

Deviant gaze processing in children with autism: an ERP study

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Abstract

This study investigated event-related potentials (ERP) during an oddball task in which detection of specific eye direction was required of children with and without autism. The detection of a change in eye direction elicited occipito-temporal negativity, which had two major differences between children with and without autism. First, while this occipito-temporal negativity predominated in the right hemisphere of typically developed children, it was distributed equally bilaterally in children with autism. Second, the amplitude of this negativity was more pronounced in typically developed children in response to the detection of direct gaze as compared to averted gaze, but was not sensitive to direct/averted gaze direction in children with autism, which converges with behavioral reports. The results concur with previous literature, suggesting the importance of the right hemisphere, especially the superior temporal sulcus, in gaze processing. Results indicate that deviant neural substrates might be involved in gaze processing in individuals with autism.

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1. Introduction

Autism is characterized by deficits in social interaction and communication, and by stereotyped, restrictive, and repetitive behavior and interests (DSM-IV, American Psychiatric Association, 1994). Among the characteristics of autism, a qualitative impairment in eye contact behavior is commonly reported in clinical and observational studies (Buitelaar, 1995; Volkmar & Mayes, 1990). Moreover, such atypical eye contact behavior can be observed from very early stage of their development (Baranek, 1999; Charman et al., 1997). Atypical fixation patterns during viewing facial stimuli in high-functioning individuals with autism were also revealed through recent studies with eye-tracking devices; their fixation time on facial features, especially the eye region, is significantly shorter than that of individuals without autism (Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Pelphrey et

al., 2002). These atypical patterns of eye gaze processing are assumed to be relevant to the characteristic social and communicative developmental deficits of this disorder in the current ‘theory of mind’ or ‘social brain’ hypothesis (Baron-Cohen, 1995). However, while several studies have found atypical neural activation while perceiving faces (Carver & Dawson, 2002; Pierce, Miller, Ambrose, Allen, & Courchesne, 2001; Schultz et al., 2000, but see also Hadjikhani et al., 2004), identifying faces (Dawson et al., 2002), and processing facial emotion (Critchley et al., 2000), to date very little is known about the neural bases of eye gaze processing in individuals with autism.

Several previous ERP or MEG studies have investigated the effect of gaze direction of perceived facial stimuli in typically developed population, but results were inconsistent. Some have found that laterally averted gaze elicited larger occipito-temporal negativity (N170; Bentin, Allison, Puce, Perez, & McCarthy, 1996; Eimer, 2000; Sagiv & Bentin, 1999) than did direct gaze (Puce, Smith, & Allison, 2000; Watanabe, Kakigi, & Puce, 2001; Watanabe, Miki, & Kakigi,

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2002) in adult participants. Farroni, Csibra, Simion, and Johnson (2002), in contrast, recorded ERPs from infants and found larger occipital negativity (infant N170) for direct gaze than for averted gaze. Others, however, failed to find differences between ERPs or event-related electro-magnetic fields (ERFs) in response to direct gaze or laterally averted gaze (Taylor, George, & Ducorps, 2001; Taylor, Itier, Allison, & Edmonds, 2001), although both direct and averted gaze elicited larger N170 than upward gaze and closed eyes.

To the best of authors' knowledge, there is only one previous study, which investigated the neural correlates of gaze perception in individuals with autism with ERP measurement (Grice et al., in press). Grice et al. (in press) recorded high-density ERPs from young children (3.5–7 years old) with autism while they are passively viewing faces with varying eye gaze directions, and found that perceived direct gaze elicited larger occipito-parietal negativity than averted gaze, just like 4-month-old infants (Ferroni, Csibra, Simion, & Johnson, 2002) but ERPs of age-matched control children or those of non-autistic adults were not sensitive to the perceived gaze direction. Their findings, which may indicate the delayed development of gaze processing in autism, are intriguing. But it is surprising they did not find any gaze-direction effect in non-autistic participants, considering the sensitivity to the perceived eye gaze direction often found in other behavioral studies (e.g., Senju & Hasegawa, in press; von Grönau & Anston, 1995). It might be due to the use of passive viewing paradigm, rather than active detection or discrimination tasks usually used in behavioral studies. Thus, neural correlates of active, rather than passive, processing of gaze direction need to be investigated in individuals with and without autism.

This study explored the electrophysiological or neurocognitive basis of active gaze processing, especially the active detection of direct gaze, by concurrent measurement of ERPs in individuals with and without autism. Because atypical orienting to social stimuli in individuals with autism has been reported (Ceponiene et al., 2003; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998), it was predicted that ERPs corresponding to active detection of change in gaze direction are deviant in individuals with autism.

During the ERP recording, stimuli with various eye gaze directions were presented according to the visual oddball paradigm, which involves presenting a series of frequent stimuli into which rare stimuli are inserted. This study used two kinds of rare stimuli: one in a direct gaze condition and the other in an averted gaze condition. The participants were instructed to respond to one of the two rare stimuli, while ignoring the other. Thus, participants in this study were required to actively detect gaze direction, rather than passively as in previous studies (Farroni et al., 2002; Puce et al., 2000; Taylor, George, et al., 2001; Taylor, Itier, et al., 2001; Watanabe et al., 2001, 2002). Although gaze discrimination has never been examined in an oddball paradigm, it seems a promising way to explore the electrophysiological activities corresponding to the detection of changeable aspects of face such as gaze di-

rection and facial expression. For example, the visual oddball paradigm was used in a previous study to record the ERPs while participants were discriminating facial expressions and found that the occipital negative component (N2) in the difference wave, accompanied by a frontal positive component (P3a), reflects the behavioral performance of the discrimination of facial expressions (Campanella et al., 2002).

2. Methods

2.1. Participants

Thirteen children with autism (all males; mean age 12:1 years, range 9:10–14:11 years) and 15 age-matched typically developing children (13 males and 2 females; mean age 12:1 years, range 9:5–14:10 years) participated in this study. All of the children were students or graduates of a primary school that is attended by both autistic and typically developing children. Informed consent was obtained from each child, his or her parents, and the school director, and the study was first approved by the Ethical Committee at Jikei University. One additional child with autism declined to participate in the experiment and was excluded from the study. All of the children with autism met the DSM-IV criteria for autistic disorder (American Psychiatric Association, 1994), and all had been diagnosed with autistic disorder by at least one child psychiatrist when they entered the school. Japanese Raven's colored progressive matrices (RCPM; Raven, 1956; Sugishita & Yamazaki, 1993) was administered to all of the children to estimate their nonverbal cognitive abilities, which were well within the normal range (>26). All of the children had normal or corrected-to-normal visual acuity. All of the experiments were conducted with the children individually in a quiet room at the National Institute of Special Education, which is near their primary school.

2.2. Stimuli

Color photographs of the laterally averted faces of three female models were cut into ovals (5° wide and 7° high, with each eyelid subtending 1.2° wide and 0.3° high) to produce one frequent and two rare stimuli for each model. Fig. 1 shows examples of each stimulus type. The frequent stimuli (Fig. 1, left) were faces glancing downward. The rare stimuli were faces either with direct gaze (Fig. 1, center) or with laterally averted gaze (Fig. 1, right). The size of each eyelid was 1.2° wide and 0.5° high for each rare stimulus. The three stimuli were produced from the same basic image, on which the same person's eyes were superimposed from other photographs according to stimulus type, on Adobe Photoshop 7.0 software. This resulted in three stimuli that were exactly the same, except for eye direction, or at least the shape of eye region. Note that all facial stimuli were laterally averted to eliminate the possibility that lower perceptual features such as symmetry of eye shape might affect the results. Ten independent typ-

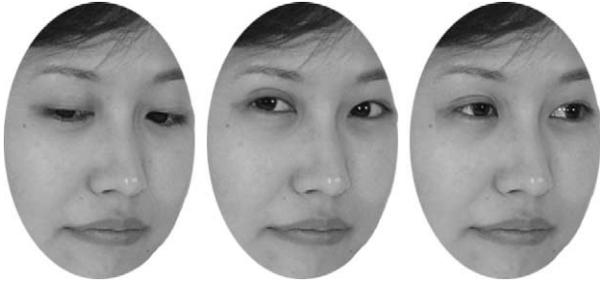


Fig. 1. Examples of frequent and rare stimuli. Left: frequent stimulus, face glancing downward. Center: rare stimulus with direct gaze (direct gaze). Right: rare stimulus with laterally averted gaze (averted gaze). Stimuli were presented in full color.

ical adults (six female, four male) judged the eye direction of the stimuli and all agreed which picture is with a direct gaze or an averted gaze. Note that our previous studies with typical adults used the same facial stimuli and found that perceived direct gaze enhances visual search (Senju, Hasegawa, & Tojo, *in press*) and delays disengagement from the facial stimuli (Senju & Hasegawa, *in press*).

In all, nine stimuli (three models \times three eye directions) were used in this experiment. In addition, a fixation point consisting of a central cross that subtended 0.5° appeared on a display screen and the children were instructed to fixate on it before the experiment started. The presentation of stimuli and the recording of reaction times (RTs) and accuracy were controlled by a personal computer with a 17-in. color monitor and commercial software (Stim; Neuroscan Inc., USA). The participants were seated approximately 130 cm from the monitor, and their performance was calculated from their button-press responses.

2.3. Design and procedure

The experiment consisted of six blocks of trials. Standards, targets, and non-targets in each block were always photographs of the same model, presented at frequencies of 82% (standard), 9% (target), and 9% (non-target). Faces with direct gaze were used as the target in half of the blocks, and those with gaze-averted faces were the targets in the other blocks. Non-targets were always the other rare stimuli, or the counterparts of targets. Block order presentation was randomized among children. The practice sequence consisted of 29 trials, while the test sequences varied from 112 to 162 trials across blocks, in order to make the end of the block unpredictable for the participants.

Each block consisted of a practice sequence followed by a test sequence. A practice sequence presented the series of standards and targets. Before beginning a practice sequence, the researcher showed the child printed photographs of the standard and target, and the child was instructed to press one button on seeing the standard and another for the target, as soon as he or she detected the stimulus. The test sequence included non-targets, in addition to standards and targets, and instructions were to press the corresponding buttons for the

standards and targets with the preferred hand, but not to press any buttons for the non-targets. As in the practice sequence, the child was instructed to press the corresponding button as quickly as possible, and as accurate as possible. The first target did not appear until at least 14 standard stimuli had been shown. Presentation of subsequent rare stimuli (both targets and non-targets) was pseudo-randomized. Each trial started with presentation of the fixation point for 200 ms, followed by presentation of one of the stimuli, which remained on the screen for 500 ms. The inter-trial interval (ITI) was 1500 ms. No feedback was given about their behavioral performances.

2.4. Electroencephalographical recording and averaging

Exploring electrodes were placed at vertex (Cz), left occipito-temporal (T5), and right occipito-temporal (T6) sites, as these are reported to be the best sites for recording face-specific ERP components (McCarthy, Puce, Belger, & Allison, 1999; Puce et al., 2000; Taylor, Edmonds, McCarthy, & Allison, 2001; Taylor, McCarthy, Saliba, & Degiovanni, 1999; Watanabe, Kakigi, & Puce, 2003; Watanabe et al., 2002). Vertical and horizontal electrooculograms (EOG) were also recorded to control for the possible artifacts caused by eye movements. All electrodes were first recorded with right earlobe reference and then recalculated to refer to the average of both earlobes off-line. Although chin or nose reference was preferred in previous ERP studies aiming at recording face-related activities (e.g., Puce et al., 2000; Taylor et al., 1999), we adopted earlobe reference to minimize the load for children with autism, some of whom have been reported to be hypersensitive (O'Neill & Jones, 1997). Electrode impedance was kept below $10\text{ k}\Omega$. Individual trials in which signal variations were greater than $\pm 100\ \mu\text{V}$ in ERP or EOG were excluded from averaging. ERP and EOG were recorded with a NeuroScan scan system (Neuroscan Inc., USA) for 400 ms following stimulus onset, with a 100-ms pre-stimulus baseline, and a bandpass of 0.1–30 Hz. The sampling rate was 250 Hz, and data were stored on disc for further off-line analysis. ERP data of two children with autism were excluded from analysis, because too few noise-free trials were recorded. Consequently, data obtained from the remaining 11 children with autism and the 15 typically developed children were used for all the ERP analyses.

2.5. Analyses

Three-way analyses of variance (ANOVAs) for group (autism versus typical development), frequency (frequent versus rare), and electrodes were conducted on peak latencies and amplitudes for each component. Difference waves were calculated in which the ERP for frequent stimuli was subtracted from the ERP in response to rare stimuli for each condition (target versus non-target and direct versus averted gaze). Peak latencies and amplitudes were examined by four-

way ANOVAs for group (autism versus typical development), gaze direction (direct versus averted), task requirement (target versus non-target), and electrodes.

3. Results

3.1. Behavioral performance

Behavioral performance has been presented elsewhere (Senju, Yaguchi, Tojo, & Hasegawa, 2003). Results with typically developing children replicated previous reports, in that stimuli with direct gaze were more accurately detected than those with averted gaze ($d' = 2.62$ for direct gaze and 1.47 for averted gaze, $F(1, 26) = 13.91$, $p < .01$). Results with children with autism, however, found no effect of gaze direction on their performance ($d' = 1.10$ for direct gaze and 0.93 for averted gaze, $F < 1$, $p > .1$). In addition, when their levels non-verbal intelligence (i.e., the score of RCPM) were introduced as a covariate, group difference was significant in direct gaze detection ($F(1, 25) = 12.84$, $p < .01$), but not in averted gaze detection ($F(1, 25) = 1.59$, ns). There was no significant effect of reaction time (RT; in children with autism, average RT = 562.6 ms for direct gaze and 563.5 ms for averted gaze; in typically developed children, average RT = 540.6 ms for direct gaze and 563.1 ms for averted gaze; all $F < 1.3$, $p > .1$).

3.2. ERP: frequent versus rare stimuli

ERPs in response to rare stimuli were averaged for each participant and compared to averages of frequent stimuli (Fig. 2); five main components, occipito-temporal P130 (at T5, T6), vertex N130 (at Cz), two peaks of occipito-temporal negativity (N170 and N270) and vertex P290 were found in the ERP waveforms in this study (Table 1). The latencies and amplitudes of the first two components, P130 and N130, were unaffected by stimulus frequency (all $F < 2.8$, $p > .1$).

An earlier peak of occipito-temporal negativity, N170, has been assumed to reflect face-specific activities in adults (Bentin et al., 1996; Eimer, 2000; Sagiv & Bentin, 1999) and in typically developing children (Taylor et al., 1999; Taylor, Edmonds, et al., 2001). A later peak, N270, was not reported in previous studies concerning gaze direction. Both N170 and N270 were larger for rare stimuli than for frequent stimuli (N170: $F(1, 24) = 9.67$, $p < .01$; N270: $F(1, 24) = 70.88$, $p < .001$). However, since these two components were overlapping, the independent effect of each component could not be determined. In addition, there was a significant interaction between frequency and electrode for N270 amplitude ($F(1, 24) = 18.21$, $p < .01$) as the frequency effect was larger for the right than for the left hemisphere. N170 peak latency was faster for the right than for the left hemisphere ($F(1, 24) = 5.29$, $p < .05$). There were no significant effects of N270 peak latency. Importantly, there were no significant effects for participant group.

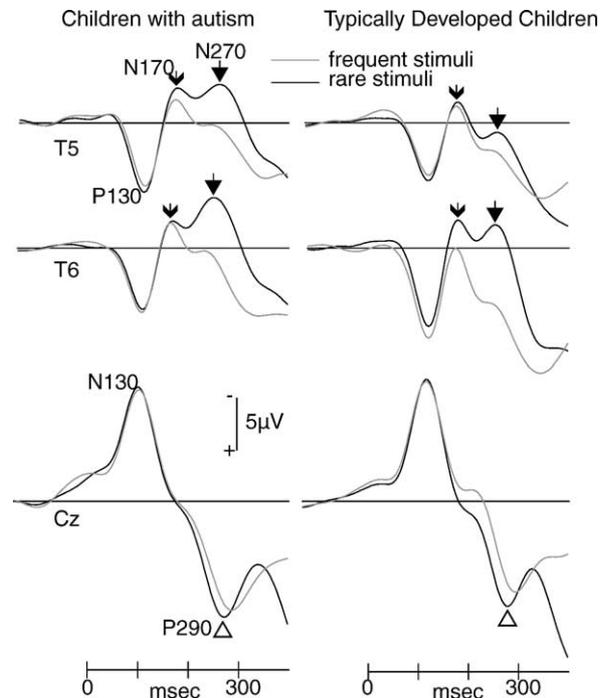


Fig. 2. Grand-average ERP waveforms of children with and without autism in response to frequent and rare stimuli at T5 (left occipito-temporal region), T6 (right occipito-temporal region), and Cz (vertex). The ERP components sensitive to stimulus frequency were occipito-temporal negativity (N170 and N270, at T5 and T6) and vertex positivity (P290, at Cz). In contrast, neither P130 nor N130 was sensitive to stimulus frequency. Left: ERPs from children with autism. Right: ERPs from typically developed children.

The positive potential at anterior sites, known as vertex positive potential (VPP), did not correspond with N170 in this experiment, which contrast to other studies. The absence of VPP may be attributable to the age of the participants, as VPP is reported to be absent in younger populations (Taylor et al., 1999). P290, whose peak latency is faster for rare than for frequent stimuli ($F(1, 24) = 11.03$, $p < .01$), was recorded at vertex (Table 1). By contrast, the peak amplitudes of P290 did not differ from each other. There were no significant effects of participant group for P290.

When analyzed separately according eye gaze direction (direct versus averted) and task requirement (target versus non-target), no effect reached significance for all components.

3.3. ERP: targets versus non-targets, direct versus averted gaze

Figs. 3 and 4 present difference waves, in which the ERPs for frequent stimuli were subtracted from the ERPs in response to rare stimuli for each condition (target versus non-target, direct versus averted gaze). Only occipito-temporal negative component (N2) and vertex positive component (P3a) amplitudes were elicited. This difference wave represents ERP in response to the detection of rare stimuli, exclud-

Table 1

Latency and amplitude of ERP components for frequent and rare stimuli at each electrode in children with autism and in typically developed children^a

	P130 (T5)	P130 (T6)	N130 (Cz)	N170 (T5)	N170 (T6)	N270 (T5)	N270 (T6)	P290 (Cz)
Latency (ms)								
Autism								
Frequent	131.3 ± 10.9	132.0 ± 9.6	128.0 ± 7.8	187.3 ± 16.8	184.7 ± 9.9 ^b	259.3 ± 25.4	259.3 ± 12.2	296.4 ± 27.5
Rare	130.0 ± 13.0	133.7 ± 11.4	127.6 ± 7.3	191.3 ± 18.0	185.8 ± 10.3 ^b	264.0 ± 24.5	269.1 ± 13.4	286.9 ± 21.7 ^c
Typical								
Frequent	137.9 ± 11.9	132.3 ± 9.1	134.4 ± 11.4	191.7 ± 11.2	186.5 ± 10.2 ^b	258.8 ± 68.9	260.8 ± 17.8	296.5 ± 13.4
Rare	133.6 ± 12.3	131.5 ± 7.5	134.9 ± 11.9	192.5 ± 10.2	185.6 ± 12.3 ^b	277.1 ± 27.9	260.8 ± 19.7	276.5 ± 29.8 ^c
Amplitude (μV)								
Autism								
Frequent	5.8 ± 4.6	6.5 ± 2.4	-10.9 ± 4.7	-2.8 ± 2.0	-2.8 ± 2.6	-1.2 ± 3.4	0.8 ± 3.0	11.2 ± 7.4
Rare	6.5 ± 4.5	5.5 ± 2.8	-11.2 ± 4.6	-4.1 ± 3.0 ^d	-3.2 ± 2.9 ^d	-4.4 ± 4.0 ^d	-4.6 ± 4.4 ^d	12.5 ± 6.1
Typical								
Frequent	5.8 ± 5.1	9.1 ± 7.2	-12.1 ± 4.2	-1.8 ± 3.2	-0.1 ± 4.1	1.8 ± 4.9	4.8 ± 5.9	9.4 ± 7.6
Rare	5.9 ± 5.0	8.3 ± 7.5	-12.4 ± 4.8	-2.8 ± 5.0 ^d	-3.5 ± 5.0 ^d	-0.9 ± 7.1 ^d	-3.8 ± 8.6 ^d	11.9 ± 6.0

^a Mean ± S.D.^b Inter-hemispheric difference: latency of N170 was faster at T6 than at T5 (main effect of electrodes, $p < .05$).^c Effect of stimulus frequency: latency of P290 was significantly faster for rare than for frequent stimuli ($p < .01$).^d Effect of stimulus frequency: amplitude of N170 and N270 was significantly larger for rare than for frequent stimuli ($p < .01$).

ing other neural activities such as visual processing or facial encoding. Table 2 presents difference wave data for the peak latencies and amplitudes of occipito-temporal N2 and vertex P3a.

Peak latencies and amplitudes of occipito-temporal N2 were analyzed. For latency, there was a significant main effect of lateralization ($F(1, 24) = 8.69, p < .01$), such that N2 was faster at the right than at the left hemisphere. No other main effects or interactions reached significance. For peak amplitude, there was both a significant main effect of lateralization ($F(1, 24) = 17.41, p < .01$), and a group \times lateralization interaction ($F(1, 24) = 8.13, p < .01$). Sim-

ple effect analyses revealed that N2 was lateralized to the right hemisphere in typically developed children ($F(1, 24) = 24.66, p < .01$), as compared to children with autism ($F(1, 24) = 0.87, ns$). A three-way interaction among groups, gaze direction and task requirement was also significant ($F(1, 24) = 7.19, p < .02$) for peak amplitude. Simple effect analyses indicated that the effect of gaze direction was significant only when typically developed children responded to the target ($F(1, 24) = 4.85, p < .05$), a pattern that mirrored their behavioral performance (Senju et al., 2003). In contrast, no significant effects were found for the latency or amplitude of P3a.

Table 2

Latency and amplitude of N2 and P3a for targets and non-targets and for direct and averted gaze at each electrode in children with autism and typically developed children^a

	Autism			Typical		
	N2 (T5)	N2 (T6)	P3a (Cz)	N2 (T5)	N2 (T6)	P3a (Cz)
Latency (ms) ^b						
Targets						
Direct	300.4 ± 31.5	294.2 ± 32.1	261.5 ± 25.3	308.8 ± 53.1	285.3 ± 35.3	262.4 ± 23.1
Averted	315.6 ± 39.2	290.9 ± 29.3	253.5 ± 26.2	304.5 ± 33.6	293.3 ± 36.6	266.4 ± 18.9
Non-targets						
Direct	320.0 ± 39.8	302.2 ± 38.8	256.4 ± 12.8	308.3 ± 42.1	286.9 ± 34.7	265.6 ± 16.8
Averted	285.8 ± 44.6	302.9 ± 29.2	267.3 ± 30.0	313.6 ± 41.0	287.2 ± 31.6	273.3 ± 35.9
Amplitude (μV)						
Targets						
Direct	-5.8 ± 4.8	-6.5 ± 2.9	5.2 ± 4.9	-5.5 ± 6.7 ^c	-11.1 ± 4.6 ^{c,d}	4.4 ± 7.2
Averted	-6.7 ± 2.8	-8.3 ± 3.8	3.1 ± 5.8	-2.8 ± 5.5	-8.2 ± 4.4 ^d	4.0 ± 4.3
Non-targets						
Direct	-7.7 ± 4.3	-8.8 ± 3.0	2.0 ± 4.7	-5.1 ± 4.8	-11.2 ± 4.1 ^d	5.6 ± 3.6
Averted	-5.4 ± 4.1	-6.1 ± 5.3	4.5 ± 4.5	-6.2 ± 6.4	-10.6 ± 4.6 ^d	2.2 ± 5.9

^a Mean ± S.D.^b Inter-hemispheric difference: latency of N2 was faster at T6 than at T5 (main effect of electrodes, $p < .01$).^c Effect of gaze direction: in typically developed children, N2 was significantly larger for targets with direct gaze than for those with averted gaze ($p < .05$).^d Inter-hemispheric difference: in typically developed children, amplitude of N2 was larger at T6 than at T5 ($p < .01$).

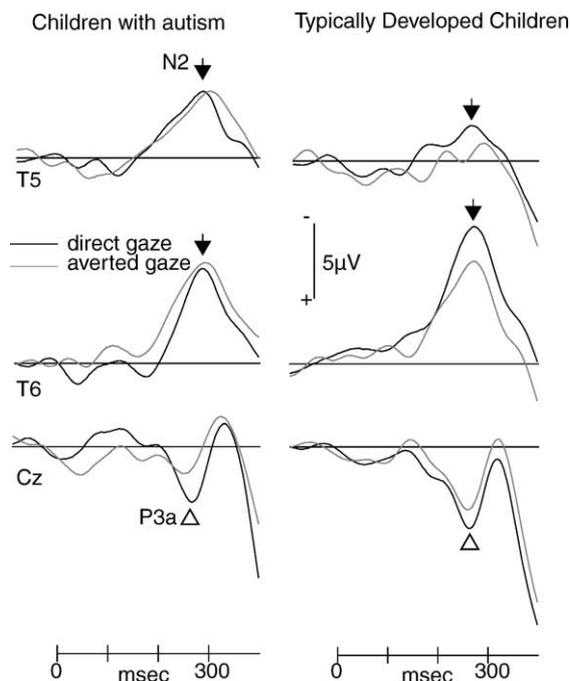


Fig. 3. Difference waves for targets, which is a subtraction of ERPs for frequent stimuli from ERPs for target stimuli. In typically developed children, N2 was larger at T6 (right hemisphere) than at T5 (left hemisphere). However, such hemispheric differences in N2 were not found in children with autism. In addition, N2 was larger for direct gaze than for averted gaze in typically developed children, but was not sensitive to gaze direction in children with autism. In contrast, P3a was not sensitive to gaze direction. Left: ERPs from children with autism. Right: ERPs from typically developed children.

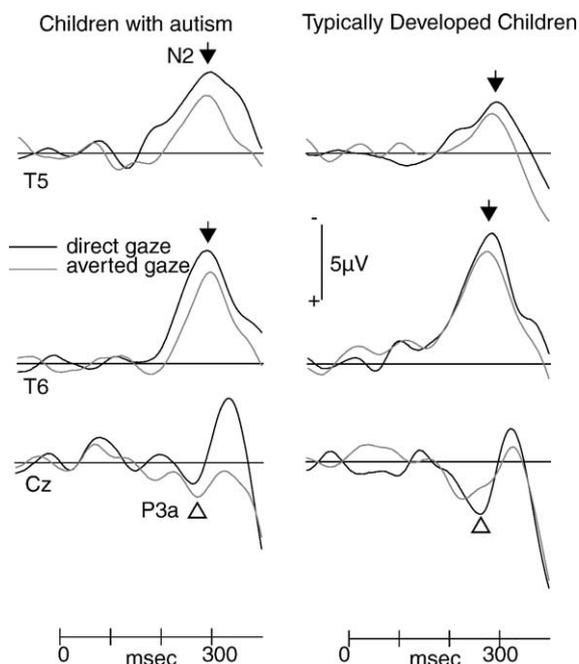


Fig. 4. Difference waves for non-targets, which is a subtraction of ERPs for frequent stimuli from ERPs for non-target stimuli. As with ERPs for target stimuli, N2 was larger at T6 (right hemisphere) than at T5 (left hemisphere) only in typically developed children. Neither N2 nor P3a was sensitive to gaze direction in this condition. Left: ERPs from children with autism. Right: ERPs from typically developed children.

To control for the possible effects related to the preparatory processes preceding the button press, ERPs from correct responses were averaged and subjected into the same analyses. The main findings presented above were still statistically significant in this subset of the data. First, the amplitude of N2 was larger in the right hemisphere in typically developed children ($F(1, 24) = 4.51, p < .05$) but not in children with autism ($F(1, 24) = 0.25, ns$). Second, direct gaze elicited larger N2 in response to the correct target detection ($F(1, 24) = 4.53, p < .05$), but not to the correct non-target rejection ($F(1, 24) = 0.20, ns$), in typically developed children. In contrast, gaze direction of the targets ($F(1, 24) = 0.07, ns$) or the non-targets ($F(1, 24) = 0.15, ns$) made no effect on the N2 of children with autism. In addition, no significant effects were found for the latency or amplitude of P3a.

4. Discussion

This study is the first to investigate the ERP correlates of active detection of gaze direction in children with and without autism, and the second to report the ERP correlates of gaze processing in children with autism. The effect of a change in eye direction was most prominent in the enhancement of the occipito-temporal negativity (N2). In typically developed children, N2 was lateralized to the right hemisphere, and N2 amplitude was greater when detecting a direct gaze as compared to an averted gaze, an effect that corresponded to behavioral performance. In children with autism, however, there was no lateralization of N2, and its amplitude was insensitive to the target's eye direction, again corresponding to behavioral patterns. We suggest that N2 correlates with neural activity for processing gaze direction, which seems to be deviant in children with autism.

Again, children with autism, as well as typically developed children, elicited N2 in response to the detection of gaze direction. Neither the overall amplitude nor latency of N2 differed between children with and without autism. There were, however, two critical differences between groups.

First, although N2 for typically developed children was lateralized to the right hemisphere, it was bilaterally distributed in children with autism. Such a lack of lateralization of ERP in children with autism has also been reported when passive facial perception was required (Carver & Dawson, 2002), even though they did not show atypical ERP lateralization when non-social visual stimuli were presented (Kemner, Verbaten, Cuperus, Camfferman, & Van Engeland, 1994). Atypical brain activation in individuals with autism was also reported during perception of faces (Pierce et al., 2001; Schultz et al., 2000) and facial expressions (Critchley et al., 2000). The results of the present study seem to suggest that gaze processing, as well as perception of faces and facial expressions, is also subserved by atypical neural substrates. However, it is quite difficult to estimate source location from the current study, and further studies utilizing high-density ERP or MEG with source analysis techniques are needed to

investigate which neural areas are responsible for gaze processing in autism.

Second, although the amplitude of N2 was larger for direct gaze than for averted gaze in typically developed children, there was no effect of gaze direction on the amplitude of N2 in children with autism, in agreement with the behavioral failure of perceived mutual gaze to facilitate detection in autism (Senju et al., 2003). Note that this does not necessarily mean the inability of children with autism to discriminate two rare stimuli from each other. As mentioned in Section 3, the discriminative accuracy of children with autism was not different from that of typically developed children when the target was averted gaze and distracter was direct gaze. It suggests that children with autism were as adept at detecting the target ignoring the distracter in this condition. So, the behavioral results seems to show the lack of facilitative effect of direct gaze on the performance of detection task, rather than a total inability in the discrimination between targets and distracters.

Current results may seem to contradict with those of Grice et al. (in press), who found that gaze direction affected ERP amplitudes of children with autism, but made no effect in non-autistic controls and adults. Several methodological differences might account for such an apparent contradiction. First of all, our study adopted active detection task, compared to the passive viewing used in Grice et al. (in press). It might be the case that the enhanced ERP response to perceived direct gaze in typically developed children, and failure to show such sensitivity to perceived gaze direction in children with autism, can only be observed under active tasks. Second, because children with autism who participated in Grice et al. (in press) were younger (3.5–7 years old) than those in our study (9–14 years old), developmental change might also account for the discrepancy between two researches. In addition, Grice et al. (in press) used facial stimuli in front view, compared to the laterally averted faces used in our experiment. It might be thus possible that lower perceptual feature such as bilateral symmetry inherent in direct gaze in front view might affect the results in Grice et al. (in press). Although such lower perceptual feature does not affect direct gaze processing in typically developing infants (Farroni, Johnson, & Csibra, 2004), it is still unknown whether it is also the case in children with autism. Further study will be required to examine if these factors affect the ERP related to gaze processing in children with and without autism.

On the other hand, several previous ERP researches have also found that the ERPs of children with autism failed to show differences between face and non-facial object (Carver & Dawson, 2002), between familiar and unfamiliar faces (Dawson et al., 2002), or between different vowels (Ceponiene et al., 2003), which concurs with current ERP results. Such a lack of sensitivity in children with autism to perceived mutual gaze and other critical social signals may correspond to their lack of interest in social stimuli (Baranek, 1999; Baron-Cohen, 1995), and might relate to atypical social cognitive development (Baron-Cohen, 1995).

As mentioned in Section 1, there are several studies which investigated ERP correlates of direct/averted gaze perception in typical adults. They have consistently found N170 (Puce et al., 2000; Taylor, Itier, et al., 2001; Watanabe et al., 2002), but they did not find occipito-temporal N270 appearing after N170, or N2. One of the likely reasons for the discrepancy between current results and those from other studies is age differences. In the studies with typically developing children, there is often a bifid component present in N170 (Taylor et al., 1999; Taylor, Edmonds, et al., 2001), and it is possible that N270 in the current study may simply be the second peak of this bifid waveform. However, previous studies with children did not report the characteristics of this latter component in detail so it is difficult to compare the current N270. The other possible explanation for different findings lies in task requirements. Passive viewing of faces, and thus implicit gaze processing, may have been required in previous studies, in contrast with active or explicit gaze processing in this study. Again, it is possible that N2 corresponds to explicit gaze processing. Explicit facial processing, and thus attention to the face, has been reported to enhance superior temporal sulcus (STS) activation (Hoffman & Haxby, 2000; Narumoto, Okada, Sadato, Fukui, & Yonekura, 2001). Preferential activation of N2 in response to direct gaze was observed only to targets, not to non-targets in the present study, which also suggests the attentional modulation of N2.

It is also possible that N2 reflects selective visual attention to targets, as in ‘processing negativity’ (Harter, Aine, & Schroeder, 1982; Näätänen, 1982) or ‘selection negativity’ (Czigler & Csibra, 1990, 1992), elicited by target detection and distributed to the occipital area. As in the present study, Campanella et al. (2002) utilized the visual oddball task in detecting changes in facial expression and found that occipital N2 was enhanced around 300 ms after stimulus onset in response to rare target stimuli. However, Harter et al. (1982) reported that processing negativity corresponding to intraspatial attention is lateralized to the left hemisphere, which contradicts the right hemisphere lateralization of N2 in this study. As right hemisphere predominance of gaze processing has been reported elsewhere (Pelphrey, Singerman, Allison, & McCarthy, 2003; Puce, Allison, Bentin, Gore, & McCarthy, 1998; Watanabe et al., 2002), the N2 seem to correspond to face-specific processing rather than domain-general selective attention. In addition, Puce et al. (2000) reported that occipito-temporal negativity was sensitive to the change in eye direction but was not affected by the configurative change in non-facial visual stimuli (checkerboard), which also support that current N2 was related to the detection of change in eye gaze direction, not the detection of the changeable part of visual stimuli in general. The data suggest that occipito-temporal N2 reflects neural activity involved in detecting changes in facial signals, such as eye gaze and facial expression. Further research will be required to confirm that the N2 data are specific to facial stimuli.

As mentioned before, it is quite difficult to estimate a source of neural activation from surface electroencephalo-

graphical distribution, but previous neuroimaging (Hoffman & Haxby, 2000; Pelphrey et al., 2003; Puce et al., 1998) studies may indeed provide the clue: they have found that direction of eye gaze is processed in the STS. Similar occipito-temporal negativity has been reported in response to detecting biological motion, which was also lateralized to the right hemisphere (N240; Hirai, Fukushima, & Hiraki, 2003). These data seem to imply that occipito-temporal N2s such as N270 and N240 reflect STS activation resulting from visual cues and social perception (Allison, Puce, & McCarthy, 2000). Although the fusiform gyrus is also known to be involved in neural circuitry regarding face perception (George, Driver, & Dolan, 2001; Hoffman & Haxby, 2000; Kanwisher, McDermott, & Chun, 1997), it is unlikely that volume-conducted current generated in the fusiform gyrus primarily influences current ERP at T5/T6. As Watanabe et al. (2003) have pointed out the dipole generated in fusiform gyrus is oriented mainly tangentially to the surface near T5/T6, which would make the electric field around T5/T6 very small. In contrast, the radially oriented dipole generated in the STS would more likely be the source of the ERP recorded in T5/T6. However, it is clear that the three electrodes used in the current study are the minimum required to estimate source location. Future studies should use a larger number of electrodes and apply source analysis techniques to estimate the source location of N2. Although there are other neuroimaging techniques such as fMRI, PET or NIRS available today, their temporal resolution seems too low to investigate specific ERP components.

Aside from N2, no other ERP components were sensitive to the active mutual gaze detection. First, current N170, in addition to N270, did not differentiate direct gaze from averted gaze, although both elicited larger amplitudes than downward-looking gaze. This replicates Taylor, George, et al. (2001) and Taylor, Itier, et al. (2001) and seems to suggest that these components relate to the detection of change in eye gaze. In addition, similar occipito-temporal negativities have reported to be face-specific (Bentin et al., 1996; Eimer, 2000; Sagiv & Bentin, 1999; Puce et al., 2000; Taylor et al., 1999; Taylor, Edmonds, et al., 2001), which also support this interpretation. However, since the frequency of presentation differed between these stimuli, we cannot totally deny the possibility that amplification of these components might have simply been caused by a novelty effect due to the novelty of the less frequent stimuli possibility, which should be investigated in further study. Second, vertex P290 was believed to reflect volume-conducted currents generated bilaterally at distant areas (possibly near T5 and T6). Since the peak latency of P290 was longer than that of N270, and since both P290 and P3a were unaffected by gaze direction, it is likely that P290 incorporates responses to other cognitive or attentional factors (Campanella et al., 2002; García-Larrea, Lukaszewicz, & Mauguère, 1992).

This study has several limitations. First, although the results strongly suggest that N2 is face-specific, it is still possible that it reflects more general neural processing, and further studies with non-facial stimuli will be required. In addition,

the current study used an earlobe reference, in response to reported hypersensitivity in some individuals with autism (O'Neill & Jones, 1997), but that may reduce the ERP in the posterior temporal region and might mask the possible gaze effect on N170 or N270. Averaging references from a large number of electrodes would be a possible solution to investigate in future studies. Second, exact fixation points of the participants during recording were not measured, even though children were strongly instructed to fixate to where the eyes of the stimuli would appear, and their gaze direction was carefully monitored by the experimenter. Because individuals with autism are known to fixate less frequently to the eye region during visual scanning of a face (Klin et al., 2002; Pelphrey et al., 2002), it might be the case that children with autism in fact fixate less to the eye region of the stimuli, which could affect the ERP results. We believe it unlikely that the participants ignored our instruction about the fixation because they followed other instructions very well. However, further study with precise recording of the fixations of participants will be required since control of fixation can affect the brain activity in response to the face processing (e.g., Hadjikhani et al., 2004). Third, the lack of non-autistic clinical controls made it difficult to determine whether such deviant ERPs in response to gaze processing are specific to autism. Impairment in sensitivity to gaze direction has also been reported in other disorders with social and communicative components, such as Turner syndrome (Elgar, Campbell, & Skuse, 2002). It is possible that deviant gaze processing is present in such disorders.

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