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Atypical visual change processing in children with autism: An electrophysiological Study

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Abstract

Children with Autism Spectrum Disorder (ASD) may display atypical behaviors in reaction to unattended changes that occur in all sensory modalities. Atypical automatic auditory change processing has been highlighted in ASD via the analysis of mismatch negativity (MMN). The present study investigated visual deviancy detection in children with ASD in order to determine whether unusual reactions to change operate in other sensory modalities. Twelve children with ASD were presented with a passive visual oddball paradigm using dynamic stimuli. Compared to controls, children with ASD showed an earlier visual mismatch response, suggesting a hypersensitivity to visual deviancy. This study is thus consistent with the hypothesis of the existence of "general" atypical change detection processing in children with ASD that might contribute to their intolerance of change.

Descriptors: Sensation/perception, Children/infants, Psychopathological, EEG/ERP

Autism Spectrum Disorder (ASD) is a severe and pervasive neurodevelopmental disorder characterized by impairments in communication and social interaction as well as high levels of repetitive, stereotypic, and ritualistic behaviors (American Psychiatric Association, 2000). This third major dimension, sometimes referred to as "resistance to change," has been less often investigated than the social and communication deficits, yet it results in major difficulties in daily life (Gabriels, Cuccaro, Hill, Ivers, & Goldson, 2005). Clinical reports of individuals with ASD show that they react in an unusual way to unattended events that occur in their environment or that interfere with their routines. These atypical reactions may be expressed in the form of tantrums as a response to change or in the form of restricted interests and repetitive or stereotyped behaviors and persist with age (Kobayashi & Murata, 1998; Richler, Huerta, Bishop, & Lord, 2010). Pervasive, stereotyped behaviors and resistance to change have been proposed to reflect poor executive abilities such as cognitive flexibility (Lopez, Lincoln, Ozonoff, & Lai, 2005). Individuals with ASD would thus have difficulties in generating novel solutions or to shift set, and they try to impose predictability, with insistence on repetition and sameness (McEvoy, Rogers, & Pennington, 1993). Resistance to change may also occur at the sensory level; children with ASD display unusual behaviors in response to changes in all sensory modalities (Boyd et al., 2010). Several behavioral studies and results of questionnaires have also shown unusual responses in all sensory modalities such as hyperreactivity or hyporeactivity (Ashwin, Ashwin, Rhydderch, Howells, & Baron-Cohen, 2009; Ben-Sasson, Carter, & Briggs-Gowan, 2009; Khalfa et al., 2004; Leekam, Nieto, Libby, Wing, & Gould, 2007; Reynolds & Lane, 2008), both being sometimes observed in the same subject. Such paradoxical responses to sensory stimuli lead to a lack of consensus on the exact nature of the underlying sensory dysfunction, but have been proposed to contribute to stereotyped behaviors and quest for sameness (Gerrard & Rugg, 2009).

Moreover, study of relationships between clinical and electrophysiological data has demonstrated that atypical brain reactivity in response to sensory changes occurring in stimulus sequence was related to the degree of behavioral intolerance of change (Gomot et al., 2011). As a whole, these features indicate that intolerance of change in ASD may be rooted in basic abnormalities in the processing of sensory information and especially in the automatic processing of changing stimuli (Gomot & Wicker, 2012).

The neural correlates of automatic sensory change detection are commonly studied through the oddball paradigm, where a sequence of repetitive standard stimuli is presented with infrequent unpredictable deviant stimuli. The event-related potential (ERP) evoked by any deviant stimulus is called mismatch negativity (MMN) and was first described in the auditory modality (Näätänen, Gaillard, & Mantysalo, 1978; Näätänen, Paavilainen, Rinne, & Alho, 2007). MMN is usually interpreted as an automatic response based on comparison of an incoming stimulus and the representation of preceding stimulus in memory. However, some investigators take the view that mismatch negativity is explained by simpler processes associated with neuronal refractoriness

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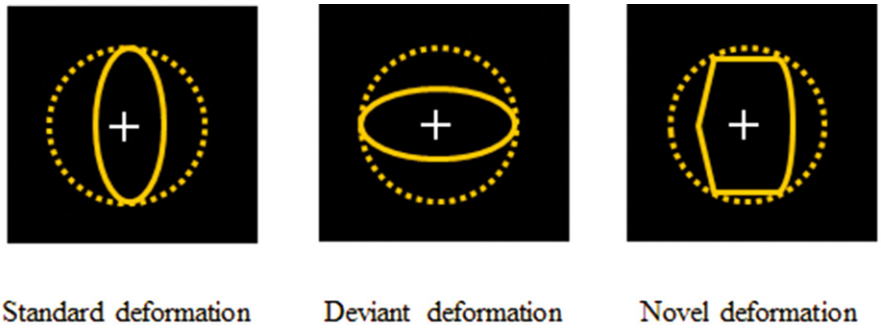

Figure 1. Dynamic stimuli consisted of the deformation of a circle into an ellipse either horizontally (standard deformation) or vertically (deviant deformation) or into a new shape (novel deformation).

(Kenemans, Jong, & Verbaten, 2003). MMN is assumed to reflect a preattentional change detection process, and its recording does not require active participation from the subject. Several studies have shown that MMN can be recorded early in development, and mechanisms underlying this response are assumed to be similar across the life span (Cheour, Leppanen, & Kraus, 2000; Gomot, Giard, Roux, Barthelemy, & Bruneau, 2000).

A number of studies have investigated the auditory MMN in patients with ASD using basic stimuli such as tones, and the results reported are rather inconsistent. For example Lepisto et al. (2005) found that children with autism displayed larger MMN amplitude. Similar findings were reported by Ferri et al. (2003) in children with a dual diagnosis of autism and mental retardation. MMN amplitude has also been reported in the normal range (Ceponiene et al., 2003; Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1995) whereas other studies indicated a reduced response (Dunn, Gomes, & Gravel, 2008; Seri, Cerquiglini, Pisani, & Curatolo, 1999). Incongruent findings regarding MMN latency have also been reported. Some studies found MMN latency in the normal range in children with ASD (Ceponiene et al., 2003; Lepisto et al., 2005), whereas others showed shorter MMN (Gomot, Giard, Adrien, Barthelemy, & Bruneau, 2002; Kujala, Tervaniemi, & Schroger, 2007) or a delayed response (Jansson-Verkasalo et al., 2003; Seri et al., 1999). Using magnetoencephalography, a similar delayed response (Oram Cardy, Flagg, Roberts, & Roberts, 2005) or a response of smaller amplitude (Tecchio et al., 2003) was obtained. Such variations in the literature may be explained by the diversity of protocols used and populations studied (for review, see Gomot & Wicker, 2012; O'Connor, 2012). However, only one study investigated the brain processes involved in automatic change detection in ASD through an auditory oddball paradigm using scalp potentials (SP) and scalp current density (SCD) mapping (Gomot et al., 2002). This study showed a shorter MMN latency in ASD with an atypical fronto-central topography, hypothesized to involve a cortical network including the cingulate region. Atypical auditory change processing in ASD was then confirmed using functional magnetic resonance imaging during an auditory oddball paradigm (Gomot et al., 2006). This study reported normal activity in the auditory cortex but unusual activation in the anterior cingulate cortex in people with ASD, a region known to be involved in attention switching and in the distribution of attentional resources (Daffner et al., 2003).

Clinical observation of individuals with ASD reveals that atypical behaviors in reaction to changes occur in all sensory modalities. Moreover, atypical brain activity associated with change processing in the auditory modality involves brain regions located outside the sensory cortices (Gomot et al., 2002, 2006). Taken together, these findings suggest the existence of atypical change processing in ASD regardless of the sensory modality.

In the visual modality, atypical sensory responses have been found in some studies in subjects with Pervasive Developmental Disorder (PDD). ERP amplitudes in response to visual stimuli measured at occipital sites are reported to be abnormally small in patients with PDD, reflecting abnormal activation of visual pathways dedicated to the processing of both high and low spatial frequencies (Boeschoten, Kenemans, van Engeland, & Kemner, 2007; Kemner & van Engeland, 2006; Milne, Scope, Pascalis, Buckley, & Makeig, 2009). Few studies have investigated visual change detection per se in ASD, and the protocols used have involved active target detection (Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1994; Sokhadze et al., 2009). Results indicated smaller P3 amplitude in response to novel visual events in people with ASD than in controls (Ciesielski, Courchesne, & Elmasian, 1990; Courchesne, Lincoln, Yeung-Courchesne, Elmasian, & Grillon, 1989). However, in everyday life, changes generally occur outside the focus of attention. No study has yet examined automatic change processing in children with ASD in the visual modality.

MMN is well defined in the auditory modality, but recent studies have provided fairly convincing evidence for the existence of its visual analogue. Electrophysiological recordings of visual automatic change detection in healthy adults have shown the emergence of a negative component in the 140–400-ms latency range and revealed the same degree of automaticity as the auditory MMN. This response would thus reflect the visual MMN counterpart (vMMN; Astikainen, Ruusuvirta, Wikgren, & Korhonen, 2004; Czigler, Balazs, & Winkler, 2002; Pazo-Alvarez, Amenedo, & Cadaveira, 2004). vMMN, characterized by a posterior negative activity, has been shown in response to deviant stimuli such as direction of movement (Kremlacek, Kuba, Kubova, & Langrova, 2006), form (Besle, Fort, & Giard, 2005), orientation (Astikainen, Lillstrang, & Ruusuvirta, 2008), spatial frequency (Maekawa et al., 2005), and color (Czigler, Balazs, & Pato, 2004). To characterize the maturation of the automatic visual change detection process, we used a visual oddball paradigm in healthy children and adults (Cléry et al., 2012). This paradigm consisted of the dynamic deformation of a circle into an ellipse either in one or another direction, thus involving two visual dimensions: object form and motion direction (Figure 1). This kind of visual stimulation involving changes in form and in motion was used to increase the chances of obtaining vMMN in children by stimulating the mismatch process within two physical stimulus features. Through use of this

paradigm, a typical visual MMN was identified in the adult group, culminating over occipito-parietal sites, followed by an additional anterior negative component. These findings were in accordance with previous vMMN literature (Amenedo, Pazo-Alvarez, & Cadaveira, 2007; Besle et al., 2005; Czigler et al., 2004; Pazo-Alvarez et al., 2004; Urakawa, Inui, Yamashiro, & Kakigi, 2010). In 11-year-old children, results showed that the organization of the visual mismatch response is still nonmature. A negative visual response to deviance was seen, culminating over occipito-parietal sites between 200 ms and 350 ms after stimulus onset. Finally, the change detection process in children was mainly characterized by a large positive wave at around 450 ms and labeled Mismatch Positivity 450 (MMP450). Only one study has examined vMMN in atypically developing children (with mental retardation; Horimoto, Inagaki, Yano, Sata, & Kaga, 2002), using a visual oddball paradigm based on color deviancy combined with a selective attention task to auditory stimuli. However, no clear findings were reported in terms of amplitude or latency of the response.

The aim of the present study was to investigate deviance processing in the visual modality in children with ASD in order to examine whether there are abnormalities comparable to those previously reported in the auditory modality and thus to determine whether unusual reactions to change might be underlain by atypical general change processing independent of the sensory modality. Using the same visual stimuli as Cléry et al. (2012), we employed ERP mapping to conduct spatiotemporal analyses of brain activation elicited by unattended changing visual stimuli.

Materials and Methods

Participants

Twelve children with ASD aged 8 to 14 years (10 boys and 2 girls) were recruited from the Child Psychiatry Centre of the University Hospital of Tours. Diagnosis was made according to DSM-IV-R criteria (American Psychiatric Association, 2000) and by using the Autism Diagnostic Interview (ADI-R; social interaction + communication scores [mean ± standard deviation]: 27 ± 7; threshold for ASD = 18) or the Autism Diagnostic Observation Schedule-Generic (ADOS-G, third module; social interaction + communication scores [mean ± standard deviation]: 13 ± 6; threshold for ASD = 7). Diagnosis was complemented by the Childhood Autism Rating Scale (CARS; mean ± standard deviation: 37 ± 7; threshold for ASD = 30). Developmental quotients (DQs) were assessed by the Echelles Différentielles d'Efficiences Intellectuelles (EDEI-R; Perron-Borelli, 1996) or the Wechsler Intelligence Scale for Children (WISC III). These two developmental scales provided overall developmental (mean ± standard deviation; DQ: 86 ± 28 and a median of 88), verbal developmental (vDQ: 80 ± 12) and nonverbal developmental (nvDQ: 92 ± 19) quotients, all within the normal range.

Patients were age and gender matched with 12 typically developing children (controls; 10 boys and 2 girls; mean age for the ASD group, 11 years, 7 months [*SD* = 1 year, 9 months], and controls 11 years, 3 months [*SD* = 1 year, 6 months]). Chronological age matching was chosen because auditory MMN latency is known to dramatically evolve throughout childhood. Several studies (Gomot et al., 2000; Kurtzberg, Vaughan, Kreuzer, & Fliegler, 1995) have shown that MMN latency significantly decreased with increasing age (e.g., from 200 ± 29 ms in a group of 5–7-year-old children to 163 ± 26 ms in a group of 8–10-year-old children). Moreover, visual ERPs in general evolve with increasing age, due to cortical maturation and myelination (Allison, Hume, Wood, & Goff, 1984; Brecelj, 2003; Emmerson-Hanover, Shearer, Creel, & Dustman, 1994; Nelson, 1997; Shaw, 1984). Matching on the basis of developmental age would thus be less relevant, as it would imply comparing children with ASD with much younger control children. The control group consisted of participants with a history of regular school attendance and normal scholar level and who had no psychiatric or developmental disorders.

All participants had normal or corrected-to-normal vision. No children reported difficulties seeing visual stimuli, and all correctly detected the target. No participants had neurological or significant medical disorders. No children were receiving psychotropic medication.

The Ethics Committee of the University Hospital of Tours approved the protocol. Signed informed consent was obtained from parents and assent was given by the children.

Stimuli and Procedures

Change detection processes were studied using a passive visual oddball paradigm with three types of dynamic stimuli: "standard" (probability of occurrence $p = .82$), "deviant" (probability of occurrence $p = .09$) and "novel" (probability of occurrence $p = .09$). As shown in Figure 1, these stimuli consisted of the deformation of a circle into an ellipse either horizontally (standard) or vertically (deviant) or into another shape (novel), adapted from Besle et al. (2005). Each stimulus consisted of seven successive images presented in 140 ms (i.e., 50 images per second), which resulted in apparent motions in the stimuli. The distinction between deviants and novels was not based on their probability of occurrence but on their salience. Whereas the deviant was always the same stimulus and only differed from the standard on the orientation of the ellipse, novel stimuli were always different nonidentifiable shapes. Stimuli were presented with a 650-ms interstimulus interval. The viewing distance was set at 120 cm (visual angle 2°). There were two runs of 815 dynamic stimuli. To control effects related to the stimuli features, deviants were swapped with standards halfway through the sequence. Total recording lasted 25 min. To present the visual stimuli within the visual field but outside the focus of attention, subjects were required to undertake a distractive task. They were asked to stare at the fixation cross (that appeared on the center of circles) and to respond as quickly as possible to its disappearance (target 9% of the trials). The disappearance of the fixation cross (target) was never in synchrony with the presentation of deviant or novel stimuli but always during a standard trial.

Acquisition and Data Analysis

The behavioral responses measured were mean reaction times (in milliseconds) and response accuracy, calculated by taking into account the rates of hits (correct response less than 2 s after target disappearance), false alarms to nontarget stimuli (response without target disappearance), and missed targets (no response within 2 s after target disappearance), according to the formula (targets − missed targets)/(targets + false alarms) * 100. Electroencephalographic (EEG) data were recorded from 31 Ag/AgCl electrodes referenced to the nose. Electrodes were placed according to the international 10–10 system (Oostenveld & Praamstra, 2001): Fz, FFz, Cz, Pz, Iz, F3, C3, P3, O1, T3, T5, FC1, CP1,

FT3, TP3, and PO3 and their homologous locations on the right hemiscalp. Additional electrodes were placed at M1 and M2 (left and right mastoid sites), IM1 and IM2 (midway between M1 and IZ and IZ and M2). The whole experiment was controlled by a Compumedics NeuroScan EEG system (Synamps amplifier, Scan 4.3 and Stim2 software). The impedance value of each electrode was less than 10 kΩ. In addition vertical eye movements (EOG) were recorded using two electrodes placed above and below the right eye. Eye-movement artifacts were eliminated using a spatial filter transform developed by NeuroScan, and EEG periods with movement artifacts were manually rejected. The EEG and vertical EOG were filtered with an analogue bandpass filter (0.3–70 Hz) and digitized at a sampling rate of 500 Hz. EEG epochs were averaged separately for the standards and the deviants over a 700-ms analysis period, including a 100-ms prestimulus baseline. The ERPs to deviants and novels included at least 120 trials for each subject. MMN was measured from the difference waves obtained by subtracting the standard-stimulus ERP from the deviant-stimulus ERP.

The ELAN software package for analysis and visualization of EEG-ERPs was used (Aguera, Jerbi, Caclin, & Bertrand, 2011). Maximum amplitudes and peak latencies of the sensory ERP and mismatch responses were measured for each subject within an 80-ms time window around the peak of the grand average waveforms specific to each group.

Scalp potential (SP) maps were generated using a two-dimensional spherical spline interpolation and a radial projection from Oz (back views) or from Cz (top views), which respects the length of the meridian arcs. Scalp current densities (SCDs) were estimated by computing the second spatial derivative of the interpolated potential distributions (Perrin, Pernier, Bertrand, & Echallier, 1989). Topographic differences were tested in the interactions between groups and electrodes on amplitude-normalized data (McCarthy & Wood, 1985). Measurements for each subject were normalized with respect to the minimum value of the measurement at each site and then were divided by the result of the max − min subtraction.

Amplitudes and latencies were analyzed using repeated measures analysis of variance (ANOVA) with Group (Controls, ASD) as the between-subjects factor and Electrodes as the within-subjects factor. As the age range of our samples was quite large, age was introduced as a covariate in statistical analyses. Within each group, the statistical significance of ERP amplitude compared to 0 was tested by Student's *t* test analysis corrected for multiple comparisons, using the statistical-graphical method of Guthrie and Buchwald (1991) as previously used in several electrophysiological studies (Colin et al., 2002; Vidal, Giard, Roux, Barthelemy, & Bruneau, 2008). This method provides a table indicating the minimum number of consecutive time samples that should be significant differences in ERP in order to have a significant effect over a given time period. For our sample of 12 subjects and an analysis period of 600 ms (from 0 to 600 ms, i.e., 300 sampling points), the minimum number corresponded to 12 consecutive time points (i.e., 24 ms) with *p* values below the .05 significance level. Direct groups' comparison of the difference waves (deviants − standards) was performed using unpaired Student's *t* test analysis corrected for multiple comparisons with the same statistical-graphical method of Guthrie and Buchwald. Such an analysis allowed determination of periods of between-groups statistical differences and constituted a good alternative for processing data from groups that do not display similar components.

Results

Behavioral Responses

Both groups performed the distractive task well, indicating that they looked at the screen and thus received visual stimuli. The autistic group showed significantly longer reaction times than the control group (with age as a covariate in the ANCOVA analysis comparing the two groups; control: 430 ± 56 ms; ASD: 514 ± 68 ms), $F(1,21) = 15.89$, $p < .001$). Moreover, the ASD group had significantly lower response accuracy for the distractive task than the control group (control: 94.7% ± 2.2%; ASD: 86.2% ± 8.4%), $F(1,21) = 12.91$, $p < .001$). This difference was due to the fact that children with ASD missed more targets (missed targets control: 2.9% ± 1.9%; ASD: 10.5% ± 8.4%), $F(1,21) = 5.19$; $p < .06$, and tended to commit more false alarms than controls, as measured according to the formula false alarms/targets * 100 (control: 2.61% ± 1.72%; ASD: 3.89% ± 4.01%; n.s.).

Electrophysiological Analysis

Responses to standard stimuli. Both groups presented the same morphology and distribution of responses to standard visual stimuli, clearly localized over occipito-parietal sites, at O1, PO3, P3, and T5 in the left hemisphere (left OPT) and at O2, PO4, P4, and T6 in the right hemisphere (right OPT; Figure 2). Evaluations of left and right OPT responses were therefore calculated by averaging values measured at these four electrode sites on each hemisphere and statistical analyses of variance were conducted on these two sets of electrodes.

The obligatory responses consisted of a positivity peaking at 130 ms and called visP130 followed by a negative wave culminating at 200 ms and referred to as visN2. The last positive wave was recorded as peaking at 330 ms (visP330). To overcome any potential age effect, age was introduced as a covariate in the ANCOVA comparing the two groups. Compared to those of the controls, the ASD responses to standard stimuli did not differ significantly in amplitude but displayed significant delayed latency of about 40 ms: visP130: $F(2,20) = 12.40$, $p < .001$; visN2: $F(2,20) = 11.49$, $p < .001$ (Table 1). Only the visP330 latency did not display significant intergroup difference, $F(2,20) = 0.61$, n.s.

Responses to deviant and novel stimuli. As shown in Figure 3, both groups had almost the same morphology and distribution of responses to the deviant as to the standard stimuli, peaking over occipito-parietal sites at left OPT and right OPT, although ASD responses to deviant stimuli were somewhat more positive than those of the control group (nonsignificant intergroup differences; cf. Table 1). For the standard stimuli, ANCOVA with age as a covariate indicated that the ASD group displayed significantly delayed latency in response to deviant stimuli on both hemispheres, for the visP130 (control: 120 ± 16 ms; ASD: 150 ± 19 ms), $F(2,20) = 8.69$, $p < .01$, visN2 (control: 190 ± 14 ms; ASD: 240 ± 17 ms), $F(2,20) = 36.40$, $p < .001$, and visP330 (control: 25 ± 16 ms; ASD: 360 ± 14 ms), $F(2,20) = 16.67$, $p < .001$. In response to novel stimuli, children of the control group had visP130 (peaking at 140 ms) followed by a visN2 (peaking at 200 ms) comparable in term of morphology and distribution (left and right OPT) with responses to deviant stimuli. However, the amplitude of the visN2 was significantly lower in response to novel stimuli than in response to deviant ones, $F(1,21) = 3.21$, $p < .001$. The novel detection process was completed by a significant novelty P3 peaking at 410 ms (Table 1).

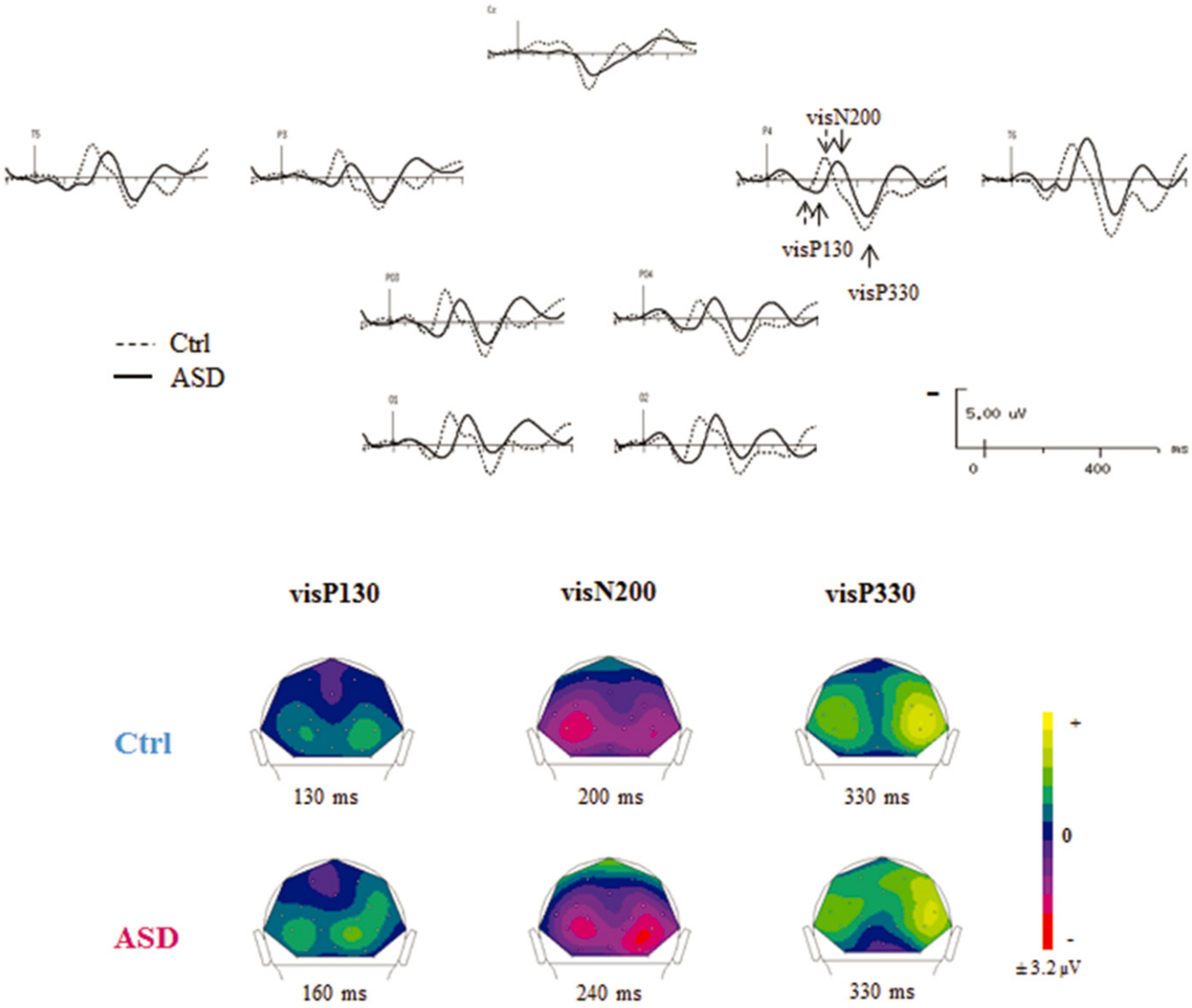

Figure 2. Grand-average ERPs to the standard visual stimuli in both groups at selected electrodes.

The ASD groups' responses to novel stimuli were morphologically different from those to deviant stimuli. The novel detection process began with a visP130 recorded over left and right OPT at 150 ms, followed by a visN2 culminating at 300 ms and a novelty P3 peaking at 380 ms. Compared to the responses to deviant stimuli, visN2 to novel stimuli appeared significantly delayed, $F(1,21) = 2.58$, $p < .01$. This delay might be explained by the presence of an additional positive wave in the ASD group recorded at 250 ms.

Compared to the control group, an additional visP2 was recorded, leading to between-group differences in the visN2 peak latency, $F(2,20) = 3.62$, $p < .01$. Nonetheless the novelty P3 culminated earlier in the ASD group than in controls, $F(2,20) = 4.63$, $p < .001$ (Table 1).

Deviance processing. The difference waves were obtained by subtracting the standard-stimulus ERP from the deviant-stimulus ERP. First observation of the control group and the ASD group difference waves revealed significant between group differences. While in the control group, the visual mismatch response was composed of a predominant negative deflection culminating over occipito-parieto temporal sites at 330 ms associated with a fronto-central positive component peaking around 280 ms and followed by a large positive wave culminating around 450 ms (labeled MMP450; Figure 4a, box), the ASD group displayed atypical change detection responses, mainly characterized by several positive deflections in the 50–300-ms latency range, followed by a significant MMP450 culminating at 400 ms over occipito-parietal regions. Visual inspection of individual ERPs revealed that these positive deflections were observed in each ASD participant in this latency range. Because the ASD groups' difference wave appeared with a morphology similar to that of controls but displaced in positivities (Figure 4a, box), a high-pass filter (1 Hz) was used to decompose the signal in both groups. The slowest positive components were thus extracted in both groups and the resulting difference waves, after filtering, were analyzed.

Table 1. *Amplitude and Latency Values of Responses to Standard, Deviant, and Novel Visual Stimuli in the Autism Spectrum Disorder (ASD) and Control Groups*

	Latency (in microseconds ± SD)		Amplitude (in microvolts ± SD)	
	Control group	ASD group	Control group	ASD group
Standard				
visP130				
L OPT	130 ± 18*	164 ± 19	1.6 ± 1.6	1.9 ± 2.1
R OPT	131 ± 17*	166 ± 17	2 ± 2.1	2.1 ± 1.7
visN2				
L OPT	200 ± 24*	242 ± 20	−3 ± 1.8	−2.9 ± 2.4
R OPT	203 ± 27*	244 ± 16	−3.1 ± 1.5	−2.9 ± 3.4
visP330				
L OPT	332 ± 18	338 ± 21	2.9 ± 2	2.3 ± 3.8
R OPT	337 ± 21	343 ± 15	3.8 ± 2.6	2.6 ± 3.6
Deviant				
visP130				
L OPT	123 ± 16*	152 ± 18	1.5 ± 2.2	3.7 ± 2.7
R OPT	121 ± 17*	149 ± 19	1.8 ± 2.2	3.2 ± 2.2
visN2				
L OPT	193 ± 11*	245 ± 18	−3.7 ± 2.8	−2.8 ± 3.7
R OPT	188 ± 18*	243 ± 16	−3.6 ± 3	−2.6 ± 3.7
visP330				
L OPT	324 ± 17*	357 ± 16	2.8 ± 2.6	4.7 ± 4.3
R OPT	328 ± 16*	358 ± 13	3.6 ± 2.8	5.1 ± 4.1
Novel				
visP130				
L OPT	143 ± 29	149 ± 26	2.6 ± 2.2	2.8 ± 2.5
R OPT	145 ± 27	156 ± 24	2.5 ± 1.9	2.9 ± 2.5
visP2				
L OPT	—	247 ± 27	—	3 ± 3
R OPT	—	247 ± 23	—	2.7 ± 3.2
visN2				
L OPT	190 ± 26*	296 ± 28	−1.1 ± 3.6	−1.6 ± 3.9
R OPT	201 ± 25*	300 ± 27	−0.9 ± 2.3	−1.3 ± 4.1
Novelty P3				
L OPT	415 ± 22*	386 ± 17	3.8 ± 2.4	3.4 ± 3.1
R OPT	423 ± 23*	381 ± 14	3.4 ± 1.7	3.9 ± 3.4

Note. L OPT: occipito-parietal sites at O1, PO3, P3, and T5 in the left hemisphere; occipito-parietal sites at O2, PO4, P4, and T6 in the right hemisphere. *$p < 0.01$.

In the control group, the resulting difference wave appeared very similar to the original one. The visual mismatch response was mainly composed of a large positive wave culminating around 450 ms and labeled Mismatch Positivity 450 (MMP450; Figure 4b). Using the criteria defined in the Materials and Methods section, two periods of statistical significant amplitude from 0 were distinguished in controls (Figure 4c, left panel): (1) from 280 to 340 ms a fronto-central positive component was revealed, and (2) from 400 to 550 ms, a large MMP450 was significant over all occipito-temporo-parietal sites.

After filtering, an early mismatch process was still observed in the ASD group as seen in Figure 4b, which showed statistically significant amplitude in the 300–400-ms latency range, revealing the MMP450 over occipito-temporo-parietal sites (Figure 4c, right panel).

ANCOVA with age as a covariate indicated that MMP450 measured at left and right OPT occurred significantly earlier in the ASD group than in controls, $F(2,20) = 30.11$, $p < .001$. MMP450 amplitude did not display a significant intergroup difference, $F(2,20) = 0.12$, n.s.

The MMP450 was the only statistically significant component observed in both groups. An unpaired Student's t test was performed to test for periods of significant between-groups differences (Figure 4c). Main differences were found from 300 to 410 ms over the centro-parietal region, highlighting the earlier MMP450 recorded in the ASD group than in controls.

Topographical analysis. Figure 5a presents the SP and SCD maps of the MMP450 in response to deviant stimuli in both groups. In controls, SP maps displayed a large bilateral positive activity over the occipito-parieto-temporal areas, slightly right lateralized, with maxima at O2 and T6. In children with ASD, SP maps revealed a more bilateral occipito-parietal positive activity than in controls, with maxima at PO3 and PO4. The topographic difference was statistically confirmed by a significant Group × Electrode (O1, O2, PO3, PO4, P3, P4, T5, T6) interaction that remained significant after data normalization, $F(7,154) = 3.89$, $p < .001$). SCD maps in controls suggested bilateral occipito-temporal current sources and a possible right parietal sink/source complex, whereas in children with ASD bilateral occipito-parietal sources with a medial occipito-parietal current sink seemed to be involved.

Finally, SP and SCD maps of the novelty P3 in response to novel stimuli are shown Figure 5b. SP maps revealed that both groups presented the same distribution of responses, characterized by a bilateral occipito-parietal positive activity. No significant groups difference or Group × Electrode interaction was found for this component. SCD maps might reflect in both groups bilateral

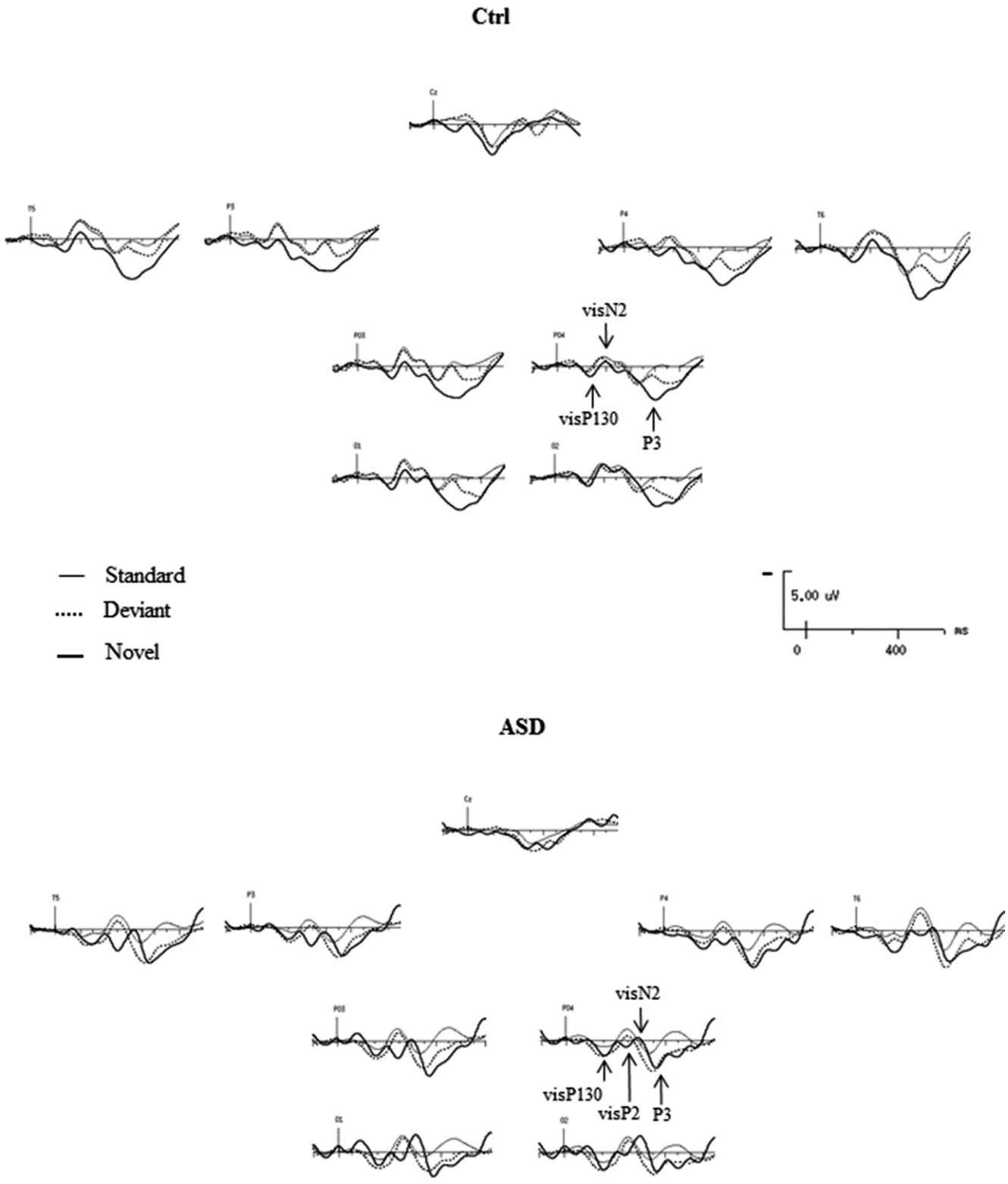

Figure 3. Grand-average event-related potentials (ERPs) to the deviant and novel visual stimuli superimposed on the grand-average ERPs to the standard visual stimuli in both groups at a selected electrode.

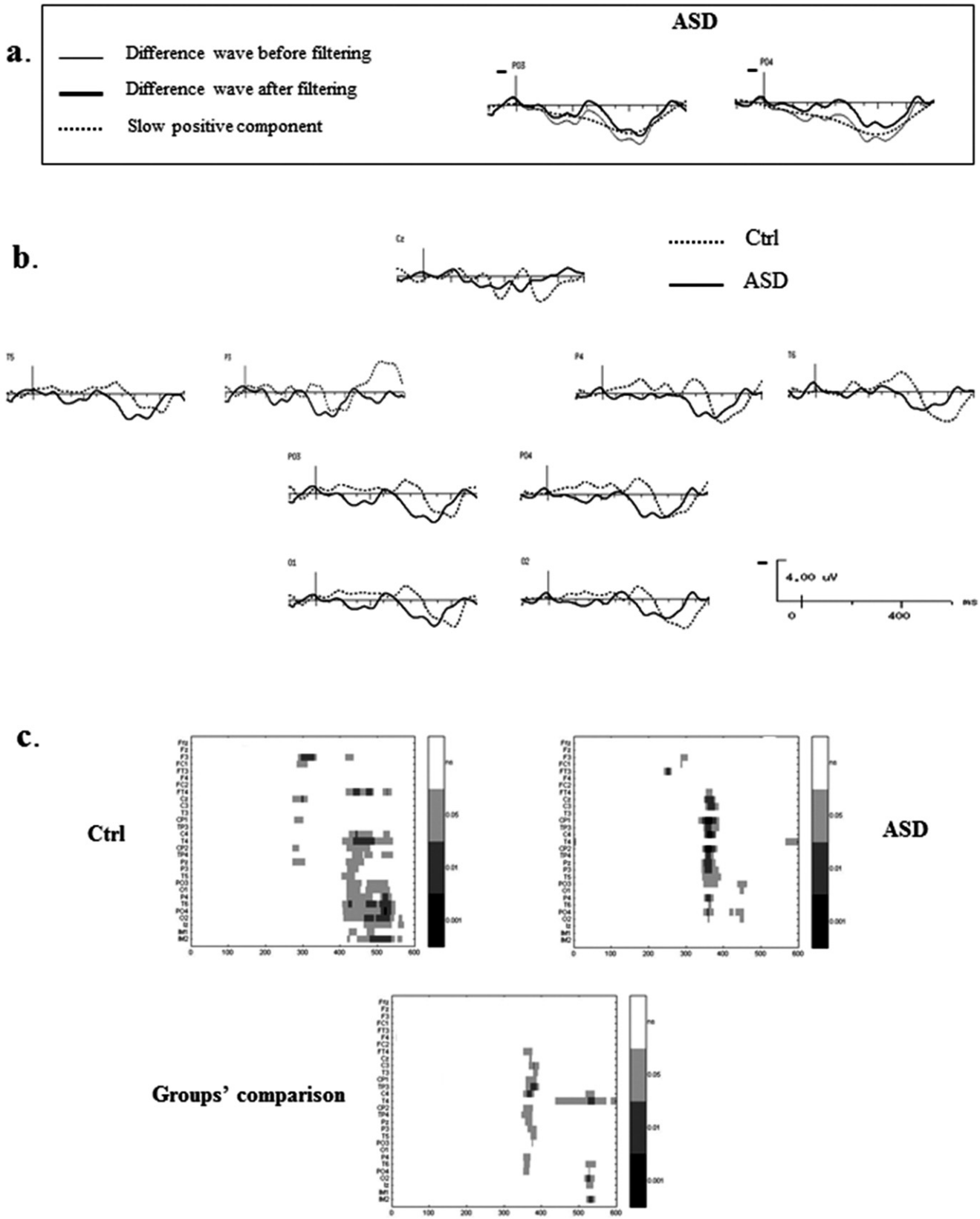

Figure 4. a: Grand-average difference wave obtained by subtracting the event-related potentials (ERPs) to the standard stimuli from those to deviant stimuli in both groups before filtering (1 Hz) and after filtering. b: Grand-average difference waves obtained by subtracting the ERPs to the standard stimuli from those to deviant stimuli in each group at selected electrodes. c: Paired Student's *t* test analysis revealing statistical significance of the amplitude of the difference wave at 29 electrodes sites in the 0–600-ms latency range in control participants (left panel) and the participants wit Autism Spectrum Disorder (ASD) (right panel). Bottom panel: Unpaired Student's *t* test analysis revealing periods of between-group statistical differences in the 0–600-ms latency range at 29 electrodes sites.

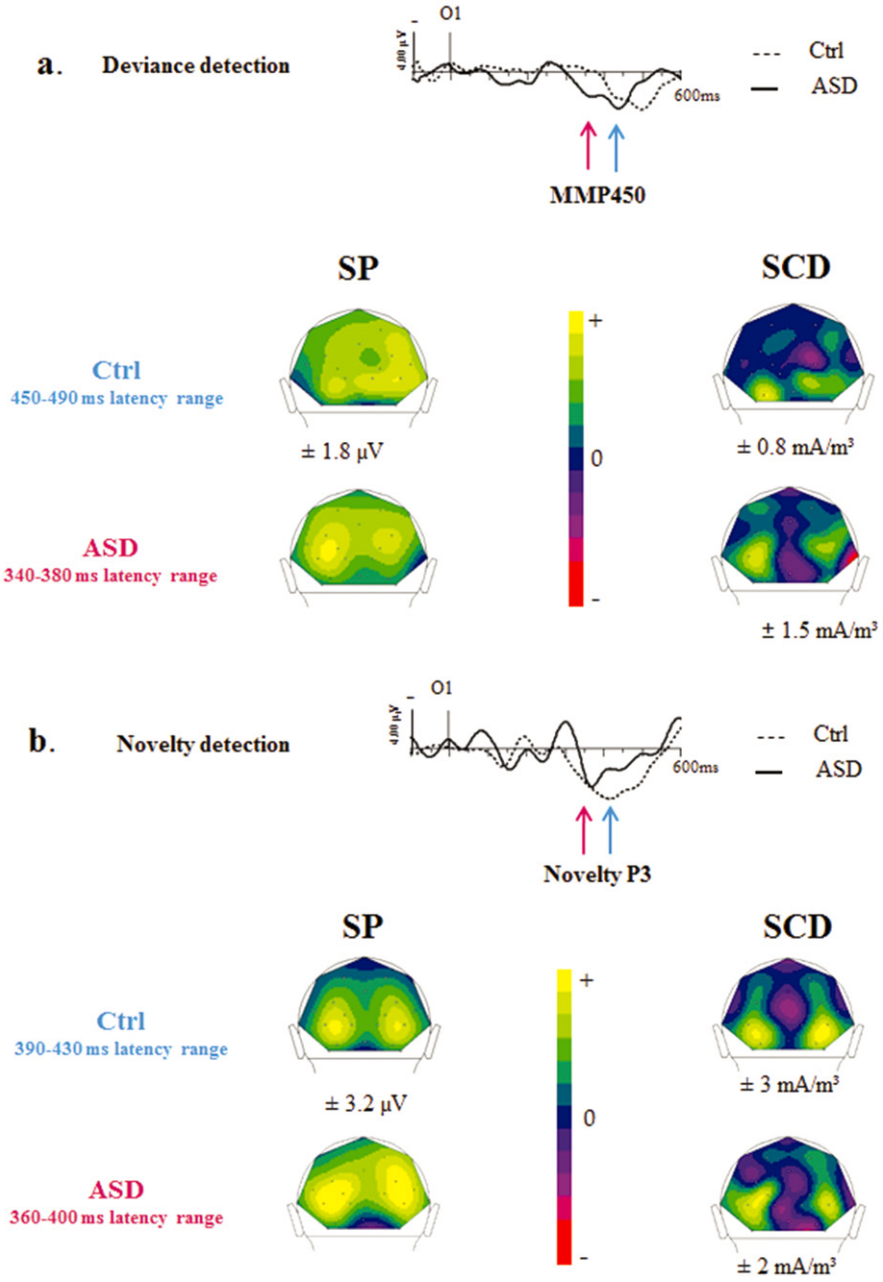

Figure 5. a: Scalp potentials (SP) and scalp current density (SCD) maps calculated at the mean peak latency of the MMP450 response for each group. Back views. b: SP and SCD maps calculated at the mean peak latency of the novelty P3 response for each group. Back views.

occipito-parietal sources associated with a medial occipito-parietal current sink.

To check if the MMP450 and the novelty P3 reflected the same component, we compared the topographies of these two responses. In contrast to the control group, which showed distinct distributions for the novelty P3 and for the MMP450 (Condition × Electrode interaction on normalized data), $F(7,154) = 6.87$, $p < .01$), the ASD group displayed novelty P3 topography similar to that of the MMP450, as no significant topographic differences were found between these two conditions in this group.

Discussion

This study is the first to characterize electrophysiological indices of deviancy processing in children with autism in the visual modality. Using a passive oddball paradigm, an earlier brain response to unattended deviant visual events was revealed in children with ASD compared to controls.

The electrophysiological pattern of the obligatory sensory responses to standard visual stimuli reported here showed the same morphology, amplitude, and topography of response in both groups, but with significantly longer latency (visP130 and visN2) in children with ASD than in controls. Such lengthened latency was also observed in response to deviant visual stimuli. These results suggest abnormalities in low level visual processing and are in accordance with findings from previous electrophysiological studies showing that the processing of basic visual information may be affected in ASD (Boeschoten et al., 2007; Jemel, Mimeault, Saint-Amour, Hosein, & Mottron, 2010; Kemner, Lamme, Kovacs,

& van Engeland, 2007; Maekawa et al., 2011; O'Connor, Hamm, & Kirk, 2007; Pei et al., 2009; Vlamings, Jonkman, van Daalen, van der Gaag, & Kemner, 2010). However, to our knowledge, no study has reported electrophysiological responses to stimuli similar to those presented in this study. As visual responses are highly dependent on the characteristics of the stimulus, it remains difficult to strictly compare the ERP components analyzed across the studies. Nonetheless, one of the most studied areas in the field of elementary visual processing in ASD is motion perception. Previous work in this domain suggested that individuals with ASD are poor at motion coherence tasks, biological motion, and second-order-motion tasks (Dakin & Frith, 2005; Simmons et al., 2009). The dynamic property of the stimuli used here could therefore have caused the delay observed in the ASD group in response to standard and deviant stimuli.

Moreover, though basic obligatory information processes were tested in this study, one cannot exclude that the slight mental age difference between our two groups might partly contribute to the differences in the ERPs in response to standards. Indeed in the ASD group the mean overall IQ was one standard deviation below the norm of 100. A developmental study including younger typically developing children should be considered and would help to determine whether minimal mental age differences could have account for the P1/N2 delay observed in those children with ASD.

First observation of the visual mismatch response revealed in the control group a predominant negative deflection peaking at 330 ms over occipito-parieto-temporal areas, accompanied by a significant brief positive component peaking at 280 ms over fronto-central sites and completed by a large positive component 450 ms after the deviant stimulus. In children with ASD, compared to controls, the mismatch process revealed an earlier atypical positive mismatch response. Mismatch processes appeared to have the same morphology in both groups, but displaced below baseline in the ASD group. A high-pass filter (1 Hz) was used to decompose the signal in both groups, and a slow positive component was identified in those with ASD. Then, after filtering, the resulting difference waves were analyzed and compared between groups. The slow positive wave observed in children with ASD seemed related to the deviant stimulus onset. Therefore, this additional wave cannot be considered as an artifact or a drift of the baseline but probably as reflecting a physiological process underlying the perception of visual change in children with ASD. In spite of this filtering, an early (but nonsignificant) positivity in the ASD group remained observable in the 100–200-ms latency range. Such a positive response to visual change has previously been described in healthy adults. In the study of Czigler et al. (2004), in which visual stimuli were presented in the visual lower or upper half-field, deviant stimuli in the lower and upper half-field elicited an anterior and a later posterior positivity, but only lower half-field stimuli elicited the vMMN. This polarity reversal was assumed to reflect the retinotopic organization of the prestriate cortex, in which the lower and upper visual hemifields are mapped in the upper and lower banks of the calcarine fissure, respectively, suggesting that visual mismatch components are generated in retinotopically organized parts of the visual system. However, this explanation cannot fully account for the polarity reversal observed in those with ASD compared to controls because in our paradigm participants were presented with stimulations at the center of the screen with a visual angle of only 2°. Such a positive ERP component in response to change in the visual modality was also obtained by Kimura, Katayama, and Murohashi (2005). The authors used a S1-S2 matching paradigm with four types of paired stimuli presented with equal probability in order to distinguish between the response associated with a change detection processing based on sensory memory and the index of regularity violation. The change detection response was characterized by a posterior positive deflection. Although differences between paradigms do not allow a strict comparison with our findings, it could be argued that, in our study using an oddball paradigm and in which both processes co-occur, in children with ASD the regularity representation would be compromised and thus the change-related positivity was observed.

The difference wave after filtering in the ASD group differed from that in controls mainly in latency. The MMP450, characteristic of the mismatch response in children, culminated at least 70 ms earlier in those with ASD than in controls. The apparent incongruity between a shortened mismatch response and a delayed sensory response in ASD might be explained in light of previous works on auditory MMN process. In this modality, the sensory processes and the mismatch process have been shown to be independent. For instance, Fischer et al. (1999) performed a study in comatose patients revealing that MMN can be observed even when no auditory N1 is recorded. Such independence might also operate in the visual modality.

Children with ASD displayed significantly shorter mismatch response latency than controls. In the auditory modality, studies conducted in healthy adults have shown that shorter MMN latencies were recorded for greater deviant–standard differences (Schroger & Winkler, 1995). This degree-of-deviance effect has also been described for the visual MMN by Czigler et al. (2002), who presented, separately, similar, slightly different (small deviance) and widely different (large deviance) pairs of colors as standard and deviant stimulus features. In the present study, it might thus be hypothesized that, compared to controls, children with ASD processed deviant stimuli as more being salient. Shorter mismatch response latencies have been described in previous studies of auditory MMN in ASD (Gomot et al., 2002; Kujala, Aho, et al., 2007). One explanation might be proposed in light of clinical reports that show that children with ASD react in an unusual way to unattended events that occur in their environment. They may possibly detect visual changes in their surroundings more rapidly than normally developing children because of a higher cerebral reactivity to the deviancy.

Compared to the control group, children with ASD showed significantly longer reaction times and lower response accuracy to this task, due to the fact that they committed more false alarms. These results partially confirm the findings of the few previous studies that examined visual novelty processing in autism using an active oddball paradigm. In two of these studies subjects were presented with letters and had to press a button whenever a target stimulus occurred (Courchesne, Lincoln, Kilman, & Galambos, 1985; Sokhadze et al., 2009). Both studies showed that control and autistic groups did not differ in the percentage of correct hits, but autistic subjects had significantly longer reaction times. In these paradigms, targets were presented sequentially embedded with the other stimuli. In our paradigm, targets (fixation cross disappearance) were presented simultaneously with the other stimuli (deformations of the circle). This particular presentation of stimuli may partly explain the lower accuracy we observed in the ASD group. Such lower discriminative capacity observed in children with ASD might reflect difficulties in selective attention.

Taken together, our results can be discussed within the framework of the mismatch system model proposed by Sussman (2007) for the auditory modality. In Näätänen's original definition, MMN was thought to reflect the automatic detection of a difference

between the active sensory memory trace of a recent repeated event (standard) and an incoming deviant stimulus (Näätänen, Jacobsen, & Winkler, 2005). On the basis of this definition, Sussman (2007) proposed a model in which MMN elicitation involved two distinct but interrelated processes: standard formation and deviance detection. The standard trace is the neural representation of stimulus reiteration extracted from the signal and maintained in the sensory memory. When a stimulus is detected as being deviant, due to the violation of the standard trace, MMN is elicited. Thus, the standard form determines the basis for the deviance detection process. Although visual MMN is now widely considered to reflect a preattentive sensory process (Heslenfeld, 2003; Pazo-Alvarez et al., 2004; Tales, Newton, Troscianko, & Butler, 1999), some studies have shown effects of attentional demands on the processing of unattended visual stimuli (Czigler & Sulykos, 2010; Lavie, 2005; Pinsk, Doniger, & Kastner, 2004; Yucel, McCarthy, & Belger, 2007). These studies have demonstrated that processing of unattended visual information is restricted by the attentional demands of a concurrent task. In our paradigm, children with ASD showed longer reaction times and lower accuracy rates in the distractive task than did controls. They also displayed a delayed ERP to the standard stimuli. These findings might thus highlight atypical allocation of attentional resources in ASD, contributing to both lower performance and abnormal standard trace formation. It cannot be excluded that the atypical automatic change detection observed in ASD is related to a disorder of the deviance detection process itself. However, in this case, responses evoked by the standard stimuli would not be different from the control group.

Both differences in latencies and statistical analysis of responses topographies to deviant and novel stimuli revealed that children in the control group displayed different responses according to the salience of the visual stimuli. In the literature, the novelty P3 is usually described as culminating around 540 ms poststimulus with an amplitude of about 20 μV in typically developing children (Stige, Fjell, Smith, Lindgren, & Walhovd, 2007). The oddball paradigm used in the present study thus allows the elicitation of the different responses to deviant and novel stimuli. However, in children with ASD, the posterior positivity in response to deviant stimuli and the response to novel stimuli were recorded at the same latency and had the same scalp distribution, more akin to those of the novelty P3 in typically developing children. Thus it could be suggested that neural networks involved in the perception of visual changes in children with ASD are less sensitive to the salience of the stimulations than in typically developing children. Moreover, clinical reports have revealed that individuals with autism often tend to be more distractible than controls, suggesting that their attention may in fact be "underselective" (Allen & Courchesne, 2001). The ability to attend selectively to meaningful sources of information while ignoring irrelevant sources is essential for competent and adaptive functioning. This may thus explain why individuals with ASD appear to ignore salient stimuli in the environment in favor of relatively discrete and apparently meaningless stimuli, but this condition may also contribute to the exceptional perceptual abilities observed in some individuals with ASD (Mottron, Dawson, Soulieres, Hubert, & Burack, 2006; Plaisted Grant & Davis, 2009). This might be a maladjustment insofar as it leads to distress at small changes in the environment (Happe & Frith, 2006).

To conclude, this study shows unusual change processing in the visual modality in children with ASD. Despite our relatively small sample size (12 typically developing children and 12 children with ASD) and the variability observed within each group, the group differences reached significance. However, future experimentation should be conducted with more participants to strengthen our findings. Finally the study of both visual and auditory automatic change detection in the same subjects would provide better support for the hypothesis of the existence of "general" atypical change detection operating in several modalities in individuals with ASD that might contribute to their intolerance of change.

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