NeuroImage: Clinical 7 (2015) 203–212

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Early neural activation during facial affect processing in adolescents with Autism Spectrum Disorder☆

Rachel C. Leung [a,b,*], Elizabeth W. Pang [b,c,d], Daniel Cassel [a], Jessica A. Brian [e,f], Mary Lou Smith [b,d], Margot J. Taylor [a,b,c,d]

[a] Diagnostic Imaging, Hospital for Sick Children, Canada
[b] University of Toronto, Canada
[c] Division of Neurology, Hospital for Sick Children, Canada
[d] Neurosciences and Mental Health Program, Research Institute, Hospital for Sick Children, Canada
[e] Bloorview Research Institute, Holland Bloorview Rehabilitation Hospital, 150 Kilgour Road, Toronto, Canada
[f] Autism Research Unit, Hospital for Sick Children, Canada

ARTICLE INFO

Article history:
Received 6 May 2014
Received in revised form 24 October 2014
Accepted 14 November 2014
Available online 18 November 2014

Keywords:
Implicit face processing
Adolescents
Autism Spectrum Disorder
Magnetoencephalography
Affect processing
Anterior cingulate cortex

ABSTRACT

Impaired social interaction is one of the hallmarks of Autism Spectrum Disorder (ASD). Emotional faces are arguably the most critical visual social stimuli and the ability to perceive, recognize, and interpret emotions is central to social interaction and communication, and subsequently healthy social development. However, our understanding of the neural and cognitive mechanisms underlying emotional face processing in adolescents with ASD is limited. We recruited 48 adolescents, 24 with high functioning ASD and 24 typically developing controls. Participants completed an implicit emotional face processing task in the MEG. We examined spatiotemporal differences in neural activation between the groups during implicit angry and happy face processing. While there were no differences in response latencies between groups across emotions, adolescents with ASD had lower accuracy on the implicit emotional face processing task when the trials included angry faces. MEG data showed atypical neural activity in adolescents with ASD during angry and happy face processing, which included atypical activity in the insula, anterior and posterior cingulate and temporal and orbitofrontal regions. Our findings demonstrate differences in neural activity during happy and angry face processing between adolescents with and without ASD. These differences in activation in social cognitive regions may index the difficulties in face processing and in comprehension of social reward and punishment in the ASD group. Thus, our results suggest that atypical neural activation contributes to impaired affect processing, and thus social cognition, in adolescents with ASD.

1. Introduction

Emotional face processing is an innate and universal ability that is integral to the acquisition of social skills (Ekman & Friesen, 1971; Meltzoff & Moore, 1977). The human face is the most important visual stimulus for human social interactions. The ability to extract the significance of expressive faces is critical for successful social interactions, as it facilitates the understanding of another's mental states and intentions and is important in guiding appropriate reciprocal behaviour. Impaired social functioning is one of the diagnostic hallmarks of Autism Spectrum Disorder (ASD). While it is generally understood that individuals with ASD experience difficulties with social cues, the current literature on emotional face processing in ASD has yielded inconsistent results with some studies finding deficits in emotional processing (e.g., Celani et al., 1999; Eack et al., 2014; García-Villamisar et al., 2010; Golan et al., 2008), with impairment in fear (Ashwin et al., 2007; Howard et al., 2000; Pelphrey et al., 2002), surprise (Baron-Cohen et al., 1993) and anger processing (Kuusikko et al., 2009), while others have noted no deficits (Adolphs et al., 2001; Balconi & Carrera, 2007; Buitelaar et al., 1999; Castelli, 2005; Tracy et al., 2011).

In typical development, emotional face processing is associated with activation in a widespread neural network, encompassing the visual, limbic, temporal, temporoparietal and prefrontal regions (Blair et al., 1999; Fusar-Poli et al., 2009; Phillips et al., 1999; Vuilleumier & Pourtois, 2007). The processing of happy facial expressions implicates a number of structures including the amygdalae, insulae, cingulate, inferior, medial and middle frontal, fusiform and middle temporal areas

☆ Data were previously presented as part of a symposium in the 18th International Conference on Biomagnetism, and as part of posters in the 18th International Conference on Biomagnetism and the International Meeting for Autism Research 2012.

* Corresponding author at: Diagnostic Imaging, Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada. Tel: +416 813 7654x304299.
E-mail address: rachel.leung@sickkids.ca (R.C. Leung).

http://dx.doi.org/10.1016/j.nicl.2014.11.009

(Breiter et al., 1996; Devinsky et al., 1995; Fusar-Poli et al., 2009; García-Villamisar et al., 2010; Hoehl et al., 2010; Kesler-West et al., 2001; Phillips et al., 1998; Thomas et al., 2001). Angry faces elicit cingulate, bilateral fusiform, inferior frontal, superior temporal, middle and medial superior frontal, and orbitofrontal activity (Blair et al., 1999; Devinsky et al., 1995; Fusar-Poli et al., 2009; García-Villamisar et al., 2010; Kesler-West et al., 2001); moreover, decreased activation to angry, relative to neutral, faces has been found in the caudate nucleus, superior temporal, anterior cingulate (ACC), and medial frontal regions (Phillips et al., 1999). While the amygdalae have been widely reported to be involved in threat processing, amygdala activation to angry faces has not been found consistently (e.g., Phillips et al., 1999; Luo et al., 2007; Whalen et al., 2001; but see Fusar-Poli et al., 2009).

Atypical activation of the social brain networks using fMRI during emotional face processing has been found in adults with ASD, including reduced left amygdala and orbitofrontal activation (Ashwin et al., 2007), greater activity in the left superior temporal gyrus and right peristriate visual cortex (Critchley et al., 2000), and reduced fusiform and extrastriate activity, while also showing activation comparable to controls in the anterior cingulate, superior temporal, medial frontal and insula regions (Deeley et al., 2007). Children and adolescents with ASD have shown reduced fusiform but greater precuneus activity during an emotion-matching task, but not during a simpler emotion labelling task (Wang et al., 2004). Collectively, these studies suggest that task demands modulate neural activity during emotional processing to a greater extent in individuals with ASD, and have likely contributed to the discrepant findings in existing literature (Wang et al., 2004).

Of the two major subsystems involved in social cognition, the ventral orbitofrontal-amygdala circuit is of particular relevance to ASD as it is implicated in socio-emotional regulation and behaviour through the processing of others' emotional states, responses and intentions (see Bachevalier & Loveland, 2006, for a review). The orbitofrontal cortex contributes to this subsystem by mediating emotional behaviour, social inhibition, reversal learning and altering of unsuitable behaviour (Blair et al., 1999; Dias et al., 1996; Elliott et al., 2000; Rolls, 2004; Van Honk et al., 2005) as well deriving positive social joy and reward (Britton et al., 2006; Morris & Dolan, 2001). Sharing a close functional and anatomical reciprocal interconnection with the orbitofrontal cortex, atypical activation in the left amygdala during affect processing has been noted in ASD (e.g., Corbett et al., 2009; Critchley et al., 2000). Hence, focusing on the orbitofrontal-amygdala circuit dysfunction may aid in delineating the profile of facial affect processing in ASD.

1.1. The spatiotemporal profile of neural activity during affect processing in ASD

There are few studies on the timing of the neural processing of emotional faces in ASD. ERP studies have noted variously a delay, reduced, or lack of activity in children and adults with ASD, relative to controls (Batty et al., 2011; Dawson et al., 2004; McPartland et al., 2004; O'Connor et al., 2005; Wong et al., 2008). A recent ERP study found that adolescents with ASD failed to show emotion-specific responses that were observed in the typically developing group (Wagner et al., 2013). Further, while face scanning was significantly associated with patterns of neural activation during face processing in typically developing adolescents, no such association was found in ASD (Wagner et al., 2013). Significant impairments in emotion recognition in adult, but not child, faces have also been noted in adolescents with ASD (Lerner et al., 2013). The same study also reported a significant association between the latency of the face-sensitive N170 component, localized to the fusiform gyri and inferior temporal areas, and deficits in emotion recognition in adolescents with ASD.

One study that investigated affective processing in adolescents with ASD using magnetoencephalography (MEG), which provides both timing and more accurate spatial information than EEG studies (Hari et al., 2010), showed reduced early emotion-specific gamma-band power, relative to controls, as well as later decreased power across all emotions (Wright et al., 2012). There do not appear to be other studies that have taken advantage of the spatio-temporal precision of MEG to determine the timing and/or brain regional activation differences in developmental ASD populations with emotional faces.

1.2. Anger processing

While emotional facial expressions of fear and anger both constitute threat-relevant signals, angry faces are more appropriate than fearful faces for investigating emotional face processing in ASD. Processing of anger requires the understanding of social norms and context, topics with which individuals with ASD struggle (Berkowitz, 1999; Zeman & Garber, 1996). Angry facial expressions are also more likely to be produced in response to repeated aggravations rather than first-time behavioural transgressions (Averill, 1982). Given that individuals with ASD are often poor at recognizing others' mental states or social norms, they have likely encountered displays of anger without understanding the implications (Bal et al., 2010; Baron-Cohen et al., 1999; Begeer et al., 2006). Past studies have specifically noted atypical angry facial processing in individuals with ASD (Ashwin et al., 2006; Kuusikko et al., 2009; Rieff et al., 2007; Rump et al., 2009). Age-effects in anger processing have also been noted, as older children and adolescents are able to correctly identify angry faces more often than younger children, regardless of diagnosis (Lindner & Rosén, 2006). There are also sharp increases in anger-specific sensitivity from adolescence to adulthood, providing support for a later maturation of anger processing (Thomas et al., 2007).

An fMRI study contrasting activations elicited by fear and anger in typical individuals showed that while both emotions activated a network of regions similarly, including the amygdalae and insulae, anger specifically elicited neural activation in a wider set of regions including the ventromedial prefrontal cortex and the posterior orbitofrontal cortex (Pichon et al., 2009). These areas have been implicated in behavioural regulation, supporting the idea that anger processing requires more resources and contextual information to adjust behaviour accordingly (Pichon et al., 2009).

1.3. Happiness processing in ASD

Happiness is the only one of the six basic emotions that is definitely positive and is the first emotion to be accurately identified in early development (Markham & Adams, 1992). Seemingly typical processing of happy affect in individuals with ASD has been observed, which may be due to the greater frequency of encountering and hence greater familiarity with happy faces (Critchley et al., 2000; Farran et al., 2011). However, while happy faces are socially rewarding for typically developing individuals (Phillips et al., 1998), insensitivity towards social reward derived from happy faces has been shown in individuals with ASD (Sepeta et al., 2012). Hence, it is important to investigate the underlying neural processes involved in the processing of happy faces in ASD to determine whether social reward systems are appropriately activated.

1.4. Adolescence

In typically developing individuals, recognition of emotional face expressions follows a protracted developmental trajectory that extends into late adolescence (e.g., Batty & Taylor, 2006; Kolb et al., 1992). Asynchronous development of emotion recognition is well established (De Sonneville et al., 2002; Pichon et al., 2009) and neuroimaging findings have demonstrated the shifting involvement of different neural networks over the course of development (Hung et al., 2012; Killgore & Yurgelun-Todd, 2007; Monk et al., 2003; Thomas et al., 2001). At around 11 years of age emotional processing abilities undergo marked improvement, which would implicate greater demands on neural

processes involved in emotional processing in early adolescence (Tonks et al., 2007).

There are few studies on emotional face processing in adolescents with ASD, representing a serious gap in the literature, as adolescence is a period of vulnerability, volatility and increased stress (Spear, 2000) during which the prevalence of negative emotions peaks and shows greater variability (Compas et al., 1995; Hare et al., 2008). Behavioural studies investigating emotional face processing in adolescents with ASD have shown affective processing comparable to controls (Grossman et al., 2000; Rieffe et al., 2007). Adolescents with ASD in these studies showed deficits in decoding emotions from static and dynamic facial affect overall, and, although they have been shown to identify specific emotions (Rump et al., 2009) such as happiness and sadness readily, they have difficulties with more complex emotions such as embarrassment (Capps et al., 1992) and identifying emotions when shown videos (Koning & Magill-Evans, 2001). Individuals with Asperger Syndrome but not high-functioning autism have shown intact emotion perception (Mazefsky & Oswald, 2007).

Adults with ASD continue to experience difficulties when presented with brief or subtle emotions, and may never reach the same level of competency in emotional processing as typically developing adults (Begeer et al., 2006; Rieffe et al., 2007). The impairment in emotional processing in adults with ASD is consistent with the notion that individuals with ASD require compensatory strategies to achieve average performance. Although competency with emotional recognition in ASD improves with age, this skill often plateaus at a performance level below that of typically developing peers, or is associated with atypical brain activations to achieve comparable performance levels. These results underscore the need to examine the adolescent period of emotional processing in ASD to obtain a clearer understanding of the emotional development in this population.

Thus, the present study explored the neural substrates of implicit emotional face processing in adolescents with ASD using MEG, providing both temporal and spatial measures of brain processes, focusing on the neural areas implicated in emotional processing. We hypothesized that adolescents with ASD would show (1) shorter response latencies to emotional faces as they are not distracted by the emotions and (2) reduced and delayed patterns of neural activation in the frontal, limbic and temporal areas, key constituents of the social brain.

2. Materials and methods

2.1. Participants

Twenty-four adolescents (age range = 12–15 years) diagnosed with ASD (20 males, 14.03 ± 1.20 years, 23 right-handed, 7 medicated, IQ = 90.79 ± 23.76) and 24 healthy controls (19 males, 14.27 ± 1.12 years, 23 right-handed, IQ = 110.04 ± 12.21) were recruited. Participants in the clinical group had a diagnosis of ASD, informed by the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 2000), or Autism Diagnostic Observation Schedule-2 (ADOS-2; Rutter et al., 2012), and confirmed by expert clinical judgment. Exclusion criteria for both groups included a history of neurological or neurodevelopment disorders (other than ASD for participants in the clinical group), acquired brain injury, uncorrected vision, colour blindness, IQ ≤ 65 and standard contraindications to MEG and MRI. Use of psychotropic medications was an exclusion criterion for control participants only, due to difficulty in recruiting medication-naïve adolescents with ASD. Seven participants with ASD were on medication, which included Bicentin, Celexa, Cipralex, Concerta, Gabapentin, Ritalin, Seroquel, Strattera and Zeldox. The study was approved by The Hospital for Sick Children Research Ethics Board and written informed consent was obtained from all participants and their legal guardians.

2.2. Characterization measures

2.2.1. Autism Diagnostic Observation Schedule

The ADOS-G (Lord et al., 2000) and ADOS-2 (Rutter et al., 2012) are semi-structured clinical assessments for diagnosing and assessing ASD. Research-reliable team members administered either module 3 or module 4 of the ADOS-G or ADOS-2 to all eligible participants with ASD. The mean and standard deviation of total scores (ADOS and ADOS-2 pooled) were 11.30 ± 3.30, which was well above the clinical threshold.

2.2.2. Wechsler Abbreviated Scales of Intelligence (WASI)

IQ was estimated using two subtests (vocabulary and matrix reasoning) of the Wechsler Abbreviated Scale of Intelligence (WASI-2; Wechsler, 2002). The two-subtest WASI-2 takes a shorter time to complete and has comparable validity to the full WASI-2.

2.3. MEG task

The task stimuli consisted of a face (happy, angry or neutral) presented concurrently with a scrambled pattern, each on either side of a central fixation cross (Fig. 1). Twenty-five colour photographs of different faces (13 males, 12 females) for each of the three expressions were selected from the NimStim Set of Facial Expressions; only happy and angry faces correctly categorized at a minimum of 80% accuracy were selected (Tottenham et al., 2009). To create unique scrambled patterns corresponding to each face, each of the selected faces from the NimStim set was divided into 64 cells and randomized. A mosaic was applied to the image (15 cells per square) after which a Gaussian blur was applied (10.0°) using Adobe Photoshop. Face–pattern pairs were matched for luminosity and colour.

Fifty trials of each of the three expressions in the left and right hemifields (each face was presented twice in each hemifield) were shown in randomized order such that the task included 300 trials in total. Emotions were irrelevant to the task as participants were instructed to fixate on the central cross and respond to the location of the scrambled pattern by pressing left or right buttons on a button box. Stimuli were presented using *Presentation* (http://www.neurobs.com/). Stimuli in each trial were presented for 80 ms with an ISI varying from 1300 to 1500 ms. Images were back-projected through a set of mirrors onto a screen positioned at a viewing distance of 79 cm. The visual angle of the stimuli was 6.9° and fell within the parafoveal region of view. Response latency was recorded for each trial. All participants performed the task in the MEG, following a practice session outside the MEG such that they were familiar with and understood the task.

2.4. Neuroimaging data acquisition

MEG data were recorded using a 151-channel CTF MEG system (MISL, Coquitlam, BC, Canada) at a 600 Hz sampling rate in a magnetically shielded room at the Hospital for Sick Children. A third order spatial gradient was used to improve signal quality with a recording bandpass of 0–150 Hz. All participants lay in a supine position with their head in the MEG dewar while they completed the experimental paradigm. Fiducial coils were placed on the left and right pre-auricular points and the nasion to monitor head position and movement within the dewar. These were replaced by radio-opaque markers for MRI co-registration. Each adolescent 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, 256 × 256 matrix, 192 slices, slice thickness = 1.0 mm isotropic voxels) obtained from a 3T MR scanner (MAGNETOM Tim Trio, Siemens AG, Erlangen, Germany), with a 12-channel head coil. Unique inner skull surfaces were derived using FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) from each MR image and multi-sphere head models were fit to this surface (Lalancette et al., 2011).

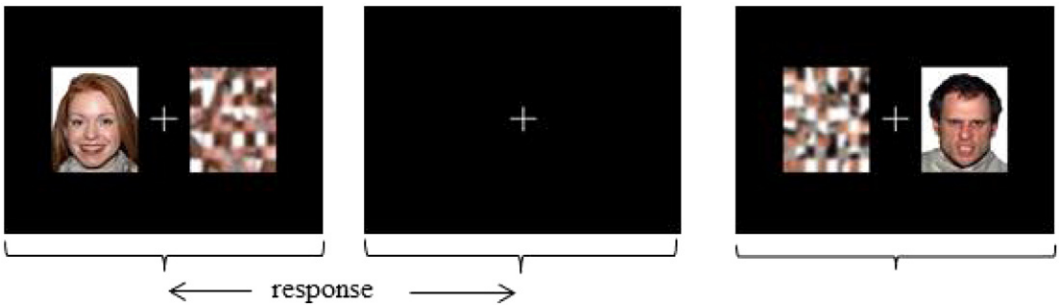

Fig. 1. Implicit emotional face processing task. A scrambled pattern (target) is randomly located in either left or right hemifield and presented concurrently with an emotional (happy, angry or neutral) face in the other hemifield with a fixation cross in the center. Participants were instructed to press a button corresponding to the side of the target (scrambled pattern) on a response button box. To minimize any saccades during the trials, stimuli were presented for 80 ms; the inter-stimulus interval varied between 1300 and 1500 ms.

2.5. Behavioural analyses

Group effects in IQ, response accuracy and response latencies across emotions were assessed using SPSS 20.0 software (SPSS Inc., Chicago, IL). Repeated measures ANCOVAs, with IQ as a covariate, were conducted to examine group (ASD vs. control) and emotion (angry vs. happy) effects.

2.6. Neuroimaging analyses

MEG activity was filtered off-line with a fourth order Butterworth filter with a bandpass of 1–30 Hz. MEG trials were epoched into 650 ms time windows with a 150 ms pre-stimulus baseline. Data were time-locked to trial onset and averaged by emotion type across subjects. Continuous head localization recording allowed us to manually exclude trials with head movement exceeding 10 mm (relative to median head position) using software developed in-house. Artefacts in MEG data were rejected using independent component analysis (ICA; EEGlab, http://www.sccn.ucsd.edu/eeglab), which allowed for the removal of eye and heart artefacts from the data while preserving neural activity of interest. Thirty components were examined for artefacts; there was no between-group difference in the number of components removed (ASD: 2.1 ± 1.2, Controls $= 1.5 \pm 1.3$), $t(23) = 1.55$, $p = 0.13$.

Activation sources for each emotion were estimated using an event-related vector beamforming (ERB) method (Quraan et al., 2011) developed in-house from 50 to 400 ms, using sliding time windows of 50 ms in duration, overlapping by 25 ms (e.g., 50–100, 75–125 ms) for a total of 13 time windows. To beamform the ICA-cleaned data, the covariance matrix for each subject was regularized by the smallest non-zero eigenvalue (Fatima et al., 2013; Lancaster et al., 2000). Beamformer images with a spatial resolution of 5 mm were normalized to a template using Advanced Normalization Tools (ANTS; http://picsl.upenn.edu/software/ants/).

While neutral faces were originally intended as emotional baselines, the 'emotional neutrality' of neutral faces has been subject to debate given their ambiguity and tendency to be misinterpreted, especially in children (Carrera-Levillain & Fernandez-Dols, 1994; Lobaugh et al., 2006; Thomas et al., 2001). In light of similar findings in individuals with ASD, who have recently been shown to misinterpret neutral faces and assign negative valence to emotionally neutral faces (Eack et al., 2014), we chose not to use neutral faces as an emotional baseline. Instead, two-sample unpaired non-parametric random permutation tests ($p < 0.05$, Sidak-corrected for multiple comparisons, 10,000 permutations) were conducted on beamformer images to determine significant differences between group activity to happy and angry emotions. Non-parametric random permutation tests determine whether the sample means from two groups, in this case, ASD and controls, are from the same distribution, with the null hypothesis being that the two groups do come from the same distributions. The distribution of the test statistic under the null hypothesis is obtained by calculating all possible values of the test statistic by rearranging membership of participants' voxel values; the difference in sample means is calculated and recorded for many re-shufflings of group membership. The set of these calculated differences makes up a distribution of possible differences under the null hypothesis. The null hypothesis is rejected if the observed test value falls within the alpha level ($\alpha = 0.05$).

Analysis of Functional Neuroimages (AFNI; Cox, 1996) was used to visualize images and in-house developed software was used to identify peak activity. To investigate between-group differences in the timing of emotion-related neural activation, the time courses of significant areas of peak activity identified from the average contrasts were computed. Two-sample non-parametric permutation tests ($p < 0.05$, Sidak-corrected, 10,000 permutations) were conducted on each normalized time point (pseudo-Z) to identify emotion-relevant between-group differences in neural activity across time. Lastly, MRIcron software (Rorden, 2012) was used to create 3D renderings of between group activations on spatially normalized brain images.

3. Results

3.1. Behavioural results

3.1.1. IQ

The 2-sub-test IQ scores were significantly lower in adolescents with ASD ($M = 90.79$, $SD = 23.76$) than in controls ($M = 110.04$, $SD = 12.21$), $t(46) = -3.53$, $p = 0.001$.

3.1.2. Accuracy

A 2 (emotion: happy, angry) × 2 (group: ASD, controls) repeated measures ANCOVA with IQ as a covariate showed a between-group effect on accuracy, $F(1, 42) = 4.32$, $p = 0.04$. Follow-up ANCOVAs revealed lower accuracy in responses (proportion correct) to angry faces (ASD: $M = 0.87$, $SD = 0.10$; Controls: $M = 0.95$, $SD = 0.04$; $F(1, 42) = 5.53$, $p = 0.02$). No other significant effects or interactions were found.

3.1.3. Response latency

A 2 (emotion: happy, angry) × 2 (group: ASD, controls) ANCOVA with IQ as a covariate showed no main or interaction effects on response latency.

3.2. MEG results: time course and source localization of neural activity

Significant between-group activations for happy and angry faces ($p < 0.05$, two-tailed, Sidak-corrected for multiple comparisons, 10,000 permutations) are listed in Table 1.

3.2.1. Angry

Apart from earlier and larger orbitofrontal activation in controls (75–125 ms; Fig. 2A), relative to adolescents with ASD, the other early activations (50–175 ms) in the presence of angry faces were all larger in the ASD group. These activations were lateralized to the left hemisphere, including the inferior frontal, inferior parietal and particularly

Table 1
MNI coordinates and pseudo-Z values for locations of significant ($p < 0.05$, Sidak-corrected, two-tailed, 10,000 permutations) peak activations for adolescents with ASD and controls in response to a) angry and b) happy faces. 'C > A' denotes less activation in the ASD group. 'A > C' denotes greater activation in the ASD group.

Time	Directionality	Laterality	Label	MNI (x, y, z)	PseudoZ
A) Angry					
50–100	A > C	Left	Middle temporal	−66 −62 −3	0.26915
75–125	C > A	Left	Orbital	−21 63 −13	−0.19609
100–150	A > C	Left	Middle temporal	−41 −62 17	0.51194
		Left	Inferior temporal	−61 −57 −8	0.3918
125–175	A > C	Left	Middle temporal	−51 −527	0.46754
		Left	Inferior parietal lobule	−36 −77 47	0.36086
		Left	Inferior frontal	−56 13 2	0.34214
150–200	C > A	Right	Supramarginal	64 −27 37	−0.37792
200–250	C > A	Right	Inferior temporal	59 −52 −23	−0.65202
		Right	Supramarginal	64 −22 22	−0.54374
		Left	Orbital	−36 58 −18	−0.33306
		Left	Middle frontal	−36 23 37	−0.32241
		Left	Frontal	−21 68 12	−0.23263
		Right	Orbital	14 43 −28	−0.22281
		Left	Inferior frontal	−46 23 17	−0.22192
225–275	C > A	Left	ACC	−11 18 37	−0.34908
		Left	Orbital	−11 33 −23	−0.28874
		Right	Middle frontal	24 43 32	−0.27495
250–300	C > A	Right	Middle temporal	59 −67 12	−0.72073
		Right	Middle frontal	49 33 32	−0.37361
		Left	Middle frontal	−36 58 12	−0.27187
		Right	Superior medial frontal	9 58 17	−0.26903
275–325	A > C	Left	Inferior parietal lobule	−51 −62 42	0.44563
300–350	C > A	Right	Middle temporal	59 −67 2	−0.46734
		Right	Inferior parietal lobule	59 −57 42	−0.36487
		Right	Superior medial frontal	9 53 42	−0.28971
325–375	C > A	Right	PCC	−1 −27 27	−0.44271
350–400	A > C	Left	Middle temporal	−66 −7 −3	0.30618
B) Happy					
50–100	C > A	Right	Lingual	29 −92 −13	−0.22022
75–125	A > C	Left	Middle temporal	−56 −37 −13	0.23831
100–150	A > C	Left	Middle temporal	−41 −62 22	0.51573
	A > C	Left	Angular	−41 −72 42	0.41101
	C > A	Left	Superior medial frontal	−1 53 22	−0.28468
		Right	ACC		
125–175	A > C	Left	Angular	−51 −77 37	0.38497
	A > C	Left	Middle temporal	−66 −7 −23	0.28924
150–200	A > C	Left	Supramarginal	−61 −27 42	0.32369
	C > A	Right	Inferior temporal	64 −32 −28	−0.52298
	C > A	Right	Supramarginal	69 −37 27	−0.49436
	C > A	Left	Orbital	−11 58 −28	−0.25784
175–225	C > A	Right	Inferior temporal	59 −52 −23	−0.45881
200–250	C > A	Right	Inferior temporal	59 −57 −18	−0.66925
		Right	Precuneus/PCC	4 −47 17	−0.43326
		Right	Superior frontal	14 53 37	−0.31553
225–275	C > A	Right	Angular	64 −57 27	−0.59196
		Right	Middle temporal	69 −37 −13	−0.43618
250–300	C > A	Right	Inferior temporal	59 −67 −3	−0.62755
		Right	Angular	59 −67 27	−0.59687
		Right	Middle frontal	49 13 42	−0.37255
		Right	Inferior frontal	44 38 12	−0.29916
275–325	A > C	Left	Inferior temporal	−61 −22 −23	0.31107
	C > A	Right	Angular	39 −67 52	−0.46264
300–350	C > A	Right	Fusiform	24 −82 −13	−0.42226
		Right	Superior medial frontal	9 68 17	−0.26521
350–400	C > A	Right	Inferior temporal	59 −42 −23	−0.45328
		Right	PCC	4 −37 22	−0.38185
		Left	Insula	−26 −32 22	−0.31002
		Right	Superior frontal	19 33 52	−0.28764

the middle temporal areas. These latter two regions also showed greater activation in the ASD group later in the time-course: inferior parietal (275–325 ms) and middle temporal (350–400 ms) gyri. Otherwise to angry faces, there was significantly greater activity in the typically developing adolescents from 150 to 375 ms, involving the bilateral middle and orbital frontal areas, right middle temporal (250–350 ms), left ACC (225–275 ms; Fig. 2B), as well as right inferior temporal and supramarginal gyri (200–250 ms), and right posterior cingulate (325–375 ms; Fig. 2C).

3.2.2. Happy

To happy faces, the adolescents with ASD again showed early left-sided activity in the left middle temporal area (75–175 ms), and left angular (100–175 ms) and supramarginal gyri (150–200 ms). The left inferior temporal region also showed greater activation (275–325 ms) in the ASD group. Otherwise, there was extensive, greater activity in the control adolescents, almost entirely in the right hemisphere. The right inferior temporal gyrus showed sustained greater activity from 150 to 400 ms, with the middle temporal region more active from 225 to

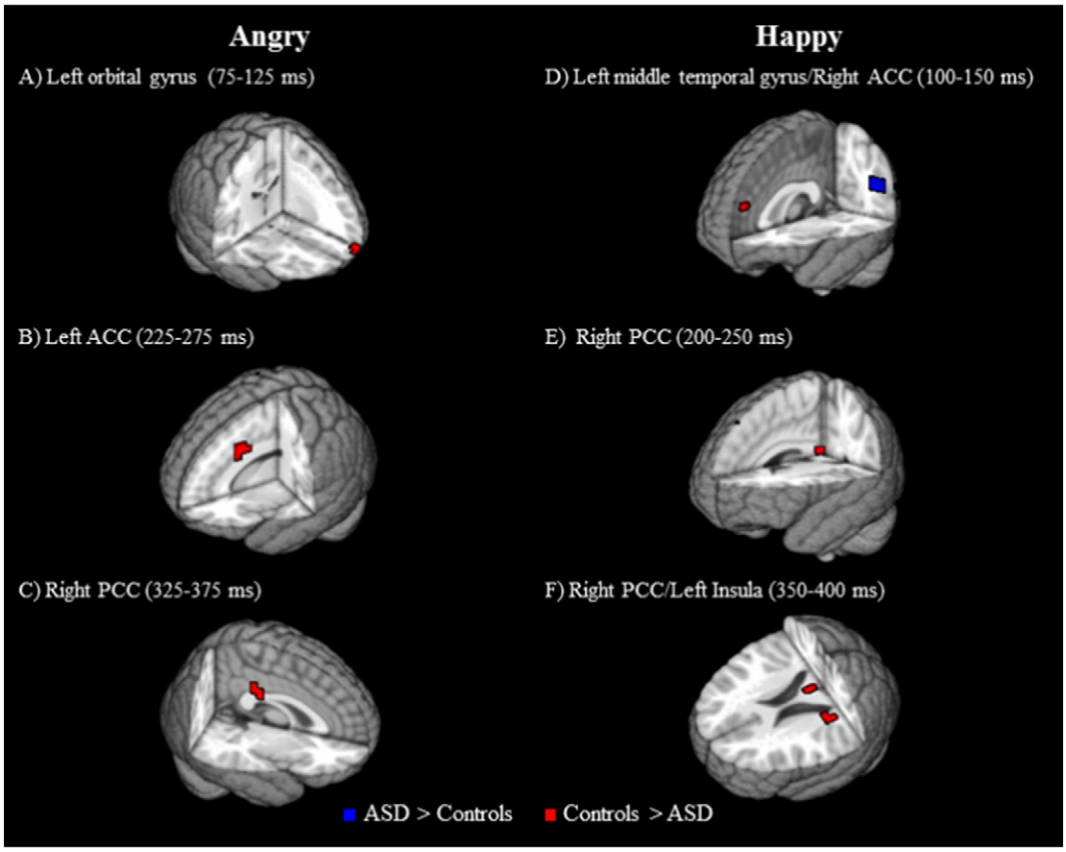

Fig. 2. Source localization of significant between-group differences. Blue indicates areas where ASD showed significantly greater activation than the control group, and red indicates areas where ASD showed less activation relative to the control group. ACC = anterior cingulate cortex; PCC = posterior cingulate cortex.

275 ms. To the happy faces, controls also had greater activity than the ASD group in the right ACC (100–150 ms; Fig. 2D), supramarginal (150–200 ms) and angular (225–325 ms) gyri, in the superior, middle and inferior frontal areas between 200 and 400 ms, all in the right hemisphere, and in the right PCC (200–250 ms; 350–400 ms; Fig. 2E, Fig. 2F). The only left hemisphere regions with greater activation in the controls were in the left superior medial (100–150 ms) and orbital frontal cortices (150–200 ms) and in the left insula (350–400 ms; Fig. 2F).

4. Discussion

The present study examined neural activity during emotional face processing in adolescents with ASD compared to typically developing adolescents using MEG. This approach allowed us to determine both the timing and spatial localization of ongoing brain activity. Behavioural analyses showed poorer anger-specific accuracy in ASD, while neuroimaging analyses revealed atypical recruitment of neural regions in ASD during angry and happy face processing.

4.1. Behavioural results

While there were no significant between- or within-group differences in response latency, adolescents with ASD showed significantly lower accuracy, relative to controls, on trials with angry faces only. Despite poorer accuracy, however, the absence of significant between-group differences in response latencies indicates a lack of attentional bias across emotions or groups. A deficit in anger processing corroborates previous findings, as young individuals with ASD have been shown to make significantly more errors in identifying angry faces and also to mislabel faces with ambiguous emotions as angry more frequently than controls (Kuusikko et al., 2009; Philip et al., 2010). A lack of difference in response latency, despite poorer anger-specific accuracy, shows comparable subjective experiences of task difficulty between groups in processing the two emotions. Hence, our behavioural findings are consistent with the concept that social difficulties experienced by individuals with ASD may be, in part, attributable to the inaccurate perception or interpretation of other individuals' facial expressions.

4.2. Neuroimaging

Our MEG findings demonstrate a complex progression of both over- and under-activation in the frontal, temporal, tempo-parietal, and limbic brain regions. Of particular interest was the abnormal neural activity in areas of the 'social brain', which encompass the ACC and orbitofrontal cortex (Brothers, 2002). The network of neural areas showing atypical activation is consistent with the model of anomalous long-range projections and the subsequent recruitment of greater processing networks in ASD (Courchesne & Pierce, 2005; Just et al., 2004). While typically developing individuals successfully integrate and coordinate multiple cognitive domains within a network of neural structures, our data suggest that individuals with ASD have deficits in the recruitment of comparable brain regions, including the orbitofrontal, limbic, and temporal regions, which impact their abilities with facial affect processing.

4.2.1. Atypical cingulate activation: delayed functional specialization of threat-relevant affective processing in ASD

Adolescents with ASD showed reduced left ACC and late right posterior cingulate (PCC) activation to angry faces and early right ACC and PCC underactivation to happy faces. The cingulate gyrus is functionally and cytoarchitecturally heterogeneous, with the anterior and posterior regions reciprocally connected with different regions of the brain (see Vogt et al., 1992 for a review). Classically, the cingulate gyrus is divided into the ACC and PCC, with the former linked to executive functioning,

including affective processing, and the latter associated with evaluative processes (Vogt et al., 1992).

In ASD structural, functional and cyto-architectural idiosyncrasies of the ACC have been reported (e.g., Haznedar et al., 1997; Simms et al., 2009). In typically developing children, a shift from only the amygdala to the amygdala and ACC activity during threat-relevant affect processing has been shown, with children utilizing the earlier-developing subcortical structures involving the amygdala and adolescents employing the later maturing functionally specialized cortical route that includes the ACC (Hung et al., 2012). Our data showing consistently reduced ACC activation in ASD is congruent with the notion of immature processing of angry faces in adolescents with ASD, relative to their typically developing peers.

Interestingly, decreased right PCC activation in ASD was noted only to happy faces. As a canonical 'evaluative' region, the PCC is implicated in monitoring and assessing the external environment (Vogt et al., 1992). In typically developing children increased PCC activity to both happy and fearful faces relative to a non-emotional cognitive task has been noted (Habel et al., 2005). Reduced activation in the PCC in adolescents with ASD suggests its inadequate recruitment and, is in line with overall limbic underactivation in ASD.

4.2.2. Orbitofrontal underactivation in ASD to angry faces

Adolescents with ASD showed less orbitofrontal activity first in the left orbitofrontal area and then bilaterally compared to controls in response to angry faces. Closely connected to the amygdala, insula and ACC, the orbitofrontal cortex has been implicated in social inhibition and behaviour mediation (Blair et al., 1999; Dias et al., 1996; Elliott et al., 2000; Rolls, 2004; Van Honk et al., 2005). Insensitivity to both punishment and reward and emotion dysregulation has been observed following orbitofrontal damage (Berlin et al., 2004). Furthermore, the orbitofrontal cortex has been implicated in associating stimuli with behavioural outcome, which is integral for outcome predictions for adaptive behaviour (see Rushworth et al., 2007 for a review) as well as inferring others' emotional states (Baron-Cohen et al., 1999). Impairments in representing and associating outcome expectations with aversive stimuli could result in failure to plan and adjust future behaviour. In light of these findings, our observations of orbitofrontal underactivation to angry faces in ASD suggest that atypical integration of information concerning punishment, and difficulty deriving social averseness from angry faces, could contribute to social impairment in ASD. This is consistent with observations that anger processing recruits additional neural areas, supporting the idea that anger requires more resources and contextual information to respond appropriately (Lindner & Rosén, 2006; Pichon et al., 2009). It is interesting to note a lack of orbitofrontal activity differences between adolescents with and without ASD to happy faces, which may be due to reduced need for behavioural adaptation, and mediation following perception of positive emotion. This contrast may explain why adolescents with ASD, with their reduced processing of angry faces, show difficulties in recognizing and interpreting anger.

4.2.3. Atypical angular gyrus activation in ASD to happy faces

The angular gyrus is a multi-modal hub that is implicated in a variety of functions, including playing a key role in mentalizing and social cognition (see Seghier, 2013 for a review). This model of the angular gyrus as a central hub of information processing coupled with our findings of atypical angular gyrus activation in ASD suggests a deficit in integrating and coordinating multiple cognitive domains, which manifests in affective processing difficulties. In adolescents with ASD, early left angular over-activation was followed by subsequent underactivation to happy faces, relative to controls. Left angular activation in controls to happy faces versus non-emotional stimuli (Habel et al., 2005) or neutral faces (Trautmann et al., 2009) has been observed, an effect that was not seen when shown negative faces. Angular gyrus activation for happy faces specifically is consistent with our data as there were differences in angular gyrus activation between adolescents with and without ASD to happy faces only.

4.2.4. Lateralization of atypical temporal activation in ASD

Temporal lobe areas are implicated in face processing and visuospatial processing (see Haxby et al., 2000 for a review). In response to viewing angry faces, a pattern of overactivation in the left middle and inferior temporal regions in ASD was noted, as well as underactivation in the right homologous temporal areas. Group effects in laterality were also seen in response to happy faces, with greater left superior, middle, and inferior temporal activation in ASD while the controls showed greater right inferior and middle temporal activation.

Cortical lateralization for specific types of information processing is often seen, such as language and visuo-spatial specialization in the left and right hemispheres, respectively. Stemming from lesion, electrophysiological and neuroimaging findings, the right hemisphere model/hypothesis of emotional processing posits a right cortical specialization for emotional processing (e.g., McLaren & Bryson, 1987), in contrast to a valence-specific bias, where implicit emotional processing in particular has hemispheric lateralization with the right hemisphere dominant for negative emotions (e.g., Sato & Aoki, 2006). A meta-analysis favoured the notion of a complex 'emotional brain' that encompasses bilateral neural regions (Demaree et al., 2005; Fusar-Poli et al., 2009) and other papers have also shown that the two models need to be considered (Smith & Bulman-Fleming, 2005). Few studies have investigated cortical specialization during emotional processing in ASD. Children with and without ASD have shown comparable right hemispheric advantage for perception of emotional expression of prosody (Baker et al., 2010). Adults with ASD showed a left visual field bias for affective faces, similarly to controls, but also showed a left visual bias in non-social conditions and on a task judging facial identity, which was not observed in controls (Ashwin et al., 2005). Our findings of consistently greater left hemisphere activity and reduced right activation in the temporal regions to affective faces in ASD suggest that their difficulties in affective processing may be attributable to increased left hemispheric lateralization at the expense of typical right hemispheric or bilateral processing.

Lastly, reduced right inferior temporal activation to happy faces was noted from 150 to 250 ms, in the time window associated with the M170/N170, a component typically showing greater amplitudes in the right hemisphere, sensitive to face processing and facial affect (Batty & Taylor, 2003; Bentin et al., 1996; Hung et al., 2010). Thus, these results suggest that atypical processing during this time window may contribute to impairments in processing happy faces in adolescents with ASD.

4.2.5. Left insula underactivation in ASD to happy faces

The insulae, well connected to other limbic structures such as the amygdalae and the orbitofrontal cortices, are activated in response to a range of emotional processes (Duerden et al., 2013; Fusar-Poli et al., 2009; Sprengelmeyer et al., 1998). Given the key role of the insulae in emotional processing, left insula under-activation to happy faces in adolescents with ASD is consistent with the insensitivity towards social reward derived from happy faces shown in individuals with ASD. This highlights that despite the relative ease with which happy expressions are recognized in individuals with ASD, cognitive mechanisms underlying happy face processing in ASD remain impaired (Farran et al., 2011), and corroborates findings of social reward deficits as the insulae have extensive effective connectivity with the nucleus accumbens, a vital structure involved in reward processing (Breiter et al., 2001; Craig, 2003; Menon & Levitin, 2005).

4.2.6. Conclusions

The present study demonstrated differences in the spatiotemporal properties of neural activity during happy and angry face processing in adolescents with ASD. Our findings show discrepant neural recruitment patterns in adolescents with ASD, particularly in their failure to adequately integrate frontal, temporal, tempo-parietal and limbic

brain regions into the facial affect processing network. These results suggest that impairments in face processing and possible deficits in appreciating social reward and punishment from positive and negative faces, respectively, may play a role in facial affect processing deficits in adolescents with ASD.

As the period of adolescence is accompanied by marked affective changes, a peak in the prevalence of negative emotional states, and heightened and more variable emotional responses, future longitudinal studies examining the neural networks recruited during emotional face processing in clinical child and adult populations can determine if these group differences increase or decrease from childhood through adolescence and into adulthood (Compas et al., 1995; Hare et al., 2008). Such findings will be critical to understanding when in development this skill acquisition is disturbed. Characterizing the developmental trajectory of emotional face processing in ASD will ultimately contribute to the understanding of the processes that underlie social impairment in ASD.

Acknowledgements

Rachel Leung was supported through a studentship, fully or in part, by the Matching Funds Program Hospital for Sick Children Foundation Student Scholarship Program.

This study was supported by a Canadian Institutes of Health Research grant (MOP-119541) to M.J.T and E.W.P.

The authors would like to thank Marc Lalancette, Tammy Rayner and Ruth Weiss for their assistance with data collection and/or analyses, Heather Leckey and Becky Baatjes for their assistance with ADOS administration, and Rina Goukon, Jane Kouptsova, Tamara Powell, Anjili Vara and Vanessa Vogan for their assistance with data collection.

References

Adolphs, R., Sears, L., Piven, J., 2001. Abnormal processing of social information from faces in autism. J. Cogn. Neurosci. 13 (2), 232–240. http://dx.doi.org/10.1162/089892901564289112445 48.

Ashwin, C., Baron-Cohen, S., Wheelwright, S., O'Riordan, M., Bullmore, E.T., 2007. Differential activation of the amygdala and the 'social brain' during fearful face-processing in Asperger syndrome. Neuropsychologia 45 (1), 2–14. http://dx.doi.org/10.1016/j.neuropsychologia.2006.04.01416806312.

Ashwin, C., Chapman, E., Colle, L., Baron-Cohen, S., 2006. Impaired recognition of negative basic emotions in autism: a test of the amygdala theory. Soc. Neurosci. 1 (3–4), 349–363. http://dx.doi.org/10.1080/17470910601040772186337 99.

Ashwin, C., Wheelwright, S., Baron-Cohen, S., 2005. Laterality biases to chimeric faces in Asperger syndrome: what is 'right' about face-processing? J. Autism Dev. Disord. 35 (2), 183–196. http://dx.doi.org/10.1007/s10803-004-1997-315909405.

Averill, J.R., 1982. Anger and Aggression: An Essay on Emotion. Springer-Verlag, New York.

Bachevalier, J., Loveland, K.A., 2006. The orbitofrontal–amygdala circuit and self-regulation of social–emotional behavior in autism. Neurosci. Biobehav. Rev. 30 (1), 97–117. http://dx.doi.org/10.1016/j.neubiorev.2005.07.00216157377.

Baker, K.F., Montgomery, A.A., Abramson, R., 2010. Brief report: perception and lateralization of spoken emotion by youths with high-functioning forms of autism. J. Autism. Dev. Disord. 40 (1), 123–129. http://dx.doi.org/10.1007/s10803-009-0841-119653088.

Bal, E., Harden, E., Lamb, D., Van Hecke, A.V., Denver, J.W., Porges, S.W., 2010. Emotion recognition in children with autism spectrum disorders: relations to eye gaze and autonomic state. J Autism Dev Disord 40 (3), 358–370. http://dx.doi.org/10.1007/s10803-009-0884-319885725.

Balconi, M., Carrera, A., 2007. Emotional representation in facial expression and script: a comparison between normal and autistic children. Res. Dev. Disabil. 28 (4), 409–422. http://dx.doi.org/10.1016/j.ridd.2006.05.00116828256.

Baron-Cohen, S., O'Riordan, M., Stone, V., Jones, R., Plaisted, K., 1999. Recognition of faux pas by normally developing children and children with Asperger syndrome or high-functioning autism. J. Autism Dev. Disord. 29 (5), 407–418. http://dx.doi.org/10.1023/A:1023035012436105878 87.

Baron-Cohen, S., Spitz, A., Cross, P., 1993. Can children with autism recognize surprise? Cogn. Emotion 7, 507–516.

Batty, M., Meaux, E., Wittemeyer, K., Rogé, B., Taylor, M.J., 2011. Early processing of emotional faces in children with autism: an event-related potential study. J Exp Child Psychol 109 (4), 430–444. http://dx.doi.org/10.1016/j.jecp.2011.02.00121458825.

Batty, M., Taylor, M.J., 2003. Early processing of the six basic facial emotional expressions. Brain Res. Cogn. Brain Res. 17 (3), 613–620. http://dx.doi.org/10.1016/S0926-6410(03)00174-514561449.

Batty, M., Taylor, M.J., 2006. The development of emotional face processing during childhood. Dev. Sci. 9 (2), 207–220. http://dx.doi.org/10.1111/j.1467-7687.2006.00480.x16472321.

Begeer, S., Rieffe, C., Terwogt, M.M., Stockmann, L., 2006. Attention to facial emotion expressions in children with autism. Autism 10 (1), 37–51. http://dx.doi.org/10.1177/136236130605786216522709.

Bentin, S., Allison, T., Puce, A., Perez, E., McCarthy, G., 1996. Electrophysiological studies of face perception in humans. J Cogn Neurosci 8 (6), 551–565. http://dx.doi.org/10.1162/jocn.1996.8.6.55120740065.

Berkowitz, L., 1999. Anger. In: Dalgleish, T., Power, M.J. (Eds.), Handbook of Cognition and Emotion. John Wiley and Sons, Chichester, England, pp. 411–428.

Berlin, H.A., Rolls, E.T., Kischka, U., 2004. Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. Brain 127 (5), 1108–1126. http://dx.doi.org/10.1093/brain/awh13514985269.

Blair, R.J., Morris, J.S., Frith, C.D., Perrett, D.I., Dolan, R.J., 1999. Dissociable neural responses to facial expressions of sadness and anger. Brain 122 (5), 883–893. http://dx.doi.org/10.1093/brain/122.5.88310355673.

Breiter, H.C., Aharon, I., Kahneman, D., Dale, A., Shizgal, P., 2001. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron 30 (2), 619–639. http://dx.doi.org/10.1016/S0896-6273(01)00303-811395019.

Breiter, H.C., Etcoff, N.L., Whalen, P.J., Kennedy, W.A., Rauch, S.L., Buckner, R.L., 1996. Response and habituation of the human amygdala during visual processing of facial expression. Neuron 17 (5), 875–887. http://dx.doi.org/10.1016/S0896-6273(00)80219-68938120.

Britton, J.C., Phan, K.L., Taylor, S.F., Welsh, R.C., Berridge, K.C., Liberzon, I., 2006. Neural correlates of social and nonsocial emotions: an fMRI study. Neuroimage 31 (1), 397–409. http://dx.doi.org/10.1016/j.neuroimage.2005.11.02716414281.

Brothers, L., 2002. The social brain: a project for integrating primate behavior and neurophysiology in a new domain. Found. Soc. Neurosci. 367–385.

Buitelaar, J.K., Van der Wees, M., Swaab-Barneveld, H., Van der Gaag, R.J., 1999. Theory of mind and emotion-recognition functioning in autistic spectrum disorders and in psychiatric control and normal children. Dev. Psychopathol. 11 (1), 39–58. http://dx.doi.org/10.1017/S0954579499001947102083 55.

Capps, L., Yirmiya, N., Sigman, M., 1992. Understanding of simple and complex emotions in non-retarded children with autism. J. Child Psychol. Psychiatry 33 (7), 1169–1182. http://dx.doi.org/10.1111/j.1469-7610.1992.tb00936.x1400699.

Carrera-Levillain, P., Fernandez-Dols, J.M., 1994. Neutral faces in context: their emotional meaning and their function. J. Nonverbal Behav. 18 (4), 281–299.

Castelli, F., 2005. Understanding emotions from standardized facial expressions in autism and normal development. Autism 9 (4), 428–449. http://dx.doi.org/10.1177/136236130505608216155058.

Celani, G., Battacchi, M.W., Arcidiacono, L., 1999. The understanding of the emotional meaning of facial expressions in people with autism. J. Autism Dev. Disord. 29 (1), 57–66. http://dx.doi.org/10.1023/A:1025970600181100979 95.

Compas, B.E., Hinden, B.R., Gerhardt, C.A., 1995. Adolescent development: pathways and processes of risk and resilience. Annu. Rev. Psychol. 46 (1), 265–293. http://dx.doi.org/10.1146/annurev.ps.46.020195.0014057872731.

Corbett, B.A., Carmean, V., Ravizza, S., Wendelken, C., Henry, M.L., Carter, C., Rivera, S.M., 2009. A functional and structural study of emotion and face processing in children with autism. Psychiatry Res. 173 (3), 196–205. http://dx.doi.org/10.1016/j.pscychresns.2008.08.00519665877.

Courchesne, E., Pierce, K., 2005. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. Curr. Opin. Neurobiol. 15 (2), 225–230. http://dx.doi.org/10.1016/j.conb.2005.03.00115831407.

Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29 (3), 162–173. http://dx.doi.org/10.1006/cbmr.1996.00148812068.

Craig, A.D., 2003. Interoception: the sense of the physiological condition of the body. Curr. Opin. Neurobiol. 13 (4), 500–505. http://dx.doi.org/10.1016/S0959-4388(03)00090-412965300.

Critchley, H.D., Daly, E.M., Bullmore, E.T., Williams, S.C., Van Amelsvoort, T., Robertson, D.M., 2000. The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions. Brain 123 (11), 2203–2212. http://dx.doi.org/10.1093/brain/123.11.220311050021.

Dawson, G., Webb, S.J., Carver, L., Panagiotides, H., McPartland, J., 2004. Young children with autism show atypical brain responses to fearful versus neutral facial expressions of emotion. Dev Sci 7 (3), 340–359. http://dx.doi.org/10.1111/j.1467-7687.2004.00352.x15595374.

De Sonneville, L.M., Verschoor, C.A., Njiokiktjien, C., Op het Veld, V., Toorenaar, N., Vranken, M., 2002. Facial identity and facial emotions: speed, accuracy, and processing strategies in children and adults. J. Clin. Exp. Neuropsychol 24 (2), 200–213. http://dx.doi.org/10.1076/jcen.24.2.200.98911992203.

Deeley, Q., Daly, E.M., Surguladze, S., Page, L., Toal, F., Robertson, D., 2007. An event related functional magnetic resonance imaging study of facial emotion processing in Asperger syndrome. Biol. Psychiatry 62 (3), 207–217. http://dx.doi.org/10.1016/j.biopsych.2006.09.03717400195.

Demaree, H.A., Everhart, D.E., Youngstrom, E.A., Harrison, D.W., 2005. Brain lateralization of emotional processing: historical roots and a future incorporating "dominance". Behav. Cogn. Neurosci Rev. 4 (1), 3–20. http://dx.doi.org/10.1177/153458230527683715886400.

Devinsky, O., Morrell, M.J., Vogt, B.A., 1995. Contributions of anterior cingulate cortex to behaviour. Brain 118 (1), 279–306. http://dx.doi.org/10.1093/brain/118.1.2797895011.

Dias, R., Robbins, T.W., Roberts, A.C., 1996. Dissociation in prefrontal cortex of affective and attentional shifts. Nature 380 (6569), 69–72. http://dx.doi.org/10.1038/380069a08598908.

Duerden, E.G., Arsalidou, M., Lee, M., Taylor, M.J., 2013. Lateralization of affective processing in the insula. Neuroimage 78, 159–175. http://dx.doi.org/10.1016/j.neuroimage.2013.04.01423587690.

Eack, S.M., Mazefsky, C.A., Minshew, N.J., 2014. Misinterpretation of facial expressions of emotion in verbal adults with autism spectrum disorder. Autism http://dx.doi.org/10.1177/1362361314520755524535689.
Ekman, P., Friesen, W.V., 1971. Constants across cultures in the face and emotion. J. Pers. Soc. Psychol. 17 (2), 124–129. http://dx.doi.org/10.1037/h00303775542557.
Elliott, R., Friston, K.J., Dolan, R.J., 2000. Dissociable neural responses in human reward systems. J. Neurosci. 20 (16), 6159–616510934265.
Farran, E.K., Branson, A., King, B.J., 2011. Visual search for basic emotional expressions in autism; impaired processing of anger, fear and sadness, but a typical happy face advantage. Res. Autism Spec. Disord. 5 (1), 455–462.
Fatima, Z., Quraan, M.A., Kovacevic, N., McIntosh, A.R., 2013. ICA-based artifact correction improves spatial localization of adaptive spatial filters in MEG. Neuroimage 78, 284–294. http://dx.doi.org/10.1016/j.neuroimage.2013.04.03323603349.
Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., 2009. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J. Psychiatry Neurosci. 34 (6), 418–43219949718.
García-Villamisar, D., Rojahn, J., Zaja, R.H., Jodra, M., 2010. Facial emotion processing and social adaptation in adults with and without autism spectrum disorder. Res. Autism Spec. Disord. 4 (4), 755–762.
Golan, O., Baron-Cohen, S., Golan, Y., 2008. The 'Reading the Mind in Films' task [child version]: complex emotion and mental state recognition in children with and without autism spectrum conditions. J. Autism Dev. Disord. 38 (8), 1534–1541. http://dx.doi.org/10.1007/s10803-007-0533-718311514.
Grossman, J.B., Klin, A., Carter, A.S., Volkmar, F.R., 2000. Verbal bias in recognition of facial emotions in children with Asperger syndrome. J. Child Psychol. Psychiatry 41 (3), 369–379. http://dx.doi.org/10.1111/1469-7610.0062110784084.
Habel, U., Klein, M., Kellermann, T., Shah, N.J., Schneider, F., 2005. Same or different? Neural correlates of happy and sad mood in healthy males. Neuroimage 26 (1), 206–214. http://dx.doi.org/10.1016/j.neuroimage.2005.01.01415862220.
Hare, T.A., Tottenham, N., Galvan, A., Voss, H.U., Glover, G.H., Casey, B.J., 2008. Biological substrates of emotional reactivity and regulation in adolescence during an emotional go–nogo task. Biol. Psychiatry 63 (10), 927–934. http://dx.doi.org/10.1016/j.biopsych.2008.03.01518452757.
Hari, R., Parkkonen, L., Nangini, C., 2010. The brain in time: insights from neuromagnetic recordings. Ann. N. Y. Acad. Sci. 1191 (1), 89–109. http://dx.doi.org/10.1111/j.1749-6632.2010.05438.x20392277.
Haxby, J.V., Hoffman, E.A., Gobbini, M.I., 2000. The distributed human neural system for face perception. Trends Cogn. Sci. (Regul. Ed.) 4 (6), 223–233. http://dx.doi.org/10.1016/S1364-6613(00)01482-010827445.
Haznedar, M.M., Buchsbaum, M.S., Metzger, M., Solimando, A., Spiegel-Cohen, J., Hollander, E., 1997. Anterior cingulate gyrus volume and glucose metabolism in autistic disorder. Am. J. Psychiatry 154 (8), 1047–10509247387.
Hoehl, S., Brauer, J., Brasse, G., Striano, T., Friederici, A.D., 2010. Children's processing of emotions expressed by peers and adults: an fMRI study. Soc. Neurosci. 5 (5–6), 543–559. http://dx.doi.org/10.1080/17470911003708206204860l3.
Howard, M.A., Cowell, P.E., Boucher, J., Broks, P., Mayes, A., Farrant, A., Roberts, N., 2000. Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. Neuroreport 11 (13), 2931–2935. http://dx.doi.org/10.1097/00001756-200009110-0002011006968.
Hung, Y., Smith, M.L., Bayle, D.J., Mills, T., Cheyne, D., Taylor, M.J., 2010. Unattended emotional faces elicit early lateralized amygdala–frontal and fusiform activations. Neuroimage 50 (2), 727–733. http://dx.doi.org/10.1016/j.neuroimage.2009.12.09320045736.
Hung, Y., Smith, M.L., Taylor, M.J., 2012. Development of ACC–amygdala activations in processing unattended fear. Neuroimage 60 (1), 545–552. http://dx.doi.org/10.1016/j.neuroimage.2011.12.00322182768.
Just, M.A., Cherkassky, V.L., Keller, T.A., Minshew, N.J., 2004. Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain 127 (8), 1811–1821. http://dx.doi.org/10.1093/brain/awh19915215213.
Kesler-West, M.L., Andersen, A.H., Smith, C.D., Avison, M.J., Davis, C.E., Kryscio, R.J., Blonder, L.X., 2001. Neural substrates of facial emotion processing using fMRI. Brain Res. Cogn. Brain Res. 11 (2), 213–226. http://dx.doi.org/10.1016/S0926-6410(00)00073-211275483.
Killgore, W.D., Yurgelun-Todd, D.A., 2007. Unconscious processing of facial affect in children and adolescents. Soc. Neurosci. 2 (1), 28–47. http://dx.doi.org/10.1080/17470910701214186186338O5.
Kolb, B., Wilson, B., Taylor, L., 1992. Developmental changes in the recognition and comprehension of facial expression: implications for frontal lobe function. Brain Cogn. 20 (1), 74–84. http://dx.doi.org/10.1016/0278-2626(92)90062-Q1389123.
Kuusikko, S., Haapsamo, H., Jansson-Verkasalo, E., Hurtig, T., Mattila, M.L., Ebeling, H., Jussila, K., Bölte, S., Moilanen, I., 2009. Emotion recognition in children and adolescents with autism spectrum disorders. J. Autism Dev. Disord. 39 (6), 938–945.
Koning, C., Magill-Evans, J., 2001. Social and language skills in adolescent boys with Asperger syndrome. Autism 5 (1), 23–36. http://dx.doi.org/10.1177/1362361301005001003117083870.
Lalancette, M., Quraan, M., Cheyne, D., 2011. Evaluation of multiple-sphere head models for MEG source localization. Phys. Med. Biol. 56 (17), 5621–5635. http://dx.doi.org/10.1088/0031-9155/56/17/01021828900.
Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L., 2000. Automated Talairach atlas labels for functional brain mapping. Hum. Brain Mapp. 10 (3), 120–131. http://dx.doi.org/10.1002/1097-0193(200007)10:3<120::AID-HBM30>3.0.CO;2-810912591.
Lerner, M.D., McPartland, J.C., Morris, J.P., 2013. Multimodal emotion processing in autism spectrum disorders: an event-related potential study. Dev. Cogn. Neurosci. 3, 11–21. http://dx.doi.org/10.1016/j.dcn.2012.08.00523245216.
Lindner, J.L., Rosén, L.A., 2006. Decoding of emotion through facial expression, prosody and verbal content in children and adolescents with Asperger's syndrome. J. Autism Dev. Disord. 36 (6), 769–777. http://dx.doi.org/10.1007/s10803-006-0105-216639533.
Lobaugh, N.J., Gibson, E., Taylor, M.J., 2006. Children recruit distinct neural systems for implicit emotional face processing. Neuroreport 17 (2), 215–219. http://dx.doi.org/10.1097/01.wnr.0000198946.00445.2f16407774.
Lord, C., Risi, S., Lambrecht, L., Cook Jr, E.H., Leventhal, B.L., DiLavore, P.C., 2000. The Autism Diagnostic Observation Schedule—Generic: a standard measure of social and communication deficits associated with the spectrum of autism. J. Autism Dev. Disord. 30 (3), 205–223. http://dx.doi.org/10.1023/A:10055924019471105545 7.
Luo, Q., Holroyd, T., Jones, M., Hendler, T., Blair, J., 2007. Neural dynamics for facial threat processing as revealed by gamma band synchronization using MEG. Neuroimage 34 (2), 839–847. http://dx.doi.org/10.1016/j.neuroimage.2006.09.02317095252.
Markham, R., Adams, K., 1992. The effect of type of task on children's identification of facial expressions. J. Nonverbal. Behav. 16 (1), 21–39. http://dx.doi.org/10.1007/BF00986877.
Mazefsky, C.A., Oswald, D.P., 2007. Emotion perception in Asperger's syndrome and high-functioning autism: the importance of diagnostic criteria and cue intensity. J. Autism Dev. Disord. 37 (6), 1086–1095. http://dx.doi.org/10.1007/s10803-006-0251-617180461.
McLaren, J., Bryson, S.E., 1987. Hemispheric asymmetries in the perception of emotional and neutral faces. Cortex 23 (4), 645–654. http://dx.doi.org/10.1016/S0010-9452(87)80054-03442998.
McPartland, J., Dawson, G., Webb, S.J., Panagiotides, H., Carver, L.J., 2004. Event-related brain potentials reveal anomalies in temporal processing of faces in autism spectrum disorder. J. Child Psychol. Psychiatry 45 (7), 1235–1245. http://dx.doi.org/10.1111/j.1469-7610.2004.00318.x15335344.
Meltzoff, A.N., Moore, M.K., 1977. Imitation of facial and manual gestures by human neonates. Science 198 (4312), 75–78. http://dx.doi.org/10.1126/science.198.4312.7517741897.
Menon, V., Levitin, D.J., 2005. The rewards of music listening: response and physiological connectivity of the mesolimbic system. Neuroimage 28 (1), 175–184. http://dx.doi.org/10.1016/j.neuroimage.2005.05.05316023376.
Monk, C.S., McClure, E.B., Nelson, E.E., Zarahn, E., Bilder, R.M., Leibenluft, E., 2003. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. Neuroimage 20 (1), 420–428. http://dx.doi.org/10.1016/S1053-8119(03)00355-014527602.
Morris, J.S., Dolan, R.J., 2001. Involvement of human amygdala and orbitofrontal cortex in hunger-enhanced memory for food stimuli. J. Neurosci. 21 (14), 5304–531011438606.
O'Connor, K., Hamm, J.P., Kirk, I.J., 2005. The neurophysiological correlates of face processing in adults and children with Asperger's syndrome. Brain Cogn. 59 (1), 82–95. http://dx.doi.org/10.1016/j.bandc.2005.05.00416009478.
Pelphrey, K.A., Sasson, N.J., Reznick, J.S., Paul, G., Goldman, B.D., Piven, J., 2002. Visual scanning of faces in autism. J. Autism Dev. Disord. 32 (4), 249–261. http://dx.doi.org/10.1023/A:10163746173691219913 1.
Philip, R.C., Whalley, H.C., Stanfield, A.C., Sprengelmeyer, R., Santos, I.M., Young, A.W., 2010. Deficits in facial, body movement and vocal emotional processing in autism spectrum disorders. Psychol. Med. 40 (11), 1919–1929. http://dx.doi.org/10.1017/S0033291709992364201026 66.
Phillips, M.L., Bullmore, E.T., Howard, R., Woodruff, P.W., Wright, I.C., Williams, S.C., 1998. Investigation of facial recognition memory and happy and sad facial expression perception: an fMRI study. Psychiatry Res. 83 (3), 127–138. http://dx.doi.org/10.1016/S0925-4927(98)00036-59849722.
Phillips, M.L., Williams, L., Senior, C., Bullmore, E.T., Brammer, M.J., Andrew, C., 1999. A differential neural response to threatening and non-threatening negative facial expressions in paranoid and non-paranoid schizophrenics. Psychiatry Res. 92 (1), 11–31. http://dx.doi.org/10.1016/S0925-4927(99)00031-110688157.
Pichon, S., de Gelder, B., Grèzes, J., 2009. Two different faces of threat. Comparing the neural systems for recognizing fear and anger in dynamic body expressions. Neuroimage 47 (4), 1873–1883. http://dx.doi.org/10.1016/j.neuroimage.2009.03.08419371787.
Quraan, M.A., Moses, S.N., Hung, Y., Mills, T., Taylor, M.J., 2011. Detection and localization of hippocampal activity using beamformers with MEG: a detailed investigation using simulations and empirical data. Hum. Brain Mapp. 32 (5), 812–827. http://dx.doi.org/10.1002/hbm.2106821484951.
Rieffe, C., Meerum Terwogt, M., Kotronopoulou, K., 2007. Awareness of single and multiple emotions in high-functioning children with autism. J. Autism Dev. Disord. 37 (3), 455–465. http://dx.doi.org/10.1007/s10803-006-0171-516868846.
Rolls, E.T., 2004. The functions of the orbitofrontal cortex. Brain Cogn. 55 (1), 11–29. http://dx.doi.org/10.1016/S0278-2626(03)00277-X15134840.
Rorden, C., 2012. MRIcron. http://www.mccauslandcenter.sc.edu/mricro/mricron/.
Rump, K.M., Giovannelli, J.L., Minshew, N.J., Strauss, M.S., 2009. The development of emotion recognition in individuals with autism. Child Dev. 80 (5), 1434–1447. http://dx.doi.org/10.1111/j.1467-8624.2009.01343.x19765010.
Rushworth, M.F., Behrens, T.E., Rudebeck, P.H., Walton, M.E., 2007. Contrasting roles for cingulate and orbitofrontal cortex in decisions and social behaviour. Trends Cogn. Sci. (Regul. Ed.) 11 (4), 168–176. http://dx.doi.org/10.1016/j.tics.2007.01.00417337237.
Rutter, M., DiLavore, P.C., Risi, S., Gotham, K., Bishop, S., 2012. Autism Diagnostic Observation Schedule: ADOS-2. Western Psychological Services, Torrance, CA.
Sato, W., Aoki, S., 2006. Right hemispheric dominance in processing of unconscious negative emotion. Brain Cogn. 62 (3), 261–266. http://dx.doi.org/10.1016/j.bandc.2006.06.00616899333.
Seghier, M.L., 2013. The angular gyrus: multiple functions and multiple subdivisions. Neuroscientist 19 (1), 43–61. http://dx.doi.org/10.1177/1073858412440596225475 30.

Sepeta, L., Tsuchiya, N., Davies, M.S., Sigman, M., Bookheimer, S.Y., Dapretto, M., 2012. Abnormal social reward processing in autism as indexed by pupillary responses to happy faces. J. Neurodev. Disord. 4 (1), 17. http://dx.doi.org/10.1186/1866-1955-4-1722958650.

Simms, M.L., Kemper, T.L., Timbie, C.M., Bauman, M.L., Blatt, G.J., 2009. The anterior cingulate cortex in autism: heterogeneity of qualitative and quantitative cytoarchitectonic features suggests possible subgroups. Acta Neuropathol. 118 (5), 673–684. http://dx.doi.org/10.1007/s00401-009-0568-219590881.

Smith, S.D., Bulman-Fleming, M.B., 2005. An examination of the right-hemisphere hypothesis of the lateralization of emotion. Brain Cogn. 57 (2), 210–213. http://dx.doi.org/10.1016/j.bandc.2004.08.04615708218.

Spear, L.P., 2000. The adolescent brain and age-related behavioral manifestations. Neurosci. Biobehav. Rev. 24 (4), 417–463. http://dx.doi.org/10.1016/S0149-7634(00)00014-210817843.

Sprengelmeyer, R., Rausch, M., Eysel, U.T., Przuntek, H., 1998. Neural structures associated with recognition of facial expressions of basic emotions. Proc. Biol. Sci. 265 (1409), 1927–1931. http://dx.doi.org/10.1098/rspb.1998.05229821359.

Thomas, K.M., Drevets, W.C., Whalen, P.J., Eccard, C.H., Dahl, R.E., Ryan, N.D., Casey, B.J., 2001. Amygdala response to facial expressions in children and adults. Biol. Psychiatry 49 (4), 309–316. http://dx.doi.org/10.1016/S0006-3223(00)01066-011239901.

Thomas, L.A., De Bellis, M.D., Graham, R., LaBar, K.S., 2007. Development of emotional facial recognition in late childhood and adolescence. Dev. Sci. 10 (5), 547–558. http://dx.doi.org/10.1111/j.1467-7687.2007.00614.x17683341.

Tonks, J., Williams, W.H., Frampton, I., Yates, P., Slater, A., 2007. Assessing emotion recognition in 9–15-years olds: preliminary analysis of abilities in reading emotion from faces, voices and eyes. Brain Inj. 21 (6), 623–629. http://dx.doi.org/10.1080/02699050701426865517577713.

Tottenham, N., Tanaka, J.W., Leon, A.C., McCarry, T., Nurse, M., Hare, T.A., 2009. The NimStim set of facial expressions: judgments from untrained research participants. Psychiatry Res. 168 (3), 242–249. http://dx.doi.org/10.1016/j.psychres.2008.05.00619564050.

Tracy, J.L., Robins, R.W., Schriber, R.A., Solomon, M., 2011. Is emotion recognition impaired in individuals with autism spectrum disorders? J. Autism Dev. Disord. 41 (1), 102–109. http://dx.doi.org/10.1007/s10803-010-1030-y20464465.

Trautmann, S.A., Fehr, T., Herrmann, M., 2009. Emotions in motion: dynamic compared to static facial expressions of disgust and happiness reveal more widespread emotion-specific activations. Brain Res. 1284, 100–115. http://dx.doi.org/10.1016/j.brainres.2009.05.07519501062.

Van Honk, J., Peper, J.S., Schutter, D.J., 2005. Testosterone reduces unconscious fear but not consciously experienced anxiety: implications for the disorders of fear and anxiety. Biol. Psychiatry 58 (3), 218–225. http://dx.doi.org/10.1016/j.biopsych.2005.04.00315939408.

Vogt, B.A., Finch, D.M., Olson, C.R., 1992. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. Cereb. Cortex 2 (6), 435–443. http://dx.doi.org/10.1093/cercor/2.6.435-a1477524.

Vuilleumier, P., Pourtois, G., 2007. Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. Neuropsychologia 45 (1), 174–194. http://dx.doi.org/10.1016/j.neuropsychologia.2006.06.00316854439.

Wagner, J.B., Hirsch, S.B., Vogel-Farley, V.K., Redcay, E., Nelson, C.A., 2013. Eye-tracking, autonomic, and electrophysiological correlates of emotional face processing in adolescents with autism spectrum disorder. J. Autism Dev. Disord. 43 (1), 188–199. http://dx.doi.org/10.1007/s10803-012-1565-122684525.

Wang, A.T., Dapretto, M., Hariri, A.R., Sigman, M., Bookheimer, S.Y., 2004. Neural correlates of facial affect processing in children and adolescents with autism spectrum disorder. J. Am. Acad. Child Adolesc. Psychiatry 43 (4), 481–490. http://dx.doi.org/10.1097/00004583-200404000-0001515187809.

Wechsler, D., 2002. Wechsler Abbreviated Scales of Intelligence. Psychological Corporation, San Antonio, TX.

Whalen, P.J., Shin, L.M., McInerney, S.C., Fischer, H., Wright, C.I., Rauch, S.L., 2001. A functional MRI study of human amygdala responses to facial expressions of fear versus anger. Emotion 1 (1), 70–83. http://dx.doi.org/10.1037//1528-3542.1.1.7012894812.

Wong, T.K., Fung, P.C., Chua, S.E., McAlonan, G.M., 2008. Abnormal spatiotemporal processing of emotional facial expressions in childhood autism: dipole source analysis of event-related potentials. Eur. J. Neurosci. 28 (2), 407–416. http://dx.doi.org/10.1111/j.1460-9568.2008.06328.x18702712.

Wright, B., Alderson-Day, B., Prendergast, G., Bennett, S., Jordan, J., Whitton, C., 2012. Gamma activation in young people with autism spectrum disorders and typically-developing controls when viewing emotions on faces. PLoS ONE 7 (7), e41326. http://dx.doi.org/10.1371/journal.pone.004132622859975.

Zeman, J., Garber, J., 1996. Display rules for anger, sadness, and pain: it depends on who is watching. Child Dev. 67 (3), 957–973. http://dx.doi.org/10.1111/j.1467-8624.1996.tb01776.x8706538.