The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry 62:12 (2021), pp 1412–1424 doi:10.1111/jcpp.13412

Brain activity during facial processing in autism spectrum disorder: an activation likelihood estimation (ALE) meta-analysis of neuroimaging studies

Cristiano Costa,[1,*] Ioana Alina Cristea,[2,3,*] Elisa Dal Bò,[1,4] Caterina Melloni,[1] and Claudio Gentili[1,4]

[1]Department of General Psychology, University of Padua, Padua, Italy; [2]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy; [3]IRCCS Mondino Foundation, Pavia, Italy; [4]Padova Neuroscience Center (PNC), University of Padua, Padua, Italy

Background: Though aberrant face processing is a hallmark of autistic spectrum disorder (ASD), findings on accompanying brain activity are divergent. Therefore, we conducted an activation likelihood estimation (ALE) meta-analysis of studies examining brain activity during face processing. **Methods:** We searched PubMed and PsycINFO using combinations of terms as 'fMRI', 'Autism Spectrum Disorder', 'Face Perception'. Eligible studies reported on DSM-diagnosed ASD individuals, compared to controls (HC), using face stimuli presented in fMRI and reporting whole-brain analysis coordinates. We compared two approaches: 'convergence of differences' (primary analysis) using study-level coordinates from ASD vs. HC contrasts, and 'differences in convergence' (secondary) pooling coordinates within each group separately, and contrasting the resultant ALE maps. **Results:** Thirty-five studies (655 ASD and 668 HC) were included. Primary analysis identified a cluster in amygdala/parahippocampus where HC showed greater convergence of activation. Secondary analysis yielded no significant results. **Conclusions:** Results suggest that ASD dysfunction in face processing relies on structures involved in emotional processing rather than perception. We also demonstrate that the two ALE methodologies lead to divergent results. **Keywords:** Functional MRI (fMRI); autism spectrum disorders; face perception; meta-analysis.

Introduction

Autism spectrum disorder (ASD) circumscribes a set of heterogeneous and lifelong neurodevelopmental disorders, defined by deficits in social communication and social interaction, and restricted, stereotyped, and highly repetitive behaviors, interests, or activities (American Psychiatric Association, 2013).

Sensory deficits, already present in early developmental stages (Baranek et al., 2013), are cardinal characteristics of ASD and strong predictors of social communication and social interaction impairments (Turner-Brown, Baranek, Reznick, Watson, & Crais, 2013), as well as of stereotyped and repetitive behavior (Boyd et al., 2010). Specifically, ASD individuals show substantial deficits in face perception (Grelotti, Gauthier, & Schultz, 2002), owing to abnormal face processing strategies (Hobson, Ouston, & Lee, 1988), possibly caused by perceptual abnormalities, such as a locally oriented rather than global visual analysis (Morin et al., 2015), or more complex alterations of the social brain network (Pelphrey, Yang, & McPartland, 2014; Schultz et al., 2003). Impaired face perception could also underpin social interaction difficulties (Bi & Fang, 2017). Several studies (Dawson, Webb, & McPartland, 2005; Harms, Martin, & Wallace, 2010; Hileman, Henderson, Mundy, Newell, & Jaime, 2011) suggested that, compared to developmentally typical individuals, ASD individuals show reduced accuracy and longer reaction times for identity or expression recognition.

Face perception is a highly sophisticated process subtended by two systems: the 'core system' and the 'extended system' (Haxby, Hoffman, & Gobbini, 2000). The 'core system' is mainly related to visual face processing. The 'extended system' includes nonvisual areas extracting information from faces, such as the amygdala, insula, other limbic structures implicated in the emotional response to faces and other areas involved in autobiographic memory. Research on face perception in ASD suggested alterations in both systems, though findings were often inconsistent (Baron-Cohen et al., 2000; Robertson & Baron-Cohen, 2017). Abnormal brain activity in ASD individuals, specifically a reduced neural response, was identified in regions related to social cognition and face processing, such as the orbitofrontal cortex, superior temporal gyrus, amygdala (Baron-Cohen et al., 1999), and fusiform gyrus (Deffke et al., 2007). Yet despite a wealth of neuroimaging studies on sensory deficits in ASD, findings were inconsistent, revealing a multitude of abnormalities in early visual (Robertson & Baron-Cohen, 2017) or face perception-related areas (Weigelt et al., 2012), as well as in structures involved in emotional processing (Baron-Cohen et al., 2000). Inconsistency could also be attributed to the diversity of tasks employed. Faces as stimuli were used in simple passive viewing tasks

*These two authors contributed equally.

Conflict of interest statement: No conflicts declared.

(Davies, Dapretto, Sigman, Sepeta, & Bookheimer, 2011; Hadjikhani et al., 2014), as well as in simple cognitive tasks such as emotion (Critchley et al., 2000) and gender recognition (Dalton et al., 2005) or memory tasks such as delayed recall (Greimel et al., 2012) or n-back (Koshino et al., 2008). Typically, in the cases where a simple task was employed, its role was to orient the participants' attention to the faces, and the performance in the task *per se* was not the focus of the study. Conversely, faces, as powerful emotional stimuli, were often used in more complex cognitive tasks such as go/no-go (Shafritz, Bregman, Ikuta, & Szeszko, 2015; Velasquez et al., 2017), where the focus of the study was on emotional modulation or processing, not face perception.

Activation likelihood estimation (ALE) meta-analyses aim to summarize and identify consistency across neuroimaging findings. Briefly, this method computes the agreement of statistically significant foci across experiments in terms of probability distributions centered at the each set of focus coordinates (Eickhoff et al., 2009). Though it can only quantify convergence probabilities and not magnitude of activations, this method is particularly useful for fields with a suite of diverse and often inconsistent findings such as mental health disorders, as it can theoretically parse out the most robust alterations in brain activity (Goodkind et al., 2015; Muller et al., 2017).

Two previous fMRI meta-analyses (Aoki, Cortese, & Tansella, 2015; Nickl-Jockschat et al., 2015) examined emotional face processing in autism: one reported ASD-related hyperactivation in bilateral thalamus, caudate, and right precuneus, and ASD-related hypoactivation in the hypothalamus (Aoki et al., 2015), while the other a cluster in the left fusiform gyrus due to reduce activations in ASD at single study level (Nickl-Jockschat et al., 2015). However, these meta-analyses used a small number of studies (13), including those relying on ROI analysis, a practice recently criticized (Eickhoff et al., 2016; Gentili, 2019; Muller et al., 2018).

Consequently, we conducted a systematic review and (ALE) meta-analysis of neuroimaging studies of face-related stimuli in individuals with ASD, with the aim of highlighting the more consistent neurobiological alterations. We also tested whether findings diverged depending on the two possible ALE meta-analysis approaches (Muller et al., 2018) (i.e., 'differences in convergence' vs 'convergence of differences'). The first approach pools differences between groups (e.g., patient vs healthy) as reported in each study. The second approach combines single group activations (e.g., patient and healthy) across included studies separately and subsequently contrasts the resultant group-level ALE maps. This latter approach is less frequently employed because many studies do not report single group activations. However, it could provide additional insight into the neurobiological substrate of face perception in each group. Though theoretically both methods should produce similar results, they have not previously been directly compared on the same sample of studies.

Methods

Study selection

Eligible studies were identified by searching the National Library of Medicine/PubMed and PsycINFO bibliographic databases (through the OVID searching engine) from inception until 30th of July 2020. We used combinations of database-specific terms as 'fMRI', 'Autism', 'Face', 'Facial, 'Visual Attention', 'Visual Processing' 'Fusiform Gyrus', 'Developmental disorder' (Figure 1 and Appendix S1 for the exact search string). Eligible studies were as follows: (a) neuroimaging studies using functional magnetic resonance imaging (fMRI) in (b) participants of any age diagnosed with ASD according to DSM IV, IV-TR or 5, including comorbid disorders, (c) compared to a matched healthy control group (HC), (d) in a task employing faces or face parts (e) within the same experimental paradigm for both ASD and HC, (f) and conducting a direct univariate comparison of brain activation between ASD and HC (i.e., HC > ASD and/or ASD > HC), (g) for which 3D coordinates of peak activations in stereotactic space of the Montreal Neurological Institute (MNI) or Talairach were reported, (h) employing whole brain and not just to region of interest (ROI) analysis. ASD participants could be undergoing any kind of therapy (e.g., psychological, pharmacological). Reviews and meta-analyses were excluded. Two authors (CM and CG) independently screened and selected studies.

Data extraction

From each paper, the following information was extracted: (a) participant reported sex and mean age; (b) diagnosis; (c) comorbidity; (d) concurrent treatments; (e) type of task and stimuli; (f) brain activation coordinates for the direct comparison between ASD and HC; and (g) where available, activation coordinates within each single group (ASD and HC). Data were extracted independently by two researchers (CC and CM).

Study quality

The quality and risk of bias (RoB) of included studies were evaluated with a modified version of the Newcastle–Ottawa scale (NOS) (Wells, 2001), (mNOS), adapted to fMRI data (Gentili et al., 2018). This version uses a different set of items adapted to fMRI studies (e.g., use of appropriate statistical corrections). Scores on the mNOS range from 0 to 11, with 0 to 3 considered indicative of high risk, 4 to 7 as intermediate, and 8 to 11 as low risk. RoB was independently assessed by two researchers (CM and EDB). Inter-rater agreement was measured with the Kappa statistic, and disagreements were subsequently resolved by discussion with a third author (CG).

ALE meta-analysis

Stereotactic coordinates (x, y, z) were extracted from the studies to be used in the activation likelihood estimation (ALE) meta-analysis. The ALE algorithm was used as implemented in the GingerALE 2.3.6 software (Eickhoff et al., 2009). We used the correction for multiple comparisons derived from the same dataset implemented in GingerALE (Turkeltaub et al., 2012). Sample size for each foci experiment has been used to calculate the full-width half-maximum (FWHM) of the Gaussian function used to blur the foci. Coordinates in the MNI 152

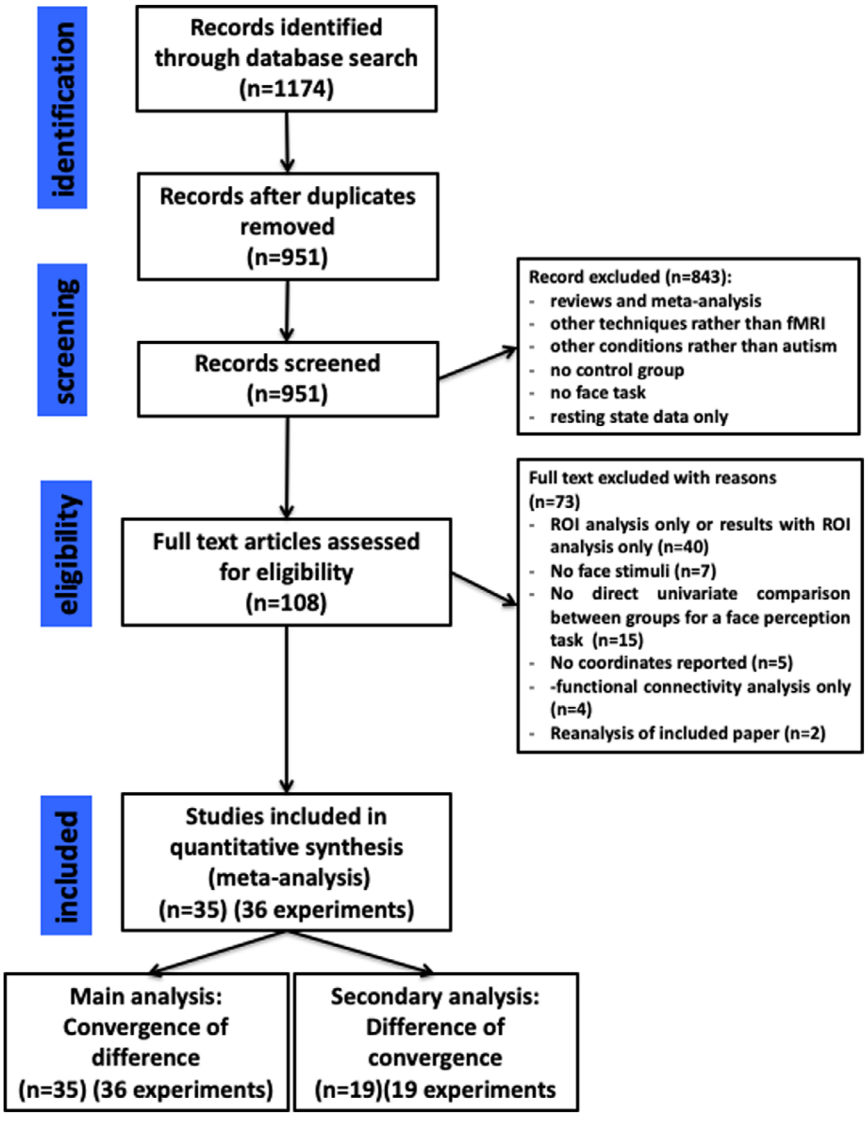

Figure 1 PRISMA flowchart illustrating the selection process of the present meta-analysis

standard space were converted into the Talairach space using the GingerALE foci converter tool.

Two approaches can be employed in an ALE meta-analysis of two groups. The first ('convergence of activation differences') uses coordinates from the contrast 'patients vs. controls' (i.e., patients > controls and controls > patients). The second ('differences in convergence') pools the activation reported within each group separately and subsequently computes a contrast between the resultant ALE maps. The two approaches have never been compared on the same data.

We used convergence of activation differences as the primary analysis because it used data from all included studies. We computed two independent meta-analyses (one for HC > ASD and the other for ASD > HC). Statistical significance was assessed and corrected for multiple comparisons using the cluster-wise method embedded in GingerALE: $p < .001$ cluster forming threshold, $p < .01$ cluster corrected FWE and $N = 2{,}000$ permutations.

To check the robustness of the findings, we also performed two subgroup analyses and two sensitivity analyses. In order to explore possible effects of age on face perception, we conducted two sensitivity analyses considering separately studies including mostly children and adolescent (mean age ≤ 16) ($n = 19$), and, respectively, studies including mostly adults (mean age > 16) ($n = 17$). The threshold of 16 years for mean age was selected post hoc. Given the heterogeneity of tasks employed, we performed another sensitivity analysis limited to studies using solely face perception as task (see Appendix S1 and Table S1). Finally, we also conducted a third sensitivity analysis as a pooled analysis across ASD > HC and HC > ASD. This analysis might reflect a better summary of group differences as differences between analysis approaches and control conditions between single studies may have influenced the direction of group differences. For all sensitivity analyses, we used the same parameters used in the primary analysis.

For the secondary analysis (differences in convergence), we computed a meta-analysis for activations of controls and ASD separately and contrasted them in a meta-analysis. For the single group meta-analysis, we used the same parameters described above, while to compute the differences of convergence, we used an uncorrected p value < .001, $N = 10{,}000$ permutations and a cluster threshold of 100 mm^3. Gaussian smoothing for each meta-analysis was independently calculated by the software (Eickhoff et al., 2009).

The difference in convergence analysis was restricted to studies that reported single group results, which were only a share of the entire pool. Therefore, differences between this analysis and the primary one (convergence of differences) could be due to the different number of included studies and not to genuine discrepancies between the methods. To account

for this possibility, we also conducted sensitivity analyses in which the primary method was performed only on the studies also reporting the single group activations (Figure 1 and Appendix S1). To maintain consistency with the primary analysis, we excluded one study (Zürcher et al., 2013) in which the contrast used in the single group analysis was different from that used in the convergence of difference. For each study, we included coordinates for single groups analysis for the same contrasts used in the convergence of differences analysis or, if there was no such overlap, the most similar contrast (e.g., faces vs. baseline used in single group analysis and faces vs. objects and houses used in HC vs ASD analysis).

Finally, as post hoc analysis, we examined whether results obtained with each of the two meta-analysis methods were also mirrored by the single studies. Specifically, for each included study, we checked whether (a) activation was reported in a cluster or region overlapping the one resulting from the meta-analysis and (b) if activation was present, whether it was discussed in the paper.

Results

Study selection

The search produced 1,174 entries (951 after removal of duplicates), 843 of which were excluded based on the abstract, that is, failing to specify the method for diagnosing ASD or inadequately describing imaging methods. The remaining 108 were retrieved, and full texts were assessed. A total of 73 articles were excluded due to (A) use of face stimuli but: (a) lack of direct univariate comparison between ASD and HC for a face perception task or no significant results for the comparison (n = 15), or comparison restricted to functional connectivity analysis (n = 4); (b) lack of reporting of coordinates for contrasts (n = 5) or ROI only reported (n = 40); (3) re-analyses of previous, already included, studies (n = 2); and (B) lack of face stimuli (n = 7). A total of 35 articles (describing 36 experiments) were included in the meta-analysis, as described in the PRISMA flow diagram (Figure 1). A list of the excluded full text is reported in Appendix S2.

Characteristics of included studies

The 36 experiments included 1,323 subjects (655 ASD and 668 HC) (Table 1, Table S1, Appendix S2). All studies performed whole-brain analyses: 17 reported both contrasts HC > ASD and ASD > HC, 15 the HC > ASD contrast only, whereas three the ASD > HC contrast only. Twenty-one studies also reported single group analyses (Figure 1). Due to the limited number of studies including participants with comorbidities or concomitant medication and to the reduced number of ASD participants with these characteristics within these studies, we could not conduct further sensitivity analyses (Appendix S1).

Study quality

The overall Cohen kappa (mean ± *SD*) was 0.88 ± 0.12 ranging from 1 to 0.63 (Appendix S2, Figure S1, Table S2). Consensus and Cohen kappa for each item of the mNOS are reported in Table S2 and Figure S1. The lower agreement was for definition (0.63) and selection (0.69) of controls. Three studies were considered as low RoB, twenty-nine as intermediate risk, and three as high risk of bias. A detailed description of the quality of each study is presented in the supplementary results. Of interest, only 7/35 studies reported high quality for type I correction (i.e., unthresholded p value < .001 – as defined in (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Eklund, Nichols, & Knutsson, 2016) – and an adequate method for type I error correction), while 22 reported an adequate type I error correction (e.g., false discovery rate, cluster-wise correction) with an unthresholded p value higher than .001.

Primary analysis: convergence of differences

For the voxel-wise whole-brain analysis, all the 36 experiments were considered. For the HC > ASD meta-analysis, we included 32 experiments and the simulation obtained a minimum cluster size of 920 mm^3, while for the ASD > HC meta-analysis, we included 20 experiments and a cluster size of 688 mm^3. We identified a single significant cluster in which the difference for the contrast HC > ASD showed a significant convergence. The cluster mainly belonged to left amygdala (64.4%) extending to the parahippocampus (Table 2, Figure 2). Post hoc analysis revealed that eleven studies reported amygdala activation for the contrast HC vs. ASD, comprising of a left-lateralized cluster in 5 and a bilateral cluster in 5, while only one paper reported a right-lateralized cluster. Only one paper discussed the possible meaning of lateralization (Critchley et al., 2000).

Secondary analysis: difference in convergences

A total of 21 experiments reported coordinates for single group analyses although two were excluded, leading to 19 studies included in this analysis (19 for HC and 16 for ASD) (see Appendix S1 and Table S3). Results for the meta-analysis within each group are reported in the supplement (Table S4, Figure S2). No significant clusters were identified for either HC > ASD and ASD > HC contrasts.

Sensitivity analyses for the primary analysis

Sensitivity analyses for age. For the HC > ASD meta-analysis, the children/adolescent group included 14 experiments with no identified significant cluster of convergence. The adult group included 18 experiments with a significant cluster of convergence in the left amygdala largely, overlapping with the results of the primary analysis (Table 2, Figure S3). For the ASD > HC meta-analysis, there were 10 experiments in each of the two

Table 1 Characteristics of the studies included in the meta-analysis

	Autism spectrum disorder						Healthy controls			
Study	*N*	M/F	Age (*SD*)[1]	Diagnosis[2]	Comorbidity[3]	Medication[4]	*N*	M/F	Age (*SD*)[1]	Task & stimuli[5]
Baron-Cohen (1999)[a]	6	4/2	26.3 (2.1)	ASD	?	?	12	6/6	25.5 (2.8)	Mental state & gender identification
Bölte (2015)[a]	32	30/2	19.3 (4.75)* (range 14–33)	ASD (10 Au, 14 Asp, 8 PDD-NOS)	-	1 AAP	25	4/21	19.7 (3.25)* (range 14–27)	Face affect recogn
Brandenburg-Goddard (2014)[c]	17	17/0	12.41 (1.94)	ASD	?	?	19	19/0	12.03 (2.36)	Face match & em label
Ciaramidaro (2018)[c]	33	31/2	18.76 (4.98)	ASD (10 Au, 15 Asp, 8 PDD-NOS	?	?	25	21/4	19.68 (3.45)	Em recogn
Corbett (2009)[c]	12	0/12	9.01 (1.60)	HFA	-	?	15	13/2	9.17 (1.44)	Face em & identity match
Critchley (2000)[a]	9	9/0	37 (7)	HFA (2 Au, 7 Asp)	-	?	9	9/0	27 (7)	Gender & em discrim
Dalton (2005) St 1[c]	14	14/0	15.9 (4.71)	Au (1 non-vb; 2 min vb)	?	?	17	17/0	17.1 (2.78)	Em recogn
Dalton (2005) St 2[c]	16	16/0	14.5 (4.60)	Au (2 min vb)	?	?	16	16/0	14.5 (4.56)	Face recogn
Dapretto (2006)[c]	10	9/1	12.05 (2.50)	ASD	?	?	10	9/1	12.38 (2.22)	Observe/imitate em express
Davies (2011) [c]	16	14/2	11.69 (2.71)	ASD	?	?	16	14/2	12.30 (1.88)	Passive view (direct/averted gaze)
Deeley (2007)[a]	9	9/0	34 (10)	Asp	-	-	9	9/0	27 (5)	Gender discrim
Doyle-Thomas (2013)[c]	18	18/0	14.94 (1.55)	ASD	5 ADHD, 1 CAPD, 1 VLPD, 1 Enc	5 MNS	16	16/0	14.69 (1.70)	Em match
Duerden (2013)[a]	19	14/5	26.8 (5.7)	ASD	-	-	20	15/5	33.7 (9.6)	Faces Go/No-Go
Greimel (2012)[c]	13	13/0	15.9 (3.0)	ASD (7 Asp, 5 HFA, 1AtA)	1 ADHD, 1 CTD	1 AAP	13	13/0	14.2 (2.8)	Recall Memory task
Greimel (2010)[c]	15	15/0	15 (1.4)	ASD	-	1 AAP, 1 TAP, 2 Ato	15	15/0	14.9 (1.6)	Infer em state & empathize
Hadjikhani (2014)[a]	36	33/3	23.5 (8.7)	ASD	?	?	31	28/3	22.5 (7.5)	Passive view (video)
Herrington (2015)[c]	12	12/0	13.4 (4.2)	ASD	?	?	19	19/0	13.4 (3.5)	1-back (faces & houses)
Holt (2014)[c]	49	33/16	M: 14.66 (1.6) F: 14.45 (1.95)	ASD/HFA	-	-	40	20/20	M: 15.27 (1.62) F:14.85 (1.66)	'Reading the Mind in the Eyes'
Ishitobi (2011)[a]	9	8/1	23.2 (6.9)	ASD	?	?	24	12/12	23.1 (4.4)	Em valence discrim
Kim (2015)[c]	17	16/1	10.89 (2.06)	ASD	-	7 Met, 1 Ato, 1 Met and Val	24	17/7	10.18 (2.04)	Passive view (attention to gender)
Klapwijk (2016)[c]	23	23/0	17.0 (1.2)	ASD (3 Au, 11 Asp, 9 PDD-NOS)	4 ADHD, 2 Dys, 1 MDD	3 AAT, 3 PS, 3 SSRI, 3 MM	33	33/0	17.1 (1.2)	Em recogn or judge own em
Koshino (2008)[a]	10	10/0	24.5 (10.2)	ASD	?	4 Tgr, Alb, Fluv, Bec°	10	10/1	28.7 (10.9)	N-back
Lassalle (2017)[a]	27	27/0	23.63 (9.86)	ASD	?	?	21	21/0	19.70 (7.74)	Passive view
Loveland (2008)[a]	5	4/1	219 (15.9) mths)	ASD	-	?	4	3/1	212 (13.7) (mths)	Em congr
Morita (2012)[a]	15	14/1	23.7 (4.3)	ASD (15 Au, 5 Asp)	?	?	15	13/2	23.3 (3.6)	Rating face fotogenicity (self & others)
Perlman (2011)[a]	12	11/1	25.5 (7.47)	ASD	?	?	7	7/0	28.57 (5.74)	Passive view
Rahko (2012)[c]	25	17/8	14.8 (1.6)	ASD	-	-	27	18/9	14.5 (1.5)	Passive view
Sabatino (2013)[a]	15	13/2	26.3 (9.4)	ASD (2 Asp 13 HFA)	?	?	17	12/5	24.3 (3.7)	Odd-ball target detect
Scherf (2015)[c]	20	20/0	14.1 (2.23)**	HFA	?	?	12	12/0	13.8 (2.40)**	Image repetition detect
Shafritz (2015)[c]	20	17/3	18.1***	HFA (14 Au, 6 Asp)	-	3 SSRI, 1 Alp, 1 Ven, 2 Arip, 1 Clom, 1 Lith, 1 Gua	18	15/3	18.4***	Faces Go/No-Go
Stanfield (2017)[a]	28	22/6	39.5 (11.6)	Au/Asp	-	2 AP	33	23/10	36.5 (9.3)	Social judge & gender discrim
Velasquez (2017)[a]	19	13/6	25.84 (4.39)	ASD	?	?	22	16/6	29.03 (9.40)	Faces Go/No-Go
Weng (2011)[c]	22	17/5	14.36 (1.70)	ASD (6 Au, 3 Asp, 13 PDD-NOS)	?	12 PTM°°	20	19/1	14.97 (1.95)	Gender discrim

(continued)

Table 1 (continued)

Study	Autism spectrum disorder						Healthy controls			Task & stimuli[5]
	N	M/F	Age (*SD*)[1]	Diagnosis[2]	Comorbidity[3]	Medication[4]	*N*	M/F	Age (*SD*)[1]	
Whyte (2016)[c]	14	13/1	15 (2)	HFA	?	NS°°°	14	13/1	15 (2)	N-Back with human & animal faces
Zürcher (2013a)[a]	22	19/3	27.6 (7.7)	ASD	?	?	22	19/3	23.7 (5.9)	Passive view (diff gazes)
Zürcher (2013b)[a]	16	13/3	23.5 (6.8)	ASD (7 Au, 7 Asp, 2 PDD-NOS)	?	?	18	16/2	25.8 (5.3)	Thatcher illusion

[1]Age in years unless otherwise specified. Mths, months.
[2]ASD, Autism Spectrum Disorder; Au, Autism Disorder; Asp, Asperger Syndrome; HFA, High Functioning Autism; AtA, Atypical Autism; Non-vb, Nonverbal; PDD-NOS, Pervasive Developmental Disorder, Not Otherwise Specified; Vb, Verbal.
[3]?, comorbidity was not declared; -, comorbidity was an exclusion criteria; ADHD, Attention Deficit and Hyperactivity Disorder; CAPD, Central Auditory Processing Disorder; VPLD, Visual Perceptual Learning Disorder; Enc, Encopresis, CTD, Chronic Tic Disorder; Dys, Dysthymia; MDD, Major Depressive Disorder.
[4]?, the medication status of the subjects was not described; - ongoing medication was an exclusion criteria AAP, Atypical AntiPsychotic; MNS, Medication type not specified; TAP, Typical AntiPsychotic; Ato, Atomoxetine; Met, Methylphenidate; Val, Valproate; PS, Psychostimulant; SSRI, Selective Serotonin Reuptake Inhibitor; MM: Multiple Medication; Tgr, Tegretol; Alb, Albuterol; Fluv, Fluvoxamine, Bec, Beclometasone; Alp, Alprazolam; Ven, Venlafaxine; Arip, Aripiprazole; Clom, Clomipramine; Lith, Lithium; Gua, Guanfacine; AP, AntiPsychotic; PTM, psychotropic medication; NS Not Specified.
[5]Congr, congruence; Detect, Detection; Diff, Different Discrim, Discrimination; Em, Emotion(al); Express, Expression; Fam, Familiar; Judge, Judgment; Label, Labeling; Match, Matching; Non-fam, Nonfamiliar; Recogn, Recognition.
[a]Sensitivity analysis on age groups: adult group.
[c]Sensitivity analysis on age groups: child/adolescent group.
°Four subjects were under the specified medications but is not specified whether each subject was tacking only one drug.
°°Twelve subjects were under medication with a not specified combination of the following (2 SSRI, 10 medication for ADHD, 4 AAP, 1 anxiolytic medication).
°°°In the paper was only stated that '… participants were not asked to withhold medication prior to testing'.
*Only ranges were provided: standard deviation was approximated according to the formula: (max_value – min_value)/4 as described inHozo, Djulbegovic, & Hozo, 2005.
**Standard deviation was calculated: in the paper the ages of each participant were presented.
***Only mean age was reported.

Table 2 Significant clusters for the comparison between autism spectrum disorder (ASD) and healthy controls (HC) using the primary analysis convergence of difference method

Contrast	Hemisphere	Region	BA	Center of mass			Peak			Peak ALE *p* value	Volume (mm3)
				x	y	z	x	y	z		
HC > ASD											
Whole sample				−25.3	−1.4	−12.1					1,112
	L	Amygdala					−28	−4	−10	.021	
	L	PHG	34				−24	0	−14	.020	
Adult sample				−25.6	0.3	−11.7					1,208
	L	Amygdala					−28	−4	−12	.019	
	L	PHG	34				−24	0	−14	.019	

ASD, autism spectrum disorder; HC, healthy controls; L, left; R, right; PHG, parahippocampal gyrus; $p < .01$ corrected.

groups and no significant cluster of convergence identified for either. Post hoc analysis (Table S5) showed that only two studies (Kim et al., 2015; Whyte, Behrmann, Minshew, Garcia, & Scherf, 2016) in children/adolescent group versus nine in the adult group reported amygdala activation for the HC vs. ASD contrast.

'Pure' face perception. The results were significant in the right amygdala for the HC > ASD (21 experiments) (Table S6 and Figure S4). For the ASD > HC meta-analysis (11 experiments), we did not find significant results.

Pooled analysis. The pooled analysis found a convergence of differences in the two amygdalae (Table S7 and Figure S5).

Sensitivity analyses for the secondary analysis

No significant cluster was evidenced for the ASD > HC meta-analysis (11 studies) using the same threshold of primary analysis. However, with a more liberal threshold ($p < .01$ uncorrected) we found a significant cluster of convergence in a cluster including the left amygdala and parahippocampus, largely overlapping with that in the primary analysis. (Table S8, Figure S6). The HC > ASD meta-analysis (18 experiments) did not yield significant results.

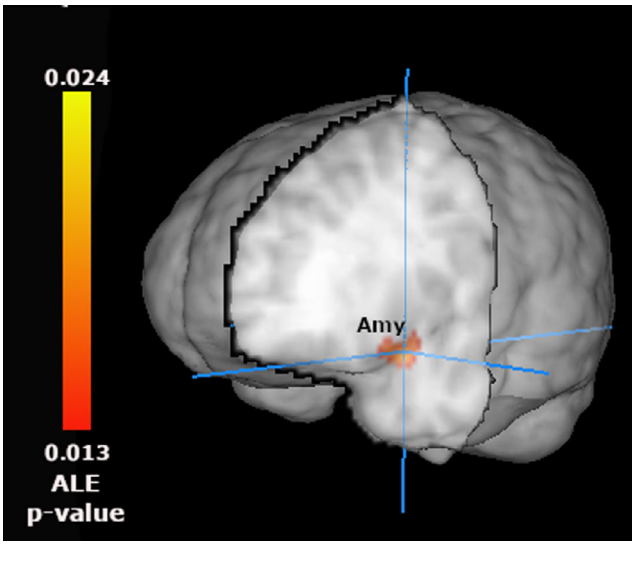

Figure 2 Significant results for the HC > ASD contrast of interest ($p < .01$ corrected). Amy: amygdala. ALE *p*-value: activation likelihood estimation probability

Discussion

ALE meta-analysis results

In this voxel-wise whole-brain ALE meta-analysis, we did not uncover differences in convergence in the 'core system' for face perception, particularly the fusiform gyrus, contradicting previous single studies (e.g., Deffke et al., (2007)). However, our findings support a crucial role for the 'extended system', confirming the involvement of limbic and subcortical structures, such as the amygdala and parahippocampal gyrus. Specifically, in the primary analysis including all studies reporting direct comparisons between HC and ASD, we found differences in convergence in the left amygdala extending to the parahippocampal gyrus. Findings were supported in the pooled analysis, which revealed a bilateral amygdala cluster. A sensitivity analysis limited to 'pure' face perception tasks also highlighted the altered activity of the amygdala, although with a different location (contralateral – right – amygdala). Examination of single studies indicated this difference was related to a higher activation of these regions in controls versus ASD participants during visual processing of face stimuli. Of note, very similar results were obtained in analyses restricted to studies in which participant mean age was over sixteen years (adult subgroup). Conversely, analyses limited to studies with participant mean age of 16 years or less (children/adolescent group) did not identify any significant clusters. Examination of the primary studies corroborated these findings, showing that only two studies of the children/adolescent group versus nine in the adult group reported differences in amygdala. These findings are consistent with behavioral studies suggesting that

impairments in face perception in ASD might not be present in childhood, but develop from the age of fifteen (Guy, Habak, Wilson, Mottron, & Bertone, 2017). Moreover, neuroimaging studies demonstrated that the neural network underpinning face perception undergoes a slow process of maturation during childhood and adolescence, including a blunted response of the amygdala in normally developing children (Behrmann, Scherf, & Avidan, 2016; Pfeifer et al., 2011). However, there are important caveats to consider in the interpretations of these findings. First, the children/adolescent group included only 14 studies for the HC > ASD meta-analysis and, respectively, 10 for ASD > HC meta-analysis, making both analyses underpowered and possibly unreliable. Indeed, simulation studies suggest that ALE meta-analysis results can be considered stable with at least 17 to 20 studies (Eickhoff et al., 2016). Secondly, a mean age of 16 years is an arbitrary threshold. We chose it because, assuming a Gaussian (or almost Gaussian) distribution, at least half of the participants would have been 16 years old or under. Finally, participants' age varied greatly both between and within studies, as indicated by the often-large standard deviations and ranges of mean age. By using study--level estimates, we could not test the possible confounding role of age variability within the single study samples, which would have required using unthresholded individual participant maps.

The amygdala is crucial for emotional processing. Its abnormal activity may contribute to impairments in social interactions, face and emotional recognition (Donovan & Basson, 2017). Both structural and functional amygdala alterations were often reported in ASD participants (Donovan & Basson, 2017; Kemper & Bauman, 1993). For instance, adults with ASD showed no amygdala activation during the *'Judging the Mind in the Eyes'* task, whereas healthy participants showed activation of the left amygdala (Baron-Cohen et al., 1999). In an in-depth examination of the included studies, we discovered that one third reported a unilateral amygdala activation, which was left-localized in eight studies and right-localized in four. However, only one study included a discussion of lateralization (Baron-Cohen et al., 1999) (Table S5). Differences in convergence in the left amygdala lend further support to the oft-cited notion that the two amygdalae underpin different functions (Gainotti, 2018; Gläscher & Adolphs, 2003; Zalla et al., 2000), with the left involved in more 'cold' cognitive and detailed processing of emotions (Dyck et al., 2011; Gainotti, 2018; Gläscher & Adolphs, 2003). As we included all studies involving faces as stimuli regardless of the task, our findings offer additional evidence for the specific involvement of the left amygdala in the ability of inferring mental state from complex visual stimuli (e.g., eyes region), frequently impaired in ASD (Baron-Cohen et al., 1999; Ketter et al., 1996). Finally, it is important to underscore that our results are derived from whole-brain analysis only. Conversely, significant amygdala findings are often only detected in studies relying on ROI analyses, given its small volume and the use of stringent type I error methods, like the frequently used cluster-wise approach (Gentili, Cecchetti, Handjaras, Lettieri, & Cristea, 2020). The use of other, less conservative but still valid methods for type I error correction, like false discovery rate, voxel-wise correction, equitable thresholding, and clustering (Cox, 2019), appear better suited to detect differences in amygdala activation. Alternatively, preregistration of ROI analyses might be a way of reducing the risk of false positives and effect inflation (Gentili et al., 2020).

Our findings failed to replicate the results of two previous meta-analyses (Aoki et al., 2015; Nickl--Jockschat et al., 2015) which found ASD-related hyperactivation in thalamus, caudate, and precuneus, and ASD-related hypoactivation in the hypothalamus (Aoki et al., 2015) in one case and a ASD-related hypoactivation in the fusiform gyrus in the other (Nickl-Jockschat et al., 2015). Divergences could be explained by different reasons. Importantly, we diverged from the two previous meta-analyses in the inclusion criteria. Specifically, both previous works included coordinates from ROI-based analyses, which we excluded. The use of coordinates from ROI-based analyses in neuroimaging meta-analysis was shown to increase the risk of inflated significance for those regions which are overrepresented in ROI analyses as, for example, amygdala (Gentili et al., ,,2019, 2020; Muller et al., 2018) and is currently discouraged. Furthermore, the two previous meta-analyses included a limited number of studies (13 in Aoki et al., (2015) and 14 in Nickl-Jockschat et al., (2015)), making analyses likely underpowered. For the ALE approach, Eickhoff et al., (2016), the developers of the method, underline how for less than 17 experiments there is a high risk of findings being driven by clusters of one or a few studies (false positives cluster). In contrast, the current meta-analysis synthesizes almost a double number of studies. Finally, while our study and that of Nickl-Jockschat et al., (2015) used the ALE approach to coordinate-based meta-analysis, Aoki et al., (2015) used the signed differential mapping (SDM) (Radua & Mataix-Cols, 2009) with random effects mode. This latter approach combines feature of ALE and multilevel kernel density analysis (MKDA) (Wager, Lindquist, & Kaplan, 2007) approaches. It is possible that different results were also due to the different methods used, especially since we are not aware of a direct comparison between the ALE and SDM methodologies, though comparisons of ALE with other approaches including MKDA showed consistent findings (Salimi-Khorshidi, Smith, Keltner, Wager, & Nichols, 2009).

'Convergence of differences' OR 'differences in convergence'?

From a methodological standpoint, we report on the first, to our knowledge, comparison within the same dataset of the two current ALE meta-analysis approaches: convergence of differences, which combines study-level activations for the contrast of ASD and HC, and differences in convergence, which combines study-level activations within each group to compute two separate meta-analyses, one for ASD and one for HC, and subsequently contrasts these single group results (Muller et al., 2018). Such meta-analytic contrast highlighted the locations where in one group stronger convergence is found compared to the other.

We demonstrate that the two approaches yield highly divergent results. The first resulted into a significant cluster of convergence of differences in the left amygdala, whereas the second yielded no differences between groups. However, the second approach was limited to studies that reported results within single groups and consequently relied on fewer studies. To test for the possibility that divergences between the two methods would be explained by differences in the number of included studies, we conducted a sensitivity analysis applying the first method to the pool of studies used in the second: a single cluster was evidenced, consistent with the primary findings.

Despite the limitation of this analysis (lower threshold and small number of experiments included – 11), it is unlikely that the divergent findings yielded by the two methods can be attributed to variations in the number of included studies. Rather, the discrepancy is probably grounded within the structure of ALE meta-analysis, which combines activations reported as significant within each study into a measure of convergence, that is, declaring higher convergence if more studies reported activations in the same area. Unavoidably, the method draws heavily on the data analysis approach employed in each single study. For instance, a study with a more lenient or even inappropriate correction for the statistical threshold of activation will still contribute to convergence results. This problem is likely enhanced in meta-analyses examining convergence of single group activations (i.e., the 2nd method) rather convergence of reported differences in activation. For instance, assuming an fMRI study uses 20 patients and 20 matched controls performing the same task, comparisons in brain activation between the two groups rely on more participants and therefore have more power than the examination of task-related activations within each group.

Moreover, examining convergence resulting from activations within single groups (e.g., patients or controls), rather than convergence resulting from contrasts between groups, might obscure important differences, as well as elevate marginal ones. For instance, using the differences in convergence approach, we found no differences in the activation of the amygdala between ASD and controls, despite the fact one third of the studies reported significant activation for this contrast. This result is probably explained by the fact that the amygdala was activated, albeit differentially in the two groups, resulting in a significant convergence within both ASD and HC. While differences in magnitude of activations are significant at a single experiment level in many cases, difference of convergence may not be significant.

Limitations and conclusions

One important limitation regards a considerable number of studies (n = 73) that were excluded for not reporting between groups contrasts for the face perception task (n = 20), performing only a comparison of functional connectivity (n = 4), not providing brain activation coordinates for a contrast (n = 6), or reporting only ROI analyses (n = 40). Since studies were not prospectively registered, the decision to not report or selectively report contrast data might have hinged on statistical significance, with negative or inconsistent findings suppressed. The high number of excluded papers is in itself an indication of heterogeneity in the literature reviewed. Although the total number of included studies was adequate, some sensitivity analysis (e.g., those with less than 17 studies) is underpowered and needs to be considered as preliminary (Eickhoff et al., 2016). Furthermore, though all included studies used faces, tasks were heterogeneous and differences among them could account for the few significant findings reported in this meta-analysis. This is an unavoidable limitation of the ALE approach, which aims to highlight the commonalities across studies. However, given the limited number of experiments using ASD participants and faces, stricter inclusion criteria would have resulted into a restricted pool of studies and considerably reduced the power to reliably detect any differences. Another limit related to ALE approach, as to every coordinate-based meta-analysis, is the risk of information lost as compared to maps meta-analysis (Salimi-Khorshidi et al., 2009): more differences between ASD and HC could be found in the original spatial maps and lost using this technique. However, coordinate-based meta-analysis represents a good trade-off given the relatively low amount of available original data. A more general issue in relying on collections of different neuroimaging studies, even when systematically identified, is the lack of a gold standard for preprocessing and data analysis and reporting. For instance, although our evaluation of possible biases suggests an overall good quality of the studies included, only few of them upheld updated 'good practices' for type I error correction, meaning that false positive or inflated findings could have made

their way into the meta-analysis. Biases related to the use of different analysis software or pipelines are even more complex to address. While the more widely used softwares (including AFNI, FSL, SPM) are all accepted by the scientific community for fMRI data analysis, there have been growing concerns about the passivity they could produce different results (Bowring, Maumet, & Nichols, 2019). Similar concerns were raised for differences in analytic pipelines, though there is no agreement on whether a pipeline is better than another. Yet, even slight changes in the order of preprocessing or analysis steps could impact the final results (Alakörkkö, Saarimäki, Glerean, Saramäki, & Korhonen, 2017; Carp, 2012). Finally, the current meta-analysis was not pre-registered, although we planned it as inclusive and straightforward as possible.

In sum, using ALE meta-analysis, we found support for a key role of amygdala dysfunctions in underpinning face processing in individuals with autism spectrum disorders. Our findings would suggest that the core alteration of ASD relies on brain structures involved in emotional processing rather than perception, particularly since we did not report any significant differences in the core face perception system. Combining participant-level unthresholded maps from all eligible studies could offer a more definitive answer on brain activity alterations in ASD individuals. Furthermore, we demonstrate that the two current ALE meta-analysis approaches can lead to highly divergent results. Neither represents a meta-analysis in a strict sense (Müller et al., 2018), since essential features such weighting of included studies or quantification of heterogeneity are absent from the ALE methodology or indeed any neuroimaging meta-analysis (Higgins & Green, 2011). Hence, both methods should be viewed as tools for descriptively summarizing neuroimaging literature. Crucially, only statistically significant results are combined in an ALE meta-analysis, leading to an unavoidably biased summary of the literature. These limitations notwithstanding, the approach based on the convergence of differences appears to mirror single study findings more closely and is thus probably better suited for summarizing available data. The more complex question as to whether either method describes 'real' rather than spurious differences in brain activity remains open.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Methods.

Appendix S2. Results.

Table S1. Description of contrasts/experiments (exp) reporting a direct comparison between autistic spectrum disorder patients and healthy controls in each included study.

Table S2. Study-level risk bias ratings (after consensus) and the kappa inter-rater agreement (before consensus).

Table S3. Studies and contrasts within studies included in the secondary analysis (differences in convergence).

Table S4. Significant clusters of convergence during facial processing within each of the HC and ASD groups.

Table S5. Post hoc study-level examination of significant clusters (Amygdala) evidenced with the primary analysis (convergence of differences).

Table S6. Sensitivity analysis: pure face perception.

Table S7. Sensitivity analysis: pooled analysis.

Table S8. Sensitivity analysis: secondary analysis (differences in convergence).

Figure S1. Study quality according to the modified version of the Newcastle–Ottawa Scale.

Figure S2. Significant clusters of convergence within HC and ASD groups during face perception tasks.

Figure S3. Sensitivity analysis for age subgroups.

Figure S4. Sensitivity analysis: 'pure' face perception.

Figure S5. Sensitivity analysis: pooled analysis.

Figure S6. Significant clusters for the comparison between autism spectrum disorder (ASD) and healthy controls (HC) in studies reporting single group activation using the convergence of difference method.

Acknowledgments

This work was carried out within the scope of the project 'use-inspired basic research', for which the Department of General Psychology of the University of Padova has been recognized as 'Dipartimento di Eccellenza' by the Ministry of University and Research. The authors declared the following author contributions. C. G. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: C.G. Acquisition, analysis, or interpretation of data: C.C., E.D-B., C.M., C.G. Statistical analysis: C.G., C.C., C.M., E.D-B. Study supervision: C.G. Manuscript Draft: C.C., C.G., I.A.C.

Critical revision of the manuscript for important intellectual content: C.G., I.A.C. Review of the final version of the manuscript: all. The authors have declared that they have no competing or potential conflicts of interest.

Correspondence

Claudio Gentili, Department of General Psychology, University of Padova, Via Venezia 8, 35135, Padova Italy; Email: c.gentili@unipd.it

Key points

- An increasing number of neuroimaging studies evaluated face perception in autism spectrum disorders (ASD) suggesting both an alteration of emotional structures (e.g., amygdala complex) and perceptive structures (e.g., fusiform gyrus).
- We compared two ALE meta-analysis approaches examining face processing in autism, Convergence of differences: using studylevel coordinates from ASD vs. healthy controls contrasts and Difference in convergence: contrast between two ALE-maps (one per group).
- Single significant result was found in amygdala for the convergence of differences analysis.
- While the two ALE methodologies lead to divergent results our findings suggest a primary role of amygdala dysfunction in altered face perception in ASD.

References

Alakörkkö, T., Saarimäki, H., Glerean, E., Saramäki, J., & Korhonen, O. (2017). Effects of spatial smoothing on functional brain networks. *European Journal of Neuroscience*, *46*, 2471–2480.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub.

Aoki, Y., Cortese, S., & Tansella, M. (2015). Neural bases of atypical emotional face processing in autism: A meta-analysis of fMRI studies. *The World Journal of Biological Psychiatry*, *16*, 291–300.

Baranek, G.T., Watson, L.R., Boyd, B.A., Poe, M.D., David, F. J., & McGuire, L. (2013). Hyporesponsiveness to social and nonsocial sensory stimuli in children with autism, children with developmental delays, and typically developing children. *Development and Psychopathology*, *25*, 307–320.

Baron-Cohen, S., Ring, H., Bullmore, E., Wheelwright, S., Ashwin, C., & Williams, S. (2000). The amygdala theory of autism. *Neuroscience and Biobehavioral Reviews*, *24*, 355–364.

Baron-Cohen, S., Ring, H.A., Wheelwright, S., Bullmore, E.T., Brammer, M.J., Simmons, A., & Williams, S.C. (1999). Social intelligence in the normal and autistic brain: An fMRI study. *European Journal of Neuroscience*, *11*, 1891–1898.

Behrmann, M., Scherf, K.S., & Avidan, G. (2016). Neural mechanisms of face perception, their emergence over development, and their breakdown. *Wiley Interdisciplinary Reviews: Cognitive Science*, *7*, 247–263.

Bi, T., & Fang, F. (2017). Impaired face perception in individuals with autism spectrum disorder: Insights on diagnosis and treatment. *Neuroscience Bulletin*, *33*, 757–759.

Bölte, S., Ciaramidaro, A., Schlitt, S., Hainz, D., Kliemann, D., Beyer, A., … Walter, H. (2015). Training-induced plasticity of the social brain in autism spectrum disorder. *British Journal of Psychiatry*, *207*, 149–157.

Bowring, A., Maumet, C., & Nichols, T.E. (2019). Exploring the impact of analysis software on task fMRI results. *Human Brain Mapping*, *40*, 3362–3384.

Boyd, B.A., Baranek, G.T., Sideris, J., Poe, M.D., Watson, L.R., Patten, E., & Miller, H. (2010). Sensory features and repetitive behaviors in children with autism and developmental delays. *Autism Research*. https://doi.org/10.1002/aur.124

Brandenburg-Goddard, M.N., van Rijn, S., Rombouts, S.A., Veer, I.M., & Swaab, H. (2014). A comparison of neural correlates underlying social cognition in Klinefelter syndrome and autism. *Social Cognitive and Affective Neuroscience*, *9*, 1926–1933.

Ciaramidaro, A., Bölte, S., Schlitt, S., Hainz, D., Poustka, F., Weber, B., … Walter, H. (2018). Transdiagnostic deviant facial recognition for implicit negative emotion in autism and schizophrenia. *European Neuropsychopharmacology*, *28*, 264–275.

Carp, J. (2012). The secret lives of experiments: Methods reporting in the fMRI literature. *NeuroImage*, *63*, 289–300.

Cox, R.W., Chen, G., Glen, D.R., Reynolds, R.C., & Taylor, P.A. (2017). fMRI clustering and false-positive rates. *Proceedings of the National Academy of Sciences*, *114*, E3370–E3371.

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 Research*, *173*, 196–205.

Cox, R.W. (2019). Equitable thresholding and clustering: a novel method for functional magnetic resonance imaging clustering in AFNI. *Brain Connect*, *9*, 529–538.

Critchley, H.D., Daly, E.M., Bullmore, E.T., Williams, S.C., van Amelsvoort, T., Robertson, D.M., … & Murphy, D.G. (2000). The functional neuroanatomy of social behaviour: Changes in cerebral blood flow when people with autistic disorder process facial expressions. *Brain: A Journal of Neurology*, *123*, 2203–2212.

Dalton, K.M., Nacewicz, B.M., Johnstone, T., Schaefer, H.S., Gernsbacher, M.A., Goldsmith, H.H., … & Davidson, R.J. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience*, *8*, 519–526.

Dapretto, M., Davies, M.S., Pfeifer, J.H., Scott, A.A., Sigman, M., Bookheimer, S.Y., & Iacoboni, M. (2006). Understanding emotions in others: Mirror neuron dysfunction in children with autism spectrum disorders. *Nature Neuroscience*, *9*, 28–30.

Davies, M.S., Dapretto, M., Sigman, M., Sepeta, L., & Bookheimer, S.Y. (2011). Neural bases of gaze and emotion processing in children with autism spectrum disorders. *Brain and Behavior*, *1*, 1–11.

Dawson, G., Webb, S.J., & McPartland, J. (2005). Understanding the nature of face processing impairment in autism: Insights from behavioral and electrophysiological studies. *Developmental Neuropsychology*, *27*, 403–424.

Deeley, Q., Daly, E.M., Surguladze, S., Page, L., Toal, F., Robertson, D., … Murphy, D.G. (2007). An event related functional magnetic resonance imaging study of facial emotion processing in asperger syndrome. *Biological Psychiatry*, *62*, 207–217.

Deffke, I., Sander, T., Heidenreich, J., Sommer, W., Curio, G., Trahms, L., & Lueschow, A. (2007). MEG/EEG sources of the 170-ms response to faces are co-localized in the fusiform gyrus. *NeuroImage*, *35*, 1495–1501.

Donovan, A.P.A., & Basson, M.A. (2017). The neuroanatomy of autism - A developmental perspective. *Journal of Anatomy*, *230*, 4–15.

Doyle-Thomas, K.A., Goldberg, J., Szatmari, P., & Hall, G.B. (2013). Neurofunctional underpinnings of audiovisual emotion processing in teens with autism spectrum disorders. *Frontiers in Psychiatry*, *4*, 48.

Duerden, E.G., Taylor, M.J., Soorya, L.V., Wang, T., Fan, J., & Anagnostou, E. (2013). Neural correlates of inhibition of socially relevant stimuli in adults with autism spectrum disorder. *Brain Research*, *1533*, 80–90.

Dyck, M., Loughead, J., Kellermann, T., Boers, F., Gur, R.C., & Mathiak, K. (2011). Cognitive versus automatic mechanisms of mood induction differentially activate left and right amygdala. *NeuroImage*, *54*, 2503–2513.

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., & Fox, P.T. (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping*, *30*, 2907–2926.

Eickhoff, S.B., Nichols, T.E., Laird, A.R., Hoffstaedter, F., Amunts, K., Fox, P.T., … & Eickhoff, C.R. (2016). Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation. *NeuroImage*, *137*, 70–85.

Eklund, A., Nichols, T.E., & Knutsson, H. (2016). Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences*, *113*, 7900–7905.

Gainotti, G. (2018). A historical review of investigations on laterality of emotions in the human brain. *Journal of the History of the Neurosciences*, *28*, 23–41.

Gentili, C., Cecchetti, L., Handjaras, G., Lettieri, G., & Cristea, I.A. (2020). The case for preregistering all region of interest (ROI) analyses in neuroimaging research. *European Journal of Neuroscience*, *53*, 357–361.

Gentili, C., Messerotti Benvenuti, S., Lettieri, G., Costa, C., & Cecchetti, L. (2018). ROI and phobias: The effect of ROI approach on an ALE meta-analysis of specific phobias. *Human Brain Mapping*, *40*, 1814–1828.

Gläscher, J., & Adolphs, R. (2003). Processing of the arousal of subliminal and supraliminal emotional stimuli by the human amygdala. *The Journal of Neuroscience*, *23*, 10274–10282.

Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., … & Etkin, A. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry*, *72*, 305–315.

Greimel, E., Nehrkorn, B., Fink, G.R., Kukolja, J., Kohls, G., Muller, K., … & Schulte-Ruther, M. (2012). Neural mechanisms of encoding social and non-social context information in autism spectrum disorder. *Neuropsychologia*, *50*, 3440–3449.

Greimel, E., Schulte-Rüther, M., Kircher, T., Kamp-Becker, I., Remschmidt, H., Fink, G.R., … Konrad, K. (2010). Neural mechanisms of empathy in adolescents with autism spectrum disorder and their fathers. *NeuroImage*, *49*, 1055–1065.

Grelotti, D.J., Gauthier, I., & Schultz, R.T. (2002). Social interest and the development of cortical face specialization: What autism teaches us about face processing. *Developmental Psychobiology*, *40*, 213–225.

Guy, J., Habak, C., Wilson, H.R., Mottron, L., & Bertone, A. (2017). Face perception develops similarly across viewpoint in children and adolescents with and without autism spectrum disorder. *Journal of Vision*, *17*, 38.

Hadjikhani, N., Zürcher, N.R., Rogier, O., Hippolyte, L., Lemonnier, E., Ruest, T., … & Gillberg, C. (2014). Emotional contagion for pain is intact in autism spectrum disorders. *Transl Psychiatry*, *4*, e343.

Harms, M.B., Martin, A., & Wallace, G.L. (2010). Facial emotion recognition in autism spectrum disorders: A review of behavioral and neuroimaging studies. *Neuropsychology Review*, *20*, 290–322.

Haxby, J.V., Hoffman, E.A., & Gobbini, M.I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences*, *4*, 223–233.

Herrington, J.D., Riley, M.E., Grupe, D.W., & Schultz, R.T. (2015). Successful face recognition is associated with increased prefrontal cortex activation in autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *45*, 902–910.

Higgins, J.P.T., & Green, S. (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration.

Hileman, C.M., Henderson, H., Mundy, P., Newell, L., & Jaime, M. (2011). Developmental and individual differences on the P1 and N170 ERP components in children with and without autism. *Developmental Neuropsychology*, *36*, 214–236.

Hobson, R.P., Ouston, J., & Lee, A. (1988). What's in a face? The case of autism. *British Journal of Psychology*, *79*, 441–453.

Holt, R.J., Chura, L.R., Lai, M.C., Suckling, J., vondem Hagen, E., Calder, A.J., … Spencer, M.D. (2014). 'Reading the Mind in the Eyes': An fMRI study of adolescents with autism and their siblings. *Psychological Medicine*, *44*, 3215–3227.

Hozo, S.P., Djulbegovic, B., & Hozo, I. (2005). Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology*, *5*, 13.

Ishitobi, M., Kosaka, H., Omori, M., Matsumura, Y., Munesue, T., Mizukami, K., … Wada, Y. (2011). Differential amygdala response to lower face in patients with autistic spectrum disorders: An fMRI study. *Research in Autism Spectrum Disorders*, *5*, 910–919.

Kemper, T.L., & Bauman, M.L. (1993). The contribution of neuropathologic studies to the understanding of autism. *Neurologic Clinics*, *11*, 175–187.

Ketter, T.A., Andreason, P.J., George, M.S., Lee, C., Gill, D.S., Parekh, P.I., … & Post, R.M. (1996). Anterior paralimbic mediation of procaine-induced emotional and psychosensory experiences. *Archives of General Psychiatry*, *53*, 59–69.

Kim, S.Y., Choi, U.S., Park, S.Y., Oh, S.H., Yoon, H.W., Koh, Y. J., … & Lee, C.U. (2015). Abnormal activation of the social brain network in children with autism spectrum disorder: An FMRI study. *Psychiatry Investigation*, *12*, 37–45.

Klapwijk, E.T., Aghajani, M., Colins, O.F., Marijnissen, G.M., Popma, A., van Lang, N.D., … Vermeiren, R.R. (2016). Different brain responses during empathy in autism spectrum disorders versus conduct disorder and callous-unemotional traits. *Journal of Child Psychology and Psychiatry*, *57*, 737–747.

Koshino, H., Kana, R.K., Keller, T.A., Cherkassky, V.L., Minshew, N.J., & Just, M.A. (2008). fMRI investigation of working memory for faces in autism: Visual coding and underconnectivity with frontal areas. *Cerebral Cortex*, *18*, 289–300.

Lassalle, A., Johnels, J.A., Zurcher, N.R., Hippolyte, L., Billstedt, E., Ward, N., … Hadjikhani, N. (2017). Hypersensitivity to low intensity fearful faces in autism when fixation is constrained to the eyes. *Human Brain Mapping*, *38*, 5943–5957.

Loveland, K.A., Steinberg, J.L., Pearson, D.A., Mansour, R., & Reddoch, S. (2008). Judgments of auditory-visual affective congruence in adolescents with and without autism: A pilot study of a new task using fMRI. *Perceptual and Motor Skills*, *107*, 557–575.

Morin, K., Guy, J., Habak, C., Wilson, H.R., Pagani, L., Mottron, L., & Bertone, A. (2015). Atypical face perception in autism: A point of view? *Autism Research*, *8*, 497–506.

Morita, T., Kosaka, H., Saito, D.N., Ishitobi, M., Munesue, T., Itakura, S., … Sadato, N. (2012). Emotional responses

associated with self-face processing in individuals with autism spectrum disorders: An fMRI study. *Social Neuroscience*, *7*, 223–239.

Muller, V.I., Cieslik, E.C., Laird, A.R., Fox, P.T., Radua, J., Mataix-Cols, D., … & Eickhoff, S.B. (2018). Ten simple rules for neuroimaging meta-analysis. *Neuroscience and Biobehavioral Reviews*, *84*, 151–161.

Muller, V.I., Cieslik, E.C., Serbanescu, I., Laird, A.R., Fox, P.T., & Eickhoff, S.B. (2017). Altered brain activity in unipolar depression revisited: Meta-analyses of neuroimaging studies. *JAMA Psychiatry*, *74*, 47–55.

Nickl-Jockschat, T., Rottschy, C., Thommes, J., Schneider, F., Laird, A.R., Fox, P.T., & Eickhoff, S.B. (2015). Neural networks related to dysfunctional face processing in autism spectrum disorder. *Brain Structure & Function*, *220*, 2355–2371.

Pelphrey, K.A., Yang, D.Y.J., & McPartland, J.C. (2014). Building a social neuroscience of autism spectrum disorder. *Current Topics in Behavioral Neurosciences*, *16*, 215–233.

Pfeifer, J., Masten, C., Moore, W., Oswald, T., Mazziotta, J., Iacoboni, M., & Dapretto, M. (2011). Entering adolescence: Resistance to peer influence, risky behavior, and neural changes in emotion reactivity. *Neuron*, *69*, 1029–1036.

Perlman, S.B., Hudac, C.M., Pegors, T., Minshew, N.J., & Pelphrey, K.A. (2011). Experimental manipulation of faceevoked activity in the fusiform gyrus of individuals with autism. *Social Neuroscience*, *6*, 22–30.

Radua, J., & Mataix-Cols, D. (2009). Voxel-wise meta-analysis of grey matter changes in obsessive–compulsive disorder. *British Journal of Psychiatry*, *195*, 393–402.

Rahko, J.S., Paakki, J.J., Starck, T.H., Nikkinen, J., Pauls, D. L., Kätsyri, J.V., … Kiviniemi, V. (2012). Valence scaling of dynamic facial expressions is altered in high-functioning subjects with autism spectrum disorders: An fMRI study. *Journal of Autism and Developmental Disorders*, *42*, 1011–1024.

Robertson, C.E., & Baron-Cohen, S. (2017). Sensory perception in autism. *Nature Reviews Neuroscience*, *18*, 671–684.

Salimi-Khorshidi, G., Smith, S.M., Keltner, J.R., Wager, T.D., & Nichols, T.E. (2009). Meta-analysis of neuroimaging data: A comparison of image-based and coordinate-based pooling of studies. *NeuroImage*, *45*, 810–823.

Sabatino, A., Rittenberg, A., Sasson, N.J., Turner-Brown, L., Bodfish, J.W., & Dichter, G.S. (2013). Functional neuroimaging of social and nonsocial cognitive control in autism. *Journal of Autism and Developmental Disorders*, *43*, 2903–2913.

Scherf, K.S., Elbich, D., Minshew, N., & Behrmann, M. (2015). Individual differences in symptom severity and behavior predict neural activation during face processing in adolescents with autism. *NeuroImage Clinical*, *7*, 53–67.

Schultz, R.T., Grelotti, D.J., Klin, A., Kleinman, J., van der Gaag, C., Marois, R., & Skudlarski, P. (2003). The role of the fusiform face area in social cognition: Implications for the pathobiology of autism. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *358*, 415–427.

Shafritz, K.M., Bregman, J.D., Ikuta, T., & Szeszko, P.R. (2015). Neural systems mediating decision-making and response inhibition for social and nonsocial stimuli in autism. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *60*, 112–120.

Stanfield, A.C., Philip, R.C.M., Whalley, H., Romaniuk, L., Hall, J., Johnstone, E.C., & Lawrie, S.M. (2017). Dissociation of brain activation in autism and schizotypal personality disorder during social judgments. *Schizophrenia Bulletin*, *43*, 1220–1228.

Turkeltaub, P.E., Eickhoff, S.B., Laird, A.R., Fox, M., Wiener, M., & Fox, P. (2012). Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. *Human Brain Mapping*, *33*, 1–13.

Turner-Brown, L.M., Baranek, G.T., Reznick, J.S., Watson, L. R., & Crais, E.R. (2013). The First Year Inventory: a longitudinal follow-up of 12-month-old to 3-year-old children. *Autism*, *17*, 527–540.

Velasquez, F., Qin, X.A., Reilly, M.A., Neuhaus, E., Estes, A., Aylward, E., & Kleinhans, N.M. (2017). Neural correlates of emotional inhibitory control in autism spectrum disorders. *Research in Developmental Disabilities*, *64*, 64–77.

Wager, T.D., Lindquist, M., & Kaplan, L. (2007). Meta-analysis of functional neuroimaging data: Current and future directions. *Social Cognitive and Affective Neuroscience*, *2*, 150–158.

Weigelt, S., Koldewyn, K., & Kanwisher, N. (2012). Face identity recognition in autism spectrum disorders: a review of behavioral studies. *Neurosci Biobehav Rev.*, *36*, 1060–84. https://doi.org/10.1016/j.neubiorev.2011.12.008.

Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2014). Newcastle-Ottawa quality assessment scale cohort studies. University of Ottawa.

Weng, S.J., Carrasco, M., Swartz, J.R., Wiggins, J.L., Kurapati, N., Liberzon, I., … Monk, C.S. (2011). Neural activation to emotional faces in adolescents with autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *52*, 296–305.

Whyte, E.M., Behrmann, M., Minshew, N.J., Garcia, N.V., & Scherf, K.S. (2016). Animal, but not human, faces engage the distributed face network in adolescents with autism. *Developmental Science*, *19*, 306–317.

Zalla, T., Koechlin, E., Pietrini, P., Basso, G., Aquino, P., Sirigu, A., & Grafman, J. (2000). Differential amygdala responses to winning and losing: a functional magnetic resonance imaging study in humans: Amygdala response to winning and losing. *European Journal of Neuroscience*, *12*, 1764–1770.

Zürcher, N.R., Donnelly, N., Rogier, O., Russo, B., Hippolyte, L., Hadwin, J., … & Hadjikhani, N. (2013). It's all in the eyes: Subcortical and cortical activation during grotesqueness perception in autism. *PLoS One*, *8*, e54313.

Zürcher, N.R., Rogier, O., Boshyan, J., Hippolyte, L., Russo, B., Gillberg, N., … Hadjikhani, N. (2013a). Perception of social cues of danger in autism spectrum disorders. *PLoS One*, *8*, e81206.

Zürcher, N.R., Donnelly, N., Rogier, O., Russo, B., Hippolyte, L., Hadwin, J., … Hadjikhani, N. (2013b). It's all in the eyes: Subcortical and cortical activation during grotesqueness perception in autism. *PLoS One*, *8*, e54313.

Accepted for publication: 20 January 2021