Early VEPs to pattern-reversal in autism

Klara Kovarski, Alix Thillay, Emmanuelle Houy-Durand, S. Roux, A. Bidet-Caulet, Frédérique Bonnet-Brilhault, M. Batty

Brief Report: Early VEPs to pattern-reversal in adolescents and adults with autism

Kovarski, K. [1], Thillay, A. [1], Houy-Durand E. [1], Roux, S. [1], Bidet-Caulet, A. [2], Bonnet-Brilhault, F. [1], Batty, M. [1]

1 Inserm, UMR U930 Imagerie et Cerveau, Université François-Rabelais de Tours, CHRU de Tours, Centre Universitaire de PédoPsychiatrie, Tours, France

2 Inserm, U1028, CNRS UMRS5292, Centre de Recherche en Neurosciences de Lyon, Bron, France.

Abstract

Autism Spectrum Disorder (ASD) is characterized by atypical visual perception both in the social and nonsocial domain. In order to measure a reliable visual response, visual evoked potentials (VEPs) were recorded during a passive pattern-reversal stimulation in adolescents and adults with and without ASD. While the present results show the same age-related changes in both autistic and non-autistic groups, they reveal a smaller P100 amplitude in autism compared to controls. These results confirm that early visual responses are affected in ASD even with a simple, non social and passive stimulation and suggest that they should be considered in order to better understand higher-level processes.

Keywords Autism spectrum disorder, Visual evoked potentials, pattern-reversal paradigm, sensory symptoms

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder diagnosed according to behavioral criteria. As core symptoms, ASD is characterized by difficulties in communication and social interaction as well as by repetitive and stereotyped behaviors. In the DSM-5, sensory abnormalities have gained a crucial weight in the diagnostic criteria. These have been reported in all sensory domains as hypo- and/or hyper-responsiveness to stimuli (Marco et al. 2011; Hazen et al. 2014; Wigham et al. 2015). In the visual domain, increasing evidence reveals that perception is atypical in ASD since infancy (see Simmons et al. 2009) and across development. Unusual visual strategies and behaviors such as visual auto-stimulation and search for bright sources are observed. Similarly, eye movements in ASD children are often characterized by frequent lateral glances (Mottron et al. 2007), suggesting a neural origin of visual abnormalities in ASD. In line with reports of affected low-level visual functioning, ophthalmological impairments have been also described (Ikeda et al. 2013; Milne et al. 2009a) confirming the importance of considering primary visual functioning on brain circuitry.

Recently, it has been suggested that the sensorial abnormalities could explain the difficulties in communication and social interaction (Hileman et al. 2011) as well as the repetitive and stereotyped behaviors (Wigham et al. 2015). For example, it has been proposed that the atypical face processing in ASD could be associated with difficulties in integrating the global information (Frith and Happe 1994), and/or with an enhanced ability to process details (Mottron et al. 2006). This local/global unbalance has also been linked to an atypical processing of spatial frequencies (Deruelle et al. 2008; Jemel et al. 2010), in line with the hypothesis of an impairment of the magnocellular pathway (Sutherland and Crewther 2010). Studies on neuropathology revealed alterations in the minicolumn organization as microcolumns were found to be smaller in ASD patients (Casanova et al. 2006; Courchesne et al. 2011). Abnormalities in both grey and white matter and atypical connectivity have also been reported

in MRI studies (see Anagnostou and Taylor 2011). In particular, abnormal cortical thickness and connectivity were found in areas implicated in social and non social autistic symptoms (Hyde et al. 2010; Anagnostou and Taylor 2011). In line with sensory symptoms in ASD, atypical neural organization of the visual network, have been reported in children (Shi et al. 2013), adolescents (Moseley et al. 2015), and adults (Belmonte and Yurgelun-Todd 2003; Ecker et al. 2010; Hyde et al. 2010; Bangel et al. 2014).

Visual evoked potentials (VEPs) recorded by electroencephalography (EEG) are a useful tool to investigate the integrity of visual pathways in neurodevelopmental disorders. Visual responses generated by the prestriate and striate visual cortices have been shown to be affected in children and adults with ASD when participants were presented with gabor patches, black and white patterns, gratings or other simple shapes (Milne et al. 2009b; Constable et al. 2012; Vandenbroucke et al. 2008; Pei et al. 2014; Baruth et al. 2010; Takarae et al. 2014). Recently, in an event related potentials (ERPs) study, Kornmeier et al. (2014) presented checkerboards with checks of two different spatial frequencies in an oddball paradigm where subjects were instructed to detect rare stimuli. They found a smaller early checksize effect 100ms after stimulus and stronger right-hemisphere lateralization of P3b component in Asperger adults compared to matched controls, revealing that early and later visual stages are both affected in ASD. In agreement with those findings, early visual processing has also been found impaired when evoked by social stimuli (Batty et al. 2011; Hileman et al. 2011). Taken together, these results suggest that atypical visual perception might depend on abnormalities in both single brain areas and networks (see Ecker et al. 2010). Moreover, these visual processing deficits in the early visual stages might be critical factors in the bottom-up cascading mechanism underlying higher processing, including integration and social processes.

In clinical settings, VEPs have been traditionally triggered with reversing checkerboard stimuli to monitor the functioning of the visual brain and detect abnormalities within it. While

the checkerboard pattern stimulation produces very early VEPs at around 30ms (ref Shigihara et al., 2016), most of the studies have focused on the pattern of three successive components: N75, P100 and N135 peaks [1]. While the generator of the N75 (also called C1) is mostly found in the primary visual area (striate cortex, area 17), the P100 source is more debated. Evidence from EEG/ MEG and functional MRI has supported for P100 and N135 being generated in dorsal extrastriate cortex of the middle occipital gyrus and the ventral extrastriate cortex of the fusiform gyrus (ref di Russo et al., 2001, ref Di Russo et al. 2005). The C1 component is sensitive to the position of the stimulus in the visual field, its polarity reverses depending on whether the upper or lower visual field is stimulated (ref Rauss et al., 2011), it also emerges when large stimuli (projecting on both foveal and peripheric retina) were used. The P1 and N1 are influenced by the content of the stimulus or the task rather than stimulus location. The P100 (also called C2 by jeffreys & Axford, 1972 ref) is known to reflect low level visual processing as P100 is highly modulated by experimental parameters, such as spatial frequency, luminance or contrast (Tobimatsu et al. 1993; Mahajan and McArthur 2012). Finally, the posterior negative component (recorded around 120-180ms) vary substantially with the kind of visual material presented. This visual component reflects a discriminative process (ref Luck, 1995; Vogel an Luck 2000), meaning that a pattern recognition mechanism is operated at this latency. When elicited by faces this component is particularly large and has been termed the N170 (ref Bentin et al., 1996; ref Rossion et al., 2011, ref Itier and Taylor, 2004).

VEPs recording during pattern-reversal paradigm have played a crucial role in determining the healthy functioning of the visual pathways up to and including the visual cortex (ref Shigihara at el., 2016). Easy to identify, the VEPs are obtained after a short period of passive viewing, moreover the reversal checkerboard may be quite captivating), making it easily applicable for young children and/or patients with poor cooperation. In general, developmental studies

[1] In this article, we used the label N75, P100 and N135 to refer to the visual evoked potentials evoked by a pattern reversal (Odom et al., 2004).

revealed a decrease in latency and an amplitude diminution in VEPs during maturation (ref Emmerson-Hanover et al., 1994). Moreover, a decrease of N75 and P100 amplitudes has been reported throughout adolescence (Mahajan and McArthur 2012).

Therefore, VEPs to pattern-reversal stimulation constitute a robust measurement for the integrity of the visual system and could be considered a promising candidate as marker of early visual functioning throughout maturation (Mahajan and McArthur 2012). In particular, adolescence is an intermediate period of continued neural development (Blakemore 2012; Mahajan and McArthur 2012; Thillay et al. 2015), representing a sensitive stage to understand maturation of visual processing. However, in autism research, adolescence is often neglected in a developmental perspective, and often confounded in children or young adults groups.

We believe that a better understanding of early-stage visual processing is necessary in order to understand higher level processing in ASD, especially when tasks require the visual modality (i.e. face processing, emotion recognition, decision making, and attention). The current study aims to investigate the early stages of low level visual processing in ASD adolescents and adults, matched to controls, using pattern-reversal VEPs.

Methods

Participants

Participants were recruited from the Child Psychiatry Hospital specialized in autism, University Hospital of Tours, France. Diagnosis of ASD was made according to the DSM-IV-TR criteria (American Psychiatric Association 2000) by a team of experienced clinicians using the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al. 2000) and/or the Autism Diagnostic Interview-Revised (ADI-R; Lord et al. 1994). In order to control for intellectual disability, global, verbal and performance age equivalent were assessed by the Wechsler intelligence scales (Wechsler 1997, 2005). 10 ASD adults (range 18-27; mean age = 21.5; SD = 3.01; 2 females) were matched for chronological age to 11 Typical Development (TD) adults (mean age = 22; SD = 2.69; 3 females), and 10 ASD adolescents (range 13-16; mean age = 14.9; SD = 1.51; 2 females) were matched for chronological age to 11 TD adolescents (mean age = 14.8; SD = 1.37; 2 females), (see Table 1). Because chronological age significantly differed from verbal age equivalent in ASD adolescents (12.8, SD = 2.18, $t = 2.42$, $p = 0.026$), we also matched this sample with another group of 11 typically developing children according to verbal developmental age (mean age = 13.1; SD = 2.09; 2 females). All participants had a normal or corrected to normal vision and no epilepsy. The local ethical committee board approved the protocol. Written informed consent was obtained from the parents and adults, and assent from the adolescents.

Table 1 Description of the ASD adolescents and adults and matched TD groups, by chronological age and verbal age (for adolescents only). Means, standard deviations, ranges and p-Values are reported.

ADOLESCENTS	**ASD**	**TD**	*p*-Value
N (*M:F* ratio)	10 (8:2)	11 (9:2)	
Chronological age	14.9 (1.5) (range = 13-17)	14.8 (1.4) (range = 13-17)	0.88
Verbal age	12.8 (2.2) (range = 10-17)	13.1 (2.1) (range = 10-17)	0.74
p-Value	0.03		
ADULTS	**ASD**	**TD**	*p*-Value
N (*M:F* ratio)	10 (8:2)	11 (8:3)	
Chronological age	21.5 (3) (range = 18-27)	22 (2.7) (range = 18-27)	0.66
Verbal age	21.1 (4.2) (range = 15-30)	-	
p-Value	0.82		

Stimuli and Procedure

Experiment consisted of a passive visual task. Participants were comfortably seated in a chair in a slightly lit room, and were asked to look at the screen for two minutes (120 stimuli). During the recording session, participants were monitored with a camera. The stimuli were presented in a pattern-reversal paradigm. Pattern-reversals consist in a black and white checkerboard that changes phase. In this experiment, check size was 1.9° (width) x 1.5° (height) visual angle, and the pattern fitted in a screen of 21.7° (width) x 16.3° (height) visual angle. Stimuli were generated by Presentation® software and were presented binocularly in the central visual field at a distance of 95 cm from participants' eyes. Pattern-reversal was generated using a temporal frequency of 1Hz (1000 ms phase/ 1000 ms reversed phase).

EEG Recording and Preprocessing

EEG was recorded using a 64-channel ActiveTwo system (Biosemi®, The Netherlands). Horizontal and vertical eye movements were monitored using electrodes placed to the outer canthi of the eyes and below the left eye. Two additional electrodes were applied on earlobes

for offline reference. The signal was recorded with a sampling frequency of 512 Hz and filtered at 0–104 Hz. Data were re-referenced offline to the average potential of the two earlobe electrodes. Electrooculographic activity was detected using independent component analysis (ICA) and was selectively removed via inverse ICA transformation. Other muscles or recording artifacts were discarded manually using ELAN software (Aguera et al. 2011). The continuous EEG was time-locked and trials were extracted in a 500 ms time-window (100 ms pre-stimulus to 400 ms post-stimulus). ERPs were digitally band-pass filtered between 0.5 and 30 Hz. ERPs were corrected with a -100 to 0 ms baseline before stimulus onset. Based on the minimum number of trials suggested for pattern-reversal stimuli analysis (see Odom et al. 2010), at least 64 stimuli were averaged for each participant (mean ± SD = 98.26 ± 20.92).

Statistical analysis

N75 and N135 were defined as the greatest negative deflections in the 35-75ms and 110-160ms latency range respectively and P100 was measured by identifying the greatest positive deflection in the 70-110ms latency range. N75 and P100 components were visually inspected at six occipital and parieto-occipital electrodes (OZ, O1, O2, POZ, PO3 and PO4). As these visual components were elicited in all subjects, mean amplitude and mean latency were measured at the occipital region (OZ, O1, and O2) and parieto-occipital region (POZ, PO3 and PO4). N135 peak was not very pronounced. Even if a deflection was observed, the peak hardly reached negative values, especially at occipital and medial electrodes. Consequently, analysis was carried out on PO3 and PO4 only, according to N135 extrastriate cortex generator (see Mahajan and McArthur 2012). N75 and P100 components are indicated by arrows in Fig. 1a, and their scalp distributions are shown in Fig. 2. Statistical analyses were completed with the TD group matched for chronological age. When a group effect was found, additional analysis were carried out with verbal age TD group as control group for developmental delay. For peak latency and amplitude of N75 and P100 analysis of variance with repeated measures

(ANOVAs) were performed with diagnostic group (ASD, TD) and age group (Adolescents, Adults) as between-subject factors, and electrode site (mean values at parieto-occipital vs. occipital electrodes) as within-subject factor. The same analysis was carried out for N135 with PO3 and PO4 only, with electrode site as a factor. ANOVAs *F* values, probability levels and effect sizes (partial eta squared η_p^2) were provided. Further analysis of significant effects were performed using Bonferroni post-hoc tests. Statistical analyses were completed using Statistica software.

Result

N75

A main effect of age group showed that N75 latency significantly decreased with age (at Oz, adolescents: 57.85 ± 3.73 ms, adults: 53.85 ± 4.56 ms; $F(1,38) = 5.70$, $p = 0.022$, $\eta_p^2 = 0.130$; see Fig. 1a). An effect for electrode site was also significant ($F(1,38) = 23.80$, $p < 0.001$, $\eta_p^2 = 0.385$) with latency being shorter in the parieto-occipital region compared to the occipital. No other interactions or diagnostic group effect were significant for N75 latency ($p > 0.06$).

For N75 amplitude, ANOVA indicated a main effect of age group ($F(1,38) = 11.60$, $p = 0.002$, $\eta_p^2 = 0.234$), with adults presenting smaller amplitude (at Oz, -2.48 ± 1.59 μV) than adolescents (at Oz, -5.83 ± 2.64 μV). An effect of the electrode site ($F(1,38) = 14.81$, $p < 0.001$, $\eta_p^2 = 0.280$) revealed occipital site being more negative than parieto-occipital. As revealed by significant interaction between site and age group ($F(1,38) = 26.33$, $p < 0.001$, $\eta_p^2 = 0.409$), adolescents presented more negative responses in the occipital region then adults ($p < 0.001$), but amplitude did not differ in the parieto-occipital region ($p = 0.576$).

No diagnostic group or other effects were found for N75 amplitude ($p > 0.08$).

P100

For P100 latency, the interaction between site and age group was significant ($F(1,38) = 5.92$, $p = 0.020$, $\eta_p^2 = 0.134$), with latency at parieto-occipital regions being shorter than at occipital regions only for adults. No other significant effects were found for P100 latency ($p > 0.08$).

Regarding amplitude, a significant effect for age group was found ($F(1,38) = 11.97$, $p = 0.001$, $\eta_p^2 = 0.239$) revealing that P100 amplitude decreases with age (at Oz, adolescents: 12.61 ± 5.57 μV; adults: 7.60 ± 3.65 μV; see Fig. 1a). Subjects with ASD presented a smaller P100 amplitude (at Oz, 10.52 ± 3.95 μV) than TD (13.37 ± 5.33 μV; $F(1,38) = 4.63$, $p = 0.038$, $\eta_p^2 = 0.108$; see Fig. 1b). The same result was confirmed when ASD were matched to controls for

verbal age ($F(1,38) = 6.10$, $p = 0.018$, $\eta_p^2 = 0.138$; see Fig. 3). Main effect of the electrode site was also significant ($F(1,38) = 87.47$, $p < 0.001$, $\eta_p^2 = 0.697$) revealing occipital site amplitude being greater than over parieto-occipital site. Also, a significant interaction between electrodes site and age group was found ($F(1,38) = 5.80$, $p = 0.021$, $\eta_p^2 = 0.132$), with adolescents presenting a larger response in the occipital site than adults ($p < 0.001$), but not in the parieto-occipital site ($p = 0.139$). No other significant effects were found for P100 amplitude ($p > 0.12$).

N135

No significant effects were found for N135 latency nor amplitude ($p > 0.12$).

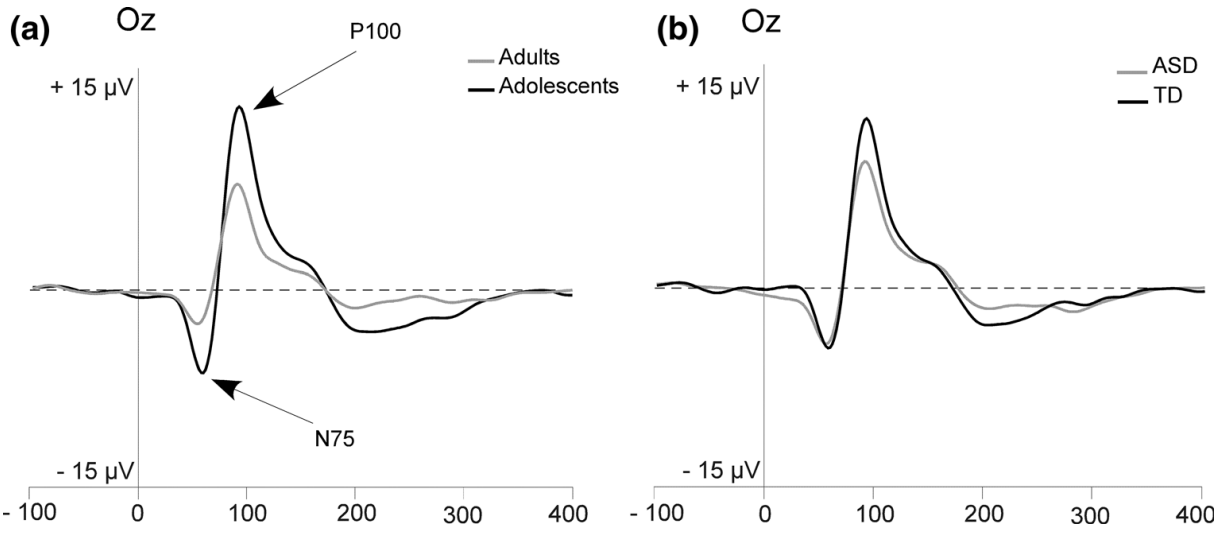

Fig.1 Grand average ERP waveforms at Oz electrode. (a) Age group effect. Black line: adults; gray solid line: adolescents (ASD and chronological age TD confounded). (b) Clinical group effect. Black line: TD (chronological age); gray solid line: ASD (adolescents and adults confounded)

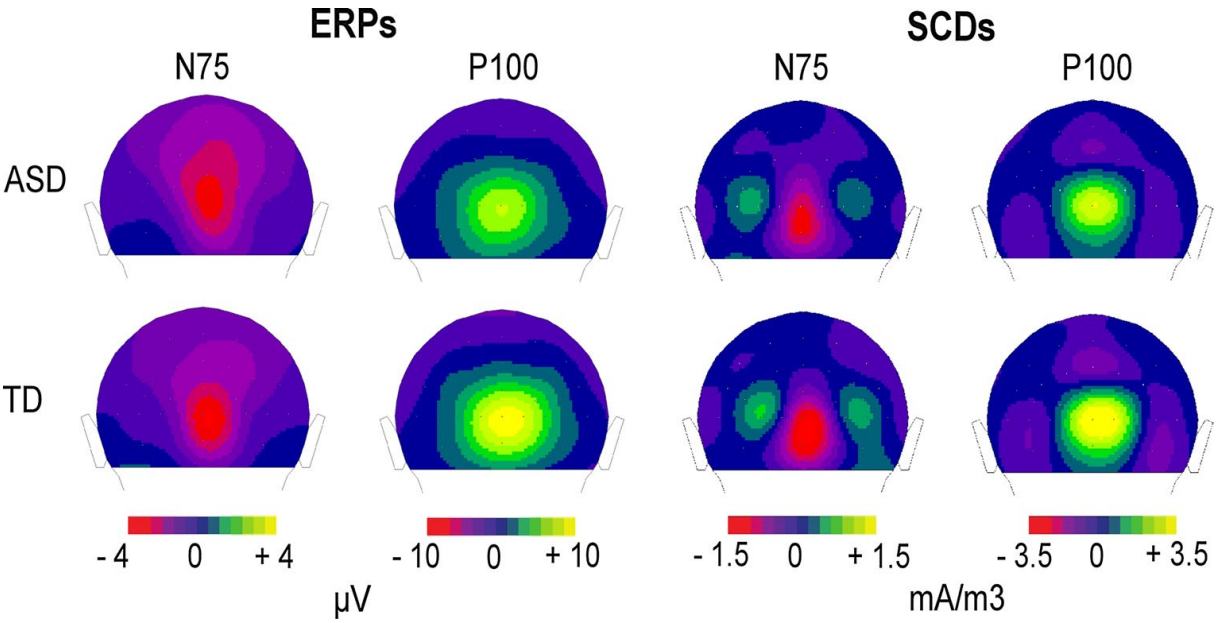

Fig.2 Back views of ERPs and SCD maps at N75 peak latency (ASD = 55 ms; TD = 57 ms) and at P100 peak latency (ASD = 91 ms; TD = 92 ms) for ASD and TD groups including both age groups (adolescents and adults). SCD maps show a different topographical distribution for N75 and P100. SCDs are estimated (surface Laplacian) using spherical spline interpolation (Perrin et al. 1989). By providing sharper spatial peaks, SCDs allow to spatio-temporally disentangle neural sources, and facilitating ERPs interpretation

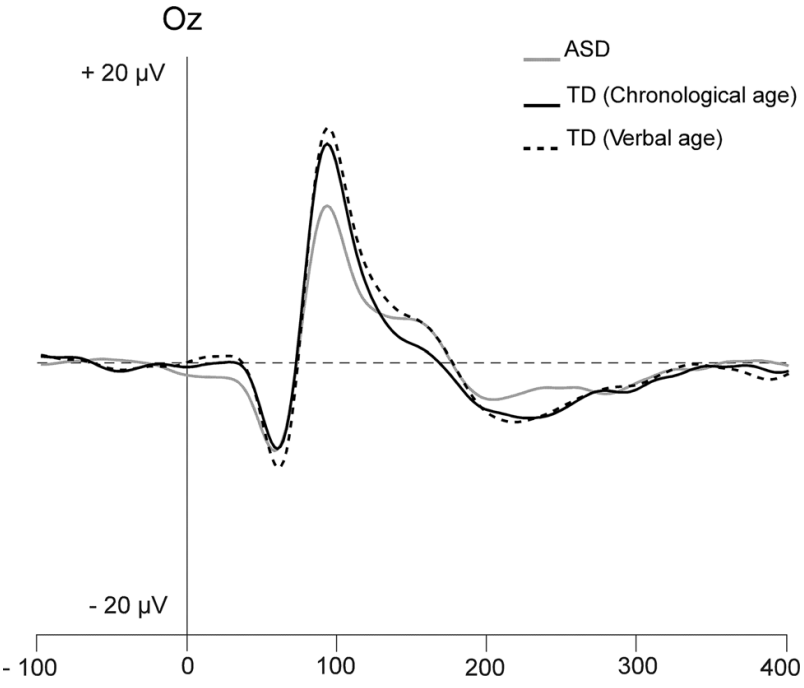

Fig.3 Grand average ERP waveforms at Oz electrode. Clinical group effect: control of the verbal development delay in adolescents. Black line: chronological age TD; black dotted line: verbal age TD; gray solid line: ASD

Discussion

The present study aimed to investigate early visual responses in adolescents and adults with autism. To evaluate early visual functioning, VEPs were recorded during a passive pattern-reversal paradigm. The results show that ASD adolescents and adults presented a smaller P100 amplitude compared to controls. These results also revealed a decrease of N75 and P100 amplitudes and a decrease of N75 latency with age.

Age effect

In line with previous developmental findings (Mahajan and McArthur 2012), N75 and P100 amplitudes decreased with age, implying that maturation proceeds until adulthood in all subjects (Emmerson-Hanover et al. 1994), and that the visual generators are not yet fully developed during adolescence. The results of the present study clearly showed that age related effects in N75 and P100 components were observed in both ASD and control groups. In agreement with a previous study, no age effect was found for P100 latency (Mahajan and McArthur 2012).

Most of the developmental studies have focused on the P100 component (ref Moskowitz & Sokol 33, Tobimatsu,1993, Kuba2012, Allsison et al, 1983), the N75 was more rarely investigated. Three studies reported an increase in N75 latency with age across the lifespan (Allison et al, 1984; ; Emmerson-Hanover et al. 1994) or adulthood (celesia et al., 1987). This increase in latency has been linked to senescence (deterioration in optics, cell death in lateral geniculate loss of dendritic spines and synaptic contacts in visual cortices, Celesia et al., 1987). To our knowledge, only one study (Mahajan and McArthur 2012) investigated the age related changes in the N75 using reversal checkerboard in the same age range as ours participants, unlike us they found no effect of age on N75 latency. However, this decrease of latency during adolescence is in agreement with the development of the equivalent auditory component. The auditory P1 (peaking between 40-60ms, known to be generated in the primary auditory cortex)

is marked by a strong latency decreased across adolescence related to synaptic pruning and myelination of axons in this region (ref attention il y en a deux la même année Mahajan &McArthur, 2012).

Group effect

- P100

P100 was smaller in ASD compared to controls matched for real age, but there was no interaction between age group and diagnostic group. The same effect was confirmed when adolescents with autism were matched for verbal age equivalent, suggesting that intellectual disability cannot explain early visual impairments (Fig. 3). This is not surprising as younger children included in the verbal age control group presented larger P100 responses, in line with previous developmental observations (Emmerson-Hanover et al. 1994) and with the age effect found in this study.

Atypical processing has been largely reported in individuals with ASD during perception of simple visual stimuli (Kornmeier et al. 2014; Pei et al. 2014; Jemel et al. 2010; Milne et al. 2009b; Constable et al. 2012 ref). Unfortunately, those studies do not always directly analyze the P100 component. For example, Kornmeier and collaborators (2014) presented checkerboards of two different size (i.e. spatial frequencies) in an oddball paradigm while Asperger patients were instructed to count for rare stimuli. They reported a smaller checksize effect (measured on the ERP difference) for the Asperger patients compared to controls at P100 latency. While their results focused on ERP difference traces only, the ERP traces for each checkerboard size were visible in the paper, and the P100 amplitude seem smaller in Asperger group compared to controls. Few studies measured directly the P100 component and the results were contradictory. In agreement with our data, a smaller P100 was found in children with high functioning ASD that in controls for both high- and low-frequency gratings (Boeschoten ref). However, other reported no differences in the properties of the P100 using pattern reversal with

low spatial frequencies gratings in adults (Jemel 2010, Constable 2012), suggesting a specific deficit in processing high frequencies. While all those studies varied by different experimental settings, levels of attention required and also age range tested, they converged to an abnormal spatial frequency processing in ASD (see also pei 2014, Milne 2009b) that has contributed to the development of the weak central coherence hypothesis (Frith, 1989) and the enhanced perceptual functioning hypothesis (Mottron et al.,2006) of ASD.

Other studies also showed that P100 component is affected in children with autism in social contexts, such as face perception (Batty et al. 2011; Hileman et al. 2011) or biological motion perception (Kroger et al. 2014). Obviously this abnormal P100 when evoked by face could be linked to abnormal spatial frequencies processes (see Jemel et al.,) but also to attention and/or social attention (discussed below). Moreover, in individuals with typical development, the properties of the P100 component were associated with social cognitive skills (Hileman,)

- N75

In the present study, P100 component was found atypical in ASD, implying impairment at this or at an earlier processing stage. However, we do not find any group effect on the N75, suggesting that this first visual processing stage could be preserved in ASD. In the present study, visual inspection of scalp current density (SCD) maps suggest that the N75 and P100 originate from different neural sources (Fig. 2) in agreement with previous studies ~~that have used an indirect measure to localize neural sources of the VEP components. While these studies used an inverse solution calculation~~ (Vanni et al.,2004, Di Russo et al., 2001, 2005) ~~and should be considered precautiously, the latencies and localization of these sources correspond to monkeys data (Nowak & Bullier 1997)~~. Therefore, the absence of a diagnostic group effect on the N75 suggests that the visual information could progress normally from the optics to V1, and allows to locate the first atypical processing at the level of the extrastriate cortices. However, atypical source activations have been reported in the occipital cortex in ASD during

a facial emotions task while the P100 and N170 components were not significantly different between ASD and control children, suggesting that source analysis represents an additional information in order to identify neural differences between groups (Wong et al. 2008), and could help to confirm the present data.

Finally, previous findings reported that the C1 component is not modulated as function of attention (Clark and Hillyard, 1996; Gomez-Gonzales et al., 1994; Mangun,1995; Martı´nez et al., 1999, 2001a, 2001b; Wijers et al., 1997, Ding et al., 2014) contrary to the later P1 and N1 components (e.g., Heinze et al., 1990; Hillyard Anllo-Vento, 1998; Luck et al., 1994; Mangun, 1995; Mangun and Hillyard, 1990, see also Taylor, 2002). One possible interpretation of our data is that the smaller P100 in ASD could result from an abnormal visual attention, justifying why no group differences was found on the previous component (N75). However, an increasing number of studies have shown that top-down modulations may influence the earliest VEP (N75/C1, Rauss et al., 2009; see also Rauss et al., 2011, Poghosyan & Ioannides, 2008).

N135

On the logic that each component reflects a higher level process of information that the preceding one, the smaller P100 amplitude would affect the following negative component. In the present study, no group effect was found on the N135. As already mentioned, the N135 was not very pronounced. Even if a deflection was observed, a clear peak is not always present. This is in agreement with another study using reversing checkerboard in a passive viewing condition, the N135 was not always elicited or measurable, often masked by the preceding P100 (see Mahajan and McArthur 2012). Known as an index of a discrimination process, the N135 is particularly sensitive to the visual material presented and the task. In the present study, the same reversal pattern was presented without any task, the subjects were simply instructed to look at the screen, no discrimination process was required which could explain the slight negative

deflection recorded. As the N135 is more driven by categorical processing, using either more complex stimuli (belonging to a visual category, eg. face) or at least two different stimuli, a larger N135/ N1 could be elicited.

Our results suggest the integrity of visual pathways, from retina to primary visual area, through the geniculate nucleus. However, only one check size was presented, including another check size would have allowed to investigate more specifically magnocellular and parvocellular pathways. The smaller P100 amplitude suggest an abnormal functioning at the first stages of extra striate cortices. While our study do not allow to identify any repercussion at the level of discrimination process, we suggest that the atypical ERPs responses revealed after 150ms in more complex and/or social tasks could result from atypical low-level visual processing (P100). This is in line with previous findings in the auditory modality, showing that a dysfunction in primary auditory cortex could be responsible for severe impairment in verbal and non-verbal communication in children with ASD (Bruneau et al. 1999). Although early processing might be partly compromised by lower-level impairments, compensatory mechanisms at higher levels processing should be considered in order to account for typical behavioral responses (Belmonte and Yurgelun-Todd 2003; Shi et al. 2013), but also for developmental and maturational changes. While P100 amplitude was found atypical in both adolescents and adults with ASD, VEPs to pattern reversal stimuli should be also investigated in younger children with ASD, in order to consider the entire developmental trajectory.

Finally, a parallel can be done with findings from other pathological conditions such as 22q11 deletion syndrome (McCabe et al. 2011) or schizophrenia. Many studies have examined the neural correlates of face and affect processing deficits in schizophrenia focusing on the N170 component. However, deficits may stem from earlier visual processing stages as those indexed by the P100 component. Indeed, the P100 amplitude is smaller in patients with

schizophrenia, when evoked by face stimuli but also by non face and simple stimuli varying in luminance and contrast, showing that here again an early sensory processing deficit may precede higher order processing deficits (Earls, 2015, Tanaka 2013). While this similitude enhances the absence of specificity, it suggests that rehabilitation of social functioning should focus on early stages of processing, and that children with ASD would also benefit from perceptual experience training.

Compliance with Ethical Standards

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Ethical approval

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local ethical committee board approved the protocol.

Informed consent

Written informed consent was obtained from the parents and adults, and assent from the adolescents.

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