2.2. Forced-choice verification task

A forced-choice verification task included the following categories: familiar faces (six family members for DD and four family members and two friends for TDC), familiar nonface objects (four images of four species each of insects, flowers, birds, and dogs), Digimon (eight images of recurring Digimon characters), and, for TDC only, Pokémon (eight images of recurring Pokémon characters). Each stimulus was presented twice in each of two different experiments along

with a true or false label (e.g., the label ‘mom’ paired with a picture of the participant’s mother [true] or the label ‘augumon’ paired with a picture of the Digimon, Gabumon [false]). The stimuli were presented on the screen of a Macintosh G3 Powerbook computer and the participant responded true or false by key press. DD was concurrently read the labels aloud because of concerns about his ability to quickly read the labels. The same accommodation was made for TDC, but because in the first few trials TDC responded before the label was said in its entirety (his average response time was less than 1 s), he was not read the label aloud for the remainder of the trials. Images were color, displayed on a gray background, and presented randomly followed by a brief color mask for 0.050 s, and then followed by the label that stayed on as long as it took the participant to respond (experiments were written in PsyScope 1.2.5 PPC, Carnegie Mellon University, Pittsburgh, PA). The stimuli were presented twice in two different formats, following the methods of Tanaka (2001). In the “long” condition, the image was displayed for 0.950 s, and in the “short” condition, the image was presented for 0.075 s. In the short condition, the mask was followed 0.875 s of blank screen so that in both the short and long conditions, the word label appeared 1 s after the presentation of the image. Outliers were removed before accuracy and mean reaction times for each condition were analyzed. Analysis of variance (ANOVA) and independent samples *t*-tests (for post-hoc comparisons) were used to assess significance.

2.3. Neuroimaging parameters

Scanning was conducted at Yale University School of Medicine MRI Center in New Haven, Connecticut on a 1.5 T GE Signa scanner (LX operating system, Version 8.4) equipped for echo planar imaging. A gradient echo, single shot echo planar pulse sequence (TR = 1.5 s, TE = 40 ms, flip angle = 60°) was employed. Eighteen coronal oblique slices 9 mm thick with a 1 mm skip and a 3.125 mm × 3.125 mm in plane resolution were collected. This protocol was selected because it afforded whole brain coverage, but some amygdala data may have been lost due to volume averaging or loss of scanner signal. Partial voluming of the amygdala was minimized by positioning a slice through the center of the amygdala and aligning the acquisition in the anatomical plane of the amygdala (i.e., perpendicular to the long axis of the right hippocampus). Eighteen T1-weighted coronal oblique slices (TE = 14 ms, TR = 500 ms, field of view = 20 cm × 20 cm, slice thickness = 9 mm, gap = 1 mm, 192 × 192 data matrix) were acquired to serve as anatomical underlays for functional images collected at the same locations.

2.4. Neuroimaging tasks

Both DD and CC were scanned during the first imaging experiment (E1). In E1, black and white images of unfamiliar faces (cropped to remove hair but not head shape), Digimon, and nonface objects (an assortment of furniture)

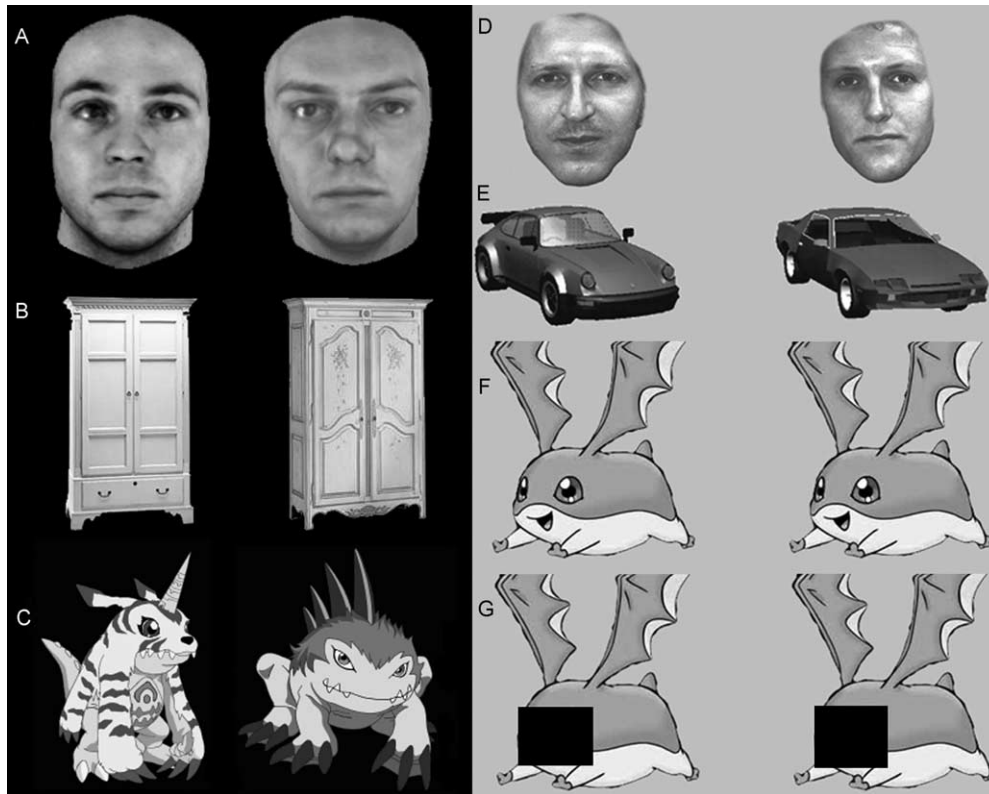


Fig. 1. Example stimuli pairs from E1 and E2. Stimulus pairs of faces, objects, and Digimon are displayed in A–C. Stimulus pairs of faces, objects, Digimon, and masked Digimon are displayed in D–G. Although the Digimon characters shown in C were paired during E1, the images used in the experiment were replaced by those displayed in this figure because we received permission only to publish these particular images of the characters. DIGIMON Digital Monsters © 2004 AKIYOSHI HONGO, TOEI ANIMATION. Co., LTD.

were back projected onto a translucent screen. They were presented side-by-side on a black background for 3.9 s, with a 0.3 s interstimulus interval, and were arranged into blocks of five image pairs (Fig. 1A–C). Each image was paired with an object from the same class or subclass. Each block was separated by a 12 s fixation period when “+ +” flashed on the screen three times, each with a duration of 3.6 s, separated by 0.4 s of blank screen. The participant was instructed to determine whether the two images were the same or different and to answer using a button box. There were three runs and three blocks of each image type per run arranged in a pseudorandom order. For the entire experiment, each task condition had 112 echo planar volumes, and the fixation baseline had 132 volumes.

A possible confounding factor to the interpretation of the findings from E1 was that DD was familiar with Digimon and that Digimon characters have faces; therefore, in order to test whether activation was related specifically to the face of the Digimon or DD’s familiarity with them, we invited DD back for another experiment (E2). E2 involved a comparison of intact Digimon, Digimon with their faces masked, different human faces, a separate “familiar” face condition, and nonface objects (Fig. 1D–G). TDC, who completed the behavioral experiments described above, was also scanned under the E2 protocol. In E2, black and white images of familiar faces (family members, teachers, and/or neighbors),

unfamiliar faces, Digimon, Digimon with faces masked by a dark gray strip (masked Digimon), and nonface objects (an assortment of cars, furniture, planes, etc.) were presented side-by-side on a light gray background for 3.3 s and arranged into blocks of five image pairs separated by 0.3 s (Fig. 1D–G). Each block was separated by a 10.5 s fixation period when “+ +”, “– –”, “+ –”, or “– +” flashed on the screen three times for 3.2 s, with each fixation separated by 0.3 s. Images were back projected onto a translucent screen. Faces were cropped to remove hair but not head shape. The participant was instructed to determine whether the two images were the same or different and to answer using a button box. There were three runs and two blocks of each stimulus type per run arranged in a pseudorandom order. The same correction for motion and linear drift in scanner signal was applied to these data. Each task condition contained 66 volumes with the exception of fixation which contained 108 volumes.

2.5. Data analysis

Motion correction software, SPM 99 (Wellcome Department of Cognitive Neurology, London, UK), was used to correct for motion between successive images within each run. For patient DD in E1, images from the last third of the second run (three blocks, one of each condition, and two blocks of fixation) were discarded due to excessive motion. Because of

expected habituation effects, analyses of the amygdala were done separately for each scan series. *t*-maps were generated from the mean percent signal change for each voxel (corrected for linear drift in scanner signal unrelated to the experiment) using software developed locally (Skudlarski, Constable, & Gore, 1999).

For each scan in E1 and E2, anatomically-defined regions of interest (ROIs) were created. No Talairach transformation, spatial smoothing, or correction for multiple comparisons was made in these hypothesis-driven analyses. The ROI boundaries for the FFA in the lateral aspect of the right FG were based on observed anatomy and anterior and posterior boundaries reported by past studies (see Table 1 in Gauthier et al., 1999b). Each participant's ROI encompassed two coronal oblique slices, and each ROI contained 29–32 voxels. ROIs for the right and left amygdala were from the single slice through the amygdala; data from right and left were analyzed separately, and each ROI contained 8–14 voxels. The differences in the number of voxels for each ROI are a result of anatomical variation between subjects, slight variations in acquisition for DD in E1 and E2, and, especially relevant for the amygdala, loss of signal due to susceptibility artifact. For each voxel in the FG ROIs, we obtained a mean percent signal change for each condition (i.e., unfamiliar face, Digimon, nonface objects, familiar face (in E2)) and masked Digimon (in E2) compared to fixation for the purpose of making statistical comparisons, each condition compared to object for the purpose of making figures, and a *t*-value for unfamiliar faces compared to nonface objects. For each voxel in the amygdala ROIs, we obtained a mean percent signal change for unfamiliar face and Digimon compared to fixation for the purpose of making statistical comparisons and figures. Data from voxels with low signal intensity, signifying loss of signal due to susceptibility artifact, were not analyzed. The remaining data were averaged to create the mean percent signal change for each region. Voxel-based paired samples *t*-tests were used to assess significance.

For the purposes of making parametric maps and determining Talairach coordinates of DD's results in E1, the corrected images were spatially smoothed using a Gaussian filter with a full width at half maximum of 6.25 mm. Talairach coordinates (Talairach & Tournoux, 1988) for the center of activation are given for the location of the activation with the highest *t*-value.

3. Results

3.1. Subject characterization and behavioral task performance

3.1.1. Neuropsychological and clinical evaluation

DD and CC met criteria for autism using all diagnostic instruments. The consensus of the experienced clinicians (AK, FRV) who evaluated the two patients was that they had a "classical" presentation, similar to those individuals with

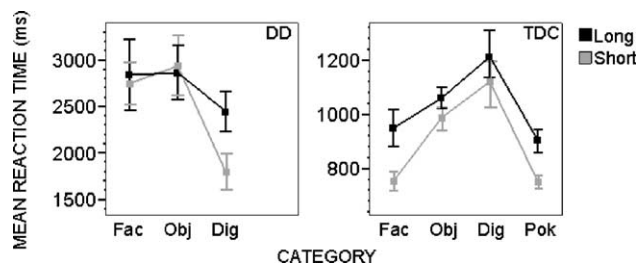


Fig. 2. The results of behavioral testing. DD and TDC's mean reaction times for correct answers in each category for both behavioral experiments. In the "short" experiment, images were presented for only 0.075 s. In the "long" experiment, images were presented for .950 s. "Fac" is face, "Obj" is object, "Dig" is Digimon, and "Pok" is Pokémon. Error bars represent standard error of the mean.

autism first described by Leo Kanner (1943). Clinicians using standard diagnostic instruments (i.e., the Autism Diagnostic Observation Schedule (ADOS) (Lord, Rutter, DiLavore, & Risi, 1999) and the Autism Diagnostic Interview—Revised (ADI-R) (Lord et al., 1994) documented the patients' stereotyped and idiosyncratic language, unusual prosody, poorly modulated eye contact and use of facial expressions, lack of social reciprocity, and restricted interests and stereotyped behaviors (Table 1). The similarity of their symptomatology underlies the similarity of their scores on these instruments. Consistent with reported face processing deficits in persons with autism, DD and CC were impaired in visuo-perceptual discrimination of unfamiliar faces as documented by the Benton Test of Face Recognition, whereas TDC's performance was normal for his age.

Although the differences in age between CC and DD and the differences in IQ between DD and TDC do not make for ideal comparisons, we have concentrated our interpretation of the data to comparing patterns of response within each subject rather than directly comparing subjects. Thus, we believe we have minimized the potentially confounding influence of age and IQ, which are factors whose influence on face-selectivity is currently unknown.

3.1.2. Forced-choice verification task

We used the forced-choice verification task to discern the relative speed at which DD and TDC individuate Digimon (and Pokémon for TDC), faces of persons well known to the participant, and nonface objects (i.e., common dogs, birds, flower, and insects) (Fig. 2). These tests required a familiarity with the labels for the common objects and Digimon presented; fortunately, TDC knew the names of the eight most popular Digimon although his real interest was Pokémon. TDC's performance was near perfect and made only two mistakes (Table 2). DD performed very well and achieved an accuracy of 75% or greater in each category (Table 2).

Although TDC was faster overall than DD (ANOVA, $F(1,204) = 169.00$, $P < 0.001$), this result is expected based on TDC's higher cognitive abilities; more informative for the questions addressed here are the differences in the relative speed at which the two cases responded to the different cate-

Table 2
Percent accuracy in forced choice verification task

	Subject			
	DD		TDC	
	Short ^a	Long ^a	Short ^a	Long ^a
Face	88	100	100	100
Object	88	75	97	100
Digimon	100	94	97	100
Pokémon			100	100

^a Condition.

gories (a significant subject by category interaction, $F(2,204) = 6.30$, $P = 0.002$). TDC was equally fast to individuate human faces and Pokémon ($t(52) = 0.49$; NS), and faster at individuating Pokémon and human faces than individuating objects (Pokémon: $t(83) = 4.32$, $P < 0.001$; faces: $t(75) = 3.12$, $P = 0.003$) or Digimon (Pokémon: $t(24) = 4.31$, $P < 0.001$; faces: $t(31) = 3.63$, $P = 0.001$). TDC was slowest with Digimon, which he did not individuate faster than common objects ($t(25) = 1.74$, $P = 0.094$). In contrast, DD was faster at individuating Digimon than both faces ($t(47) = 2.43$, $P = 0.019$) and common objects ($t(68) = 2.79$, $P = 0.007$). There was no difference in the speed at which he individuated faces and common objects ($t(60) = 0.29$, NS).

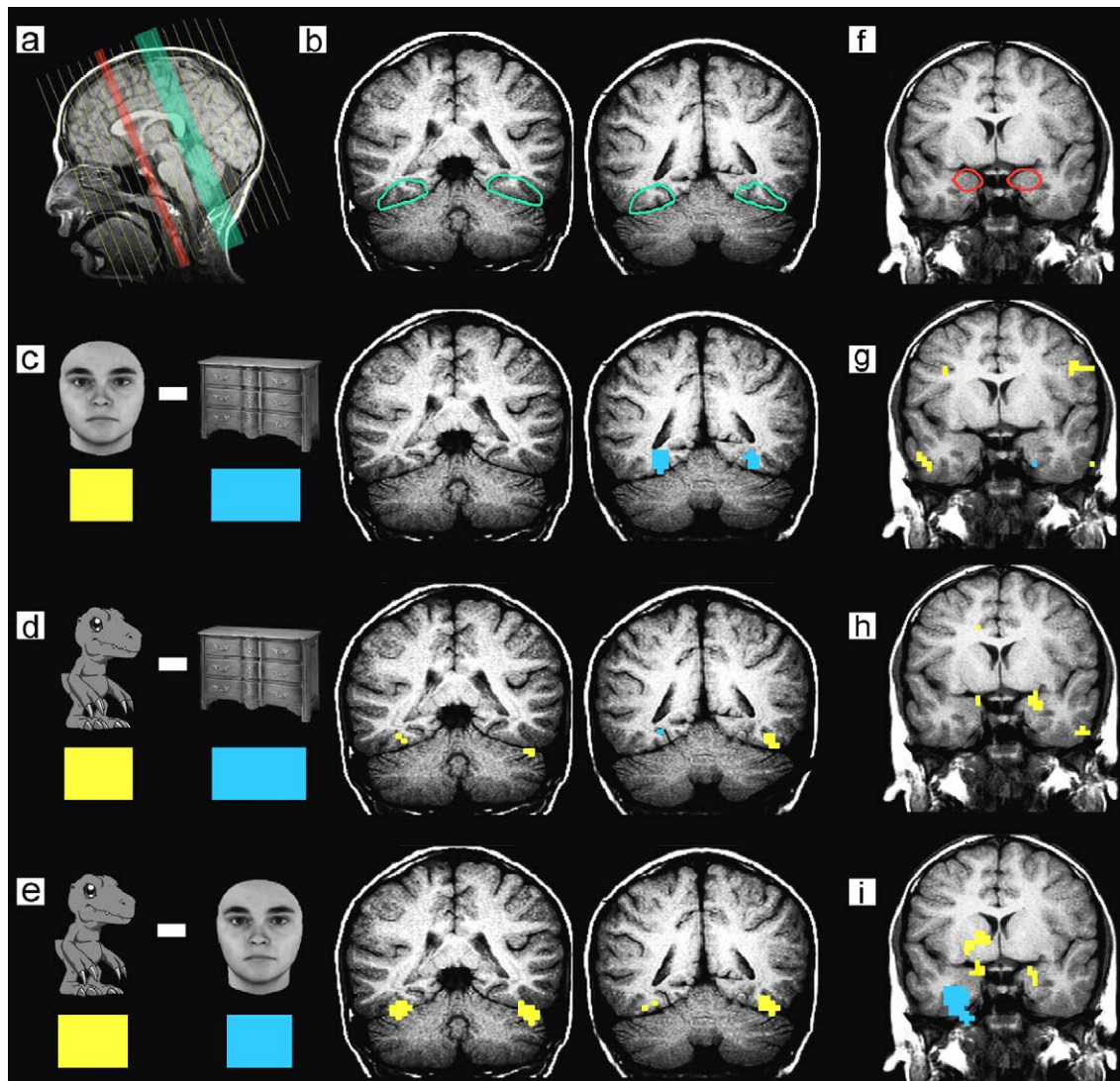


Fig. 3. Activation of the FG and amygdala to Digimon but not to faces in patient DD. The slices containing the FG are highlighted in green, A. The FG is outlined in green, B. Right and left are reversed by radiological convention. Voxels from E1 are colored if the smoothed data had a $t \geq 4$ (which corresponds to $P < 0.0001$ uncorrected). Activation of the medial aspect of the FG to objects is blue and evident in both comparisons with faces, C, and Digimon, D. Digimon activations in the lateral FG (i.e., the location of the would-be FFA) are yellow and evident in comparisons with objects, D, and faces, E. The right and left amygdala are outlined in red, F. Again, right and left are reversed by radiological convention. Whereas no voxel in the amygdala was active when faces and objects were compared, G, Digimon activations in the right and left amygdala are yellow and evident in comparisons with objects, H, and faces, I. DIGIMON Digital Monsters © 2004 AKIYOSHI HONGO, TOEI ANIMATION. Co., LTD.

3.1.3. Behavioral data from E1 and E2

Analysis of data from the same–different judgment tasks collected while the participants were being scanned demonstrates that each participant was engaged in the task and could perform it well. Whereas we monitored DD's responses during E1, no responses were recorded as a result of a faulty connection to the computer attached to the button box. DD's accuracy in E2 was quite good, and although we do not have the data for E1, we assume his performance in E1 was similar to that of E2. Although the subjects with autism discriminated faces less well than objects from the other categories, accuracy for each subject for each condition was 75% or greater.

3.2. Neuroimaging

3.2.1. Activation of the fusiform gyrus

A *t*-map created by comparing signal during the different conditions of E1 is displayed in Fig. 3A–E (see also Fig. 1A–C for example stimuli). A threshold for displaying activations of $t \geq 4$, corresponding to $P < 0.0001$ (uncorrected) was selected for these analyses. We found that DD had no FFA activation to unfamiliar faces but significant activation to Digimon in the area where we would expect his FFA. Activations to Digimon in the right lateral FG were similar to those typically found for faces in normative studies (see Table 1 in Gauthier et al., 1999b), as demonstrated by the Talairach coordinates for the center of the activations (Table 3). DD responded to Digimon in both his left and right FG, and we focused on activity in the right FG because the right FFA has been better characterized and studied than the left (Gauthier et al., 1999b). Activation to nonface objects in the medial FG was also consistent with other studies reported in the literature (Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999).

3.2.2. ROI analysis of the right FFA

For each category, we assessed the amount of FG involvement using unsmoothed data from a region of interest (ROI)

analysis of the right lateral FG, the region where the FFA is typically found. The results of the two experiments are presented in Fig. 4A, which shows the mean percent signal change relative to objects for the ROIs of each condition and participant. As expected, TDC showed a greater response to unfamiliar faces than objects in this ROI ($t(31) = 3.44$, $P = 0.002$), unlike the two participants with autism who show a greater response to objects than unfamiliar faces (DD: E1: $t(31) = 0.18$, NS; DD: E2: $t(30) = 2.78$, $P = 0.009$; CC: $t(28) = 4.34$, $P < 0.001$). TDC showed no difference between Digimon and nonface objects ($t(31) = 0.81$, NS). In E1 and again in E2, however, patient DD had greater activation to Digimon compared to both unfamiliar faces (E1: $t(31) = 5.85$, $P < 0.001$; E2: $t(30) = 6.38$, $P < 0.001$) and objects (E1: $t(31) = 6.20$, $P < 0.001$; E2: $t(30) = 5.84$, $P < 0.001$). Moreover, our comparison participant with autism, CC, had less signal to unfamiliar faces (reported above) and Digimon ($t(28) = 2.90$, $P = 0.007$) than he had to objects.

To test the importance of Digimon faces and DD's familiarity with the characters in Digimon activation of the right lateral FG, we compared Digimon with their faces masked and familiar faces to intact Digimon, unfamiliar faces, and objects in subjects who took E2. TDC had more signal to masked Digimon than Digimon ($t(31) = 4.80$, $P < 0.001$) and nonface objects ($t(31) = 5.19$, $P < 0.001$), but not to human faces ($t(31) = 1.35$, NS). Surprisingly, TDC had less activity for familiar faces than for unfamiliar faces ($t(31) = 6.04$, $P < 0.001$), Digimon ($t(31) = 4.40$, $P < 0.001$), masked Digimon ($t(31) = 3.42$, $P = 0.002$), and objects ($t(31) = 2.69$, $P = 0.011$). DD, on the other hand, had a greater response to masked Digimon than to unfamiliar faces ($t(30) = 3.91$, $P < 0.001$) and objects ($t(30) = 2.27$, $P = 0.031$), although this response was less than that to intact Digimon ($t(30) = 3.186$; $P = 0.003$). DD had a greater response to familiar faces when compared to unfamiliar faces ($t(30) = 3.47$, $P = 0.002$), however, the response to familiar faces was less than that to Digimon ($t(30) = 7.35$, $P < 0.001$) and masked Digimon ($t(30) = 3.91$, $P < 0.001$). There was no difference between his response to familiar faces and nonface objects ($t(30) = 1.11$, NS).

Another test of face specificity in this cortical area is to investigate activity in only the most face-selective voxels. We compared the mean percent signal changes for each condition relative to objects in the five most face-selective voxels of the ROIs (Fig. 4B). The five most face-selective voxels were those with the highest *t*-value for unfamiliar faces when compared to objects. In TDC's most face-selective voxels, activity for faces is higher than activity for Digimon. However, even in DD's most face-selective voxels, DD's activity for Digimon is higher than activity for faces.

3.2.3. Activation of the amygdala

Because it has been reported that amygdala activity habituates over repeated trials (Buchel, Morris, Dolan, & Friston, 1998; Breiter et al., 1996), activity in the amygdala was analyzed for each of three scan series separately. As expected, DD's amygdala showed habituation to Digimon relative to

Table 3
Talairach coordinates for peak of activation in E1 (DD only)

Anatomical location	Condition (comparison)	Coordinates (x, y, z)
Right lateral fusiform gyrus	Digimon (vs. object)	38, -48, -13
	Digimon (vs. face)	40, -50, -15
Left lateral fusiform gyrus	Digimon (vs. object)	-42, -58, -11
	Digimon (vs. face)	-40, -58, -10
Right medial fusiform gyrus	Object (vs. face)	30, -48, -4
	Object (vs. Digimon)	30, -48, -4
Left medial fusiform gyrus	Object (vs. face)	30, -54, -6
Right amygdala	Digimon (vs. object)	19, 2, -15
	Digimon (vs. face)	19, 2, -15
Left amygdala	Digimon (vs. object)	-22, 0, -15
	Digimon (vs. face)	-23, 0, -15

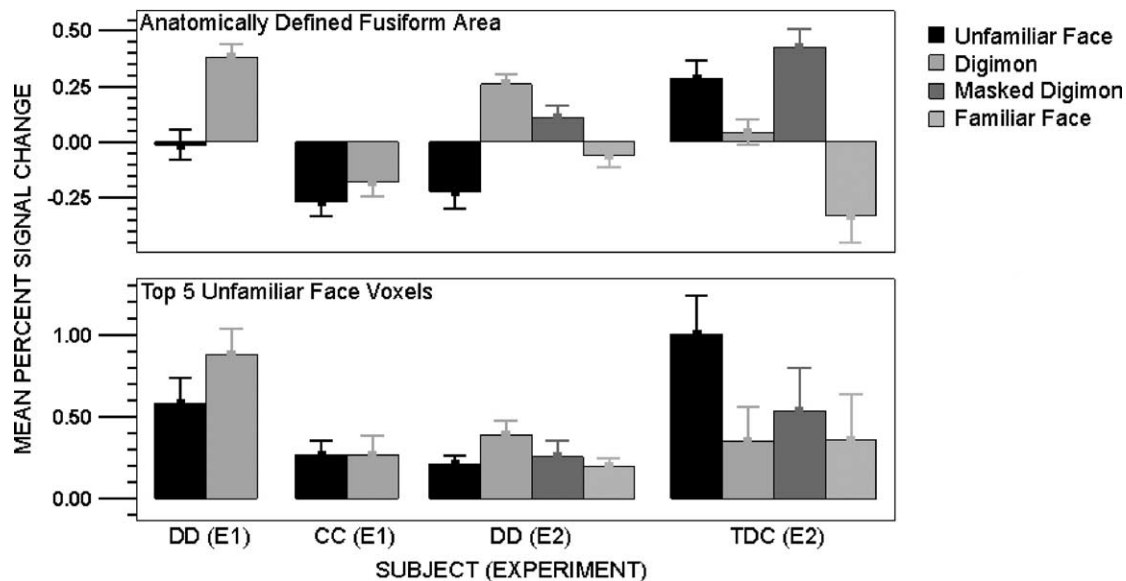


Fig. 4. Results of ROI analysis in the right lateral FG. Mean percent signal changes for each condition relative to objects over the entire FFA ROI and in the five most face-selective voxels are displayed for each participant. Error bars represent standard error of the mean across voxels.

fixation across runs, in much the same way TDC's amygdala showed habituation to the human face (data not shown). Therefore, only smoothed data from the first run were used to make *t*-maps. DD showed bilateral amygdala activation for Digimon relative to both faces and nonface objects (Fig. 3F–I) at a threshold of $t \geq 4$, corresponding to an uncorrected $P < 0.0001$.

3.2.4. ROI analysis of the right and left amygdala

Using unsmoothed data in a comparison of activity for faces and Digimon from the first run in the amygdala ROIs, we tested the right and left amygdalae for differences between activity to faces and Digimon within subjects. Signal for faces was greater than signal for Digimon in TDC in both the right and left amygdalae (Left: $t(9) = 4.01$, $P = 0.003$; Right: $t(12) = 4.40$, $P < 0.001$). For DD, however, signal was higher for Digimon than faces (E1 Left: $t(9) = 3.81$, $P = 0.004$; E1 Right: $t(11) = 3.44$, $P = 0.006$; E2 Left: $t(7) = 9.26$, $P < 0.001$; E2: Right $t(12) = 2.61$, $P = 0.023$). For CC, signal was higher for Digimon in the left amygdala but not different than for faces on the right (Left: $t(13) = 3.04$, $P = 0.009$; Right: $t(10) = .521$, NS).

4. Discussion

4.1. Behavioral testing

Using the forced-choice verification test, we wanted to measure differences in DD's responses to familiar faces, Digimon, and familiar nonface objects to assess his expertise for faces and Digimon. Generally, people can categorize objects faster at the basic level (e.g., "dog" or "car") than at more specific levels (e.g., "beagle" or "Ford Explorer"). However,

experts in a domain, such as dog or bird experts, can categorize objects at the individual level as fast as at the basic level (Tanaka & Taylor, 1991). Consistent with this finding, typically developing individuals (i.e., face experts), such as TDC, show an advantage for individuating familiar faces over nonface objects (Tanaka, 2001). The face deficits of persons with autism suggest that they may lack a perceptual advantage for individuating people by their face (Grelotti et al., 2002). Our results with DD are consistent with this, as he was no faster at individuating familiar faces than common objects. DD's perceptual advantage for Digimon over familiar faces and common objects, on the other hand, is indicative of Digimon expertise. This face-like advantage for Digimon is consistent with our prediction that DD, who demonstrates more interest for Digimon than for faces, has acquired expertise for Digimon at the individual level. Interestingly, he does not appear to have the same expertise for faces.

4.2. The fusiform gyrus

Because of DD's expertise for individuating Digimon and his deficit in individuating faces, we predicted not only hypoactivation of the FFA to familiar and unfamiliar faces (compared to objects) but also that Digimon would elicit activity in the area of the FG that is normally recruited for faces. As predicted, the middle region of DD's FG responded more to Digimon and masked Digimon than to familiar and unfamiliar faces and nonface objects. Given that neither TDC nor CC had greater activation to Digimon than objects, DD's activation to Digimon seems special. We believe that DD's FG activation to Digimon and his lack of cortical specialization for faces are consistent with differences in the amount of time he has spent looking at or thinking about people and Digimon over his lifetime.

What are the implications of these findings for understanding the nature and origin of the FFA? One possibility is that DD's "face module" is damaged and dysfunctional and that nearby cortex can nonetheless support the individuation of non-face objects like Digimon. Indeed, the fact that some individuals with acquired prosopagnosia are reported to have relearned objects but not faces (McNeil & Warrington, 1993) would be consistent with this account. In addition, a unique individual with visual object agnosia was reported to have face recognition preserved (Moscovitch, Winocur, & Behrmann, 1997), suggesting that areas of the cortex can subservise a discrete function and can be selectively damaged, without impacting the function of adjacent areas. DD could be an example of a person with autism who has a dysfunctional face module but an otherwise intact FG cortex that responds to objects that have a special meaning to him.

A second explanation for the observed face and Digimon dissociation in DD emphasizes the perceptual processes that underlie face processing and expert non-face object processing. Although some studies have reported individual patients whose face processing deficits are disproportionately more impaired than their within category object discrimination (Farah et al., 1995) or configural processing (Duchaine, 2000), face recognition deficits in persons with prosopagnosia are often accompanied by marked difficulty in discriminating between visually similar objects (Damasio, 1990) and sensitivity to an object's level of categorization (Gauthier, Behrmann, & Tarr, 1999a). Additionally, objects of expertise are found to recruit the FFA (Gauthier et al., 1999b; Gauthier et al., 2000a), suggesting that specialization for faces in the FFA is an example of a more general phenomenon related to experience, individuation, and configural processing (Tarr & Gauthier, 2000). Accordingly, a lack of experience with faces may underlie the face processing deficit in persons with autism and hypoactivation of the FFA in neuroimaging studies of face perception. Within this framework, DD's activation to Digimon is conceived as the equivalent of the FFA for faces, a result of his acquisition of Digimon expertise.

These two alternative explanations are very difficult to tease apart, partly because it is impossible to know for sure whether DD's "Digimon area" falls exactly where his absent FFA would have been. The Talairach coordinates for the center of Digimon activation places the fusiform Digimon area squarely within the region in which one would expect the FFA. For example, in a classical study on the FFA, the centers of activation for a comparison of faces and objects ranged from 31 to 50 in the X-axis, -39 to -69 in the Y-axis, and -3 to -18 in the Z-axis (Kanwisher et al., 1997). The center of DD's activation to Digimon compared to faces in the right FG falls squarely within this region (DD: 38, -48, -13). On the other hand, there is enough variability between individuals in the exact location of face-selective voxels to make it possible that the Digimon region and the absent face region would not overlap. However, it is important to consider that even if the two areas were different, it appears likely that a Digimon area in the FG, induced by DD's expertise,

would be functionally related to the FFA in some important way. In other words, the mechanisms responsible for cortical specialization to Digimon (or other objects of expertise) can reasonably be expected to be similar to those responsible for the acquisition of nearby cortical specialization for faces. In that respect, our results have an important implication: neither specialization for faces nor an innate bias to process a given geometry appears to be necessary for expertise to be associated with a specialized response to Digimon in the FG.

Many authors have reported that stimuli other than faces (including animals) activate the FFA (Chao, Martin, & Haxby, 1999; Kanwisher, Stanley, & Harris, 1999), but our study demonstrates how this kind of activation is possible even in the absence of activation to or prior "specialization" for faces. It has been suggested that expertise effects in the FFA merely demonstrate that a face module will respond to nonface objects of one's expertise by the ulterior recruitment of the face processing module (e.g., Greebles, cars, and birds (Kanwisher, 2000)). One way to interpret our findings is to think of Digimon as animals and activation to Digimon in the FFA as a result of similarities between Digimon and faces (whereby, the argument goes, Digimon, like animals, co-opt the face circuits of the FFA). It is impossible to say with certainty with our data whether or not activation to Digimon is influenced in some way by the fact that Digimon have faces. This limitation may be overcome by testing persons with autism with expertise in objects without faces. Nonetheless, even if we assume that Digimon are treated like animals, that animals engage the FFA, and thus that DD's Digimon area is really a response to animals in his putative FFA, our results indicate that this response can be obtained in the absence of specialization for faces. Therefore, DD did not use existing FFA circuitry to obtain his expertise for Digimon although it is in the region where one would expect face specialization.

Could the faces of Digimon be responsible for our results? If this were the case we might expect no difference in signal between masked Digimon and objects. However, as shown in Fig. 4, masked Digimon elicit greater activation in the FG ROI than objects and familiar and unfamiliar faces. These results suggest that a class of objects can selectively engage the right lateral FG independent of any specialized network for processing human faces. Patient DD may be an existence proof that the FFA can show greater activation for something other than human faces. However, this result is complicated by the finding that TDC's FFA also responds more to masked Digimon than to objects, despite the fact that his FFA does not respond more to intact Digimon with faces compared to objects. This intriguing result could be related to the findings of a recent study where contextually defined faces (a blurred patch over a body where the head would be) engaged the FFA at least as well as intrinsically defined (normal) faces (Cox, Meyers, & Sinha, 2004). While the faces of actual Digimon may not resemble human faces sufficiently to activate TDC's FFA, the faces that were "filled in" during the masked condition may have resembled human faces much more, especially in TDC who is not a Digimon expert. Finally, it is unlikely

that DD's response to masked Digimon could be explained by the same phenomenon, since he shows no more response to normal faces than objects.

We contend that theories that support the role of experience and individuation in cortical face specialization provide the most parsimonious explanation for both the Digimon findings and the expertise effects that have been shown in the FFA for nonface objects in typically developing individuals. Indeed, an alternative account for the behavioral and neuroimaging face processing abnormalities based on a selectively damaged face module in persons with autism would require a separate explanation for the profound social disability of persons with autism (which is not recapitulated in adults with prosopagnosia) (Grelotti et al., 2002). This renders the modular explanation for the lack of FFA activity in persons with autism less parsimonious than an explanation based on the expertise model. We have argued that a single neurodevelopmental abnormality could disrupt social motivation in persons with autism, as well as social reciprocity skills and face perception skills (Grelotti et al., 2002; Schultz et al., 2000a; Schultz et al., 2000b). More specifically, we hypothesize that an early failure to develop an appropriate degree of interest in other people has the consequence of curtailing experience with people and concomitantly time looking at and processing faces which in turn is at least partially responsible for the deficits in face individuation and the related FFA hypoactivation to faces (see also Schultz et al., 2003 for additional consequences of this early social motivation deficit vis-à-vis social cognition and the FFA).

Interestingly, DD's response to familiar faces was greater than his response to unfamiliar faces, although it was no different than his response to objects. Findings of FG activation to simple geometric shapes engaged in social interactions and necessitating individuation (Castelli, Happe, Frith, & Frith, 2000; Schultz et al., 2003 but see also Castelli, Frith, Happe, & Frith, 2002) may provide an explanation of this. Indeed, Schultz et al. (2003) speculate that the response of the FG to shapes engaged in social interactions is related to the FG's encoding of abstract semantic information about people after repeated perceptual experiences with faces. These same mechanisms may participate in the response of DD's FG to familiar faces and Digimon. It is possible that a combination of individuation, semantic knowledge, increased attention to the stimuli, and experience influences activity to familiar faces and Digimon in this region. However, unlike the Digimon stimuli, DD did not spontaneously recognize any of the cropped familiar faces—not even his mother's face or his own face—and would not accept that they were pictures of his family until we showed him the original photos. It is impossible to tell what his fMRI response to familiar faces would have been if we did not demonstrate to him before testing that they were images of family members.

Unlike DD, TDC's response to familiar faces was less than his response to all other conditions. However, this analysis

is confounded by the fact that there were only twelve different photos of each subject's family members and friends, and they were recycled throughout the experiment unlike the other stimuli. Because there are well documented FFA decreases with repeated presentation of the same face (Buckner et al., 1998; Gauthier et al., 2000b; Henson & Rugg, 2003), we cannot separate the familiarity from the effects of repetition suppression for TDC's findings. It remains possible that the familiarity and repetition suppression effects differ between individuals with autism and those who are typically developing.

4.3. *The amygdala*

Amygdala activation to neutral, unfamiliar faces has been shown in typically developing individuals but not in individuals with autism (Pierce et al., 2001). Consistent with this, TDC and not DD had activity in the amygdala when viewing unfamiliar faces. Amygdala activity has been associated with marking certain percepts as salient or important (Aggleton, 1993; Anderson & Phelps, 2001; Breiter et al., 1996). We reasoned that because DD found Digimon to be emotionally meaningful, that they would elicit activity in his amygdala. Indeed, DD had activity in his right and left amygdala to Digimon that was similar to TDC's activity to unfamiliar faces (Fig. 5). In contrast, CC had significantly more activity to Digimon in his left amygdala, but not his right. Some data suggest that the left amygdala responds more than the right to highly arousing stimuli, such as fearful stimuli (Breiter et al., 1996). While differences between the functions of the left and right amygdala remain speculative, one recent model suggests that activity in the right amygdala is related to an emotional reaction to stimuli, whereas the left amygdala is more involved in the analysis and processing of arousing stimuli (Glascher & Adolphs, 2003). It follows that left amygdala activity in both persons with autism may be related to the processing of select, highly arousing attributes of the stimuli (e.g., the teeth, claws, or weapon-like features of some Digimon). Activity in DD's right amygdala suggests a sustained arousal by the stimulus not shared by CC that would likely be related to his general fascination and preoccupation with the Digimon fantasy world and how engaging and interesting he found the characters. In any case, it appears that the amygdala of persons with autism may become significantly engaged when percepts are particularly salient or have a high reward value; for DD, Digimon appear to be much more salient and rewarding than human faces.

We looked specifically at the FG and amygdala in this case because of reported abnormalities in these areas for persons with autism, and the results of this study are also consistent with hypotheses of a special relationship between the FG and amygdala. The amygdala may influence the FG through attention (George, Driver, & Dolan, 2001), modulating short-term plasticity (Rotshtein et al., 2001), or directly and/or indirectly shaping long-term specialization in the FG (Grelotti et al., 2002; Schultz et al., 2000a; Schultz et al., 2000b).

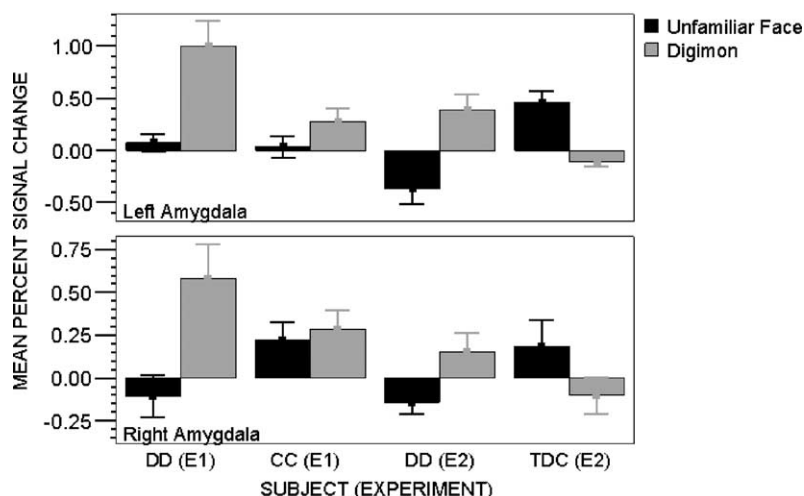


Fig. 5. The response of the amygdala to Digimon. Mean percent signal change in the first run for Digimon and unfamiliar faces relative to fixation in the right and left amygdalae are displayed for each participant. Error bars represent standard error of the mean across voxels.

5. Conclusion

Neither expertise effects for objects in the FFA (Gauthier et al., 1999b; Gauthier et al., 2000a) nor a lack of activity for faces in the FFA or amygdala of a person with autism (Critchley et al., 2000; Pierce et al., 2001; Schultz et al., 2000a) are new findings, but the combination of these findings and the amygdala activity to Digimon in the same person has important implications for the study of autism. It suggests that the FG and amygdala of individuals with autism function normally under certain conditions. We hypothesize that social interest is a key precondition for normal development of these regions. This then begs the very important question of why there are social motivational impairments among persons with autism. In this regard, further studies of expertise for nonface objects and the motivational underpinnings for special interests in autism may be quite informative as to the key mechanisms underlying the development of social deficits in autism.

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