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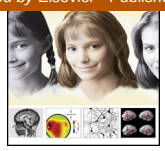

Neurophysiological responses to faces and gaze direction differentiate children with ASD, ADHD and ASD + ADHD

Charlotte Tye[a,*], Evelyne Mercure[b], Karen L. Ashwood[c], Bahare Azadi[c], Philip Asherson[a], Mark H. Johnson[d], Patrick Bolton[a,c], Gráinne McLoughlin[a,e]

[a] MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College, London, UK
[b] Institute of Cognitive Neuroscience, University College, London, UK
[c] Child and Adolescent Psychiatry, Institute of Psychiatry, King's College, London, UK
[d] Centre for Brain and Cognitive Development, Birkbeck, University of London, UK
[e] Swartz Center for Computational Neuroscience, Institute for Neural Computation, University of California, San Diego, USA

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ABSTRACT

Children with autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) demonstrate face processing abnormalities that may underlie social impairment. Despite substantial overlap between ASD and ADHD, ERP markers of face and gaze processing have not been directly compared across pure and comorbid cases. Children with ASD ($n = 19$), ADHD ($n = 18$), comorbid ASD + ADHD ($n = 29$) and typically developing (TD) controls ($n = 26$) were presented with upright/inverted faces with direct/averted gaze, with concurrent recording of the P1 and N170 components. While the N170 was predominant in the right hemisphere in TD and ADHD, children with ASD (ASD/ASD + ADHD) showed a bilateral distribution. In addition, children with ASD demonstrated altered response to gaze direction on P1 latency and no sensitivity to gaze direction on midline-N170 amplitude compared to TD and ADHD. In contrast, children with ADHD (ADHD/ASD + ADHD) exhibited a reduced face inversion effect on P1 latency compared to TD and ASD. These findings suggest children with ASD have specific abnormalities in gaze processing and altered neural specialisation, whereas children with ADHD show abnormalities at early visual attention stages. Children with ASD + ADHD are an additive co-occurrence with deficits of both disorders. Elucidating the neural basis of the overlap between ASD and ADHD is likely to inform aetiological investigation and clinical assessment.

1. Introduction

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are both common and severely impairing neurodevelopmental disorders with childhood onset. Although current diagnostic criteria preclude a co-diagnosis, high rates of co-occurrence have been documented and evidence is accumulating to suggest substantial clinical, neuropsychological and genetic overlap (Rommelse et al., 2011). In particular, while social difficulties are a core impairment in ASD, children with ADHD also frequently exhibit social difficulties comparable to those shown in ASD (Clark et al., 1999; Greene et al., 1996; Landau et al., 1998; Luteijn et al., 2000; Mulligan et al., 2009; Santosh & Mijovic, 2004). Nevertheless, the interaction and mode of co-occurrence between these conditions is still not well understood (Taurines et al., 2012). In order to determine whether the comorbid condition differs from the simple additive combination of the deficits or pathophysiology associated with ASD and ADHD when they occur alone, the next essential step is to investigate whether associated features differentiate between

* Corresponding author. Tel.: +44 207 848 0784; fax: +44 207 848 0866.
E-mail address: charlotte.tye@kcl.ac.uk (C. Tye).

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conditions (Banaschewski et al., 2005). It is therefore necessary to stratify groups and compare underlying risk factors in the comorbid group to pure disorders (ASD-only vs. ADHD-only vs. ASD + ADHD) when investigating the underlying mechanisms of social difficulties (Banaschewski et al., 2007).

The ability to process faces is considered fundamental to typical development of social abilities (Dawson et al., 2005). In particular, gaze direction detection is linked to Theory of Mind (ToM) abilities, successful face and emotion recognition, and orienting of social attention, which has led to the proposition of a specialised neural mechanism (Baron-Cohen, 1995; Emery, 2000; Itier & Batty, 2009). Event-related potentials (ERPs) provide the excellent temporal resolution necessary to investigate different temporal stages of information processing when attending to face stimuli. In typical individuals the right-lateralised temporo-occipital N170 ERP component appears to be particularly sensitive to face stimuli, notably demonstrated by amplitude enhancement for faces compared to other non-face stimuli (Bentin et al., 1996; Halit et al., 2000; Itier & Taylor, 2004b). The N170, along with the preceding occipital P1 component, are affected by disruptions of the configuration of facial features, as they show longer latency and larger amplitude to inverted faces compared to upright faces ("face inversion effect") (Bentin et al., 1996; de Haan et al., 2002; Itier & Taylor, 2002, 2004a; Rossion et al., 1999, 2000; Rossion & Gauthier, 2002). While the N170 is also sensitive to eyes alone (Bentin et al., 1996), most studies of children and adults do not find modulation of the N170 by gaze direction (Grice et al., 2005; Klucharev & Sams, 2004; Schweinberger et al., 2007; Taylor et al., 2001). Behavioural studies suggest that an upright face is required for enhanced processing of direct gaze (Senju et al., 2005a). While one study found no modulation by gaze when presented in inverted faces on a component peaking at 240 ms in 4-month-old infants (proposed to be the infant precursor to the adult N170) (de Haan et al., 2002; Farroni et al., 2004), further investigation of the N170 is required to confirm the reliance of gaze perception on configural processing and overlap in the neural mechanisms subserving these processes.

While typically developing infants as young as 3 months old show a preference for face like-stimuli (Hood et al., 1998), individuals with ASD look less at human faces and this is evident in children as young as 6–12 months old (Maestro et al., 2002; Osterling & Dawson, 1994). Behavioural studies demonstrate impairment in face discrimination and recognition in autism (Boucher et al., 1998; Gepner et al., 1996). ERP studies suggest abnormal responses to face stimuli, notably a reduction or absence of the face inversion effect, on P1 and N170 amplitude in individuals with autism (Batty et al., 2011; Dawson et al., 2002, 2005; Hileman et al., 2011; McCleery et al., 2009; McPartland et al., 2004, 2011; O'Connor et al., 2005, 2007; Webb et al., 2006, 2009). The lack of sensitivity to face inversion has been used to support theories of 'weak central coherence' in ASD, referring to a cognitive bias toward local detail (Happé, 1999), which could be associated with a reliance on features to process faces and/or an impairment in configural face processing.

Behavioural studies show that while typically developing children are more accurate and faster at detecting direct gaze than averted gaze, children with ASD show equal detection of direct and averted gaze (Senju et al., 2005a, 2008). ERP studies support abnormalities in gaze direction detection. Firstly, using passively viewed front-view face stimuli, a larger N170 over midline channels to direct than averted gaze was observed in young children with autism with no such effect for age-matched controls (Grice et al., 2005), similar to that shown in 4-month-old typically developing infants (Farroni et al., 2004). In older children explicitly processing gaze direction in laterally averted faces, the N170 was enhanced by direct gaze in controls but remained uninfluenced by gaze in autism (Senju et al., 2005b). Abnormal ERP responses to gaze direction are also observed in infant siblings of children with ASD (Elsabbagh et al., 2009a, 2012) and are predictive of subsequent ASD diagnosis (Elsabbagh et al., 2012). In addition, while the N170 is larger in the right hemiscalp compared to the left hemiscalp in typically developing individuals, individuals with autism show an atypical bilateral scalp distribution (Carver & Dawson, 2002; McCleery et al., 2009; McPartland et al., 2004; Senju et al., 2005b) suggestive of abnormal cortical specialisation for faces (Dawson et al., 2005). As abnormalities in these face-sensitive ERPs have been associated with impaired social skills (Hileman et al., 2011), it is likely that these abnormalities reflect the social and communication deficits observed in autism.

There is limited knowledge regarding basic face processing in ADHD at the neural level and particularly how this compares to deficits reported in ASD. While there is consistent evidence for impaired emotion perception and recognition in ADHD (Dickstein & Castellanos, 2012), it is unclear whether emotion deficits are accompanied by or temporally preceded by abnormalities in structural face processing and gaze direction detection. Studies of ERP responses to emotional face expressions report reduced P1 amplitude, increased N170 amplitude and reduced P300 amplitude in temporal regions to neutral faces compared to controls (Williams et al., 2008). A recent ERP study reports deficits in N170 modulation to emotional face stimuli that were not accompanied by impairments in basic face processing, as supported by an enhanced N170 response to face stimuli compared to word stimuli (Ibanez et al., 2011). Importantly no study has assessed P1 and N170 responses to face stimuli in individuals with ASD + ADHD. As social difficulties in ADHD are associated with greater impairment (Nijmeijer et al., 2008), a closer investigation of the neural correlates of face processing in ADHD and their overlap with ASD is required.

The aim of this study was to investigate whether the ERP abnormalities in face and gaze processing associated with ASD are also found in ADHD and comorbid ASD + ADHD. We presented upright and inverted faces with direct and averted gaze in an experimental design previously used (Farroni et al., 2004; Grice et al., 2005) to cases of ASD, ADHD, ASD + ADHD and typically developing children that were systematically assessed to ensure minimal misspecification in group allocation. We hypothesized that the clinical groups would not show the typical amplitude enhancement in the right hemiscalp or sensitivity to face

orientation and gaze direction as indexed by the P1 and N170 ERPs. We expected the ASD and comorbid group to show a more profound impairment in face and gaze processing compared to ADHD children, and the magnitude of the deficits to be associated with the number of autism symptoms reported by parents. In addition, as reported by previous studies suggesting overlap between face and gaze processing, modulation of neural responses by gaze were expected in upright faces only, particularly in the TD group who have been shown to rely on configural processing.

2. Methods

2.1. Sample

Nineteen male participants with ASD, 18 with ADHD, 29 with ASD and ADHD, and 26 typically developing controls (TD) took part in the study. Only males were included in the study to reduce sample heterogeneity and due to the higher ratio of males diagnosed with ASD compared to females. The age range was 8–13 years and participants were age-matched at the group level (Table 1). All participants were required to have an IQ > 70, normal or corrected-to-normal vision, and not to be taking any medication except for stimulants, which had to be interrupted 48 h prior to the experiment. Exclusion criteria included English not as the main language, specific medical disorders, history of traumatic brain injury, a diagnosis of epilepsy and other comorbid psychiatric disorders not including ODD.

The participants were recruited from out-patient neurodevelopmental clinics and local parent support groups. All participants had a clinical diagnosis made according to ICD-10 or DSM-IV criteria (autism, Aspergers syndrome, ADHD combined type/hyperkinetic disorder). Upon recruitment, cases then underwent a comprehensive assessment to ascertain present symptomatology and provide a pure or comorbid research diagnosis. All cases were initially evaluated with Conners 3rd Edition Parent Rating Scale short form (Conners, 2008) and Social Communication Questionnaire (SCQ; Rutter et al., 2003). Cases of ASD were diagnosed using the Autism Diagnostic Interview-Revised (ADI-R; modified criteria; IMGSAC, 1998) and the Autism Diagnostic Observation Schedule (ADOS-G; Gotham et al., 2007). Cases of ADHD were diagnosed using Parent Account of Childhood Symptoms (PACS) (Taylor et al., 1986). Co-morbid ASD + ADHD cases met full diagnostic criteria for ASD and full diagnostic criteria for ADHD using the ADI-R/ADOS and PACS. In addition, the ADI-R was conducted for ADHD participants who scored above threshold on the SCQ, and the PACS for ASD participants who scored above threshold on the Conners'. Of the children clinically diagnosed with ASD, 47% (n = 16/34) met research diagnostic criteria for ADHD and 14% (n = 3/21) of children clinically diagnosed with ADHD met criteria for ASD and were reallocated to the comorbid group. In addition, 91% (n = 10/11) of the children clinically diagnosed with ASD + ADHD retained their diagnosis following research assessments. One participant clinically diagnosed as ASD + ADHD did not reach ADHD diagnosis as defined by the PACS interview and therefore was reallocated into the ASD-only group.

Table 1
Clinical and demographic characteristics.

	Diagnosis								F	p	Post hoc
	TD (n = 26)		ASD (n = 19)		ADHD (n = 18)		ASD + ADHD (n = 29)				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Age	10.56	1.79	11.69	1.70	10.48	1.91	10.53	1.69	2.20	.093	n.s.d.
Right-handed (%)	23	88%	18	95%	17	94%	21	72%	chi^2 = 6.79	.079	n.s.d.
Verbal IQ	120.00	14.40	113.79	23.87	105.94	18.47	110.41	15.67	2.48	.066	n.s.d.
Performance IQ	115.73	13.89	111.05	13.31	101.67	11.60	106.72	11.97	4.86	.004	TD > ADHD
Full-scale IQ	120.04	13.42	115.68	15.73	104.11	14.23	109.72	13.41	5.31	.002	TD > ASD + ADHD, ADHD
SCQ	3.88	3.54	20.11	6.42	10.89	5.36	24.79	5.71	81.12	<.001	TD < ADHD < ASD < ASD + ADHD
Conners DSM-inattentive	56.08	11.05	67.11	14.13	83.94	7.41	80.21	11.59	29.85	<.001	TD < ASD < ASD + ADHD, ADHD
Conners DSM-hyperactive	58.88	17.02	66.11	12.99	87.89	3.25	84.00	7.63	32.76	<.001	TD, ASD < ASD + ADHD, ADHD

Abbreviations: TD, typically developing controls; ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; ASD + ADHD, comorbid ASD and ADHD; Conners, Conners third edition parent rating scale short form; DSM, Diagnostic and statistical manual of mental health disorders; IQ, intelligence quotient; SCQ, social communication questionnaire. n.s.d. = non-significant difference.

The TD group consisted of children recruited through local schools and forums. Children were not included if they had any psychiatric diagnosis and were assessed with the SDQ, SCQ and Conners' questionnaires. Eleven TD participants scored above threshold on the Conners'. Further assessment of 9 of these children with the PACS interview confirmed that these children did not reach a diagnosis of ADHD and thus were retained in the study. A more stringent approach to control selection (excluding the 2 participants who were not assessed on the PACS and those scoring 5 or above on either domain of the PACS interview), which did not affect any of the results reported. In addition, boys who had a sibling with a diagnosis of ASD and/or ADHD were not included. The study protocol was approved by a medical ethics committee. Parental written consent was given before the experiment began.

2.2. Task and stimuli

The stimuli were colour images of three female faces with direct or averted gaze (looking right or left). These images were presented either in upright or inverted orientation on a grey background. Faces subtended $15.8^\circ \times 10.2^\circ$ from a viewing distance of 90 cm. Each trial began with the presentation of a fixation stimulus that had a variable inter-trial interval of 800 and 1200 ms to reduce stimulus repetition effects and ensure the child could not predict the onset of the face stimulus. The fixation stimuli consisted of various static cartoon images that were used to stimulate the child's participation and attention and were not analyzed. Face stimuli were presented for 500 ms followed by a 500 ms interval without visual stimulus, and were aligned vertically so that the eyes appeared at the same height as the fixation stimuli, in order to orient attention towards the eyes. 360 trials were presented in four blocks of 80 trials with randomized presentation. Participants were asked to count the appearances of flags among the fixation stimuli, in order to stimulate the child's participation and attention. The approximate number of flags counted per block was used as a benchmark for attention to task and participants were also continually monitored by video recording. This method has been used previously in ASD and infant samples (Farroni et al., 2004; Grice et al., 2005). The task was administered as part of a larger EEG/ERP test battery (not presented here) with a duration of 65 min. Presentation of the tasks was ordered in the same way for each group to control for effects of practice and fatigue. IQ was assessed using four subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) (Block Design, Vocabulary, Matrix Reasoning and Similarities) and took 45 min.

2.3. Electrophysiological recording and analysis

EEG was recorded using a 62 active electrode recording system (ActiCap, Brain Products, Munich, Germany; extended 10–20 montage). The reference electrode was positioned at FCz. Vertical and horizontal electrooculograms (EOGs) were simultaneously recorded from electrodes above and below the left eye and at the outer canthi. The signal was digitized at 500 Hz sampling rate, stored and analyzed offline.

Data were analyzed in Brain Vision Analyzer (2.0; Brain Products, Munich, Germany). The signal was re-referenced offline to the average reference and downsampled to 256 Hz. We applied 0.1–30 Hz (24 dB/Oct) Butterworth filters. Ocular artifacts were removed from the data using biased infomax Independent Component Analysis (ICA, Jung et al., 2000). The extracted independent components were manually inspected and ocular artefacts were removed by back-projection of all but those components. Remaining artefacts exceeding 200 μV peak-to-peak in any channel were rejected from the data. Baseline correction was performed using a 200 ms pre-stimulus reference period. Stimulus-locked epochs (−200 to 700 ms peristimulus window) were averaged for the following trial types: upright orientation/direct gaze; upright orientation/averted gaze; inverted orientation/direct gaze; and inverted orientation/averted gaze. Averages were computed for each participant in each experimental condition on a minimum of 55 trials per stimulus (means per group: TD: 72.02; ASD: 69.60; ADHD: 69.72; ASD + ADHD: 70.63).

Based on visual inspection of the grand average and congruent with the topography and previous literature (Batty et al., 2011; Churches et al., 2010; Eimer, 2011; O'Connor et al., 2005), the N170 was scored as the maximal negative peak at P7 and P8 and the midline-N170 at Pz, in a 150–290 ms latency window, and the P1 was scored as the maximal positive peak in a 100–200 ms latency window at O1 and O2, using the semi-automatic peak detection module in Brain Vision Analyzer.

2.4. Statistical analyses

Tests of ANOVA assumptions included checking for equality of error variances (Levene's test) and equality of covariance matrices (Box's test). Multivariate ANOVA is relatively robust to small violations of non-normality, as long as the skew is not caused by univariate or multivariate extreme outliers (Tabachnick and Fidell, 2001). By removing extreme outliers (±3.5 SD) at the start of the analysis procedure it was possible to employ multivariate approaches to overcome any potential problems.

One ASD subject was removed due to extreme outlier scores on the P1 and N170 and an additional ASD subject from the N170 peak-to-peak analysis. One TD subject was removed from analysis due to insufficient segments for reliable ERP analysis. One ADHD and one TD subject were removed from analysis due to poor attention to task shown in video recording. A repeated-measures ANOVA was conducted on each ERP parameter (P1 amplitude, P1 latency, N170 amplitude, P1–N170 amplitude difference, N170 latency, N170 midline amplitude, N170 midline latency) with orientation (upright/inverted), gaze (direct/averted) and, for P1 and occipito-temporal N170 hemisphere (left/right), as the within-subjects factors, and group as the between-subjects factor. In order to evaluate the utility of this method to dissociate clinical groups and elucidate the basis of comorbidity, the between-subjects factor was defined in two ways: (1) a comparison of 4 groups of ASD-only, ADHD-only, ASD + ADHD and TD to

assess differences between pure and comorbid groups and (2) 2 × 2 comparisons with ADHD (ADHD/ASD + ADHD) and ASD (ASD/ASD + ADHD) to examine the interaction between the disorders. A non-significant interaction between the disorders is compatible with an additive model. Post hoc analyses were carried out when necessary using Tamhane correction that caters for unequal variances. Effect sizes (Cohen's *d*) were calculated using the difference in the means, divided by the pooled standard deviation of the data.

IQ was not a significant covariate on any analyses and therefore was removed. Age was not a significant predictor of P1 amplitude, P1 latency, midline-N170 amplitude or midline-N170 latency and therefore was removed as a covariate. However, due to reported developmental changes on the P1 and N170 components (Taylor et al., 2004), any changes to reported significant findings when age was included as a covariate are noted (main effects on P1 amplitude and latency).

In order to limit the number of comparisons, Spearman's correlations were run between ERP parameters and parent-rated symptom scores where significant group differences were found, with age partialled out where appropriate. Due to a highly skewed distribution of Conners scores, and moderate correlations between scores on the SCQ and Conners rating scales (SCQ-Conners inattention: $r = .37$, $p < .001$; SCQ-Conners hyperactivity–impulsivity: $r = .39$, $p < .001$), rating-scale-corrected residuals were entered into the correlation analysis, in order to control for the effect of measures that are correlated with both ASD and ADHD. Correlations that were significant across groups were taken forward for hierarchical multiple regression, in order to ascertain the relative contribution of each measure in predicting the ERP measure whilst controlling for the other.

3. Results

3.1. P1 amplitude

Grand average ERPs are shown in Fig. 1. There was a main effect of gaze on P1 amplitude [F (1, 84) = 4.49, $p = .04$, $d = 0.07$], indicating greater amplitude for averted gaze compared to direct gaze, that did not remain when controlling for age [F (1, 84) = 01, $p = .93$]. There was also a main effect of hemisphere (left vs. right) on P1 amplitude [F (1, 84) = 7.77, $p = .01$, $d = 0.23$]: greater amplitude was shown in the right hemisphere compared to the left hemisphere in all groups across all conditions, which did not remain when controlling for age [F (1, 84) = 0.12, $p = .73$].

There was no main effect of group on P1 amplitude [F (3, 84) = 0.12, $p = .95$], and no significant interactions with orientation [F (3, 84) = 1.47, $p = .23$], gaze [F (3, 84) = 0.96, $p = .42$] or hemisphere [F (3, 84) = 0.46, $p = .71$], nor were effect sizes beyond small observed for these contrasts (all $d < .20$). No group effects emerged when combining the groups by the presence of ASD [F (1, 86) = 0.03, $p = .87$] or ADHD diagnosis [F (1, 86) = 0.17, $p = .68$], indicating that P1 amplitude effects described above are characteristic of all groups. There was no interaction between ASD and ADHD on these parameters (all $p > .05$).

3.2. P1 latency

Across all groups there was a main effect of orientation of faces on the latency of the P1 [F (1, 84) = 24.79, $p < .001$, $d = 0.46$]: latency was longer for inverted faces compared to upright faces, which did not remain when age was controlled for [F (1, 84) = 1.09, $p = .30$]. There was no main effect of group on P1 amplitude [F (3, 84) = 95, $p = .42$], and no significant interactions with orientation [F (3, 84) = 1.52, $p = .22$] or gaze [F (3, 84) = 1.46, $p = .23$]. There was, however, a significant interaction between group and hemisphere [F (3, 84) = 4.51, $p = .01$]. Post hoc analyses revealed that TD children showed longer latency in the RH whereas the ASD + ADHD group showed longer latency in the LH ($p = .02$, $d = 0.94$) with a similar non significant tendency in the ASD-only ($p = .08$, $d = 0.88$), but a non-significant effect for ADHD-only ($p = .18$, $d = 0.72$; Fig. 2).

Interesting group differences emerged when combining the groups by the presence or absence of ADHD or ASD diagnosis. The interaction between group and hemisphere remained when grouping subjects by the presence or absence of ASD (ASD/ASD + ADHD: F (1, 84) = 6.36, $p = .01$, $d = 0.60$) with a trend for ADHD (ADHD/ASD + ADHD: F (1, 84) = 3.10, $p = .08$, $d = 0.46$). There was no significant interaction between ASD and ADHD [F (1, 84) = 2.34, $p = .13$].

When combined by the presence or absence of ASD, a three-way interaction between ASD, gaze and orientation emerged [F (1, 84) = 6.68, $p = .01$, $d = 0.50$]. Planned contrasts revealed that in upright faces, there was a significant interaction between group and gaze: TD and ADHD children showed longer latency to direct than averted gaze, whereas children with ASD and ASD + ADHD showed shorter latency to direct than averted gaze ($p = .026$ $d = 0.48$). In inverted faces, however, there were no significant differences between groups (all $p < .05$), supporting a gaze effect specific to upright faces (Fig. 3). This interaction was not shown when combining the groups by ADHD [F (1, 84) = 1.72, $p = .19$], nor was there a significant interaction between ASD and ADHD [F (1, 84) = 0.21, $p = .65$].

When combining the groups by the presence or absence of ADHD diagnosis, an interaction between group and orientation emerged [F (1, 84) = 6.03, $p = .02$, $d = 0.49$] indicating a reduced effect of face inversion in children with ADHD diagnosis (Fig. 4) that was not present when combining by ASD diagnosis [F (1, 84) = 1.26, $p = .26$, $d = 0.13$]. There was no interaction between ASD and ADHD [F (1, 84) = 0.20, $p = .66$), suggesting additive effects.

3.3. N170 amplitude

Grand average ERPs and topographical maps are shown in Fig. 5. Across the whole sample there was a main effect of orientation on the amplitude of the N170 [F (1, 83) = 10.51, $p = .002$] with increased amplitude for inverted compared to upright faces. An orientation by age interaction [F (1, 83) = 12.18, $p = .001$] indicated that enhanced amplitude of the N170 to inverted faces increases with development ($r = -.30$, $p = .004$). An interaction between orientation and gaze was found [F (1, 83) = 5.34, $p < .05$, $d = 0.11$]. Post hoc

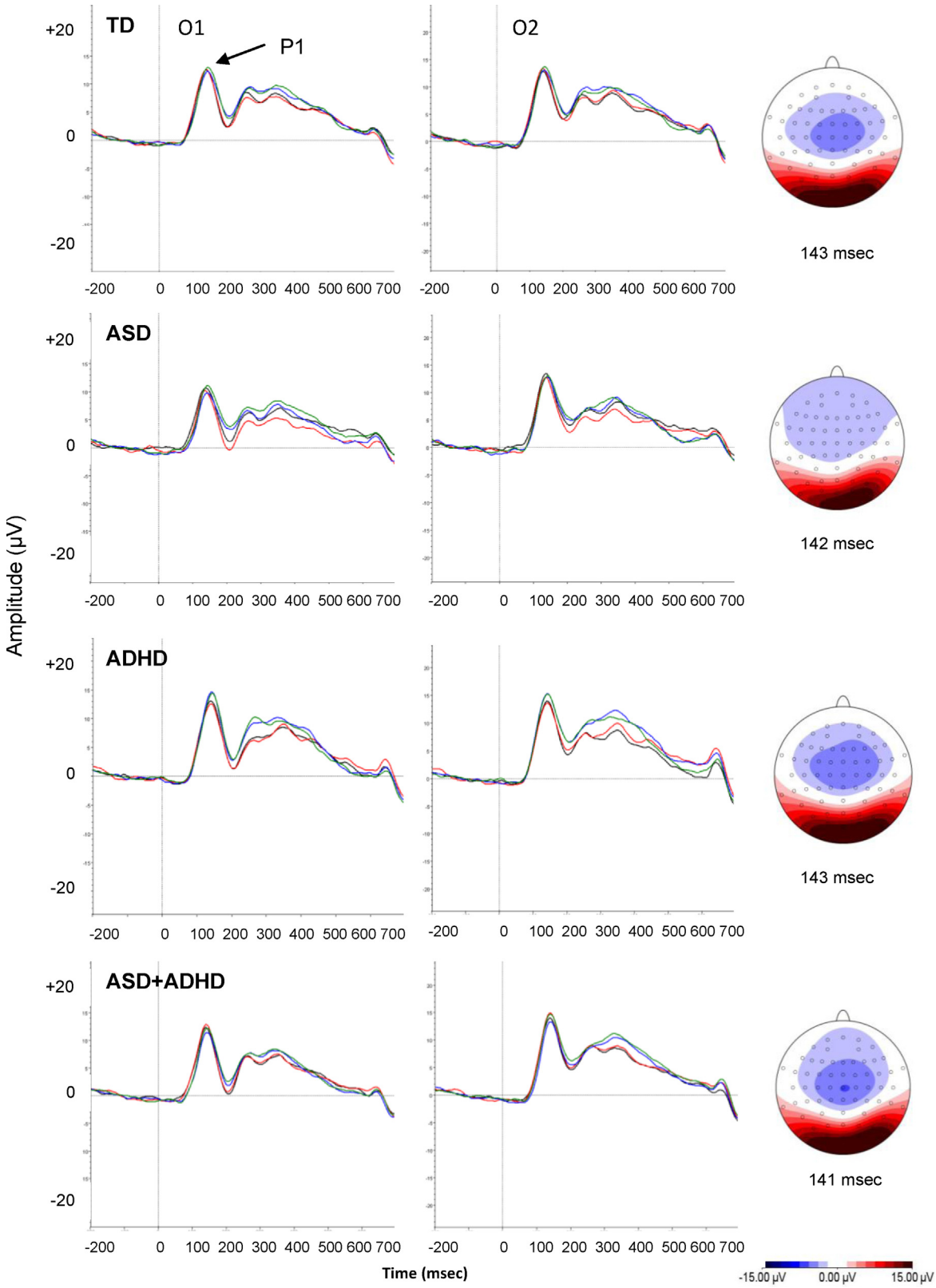

Fig. 1. Grand mean P1 ERPs to face stimuli for each group and isocontour maps derived for the grand-average at average peak latency for each group. Black represents upright-direct, red represents upright-averted; blue represents inverted-direct; green represents inverted-averted.

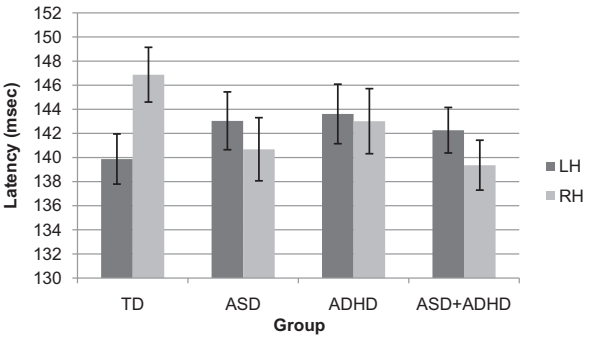

Fig. 2. The interaction between hemisphere and diagnostic group on P1 latency (±1 SE). TD, typically developing controls; ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; ASD + ADHD, comorbid ASD and ADHD; LH, left hemisphere; RH, right hemisphere.

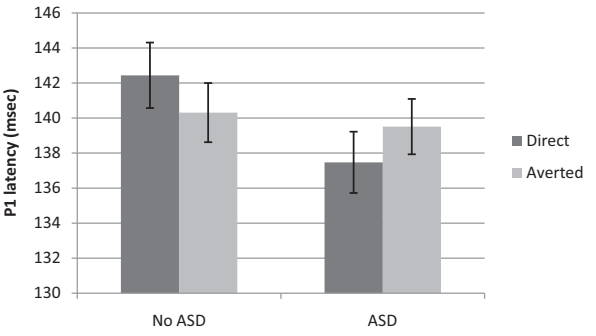

Fig. 3. The interaction between gaze direction and ASD diagnosis on P1 latency in upright faces (±1 SE). No ASD = TD and ADHD ASD = ASD and ASD + ADHD.

analyses revealed enhanced N170 amplitude for averted gaze compared to direct gaze in upright faces only. There was a three-way interaction between orientation, gaze and age [F (3, 83) = 4.97, p = .03], indicating that the gaze effect in upright faces only is shown with increasing age (r = .23, p = .03).

Although no main effect of group emerged on N170 amplitude [F (1, 83) = 59, p = .63], an interaction between group and hemisphere was found [F (3, 83) = 4.09, p = .01]. Post hoc analyses revealed enhanced N170 in the left hemisphere for ASD + ADHD subjects compared to enhanced amplitude in the right hemisphere for TD (p = .01, d = 0.94) with a trend compared to ADHD (p = .07, d = 0.78). When combining the groups by the presence or absence of ASD or ADHD, this interaction appeared to be driven by ASD diagnosis [F (1, 83) = 8.23, p = .01, d = 0.71] and not by ADHD diagnosis [F (1, 83) = 1.60, p = .21, d = 0.38]. There was no interaction between ASD and ADHD on this measure [F (1, 83) = 0.01, p = .93].

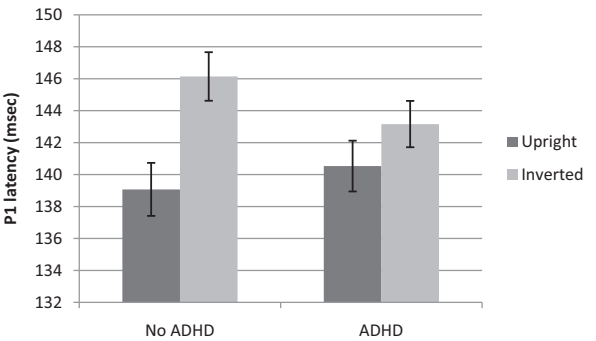

Fig. 4. The interaction between face orientation and ADHD diagnosis on P1 latency across upright and inverted faces (±1 SE). No ADHD = TD and ASD ADHD = ADHD and ASD + ADHD.

There was also a trend towards an interaction between ASD and orientation with a small effect size [F (1, 83) = 3.38, p = .07, d = 0.24], indicating greater N170 amplitude enhancement to inverted faces compared to upright faces in TD/ADHD, compared to participants with an ASD diagnosis (ASD/ASD + ADHD). An effect of orientation was not found when combining by the presence of an ADHD diagnosis [F (1, 83) = 2.74, p = .10, d = 0.16], nor was there an interaction between ASD and ADHD on orientation [F (1, 83) = 0.00, p = .96]. There was no interaction between group and gaze [F (2, 83) = 1.14, p = .34].

Any effect on the P1 could be propagated to be amplified at the N170 level, supported by moderate correlations between the P1 and N170 measured at P7 and P8 (P7: r = .34, p < .001; P8: r = .38, p < .001). The above analyses were repeated using a peak-to-peak approach, revealing a significant main effect of orientation on the amplitude of the P1–N170 [F (1, 81) = 10.75, p = .002] with increased amplitude for inverted compared to upright faces. An orientation by age interaction [F (1, 81) = 14.47, p < .001] indicated that enhanced amplitude of the P1–N170 to inverted faces increases with development (r = –.36, p = .001).

There was no main effect of group [F (3, 81) = 1.26, p = .30], although when combined by ADHD diagnosis a trend toward greater amplitude of the P1–N170 was shown in children with ADHD [F (1, 81) = 3.48, p = .07, d = 0.41], which was not shown when combined by ASD diagnosis [F (1, 81) = 0.10, p = .75, d = 0.07] nor was there an interaction between ASD and ADHD [F (1, 81) = 0.26, p = .61].

There was no interaction between orientation and gaze as noted for the above analyses [F (1, 81) = 0.17, p = .69], although when combined by the presence of ADHD diagnosis, this effect was significant [F (1, 81) = 5.62, p = .02], indicating that in upright faces all groups show enhanced amplitude to averted gaze compared to direct gaze, whereas in inverted faces ADHD subjects show no effect of gaze (p = .001, d = 0.72). This effect was not shown when combining subjects by the presence of ASD diagnosis [F (1, 81) = 0.08, p = .79, d = 0.08], nor was there an interaction between ASD and ADHD on this measure [F (1, 81) = 1.79, p = .19].

No interaction between group and hemisphere was found in contrast to above [F (3, 81) = 1.39, p = .25], although when combined by ASD diagnosis there was a trend towards reduced hemispheric effects in subjects with ASD compared to those without ASD [F (1, 81) = 3.31, p = .07, d = 0.39], which was not shown when combining by the presence of ADHD [F (1, 81) = 0.04, p = .85, d = 0.04], nor was there an interaction between ASD and ADHD [F (1, 81) = 1.46, p = .23].

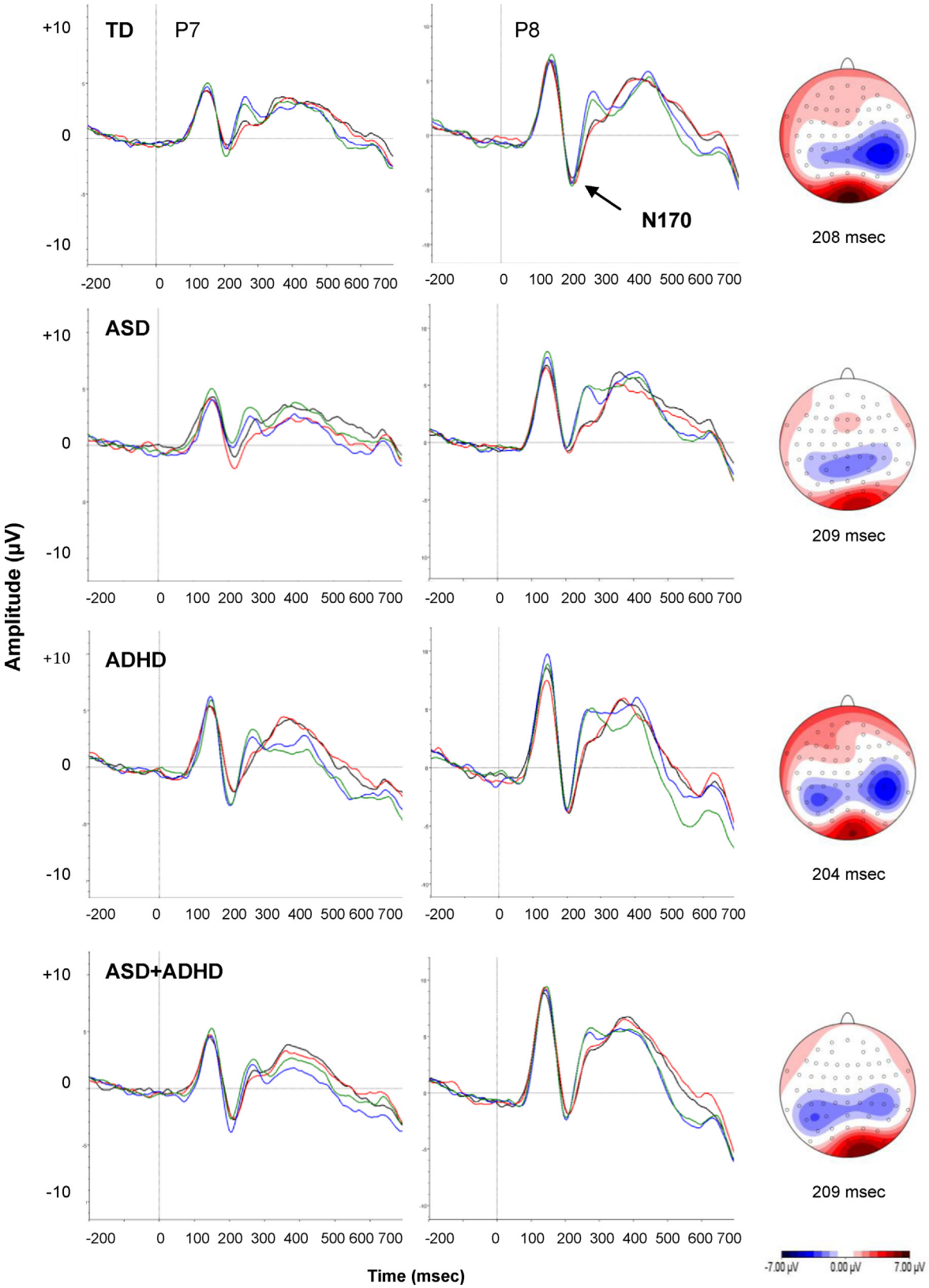

Fig. 5. Grand mean N170 ERPs to face stimuli for each group and isocontour maps derived for the grand-average at peak latency for each group. Black represents upright-direct, red represents upright-averted; blue represents inverted-direct; green represents inverted-averted.

3.4. N170 latency

Across the whole sample there was a main effect of age [$F(1, 83) = 19.92$, $p < .001$] showing decreased latency of the N170 with increasing age ($r = -.43$, $p < .001$). There was a significant interaction between gaze direction and age [$F(1, 83) = 4.01$, $p < .05$] indicating longer latency of the N170 to averted gaze is shown only in older subjects ($r = .21$, $p = .05$).

Although there was no main effect of group overall on N170 latency [$F(3, 83) = 1.88$, $p = .14$], when combined by ASD diagnosis there was a trend toward a main effect of group on N170 latency [$F(1, 83) = 3.68$, $p = .06$, $d = 0.23$], indicating slightly longer N170 latency in participants with ASD/ASD + ADHD compared to TD/ADHD. In addition, a weaker trend toward a main effect of ADHD diagnosis [$F(1, 83) = 3.07$, $p = .08$, $d = 0.13$], suggested shorter N170 latency in ADHD and ASD + ADHD when combined. There was no interaction between ASD and ADHD diagnosis suggesting an additive effect of the conditions [$F(1, 83) = 0.08$, $p = .78$]. There was no interaction between group and orientation [$F(3, 83) = 2.06$, $p = .11$], nor between group and gaze [$F(3, 83) = 1.33$, $p = .27$] on N170 latency.

3.5. Midline N170 amplitude

Grand average ERPs and topographical maps are shown in Fig. 6. There was no main effect of group on midline-N170 amplitude [$F(1, 83) = 0.88$, $p = .46$], nor an interaction between group and orientation [$F(3, 83) = 1.68$, $p = .18$]. A main effect of gaze was shown across the whole sample [$F(1, 84) = 5.82$, $p = .02$], revealing enhanced amplitude to averted gaze compared to direct gaze. There was a trend towards an interaction between group and gaze [$F(3, 83) = 2.30$, $p = .08$], and when combined by the presence of ASD diagnosis, there was a significant interaction between group and gaze [$F(1, 84) = 4.24$ $p = .04$, $d = 0.44$], indicating a reduced gaze effect in children with ASD (ASD/ASD + ADHD) compared to those without an ASD diagnosis (TD/ADHD). This effect was not shown when combining by the presence of ADHD diagnosis [$F(1, 84) = 0.46$, $p = .50$, $d = 0.04$]. In addition, there was no significant interaction between ASD and ADHD, suggesting an additive effect of the disorders [$F(1, 84) = 2.46$, $p = .12$].

There was a trend toward age being significant as a covariate [$F(1, 83) = 3.08$, $p = .08$]. Therefore the analyses were run with and without age, revealing that the main effect of gaze was not present when controlling for age [$F(1, 83) = 0.39$, $p = .53$]. Effects of ASD diagnosis on midline-N170 amplitude remained the same regardless of age [$F(1, 85) = 4.24$, $p = .04$]. No other effects of task manipulation were significant (all $p > .05$).

3.6. Midline N170 latency

There was no significant main effect of group on the midline-N170 latency [$F(1, 84) = 1.17$, $p = .33$], nor an interaction between group and orientation [$F(1, 84) = 1.59$, $p = .20$] and gaze [$F(3, 84) = 1.45$, $p = .24$]. There was, however, a trend toward a main effect of orientation across the whole sample [$F(1, 84) = 3.41$, $p = .07$], indicating increased latency to inverted faces compared to upright faces. All other effects were non-significant (all $p > .10$).

3.7. Dimensional analyses

In order to examine whether ERP parameters are related to quantitative trait measures of the disorders, correlations were conducted between parameters that showed differences between diagnostic groups (based on calculation of difference scores) and parent-rated symptom scores (see Table 2). Across the whole sample, the interaction between group and hemisphere on N170 amplitude showed a significant association with parent-rated symptom scores on the SCQ ($r = -.31$, $p = .004$) and not on the Conners (inattention: $r = -.01$, $p = .91$; hyperactivity–impulsivity: $r = -.01$, $p = .93$). A hierarchical regression model confirmed this correlation supporting the SCQ as a predictor of reduced lateralisation of N170 amplitude; the regression model showed a significant R^2 increase (R^2 change = .09, $p = .003$) indicating enhanced prediction of the ERP parameter, which remained after controlling for the potential effect of the Conners rating scale (R^2 change = .08, $p = .01$). Conversely, the Conners rating scale did not significantly enhance prediction of the N170 amplitude lateralisation (R^2 change = .02, $p = .44$). All other correlations were non-significant.

4. Discussion

This study compared ERP markers of face and gaze processing in cases of ASD, ADHD and ASD + ADHD that were individually assessed using screening questionnaires and diagnostic interviews. The disorders were associated with distinct abnormalities: children with ASD showed abnormalities on the face-sensitive N170 component, namely in hemispheric distribution and processing of gaze direction, whereas children with ADHD exhibited a similar response to upright and inverted faces on the latency of earlier P1 component, indicating a reduced effect

Table 2
Correlations between ERP parameters and symptom scores.

ERP	Effect	SCQ	Conners inattention	Conners hyperactivity-impulsivity
P1 latency	Hemisphere	−.16	.02	.01
P1 latency	Gaze	−.09	.01	.03
P1 latency	Orientation	−.03	−.08	−.09
N170 amplitude	Gaze	−.09	.02	.17
N170 amplitude	Hemisphere	−.31**	−.01	−.01

Abbreviations: Conners, Conners third edition parent rating scale short form; ERP, event-related potential; SCQ, social communication questionnaire.
** $p < .01$.

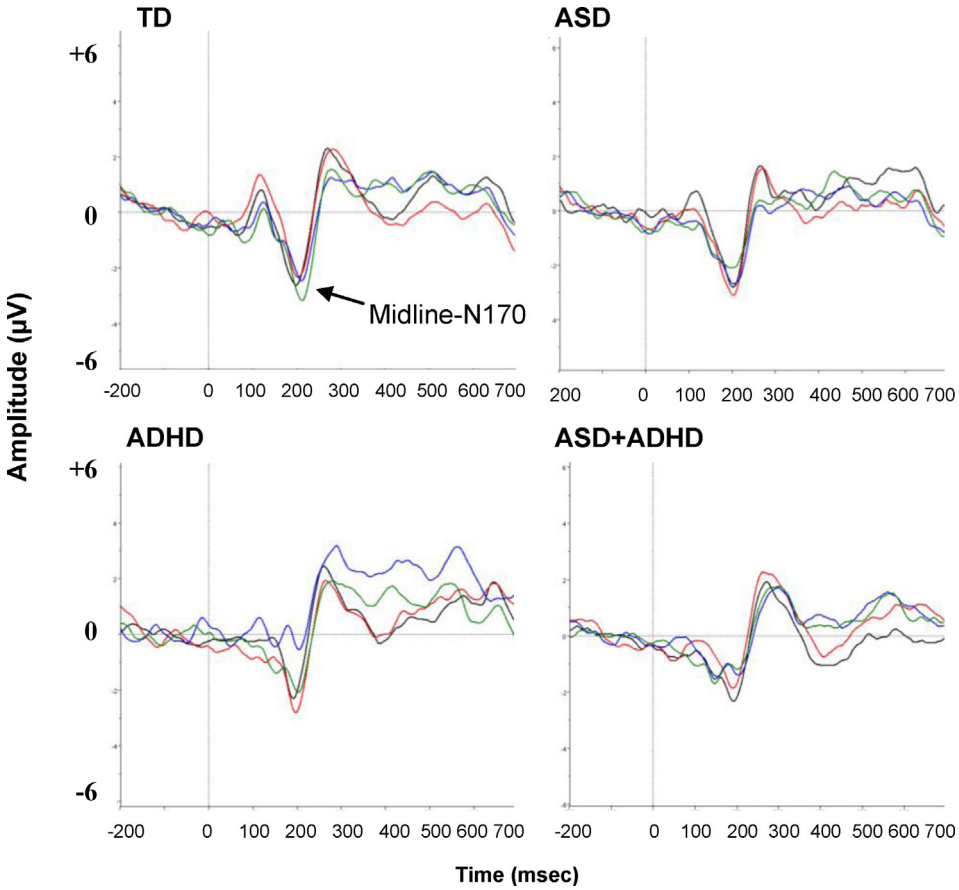

Fig. 6. Grand mean midline-N170 ERPs at Pz to face stimuli for each group and isocontour maps derived for the grand-average at peak latency for each group. Black represents upright-direct, red represents upright-averted; blue represents inverted-direct; green represents inverted-averted.

of face inversion. Children with ASD + ADHD present as an additive condition with the unique deficits of both disorders.

4.1. Face inversion effects

Across all groups, inverted faces elicited delayed P1 (when age was not controlled) and enhanced N170 components, both absolute and peak-to-peak, consistent with previous findings (Bentin et al., 1996; Taylor et al., 2004). This might reflect disruption of configural processing both in early sensory components associated with low-level visual processes (Itier et al., 2007) and later components associated with higher-level category recognition. However, while TD and ASD groups showed delayed P1 latency to inverted faces compared to upright faces, both ADHD groups displayed similar P1 latency across upright and inverted faces. This suggests children with ADHD may not process faces configurally and employ an alternative strategy, although evidence for a featural processing style in ADHD is limited (Booth et al., 2003). As group differences on the inversion effect are shown on the early visual P1 component, deficits in the ADHD group may be sensory or perceptual in nature, although importantly this would not due to visual properties of the stimuli that were identical across conditions. The P1 can also reflect early modulation of top-down attention (Taylor, 2002), which is supported by it's modulation by inversion itself (Doi et al., 2007). Thus an alternative explanation is that typically developing children expect an upright face, whereas in ADHD these predictive/attentive mechanisms do not operate. Reduced amplitude of the P1 has been reported in ADHD toward emotional faces, which correlated with poor emotion recognition (Williams et al., 2008). While previous behavioural and electrophysiological research suggests poor processing of emotional expressions, this effect may not reflect a specific deficit to faces (Dickstein & Castellanos, 2012; Ibanez et al., 2011). Future work should measure responses to a control stimulus with no social value (e.g. a building) incorporated into the design, to examine whether these responses are specific to faces or simply a response to an inverted or incongruous stimulus, reflecting these predictive/attentive deficits. Our findings may suggest comorbid ADHD or core symptoms of ADHD explain the reduced inversion effect previously demonstrated in adults with ASD, although these effects are typically observed for the N170 rather than the P1 (McPartland et al., 2004; Webb et al., 2009). Indeed, most recent behavioural studies have shown an intact inversion effect in ASD (Gross, 2008; Jemel et al., 2006; Lahaie et al.,

2006; Teunisse & de Gelder, 2003). Still, the trend toward a reduced inversion effect on the N170 in the ASD groups may suggest limited power to detect this effect on this component.

4.2. Gaze effects

Several ERP parameters were modulated by gaze direction. Firstly, across all groups averted gaze produced larger P1 (when age was not controlled) and delayed N170 components, suggesting slower and enhanced processing for averted gaze. In addition, the modulation of gaze processing by face orientation on P1 and N170 components suggests gaze direction detection was diminished in inverted faces (Farroni et al., 2004; Itier et al., 2007; Senju et al., 2005a). This supports theories of configural/holistic processing of the face and featural processing of the eyes occurring in parallel (Bentin et al., 1996; Itier et al., 2007). As there was no difference by group on the N170 for the interaction between face orientation and gaze direction, this suggests that gaze direction is mediated by configural processing in all groups. Analyses that controlled for the preceding P1 component, however, revealed differences in the ADHD groups, whereby children with no ADHD diagnosis demonstrated a gaze effect regardless of the orientation of the face, whereas children with ADHD (ADHD/ASD + ADHD) only showed a gaze effect for upright faces. This may suggest that earlier components influence the distinction between processing of these facial features (i.e. gaze effects dependent on face orientation), whereas the ADHD groups show the same effect as absolute N170. The trend toward enhanced P1–N170 peak-to-peak amplitude in the ADHD groups may indicate abnormal enhanced processing of these stimuli, which may occur as a cascading effect from early predictive/attentional processing deficits described above (Williams et al., 2008) and reflect the unanticipated presentation of averted gaze. The social relevance of these responses should be explicitly tested. These findings suggest previous activity may influence components evoked by faces, although shared method variance between P1 and N170 amplitude attributable to the EEG technique rather than a particular construct of interest may be an issue. The lack of an interaction between orientation and gaze at midline regions suggests topographical differences in this effect that should be explored.

Secondly, noteworthy group differences on P1 and N170 responses to gaze direction emerged suggesting specific abnormalities in gaze processing in ASD. In upright faces, participants with ASD diagnosis (ASD and ASD + ADHD) had delayed latency to averted gaze compared to delayed P1 latency to direct gaze in controls. These group differences show a sensitivity to gaze direction in both groups that varied as to which gaze direction they were sensitive to, corresponding to recent fMRI work (Pitskel et al., 2011) and suggests ASD children recruit distinct mechanisms for processing gaze at early sensory processing stages. In addition, enhanced N170 at midline scalp locations to averted gaze shown in TD and ADHD children was absent in children with ASD symptoms. This midline-specific effect is consistent with previous research (Grice et al., 2005), and indicates equivalent processing of direct and averted gaze. Enhanced processing of *averted* gaze, however, is contradictory to some previous findings suggesting faster detection of or enhanced N170 response to direct gaze in typical development, although task differences (behavioural vs. ERP; passive vs. active; front view vs. lateral view; static vs. dynamic gaze shifts (Conty et al., 2007; Senju et al., 2005b) and developmental effects (Elsabbagh et al., 2009a; Watanabe et al., 2002) are likely to underlie these discrepancies. Because averted gaze can be used to infer the locus of attention of others, these findings may signify the increasing importance of and therefore enhanced processing of averted gaze with development, which corresponds with behavioural failure to detect direct gaze in ASD (Klin et al., 2002; Pelphrey et al., 2002; Senju et al., 2005a). Alternatively, this might also imply the use of a different strategy, for example using low level information such as the position of the pupil/iris rather than social cues (Ristic et al., 2005) or deficits in visual attention or perception, supported by consistent sensory processing deficits in ASD (Leekam et al., 2007). Nevertheless, studies support occipito-temporal negative components as modulated specifically by gaze direction as compared to changes in non-facial visual stimuli (Puce et al., 2000).

4.3. Hemispheric effects

Enhanced amplitude of the N170 component in the right hemisphere in control and ADHD children was not shown in ASD groups. Converging with previous work, this suggests reduced or altered neural specialisation of face and gaze processing is specific to children with ASD symptoms (Carver & Dawson, 2002; McCleery et al., 2009; McPartland et al., 2004; Senju et al., 2005b) supported by structural imaging studies (Pierce et al., 2001; Schultz et al., 2000). In addition, this association transcended diagnostic grouping, as supported by correlations with parent-rated symptom scores of ASD. Bilateral scalp activity in response to faces is also shown in younger children, suggesting this effect may indicate delayed development in ASD (Mercure et al., 2009). It is likely, therefore, that individuals with ASD employ alternative face processing strategies that are perhaps more akin to object processing and associated with immature development (Behrmann et al., 2006). This hemispheric effect was reduced to a trend level when the amplitude of the preceding P1 component was controlled for.

4.4. Limitations and considerations

Sample ascertainment is important to consider as a limitation. Firstly, the reallocation of a substantial amount of ASD and ADHD cases raises the possibility that these individuals are unrepresentative of individuals seen at neurodevelopmental clinics. In addition, a greater number of children with ASD were reallocated to the ASD + ADHD group, compared to the number of children with ADHD. This pattern of results is in line with previous work (e.g. Hattori et al., 2006), and may reflect the ASD diagnosis in effect subsuming any secondary diagnoses due to its higher level of severity, leaving in-depth assessment of ADHD 'below the radar', or inflation by less obvious similarities

in the defining features of the disorders, such as idiosyncratic attention–inattention patterns in ASD (Dawson & Lewy, 1989). The comprehensive assessments and stringent criteria employed, however, reduce the likelihood of misspecification in group allocation and other confounding factors (such as additional comorbidity), and extend previous research that failed to include a comorbid group or acknowledge potential comorbidity. The ascertainment process also emphasised unequal group sizes and a relatively small sample size, which limits firm conclusions and necessitates further replication.

The findings reported are dependent on task type. For example, children with ASD can discriminate gaze direction when they are cued or told explicitly to pay attention to gaze (Lopez et al., 2004; Ristic et al., 2005) and therefore the passive nature of the present task may exacerbate the impairment. While participants who did not attend to the task sufficiently were excluded from analysis, it is possible that findings are affected by group differences in face scanning patterns and reduced foveation, and as such this study would benefit from the concurrent recording of eye movements using eye tracking equipment (Dalton et al., 2005; Elsabbagh et al., 2009b). Likewise, there were no task performance parameters for the tasks, thus it is possible that undetected poor attention may impact the results. The identification of aberrant covert processing of social stimuli supports the use of ERP measures, but ideally concurrent behavioural performance should be measured. The lack of behavioural data renders it difficult to make firm conclusions regarding the social nature of the tasks and the ERP components they evoke. For example, a behavioural measure may provide further insight on the nature of the reduced face inversion effect in ADHD.In addition, further research in other groups with ASD would be of interest. Firstly, only males were included in the study and as such a comparison of female patients would be informative, although similar deficits across genders have been found on tasks of social cognition (Lai et al., 2012). Findings also vary depending on autistic severity and therefore studies investigating neural correlates of social cognition should be extended to low-functioning individuals. For example, case-control differences on the N170 when viewing faces with different emotional expressions disappear when the groups are matched by verbal age rather than chronological age (Batty et al., 2011), suggesting findings may be due to a delay in the development of face processing, rather than a deviant trajectory (Jemel et al., 2006).

4.5. Implications

The findings revealed that ASD and ADHD can be dissociated on the basis of ERP abnormalities in the first stages of face processing. A lack of face inversion effects around 100 ms suggests basic face processing impairments in ADHD that may be a consequence of differences in perceptual processing style and/or visual attention deficits. In contrast, specific abnormalities shown in gaze processing and on the "face-sensitive" N170 in ASD are likely to be more relevant to the characteristic social deficits of autism and theories suggesting a lack of interest for the human face from early in development (Jemel et al., 2006), which may then in turn lead to ToM deficits and problems in social interactions (Baron-Cohen, 1995; Dawson et al., 2005). The comorbid ASD + ADHD group demonstrated unique deficits of both disorders, shown by both reduced face inversion effects, altered gaze processing and topographical differences suggestive of an additive condition, and these additive effects held for peak-to-peak analysis. It is possible, therefore, that different subgroups within the autism spectrum have a difficulty with configural processing and these subgroups can be defined by comorbid symptoms of other disorders. As the comorbid group demonstrated the most bilateral distribution of the N170, the sensitivity of ERP correlates of social cognition to ASD may be dependent on the presence of comorbid conditions. An additive model is supported by findings in the same sample reporting specific neural deficits of inhibition and attentional orienting in ADHD and ASD + ADHD that were not shown in ASD-only (Tye et al., unpublished results). These findings converge to suggest the disorders can be dissociated on the basis of inhibitory deficits and gaze processing impairments at the neural level, which is supported by previous behavioural investigations of inhibition and ToM (Ames & White, 2011; Bühler et al., 2011).

5. Conclusion

This study reports novel distinct impairments in face and gaze processing in children with ASD, ADHD and comorbid ASD + ADHD and extends electrophysiological studies of the temporal stages in face and gaze processing. A better understanding of the nature of the comorbid condition is likely to aid in enhanced assessment and treatment of these complex cases, such as early interventions that improve social attention. This supports the adoption of a broader view of psychiatric disorders when examining underlying mechanisms, and warrants systematic assessment of clinical cases to ensure minimal misspecification in group allocation in future research.

Conflict of interest

The authors declare no conflict of interest.

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