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Age-dependent atypicalities in body- and face-sensitive activation of the EBA and FFA in individuals with ASD

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ABSTRACT

Individuals with autism spectrum disorder (ASD) have difficuly in recognizing bodies and faces, which are more pronounced in children than adults. If such difficulties originate from dysfunction of the extrastriate body area (EBA) and the fusiform face area (FFA), activation in these regions might be more atypical in children than in adults. We preformed functional magnetic resonance imaging while children and adults with ASD and age-matched typically developed (TD) individuals observed face, body, car, and scene. To examine various aspects, we performed individual region of interest (ROI) analysis, as well as conventional random effect group analysis. At individual ROI analysis, we examined the ratio of participants showing a category-sensitive response, the size of regions, location and activation patterns among the four object categories. Adults with ASD showed no atypicalities in activation of the EBA and FFA, whereas children with ASD showed atypical activation in these regions. Specifically, a smaller percentage of children with ASD showed face-sensitive activation of the FFA than TD children. Moreover, the size of the EBA was smaller in children with ASD than in TD children. Our results revealed atypicalities in both the FFA and EBA in children with ASD but not in adults with ASD.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition that is characterized by difficulties in social communication and interaction, as well as restricted, repetitive patterns of behaviors, interests, or activities (DSM5). Within the social communicative difficulty, it is well known that individuals with ASD have

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atypicalities in recognizing body actions (Cossu et al., 2012) and identifying faces (Weigelt et al., 2012). However, previous behavioral studies have shown that atypicalities in the body- and face-recognition of children with ASD decrease through the course of development (Dowell et al., 2009; Serra et al., 1998; Strauss et al., 2012). These behavioral findings indicate that children with ASD show more atypical neural responses in the brain regions that are associated with body and face recognition than adults with ASD.

A number of previous neuroimaging studies on typically developed (TD) individuals have identified the brain networks that underlie recognition of bodies or faces. Core nodes of such networks reside in the occipito-temporal cortex, and are specialized for the visual processing of specific object categories. For instance, the extrastriate body area (EBA) (Downing et al., 2001; Weiner and Grill-Spector, 2011) has been shown to be involved in the recognition of body forms or actions (Vangeneugden et al., 2014; Wiggett and Downing, 2011). The fusiform face area (FFA), a focal region in the fusiform gyrus sensitive to observed faces (Kanwisher et al., 1997; Kanwisher and Yovel, 2006), is considered to represent invariant features of faces that can be used for identification (Haxby and Gobbini, 2011). Thus, dysfunction of the EBA and FFA might be one of the cause of atypicalities in body- and face- recognition, respectively. If this is the case, there are two possible mechanisms that could explain the improvement in face and body recognition in individuals with ASD over the course of development. First, atypical activation in the FFA and EBA in children with ASD may become normalized as they approach adulthood. Alternatively, brain networks beyond the FFA and EBA may show distinct patterns over the course of development, possibly due to compensatory strategies. Despite these claims, neural responses in the EBA and FFA of individuals with ASD are not yet fully understood from a developmental perspective.

To date, few studies have examined neural responses in the EBA of individuals with ASD. In our previous study, we demonstrated similar body-sensitive responses of the EBA in both TD adults and those with ASD when viewing body parts (Okamoto et al., 2014). However, atypicalities in body recognition of children with ASD decrease through the course of development (Dowell et al., 2009; Serra et al., 1998). For instance, Dowell et al. (2009) have shown a positive correlation between the recognition of a skilled gesture and the age of children with ASD (Dowell et al., 2009). These findings indicate that activation in the EBA might be atypical for children with ASD, unlike adults with ASD. Nevertheless, there have been no studies examining activation of the EBA in children with ASD.

In contrast to the EBA, a number of studies have examined neural responses in the FFA in individuals with ASD, however, such studies have reported inconsistent results (Nomi and Uddin, 2015). Although several factors may contribute to such inconsistent findings, such as gaze pattern (Dalton et al., 2005; Perlman et al., 2011) and familiarity of faces (Pierce and Redcay, 2008), task-demands on visually-presented faces is one of the relevant factors. In terms of adults with ASD, several functional magnetic resonance imaging (fMRI) studies using passive viewing tasks have found similar activation in the FFA between adults with and without ASD (Hadjikhani et al., 2004; Hadjikhani et al., 2007). These findings indicate that, similar to TD adults, there is a clustered region that is sensitive to facial recognition in the fusiform gyrus of adults with ASD. In contrast, other studies have shown hypo-activation of the FFA in adults with ASD when compared to TD adults e.g. (Critchley et al., 2000; Humphreys et al., 2008; Kleinhans et al., 2010; Pierce et al., 2001; Piggot et al., 2004; Pinkham et al., 2008; Schultz et al., 2000). In most of these studies, however, FFA activation was measured when participants performed a task, such as memorizing on identities of face including working memory or identification of facial emotions. Collectively, these fMRI studies have suggested that there is a face-sensitive cluster in the fusiform gyrus (i.e. FFA) in both adults with and without ASD, but that involvement of the FFA in facial memorization and recognition of emotion might be different between adults with and without ASD.

In contrast to the above-described studies on the adult population, there are few studies examining FFA activity in children with ASD and all studies have reported hypo-activation in the FFA as compared to TD children (Corbett et al., 2009; Grelotti et al., 2005; Malisza et al., 2011; Pierce and Redcay, 2008; Scherf et al., 2010). However, almost all fMRI studies examined FFA activation during facial memorization or the recognition of emotion (Corbett et al., 2009; Grelotti et al., 2005; Malisza et al., 2011; Pierce and Redcay, 2008). Therefore, the following two possibilities might explain these results. First, unlike adults with ASD, children with ASD might lack a face-sensitive cluster in the fusiform gyrus (i.e. FFA). Alternatively, and similar to adults with ASD, involvement of the FFA in the performance of these tasks might be atypical in children with ASD. To investigate the existence of the FFA in children with ASD, FFA activation should be investigated when participants passively observe pictures of faces (i.e., without performing a task such as memorization or emotional recognition) in order to follow up on studies previously conducted on adults with ASD (Hadjikhani et al., 2004; Hadjikhani et al., 2007).

The main goal of the present study was to examine whether children with ASD showed atypical activation in the EBA and FFA when they passively observed faces and bodies (i.e., in the absence of the performance of tasks related to these objects). In the present study, we initially confirmed that adults with and without ASD showed similar activation in both the EBA and FFA when performing a task free of cognitive demand (Experiment 1). We then examined whether children with ASD showed atypical activation in the EBA and FFA using the same task performed by adults (Experiment 2). Participants of both experiments observed pictures of neutral faces, non-face-related body parts, outdoor scenes, and cars. To ensure attention was maintained on the presented pictures, participants were required to detect a change in color of a fixation cross, which was presented irrespective of each object. We predicted that, unlike adults with ASD, children with ASD would exhibit prominent atypical activation in the EBA and FFA.

2. Methods

2.1. Participants

In this study, adults with and without ASD participated in Experiment 1, and children with and without ASD, as well as TD adults, participated in Experiment 2 (Table 1). Our protocol was approved by the Ethics Committee of the University of Fukui (Japan) for Experiment 1 and the National Tottori Medical Center (Japan) for Experiment 2, and both experiments were conducted in accordance with the Declaration of Helsinki. Participants were excluded if they had a history of major medical or neurological illness including epilepsy, significant head trauma, or a lifetime history of alcohol or drug dependence. After the study was explained in detail, written informed consent was obtained from each participant or, in the case of children, their legal guardian. Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). We obtained intelligence quotient (IQ) scores using the Wechsler Adult Intelligence Scale-III (Wechsler, 1997) for adults in Experiment 1 and the Wechsler Intelligence Scale for Children–Third Edition (Wechsler, 1991) for children in Experiment 2. We also measured the Autism Spectrum Quotient (AQ) scores for all participants using different versions for adults (Baron-Cohen et al., 2001) and children (Auyeung et al., 2008; Wakabayashi et al., 2007).

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Table 1
Demographic data and rating scale scores.

		Experiment1				Experiment2				
		ASD Adults	TD Adults	t values	p values	TD Adults	ASD Children	TD Children	t values	p values
Number		17	17			12	11	12		
	Males	16	16			11	10	11		
	Females	1	1			1	1	1		
Handedness(right/left)		17/0	17/0			11/1	10/1	11/1		
Age		24.2 ± 4.3	24.2 ± 3.9	0.00		22.4 ± 1.9	11.2 ± 1.6	11.3 ± 1.3	0.11	
IQ										
	Full-scale IQ	107.3 ± 13.3	111.5 ± 6.1	1.19		–	97.6 ± 16.1	101.0 ± 8.8	0.61	
	Verbal IQ	110.5 ± 15.0	112.3 ± 9.4	0.43		–	97.7 ± 17.0	104.6 ± 12.0	1.13	
	Performance IQ	101.6 ± 14.1	107.1 ± 8.5	1.37		–	98.9 ± 17.3	96.9 ± 10.1	0.34	
AQ										
	Total	33.5 ± 5.7	13.2 ± 3.6	12.43	< 0.001	20.9 ± 7.2	30.4 ± 7.9	13.7 ± 5.7	5.85	< 0.001
	Social skill	7.4 ± 2.0	1.9 ± 1.8	8.19	< 0.001	3.8 ± 2.7	6.4 ± 2.4	2.6 ± 2.4	3.80	< 0.01
	Attention switching	7.6 ± 1.6	3.4 ± 1.7	7.56	< 0.001	5.7 ± 2.0	6.1 ± 1.6	2.4 ± 1.6	5.50	< 0.001
	Attention to detail	5.4 ± 2.7	3.4 ± 1.5	2.72	< 0.01	3.9 ± 2.1	4.9 ± 2.5	3.8 ± 1.8	1.27	
	Communication	7.2 ± 2.5	1.7 ± 1.4	7.98	< 0.001	4.0 ± 2.5	6.5 ± 1.9	1.6 ± 1.4	7.30	< 0.001
	Imagination	5.8 ± 2.1	2.8 ± 1.6	4.70	< 0.001	3.5 ± 1.6	6.5 ± 2.4	3.3 ± 1.7	3.58	< 0.01

IQ; Wechsler Adult Intelligence Scale Third Edition (Wechsler, 1997) for adults in Experiment 1 and Wechsler Intelligence Scale for Children (Wechsler 1991) for children in Experiment 2. Number, Number of participants. AQ, Autism Spectrum Quotient (Baron-Cohen et al., 2001; Auyeung et al., 2008; Wakabayashi et al., 2007). Handedness was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Age, IQ scores, and AQ scores are shown as mean ± SD. $p < 0.01$, $p < 0.001$ indicate the results of independent-samples *t*-tests that compared adults with ASD to TD adults in Experiment 1 and compared children with ASD and TD children in Experiment 2.

2.1.1. Experiment 1 (Adults)

To examine body- and face-sensitive activation in the EBA and FFA of adults with ASD, we utilized data originally acquired as a part of our previous study (Okamoto et al., 2014). Participants included 22 TD adults and 19 adults with ASD. In order to match full-scale intelligence quotient (FSIQ) between the two groups, five TD adults with higher FSIQs and two adults with ASD and lower FSIQs were excluded from the analysis. Therefore, the data of 17 adults with ASD and 17 TD adults were analyzed (Table 1). Two psychiatrists (H.K and T.M) diagnosed the participants with ASD based on DSM-5 classifications (DSM5) and standardized criteria using the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing et al., 2002). The DISCO has good psychometric properties (Nygren et al., 2009) and includes items on early development and activities of daily living, giving the interviewer a sense of an individual's level of function in several different areas besides social functioning and communication (Wing et al., 2002). Seventeen age-matched TD adults (16 males and one female, 24.2 ± 3.9 years) were recruited from the local community (Table 1). The full-scale IQ (FSIQ) was not different between the two groups ($p > 0.2$, independent-sample *t*-test) and the scores of all participants were >75. The AQ total score was significantly higher in adults with ASD than in TD adults ($p < 0.001$, independent-sample *t*-test) (Table 1).

2.1.2. Experiment 2 (Children)

Ten boys and one girl with ASD (11.2 ± 1.6 years) were recruited at the National Tottori Medical Center (Japan) (Table 1). One expert pediatrician and certified child neurologist (T.K, 15th author) diagnosed the participants based on DSM-5 classifications (DSM5). Twelve age-matched TD children (11 boys and one girl, 11.3 ± 1.3 years) were recruited from the local community (Table 1). The FSIQ scores of all participants were >75, and there were no significant differences in these scores between children with ASD and TD children ($p > 0.05$, independent-sample *t*-test). However, the AQ total score was significantly higher in children with ASD than in TD children ($p < 0.001$, independent-sample *t*-test, Table 1). As we utilized different magnetic resonance imaging (MRI) scanners for Experiments 1 and 2, it was necessary to confirm that the FFA and EBA were similarly depicted by both machines. Therefore, an additional control group of 12 TD adults (11 males and one female; 22.4 ± 1.9 years), who were recruited from the same local community, participated in Experiment 2 (Table 1).

2.2. MRI parameters

2.2.1. Experiment 1 (Adults)

All volumes were acquired with a 3-T magnetic resonance (MR) imager (Sigma Horizon; GE Medical Systems, Milwaukee, WI, USA). Functional volumes were acquired using T2*-weighted gradient-echo echo-planar imaging (EPI) sequences (37 oblique slices, 3.0 mm in thickness, 15% gap, repetition time (TR) = 2500 ms, flip angle (FA) = 80°, echo time (TE) = 30 ms, field of view (FOV) = 192 × 192 mm, digital in-plane resolution = 64 × 64 pixels, and pixel dimension = 3 × 3 mm). Axial slices were sequentially acquired in ascending order. For each participant, a high-resolution anatomical T1-weighted image was also acquired by three-dimensional inversion recovery-prepared fast spoiled-gradient recalled acquisition in the steady state sequencing (TR = 11.3 ms, TE = 5.3 ms, FA = 10°; 320 × 192 matrix, voxel dimensions = 0.75 × 1.25 × 1.60 mm).

2.2.2. Experiment 2 (Children)

All volumes were acquired with a 1.5-T MR imager (Magnet Symphony; Siemens, Erlangen, Germany). Functional volumes were acquired using T2*-weighted gradient-echo EPI sequences (32 oblique slices, 3.0 mm in thickness, 33% gap, TR = 3000 ms, FA = 90°, TE = 33 ms, FOV = 192 × 192 mm, digital in-plane resolution = 64 × 64 pixels, and pixel dimension = 3 × 3 mm). Axial slices were acquired sequentially in ascending order. A high-resolution anatomical T1-weighted image was acquired by three-dimensional magnetization prepared rapid gradient echo sequencing (TR = 1900 ms, TE = 2.13 ms, FA = 15°; 192 × 192 matrix, voxel dimensions = 1 × 1 × 1.3 mm).

2.3. Experimental setup

Visual stimuli presentation and response collection were conducted with Presentation software (Neurobehavioral Systems, Berkeley, CA, USA) implemented on a Windows-based desktop computer. Visual stimuli were presented on a screen by a liquid-crystal display (LCD) projector for Experiment 1 and an LCD monitor for Experiment 2. Participants viewed visual stimuli via a mirror attached to the head coil of the MRI scanner. Head motion was minimized by placing comfortable but tight-fitting foam padding around each participant's head.

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2.4. Task procedures

We employed the conventional localizer task, of which the task paradigm has been exhaustively explained in a previous study (Okamoto et al., 2014). In short, participants completed two runs of the task, each of which consisted of 21 15-s blocks (Fig. 1). The first, sixth, 11th, 16th, and 21st blocks were fixation-only baseline conditions. We prepared four categories of objects: faces, non-face-related body parts, scenes, and cars. Twenty achromatic photographs from one of the four object categories were presented successively in each block. Each photograph was presented for 300 ms, and the inter-stimulus interval (ISI) was 450 ms. Each object category block was repeated four times. Four volumes of a fixation-only baseline condition (10 s for Experiment 1 and 12 s for Experiment 2) was added before the first baseline block. Each participant was asked to observe the presented pictures. In order to keep the participants' gaze on the picture, they completed a color-detection task which required them to press a button when the fixation cross changed from white to red during the ISIs.

2.5. Data analysis

2.5.1. Behavioral data

Accuracy and RT on the color-detection task were measured for each participant to confirm that attention was maintained on the visual stimuli throughout the course of the experiments; these values were compared between individuals with ASD and TD individuals within each experiment.

2.5.2. fMRI analysis

2.5.2.1. Preprocessing. The first four volumes of each run were discarded because of unsteady magnetization. The remaining 126 (Experiment 1) and 105 vols (Experiment 2) per run were analyzed with Statistical Parametric Mapping software (SPM8; Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB (MathWorks, Natick, MA, USA). After functional image realignment, we performed slice timing correction. Then, the high-resolution anatomical images were coregistered to the functional images and normalized to a template T1 image (ICBM 152) that was already fitted to the Montreal Neurological Institute space. The parameters from this normalization process were then applied to all of the functional images, which were resampled to a final resolution of $2 \times 2 \times 2\,mm^3$. The normalized fMRI images were filtered using a Gaussian kernel of 8 mm (full-width at half-maximum) in the x–z axes.

2.5.2.2. Statistical analysis. We initially confirmed that adults with and without ASD showed similar EBA and FFA activation in Experiment 1. For Experiment 2, we then examined if children with ASD showed different activation of the EBA and FFA when compared to TD children. In order to examine activation in these regions, we performed a random-effect group analysis, examining overall activation patterns, as well as an individual region of interest (ROI) analysis, examining detailed features.

2.5.2.2.1. Random-effect group analyses. In order to examine overall activation patterns at the group level, we conducted classical analyses at the following two levels. For first-level individual analyses, we fit a general linear model to the fMRI data of each participant (Friston et al., 1994; Worsley and Friston, 1995). Blood-oxygen-level dependent signal was modeled with box-car functions convolved with the canonical hemodynamic response function. Each run included four regressors of each object category, a regressor for a participant's response to the color-detection task, and six regressors of motion-related artifacts (three displacements and three rotations obtained by the rigid-body realignment procedure). The time series for each voxel was high-pass filtered at 1/128 Hz. Assuming a first-order autoregressive model, the serial autocorrelation was estimated from a set of pooled active voxels with the restricted maximum likelihood procedure and was used to whiten the data (Friston et al., 2002). Global signal changes were utilized to remove global confounding such as scanner gain. Parameter estimates for each condition in each individual were compared using linear contrasts.

We then conducted the second-level group analysis in which contrast images from the individual analyses were entered into the analysis, with between-participants variance modeled as a random factor. We used two full factorial designs, each of which included two factors (object and group) for each experiment. Thus, a design matrix included the contrast images of faces, non-face-related body parts, outdoor scenes, and cars presented to adults with ASD and TD adults in Experiment 1. Similarly, the other design matrix included the contrast images of four objects that were presented to children with ASD, TD children, and TD adults in Experiment 2. An object factor was modeled as a within-subject (dependent) level, whereas a group factor was modeled as separate between-subject (independent) levels. In all design matrices, estimates for the conditions were compared using linear contrasts. The resulting set of voxel values for each contrast constituted the SPM{t}. The statistical threshold of SPM{t} was set at $p < 0.05$ and corrected for multiple comparisons at the cluster level over the search volume (family-wise error) with a height threshold of $p < 0.001$ (Friston et al., 1996). The FFA and other face-related regions were depicted by the contrast of faces against the mean of the other three object categories (face-sensitive activation). As the FFA is a small region within the fusiform gyrus that is dominant in the right hemisphere (Kanwisher et al., 1997), the search for the FFA was restricted to the anatomically-defined right fusiform gyrus by a probabilistic atlas (Shattuck et al., 2008). We also depicted the EBA by contrasting non-face-related body parts against the mean of the other three object categories (body-sensitive activation). The search volume for the EBA was the whole brain. Other brain regions were labeled according to the same probabilistic atlas (Shattuck et al., 2008).

2.5.2.2.2. Individual region of interest analysis. While the random-effect group analysis examined similarities and differences in activity between the two groups, it was not suited for examining detailed differences between groups. Such differences included individual variability in the location of activation, as well as the size of activation in each individual. Thus, we conducted individual ROI analyses to examine the following four points. First, we calculated the ratio of participants showing a category-sensitive response. Next, for individuals showing this response, we examined the (2) size of activation (i.e. total number of voxels over a threshold), (3) location of peak coordinates for participants showing activation, and (4) activation pattern among four object categories at individual peak coordinates. We utilized the same anatomical definition of the ROI as the group analysis in the FFA. Because the EBA extends to several gyri, such as the middle temporal gyrus or the middle occipital gyrus, ROIs were defined by a sphere with an 8-mm radius of mean coordinates that had been determined by previous findings for TD children and adults ($x = 48$, $y = -70$, $z = 4$ for right hemisphere, $x = -44$, $y = -72$, $z = 8$ for left hemisphere) (Chan et al., 2004; David et al., 2007; Downing et al., 2006; Downing et al., 2001; Morris et al., 2006; Peelen and Downing, 2005; Pelphrey et al., 2009; Saxe et al., 2006; Taylor et al., 2007). The radius corresponded to the full width at half-maximum of the smoothing kernel. The statistical threshold was set at $p < 0.01$, uncorrected for multiple comparisons, in order to compare detailed differences between participants with ASD and TD individuals. We further confirmed the main results by using the same height threshold as the random effect analysis ($p < 0.001$ uncorrected).

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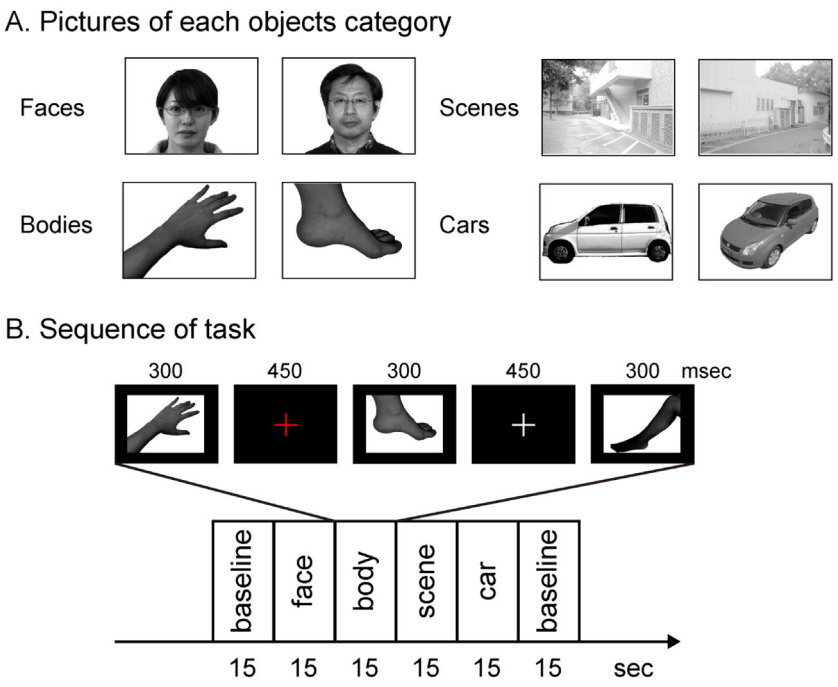

Fig. 1. Visual localizer task.
(A) Representative pictures utilized in the present study. (B) Task sequence. Participants observed pictures and were asked to press a button as soon as a red cross appeared.

3. Results

3.1. Experiment 1

We initially confirmed that adults with ASD and TD adults showed similar activation in the EBA and FFA.

3.1.1. Behavioral results of the color detection task

Mean accuracy on the color detection task in adults with ASD was 99.6 ± 1.5% (mean ± SD) and 99.4 ± 1.1% in TD adults. Independent-sample *t*-tests revealed no significant difference in accuracy between adults with ASD and TD adults ($p > 0.6$). Similarly, we found no group difference in RT (462.3 ± 43.0 ms for adults with ASD and 449.4 ± 39.5 ms for TD adults, $p > 0.3$ with an independent-sample *t*-tests). These results suggest that adults with and without ASD equally attended to visual stimuli.

3.1.2. fMRI results

3.1.2.1. Random effect group analysis.

3.1.2.1.1. Body-sensitive regions. Both TD adults and adults with ASD showed similar body-sensitive activation in the bilateral lateral occipito-temporal regions, which correspond to the EBA (Table 2; Fig. 2A). In addition to the EBA, TD adults showed body-sensitive activation in the left superior parietal lobule (SPL) and the right cerebellum, while adults with ASD showed activation in the left SPL. A conjunction analysis (with conjunction-null hypothesis (Nichols et al., 2005)) confirmed activation overlap in the bilateral EBA and the left SPL between the two groups, and response patterns to presented objects between individuals with ASD and TD in the EBA were highly similar (Fig. 2B). Furthermore, there was no significant difference between the two groups.

3.1.2.1.2. Face-sensitive regions. Adults with ASD, as well as TD adults, showed significant face-sensitive activation in the right fusiform gyrus, specifically the FFA (Table 2; Fig. 2C). In addition to the FFA, TD adults exhibited face-sensitive activation in the right precuneus and the bilateral inferior parietal lobule (IPL), while adults with ASD showed significant face-sensitive activation in the right precuneus and the right IPL. A conjunction analysis confirmed an overlap of activation in the right fusiform gyrus and the right precuneus between adults with ASD and TD adults, and both groups showed quite similar responses to object categories with the peak coordinate overlapping in activation (Fig. 2D). No brain region showed significant group differences.

3.1.2.2. Individual ROI analysis. In order to further characterize the category sensitive activation of FFA and EBA for adults with ASD and TD adults, we evaluated (1) the ratio of participants showing category-sensitive activation, (2) the number of voxels that revealed category-sensitive activation, (3) peak coordinates of the category-sensitive activation, and (4) response patterns to object categories in each region.

3.1.2.2.1. The EBA. The right EBA was identified in 17/17 TD adults and 16/17 adults with ASD and the left EBA was identified in 16/17 TD adults and 17/17 adults with ASD. In both hemispheres, chi-squared tests revealed no group differences in the ratio of participants whose EBA was identified (all p values > 0.2; Fig. 3A, E). We then compared size (the number of voxels over the threshold in the ROI), location variability, and activation pattern of the bilateral EBA between adults with ASD and TD adults. We found that the number of voxels was not different between the two groups in both hemispheres (all p values > 0.1 with an independent-sample *t*-test; Fig. 3B, F). Moreover, mean coordinates of the individually defined EBAs were quite similar between the two groups (Table 3). To examine variability in the location of the FFA, we calculated the distance between mean coordinates of each group and individual peak coordinates. Using this approach, the distance was comparable between adults with ASD and TD adults in the bilateral EBA (all p values > 0.9 with an independent-sample *t*-test; Fig. 3C, G). In order to examine response patterns, we extracted parameter estimates at peak coordinates of individually-defined EBAs. Fig. 3D, H shows activation patterns of the individually defined EBAs. In the bilateral EBA, a two-way analysis of variance (ANOVA) on object categories and groups revealed a significant main effect of object category (all p values < 0.001), while there was no significant interaction of

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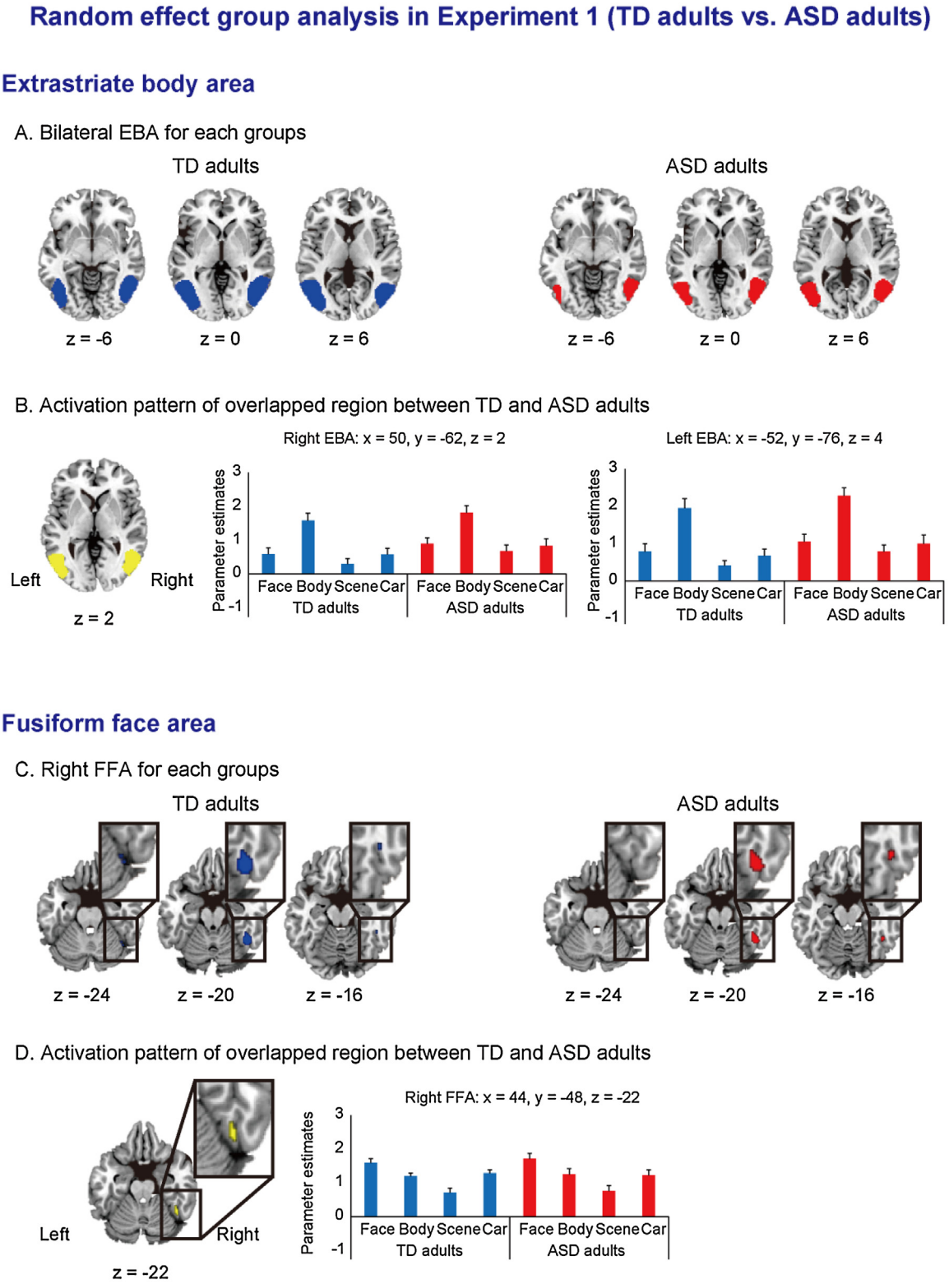

Fig. 2. Random effect group analysis in Experiment 1 (TD adults vs. ASD adults).
Body-sensitive activation in the lateral occipito-temporal region (EBA) and the face-sensitive activation in the fusiform gyrus (FFA) in adults with ASD and TD adults were superimposed on horizontal sections of a T1-weighted MR image. (A) The EBA of ASD and TD adults. (B) Activation pattern of overlapping regions of the EBA between ASD and TD adults. (C) The FFA of ASD and TD adults. (D) Activation pattern of overlapping regions of the FFA between ASD and TD adults. The size of activation was set at a threshold of $p < 0.05$ and corrected for multiple comparisons, with the height threshold set at $p < 0.001$ within the anatomically defined right fusiform gyrus.

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Table 2
Random effect group analysis of TD adults and ASD adults in Experiment 1.

Spatial extent test	P values	MNI coordinate			Z values	Hem	Anatomical region
Cluster size (mm^3)		x	y	z			
Body sensitive regions							
TD adults							
14,752	$p < 0.001$	48	−68	2	Inf	R	Middle occipital gyrus
16,096	$p < 0.001$	−54	−72	2	Inf	L	Middle occipital gyrus
9360	$p < 0.001$	−36	−52	60	4.66	L	Superior parietal lobule
11,128	$p < 0.001$	20	−52	−42	4.44	R	Cerebellum
ASD adults							
8576	$p < 0.001$	−52	−76	4	7.68	L	Middle occipital gyrus
10,960	$p < 0.001$	50	−62	2	6.22	R	Middle temporal gyrus
3696	$p < 0.01$	−30	−60	56	4.59	L	Superior parietal lobule
TD adults − ASD adults							
n.s.							
ASD adults − TD adults							
n.s.							
Intersection of ASD adults and TD adults in conjunction analysis							
8560	$p < 0.001$	−52	−76	4	7.68	L	Middle occipital gyrus
10,248	$p < 0.001$	50	−62	2	6.22	R	Middle temporal gyrus
2960	$p < 0.05$	−30	−58	56	4.48	L	Superior parietal lobule
Face sensitive regions							
TD adults							
400	$p < 0.05$ *	44	−48	−22	5.84	R	Fusifrom gyrus
22,928	$p < 0.001$	2	−66	26	6.55	R	Precuneus
14,200	$p < 0.001$	42	−66	36	5.20	R	Inferior parietal lobule
4984	$p < 0.01$	−38	−66	38	4.50	L	Inferior parietal lobule
ASD adults							
512	$p < 0.05$ *	44	−48	−22	5.28	R	Fusifrom gyrus
858	$p < 0.01$	10	−64	28	4.58	R	Precuneus
437	$p < 0.01$	60	−50	16	3.78	R	Inferior parietal lobule
TD adults − ASD adults							
n.s.							
ASD adults − TD adults							
n.s.							
Intersection of ASD adults and TD adults in conjunction analysis							
344	$p < 0.05$ *	44	−48	−22	5.28	R	Fusifrom gyrus
5824	$p < 0.01$	8	−64	26	4.47	R	Precuneus

R, right; L, left. n.s. indicates no significant activation. The statistical threshold was $p < 0.05$, corrected for multiple comparisons at the cluster level, with a height threshold of $p < 0.001$. An asterisk indicates the p value when the search region was restricted to the right fusiform gyrus.

Table 3
Mean coordinate of the EBA and FFA of TD and ASD adults in Experiment 1.

	TD adults			ASD adults		
Right EBA						
x	49.1	±	3.4	48.4	±	3.6
y	−70.7	±	3.2	−71.2	±	4.4
z	3.2	±	5.0	2.6	±	3.8
Left EBA						
x	−47.1	±	3.2	−46.1	±	3.6
y	−74.6	±	4.5	−74.9	±	3.4
z	5.8	±	2.6	6.5	±	3.4
Right FFA						
x	44.1	±	3.3	44.1	±	3.7
y	−50.4	±	6.6	−47.2	±	5.8
z	−21.1	±	3.7	−20.6	±	3.9

Mean and SD of the peak coordinates at individually defined EBAs and FFA. The analyses were conducted on participants showing significant activation in the EBAs and FFA. The statistical threshold was set with height threshold $p < 0.01$. The anatomically defined right fusiform gyrus was used as the ROI.

group and object category, as well as no main effect of group (all p values > 0.3). Thus, activation patterns of the two groups were similar.

3.1.2.2.2. The FFA. We identified the FFA in 17/17 TD adults and 15/17 adults with ASD, and the ratio of participants was not significantly different between the two groups ($\chi^2[1] = 2.1$, $p > 0.1$) (Fig. 3I). We then compared the size, location, and activation pattern of the FFA for the 17 TD adults and 15 adults with ASD. As shown in Fig. 3J, the size of the FFA was not different between the two groups ($p > 0.2$ with an independent-sample t-test). Moreover, the mean coordinates of the individually defined FFA was similar between adults with ASD and TD adults (Table 3). The distance between the mean coordinates of each group and individual peak coordinate was not significantly different between adults with ASD and TD adults (p values > 0.6 with an independent t-test; Fig. 3K). As shown in Fig. 3L, the FFA revealed highly similar response patterns between individuals with ASD and age-matched TD participants. A two-way ANOVA on object categories and groups revealed a significant main effect of object category ($p < 0.001$), no significant interaction of group and object category, and no main effect of group ($p > 0.3$). Thus, both groups showed similar activation patterns in the FFA.

3.2. Experiment 2

Experiment 1 showed highly comparable characteristics of the EBA and FFA between adults with and without ASD. In Experiment 2, we used the same procedure described in Experiment 1 to examine whether children with ASD showed atypical activation of the EBA and FFA.

3.2.1. Behavioral results of the color detection task

There was no significant difference ($p > 0.05$; independent-sample t-test) in the mean accuracy of children with ASD (95.7 ± 3.3%) and TD children (98.2 ± 2.9%). Similarly, there was no group difference in RT (523.9 ± 59.7 ms for children with ASD and 560.2 ± 93.0 ms for TD children; $p > 0.2$ with an independent-sample t-test). These results suggest that both children with and without ASD equally attended to visual stimuli. The mean accuracy

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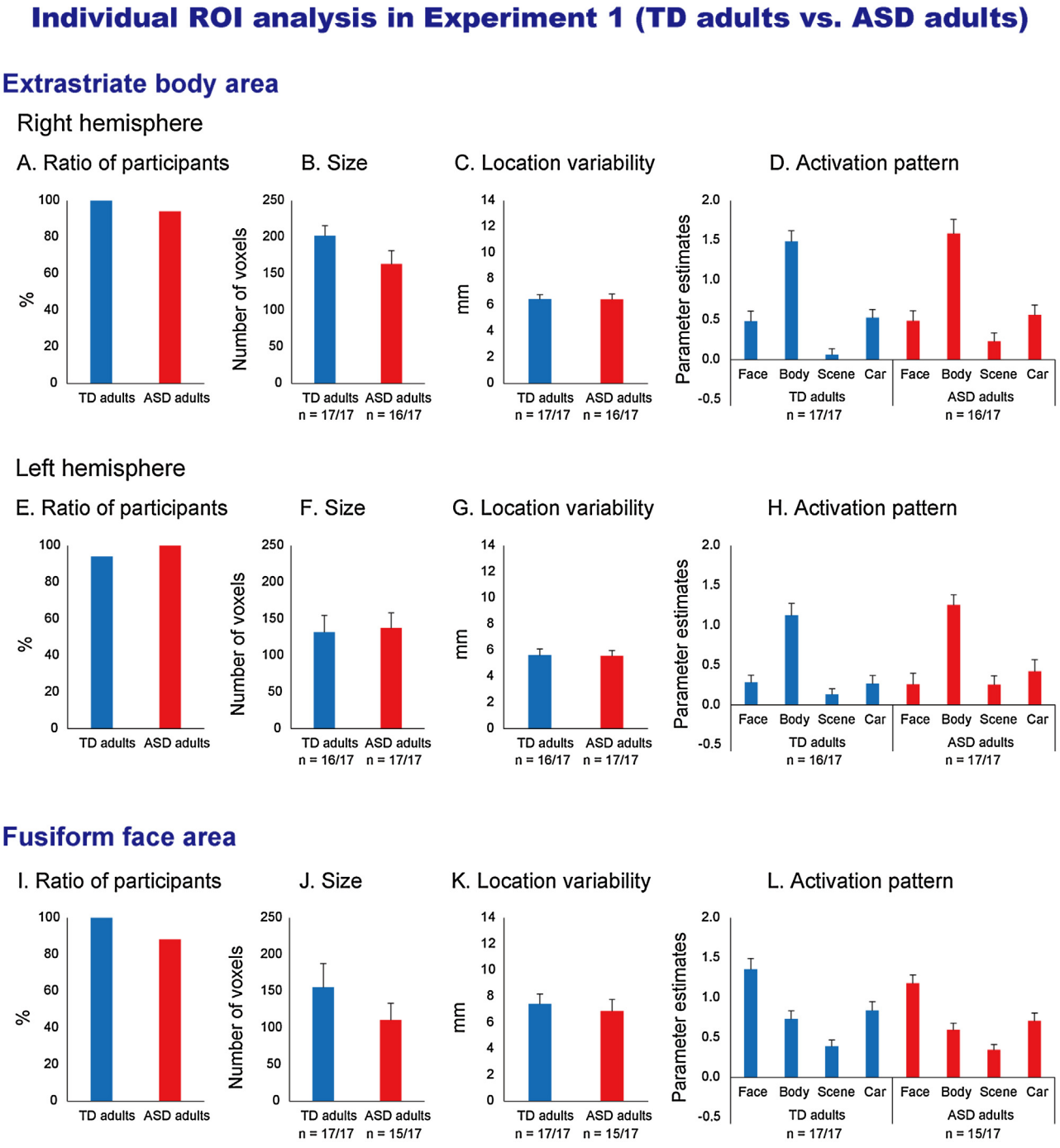

Fig. 3. Individual ROI analysis in Experiment 1 (TD adults vs. ASD adults).
Upper row (A–D) shows the right EBA, while the middle row (E–H) shows the left EBA. Lower row shows the right FFA (I–L). (A, E, I) Ratio of participants showing activation of the EBA or FFA. (B, F, J) Size, as shown by the number of voxels over the threshold within the ROI. (C, G, K) Location variability, as depicted by the distance between peak coordinates of individually defined EBAs or FFA and the mean coordinate of the EBA of FFA in each group. (D, H, L) Activation pattern of the EBAs or FFA at individually defined coordinates. The size, location variability, activation pattern were examined participants showing significant activation in the EBAs or FFA. The statistical threshold was set with a height threshold of $p < 0.01$. The ROI of EBA was defined by a sphere with an 8-mm radius of mean coordinates, as reported in previous studies ($x = 48$, $y = -70$, $z = 4$ for the right hemisphere, $x = -44$, $y = -72$, $z = 8$ for the left hemisphere). The ROI of FFA was anatomically defined the fusiform gyrus. Note that none of these parameters showed significant group difference.

and RT of TD adults was $99.4 \pm 1.5\%$ and 477.2 ± 59.8 ms, respectively.

3.2.2. fMRI results

3.2.2.1. Random effect group analysis.

3.2.2.1.1. Body-sensitive regions. Both children with ASD and TD children showed body-sensitive activation in the bilateral lateral occipito-temporal region (EBA, Table 4; Fig. 4A). In addition, TD children showed body-sensitive activation in the left postcentral gyrus and the right SPL. The conjunction analysis confirmed overlapping activation in the bilateral EBA between children with ASD and TD children, and both groups showed similar activation patterns (Fig. 4B). Moreover, we found no significant group difference.

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Table 4
Random effect group analysis of TD children and ASD children in Experiment 2.

Spatial extent test	P values	MNI coordinate			Z values	Hem	Anatomical region
Cluster size (mm^3)		x	y	z			
Body sensitive regions							
TD children							
11,976	$p < 0.001$	−50	−68	0	Inf	L	Middel temporal gyrus
14,488	$p < 0.001$	54	−74	0	6.99	R	Middle occipital gyrus
5768	$p < 0.001$	−48	−24	36	5.80	L	Postcentral gyrus
4272	$p < 0.001$	32	−48	58	4.35	R	Superior parietal lobule
ASD children							
2928	$p < 0.01$	−52	−64	2	5.09	L	Middel temporal gyrus
1416	$p < 0.05$	54	−72	−2	4.32	R	Middle occipital gyrus
TD children − ASD children							
n.s.							
ASD children − TD children							
n.s.							
Intersection of ASD children and TD children in conjunction analysis							
2928	$p < 0.01$	−52	−64	2	5.09	L	Middel temporal gyrus
1416	$p < 0.05$	54	−72	−2	4.32	R	Middle occipital gyrus
Face sensitive regions							
TD children							
2056	$p < 0.001^*$	42	−52	−18	5.05	R	Fusiform gyrus
10,448	$p < 0.001$	4	−56	28	5.60	R	Precuneus
1416	$p < 0.05$	42	20	−32	5.31	R	Superior temporal gyrus
1888	$p < 0.05$	−22	−8	−14	5.01	L	Hippocampus
2512	$p < 0.01$	18	−6	−12	4.97	R	Hippocampus
1736	$p < 0.05$	40	−72	38	4.14	R	Inferior parietal lobule
ASD children							
n.s.							
TD children − ASD children							
408	$p < 0.05^*$	42	−38	−24	3.90	R	Fusiform gyrus
ASD children − TD children							
n.s.							
Intersection of ASD children and TD children in conjunction analysis							
n.s.							

R, right; L, left. n.s. indicates no significant activation. The statistical threshold was $p < 0.05$, corrected for multiple comparisons at the cluster level, with a height threshold of $p < 0.001$. An asterisk indicates the p value when the search region was restricted to the right fusiform gyrus.

3.2.2.1.2. Face-sensitive regions. TD children showed significant face-sensitive activation in the right fusiform gyrus, right precuneus, right superior temporal gyrus, right IPL, and bilateral hippocampus (Table 4; Fig. 4C). In contrast, there was no significant activation of these regions in children with ASD. Moreover, a direct comparison revealed significantly lower face-sensitive activation in the right fusiform gyrus for children with ASD than TD children, and response patterns at the peak coordinate were quite different between TD children and those with ASD (Fig. 4D). No other brain region showed significant group differences.

3.2.2.2. Individual ROI analysis. Using the same procedure described in Experiment 1, we compared the ratio of participants showing category-sensitive activation, size, location, and activation patterns to object categories between TD children and those with ASD.

3.2.2.2.1. The EBA. The right EBA was identified in 10/12 TD children and 9/11 children with ASD. The left EBA was identified in 12/12 TD children and 8/11 children with ASD. In both hemispheres, chi-squared tests revealed no group differences in the ratio of participants where the EBA was identified (all p values > 0.05; Fig. 5A, E). Among participants showing activation in the EBA, the number of voxels in the bilateral EBA was significantly lower in children with ASD than in TD children ($t(17) = 2.1$, $p < 0.05$ for the right hemisphere, $t(16.1) = 2.3$, $p < 0.05$ for the left hemisphere, with an independent-sample t-test) (Fig. 5B, F). When we set a more stringent height threshold of $p < 0.001$, there was still a significant group difference between children with ASD and TD children in the right EBA (35.9 ± 33.1 voxels for children with ASD and 84.9 ± 54.2 voxels for TD children, $t(15) = 2.2$, $p < 0.05$) and the left EBA (23.3 ± 11.9 voxels for children with ASD and 75.6 ± 70.3 voxels for TD children, $t(9.8) = 2.3$, $p < 0.05$). Mean coordinates of the individually defined EBAs were similar between groups (Table 5). The distance between the mean coordinates of each group and the individual peak coordinate was comparable between children with ASD and TD children in the bilateral EBA (all p values > 0.3; Fig. 5C, G). As shown in Fig. 5D, H, a two-way ANOVA on object categories and groups revealed a significant main effect of object category ($p < 0.001$), no significant main effect of group, and no interaction of object category and group (all p values > 0.1).

Table 5
Mean coordinate of the EBA and FFA of TD c and ASD children in Experiment 2.

	TD children			ASD children		
Right EBA						
x	50.6	±	4.4	48.9	±	4.8
y	−71.6	±	2.3	−71.6	±	4.4
z	3.0	±	4.1	3.6	±	2.8
Left EBA						
x	−46.3	±	2.9	−48.5	±	2.6
y	−74.0	±	3.5	−72.0	±	3.7
z	5.2	±	4.0	4.3	±	6.8
Right FFA						
x	43.0	±	3.6	40.4	±	7.0
y	−50.3	±	9.5	−46.4	±	12.1
z	−21.3	±	4.7	−24.4	±	0.9

Mean and SD of the peak coordinates at individually defined EBAs and FFA. The analyses were conducted on participants showing significant activation. The statistical threshold was set with height threshold $p < 0.01$ and the anatomically defined right fusiform gyrus was used as the ROI.

3.2.2.2.2. The FFA. We identified the FFA in 12/12 TD children and 5/11 children with ASD (Fig. 5I). The ratio of participants was significantly lower in children with ASD than in TD children in Experiment 2 ($\chi^2[1] = 8.9$, $p < 0.01$). Moreover, adoption of a higher

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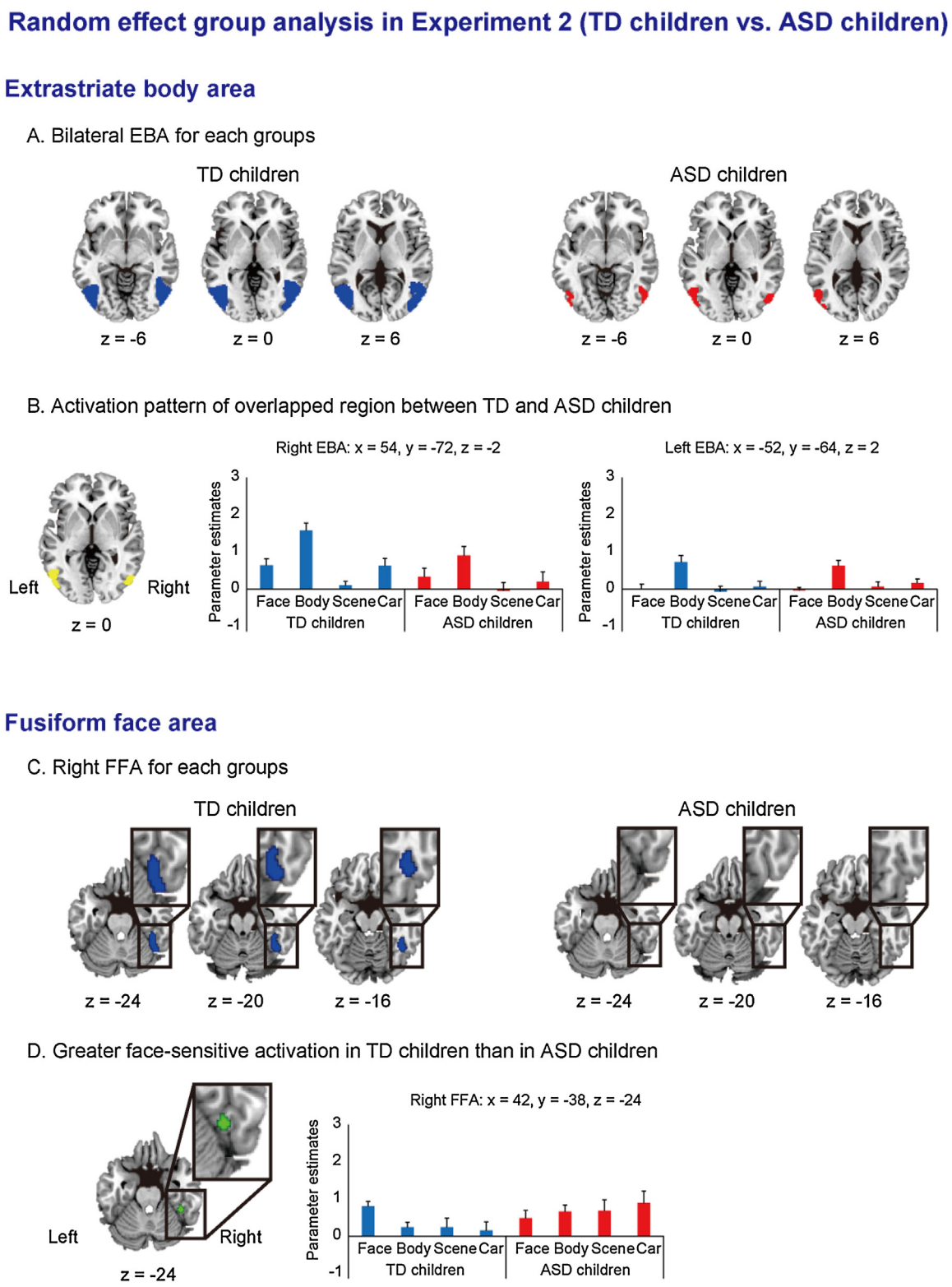

Fig. 4. Random effect group analysis in Experiment 2 (TD children vs. ASD children).
Body-sensitive activation in the lateral occipito-temporal region (EBA) and the face-sensitive activation in the fusiform gyrus (FFA) in children with ASD and TD children were superimposed on horizontal sections of a T1-weighted MR image. (A) The EBA of ASD and TD children. (B) Activation pattern of overlapping regions of the EBA between ASD and TD children. (C) The FFA of ASD and TD children. (D) Activation pattern of region showed greater face-sensitive activation in TD children than ASD children. The size of activation was set at a threshold of $p < 0.05$ and corrected for multiple comparisons, with the height threshold set at $p < 0.001$ within the anatomically defined right fusiform gyrus.

height threshold (i.e. $p < 0.001$ with height threshold) to define the FFA still yielded significant differences between TD children and those with ASD (10/12 for TD children, 2/11 for children with ASD; $\chi^2[1] = 9.8$, $p < 0.01$). Among participants showing activation in the FFA, the size was not different between children with ASD and TD children ($p > 0.2$ with an independent-sample *t*-test; Fig. 5J). More-

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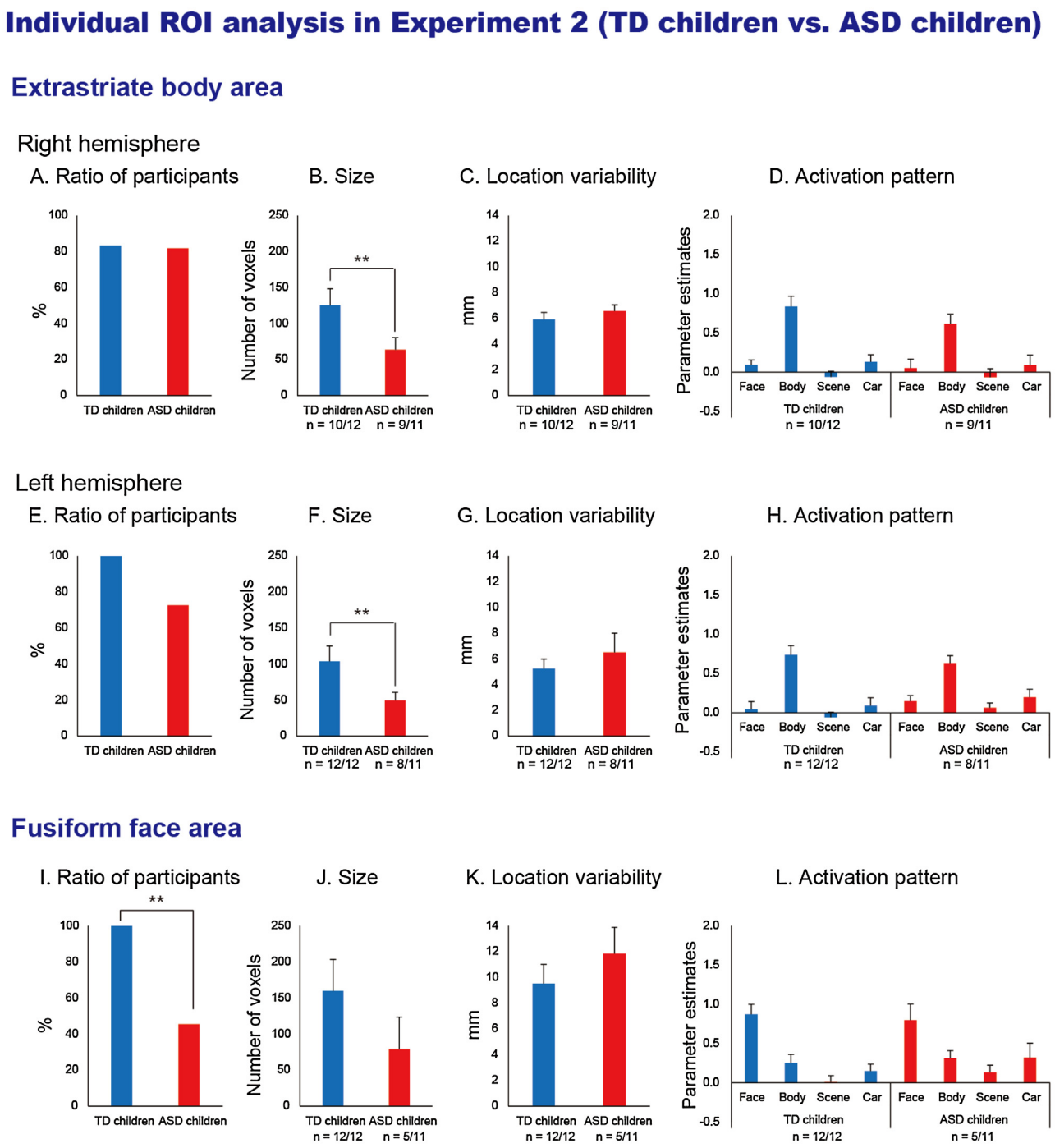

Fig. 5. Individual ROI analysis in Experiment 2 (TD children vs. ASD children).
Upper row (A–D) shows the right EBA, while the middle row (E–H) shows the left EBA. Lower row shows the right FFA (I–L). (A, E, I) Ratio of participants showing activation of the EBA or FFA. (B, F, J) Size, as shown by the number of voxels over the threshold within the ROI. (C, G, K) Location variability, as depicted by the distance between peak coordinates of individually defined regions and the mean coordinate in each group. (D, H, L) Activation pattern at individually defined coordinates. The size, location variability, activation pattern were examined participants showing significant activation in the EBAs or FFA. The statistical threshold was set with a height threshold of $p < 0.01$. The ROI of EBA was defined by a sphere with an 8-mm radius of mean coordinates, as reported in previous studies ($x = 48$, $y = -70$, $z = 4$ for the right hemisphere, $x = -44$, $y = -72$, $z = 8$ for the left hemisphere). The ROI of FFA was anatomically defined the fusiform gyrus.

over, the mean coordinates of the individually defined FFA was similar between children with and without ASD (Table 5). The distance between mean coordinates of each group and individual peak coordinates was not significantly different between children with ASD and TD children ($p > 0.3$ with an independent *t*-test; Fig. 5K). As shown in Fig. 5L, the FFA revealed highly similar response patterns between children with ASD and TD children. A two-way ANOVA on object categories and groups revealed a significant main effect of object category ($p < 0.001$), whereas there was no significant main effect of group and no interaction of object category and group (all p values > 0.3). In sum, although over half of children with ASD failed to show activation in the FFA, the remaining children with ASD showed activation in the FFA that was similar to TD children.

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3.3. Can differences between children with ASD and TD children be explained by head movement?

As head motion can affect fMRI results, it is possible that the difference in category-sensitive activation of the EBA and FFA was caused by differences in head motion between children with ASD and TD children. To explore this possibility, we compared motion parameters of three displacements (x–z axes) and three rotations (pitch, roll, and yaw) between children with ASD and TD children. More specifically, we calculated (1) the difference in the maximum and minimum values of each parameter within a run and (2) the SD of the time-series values of each parameter within a run. Supplementary Table 1 shows the mean of these values between the two tested runs. An independent-sample *t*-test revealed no significant difference between children with ASD and TD children in all values (all p values > 0.2). We then examined correlations between regressors of each object (face, body, scene, and car) and the six motion parameters for TD children and those with ASD (Supplementary Table 2). A two-way ANOVA on each motion parameter revealed no significant main effect of object or group, nor did it reveal an interaction of objects and groups (all p values > 0.05). Furthermore, we calculated the number of motion contaminated volumes defined by metric of frame-wise displacement (>0.9 mm) for each group (Siegel et al., 2014). There was no significant between-group difference for the number of motion contaminated volumes in two fMRI sessions ($t(21) = 0.59$, $p > 0.5$, independent samples *t*-test, 22.0 ± 28.0 for ASD children group and 16.1 ± 19.5 for TD children group). Thus, since head motion did not differ between children with ASD and TD children, it is unlikely that different category-sensitive activation in these regions can be explained by group differences in head motion.

3.4. Scanner differences and variability in individual characteristics did not explain age-dependent atypicalities in the EBA and FFA

As we utilized different scanners in Experiments 1 and 2, it is possible that atypicalities in category-sensitive activation of the EBA and FFA in children with ASD could be due to the difference in scanners. To consider this possibility, we examined EBA and FFA activation in 12 TD adults using the same MR scanner utilized in Experiment 2. As shown in Supplementary Table 3, TD adults showed significant body-sensitive activation in the bilateral occipito-temporal regions. Distances of the peak coordinates between the TD adults in Experiment 1 and 2 were 10.8 and 7.5 mm for the right and left hemisphere, respectively. Furthermore, we identified the right FFA and the distance of the peak coordinates between the TD adults in Experiment 1 and Experiment 2 as 8.2 mm. As the effective resolution [i.e., final smoothness] was 15.1 mm for Experiment 1, these results indicated that the locations of the EBA and FFA in TD adults were comparable between Experiments 1 and 2. In addition, the strength of the static magnetic field was higher in Experiment 1 for adults (3.0T) than in Experiment 2 for children (1.5T). Generally, MRI scanners with high-strength static magnetic fields are more sensitive than those with low-strength static magnetic fields. Nevertheless, we found a significant intergroup difference in Experiment 2 using a 1.5 T MRI scanner. Therefore, these fact suggest that atypicalities in category-sensitive activation in the EBA and FFA in children with ASD were not merely due to the difference in MR scanner.

Other than the MR scanner, it is possible that individual characteristics (e.g., autistic tendency and intellectual ability) might explain our results. If this were true, then AQ total scores and FSIQ would be different between children with ASD and adults with ASD, and these scores would be associated with the existence FFA activation or size of the EBA in children with ASD. The mean of AQ total scores amongst adults with ASD in Experiment 1 (33.5) and children with ASD in Experiment 2 (30.4) was within −1 SD of previous reports of AQ scores in Japan (37.9 ± 5.31 for adults with ASD and 31.9 ± 6.69 for children with ASD) (Wakabayashi et al., 2007; Wakabayashi et al., 2006). An independent *t*-test on the FSIQ also revealed no significant difference between children with ASD and adults with ASD ($p > 0.05$). Therefore, the autistic tendency and intellectual ability of children and adults with ASD did not substantially differ. Furthermore, the AQ total score and FSIQ were not different between children with ASD showing activation of the FFA and those without FFA activation (all p values > 0.5 with an independent sample *t*-test). There was also no correlation between the size of the EBA and AQ total score ($p > 0.5$) or the size of the EBA and FSIQ ($p > 0.2$). Thus, the existence of FFA activation and the size of the EBA in children with ASD were both not associated with FSIQ and AQ total score. These findings suggest that age-dependent atypicalities in the EBA and FFA were not due to differences in these characteristics.

4. Discussion

In the present study, we confirmed that adults with ASD showed similar activation in the EBA and FFA to TD adults. By contrast, children with ASD and TD children showed distinct activation in these region. More specifically, the size of the EBA in children with ASD was smaller than those in TD children. Furthermore, less children with ASD showed activation in the FFA, as compared to TD children.

4.1. Similar activation in the EBA and the FFA for adults with ASD

In our previous study (Okamoto et al., 2014), we reported similar activation in the EBA in a random effect group analysis between individuals with and without ASD. In the present study, we determined that the ratio of participants showing activation of the EBA, as well as its size, location, and activation pattern was also similar between adults with and without ASD. These findings suggest that visual processing of non-face body parts in the EBA is normal in adults with ASD. However, it has been suggested that the EBA is also involved in higher-order cognition, such as the sense of agency and the detection of social contingency during reciprocal imitation (David et al., 2007, 2009; Okamoto et al., 2014). Our previous study found that activation in the left EBA is attenuated in adults with ASD when participants are imitated by another person. These results suggest that adults with ASD have atypicalities in the detection of contingency between visually observing an individual's actions and executing one's own actions. Detection of social contingency, as well as the sense of agency, is considered to be processed within the network of the EBA and the front-parietal region including putative mirror neuron system (Jeannerod, 2004; Okamoto et al., 2014; Sasaki et al., 2012). Thus, it is reasonable that visual processing of non-face body parts in the EBA is intact for adults with ASD, while the network of the EBA and the frontal-parietal region, which contribute to social contingency detection or the sense of agency, are disturbed.

Similar to the EBA, we found comparable activation in the FFA for adults with and without ASD, which is consistent with previous fMRI studies that utilized passive viewing tasks (Hadjikhani et al., 2004, 2007). Although participants in the present study performed a color-detection task, they were not required to memorize or recognize facial emotion. Therefore, our current findings confirmed that adults with and without ASD exhibit equivalent activation in the FFA when observing neutral faces in the absence of cognitive demands. Moreover, these findings indicated that, similar to TD adults, adults with ASD possess a clustered region in the brain that is sensitive to viewing faces (i.e. FFA). In contrast to our findings, sev-

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eral fMRI studies which require participants to perform a task while focusing on a face, such as memorizing a face during the n-back task or judging emotion, tend to show reduced activation in the FFA for adults with ASD (e.g. Critchley et al., 2000; Humphreys et al., 2008; Kleinhans et al., 2010; Pierce et al., 2001; Piggot et al., 2004; Pinkham et al., 2008; Schultz et al., 2000). It has been proposed that several brain regions are involved in facial memorization and the recognition of emotion. For instance, the FFA and the medial temporal lobe of the hippocampus are considered to be important for encoding and retrieving facial information (Tsukiura, 2012). Moreover, Haxby and Gobbini (2011) proposed that emotional facial expressions are processed in the network between the "core system", which includes the FFA, and the "extended system", which includes the inferior parietal and frontal operculum, associated with recognizing facial expression, and the amygdala, the insula and the striatum, associated with recognizing emotion (Haxby and Gobbini, 2011). Thus, reduced activation in the FFA in adults with ASD might reflect atypicalities in network formed between the FFA and other brain regions. Collectively, although adults with ASD have atypicalities in connection between the FFA and other brain regions, such as the hippocampus and inferior parietal lobule and frontal operculum, the function of the FFA which processes invariant facial features might be intact.

4.2. Atypical activation in the EBA and the FFA in children with ASD

Even though we utilized the same task as that employed in Experiment 1, Experiment 2 revealed that children with ASD showed atypical activation in the EBA and FFA. Specifically, the size of the bilateral EBA was smaller in children with ASD than in TD children and a smaller percentage of children with ASD showed face-sensitive activation of the FFA than TD children. These findings suggested that, unlike adults with ASD, children with the disorder had atypicalities in the FFA and EBA.

An individual ROI analysis revealed that children with ASD had smaller bilateral EBA when compared to TD children. Although a random-effects group analysis showed no significant difference in the EBA, the cluster size of the bilateral EBA in TD children was over four times greater than the size of the EBA in children with ASD. Because almost all children with ASD showed activation in the EBA at the individual level (more than 70%), a smaller EBA could be an overall trend for children with ASD, rather than reflecting a specific sub-population. These results could help explain why children with ASD have difficulties in processing visual stimli such as non-face body parts; specifically, such impairments could be due to a reduction in bilateral EBA size. To our knowledge, no study has examined neural responses in the EBA in children with ASD; therefore, this is the first report showing atypicalities in the EBA in this specific population.

We showed that a smaller portion of children with ASD exhibited face-sensitive activation in the FFA than TD children. Similar to our study, previous studies have shown hypo-activation of the FFA in children with ASD (Corbett et al., 2009; Grelotti et al., 2005; Malisza et al., 2011; Pierce and Redcay, 2008; Scherf et al., 2010). However, most previous studies examined FFA activation during cognitive-demanding tasks (Corbett et al., 2009; Grelotti et al., 2005; Malisza et al., 2011; Pierce and Redcay, 2008); therefore, it is possible that the reduced activation could be explained by disturbances in connectivity between the FFA and other brain regions, rather than FFA dysfunction itself. Scherf et al. (2010) found reduced face-sensitive activation in the FFA of children with ASD when participants viewed movies of faces compared to movies showing other categories of familiar objects (Scherf et al., 2010). However, gaze atypicalities during passively observed movies have been well documented in children with ASD (Klin et al., 2002; Nakano et al., 2010). As gaze atypicalities are associated with reduced FFA activation in both adolescents and adults with ASD (Dalton et al., 2005; Perlman et al., 2011), it is also possible that the previously reported results in children with ASD might have merely been caused by atypical gaze patterns. In the current study, participants were not required to perform any cognitive tasks when presented with visual stimuli in any of the tested object categories. Therefore, the lack of FFA activation in some children with ASD could not be explained by a disturbance in the network between the FFA and extended system involved in facial recognition. Furthermore, as children with and without ASD showed similar behavioral performance in the color-detection task, our findings confirmed that they both groups of children attended similarly to visual stimuli. Therefore, results of the current study revealed that some children with ASD exhibited no FFA activation, likely reflecting a disturbance in the processing of invariant facial features in the FFA.

4.3. Possible developmental changes in EBA and FFA function in individuals with ASD

The age-dependent atypicalities observed in the EBA and FFA imply that atypiclities in these regions normalize before adulthood. Indeed, these findings are consistent with previous behavioral studies that have reported improvements in body and/or face recognition over development in individuals with ASD (Dowell et al., 2009; Serra et al., 1998; Strauss et al., 2012). For instance, Dowell et al. (2009) showed a positive correlation between the recognition of a skilled gesture and the age of children with ASD. Strauss et al. (2012) also found better gender discrimination skills (using faces alone) in adults with ASD than in children with ASD. As the FFA is relevant for facial gender discrimination (Contreras et al., 2013; Freeman et al., 2010; Wiese et al., 2012), we can speculate that normalized visual processing related to body- and/or face-related stimuli in the EBA and FFA contribute to improvements in the recognition skills of individuals with ASD.

The abovementioned findings pose the question of whether atypical development of the EBA and FFA in children with ASD is due to developmental delay or deviation from the normal course of development. Interestingly, smaller EBAs and an absence of FFA activation have been reported in young TD individuals (Gathers et al., 2004; Pelphrey et al., 2009; Ross et al., 2014; Scherf et al., 2007). For instance, TD children around 9-years-old exhibit significant body-sensitive activation of the EBA; however, the size of the activated region is smaller than what is observed in TD adults (Ross et al., 2014). Moreover, Gathers et al. (2004) found that children aged 9- to 11-years-old exhibit activation of the FFA, while younger children (5- to 8-years-old) do not [59]. These studies suggest that the atypical EBA and FFA activation observed in children with ASD in the present study reflect immaturity of these regions. In support of this, we found that adults with ASD showed comparable activation in these regions to TD adults; thus, individuals with ASD likely have delayed EBA and FFA development.

We speculate that a delay in EBA and FFA development might be due to less experience in observing other individuals. In support of this, Schultz (2005) proposed that subjects with ASDs avoid gazing at the faces of other individuals during early childhood, and that this leads to facial recognition deficits. For TD individuals, there is an inborn preference to look at other faces, and this prompts maturation of the face-perception network that includes the FFA. Conversely, avoiding faces results in immaturity of face-related brain regions in subjects with ASDs (Schultz, 2005). This theoretical account could be applicable for EBA and FFA immaturity in children with ASD. However, although children with ASD have less experience looking at faces and/or bodies, they will inevitably encounter more and more people over time. This increase in experience look-

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ing at faces and bodies could therefore explain the gradual increase in EBA and FFA function throughout development.

4.4. Limitations

We should note limitations of the present study. First, although we have proposed that atypicalities in the EBA and FFA led to difficulties in face and/or body recognition, the current study does not provide direct evidence for this. Considering that the relationship between the activation patterns and the improvement of skills are not straightforward (e.g., Naito and Hirose, 2014; Takahashi et al., 2012; Sakai, 2005), further studies examining the relationship of brain activation and recognition behaviors are therefore necessary. Second, it remains unclear why about half of the children with ASD in our sample showed activation in the FFA, while the other half did not. There are several possibilities to explain FFA atypicalities. Because ASD is highly heterogeneous, there might be sub-groups of individuals with ASD who do not have delayed functional maturation of the FFA. Although we were not able to associate differences in autistic traits or intellectual ability with FFA atypicalities, other factors (e.g., genetic background or environment) might be associated with the immaturity in this brain region. Otherwise, it is possible that the ages we examined denoted a transitional phase in FFA maturation. We predict, based on this assumption, that children with ASD who did not show EBA and FFA activation will show activation of the FFA in the near future. In this case, however, we should consider the possibility that these children show alternative activation in other regions, such as the EBA, in middle and late adolescence, which reflects the use of alternative strategies for viewing faces. To address such possibilities, future studies examining the association between FFA activation and genetic and environmental factors will help explain the individual variability observed in the current study; fMRI studies on a larger sample size than in the present study would allow this approach. Furthermore, longitudinal studies could provide more precise developmental trajectories of the FFA. Third, previous studies have shown that several factors such as gaze pattern (Dalton et al., 2005; Perlman et al., 2011) and familiarity of faces (Pierce and Redcay, 2008) also lead to controversial results regarding activation in the FFA. Therefore, examining age-difference of the activation in the FFA by manipulating familiarity of faces (e.g., viewing faces of well-known persons or strangers) or examining the contribution of gaze pattern to FFA activation using an eye-tracking system should provide more comprehensive understanding of the development of FFA in individuals with ASD. Fourth, we can speculate that developmental courses may be different network of the EBA for performing reciprocal imitation task, and FFA for recognizing facial expressions or memorizing identity of face. These possibilities should examine in the near future.

5. Conclusions

The present study showed atypicalities in EBA and FFA activity in children with ASD. More specifically, EBA size in children with ASD was smaller than in TD children. Moreover, fewer children with ASD showed face-sensitive activation of the FFA. In contrast, adults with ASD showed no such atyicalities. These findings suggest that maturation of the EBA and FFA is delayed in individuals with ASD but that such regional atypicalities normalize before adulthood.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neures.2017.02.001.

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