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ORIGINAL PAPER

Enhanced Early Visual Responses During Implicit Emotional Faces Processing in Autism Spectrum Disorder

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Abstract

Research on Autism Spectrum Disorder (ASD) has focused on processing of socially-relevant stimuli, such as faces. Nonetheless, before being 'social', faces are visual stimuli. The present magnetoencephalography study investigated the time course of brain activity during an implicit emotional task in visual emotion-related regions in 19 adults with ASD (mean age 26.3 ± 4.4) and 19 typically developed controls (26.4 ± 4). The results confirmed previously-reported differences between groups in brain responses to emotion and a hypo-activation in the ASD group in the right fusiform gyrus around 150 ms. However, the ASD group also presented early enhanced activity in the occipital region. These results support that impaired face processing in ASD might be sustained by atypical responses in primary visual areas.

Keywords Autism · MEG · Face processing · Emotion · Visual processing

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by two major groups of behavioural symptoms. The first includes difficulties in the social and communication area and the second is defined by restricted interests and stereotyped behaviours. However, atypicalities in all sensory modalities are now considered as core symptoms of autism (APA 2013; Marco et al. 2011). In the visual domain, hyper and hypo-responsiveness to external stimuli, as well as unusual visuo-motor behaviours, including abnormal scanning or auto-stimulation, are often observed from infancy (Mottron et al. 2007; Simmons et al. 2009). Enhanced perception of details, as well as difficulties in processing the *global picture*, are often reported to account for such atypical strategies and behaviours (Happé and Frith 2006; Mottron et al. 2006).

In line with general difficulties for ASD in processing the significant flow of sensory information in the environment (Gomot and Wicker 2012), facial expressions are

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particularly challenging stimuli containing both low-level and social features. Due to the holistic configuration of faces and their constantly changing features, it is difficult for those with ASD to automatically extract the information from faces and to rapidly understand the meaning of changes in facial expression (Clark et al. 2008; Lozier et al. 2014). Thus, investigating early face processing in autism is crucial to improve our understanding of both visual and social aspects of these atypical processes.

Facial expressions are critical to understand others' mental states and for successful social interactions (Haxby et al. 2002). The importance of emotional expressions is supported by the fact that emotional processing is prioritized even when attention is required in a concurrent task (Johnson 2005; Vuilleumier 2005). Several methods exist to investigate implicit processing of emotions. While one way is to manipulate the time exposure of emotional stimuli (Kouptsova et al. 2017), another way is to involve the participant in a concurrent task where explicitly processing the emotional content of faces is not necessary (e.g. gender detection task, Critchley et al. 2000). In line with this, tasks demands implicating face perception are known to differently modulate regions such as the inferior occipital and the fusiform gyri (FG) (Cohen Kadosh et al. 2010).

Both explicit and implicit social cognitive processes are often atypical in ASD, as supported by behavioural (Callenmark et al. 2014) and neuroimaging studies (Critchley et al. 2000; Johnson et al. 2005; Kana et al. 2016; Wong et al. 2008). Learning strategies can compensate for difficulties in explicit emotional understanding, while this is not the case when emotions are implicit and processed rapidly and automatically (Frith 2004). Early automatic processing of emotional faces involves bilateral posterior and temporal cortical areas in addition to activation of limbic regions such as the amygdalae (Bernstein and Yovel 2015; Johnson 2005; Rossion 2014). Threat-related stimuli are particularly salient for the attentional system and elicit enhanced activity in the visual cortex (Vuilleumier 2005; Vuilleumier et al. 2004). While increased activation in visual areas including the inferior and middle occipital gyri, the lingual gyri and the FG has been associated with face processing, responses to the emotional content have been related to brain activity in the temporal cortices, such as the superior temporal sulcus and the inferior temporal gyri (Fusar-Poli et al. 2009a, b; Vuilleumier and Pourtois 2007).

With their excellent, millisecond time resolution, electroencephalography (EEG) and magnetoencephalography (MEG) are of particular value in investigating the earliest responses in visual emotional processing (Liu et al. 2002; Rossion 2014). MEG also provides a fine spatial resolution which enables the investigation of the earliest brain activity with accurate spatial localization (Dumas et al. 2013). The event-related potentials (ERPs) and their magnetic field equivalent (event-related fields, ERFs) P/M1 and N/M170 components are usually investigated as the first indices of perceptual and attentional face processing. These components are then followed by attention reorienting and memory processes both modulated by face features and emotions (Batty and Taylor 2003; Bentin et al. 1996; Olivares et al. 2015). Furthermore, neural activity within the first 100–300 ms is modulated by facial expressions, in particular by negative emotions over the occipital and temporal cortices (Bailey et al. 2005; Braeutigam et al. 2001; Pourtois et al. 2004).

In ERP studies, the P1 and N170 components have been described as atypical in ASD (Batty et al. 2011; Dawson et al. 2005; Hileman et al. 2011; McPartland et al. 2004; O'Connor et al. 2007). However, conflicting results exist, as other studies did not find group differences in latency and/or amplitude within these components (for discussion, Feuerriegel et al. 2015; Wong et al. 2008). Of interest, Wong et al. (2008) did not find atypical ERPs (P1 nor N170) in children with ASD; however, significant differences emerged with the neural sources of these two components during implicit and explicit emotional processing. In the occipital cortex, brain activation was delayed during implicit emotional processing and larger in the left compared to the right hemisphere in the ASD group only, in both explicit and implicit conditions. Importantly, around the P1 and N170 latencies, the activity in the bilateral FG was reduced in the implicit emotional condition only.

Taken together, these results suggest a potential role for MEG in elucidating previous conflicting results, due to the greater spatial resolution compared to EEG, in investigations of atypical face processing in ASD. Two MEG studies reported that responses to faces differed between ASD adults and controls around 140 ms in the extrastriate cortices (Bailey et al. 2005) and starting before 100 ms in temporal regions in adolescents with ASD (Leung et al. 2015), confirming very early atypical face processing in ASD. These results are in line with broader disrupted visual responses (Samson et al. 2012; Simmons et al. 2009), which should also be considered while investigating emotional processing in ASD.

The present MEG study investigated early and automatic responses to emotional faces in adults with and without ASD within the first stages of the visual emotional processing at brain source level. Regions of interest (ROI) critical to the implicit emotional processing were selected for analyses including areas involved in the early visual activity and face-sensitive regions. In addition to disrupted responses in areas related to social cognitive processing, such as decreased activity in the FG, we expected to see atypical early responses in visual areas in the adults with ASD compared to typically developped (TD) controls.

Materials and Methods

Participants

Twenty-two adults in each group (ASD and controls) participated to the study. However, three in each were not included due to MEG data that were too noisy. For analyses, the 19 adults with autism (7 females, age range 20–36, mean ± standard deviation: 26.3 ± 4.4) were matched by age to 19 TD adults (8 females, age range: 20–34, mean: 26.4 ± 4; t (36) = − 0.13, $p = .69$). To ensure that participants did not present a developmental delay (intelligence quotient, IQ ≤ 70), two subtests (vocabulary and matrix reasoning) of the Wechsler Abbreviated Scale of Intelligence (WAIS, Wechsler 1999) were administered. A t test showed that the groups did not differ on IQ (ASD IQ = 115.5 ± 16, TD = 114.7 ± 9.8; t(36) = 0.19, $p = .85$).

ASD participants were diagnosed based on expert clinical judgment supported by the Autism Diagnostic Observation Schedule-Generic, ADOS-2 (ADOS-2, Lord et al. 2000) and/or by the Autism Diagnostic Interview-Revised, ADI (ADI, Lord et al. 1994). The average ADOS-2 severity score was 6.2 ± 2.5 (Corbetta and Shulman 2002; Gotham et al. 2009). In both groups, exclusion criteria included a history of neurological disorders, neurodevelopmental disorders (other than autism for the ASD group), acquired brain injury, and standard contraindications to MEG and MRI; all participants had normal or corrected-to-normal vision. As it is typical for adults with ASD, nine participants were taking medications at the time of the testing (e.g. SSRIs, anxiolytics); given their long half-life, it was not ethical to ask participants to be without clinically prescribed medications for many weeks for a short research study. The research was approved by The Hospital for Sick Children Research Ethics Board. Informed written consent was obtained from all the participants.

Stimuli and Task

The stimuli consisted of photographs of emotional faces (angry, happy or neutral) presented on the right or left side of a central fixation cross, and scrambled versions of the same faces presented concurrently on the other side (Leung et al. 2014; Mennella et al. 2017). Twenty-five faces (13 males) for each of the three facial expressions were selected from the NimStim Set of Facial Expressions, with a minimum of 80% of categorization accuracy for emotional expressions (Tottenham et al. 2009). Scrambled patterns were created from each face by dividing the images into 64 cells that were then randomized. A mosaic (15 × 15 px per tile) and a Gaussian blur (10.0 px) were applied using Adobe Photoshop. The face-pattern pairs were matched for luminance and colour. Images were back-projected through mirrors onto a screen at a distance of 79 cm, with a visual angle of 9° (wide) × 11° (high), 7° from the central fixation cross (i.e., within the parafoveal region, see Fig. 1).

A total of 300 trials (100 per emotional expression) were randomly presented using *Presentation* software (Neurobehavioral Systems, Berkley, CA). Each emotional face appeared four times, two times in the left and two times in the right visual field with equal probability. Stimuli were presented for 80 ms followed by a fixation cross with an ISI of 1300–1500 ms; stimuli were presented very briefly to avoid visual scanning. Participants were instructed to identify whether the scrambled pattern was on the left or right as quickly as possible by pressing a button with the left or right hand, respectively. Thus, emotions were implicit to the task, allowing investigation of rapid and automatic brain responses to emotional faces.

Behavioural Analysis

Mixed ANOVAs were conducted on reaction time (RT) and accuracy to examine group (ASD vs. control) and emotion (angry vs. neutral. vs. happy) effects during the task.

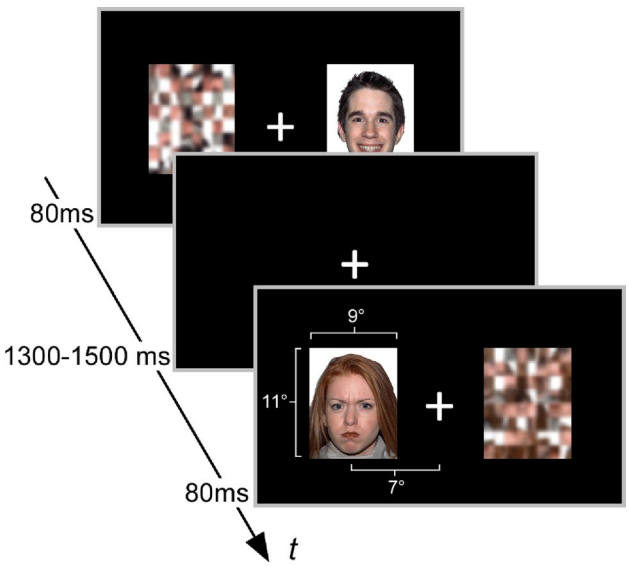

Fig. 1 Schematic of the task: a fixation cross is displayed on the center of the screen with an emotional face (angry, happy or neutral) presented in the right or left hemifield, while a scramble pattern of the same face is presented in the other hemifield. The stimuli had a visual angle of 9° (wide) × 11° (high) with a distance of 7° from the central fixation cross (parafoveal view). The participants were instructed to detect the position of the scrambled pattern by pressing a button

MEG and MRI Data Acquisition

MEG data were recorded using a 151-channel CTF MEG system (CTF, Coquitlam, BC, Canada) at a sampling rate of 600 Hz in a magnetically shielded room at the Hospital for Sick Children. A third-order spatial gradient and an offline bandpass filter of 1–150 Hz were applied. All participants were supine in the MEG while they completed the task. Fiducial coils were placed on the left and right preauricular points and the nasion to monitor head position and movement within the helmet. These were replaced by radio-opaque markers for MRI coregistration. All the participants also had a T1-weighted MR image (3D SAG MPRAGE: PAT, GRAPPA = 2, TR/TE/FA = 2300 ms/2.96 ms/90°, FOV = 28.8 × 19.2 cm, 240 × 256 matrix, 192 slices, slice thickness = 1.0 mm isotropic voxels) obtained from a 3T MR scanner (MAGNETOM TimTrio, Siemens AG, Erlangen, Germany), with a 12-channel head and neck coil.

Brain Responses at Source Level

For source reconstruction notch filters at 60 Hz and 120 Hz were applied to MEG data. Epochs were extracted from − 1500 ms before stimulus presentation to 3000 ms and were rejected when intra-trial head motion exceeded 5 mm. The head position was corrected to the median head position during the remaining trials. A realistic single-shell head model was constructed using each participant's MRI. The source time course for the 90 seeds placed at the centre of mass of each Automated Anatomical Labeling region (AAL Atlas, Tzourio-Mazoyer et al. 2002) were transformed into subject-space then estimated through a linearly constrained minimum variance beamformer (Van Veen et al. 1997). Beamformers project the recorded data from the sensors through a spatial filter to extract timeseries at ROI while suppressing sources outside the target region (Quraan and Cheyne 2010). Due to the minimization of the contribution of the sources outside the seeds of interest, MEG beamformers are a powerful method to suppress ocular and non-ocular artefacts (i.e. eye-blinks, saccades, cardiac and muscle activity), replacing artefact rejection based on visual inspection (Muthukumaraswamy 2013).

MEG source activity was estimated for each participant of the ASD and TD groups and for each condition (angry, happy, neutral), and was filtered off-line with a band pass filter of 1–30 Hz with a 200 ms pre-stimulus baseline. Data from each seed were squared to determine the evoked power in each condition for all locations. Data were time-locked to trial onset and averaged by emotion type across subjects. For each condition the number of averaged trials (± SD) in the ASD group were 94.6 ± 13.9 (angry), 94.6 ± 14.5 (neutral), 94.9 ± 13.9 (happy) and in the TD group were 99.8 ± 0.9 (angry), 99.3 ± 20.75 (neutral), 99.6 ± 1.6 (happy). A repeated measures ANOVA on trial numbers did not reveal any significant effect concerning condition or group (all $ps > 0.14$).

Preliminary Data Visualization

Ten bilateral occipital and temporal ROIs (see Table 1), known to be recruited in emotional face processing and spatial attention, were selected to compare implicit emotional processing in the ASD and control groups. Each ROI corresponded to a specific seed, as shown in Table 1. The selection was based on functional criteria, including regions involved in face processing and spatial attention described in previous studies on face and emotional face processing in typical development and autism (Fusar-Poli et al. 2009b;

Table 1 List of the ROI selected from visualization for six time-windows of 30 ms

ROI	Time windows (ms)						MNI coordinates (x, y, z)					
	90–120	105–135	135–165	155–185	200–230	225–255	Left			Right		
Calcarine		✓	✓	✓			− 8	− 79	6	15	− 73	9
Cuneus		✓	✓	✓			− 7	− 80	27	13	− 79	28
Lingual		✓	✓	✓			− 16	− 68	− 5	15	− 67	− 4
Occipital Sup		✓	✓	✓		✓	− 18	− 84	28	23	− 81	31
Occipital Mid		✓	✓	✓		✓	− 33	− 81	16	36	− 80	19
Occipital Inf		✓	✓	✓		✓	− 37	− 78	− 8	37	− 82	− 8
Fusiform	✓		✓			✓	− 32	− 40	− 20	33	− 39	− 20
Temporal Sup	✓	✓	✓		✓		− 54	− 21	7	57	− 22	7
Temporal Mid	✓	✓	✓		✓		− 57	− 34	− 2	56	− 37	− 1
Temporal Inf	✓	✓	✓				− 51	− 28	− 23	53	− 31	− 22

Only ROI and time-windows indicated by ✓ were considered for statistical analyses. Left and right MNI coordinates (x, y, z) are reported for each ROI

Sup superior, *Mid* middle, *Inf* inferior

Schultz et al. 2003; Wong et al. 2008). In a first exploratory phase, the sources' evoked power were visually inspected and six peaks of activity were clearly identifiable in the first 300 ms in each ROI.

Mean power was measured in six time windows of 30 ms over the ROIs where the peaks were identified (see Fig. 2). Table 1 shows the selected ROIs and the time windows in which the mean amplitude was measured for statistical analysis. To investigate specific responses to the emotions, bilateral ROIs were considered and data were compared between groups and across conditions.

Statistical Analysis

Repeated measures ANOVAs were performed at each ROI for the selected time windows (see Table 1). Analyses included group (ASD vs. control) and Emotion (angry vs. happy vs. neutral) and Hemisphere (left vs. right). ANOVA results were corrected with the Greenhouse–Geisser procedure and a Tukey HSD test was performed for post-hoc analyses.

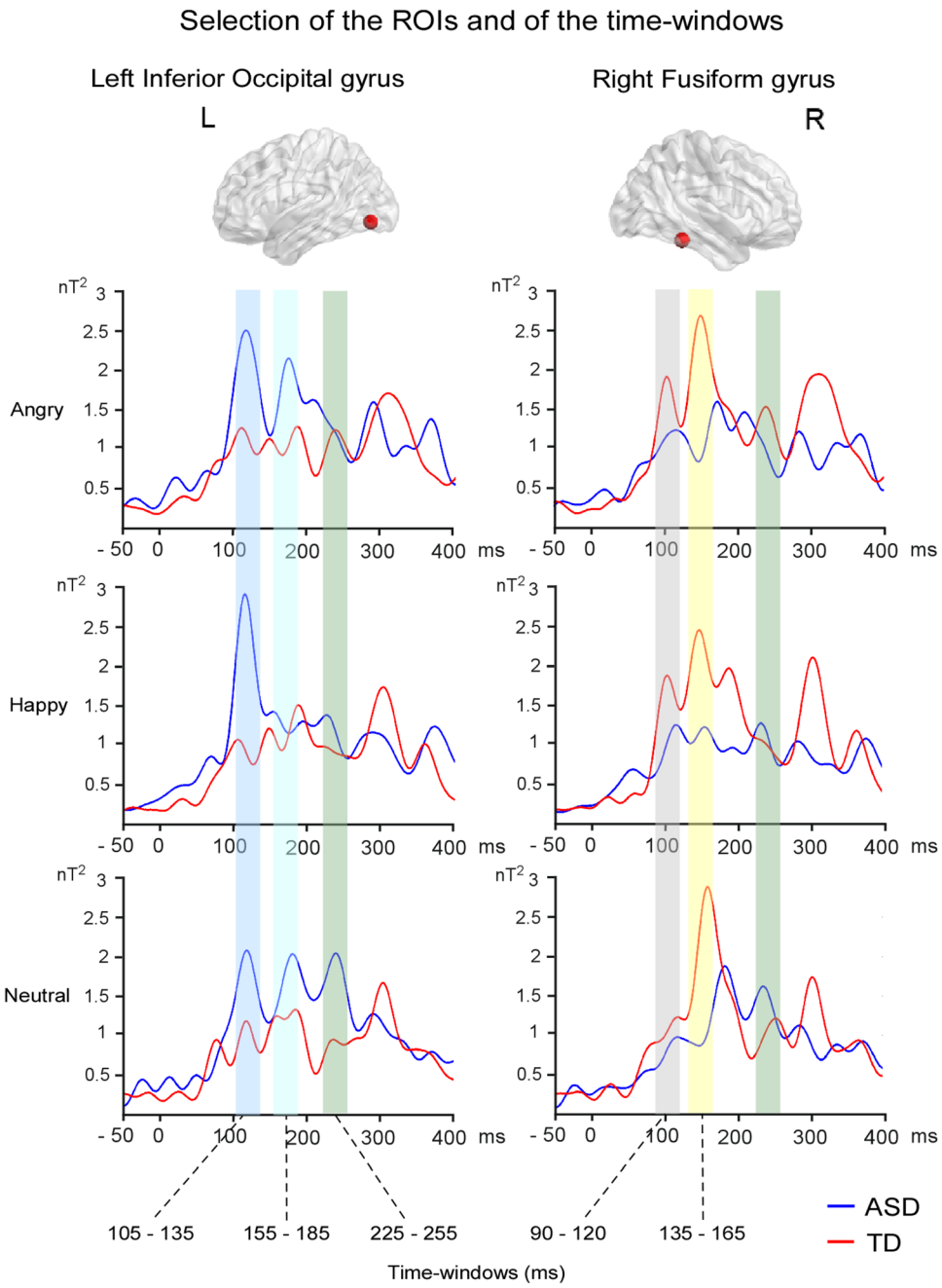

Fig. 2 Grand average evoked power for angry, happy and neutral faces at two ROI (left inferior occipital gyrus and right fusiform gyrus); the ASD group is displayed with a blue color line and the TD group with a red line. Five time windows of the six selected are shown in coloured frames

Brain–Autism Severity Correlations

Based on the previous ANOVAs, we also related the clinical characterization of the ASD participants to their occipital brain activity. Thus, according to our hypothesis that the severity of autism is influenced by social deficits as well as by sensory atypicalities, we predicted a relation between evoked activity in the visual ROIs (mean activity of the two hemispheres) and behavioural symptoms.

A General Linear Model to predict brain activation was performed including Sites (calcarine fissures, cuneus, lingual gyri and in the inferior, middle and superior occipital gyri) and emotion (angry, happy and neutral) as categorical predictors and ADOS scores as continuous variable. This allowed us to identify the brain regions where the relation between ASD severity and brain activation differed statistically as a function of emotion. Finally, in regions where the interaction between emotion and symptom severity in predicting brain activity was significant, Pearson correlations were performed ($p < .05$).

Results

Behavioural Results

Both groups performed the task close to ceiling, with accuracy > 96% for both groups, and average RTs across all emotions of 385 ± 60 ms for ASD and 366 ± 40 ms for TD (Table 2). Neither main effects nor interactions between group and emotion were significant for RT or accuracy (all $ps > 0.07$).

MEG Results

Details of ANOVA significant results are presented in Tables 3 and 4 for the occipital and the temporal regions respectively. Effects involving the between factor Group were found in four time-windows (90–120 ms, 105–135 ms, 135–165 ms and 225–255 ms); no significant between Group effects were found in the 155–185 ms and 200–230 ms time-windows. Tables 3 and 4 contain a summary of all significant effects and their directionality (e.g., TD > ASD) and Fig. 3 explains the directionality of significant interactions. All effects, significant and non-significant are reported as electronic supplementary material (see Supp. 1 and Supp. 2).

From 90 to 120 ms, angry faces elicited stronger activation than neutral faces in both groups in the FG (FDR corrected). However, only the controls showed larger responses to angry compared to both happy and neutral faces in the inferior temporal gyrus.

In the 105–135 ms time-window, in the occipital region the ASD group had enhanced neural activity compared to controls for all the facial expressions. In the ASD group, we found a left-hemisphere dominance and an emotion-specific response in the inferior occipital gyrus with happy faces eliciting a stronger activity than angry and neutral faces. After FDR correction these results were no longer significant. However, the effect of Group reached $p_{uncorr} < .05$ on all three occipital sites, suggesting that it was not due to chance. In the lingual gyrus, happy faces elicited stronger activation in the right hemisphere in controls and in the left hemisphere for the ASD group.

In the following time-window (135–165 ms) coinciding with the face-sensitive activity peaking around 150 ms, the ASD group showed a hypo-activation in the right FG, irrespective of emotion, which survived FRD correction. At this latency only controls presented a right-hemisphere dominance in the inferior occipital gyrus. No emotion effects were seen in this time-window. Emotion-sensitive responses were observed at 225–255 ms: neutral faces elicited a stronger response than happy faces in the middle occipital gyrus in the ASD group only.

Therefore, differences in neural activity between adults with ASD and matched controls were observed in several regions implicated in emotion-face processing as discussed below.

Table 2 RTs and accuracy in the behavioural task for ASD and TD group

	Facial expressions (ms)			ANOVAs		
	Angry	Happy	Neutral	Group	Emotion	Group × Emotion
RT (ms)						
ASD	384 ± 64	385 ± 65	385 ± 65	$F(1,36) = 1.09$, $p = .30$, $\eta_p^2 = .03$	$F(2,72) = 0.48$, $p = .62$, $\eta_p^2 = .01$	$F(2,72) = 0.08$, $p = .92$, $\eta_p^2 = .002$
TD	366 ± 43	366 ± 42	367 ± 42			
Accuracy (%)						
ASD	97 ± 3	97 ± 3	98 ± 3	$F(1,36) = 0.19$, $p = .67$, $\eta_p^2 = .005$	$F(2,72) = 0.01$, $p = .99$, $\eta_p^2 < .001$	$F(2,72) = 2.81$, $p = .07$, $\eta_p^2 = .07$
TD	96 ± 5	96 ± 4	96 ± 5			

On the right, the ANOVA results

Table 3 Schematic of the occipital ROIs effects (main effects and interactions) found in four time-windows

Time windows	ROI	Main effects		Interactions		
		Group F(1,36)	Hemisphere F(1,36)	Group × Hemisphere F(1,36)	Group × Emotion F(2,72)	Group × Hemi × Emo F (2,72)
105–135 ms	Lingual					9.26, $p = .0003$, $\eta_p^2 = .20$*
	Occipital Sup	4.43, $p = .042$, $\eta_p^2 = .11$: ASD > TD	15.67, $p = .0003$, $\eta_p^2 = .30$: L > R*			
	Occipital Mid	6.48, $p = .015$, $\eta_p^2 = .15$: ASD > TD	16.30, $p = .0003$, $\eta_p^2 = .31$: L > R*			
	Occipital Inf	4.17, $p = .048$, $\eta_p^2 = .10$: ASD > TD	5.47, $p = .025$, $\eta_p^2 = .13$: L > R*	7.01, $p = .012$, $\eta_p^2 = .16$		3.84, $p = .026$, $\eta_p^2 = .10$
135–165 ms	Lingual		11.73, $p = .001$, $\eta_p^2 = .25$: L > R*			
	Occipital Sup		15.69, $p = .0003$, $\eta_p^2 = .30$: L > R*			
	Occipital Mid		11.62, $p = .002$, $\eta_p^2 = .24$: L > R*			
155–185 ms	Lingual		9.38, $p = .004$, $\eta_p^2 = .21$: L > R*			
	Occipital Sup		10.58, $p = .002$, $\eta_p^2 = .23$: L > R*			
225–255 ms	Occipital Sup		8.83, $p = .005$, $\eta_p^2 = .20$: L > R*			
	Occipital Mid		4.53, $p = .04$, $\eta_p^2 = .11$: L > R		3.66, $p = .04$, $\eta_p^2 = .09$	

Non-significant results or results not explained by post-hoc analysis are not reported; asterisks indicate significant results after FDR correction. Significant interactions explained by post-hoc analyses are shown in Fig. 3

*Surviving FDR correction

Table 4 Schematic of the Temporal ROIs effects (main effects and interactions) found in four time-windows

Time windows	ROI	Main effects			Interactions	
		Group F(1,36)	Hemisphere F(1,36)	Emotion F(2,72)	Group × Hemisphere F(1,36)	Group × Hemi × Emo F (2,72)
90–120 ms	Fusiform			3.75, $p = .028$, $\eta_p^2 = .09$: A > N		
	Temporal Sup		5.84, $p = .02$, $\eta_p^2 = .14$: L > R			
	Temporal Mid		20.72, $p = .00006$, $\eta_p^2 = .36$: L > R*			
	Temporal Inf		10.14, $p = .003$, $\eta_p^2 = .22$: R > L*			3.41, $p = .040$, $\eta_p^2 = .09$
105–135 ms	Temporal Mid		9.67, $p = .004$, $\eta_p^2 = .21$: L > R*			
	Temporal Inf		8.28, $p = .007$, $\eta_p^2 = .19$; R > L*	3.38, $p = .039$, $\eta_p^2 = .09$: A > H		
135–165 ms	Fusiform	4.71, $p = .036$, $\eta_p^2 = .11$: TD > ASD	8.06, $p = .007$, $\eta_p^2 = .18$: R > L*		15.09, $p = .0004$, $\eta_p^2 = .29$*	
	Temporal Sup		11.89, $p = .001$, $\eta_p^2 = .25$: L > R*			
	Temporal Mid		19.06, $p = .0001$, $\eta_p^2 = .35$: L > R*			
	Temporal Inf		5.13, $p = .03$, $\eta_p^2 = .12$: R > L			
200–230 ms	Temporal Sup		8.68, $p = .006$ $\eta_p^2 = .19$: L > R*			
	Temporal Mid		31.02, $p = .000003$, $\eta_p^2 = .46$: L > R*			

Non-significant results or results not explained by post-hoc analysis are not reported; asterisks indicate significant results after FDR correction. Significant interactions explained by post-hoc analyses are shown in Fig. 3. Significant differences for the Emotion effect are indicated by asterisks: $p < .05$*; *L* left, *R* right; *A* angry, *H* happy, *N* neutral

*Surviving FDR correction

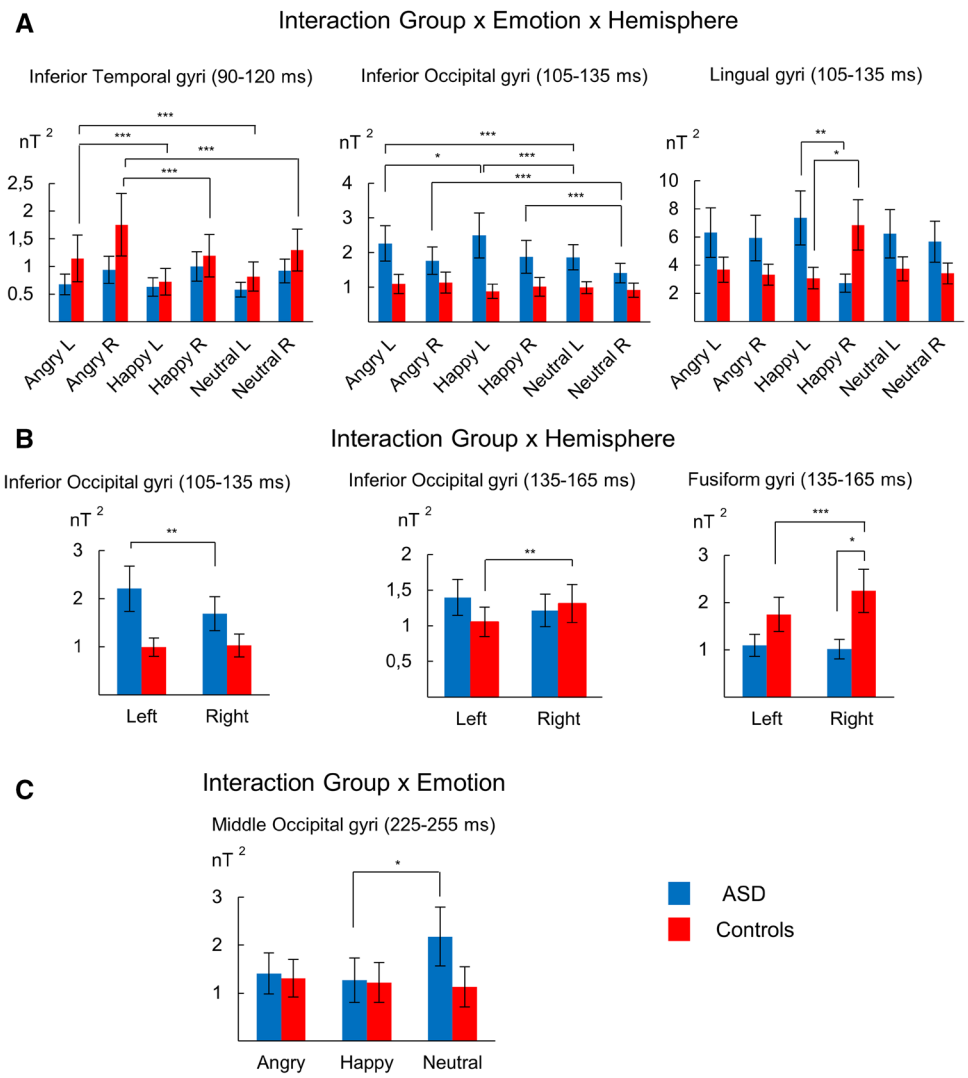

Fig. 3 **A** Post-hoc contrasts from the thee-way interactions (Group × Hemisphere × Emotion). **B** The two-way interactions (Group × Hemisphere) and **C** the two-way interactions (Group × Emotion). The ASD group is displayed in blue and the TD group in red. Error bars are standard errors of the mean. Significant planned differences are indicated by asterisks: $*p < .05$, $**p < .01$, $***p < .001$. *L* left, *R* right

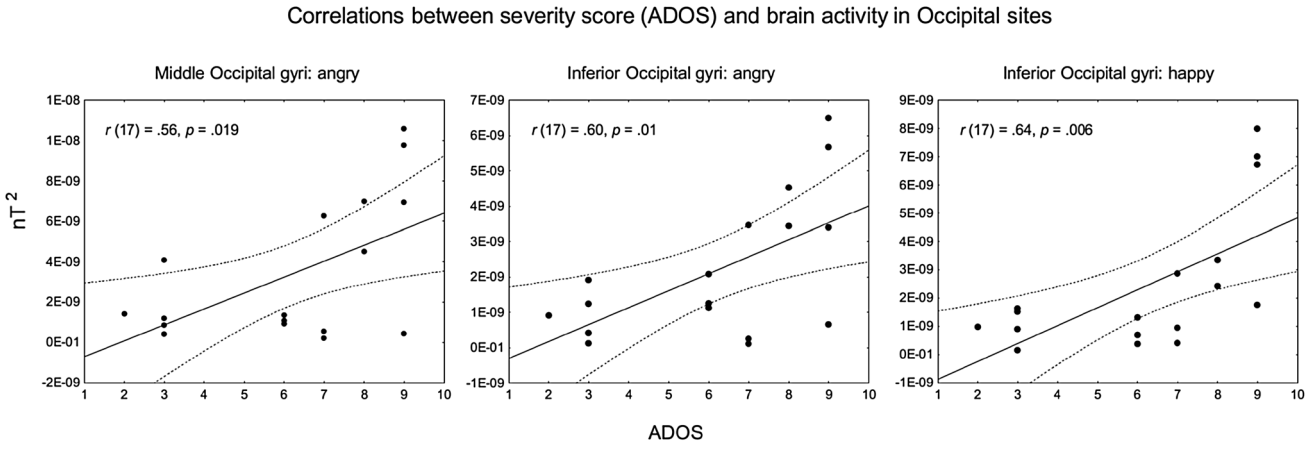

Fig. 4 Brain–autism severity (ADOS) correlation graphs for ASD participants over the middle and inferior occipital gyri for emotional faces (angry and happy) in the 105–135 ms time window

Brain–Autism Severity Correlations

Analyses showed a significant interaction between Site, Emotion and ADOS ($F(10,150) = 1.95$, $p = .042$, $\eta_p^2 = .115$). To determine which areas drove this interaction, General Linear Model analyses were performed separately for each site with Emotion as the dependent variable and ADOS severity score as the continuous variable. A significant effect of the Emotion and a significant interaction between Emotion and ADOS were found for the middle occipital gyri ($F(2,30) = 4.99$, $p = .013$, $\eta_p^2 = .250$; $F(2,30) = 4.60$, $p = .018$, $\eta_p^2 = .235$, respectively) and a trend for the interaction between Emotion and ADOS for the inferior occipital gyri ($F(2,30) = 3.18$, $p = .056$, $\eta_p^2 = .175$). Pearson correlations (FDR corrected) were performed on these two sites and significant correlations between evoked activity occurring in the 105–135 ms time-window and Autism Severity scores (ADOS) were confirmed in the middle occipital gyri for angry faces only ($r(17) = .56$, $p = .019$) and in the inferior occipital gyri for angry ($r(17) = .60$, $p = .011$; see Fig. 4) and for happy faces ($r(17) = .64$, $p = .006$). For all correlation results, see Supp. 3.

Discussion

The present MEG study investigated the time course of brain activity during an implicit emotional task in ten bilateral posterior ROIs, including visual and emotion-related areas. Differences between ASD and controls were found in both the occipital and temporal cortices, suggesting the potential role for MEG in consolidating existing findings and clarifying previous conflicting results, through a more accurate timing description of activity from the underlying brain sources.

Temporal Regions

The FG is a region responding preferentially to faces compared to other stimuli such as objects (Halgren et al. 2000; Haxby et al. 2000; McCarthy et al. 1999). Face-related responses in the FG (Halgren et al. 2000; Itier and Batty 2009; Morris et al. 2007) have often been described around 150 ms, and are affected by changes in facial expressions (Fox et al. 2009; Ganel et al. 2005; Harry et al. 2013) with the modulation depending on emotional valence (Batty and Taylor 2003; Nomi et al. 2013, but see also Harry et al. 2013; Pourtois et al. 2010).

In the present study, we found enhanced FG responses for angry faces in both groups at an early (90–120 ms) time window, in agreement with prior work reporting emotional sensitivity not only in the time window of the N170/M150, but also earlier and later (Hadjikhani and de Gelder 2003; Pizzagalli et al. 2002; Wong et al. 2008). Our results suggest that the analysis of the whole time course of emotional face processing provides additional information on the extent of emotional modulations in the FG, and should be further considered in models of emotional face processing. Moreover, these results are also supported by the fact that the magnocellular pathway, solicited by parafoveal stimulation, is characterized by a dual route pathway, with one rapid pathway reaching the ventro-occipital regions and the fusiform gyri via the amygdalae, which respond preferentially to threat stimuli (see Corradi-Dell'acqua et al. 2014; Vuilleumier et al. 2003).

The mixed findings in the literature on the emotional response in the FG may depend on attention to the emotion, which is found to be responsible for modulations of specific emotions (Etkin et al. 2004; Pourtois et al. 2010). However, as suggested by ERP and fMRI studies, the implicit/explicit nature of the task plays an important role in the modulation of early face-sensitive and emotional responses (Kana et al. 2016; Wronka and Walentowska 2011). In particular, while explicit emotional processing seems particularly to affect the FG, activity within this region responds to broader face processing when emotions are processed implicitly (Pourtois et al. 2010).

While specific responses modulated by emotion were similar between groups in the FG, we observed a hypo-activation of the right FG in ASD, as described in many other neuroimaging studies (Critchley et al. 2000; Hall et al. 2003; Humphreys et al. 2008; Schultz 2005). This suggests that hypo-activation of the FG might play a critical role in atypical face processing in ASD, especially when attention is not directed towards the emotional content of the stimuli.

In our study only controls presented emotion-sensitive activity in the inferior temporal gyrus in the earliest time-window, aligning with a previous MEG study reporting modulations of the temporal regions in processing pleasant and unpleasant pictures (Peyk et al. 2008). Conversely, the ASD participants showed a similar effect in the inferior occipital gyrus (see below), suggesting distinct spatio-temporal emotional processing rather than an absence of emotional processing per se.

Occipital Regions

In contrast to temporal regions, such as the FG which responds to both feature-based and configural information, the inferior occipital gyri respond preferentially to face features, and several visual regions in the occipital cortex have been associated with emotional processing (Fusar-Poli et al. 2009b). In particular, in the first 150 ms, emotion-sensitive visual activity has been reported, demonstrating a rapid emotional response (Batty and Taylor 2003; Pourtois et al.

2004). The present study provided insight on the timing of atypical visual responses to emotional faces in adults with ASD (see Fig. 3) in the occipital region and in the lingual gyri, previously reported in fMRI studies (Hadjikhani et al. 2004; Pierce et al. 2001).

Emotion-sensitive responses were observed only in the ASD group at 105–135 ms in the inferior occipital gyrus (Kim et al. 2015), where happy and angry faces presented stronger activity than neutral faces, and happy faces elicited stronger activity than angry faces. Interestingly, the ASD group presented the opposite emotion-response in the 225–255 ms time-window as neutral faces elicited greater neural activity than happy faces in the middle occipital gyrus.

In our study, the stimuli were presented in the parafovea, thus rapidly stimulating the magnocellular pathway (Bayle et al. 2011) through the direct subcortical route via the amygdalae and feedback projections to the visual areas (Liddell et al. 2005; Pourtois and Vuilleumier 2006; Vuilleumier et al. 2004). Thus, specific emotional responses over the occipital region seen in the ASD participants suggest an atypical early threat response, as supported by both connectivity (Kana et al. 2016) and behavioural studies (Deruelle et al. 2008). In particular, previous MEG studies reported reduced connectivity between limbic and paralimbic regions and posterior face-sensitive areas in response to threatening (i.e., angry) faces, in both adolescents and adults with ASD compared to controls (Leung et al. 2014; Mennella et al. 2017).

Here both groups presented emotion-specific responses though with different spatial distribution and with different emotional prioritization. Taken together these results suggest that implicit face processing is atypical from the earliest visual responses (Batty et al. 2011; Samson et al. 2012). Notably, this aligns with the hypotheses that those with ASD prefer feature-based strategies during behavioural tasks involving faces (Deruelle et al. 2008) and not global/configural information. Although in line with our results, this interpretation is speculative at the present time, since configural versus feature-based processing were not directly compared in the present study.

An increasing number of studies have focused on the sensory domain of atypical visual processing in autism. In investigations of low-level processes, atypical visual activity has been reported (Constable et al. 2012; Milne et al. 2009; Pei et al. 2014), suggesting that disrupted sensory processing might impact later processes, and contribute to atypical social cognition (Kornmeier et al. 2014; Kovarski et al. 2016; Thye et al. 2017). These considerations are supported by a positive correlation between the occipital region activation to emotional stimuli and the autism severity score in the ASD group (see Fig. 4), strengthening the importance of relating early sensory neural responses to clinical symptoms in populations with neurodevelopmental disorders.

Face and Emotional Processing

Emotional processing in ASD represents an important function to understand social difficulties in these participants. In the present study, specific emotion modulations were observed as early as 90–120 ms; prior studies have also shown early activity in the FG. The rapid involvement of the FG through the amygdala pathway has been suggested by fMRI (Berchio et al. 2016), but also by electrophysiological evidence. For instance, an MEG study by Hung et al. (2010) has shown a peak of activation of the left FG as early as 85 ms in response to faces presented parafoveally. Other studies have described multiple stages of activation of the FG (Barbeau et al. 2008; Cornwell et al. 2008). By using intracerebral recording Barbeau et al. (2008) reported two stages of activation of the FG at 110 ms and 160 ms in response to face stimuli. During a matching face task, a similar two-step processing of the FG was suggested by Cornwell et al. (2008) in an MEG study applying beamforming analysis. This is in accordance with a recent EEG source study reporting that the right FG was implicated in the processing of gaze direction at 100–120 ms (Berchio et al. 2016), suggesting an early dissociation of implicit gaze detection. Finally, in the study by Wong et al. (2008) the source analysis of the ERPs revealed that the FG were differently modulated between the ASD and the TD children around the P1 time-window.

Similar to the emotional modulation in the FG, an enhancement for angry faces was found in the inferior temporal gyri in controls only, suggesting broader emotional responses to threat-related stimuli in typical adults in this early time-window. However, in a later time-window a comparable emotion-sensitive response was found in the ASD group, in the inferior occipital gyri. These novel results are important in demonstrating that ASD and controls both have common responses in occipito-temporal areas indexing early emotional processing, but with spatio-temporal differences in the modulation of the emotional information of faces, rather than a simple hypo-activation. The analyses of several ROIs that are key to faces and emotional processes allowed these significant effects to be identified.

To integrate evidence from the impairment/enhancement dichotomy (Simon and Wallace 2016) into a unique model, accounts such as the weak central coherence hypothesis (WCC, Happé and Frith 2006) and the enhanced perceptual functioning (EPF, Mottron et al. 2006) have been proposed to explain the atypical perceptual functioning in autism. The WCC hypothesis proposes that perception in autism is characterized by a bias for local information coupled with

difficulty in processing global information. The EPF states that rather than a failure in global processing, ASD individuals present enhancement for details and low level processing. A third account proposed a *perceptual integration* deficit in ASD, due to a failure in the integration of sensory information into a 'big picture' (Dakin and Frith 2005). Taken together, these approaches to autistic perceptual functioning are founded on evidence of superior sensory processing (Mottron et al. 2006) as well as atypical brain activity in sensory regions such as the extrastriate cortex (Milne et al. 2009), rather than a lack of "expertise" for faces (Bolte et al. 2006; Perlman et al. 2011).

A recent meta-analysis (Samson et al. 2012) found a spatial overlap in activations in the face sensitive regions suggesting that the methodological choices might be responsible for different activation patterns in the face network, including the FG. However, in line with our study, greater bilateral activity in the extrastriate and striate regions was found in the ASD group compared to controls, demonstrating that faces are processed atypically in those with ASD within the visual face network.

Only adults with high functioning autism participated in this study, which required high compliance from the participants, to remain still and concentrate throughout the task; thus, the full autistic spectrum was not represented. Future studies, possibly relying on passive viewing designs, could be used to try to include a larger range of the spectrum.

Our study suggests that atypical visual processing in the occipital cortex is identifiable from the earliest visual stages. It is important to note, though, that contrary to the hypo-activation in the right fusiform gyrus, group differences in occipital sites did not survive multiple comparison correction. This suggests that, although uncorrected differences were present in three out of three occipital sites considered, they were not as large as the effect found in the right fusiform, in line with the fact that fusiform hypo-activation in ASD is a well replicated result in the literature. In a neurodevelopmental perspective, perceptual or sensory difficulties could undermine the development of face and emotional processing via a cascade mechanism, eventually triggering compensatory mechanisms or strategies (Baum et al. 2015; Cascio et al. 2016).

Conclusions

These findings support the existence of a distinct spatio-temporal neural organization in the ASD group during the processing of implicit emotional faces. According to the perceptual and sensory theories of autism, stronger visual responses in ASD compared to controls in an early time-window (105–135 ms) was found; interestingly, the response was reduced at longer latencies. Thus, atypical facial expression processing seems to be not only characterised by hypo-activation of the FG, but by a broader atypical processing of the emotional face network, including atypical visual processing and emotion-sensitive responses (Critchley et al. 2000; Pierce et al. 2001; Wong et al. 2008). Considering the directions of these differences in the activations and the time windows, stronger early visual responses may be partly responsible for impairment in subsequent face-sensitive processes in the FG.

The present study strengthens the hypothesis that early visual hyper-reactivity plays a role in social disturbances in ASD. Importantly, to investigate the specificity of this response, further studies are needed to compare early visual responses to social and non-social stimuli. Nonetheless, in light of the correlation with the severity of ASD symptoms, atypical early visual responses ought to be considered when studying social cognition in autism.

Finally, from a clinical perspective, these findings could have profound implications. The present results highlight the importance of properly assessing basic perceptual atypicalities in autism, which could underlie deficits in higher-order cognitive processes, such as social cognition. Treatment might need to focus not only on strengthening individuals' social skills, but also on promoting strategies to better process the stimuli in the environment, at a more basic perceptual level.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in this study 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.

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