Table 1
Mean latencies (ms) and amplitudes (μV) of the P1, N1, P2, N2, and P300 in NC and HF-ASD groups.

Stimuli	ERP peaks	Latency (SD)		Amplitude (SD)	
		NC	ASD	NC	ASD
Standard	P1	96.0 (11.9)	94.4 (12.8)	5.7 (2.8)	2.9 (1.8)*
	N1	140.2 (15.2)	137.6 (22.1)	−1.6 (3.7)	−2.6 (5.0)
	P2	224.9 (18.3)	218.4 (29.0)	8.5 (4.0)	7.5 (4.1)
Deviant	P1	97.1 (12.5)	95.1 (16.8)	6.1 (2.7)	3.0 (1.9)*
	N1	141.3 (16.9)	135.3 (26.0)	−2.2 (2.8)	−2.5 (4.9)
	P2	224.7 (16.2)	205.3 (21.9)	7.7 (3.9)	7.3 (5.2)
	N2	293.1 (18.8)	287.8 (33.7)	1.9 (2.4)	−0.1 (4.2)
Target	P1	118.4 (5.6)	121.8 (5.8)	8.5 (4.4)	6.3 (3.4)
	N1	162.5 (10.6)	167.3 (13.1)	−1.0 (2.4)	−3.0 (4.9)
	P2	191.0 (11.5)	200.0 (8.0)	1.6 (1.4)	0.8 (4.7)
	P300	392.0 (11.9)	412.4 (17.4)*	14.3 (1.9)	10.2 (4.1)*
Difference (deviant − standard)	vMMN	274.2 (27.9)	268.7 (28.1)	−2.4 (0.8)	−2.2 (1.4)

* $P < 0.05$.

amplitude for target stimulus between the two groups. There was also no statistical difference in P1 latency for each stimulus type between the two groups (see Table 1, Fig. 2A). There were no significant differences between the groups in the latencies and amplitudes of the N1 and P2. The mean peak amplitude of the P300 in the HF-ASD group was significantly smaller than that of NC group ($t(16) = -2.73$, $P = 0.015$). In addition, the mean peak latency of the P300 in HF-ASD group was significantly prolonged compared with that of the NC group ($t(16) = 2.91$, $P = 0.010$; Fig. 2B).

Although vMMN was clearly exhibited at the occipital and posteriotemporal electrodes in both groups, there was no statistical difference in either the peak latency or mean amplitude between the groups (Table 1, Figs. 2C and 3).

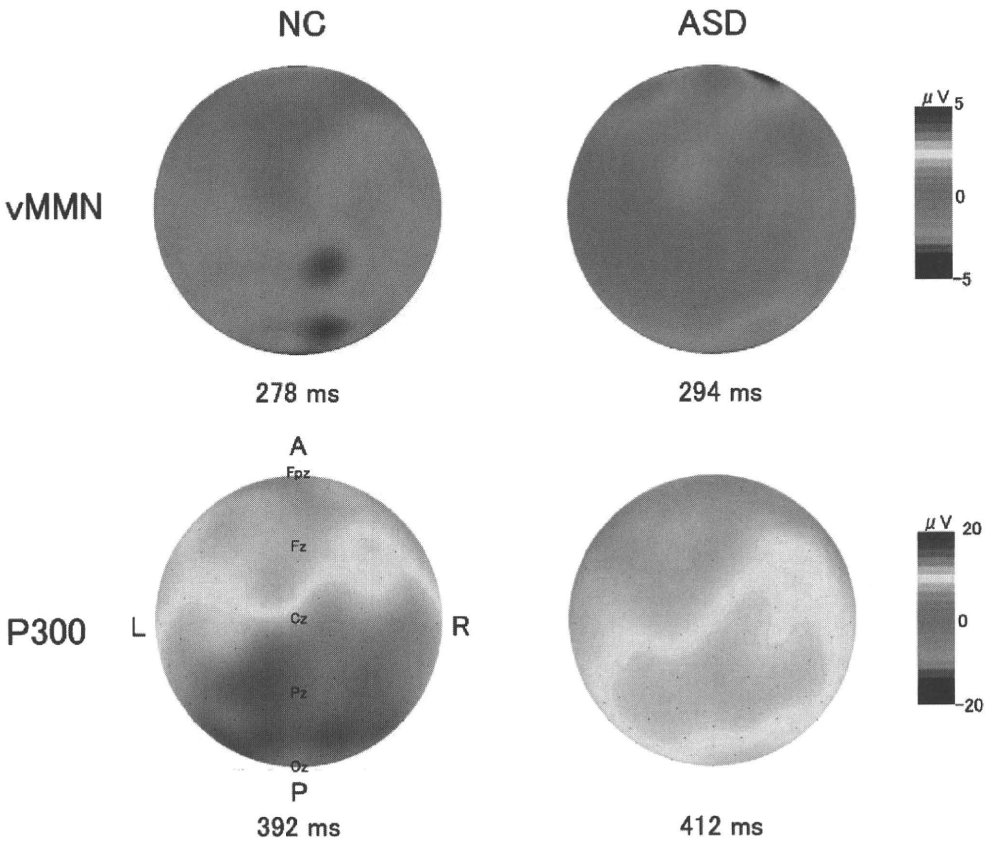

Fig. 3. Topographical maps of the vMMN (Oz) and P300 (Pz) in each group. Upper panel shows the topography of difference activity from standard to deviant stimuli of each group at vMMN peak latency. Although there was no statistically significant difference in the mean amplitude of the vMMN between the two groups, the amplitude gradient of the NC group appears to be steeper than in the ASD group. Lower panel shows the amplitude gradient of topography of response for target stimuli in each group at the P300 peak latency. The amplitude gradient of the NC group is steeper than that in the ASD group, which roughly corresponds to the statistically significant differences (Table 1).

4. Discussion

The major differences we found between the HF-ASD group and the NC group are summarized as follows. In HF-ASD individuals, (1) behavioral target detection was significantly faster, (2) the P1 response (80–120 ms) to standard and deviant stimuli was significantly smaller, (3) the P300 latency (300–500 ms) was significantly prolonged and its amplitude was decreased, and (4) both the mean amplitude and latency of vMMN (150–300 ms) were within the normal range. These findings suggest that individuals with HF-ASD exhibit differences in perceptual integration, with a unique electrophysiological processing pattern. Namely, this group exhibits abnormal lower level (P1) and top-down attentive processing (P300) while bottom-up processing (vMMN) appears to be intact. In the following section, we will discuss the pattern of unusual electrophysiological activity we observed in HF-ASD individuals in terms of bottom-up and top-down attention.

4.1. Abnormal lower visual level processing

The reduced P1 amplitude we observed in the HF-ASD group in our study suggests abnormalities in lower level visual processing, in accord with previous reports (Boeschoten et al., 2007; Hoeksma et al., 2004; Hoeksma et al., 2006; Itier and Taylor, 2002, 2004; O'Conner et al., 2005; Taylor et al., 2001; Webb et al., in press). Boeschoten et al. (2007) focused on the effect of spatial frequency (SF). They examined early visual sensory processing in HF-ASD children using two types of horizontal grating stimuli. They found that P1 responses evoked by both low- (0.75 cycles/deg or 4 bars) and high-SF (6 cycles/deg or 32 bars) gratings were significantly decreased in the HF-ASD group compared with control children. The authors suggested that atypical social perception and recognition (including deficits in face processing) in ASD may be caused by more fundamental lower level visual processes. In accord with this report, we also found that HF-ASD individuals exhibited a significantly smaller P1 in response to windmill patterns of both low (6-vane) and high (24-vane) SF, but not in response to unpatterned stimuli. Therefore, our findings are consistent with the results of Boeschoten et al. (2007), which suggested that abnormal lower level visual information processing was also exhibited by HF-ASD adolescents and adults.

Our interpretation is in accord with previous findings showing that hierarchical face processing is differentially influenced by the removal of high- and low-SF content, (Badcock, Whitworth, Badcock, & Lovegrove, 1990; Boeschoten, Kemner, Kenemans, & van Engeland, 2005; Goffax, Gauthier, & Rossion, 2003; Goffax, Hault, Michel, Vuong, & Rossion, 2005; LaGasse, 1993; Ruitz-Solar and Beltran, 2006). Thus, the local visual processing biases often found in ASD (e.g. Behrmann, Thomas, & Humphreys, 2006; Dakin & Frith, 2005; Happé & Frith, 2006; Mottron, Dawson, Soulières, Hubert, & Burack, 2006) may be related to abnormal early processing of SF. Furthermore, abnormal processing of low-SF stimuli was also found in our study. Namely, we found that HF-ASD individuals exhibited decreased P1 amplitude in response to six-vane windmill patterns. This could be related to the abnormal face and emotion recognition often reported in ASD (Baron-Cohen et al., 1999; Braverman, Fein, Lucci, & Waterhouse, 1989; Critchley et al., 2000; Dawson, Webb, Garver, Panagiotides, & McPartland, 2004; Hobson & Lee, 1989; Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004), because low-SF information is important for both face recognition and emotion perception (Pourtois, Dan, Grandjean, Sander, & Vuilleumier, 2005; Tanskanen, Näätänen, Montez, Päällysaho, & Hari, 2005; Vuilleumier, Armony, Driver, & Dolan, 2003).

4.2. Distinct electrophysiological features of HF-ASD

To our knowledge, this is the first report of vMMN in an HF-ASD group. However, there have been several previous MMN studies in the auditory modality (Ceponiene, Rinne, & Näätänen, 2002; Ceponiene et al., 2003; Dunn, Gomes, & Gravel, 2008; Kuhl, Coffey-Corina, Padden, & Dawson, 2005; Lepistö et al., 2005, 2006, 2008, 2009). Kuhl et al. (2005) found that the children with ASD showed a normal MMN to changes in non-speech sounds, but showed no MMN in response to changes in speech syllables. In general, the majority of autistic children preferred to listen to non-speech sounds, thus demonstrating an association between cortical processing of language and behavior (Kuhl et al., 2005). In the current study, we found that vMMN in response to a non-social stimulus (a windmill pattern) was preserved. This finding suggests that the pre-attentive visual information processing involved in detecting subtle changes in the visual environment is intact in HF-ASD.

On the other hand, the P300 in individuals with HF-ASD was significantly smaller than that of NCs in the present study. There have been a small number of studies examining the visual P300 in ASD (see for a review, Jeste & Nelson, 2009). In addition, there have been several reports showing a smaller auditory P300 in ASD, despite normal behavioral performance (e.g. Ciesielski, Courchensne, & Elmasian, 1990; Lincoln, Courchesne, Harms, & Allen, 1993). These findings for auditory tasks imply that individuals with ASD have altered cortical processing that may interfere specifically with speech sounds but not pitch sounds. In light of these previous findings, we expected that individuals with HF-ASD would show intact vMMN and smaller a P300 in response to a non-social stimulus such as a visual windmill pattern. Several previous studies demonstrated a smaller visual P300 in children with ASD (Gomarus, Wijers, Minderaa, & Althaus, 2009; Gunji, Inagaki, Inoue, Takeshima, & Kaga, 2009; Hoeksma et al., 2004; Hoeksma et al., 2006; Kemner, van der Gaag, Verbaten, & van Engeland, 1999; Pitchard, Raz, & August, 1987; Verbaten, Roelofs, van Engeland, Kenemans, & Slangen, 1991). However, there the P300 findings in adults with HF-ASD have not been consistent. Couchesne, Couchesne, Hicks, and Lincoln (1985), Courchesne, Lincoln, Kilman, and Galambos (1985), Courchesne, Lincoln, Yeung-Courchesne, Elmasian, and Grillon (1989), and Hoeksma et al. (2004, 2006) reported a normal P300 in HF-ASD adults, while Townsend et al. (2001) found a significantly reduced P300. In

addition, Hoeksma et al. (2006) found smaller P300 s in response to a rectangle discrimination task in children with HF-ASD, but a normal P300 in adults with HF-ASD in the same task. These findings suggest that an abnormal P300 in children with ASD may be accompanied by abnormal selective attention, but that normalization of P300 may occur by adulthood. Thus, Hoeksma et al. (2006) interpreted their results as showing that the P300 may be an index of a compensatory process. In the present study, the P300 was significantly decreased and delayed in an HF-ASD group, in direct contrast to the findings of Hoeksma et al. (2006). It is possible that windmill pattern stimuli are more sensitive in the detection of altered visual functioning than other visual stimuli such as the rectangle used in the earlier study.

4.3. Bottom-up attention may compensate top-down processing

Although a number of neuropsychological studies have investigated the neural mechanisms of both bottom-up and top-down attention, it is currently unclear whether aspects of these mechanisms are affected in HF-ASD. Our vMMN results suggest that bottom-up attention is relatively preserved in this condition, while the abnormal P300 we observed indicates that top-down attentional processing is impaired (Maekawa et al., 2005). Interestingly, individuals with HF-ASD showed faster behavioral target detection than NCs. Taking behavioral and neurophysiological findings into account, we assume that preserved bottom-up attention could cause faster target detection in our participants. There are several lines of evidence for atypical visual information processing in ASD from both neurophysiological and neuroimaging studies (see Jeste & Nelson, 2009 for a review; Müller, 2008). Superior visual performance has been more commonly observed in ASD than in other developmental cognitive disorders (see Mottron et al., 2009 for a review). Although several hypotheses (including WCC theory; Frith, 1989) have been proposed to explain this discrepancy, it remains unclear why autism is associated with superior visual task performance. Our findings may indicate that adolescents and adults with HF-ASD may exhibit involuntary or automatic processing in vMMN tasks. This idea provides a new hypothesis regarding altered visual information processing underlying the visual task performance advantage found in HF-ASD.

4.4. Methodological reservations

Although the difference in the gender ratio between the groups was not statistically significant, a possible effect of the trend towards a difference should still be considered. A number of studies have demonstrated mixed gender effects on visual and auditory oddball ERPs. Lower amplitudes in males and shorter latencies in females of early VEP components including the N50, P100, N100 and N200 have been previously reported (Ehlers, Wall, Garcia-Andrade, & Philips, 2001; Mitchell, Howe, & Spencer, 1987). Hoffman and Polich (1999) found that females exhibited a larger P300 component than males. However, other studies contradicted this finding, showing no significant gender difference in visual P300 (e.g. Steffensen et al., 2008; Rozenkrants & Polich, 2008). Thus, gender was unlikely to have significantly affected the results of the present study.

5. Conclusion

The present study is the first report focusing on bottom-up and top-down attention in HF-ASD using vMMN and the P300. Our results suggested that bottom-up involuntary attention is unaffected in HF-ASD, while lower level and top-down visual information processing are impaired in the condition.

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Electrophysiological evidence for selective impairment of optic flow perception in autism spectrum disorder

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ABSTRACT

People with autism spectrum disorder (ASD) often show inferior global motion performance with superior performance in detail form perception, suggesting dysfunction of the dorsal visual stream. To elucidate the neural basis of impaired global motion perception in ASD, we measured psychophysical threshold and visual event-related potentials (ERPs) with a 128-channel system in 12 ASD and 12 healthy control adults. Radial optic flow (OF) and horizontal motion (HO) were used as the visual stimuli. The former was related to the ventro-dorsal stream formed by the inferior parietal lobule, while the latter was conveyed from the dorso-dorsal stream formed by the superior parietal lobule. No significant group differences were observed in the motion thresholds for both OF and HO. N170 and P200 were elicited as major components of ERPs in both groups. However, the latencies of both components for OF but not HO were significantly prolonged in ASD compared with the control group. Our ERP results suggest that ASD has a selective impairment for OF processing even though the psychophysical thresholds are preserved. Therefore, we provide the first electrophysiological evidence for altered function of the higher-level dorsal visual stream in ASD, specifically the ventro-dorsal stream closely related to OF perception.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social interaction and communication impairments, as well as restricted and repetitive behaviors and interests (Frith & Happé, 2005; Kamio et al., in press). Individuals with ASD show superior performance in processing fine details (Happé & Frith, 2006; Happé, 1996; Jolliffe & Baron-Cohen, 1997), while even those with high IQ are poor at processing global structure and motion perception (Bertone, Mottron, Jelenic, & Faubert, 2003; Milne et al., 2002; Spencer et al., 2000). This unusual cognitive style of reduced global bias coupled with enhanced local bias may be related to abnormal integration of perceptual information and may affect cognitive operations. Thus, low-level perception is considered to contribute to higher-level impairments of social

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cognition in ASD (Dakin & Frith, 2005; Mottron & Burack, 2001). Consequently, to elucidate the neural basis of impaired social interaction and communication in ASD, it is important to investigate visual motion perceptual function.

Fine-form perception is mainly processed in the parvocellular (P) pathway. In contrast, global motion is processed in the magnocellular (M) pathway on a basis of parallel visual information processing (Livingstone & Hubel, 1988; Tobimatsu & Celesia, 2006). After the primary visual cortex (V1), the M pathway projects to the dorsal stream that includes V1–3, V3a, V5/MT, MST, V6, and the posterior parietal lobule. Recently, the dorsal stream has been divided into two functional streams in primates: the dorso-dorsal (d-d) and ventro-dorsal (v-d) streams (Rizzolatti & Matelli, 2003). The former consists of V6 and the superior parietal lobule (SPL), whereas the latter is formed by V5/MT and the inferior parietal lobule (IPL). Given this background, we hypothesized that the atypical visual findings seen in ASD might derive from abnormalities at higher-level processing in the M pathway.

It is well known that the higher-level dorsal pathway including V5/MT integrates local motion signals from V1 into global motion (Snowden, Treue, Erickson, & Andersen, 1991). Therefore, coherent motion stimuli have been widely used to investigate global motion processing in psychophysical, electrophysiological, and neuroimaging studies (Morrone et al., 2000; Newsome & Paré, 1988; Niedeggen & Wist, 1999). There are several types of global motion including radial optic flow (OF) and horizontal motion (HO). Radial OF is the visual motion seen during observer self-movement and is known to be important for daily life because it provides cues about the heading direction and the three-dimensional structure of the visual environment (Gibson, 1950; Warren & Hannon, 1988). Using functional magnetic resonance imaging (fMRI), we recently reported that OF is mainly processed in the v-d (IPL) stream, while HO is mostly related to the d-d (SPL) stream in healthy humans (Yamasaki & Tobimatsu, in press). Thus, the use of both stimuli can reveal the function of two distinct higher-level dorsal pathways in ASD in detail.

Many psychophysical studies have been conducted to investigate motion perception in ASD. Motion coherence thresholds for HO (Milne et al., 2002; Spencer et al., 2000), OF (Del Viva, Igliozzi, Tancredi, & Brizzolara, 2006; Tsermentseli, O'Brien, & Spencer, 2008), and plaid motion (Vandenbroucke, Steven Scholte, van Engeland, Lamme, & Kemner, 2008) were measured to evaluate the function of the dorsal stream. Conversely, several studies evaluated the function of the lower and higher levels of the dorsal streams separately. One study examined motion sensitivity to the lower level of first-order (luminance-defined) and higher level of second-order (texture-defined) motion (Bertone et al., 2003). Other studies assessed dorsal stream functioning at both lower (sensitivity to flicker contrast) and higher (sensitivity to coherent HO) levels (Pellicano & Gibson, 2008; Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005). However, it is still controversial whether impaired motion perception exists, and if it exists, it remains unclear how the M (or dorsal) pathway is functionally impaired in ASD.

Visual event-related potentials (ERPs) can detect abnormalities not only in patients with visual complaints but also in patients with no visual symptoms on examination (Tobimatsu & Celesia, 2006). Therefore, ERPs are considered to be useful for resolving the psychophysical controversy about motion perception (function of the dorsal pathway) in ASD; however, to date, there have been no such ERP studies on ASD. Therefore, in the present study, the psychophysical threshold of coherent motion (OF and HO) and ERP responses to these stimuli were measured to evaluate the function of the two distinct higher-level dorsal pathways in ASD.

2. Methods

2.1. Experiment 1: psychophysical threshold measurements

2.1.1. Subjects

Twelve ASD adults (nine males and three females, aged 20–39 years) and 12 control adults with similar chronological age and sex ratios (nine males and three females, aged 20–39 years) participated in this experiment. The ASD patients comprised six patients with Asperger's syndrome and six patients with pervasive developmental disorder not otherwise specified (PDD-NOS). These patients were diagnosed by a research team, including an experienced child psychiatrist (Y.K.), according to DSM-IV criteria (American Psychiatric Association, 1994) based on clinical interviews with patients and/or parents using semi-structured interviews that were validated for the Japanese PDD population (Pervasive Developmental Disorders Autism Society Japan Rating Scale; Kamio et al., 2006). Diagnostic agreement among the team was obtained for all subjects. Control subjects were recruited from the college student and faculty population and were confirmed as having no developmental problems by interviews.

Intellectual function of the ASD patients was evaluated using WAIS-R. ASD participants with full-scale IQ scores below 70 were not included in the study. All subjects exhibited normal or corrected-to-normal visual acuity (>1.0), evaluated using the Landolt's ring (Landolt, 1905). Autism-Spectrum Quotient (AQ) (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Wakabayashi, Baron-Cohen, Wheelwright, & Tojo, 2006) was also examined.

Informed consent was obtained after the nature of the experiment had been fully explained. The experimental procedures were approved by the ethics committee of the Graduate School of Medical Sciences, Kyushu University.

2.1.2. Visual stimuli

The visual stimuli were generated by the software Presentation (Neurobehavioral Systems, Inc., San Francisco, CA, USA), which was run on a personal computer and displayed on a gamma-corrected color monitor with a frame rate of 60 Hz

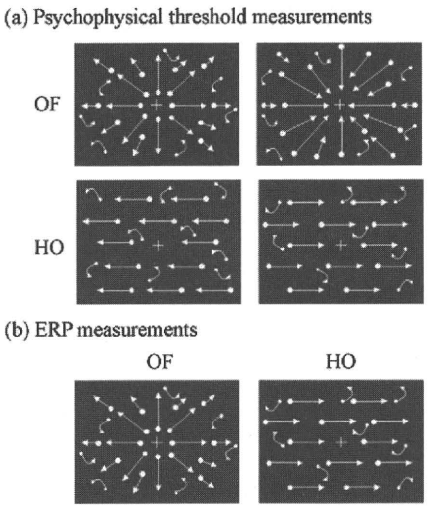

Fig. 1. Visual motion stimuli used in this study. Four hundred white square dots (visual angle, 0.2° × 0.2°; luminance, 48 cd/m^2) are randomly presented on a black background (visual angle, 50° × 48°; luminance, 0.1 cd/m^2). The contrast level is 99.6%. The white dots move at a velocity of 5.0°/s. (a) Shows two types of motion stimuli, OF and HO, for psychophysical threshold of coherent motion measurements. HO contains dots that move leftward or rightward. OF contains dots that move in a radial outward or inward pattern on the center of the screen. (b) Depicts visual motion stimuli for ERP measurements. When the white dots move incoherently, RM stimulation is created. When the white dots move coherently, OF and HO are perceived. *Abbreviations*: RM, random motion; HO, horizontal motion; OF, optic flow.

(Electron22blue IV, LaCie, Tokyo, Japan). We used coherent motion stimuli as the visual stimuli (Fig. 1). They consisted of 400 white square dots randomly presented on a black background. The white dots moved at a velocity of 5.0°/s. Two types of motion stimuli, namely OF and HO, were used (Fig. 1a). OF contained dots that moved in a radial outward or inward pattern on the center of the screen. HO contained dots that moved leftward or rightward. These coherent motion patterns were intermixed with random motion (RM), and the percentage of coherently and randomly moving dots varied between trials for the determination of motion coherent thresholds. After central fixation was established, these visual stimuli were shown for 750 ms with an interstimulus interval of 1500 ms. Both stimuli had the same dot density, luminance, contrast, and average dot speed.

2.1.3. Psychophysical testing

Participants sat on a chair in front of a monitor in a dark room and fixated on a fixation point (visual angle 0.2° × 0.2°) in the center of the monitor. In the OF condition, participants indicated whether the coherent motion was expansion or contraction. In the HO condition, participants indicated whether the coherent motion was to the left or right. Participants were instructed to press the computer mouse buttons with either thumb as soon as possible. The ratio of dots with coherent movement varied at 14 steps from 5% to 70% in a random order. Each step consisted of 40 trials (20 trials × 2); therefore, one session was 40 trials × 14 steps. Perceptual thresholds were defined as the percentage of coherent motion in stimuli (([coherently moving dots]/[coherently moving dots + random dots]) × 100) yielding 82.0% correct responses, reflecting Weibull fits to psychophysical responses (Harvey, 1986). The order of motion stimulation was counterbalanced across participants.

2.1.4. Data analysis

We performed two-way analysis of variance (ANOVA) with repeated measures to determine the effects of the participant groups and stimulus types on the coherent motion perceptual threshold. Multiple comparisons with Bonferroni correction were also conducted for paired comparisons.

2.2. Experiment 2: ERP measurements

2.2.1. Participants

Twelve ASD adults and 12 control adults participated in this experiment. The participants were the same as those in experiment 1.

2.2.2. Visual stimuli

Two types of motion stimuli, namely OF and HO, were used (Fig. 1b). OF contained dots that moved in a radial outward pattern. HO contained dots that moved leftward or rightward. The coherence level was 90% in both stimuli. The stimulus characteristics, such as visual angle, dot density, luminance, contrast, and average dot speed, were the same as the stimuli in

experiment 1. An image of RM-containing dots that moved incoherently was used as the baseline condition. In each session, the motion stimulus was fixed to one of the two stimuli, namely OF and HO, and the stimulus was presented 25 times for 750 ms with presentation of the RM for 1500–3000 ms alternating with the motion stimuli. Thus, one session lasted for about 60–90 s. In each motion stimulation, six sessions were performed, such that each motion stimulation was presented a total of 150 (25 × 6) times. The order of motion stimulation was counterbalanced among the subjects.

2.2.3. ERP recording

ERPs were recorded using a Geodesic electroencephalogram (EEG) system, NetAmps 200 (Electrical Geodesics Inc. [EGI], Eugene, OR, USA). A high-density 128-channel HydroCel Geodesic Sensor net (EGI) was applied over the scalp of the subject. This net holds each electrode in place and distributes electrodes from the nasion to the inion and from left to right mastoids at uniform intervals. Each electrode consisted of a silver-chloride carbon-fiber pellet, a lead wire, a gold-plated pin, and a potassium-chloride-soaked sponge. This electrode configuration effectively blocked out electrochemical noise and minimized triboelectric noise. Signals were amplified via an AC-coupled, 128-channel high-input impedance amplifier (NetAmps 200, EGI). Amplified analog voltages were hardware band-pass filtered at 0.1–200 Hz. All sensors were individually adjusted by the experimenter until the impedance of each electrode was less than 50 kΩ (Ferree, Luu, Russell, & Tucker, 2001). The impedance levels were comparable between the ASD and control groups. EEG data were collected using the vertex (Cz) electrode reference.

The subjects sat on a chair in front of a monitor in a dark room and fixated on a fixation point (visual angle, 0.2° × 0.2°) at the center of the monitor. The subjects were instructed to remain relaxed and as motionless as possible and to fixate on the center of the screen with both eyes. The arousal level was carefully monitored visually by the observer within the room, by the video camera outside of the room, and by EEG. If the subjects were getting drowsy, we alerted them and gave them a brief rest.

2.2.4. Data analysis

EEG data were collected using the vertex (Cz) electrode reference. Epochs that contained blinks, horizontal or non-blink eye movements, A/D saturation, or obvious occipital α-activity were rejected in offline analysis to obtain averaged waveforms. The electrodes surrounding the eyes were used to identify the artifacts of blinks and horizontal or non-blink eye movements. Then, they were re-referenced offline to the average of two channels on the cheeks. The analog data, hardware band-pass filtered at 0.1–200 Hz, were digitized at a sampling rate of 500 Hz/channel and were filtered using a 1–30 Hz band-pass filter and a 60-Hz notch filter before averaging. And then, 150 samples of 800-ms (from −100 to 700 ms) epochs were averaged using the software (EMSE Suite, Source Signal Imaging, Inc., San Diego, CA, USA).

To reveal the characteristic difference among the stimuli, the global field powers (GFP; Brandeis & Lehmann, 1986; Lehmann & Skrandies, 1980) of the major components were calculated for each stimulus for each participant as well as in averaged data for these individuals. Then, referring to the GFP peak in each grand-averaged waveform, we created the scalp topography and evaluated the difference of the scalp topography of the major components among the visual stimuli. Two-way ANOVA with repeated measures was performed to determine the effects of the subject groups and stimulus types on the GFP peak amplitudes and peak latencies of the major components. Multiple comparisons with the Bonferroni correction were also conducted for paired comparisons.

3. Results

3.1. Intellectual function

ASD patients exhibited normal IQ (verbal IQ, 103.8 ± 10.4 [mean ± SD]; performance IQ, 96.3 ± 21.5; full-scale IQ, 100.3 ± 15.7). AQ in these patients was 27.8 ± 6.4 (mean ± SD). There were no significant differences in chronological age (*t*-test) and sex ratio (χ^2-test) between the two groups.

3.2. The psychophysical thresholds for coherent motion

The motion thresholds for OF and HO in both groups are summarized in Table 1. Within the participant groups, no significant difference in the mean motion threshold between the two stimuli was found. When compared between the two groups, there were no significant differences in the mean motion threshold for both OF and HO. In sum, ASD adults showed no decline in discrimination of both OF and HO.

Table 1
The thresholds for coherent motion in control and ASD adults.

Stimuli	Control adults	ASD adults
OF	17.3 ± 3.4	22.9 ± 11.0
HO	16.7 ± 3.4	20.1 ± 5.0

Data are expressed as mean ± SD (%).

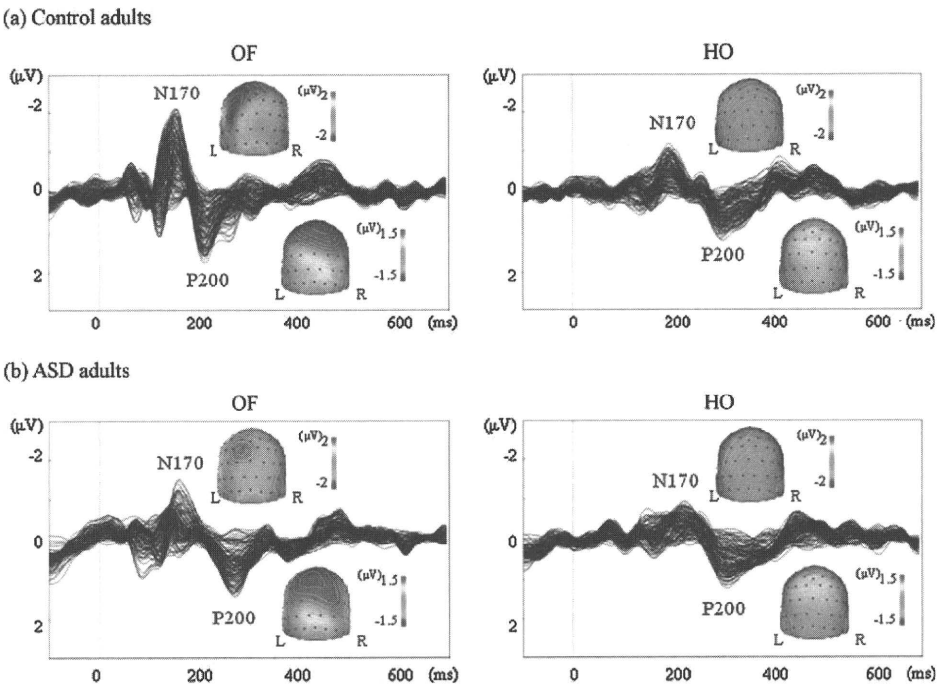

Fig. 2. The superimposed waveforms and the scalp topography of grand-averaged ERPs in response to each motion stimulus in control (a) and ASD (b) groups. In both groups, N170 and P200 are evoked by both motion stimuli. ASD adults show an apparent prolongation of P200 latency for OF compared with control adults.

3.3. ERP responses

In the control group, two major components (N170 and P200) were obtained by both motion stimuli (Fig. 2a). N170 was predominant at the occipito-temporal regions for both stimuli. P200 for OF was distributed at parietal regions, whereas P200 for HO was located at central regions (Fig. 2a). ASD adults exhibited similar patterns of ERP responses and scalp topography as observed in control adults. However, ASD adults displayed the prolongation of P200 latency for OF compared with controls (Fig. 2b).

Regarding the N170 GFP peak amplitude, there was no main effect of the participant groups or an interaction effect of the subject groups × stimulus types (Table 2). For the N170 GFP peak latency, an interaction effect of the subject groups × stimulus types was found ($F(1,22) = 13.435$, $p < 0.001$). The mean N170 latency for OF in ASD adults was significantly prolonged compared with that of controls ($p < 0.001$), while there was no difference in the mean N170 latency for HO between the two groups (Table 2). For the P200 GFP peak amplitude, there was no main effect of participant groups or interaction effect of subject groups × stimulus types (Table 2). However, for the P200 GFP peak latency, a significant main effect of the subject groups ($F(1,22) = 15.578$, $p < 0.001$) and an interaction effect of the subject groups × stimulus types ($F(1,22) = 9.749$, $p < 0.01$) were found. The mean P200 latency for OF in ASD adults was significantly prolonged compared with the controls ($p < 0.001$). In contrast, there was no difference in the mean P200 latency for HO between the two groups (Table 2).

Table 2
GFP peak amplitudes and latencies of the N170 and P200 components in control and ASD adults.

Stimuli	N170 amplitude (μV)		N170 latency (ms)	
	Control adults	ASD adults	Control adults	ASD adults
OF	8.1 ± 5.5	9.9 ± 5.7	158.5 ± 11.8*	194.5 ± 28.4*
HO	4.1 ± 1.2	5.6 ± 1.9	225.0 ± 28.2	201.5 ± 37.1
Stimuli	P200 amplitude (μV)		P200 latency (ms)	
	Control adults	ASD adults	Control adults	ASD adults
OF	8.1 ± 3.6	10.2 ± 4.7	210.1 ± 16.3*	262.3 ± 36.5*
HO	5.1 ± 1.8	6.7 ± 2.8	284.5 ± 19.3	293.5 ± 24.9

Data are expressed as mean ± SD.
* $p < 0.001$, control adults vs. ASD adults.

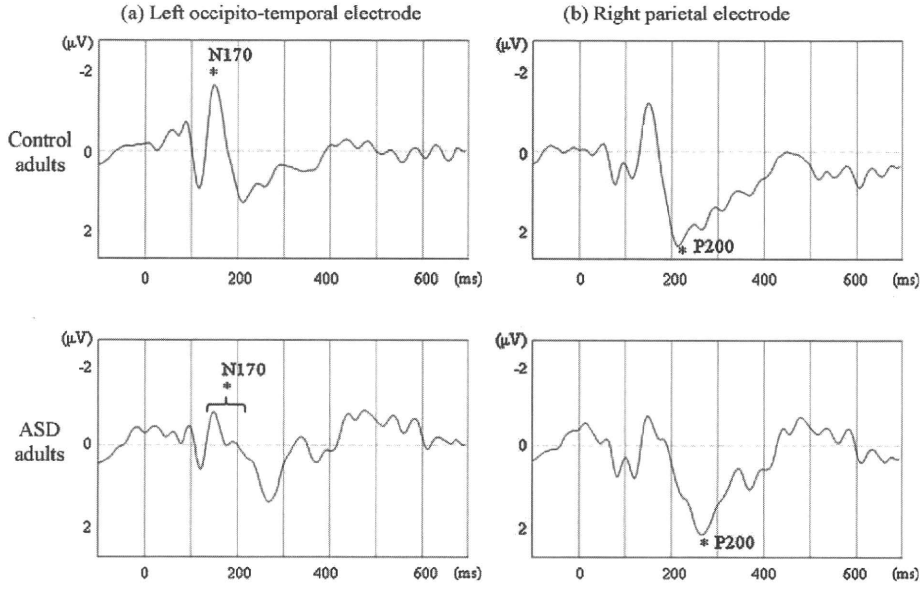

Fig. 3. Grand average of ERPs in response to OF stimulation at the left occipito-temporal electrode (a) and at the right parietal electrode (b) in control and ASD groups. ASD adults exhibit small and ill-defined N170 response (a) and prolonged P200 latency (b) compared with control adults.

Fig. 3 shows the maximal N170 response for OF at the left occipito-temporal electrode and the maximal P200 response for OF at the right parietal electrode on the basis of the scalp topography in both groups. ASD adults exhibited a small and ill-defined N170 response, which may be because of the large variability of N170 latency of ASD adults compared with control adults (Fig. 3a, Table 2). A marked prolongation of P200 latency was observed in ASD adults (Fig. 3b, Table 2). Overall, ASD adults manifested significant prolongation of both N170 and P200 latencies for OF but not HO compared with control adults.

4. Discussion

4.1. Selective impairment of OF perception in ASD adults

In the psychophysical experiment, there were no significant differences in the motion threshold for both OF and HO between the two groups. However, ERPs provided objective evidence for the decline of motion perception in ASD. We found significant prolongations of N170 and P200 latencies for OF but not HO in ASD adults, indicating the selective impairment of OF perception in ASD even though the psychophysical thresholds were preserved.

Which portion of the dorsal stream is impaired? In control adults, N170 and P200 were the two distinct major ERP components. N170 was evoked by both motion stimuli, while the parietal-distributed P200 was only elicited by OF. This suggests that N170 is a nonspecific motion component but the parietal-distributed P200 is an OF-specific component. Previous ERP studies with unidirectional coherent motion stimuli (Kuba & Kubová, 1992; Niedeggen & Wist, 1999) detected an occipito-temporal-distributed N2 component (latency, 150–200 ms) originating from in or around V5/MT (Probst, Plendel, Paulus, Wist, & Scherg, 1993). It is likely that our N170 corresponds to N2; therefore, our N170 reflects chiefly V5/MT function. In contrast, our recent fMRI study on healthy humans has revealed that the v-d (IPL) stream is significantly activated by OF compared with HO (Yamasaki & Tobimatsu, in press), which implies that P200 may represent the function of IPL. Therefore, impaired OF perception may result from the dysfunction of the higher level of the v-d (IPL) stream after V5/MT in ASD adults.

What is the meaning of selective impairment of OF perception but not HO perception in ASD adults? OF includes information about heading direction, orientation, and visual navigation in three-dimensional space, which controls posture and locomotion, as well as perception of moving objects and selection of motor actions that allow appropriate interactions with these objects (Gibson, 1950; Koenderink, 1986; Warren & Hannon, 1988). In contrast, HO has unidirectional motion information, and therefore, HO is a relatively low-level motion compared with OF. It is likely that OF information is more important for perception of the external world, including other people, compared with HO information and that impaired communication is closely related to the impaired OF perception in ASD. Gepner and Mestre (2002) demonstrated that autistic children are posturally hyporeactive to visually perceived environmental motion (visuo-postural tuning) in comparison with control children, which may support in part our OF-specific impairment in ASD.

4.2. "Pathway-specific" vs. "complexity-specific" hypotheses

Based on the atypical visual perceptual abnormalities in ASD, "pathway-specific" (Spencer et al., 2000) and "complexity-specific" (Bertone & Faubert, 2006; Bertone et al., 2003; Bertone, Mottron, Jelenic, & Faubert, 2005) hypotheses have been

proposed. The former suggests the dysfunction of the dorsal (or M) pathway with sparing of the ventral (or P) pathway, which is related to the idea of "dorsal stream vulnerability" (Braddick, Atkinson, & Wattam-Bell, 2003). In contrast, the latter implies dysfunction of neurointegrative processing at a higher cortical level for both the dorsal and ventral pathways with preserved function of the lower level of dorsal and ventral pathways (before V1).

As mentioned above, our ERP results reveal that ASD adults have selective impairment of a higher level of the v-d (IPL) stream after V5/MT. Additionally, using visual evoked potentials (VEPs) with low contrast achromatic sinusoidal gratings, our recent study showed that the function of the lower level of dorsal pathways before V1 is preserved in ASD adults (4 out of 12 subjects also participated in the current study; Fujita, Yamasaki, Kamio, Hirose, & Tobimatsu, 2011). Therefore, our consecutive studies may partly support the "complexity-specific" hypothesis rather than the "pathway-specific" hypothesis, although we could not fully test these two hypotheses. Further VEP and ERP studies are needed to evaluate the function of the ventral pathway in ASD.

4.3. Methodological limitations

Although special care was taken when creating the coherent motion stimuli, our sample size was relatively small. Clinical diagnoses were performed based on extensive clinical interviews, and standard interview tools such as the ADI-R or ADOS-G were not used. Instead, we used a widely used scale (PARS) with high sensitivity and high specificity in Japanese populations to distinguish all ages of individuals with PDD (Kamio et al., 2006). Intellectual function was not assessed in control participants, but because they were recruited from college students and faculties and reported no developmental problems, their intellectual functioning was very likely to be within the normal range.

4.4. Conclusion

The current study indicates that the higher level of the dorsal motion pathway, particularly the v-d (IPL) pathway closely related to OF perception, is selectively impaired in ASD adults. Dysfunction of the v-d (IPL) stream may contribute to higher-level impairment of social cognition in ASD.

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Parvocellular pathway impairment in autism spectrum disorder: Evidence from visual evoked potentials

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ABSTRACT

In humans, visual information is processed via parallel channels: the parvocellular (P) pathway analyzes color and form information, whereas the magnocellular (M) stream plays an important role in motion analysis. Individuals with autism spectrum disorder (ASD) often show superior performance in processing fine detail, but impaired performance in processing global structure and motion information. To date, no visual evoked potential (VEP) studies have examined the neural basis of atypical visual performance in ASD. VEPs were recorded using 128-channel high density EEG to investigate whether the P and M pathways are functionally altered in ASD. The functioning of the P and M pathways within primary visual cortex (V1) were evaluated using chromatic (equiluminant red–green sinusoidal gratings) and achromatic (low contrast black–white sinusoidal gratings) stimuli, respectively. Unexpectedly, the N1 component of VEPs to chromatic gratings was significantly prolonged in ASD patients compared to controls. However, VEP responses to achromatic gratings did not differ significantly between the two groups. Because chromatic stimuli preferentially stimulate the P-color but not the P-form pathway, our findings suggest that ASD is associated with impaired P-color pathway activity. Our study provides the first electrophysiological evidence for P-color pathway impairments with preserved M function at the V1 level in ASD.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and communication, as well as restricted and repetitive behaviors and interests (Frith & Happé, 2005). Individuals with ASD exhibit superior performance on processing fine details (Happé, 1996; Happé & Frith, 2006; Ishida et al., in press; Jolliffe & Baron-Cohen, 1997). ASD individuals with high IQ tend to be poor at processing global structure and motion perception (Bertone, Mottron, Jelenic, & Faubert, 2003; Milne et al., 2002; Spencer et al., 2000). Two distinct hypotheses have been proposed regarding abnormal early processing of the visual system in ASD. Spencer et al. (2000) proposed a 'pathway-specific' hypothesis. This hypothesis proposes that ASD involves a dysfunctional magnocellular (M) visual pathway, but preserved functioning in the parvocellular (P) pathway, causing an elevated motion coherence threshold (the minimum number of coherently moving elements supporting direction discrimination at some criterion level of performance), but

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preserved form coherence threshold (the static analog of the motion coherence threshold). Bertone et al. (2003) proposed an alternative 'complexity-specific' hypothesis. They measured sensitivity to first-order (luminance-defined) and second-order (texture-defined) motion stimuli and found a decrease in performance for second-order motion only. They proposed that inefficient neuro-integrative functioning affects complex information analysis in autism, regardless of static or dynamic visual information. The authors also evaluated the function of sub-cortical visual processing using the flicker contrast sensitivity task, and concluded that sub-cortical visual processing was intact (Bertone & Faubert, 2006; Bertone et al., 2003; Bertone, Mottron, Jelenic, & Faubert, 2005).

P and M are the two major parallel visual pathways in humans (Tobimatsu & Celesia, 2006). Both systems begin in the retina and project to the primary visual cortex (V1) via the lateral geniculate nucleus (LGN). The P pathway projects to area V4 via the P-blob (color) and P-inter-blob (form) pathways of V1, and visual information is subsequently sent to the inferior temporal cortex. The P-color pathway is important for analyzing color information and the P-form pathway for processing detailed form information. In contrast, the M pathway projects to area V5/MT and terminates in the posterior parietal cortex. The M pathway plays an important role in detecting motion and processing of global structure (Livingstone & Hubel, 1988; Tobimatsu & Celesia, 2006). These distinct features depend on the specific physiological characteristics of the P and the M pathways. The former is characterized by high spatial resolution, color sensitivity, low contrast sensitivity, and low temporal resolution, while the latter exhibits opposite characteristics of low spatial resolution, color insensitivity, high contrast sensitivity, and high temporal resolution (Livingstone & Hubel, 1988; Tobimatsu & Celesia, 2006). Based on the concept of parallel visual processing, it is possible that the atypical superior visual processing of fine detail (local structure) and the inferior global structure and impaired motion processing in ASD might be related to superior functioning of the P pathway (particularly, the P-form pathway) and dysfunction of the M pathway.

Visual evoked potentials (VEPs) are a useful experimental tool and have been extremely useful in studies investigating the physiology and pathophysiology of the human visual system, including the visual pathways and visual cortex (Regan, 1989; Tobimatsu & Celesia, 2006). VEPs can be used to detect abnormalities not only in patients with visual deficits, but also in patients without visual symptoms upon examination (Tobimatsu & Celesia, 2006). VEPs exist in two forms—transient and steady-state (Tobimatsu & Celesia, 2006). Based on the different stimulus selectivity of the P and M pathways, our group has performed a number of studies using VEPs with appropriate visual stimuli to evaluate the functioning of the parallel visual pathways in both healthy subjects and patients with various neurological disorders (Tobimatsu, Goto, Yamasaki, Tsurusawa, & Taniwaki, 2004; Tobimatsu, Goto, Yamasaki, Tsurusawa, & Taniwaki, 2006; Tobimatsu & Kato, 1998; Tobimatsu, Shigeto, Arakawa, & Kato, 1999; Tobimatsu, Tomoda, & Kato, 1995; Nakashima et al., 2008; Yamasaki et al., 2004). Transient VEPs at low temporal frequencies elicited by chromatic sinusoidal gratings with equal luminance and high spatial frequency are suitable for examining the P pathway at the lower levels within V1. This stimulus evokes a characteristic negative wave (N1) with a peak latency around 120 ms. Conversely, steady-state VEPs at high temporal frequencies that use achromatic sinusoidal gratings with low contrast and low spatial frequencies are useful for evaluating the M pathway within V1. This stimulation induces a positive peak (P1) around 120 ms followed by steady-state responses (Gutschalk, Patterson, Rupp, Uppenkamp, & Scherg, 2002).

To date, no studies have utilized VEPs to examine the neural basis of the 'pathway-specific' and 'complexity-specific' hypotheses, the two major hypotheses that have been proposed on the basis of psychophysical measurements. In addition, elemental chromatic and achromatic stimuli have not been previously used to study the parallel visual pathways within V1. Therefore, we aimed to objectively evaluate the neural substrates of the atypical visual performance observed in ASD. Special attention was paid to lower-level processing (within V1) of the P and M pathways elicited by appropriate visual stimuli.

2. Methods

2.1. Participants

Twelve ASD participants, including two adolescents and 10 adults with high-functioning ASD (eight males and four females, aged 17–38 years, mean age 28.1 years), and 12 healthy control participants, including one adolescent and 11 adults with similar chronological age and sex ratios (seven males and five females, aged 19–36 years, mean age 26.3 years), were enrolled in the study. The ASD group included six individuals with Asperger's disorder, three with autistic disorder, and three with pervasive developmental disorder not otherwise specified (PDD-NOS). A research team, including an experienced child psychiatrist (Y.K.), diagnosed the ASD participants according to DSM-IV criteria (APA, 1994) and clinical interviews with participants and/or parents using semi-structured interviews that have been validated for Japanese PDD populations (PARS, Kamio et al., 2006). Diagnostic agreement among the team was obtained for all participants. Control participants reporting no developmental problems were recruited from college classes and faculties.

The intellectual functioning of the ASD participants was evaluated using a Japanese version of the WAIS-R. ASD participants with full-scale IQ scores below 80 were not included in the study. All subjects exhibited normal or corrected-to-normal visual acuity (>1.0), evaluated using the Landolt's ring (Landolt, 1905). No subjects exhibited any color deficits, as determined by Ishihara color plates (Ishihara, 1997).

Informed consent was obtained after the nature of the experiment had been fully explained. The experimental procedures were approved by the ethics committee of the Graduate School of Medical Sciences, Kyushu University.

2.2. Visual stimuli

The stimuli were generated by ViSaGe (Cambridge Research Systems, Cambridge, UK) and were displayed on a gamma-corrected color monitor with a frame rate of 100 Hz (Electron22blue IV, LaCie, Tokyo, Japan). The P and M pathways have distinct physiological characteristics (Livingstone & Hubel, 1988; Tobimatsu & Celesia, 2006). Therefore, different types of stimuli were created to preferentially stimulate either the lower level P pathway or the lower M pathway within V1 as described below.

The P pathway is characterized by its high spatial resolution, color sensitivity, low contrast sensitivity, and low temporal resolution (Livingstone & Hubel, 1988; Tobimatsu & Celesia, 2006). Red/green chromatic sinusoidal gratings with equal luminance of red and green were used to evaluate P pathway activity (Fig. 1a). Because this stimulus was highly elemental, it would be expected to preferentially stimulate the P pathway (particularly the P-color pathway) within V1. The visual stimulus subtended 10×10 degrees of visual angle at a viewing distance of 114 cm. CIE coordinates (measured by a ChromaMeter CS 100, Konica Minolta, Tokyo, Japan) were $x = 0.601$, $y = 0.365$ (R); $x = 0.267$, $y = 0.581$ (G). Chromatic stimuli were surrounded by a homogeneous background containing a mixture of red and green (yellow). The luminance of red and green, as well as the homogeneous background, was 21 cd/m^2. The contrast level was 0% as defined by the Michelson contrast. The spatial frequency was set to 2 cycles per degree. Prior to experimentation, subjects viewed a 15-Hz alternating red/green pattern stimulus to establish psychophysical isoluminance, and relative luminance was adjusted to minimize the perception of flicker (Yamasaki, Goto, Kinukawa, & Tobimatsu, 2008). A chromatic pattern appeared for 200 ms, and was subsequently replaced by a homogeneous stimulus background for 1000 ms. This type of stimulus is known to elicit transient VEP responses (N1) (Tobimatsu et al., 1995). Subsequently, cartoon characters appeared for 1000 ms, which were then replaced by a homogeneous stimulus background for 1000 ms. Ten images of cartoon characters were randomly presented in each session. An entire sequence was 3200 ms. A session included 30 sequences (about 1–2 min) and was repeated four times. Therefore, a total of 120 sequences were presented (about 6–7 min in total).

The M pathway is characterized by high temporal resolution, high contrast sensitivity, color insensitivity, and low spatial resolution (Livingstone & Hubel, 1988; Tobimatsu & Celesia, 2006). Achromatic (black/white) sinusoidal gratings were used to evaluate the M pathway (Fig. 1b). Because this stimulus was highly elemental, it preferentially stimulated the M pathway within V1. The luminance of black was 17.5 cd/m^2, and that of white was 24.5 cd/m^2. A homogeneous background, containing a mixture of white and black (gray), surrounded the visual stimuli. The mean luminance of the achromatic gratings and the homogenous background was 21 cd/m^2, and the contrast level was 16.6%, as defined by the Michelson contrast. Spatial frequency was set to 1 cycle per degree. The stimulus pattern alternated in a square-wave fashion at a rate of 8 Hz (16 reversals/s). Stimulation was presented for 2000 ms, and was subsequently replaced by a homogenous background for 1000 ms. This stimulus condition elicited a transient VEP response (P1), followed by steady-state responses (Gutschalk et al., 2002). Ten cartoon characters then randomly appeared for 1000 ms and were subsequently replaced by a homogeneous stimulus background for 1000 ms. These cartoon characters were entirely different from those of chromatic condition. An entire sequence was 5000 ms. A single session included 30 sequences (about 2–3 min) and was repeated four times. Therefore, a total of 120 sequences were presented (about 10 min in total).

2.3. VEP recordings

VEPs were recorded using a Geodesic EEG system, NetAmps 200 (Electrical Geodesics [EGI], Eugene, OR). A high-density, 128-channel, HydroCel Geodesic Sensor net (EGI) was applied over the scalp of the participant. This net held each electrode in place, and distributed electrodes from the nasion to the inion and from the left to the right mastoid at uniform intervals.

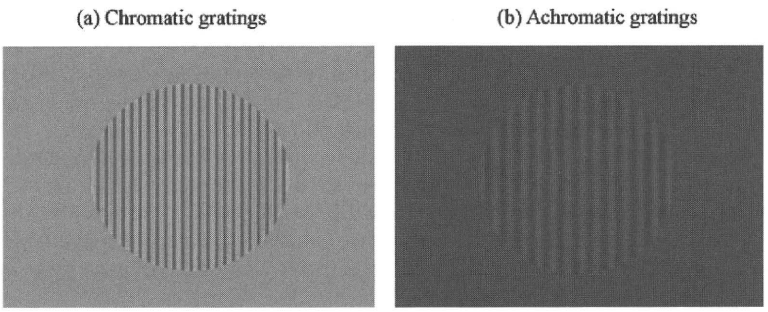

Fig. 1. Visual chromatic (a) and achromatic (b) stimuli used in this study. (a) The equal luminance red/green chromatic sinusoidal gratings (visual angle, 10° × 10°; mean luminance, 21 cd/m^2; spatial frequency, 2 cycles per degree). Visual stimulus is surrounded by a homogeneous background, with a mixture of red and green colors (mean luminance, 21 cd/m^2). This pattern stimulus appears for 200 ms and is replaced by a homogeneous stimulus background for 1 s. (b) The achromatic (black/white) sinusoidal gratings (visual angle, 10° × 10°; mean luminance, 21 cd/m^2; spatial frequency, 1 cycle per degree). The visual stimulus is surrounded by a homogeneous background, with a mixture of black and white colors (mean luminance, 21 cd/m^2; contrast, 16.6%). This stimulus is rapidly alternated in a square-wave fashion at 8 Hz (16 reversals/s) and appears for 2000 ms, followed by a homogenous background for 1 s.

Each electrode consisted of a silver chloride carbon fiber pellet, a lead wire, a gold-plated pin, and a potassium chloride-soaked sponge. This electrode configuration effectively blocked out electrochemical noise and minimized triboelectric noise. Signals were amplified via an AC-coupled, 128-channel, high-input impedance amplifier (NetAmps 200, EGI). The analog data were digitized at a sampling rate of 500 Hz/channel. Amplified analog voltages were hardware band-pass-filtered at 0.1–200 Hz. The experimenter individually adjusted all sensors until the impedance of each electrode was less than 80 kΩ (Ferree, Luu, Russell, & Tucker, 2001). Most of the electrode impedances were kept below 50 kΩ throughout the experiment, except for the electrodes surrounding the ears and neck. The impedance levels were comparable between the ASD (24.1 ± 3.6 kΩ [mean ± SD]) and control (32.1 ± 8.8 kΩ) groups. We used the vertex (Cz) electrode as a reference.

The participants were instructed to remain still and to fixate on a black fixation dot at the center of the screen. The arousal level was carefully visually monitored by an observer (T.F.) in the same room and by the EEG signal. We also recorded the participants' activity with a video camera placed outside of the room. If a participant became drowsy, he/she was alerted and provided with a brief rest. To maintain attention to the stimuli, the participants were instructed to memorize the names of the cartoon characters that were presented between stimuli. Following VEP recording, all participants were able to provide the cartoon character's names. The order of chromatic and achromatic stimuli was counterbalanced among the participants.

2.4. Offline data analyses

Epochs containing EEG deviations from the baseline greater than 50 μV were automatically rejected from the analysis. Subsequently, epochs that contained blinks, horizontal or non-blank eye movements, A/D saturation, or obvious occipital α-activity were rejected. Electrodes surrounding the eyes were used to identify blink artifacts, as well as horizontal or non-blank eye movements. Epochs were then re-referenced offline to an average of 99 channels that represented all channels except the channels surrounding the eyes, ears, and neck, because these channels were easily contaminated by muscle electric potentials.

A total of 120 VEP samples in 400-ms epochs (from −100 to 300 ms) were averaged for chromatic stimuli using Net Station software (EGI). We required at least 80 viable trials for a participant to be included in the analysis. VEPs elicited in a brief presentation of visual stimuli provided the transient VEP responses. The N1 was the first major component to emerge. Because the scalp topography of the N1 component exhibited maximal amplitude at Oz and the Oz electrode reflects activity around V1, EEG data were analyzed at Oz.

A total of 120 VEP samples with 2000-ms epochs (from 0 to 2000 ms) were averaged for achromatic stimuli using Net Station software (EGI). The required minimum number of viable trials for participation was defined as 80. The scalp topography for the major component (P1) was then created. Next, because the scalp topography of the P1 component exhibited maximal amplitude at Oz, and the Oz electrode reflected activity around V1, EEG data from Oz were used in the analysis.

Finally, scalp topography for the steady-state response (positive and negative phases) was created. Because the scalp topography of the steady-state response exhibited maximal amplitude at Oz, data from Oz were used for further analysis. The average response was then subjected to fast Fourier transforms (FFTs), which yielded the amplitude (square root of the power) and phase of the major component (EMSE Suite, Source Signal Imaging, San Diego, CA, USA).

2.5. Statistical analyses

The mean number of viable trials between the two groups was analyzed using unpaired *t*-tests. For the N1 elicited by chromatic stimuli and the P1 elicited by achromatic stimuli, the peak amplitude and latency were measured from the pre-stimulus baseline in each subject. The latency difference between the two groups was analyzed using unpaired *t*-tests. The Mann–Whitney *U* test was used to assess amplitude differences. A level of $p < 0.05$ was considered to be statistically significant.

The steady-state VEP phase was analogous to the latency of transient VEPs, but phase data were distributed on a circular scale (from 0° to 360°). These data were therefore quantified using circular statistics, which were employed for evaluating phase data (Mardia, 1972; Zar, 1999). Three parameters were calculated: mean angle, phase coherence (*r*), and circular standard deviation (CSD; Tobimatsu & Celesia, 2006). Both *r* and CSD were used as measures of dispersion in the phase data. The *r*-value varied from 0, when too much dispersion resulted in a total lack of definition of a mean angle, to 1.0, when all data were concentrated in the same direction (Mardia, 1972; Zar, 1999). The reliability of *r*-values was quantified using the Rayleigh test for randomness (Batschelet, 1981). A level of $p < 0.05$ was considered to be statistically significant for this analysis. CSD was SD for phase measurements, and appeared most similar to the linear SD (Mardia, 1972). The difference in VEP amplitude between the two groups was analyzed using unpaired *t*-tests. Because phase data were circularly distributed, the Mann–Whitney *U* test was used to assess them. A level of $p < 0.05$ was considered to be statistically significant in these analyses.

3. Results

3.1. Intellectual function

The ASD participants exhibited normal IQ (verbal IQ, 111 ± 19.2 [mean ± SD]; performance IQ, 110 ± 12.8; full-scale IQ, 112 ± 13.8). There were no significant differences in chronological age (*t*-test) and sex ratio (χ^2 test) between the two groups.

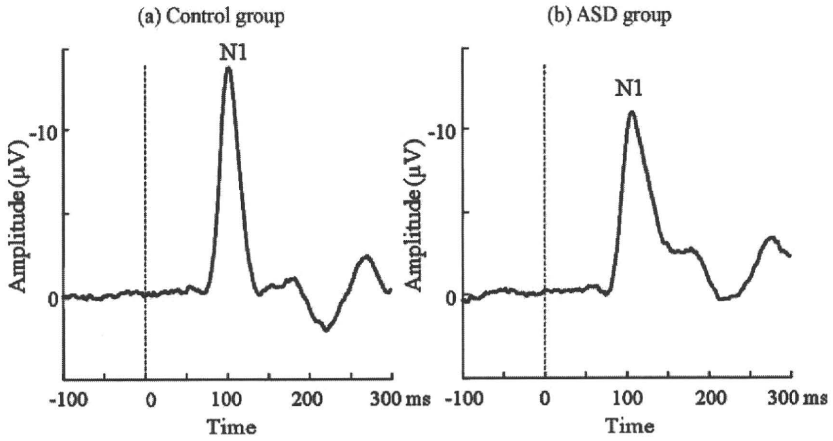

Fig. 2. Grand averaged waveforms of VEPs in response to chromatic stimuli at the Oz electrode in control (a) and ASD (b) groups. In both groups, a negative component around 100 ms (N1) was elicited, which is regarded as a major component.

3.2. Parvocellular function

In the trials designed to elicit P pathway activation, all participants correctly named the cartoon characters following VEP recording. This confirms that participants were attentive during the experiment. The numbers of trials rejected for α-activity were below five in both groups. There was no significant difference in the mean number of viable trials between groups (control group, 104.5 ± 10.3; ASD group, 100.7 ± 13.1, $p = 0.43$). These results suggest that differences in arousal and attention levels between groups did not affect VEP responses.

Grand-average VEP waveforms elicited by chromatic stimuli at Oz are shown in Fig. 2. In both groups, the negative component at approximately 100 ms (N1) was elicited as a major component. In terms of scalp topography, N1 was located at the occipital area (maximum at Oz), and there was no obvious difference in N1 distribution between the two groups (Fig. 3). The mean N1 latency in the ASD group (108.6 ± 7.7 ms) was significantly longer than in the control group (102.8 ± 5.3 ms) ($p = 0.04$). In contrast, there was no significant difference in mean N1 amplitude between control (15.5 ± 7.2 μV) and ASD groups (13.0 ± 6.3 μV) ($p = 0.47$).

Six ASD participants (50%) exhibited an N1 latency within the normal range (102.8 ± 5.3 ms). Thus, additional analyses (unpaired *t*-test) were performed to examine the characterization/phenotypic difference between the subgroups within or outside of the normal range. However, there was no significant difference between the two subgroups.

3.3. Magnocellular function

In the trials designed to elicit M pathway activation, all participants correctly named the cartoon characters following VEP recording. This confirms that participants were attentive during the experiment. The number of trials rejected for α-activity

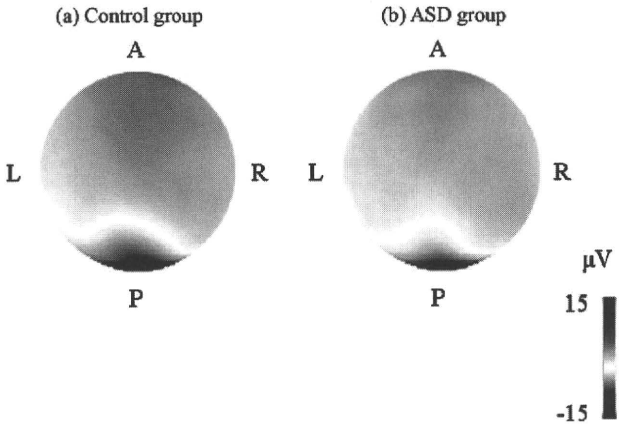

Fig. 3. Grand-averaged scalp topography of the N1 component in control (at 102 ms) (a) and ASD groups (at 108 ms) (b). In both groups, the N1 component is predominantly distributed at occipital areas (maximum at Oz). There was no obvious difference in N1 distribution between the two groups. L: left, R: right, A: anterior, P: posterior in this and Fig. 5.

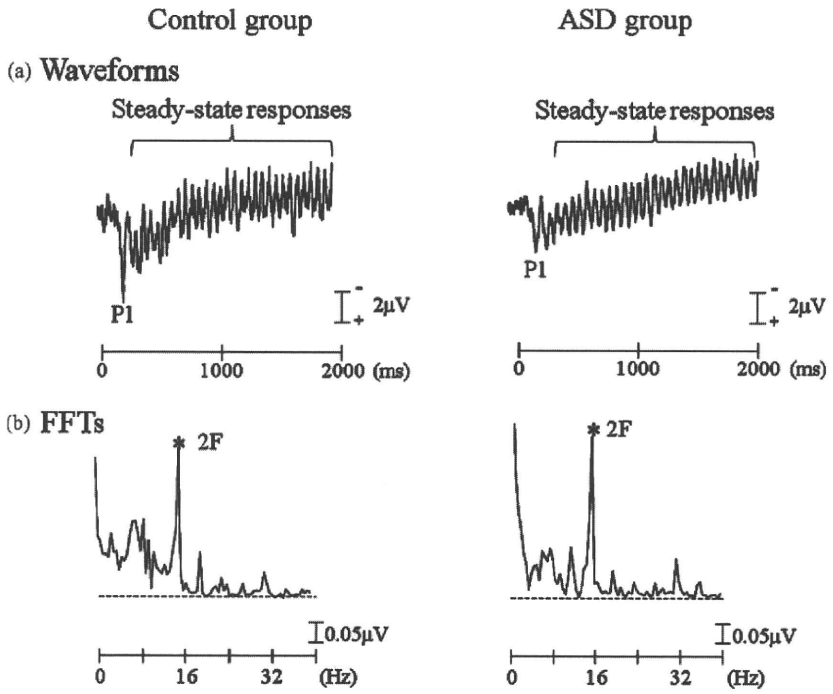

Fig. 4. Representative waveforms of VEPs (a) and fast Fourier transforms spectra (FFTs, b) in response to achromatic stimuli at the Oz electrode in control (left) and ASD (right) subjects. In both subjects, a positive component around 120 ms (P1) and quasi-sinusoidal waveforms correspond to the reversal frequency (16 Hz) (a). FFTs show that the second harmonic (2F) component is a major component in both groups (b).

in the trials designed to activate the M pathway was less than 15 in both groups. The mean number of viable trials in the ASD group was no different from the controls (control group, 105.3 ± 14.9; ASD group, 101.8 ± 11.8, $p = 0.53$). These results suggest that differences between arousal and attention levels did not affect the VEP responses.

In both groups, VEPs, in response to achromatic stimuli at Oz, exhibited a positive component (P1) at around 120 ms, as well as quasi-sinusoidal waveforms that corresponded to the reversal frequency (16 Hz; Fig. 4a). Scalp topography revealed that P1 and steady-state responses in the positive and negative phases were predominantly distributed over occipital areas (maximal at Oz). There was no obvious difference in the distribution of P1 and steady-state responses between the two groups (Fig. 5).

There was no significant difference in mean P1 latency between the control group (129.5 ± 5.3 ms) and the ASD group (132.0 ± 7.2 ms) ($p = 0.38$). In addition, no significant difference was detected in mean P1 amplitude between the control

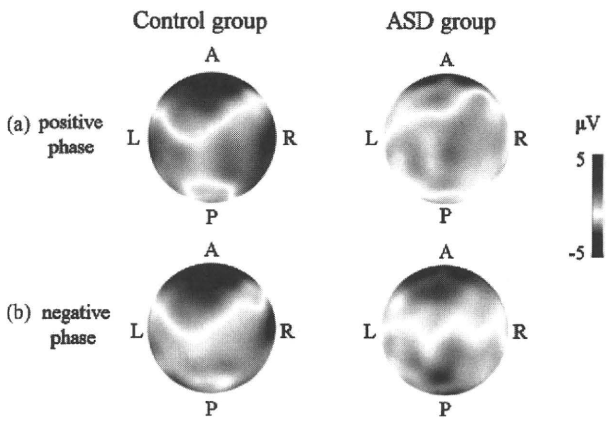

Fig. 5. Grand-averaged scalp topography of steady-state responses (positive (a) and negative (b) phases) in control (left) and ASD (right) groups. In the control group, scalp topography of positive phase at 787 ms (left, a) and negative phase at 755 ms (left, b) are mapped, while that of positive phase at 634 ms (right, a) and negative phase at 660 ms (right, b) are depicted in the ASD group. In both groups, steady-state responses are predominantly distributed at occipital areas (maximum at Oz). There is no obvious difference in the distribution of steady-state responses between the two groups.

(9.01 ± 3.34 μV) and ASD groups (7.73 ± 2.47 μV; $p = 0.43$). For the steady-state responses with FFTs, the second harmonic (2F) component was evident as a major component in both groups (Fig. 4b). As such, we analyzed the phase and amplitude of this component. In the control group, mean 2F amplitudes and phases were 0.57 ± 0.33 μV and 142.3 ± 62.9 (CSD) degrees, respectively. The r-value was 0.548 ($p < 0.05$). In the ASD groups, mean 2F amplitudes and phases were 0.51 ± 0.22 μV and 128.2 ± 53.6 (CSD) degrees, respectively. The measure of r was 0.646 ($p < 0.05$), suggesting narrow angle dispersion. There was no significant difference in mean 2F amplitudes and phases between the groups (amplitude, $p = 0.55$; phase, $p = 0.63$).

4. Discussion

4.1. Dysfunction of the parvocellular-color pathway in ASD

Chromatic stimuli with equal luminance do not stimulate M neurons. The mean N1 latency in response to chromatic stimuli in high-functioning adults with ASD was significantly longer than in the control group. The chromatic stimuli used in this study would be expected to preferentially activate the color pathway, but not the form pathway, since the form pathway preferentially responds to gratings with high spatial frequency and high contrast (Tobimatsu & Celesia, 2006). In accord with these previous findings, the present results indicate that dysfunctional activity in the P-color pathway at a relatively low level may be involved in ASD.

Although anecdotal evidence suggests that differences in color perception exist in children with autism and non-autistic children, few studies have directly examined this possibility. To the best of our knowledge, only one previous psychophysical study has investigated color perception in ASD, revealing color perception abnormalities (color memory, color search, and chromatic discrimination) in children with ASD, without color deficits in perceiving Ishihara color plates (Franklin, Sowden, Burley, Notman, & Alder, 2008). The authors concluded that abnormal color perception in ASD was due to differences in the anatomical and functional organization of the brain. In particular, disruption to one or more of the visual pathways was proposed to play a role in this color perception abnormality. Our present neurophysiological results are thus consistent with these previously described psychological findings in demonstrating that ASD is associated with dysfunctional activity in the visual pathway responsible for analyzing color information. The present study is the first to elucidate abnormal function within the P-color pathway in ASD.

The P-color pathway anatomically interacts with the P-form pathway (Yabuta & Callaway, 1998). Although the functioning of the P-form pathway itself was not assessed in the present study, the possibility of P-color dysfunction (color perception) and P-form biased function (detailed form perception) can be predicted based on the abundant evidence of superior fine form perception in ASD (Dakin & Frith, 2005). To test this hypothesis, further VEP studies are required to evaluate P-form pathway functioning using appropriate visual stimuli, such as high-contrast achromatic gratings with high spatial frequencies in children, as well as adults with ASD.

4.2. Normal function of the magnocellular pathway within V1 in individuals with ASD

P neurons respond poorly to achromatic low-contrast patterns with high temporal frequencies (Tobimatsu & Celesia, 2006). In the present study, there was no significant difference in VEP responses to achromatic stimuli between the groups. This indicates that lower-level M pathway functions are preserved in ASD adults.

Previous studies have demonstrated an elevated motion coherence threshold in ASD (Milne et al., 2002; Spencer et al., 2000). An additional psychophysical study (Bertone et al., 2003) revealed that motion sensitivity in ASD was similar to control groups for first-order (luminance-defined) motion stimuli related to V1 functioning. However, second-order (texture-defined) motion stimuli related to V2/3 activity elicited significantly decreased motion sensitivity in ASD patients compared to control groups. Moreover, relative to typical developing children (Pellicano, Maybery, & Durkin, 2005), children with ASD displayed an elevated global motion threshold, but equivalent flicker contrast sensitivity. These findings suggest abnormal functioning in the higher levels of the M pathway in ASD patients, but intact lower-level functioning, which further supports the present electrophysiological results showing normal lower-level M pathway activity.

The human visual system can detect a small percentage of coherently moving dots against a background of incoherently moving dots (Baker, Hess, & Zihl, 1991). This ability depends on V5/MT integration of local motion signals from V1 into global motion (Snowden, Treue, Erickson, & Andersen, 1991). Therefore, coherent motion stimuli are considered to be more useful than second-order motion for investigating higher-level functioning in the M pathway. Accordingly, replication of these studies is necessary for children with ASD, and further VEP studies using coherent motion stimuli are needed to confirm whether the higher-level activity in the M pathway is functionally impaired in children, as well as adults, with ASD.

4.3. Methodological limitations

Although special care was taken when creating the appropriate visual stimuli for P- and M pathways, our sample size was relatively small. Clinical diagnoses were performed based on extensive clinical interviews, and standard interview tools such as the ADI-R or ADOS-G were not used. Instead, we used a widely used scale (PARS) with high sensitivity and high specificity