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Review

A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders

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ABSTRACT

Recent years have seen a rapid increase in the investigation of autism spectrum disorders (ASD) through the use of functional magnetic resonance imaging (fMRI). We carried out a systematic review and ALE meta-analysis of fMRI studies of ASD. A disturbance to the function of social brain regions is among the most well replicated finding. Differences in social brain activation may relate to a lack of preference for social stimuli as opposed to a primary dysfunction of these regions. Increasing evidence points towards a lack of effective integration of distributed functional brain regions and disruptions in the subtle modulation of brain function in relation to changing task demands in ASD. Limitations of the literature to date include the use of small sample sizes and the restriction of investigation to primarily high functioning males with autism.

Contents

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1. Introduction

Autism spectrum disorders (ASD) are characterised by difficulties in social interactions, communication impairments and a restricted repetitive pattern of interests and behaviours (American Psychiatric Association, 2000). Neuropsychological studies have identified many differences between individuals with ASD and controls, in particular differences in sensory processing, disturbances to executive function and a reduced capacity to appreciate the mental states of others (Rajendran and Mitchell, 2007). Whilst the difficulties which are prevalent in ASD are largely accepted as neurodevelopmental in origin, the changes to brain function which underlie the conditions are only recently being recognised. A major contributor to this increase in understanding has been the development of functional magnetic resonance imaging (fMRI), a technique which exploits differences in the ferromagnetic properties of oxygenated and deoxygenated blood to produce an indirect measure of neuronal activity (Cohen and Bookheimer, 1994). Since its development, fMRI has been widely applied in individuals with ASD using a variety of populations, tasks and methods of analysis. This review and meta-analysis aims to draw together this literature in order to characterise the populations examined and the methodology used so that common findings from across studies can be identified.

The aim of this review is to (1) assess the ASD populations taking part in fMRI research in terms of how representative they are of the ASD population as a whole; (2) identify common findings across studies which indicate brain regions which function differently in ASD, relative to typically developed individuals.

2. Methods

2.1. Literature search methods

Medline, EMBASE and PsychINFO were searched for all English language studies published between January 1984 and August 2009 that reported functional MRI data in people with an autism spectrum disorder. Search terms included 'autism', 'Asperger Syndrome', 'pervasive developmental disorder' and related terms were combined using the AND operator with 'functional magnetic resonance imaging' OR 'fMRI'. Both free-text and expanded medical subject headings were used. The search strategy was supplemented using a cited reference search and by inspecting the reference lists of included articles.

2.2. Inclusion criteria

Articles were included if they were primary research studies published as peer-reviewed articles in English and they compared a sample of participants with an autism spectrum disorder with a group of neurotypical controls, using fMRI. Abstracts were assessed for inclusion, and full text articles were retrieved where appropriate.

2.3. Data extraction

For each study, data for the ASD participant group were extracted: gender, mean age and mean IQ. Where possible, data pertaining to the diagnosis of the ASD group was also extracted, including the diagnostic criteria used. The selection of the comparison group and features by which they were matched to the ASD group was also recorded. Details of the fMRI paradigm were also extracted and studies grouped according to the element of cognition under investigation. The fMRI studies were allocated to six task domains: motor tasks; visual processing tasks; executive function tasks; auditory and language tasks; basic social processing tasks (face processing, emotion processing, motion in relation to social stimuli, eye gaze) and complex social cognition tasks (imitation, irony comprehension, empathy). Many tasks contain aspects from multiple domains and where this occurred the tasks were considered in more than one analysis. fMRI studies, which analysed functional and effective connectivity, were separately considered.

Within scanner performance was examined by extracting accuracy and reaction time data where available for the ASD and the control groups. For the meta-analysis, coordinates where the BOLD response differed significantly between the ASD and control groups were extracted where available.

2.4. ALE meta-analysis

Statistically significant foci from between group contrasts were recorded for each study. MNI coordinates were converted to Talairach coordinates. The meta-analyses were conducted with activation likelihood estimation (ALE 2.0). The ALE algorithm is based on models (Eickhoff et al., 2009) implemented in BrainMap (Laird et al., 2005). ALE models the activation foci as a three-dimensional Gaussian probability density function centred at the given coordinates. In the next step ALE calculates the spatial overlap of these distributions across different experiments. The spatial

uncertainty associated with activation foci is estimated to the inter-subject and inter-experiment variability. The convergence of activation patterns across studies is computed by taking the modelled activation maps. The estimation was constrained by a grey matter mask and estimated the above chance clustering with the experiments as a random-effects factor (Eickhoff et al., 2009).

For verification of ASD-related differences in activation for each task domain, we performed ALE analyses (ASD > C, C > ASD) for all six task domains separately. In addition, in the three task domains where studies with children and adolescents were available (auditory and language tasks, basic social tasks and complex social cognition tasks), separate analyses of children/adolescents (under 18 years old) and adults (over 18 years old) were carried out. Result map overlays were produced on a standardised structural scan for localisation.

3. Results

3.1. Included papers

95 Papers were identified which reported using fMRI to investigate ASD. One article performed spectroscopy analysis in conjunction with fMRI data presented elsewhere and was therefore excluded (Kleinhans et al., 2007). Three papers presented case studies so were also excluded (Turkeltaub et al., 2004; Grelotti et al., 2005; Carmody et al., 2007). Finally, one study was excluded as it investigated a group of participants with autism pre and post treatment and did not investigate a comparison group (Bölte et al., 2006). This left 90 original research papers in which a group of participants with ASD were investigated using functional MRI paradigms and compared to a control group.

3.2. Details of ASD participants

The largest sample size was a pooled analysis of data collected together from several other studies and concerned 57 participants with ASD. The largest original study contained 19 participants with ASD, whilst the smallest concerned only 5 individuals. Overall the mean number of participants with ASD per study was 12. Seven studies failed to report the gender ratio in their sample. Of those that did, 60% of studies investigated only male participants. The ratio of males to females participating across all fMRI studies is approximately 15:1. One study did not provide details of the age of the participants in their study. Of the remaining 89 studies, 24 concerned participants with a mean age of less than 18 and 65 concerned participants with a mean age of greater than 18. Almost all studies provided intelligence quotient (IQ) scores for the ASD participants in their study. The median full scale IQ score was 104, with a reported range of 55–139. The majority of studies however only included participants with an IQ over 70.

In total, 1083 participants with an autism spectrum disorder were reported on, although there was considerable overlap between studies. In 13 studies, a total of 138 participants were described as an unspecified combination of individuals with autism/high functioning autism and/or Asperger Syndrome and/or PDD-NOS. In a further 10 studies, a total of 133 participants, were described as having an ASD, presumably encompassing the disorders mentioned above. The remainder of studies specified the diagnosis of participants; 609 had a diagnosis of autism (mainly 'high-functioning autism'), 188 had a diagnosis of Asperger Syndrome and 15 had a diagnosis of PDD-NOS. Expert clinical assessment was used for participant diagnosis which was generally supported by the use of DSM-IV criteria (in 51 studies) and ICD-10 criteria (a further 9 studies). The ADI (Lord et al., 1994) and ADOS (Lord et al., 1989) were commonly used as standardised diagnostic measures, in 73 and 65 studies respectively. However, according to some of the published scores, participants did not always meet the cut-off criteria on these instruments or scores for some participants were missing. In studies with younger participants the Childhood Autism Rating Scale assessment (CARS; Schopler et al., 1980) and the Vineland Adaptive Behaviour Scale (Sparrow and Cicchetti, 1985) were applied. The Autism Spectrum Quotient (AQ; Woodbury-Smith et al., 2005) and Social Responsiveness Scale (SRS; Constantino et al., 2003) were also used as continuous measures of autistic traits in three studies.

Table 1
Number of experiments and foci included in the analysis of each task domain.

Group	Number of experiments	Total number of subjects	Number of foci
Motor tasks	3	24	107
Visual processing tasks	4	40	83
Executive processing tasks	10	116	118
Auditory and language tasks	10	125	181
Basic social tasks	20	253	244
Complex social cognition tasks	9	122	118

3.3. Behavioural performance

No group differences in accuracy and/or reaction time between the ASD and the controls were found in most of the task domains for children/adolescents and adults. There was a group difference in accuracy and reaction time in complex social cognition tasks in adults, ($F(1,28) = 7.40$, $p < 0.05$).

3.4. ALE meta-analyses

49 Studies provided co-ordinates where significant differences between individuals with ASD and controls were identified. In the main analysis, across the six task domains there were 851 foci from 85 contrasts (see Table 1). In the three domains where separate age-related analyses were carried out 235 foci from 24 experiments were included for children/adolescents and 253 foci from 29 experiments for adults (Tables 2 and 3, Fig. 1).

3.5. Motor tasks

Individuals with autism activated the bilateral precentral gyri and the inferior/middle frontal gyri more than the control subjects. In contrast, controls displayed greater activations of the left culmen and the right superior temporal gyrus than are evident in those with ASD.

3.6. Visual processing tasks

The ASD group showed greater activation than controls in the thalamus and the medial frontal gyrus, whilst controls showed more activation than individuals with ASD in the cingulate gyrus and occipital regions (Tables 4 and 5, Fig. 2).

3.7. Executive function tasks

Individuals with ASD showed greater activation in the left middle frontal gyrus (BA11). In comparison, control subjects showed greater activation than those with ASD in the right middle frontal gyrus (BAs 6 and 9) as well as other prefrontal regions and subcortical regions (Tables 6 and 7, Fig. 3).

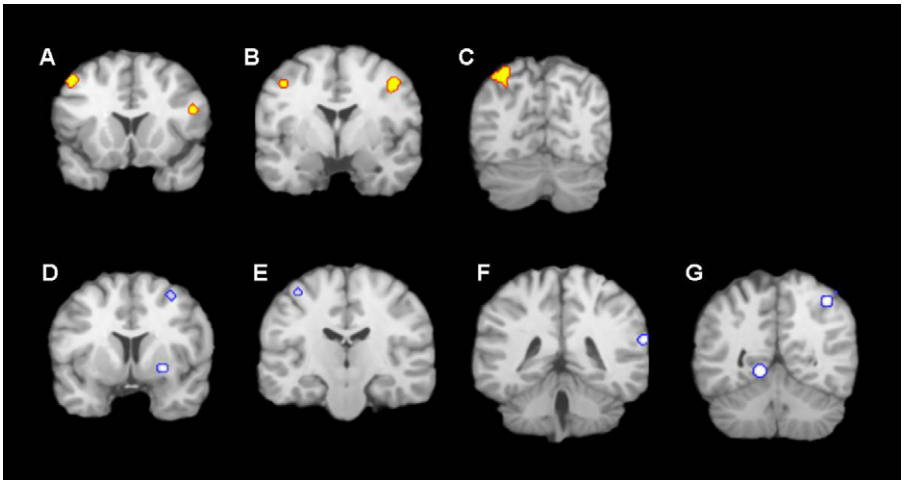

Fig. 1. Motor tasks. ALE maps ($p_{FDR} < 0.05$) are superimposed on slices from grey matter template in Talairach space. The top panel illustrates areas of greater probability of activation in ASD subjects compared to controls in a cluster centred at (a) left middle frontal gyrus ($x = -44$, $y = 14$, $z = 44$) and right inferior forntal gyrus ($x = 48$, $y = 10$, $z = 22$); (b) the bilateral precentral gyrus (left, $x = -40$, $y = -6$, $z = 42$); (right, $x = 44$, $y = -6,42$); (c) the left superior parietal lobe ($x = -30$, $y = -70$, $z = 50$). The bottom panel shows C > ASD activation likelihood estimate maps in clusters centred at (d) right lentiform nucleus ($x = 26$, $y = 4$, $z = -4$) and right middle frontal gyrus ($x = 30$, $y = 6$, $z = 52$); (e) left precentral gyrus ($x = -36$, $y = -22$, $z = 54$); (f) right superior temporal gyrus ($x = 64$, $y = -44$, $z = 18$), (g) the left culmen ($x = -12$, $y = -58$, $z = -6$) and right inferior parietal lobe ($x = 40$, $y = -54$, $z = 48$).

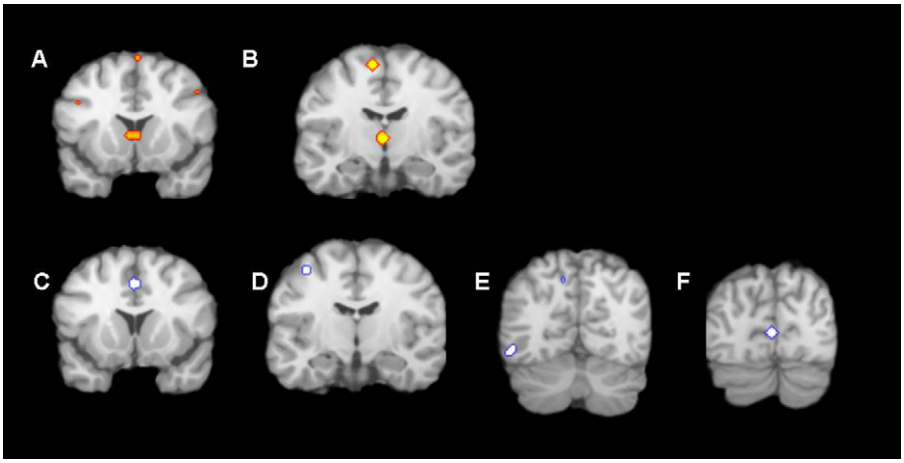

Fig. 2. Visual processing tasks. ALE maps ($p_{FDR} < 0.05$) are superimposed on slices from grey matter template in Talairach space. The top panel illustrates areas of greater probability of activation in ASD subjects compared to controls in a cluster centred at (a) left thalamus ($x = 0$, $y = -16$, $z = 4$); (b) left medial frontal gyrus ($x = -8$, $y = -12$, $z = 58$) and left caudate ($x = -4$, $y = 10$, $z = 6$). The bottom panel shows C > ASD activation likelihood estimate maps in clusters centred at (c) left cingulate gyrus ($x = 0$, $y = 10$, $z = 40$); (d) left precentral gyrus ($x = -36$, $y = -14$, $z = 50$), (e) left middle occipital gyrus ($x = -48$, $y = -66$, $z = -8$); left occipital lingual gyrus ($x = 0$, $y = -78$, $z = 4$).

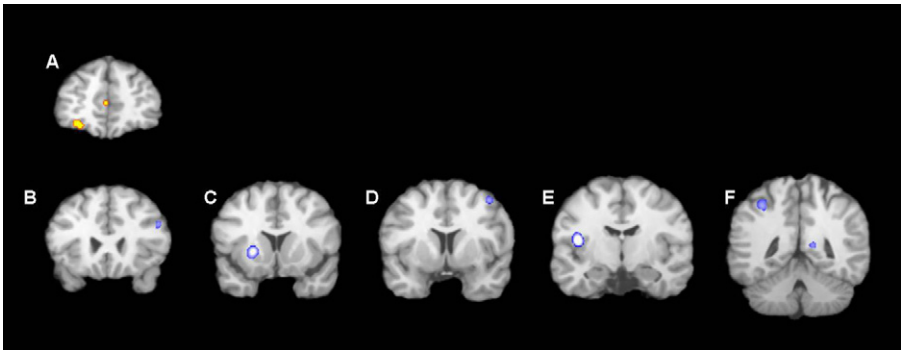

Fig. 3. Executive function tasks. ALE maps ($p_{FDR} < 0.05$) are superimposed on slices from grey matter template in Talairach space. The top panel illustrates areas of greater probability of activation in ASD subjects compared to controls in a cluster centred at (a) left middle frontal gyrus ($x = -28$, $y = 42$, $z = -8$). The bottom panel shows C > ASD activation likelihood estimate maps in clusters centred at (b) right middle frontal gyrus ($x = 40$, $y = 4$, $z = 50$); (c) left lentiform nucleus ($x = -20$, $y = 10$, $z = 2$); (d) right middle frontal gyrus ($x = 48$, $y = 20$, $z = 28$); (e) left insula ($x = -40$, $y = -12$, $z = 12$); (f) left inferior parietal lobule ($x = -34$, $y = -48$, $z = 46$) and right posterior cingulate ($x = 14$, $y = -48$, $z = 8$).

Table 2
Motor tasks. The main findings reported are significant differences in a whole brain between group contrast unless detailed in italics or otherwise stated. Abbreviations; ADI-R – autism diagnostic interview-revised, ADOS – autism diagnostic observational schedule, AQ – autism spectrum quotient, AS – Asperger symdrome, DSM-IV – diagnostic and statistical manual of mental disorders – 4th edition, HFA – high functioning autism, ICD-10 – international classification of diseases – 10th edition, IQ – intelligence quotient, PDD-NOS – pervasive developmental disorder – not otherwise specified, ROI – region of interest.

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Allen and Courchesne (2003)	7:1	26.9 (8.6)	85 (11.95)	Autism	DSM-IV, ADI-R, ADOS	Age, gender, handedness, task performance	1. Self paced button press; 'rest' as baseline. 2. Button press to target; passive viewing of visual stimuli as baseline.	1. ASD > control: cerebellum. 2. Control > ASD: cerebellum. (ROI analysis)
Allen et al. (2004)	7:1	26.9 (8.6)	85 (11.95)	Autism	DSM-IV, ADI-R, ADOS	Age, gender, handedness, task performance	Self paced button press; 'rest' as baseline.	ASD > control: ipsilateral anterior cerebellum. (ROI analysis)
Muller et al. (2001)*	8:0	28.4 (8.9)	86.5 (11.4)	Autism	DSM-IV, ADI-R, CARS	Age, gender, handedness, task performance	Visually paced motor response; passive viewing of visual stimuli.	Control > ASD: contralateral sensorimotor cortex and anterior temporal lobe including anterior insula and caudate. ASD > control: bilateral parieto-occipital and contralateral prefrontal cortex.
Muller et al. (2003)*	8:0	28.4 (8.9)	86.5 (11.4)	Autism	DSM-IV, ADI-R, CARS	Age, gender, handedness,	1. Image of hand with dot indicating appropriate button press for a 6-digit repeated sequence; single-digit stimuli as baseline.	1. Control > ASD: bilateral occipital and superior parietal cortex and right middle frontal gyrus. ASD > control: bilateral parietal lobes, premotor cortex, right medial frontal area and left middle and superior frontal gyri.
							2. Image of hand with dot indicating appropriate button press for a 6-digit repeated sequence; regular 6-digit sequence as baseline.	2. Control > ASD: bilateral premotor, superior parietal anterior inferior parietal, tempero-occipital cortex and left anterior cerebellum. ASD > control: frontal cortex anterior to premotor cortex and inferior and posterior parietal cortex.
Muller et al. (2004)*	8:0	28.4 (8.9)	86.5 (11.4)	Autism	DSM-IV, ADI-R, CARS	Age, gender, handedness	Image of hand with dot indicating appropriate button press for a 8-digit repeated sequence; single-digit stimuli as baseline.	'late learning' vs 'early learning' Control > ASD; prefrontal cortex ASD > control; right pericentral and premotor cortex

* Study included in meta-analysis.

3.8. Auditory and language tasks

When all auditory and language studies were included, the ASD group showed greater likelihood of activated clusters in the right precentral gyrus and the left declive compared to the controls. In contrast, controls showed greater activation than those with ASD in the bilateral superior temporal gyri (Tables 8 and 9, Fig. 4).

When separated by age, relative overactivation in the right precentral gyrus was seen in children/adolescents with ASD, whilst greater activation in the bilateral declive was apparent in adults with ASD. Unaffected children/adolescents activated the bilateral superior temporal gyri significantly more than those with ASD. In both age groups, control subjects displayed greater probability of activation of the left cingulate gyrus. Adults with ASD showed more clusters of relative overactivation than underactivation whilst the reverse was true in children/adolescents with ASD.

3.9. Basic social processing tasks

Within the whole group analysis for basic social processing tasks the individuals with ASD showed greater likelihood than controls of activated clusters in the bilateral superior temporal gyri, whilst controls showed greater activation than those with ASD in

Table 3
Group comparisons of regions with significantly elevated likelihood of activation in motor tasks. Brain areas activated from the ALE analysis ($p_{FDR} < 0.05$ and a minimum cluster size of 200 voxels).

Comparison – age group	Brain region	BA	Volume (mm^3)	Talairach			ALE (10^{-2})
				x	*y*	*z*	
ASD > C; Adults	Superior Parietal Lobule L	7	944	−30	−70	50	0.90
	Precentral Gyrus R	6	752	44	−6	42	1.03
	Middle Frontal Gyrus L	8	488	−44	14	44	1.03
	Inferior Frontal Gyrus R	9	432	48	10	22	1.02
	Precentral Gyrus L	6	264	−40	−6	42	0.80
C > ASD; Adults	Culmen L		912	−12	−58	−6	1.24
	Inferior Parietal Lobule R	40	560	40	−54	48	1.08
	Superior Temporal Gyrus R	22	328	64	−44	18	0.97
	Lentiform Nucleus R		288	26	4	−4	0.96
	Middle Frontal Gyrus R	6	248	30	6	52	0.85
	Precentral Gyrus L	4	216	−36	−22	54	0.85

clusters in the left fusiform gyrus and the right inferior occipital gyrus (Tables 10 and 11, Fig. 5).

Adults with ASD showed a higher likelihood of activation than controls in a cluster representing social regions like the bilateral superior temporal gyri. Controls had a greater probability of activation in the right parahippocampal gyrus and right inferior occipital gyrus, thought to be object-related processing regions, and the left fusiform gyrus. Regarding the distribution and numbers of clusters between the age groups, adults with ASD showed a mixture of over- and under-activation compared to controls whereas children with ASD tended to underactivate.

3.10. Complex social cognition tasks

When all complex social cognition tasks were entered into the analysis, the left superior temporal gyrus appeared as a region that was both over- and underactivated in individuals with ASD relative to controls. In addition a significant cluster in the right superior temporal gyrus was seen as a region of greater activation in the control group compared to individuals with ASD (Tables 12 and 13, Fig. 6).

Children and adolescents with ASD showed greater activation than controls in the left inferior frontal gyrus, left pre- and post-central gyri and the left superior temporal gyrus. Reduced activation in children/adolescents with ASD was seen in left superior frontal gyrus, right superior temporal gyrus and left inferior parietal lobule, whereas adults with ASD showed reduced activation in the right claustrum. The age-related pattern of significant clusters in this task domain is different than in the other task domains with children and adolescents with ASD showing more areas of both over- and under-activation relative to controls than are seen in adults with ASD

3.11. Connectivity

ALE meta-analysis is not possible for studies of functional and effective connectivity. However, the systematic review showed that all but two of the studies (Welchew et al., 2005; Noonan et al., 2009) examining brain connectivity identified reductions in connectivity in individuals with ASD compared to controls. Of these, the majority identified underconnectivity alone although three studies (Mizuno et al., 2006; Turner et al., 2006; Wicker et al., 2008) identified a mixed pattern of increases and decreases. Both Mizuno et al. (2006) and Turner et al. (2006) found atypically increased activations in subcortical regions in ASD whereas Wicker et al. report on altered cortico-cortical connectivity. Reductions in connectivity in individuals with ASD were identified across a wide variety of brain areas using tasks which probed aspects of executive function (Koshino et al., 2005, 2008; Just et al., 2006; Kana et al., 2007; Kleinhans et al., 2008b), language (Just et al., 2004; Mason et al., 2008), emotion processing (Wicker et al., 2008) and motor functions (Villalobos et al., 2005; Mizuno et al., 2006; Turner et al., 2006). In addition, two studies identified reductions in resting state

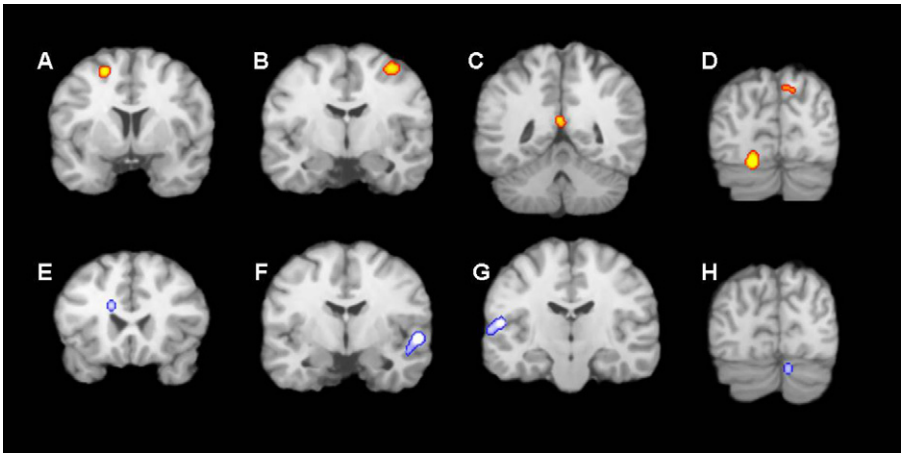

Fig. 4. Auditory and language tasks. Whole group analysis. ALE maps ($p_{FDR} < 0.05$) are superimposed on slices from grey matter template in Talairach space. The top panel illustrates areas of greater probability of activation in ASD subjects compared to controls in a cluster centred at (a) left frontal sub-gyral ($x = -20$, $y = 2$, $z = 52$); (b) right precentral gyrus ($x = 36$, $y = -10$, $z = 54$); (c) left posterior cingulate $9x = 0$, $y = -50$, $z = 14$); (d) left declive ($x = -18$, $y = -78$, $z = -18$). The bottom panel shows C > ASD activation likelihood estimate maps in clusters centred at (e) left cingulate gyrus ($x = 14$, $y = 18$, $z = 24$); (f) right superior temporal gyrus ($x = 56$, $y = -8$, $z = -2$); (g) left superior temporal gyrus ($x = -52$, $y = -20$, $z = 10$); (h) right pyramis ($x = 10$, $y = -78$, $z = -24$).

Table 4
Visual processing tasks. Abbreviations as in Table 2.

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Bölte et al. (2008)	7:0	27.7 (7.8)	98 (19.2)	Autism	ICD-10, ADI-R, ADOS	Age, IQ, gender, handedness, task performance	1. Count triangles within Block Design stimuli; fixation baseline. 2. Counting colours; fixation baseline.	1. Control > ASD: right ventral quadrant of prestriate visual cortex (V2v) and ventral posterior visual cortex (VP). 2. Control > ASD: ventral posterior visual cortex (VP). (ROI analysis)
Hadjikhani et al. (2004b)	8	35 (12)	117 (6)	Autism, AS, PDD-NOS	ADI-R, ADOS	IQ	Visual checkerboard	No qualitative difference in activation patterns between groups.
Hubl et al. (2003)	7:0	27.7 (7.8)	98 (17)	Autism	ICD-10, ADI, ADOS	Age, IQ, gender, task performance accuracy (not RT)	1. Indentify target via button press. Happy, sad, angry and neutral faces presented. Target happy (explicit emotion condition); target female (implicit emotion condition); scrambled faces as baseline condition. 2. Colour counting; shape counting within a mosaic; and a rest condition.	*Values from ROIs were extracted from each condition and investigated in an ANOVA for interactions with diagnosis, task, region and hemisphere. Activations for each task were different between ASD and controls. Different tasks activated different regions. The ASD and control groups differ with respect to the difference in activations caused by each task in different regions.*
Keehn et al. (2008)*	9:0	15.1 (2.6)	PIQ 110 (20)	ASD	DSM-IV, ADI, ADOS (but one did not meet cut off)	Age, gender, PIQ	Visual search paradigm where participants indicated via button press whether the target was present or not. There were 12 trial types; presence/absence of target, homogen-sous/heterogenous distractors, 3 set sizes. High level baseline; solitary target or distractor. Low level baseline; visual fixation.	High level baseline vs low level baseline ASD > control: right inferior frontal gyrus Homogenous/heterogenous trials vs high level baseline ASD > controls: right middle occipital gyrus, inferior frontal gyrus and middle occipital gyrus. Left supplementary motor area, superior parietal lobe and precentral gyrus.
Lee et al. (2007b)	12:5	10.37 (1.52)	109.3 (14.2)	8 HFA, 9 AS	DSM-IV, ADI-R, ADOS	Age, IQ, task performance	Embedded figures task; shape matching task as baseline.	No significant group differences. *Qualitative difference in activation maps between groups; ASD group failed to recruit medial and lateral prefrontal cortex, ventral temporal cortex and inferior parietal cortex; parietal and occipital activation was bilateral in control group and unilateral in the ASD group.*
Luna et al. (2002)	9:2	32.3 (9.3)	102.7 (12.1)	Autism	ADI, ADOS	Age, IQ	1. Visually guided saccades; fixation baseline.	1. No group differences. (Groups task performance matched)

Table 4 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
							2. Ocularmotor delayed response task; visually guided saccades.	2. Control > ASD: bilateral dorsolateral prefrontal cortex and posterior cingulate cortex. (Groups not task performance matched, ROI analysis)
Manjaly et al. (2007)	12	14.4 (2.7)	110.1 (20)	3 HFA, 9 AS	DSM-IV, ICD-10, ADI-R, ADOS	Age, IQ, gender, handedness, task performance	Embedded figures task; visuospatial control task as baseline.	No significant differences between groups. *Qualitative difference in activation maps between groups; more activation in ASD group in extrastriate cortex and calcarine sulcus than controls.*
Ring et al. (1999)*	4:2	26.3 (2.1)	108.5 (10.5)	Autism, AS	DSM-IV, ICD-10	Age, IQ, handedness, socioeconomic status, education, task performance	Embedded figures task; fixation baseline.	Control > ASD: bilateral parietal regions and occipital cortex and right dorsolateral prefrontal cortex. ASD > control: right occipital cortex extending into inferior temporal gyrus.
Sahyoun et al. (2009)	10:2	13.3 (2.1)	100.8 (12.3)	HFA	DSM-IV, ADI-R	Age, IQ, handedness, behavioural performance in scanner	Visuospatial and linguistic reasoning task. Participants filled in the blank in a matrix. Visual fixation baseline. 1. visuospatial trials 2. visuospatial and semantic trials 3. semantic trials	1. Control > ASD: Left MTG, lingual gyrus and superior precentral sulcus. Right angular gyrus. ASD > Control: Bilateral anterior MTG. Left lateral occipito-temporal sulcus, pre/post central sulcus, posterior lateral fissure. Right inferior frontal area and postcentral gyrus. 2. Control > ASD: Left MTG, lingual gyrus, superior precentral sulcus. Right angular gyrus, inferior frontal area and STS. ASD > Control: Bilateral anterior MTG. Left lateral occipito-temporal sulcus, posterior lateral fissure, inferior parietal sulcus, occipital cortex. Right postcentral gyrus. 3. Control > ASD: Left MTG, lingual gyrus, and superior precentral sulcus. Right supermarginal gyrus, occipito-temporal cortex. ASD > Control: Left lateral occipito-temporal sulcus, posterior lateral fissure. Right insula, anterior MTG, inferior frontal area.

Table 4 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Silk et al. (2006)	7:0	14.7 (2.9)	114 (16.9)	Autism, AS	DSM-IV, ADI-R	Age, IQ, gender, handedness	Mental rotation and matching of shapes; shape matching as baseline.	Control > ASD: right inferior and medial frontal gyri including caudate and dorsal premotor cortex.
Thakkar et al. (2008)*	10:2	30 (11)	114 (9)	8 autism, 2 AS, 2 PDD-NOS	DSM-IV, ADI, ADOS	Age, verbal IQ, gender, handedness, socioeconomic status, education	Pro-saccade and anti-saccade events; fixation baseline.	1. Error vs correct events Control > ASD: right medial superior frontal gyrus. 2. Correct responses vs fixation ASD > control: right rostral anterior cingulated gyrus.
Takarae et al. (2007)*	13	24.5 (7.7)	105.9 (12.3)	Autism	DSM-IV, ADI, ADOS	Age, IQ	1. Visually guided saccades; fixation baseline.	1. Control > ASD: bilateral frontal and supplementary eye fields, posterior parietal cortex and cerebellum. ASD > control: bilateral dorsolatrel prefrontal cortex, anterior and posterior cingulate cortex, medial thalamus, caudate nucleus and right dentate nucleus.
							2. Smooth pursuit of a visual target; fixation baseline.	2. Control > ASD: bilateral frontal eye fields, posterior parietal cortex, posterior cingulate cortex, cingulate motor area, cerebellum, dorsolateral prefrontal cortex, precuneus and pre-supplementary motor area.

* Study included in meta-analysis.

connectivity in individuals with ASD (Cherkassky et al., 2006; Kennedy and Courchesne, 2008) (Table 14).

4. Discussion

4.1. Methodology of included literature

4.1.1. Study participants

The majority of studies including individuals with a diagnosis of autism used appropriate diagnostic tools to confirm this, usually the ADI-R and the ADOS. It should be noted however that, whilst the ADOS allows a category of autism spectrum disorders in addition to autism, the ADI-R allows only for the diagnosis of autism to be made. Confusingly several studies also reported using the ADI-R to confirm diagnosis in individuals with autism spectrum disorders. Also, as concepts of the autism spectrum have broadened, increasing numbers of individuals are receiving a diagnosis of PDD-NOS, which these tools are not designed to assess. Due to differences in reporting between studies it is not possible to determine exactly the number of individuals included in this review with PDD-NOS, but it appears to be low.

Table 5
Group comparisons of regions with significantly elevated likelihood of activation in visual processing tasks. Brain areas activated from the ALE analysis ($p_{FDR} < 0.05$ and a minimum cluster size of 200 voxels).

Comparison – age group	Brain region	BA	Volume (mm^3)	Talairach			ALE (10^{-2})
				x	*y*	*z*	
ASD > C; Adults	Thalamus L		448	0	−16	4	1.24
	Medial Frontal Gyrus L	6	368	−8	−12	58	1.10
	Caudate L		256	−4	10	6	0.80
C > ASD; Adults	Cingulate Gyrus L	32	368	0	10	40	1.12
	Precentral Gyrus L	4	296	−36	−14	50	0.97
	Occipital Lingual Gyrus	18	264	0	−78	4	1.01
	Middle Occipital Gyrus	37	224	−48	−66	−8	0.90

Table 6
Executive function tasks. Abbreviations as in Table 2.

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Belmonte and Yurgelun-Todd (2003)*	5:1	32.7 (9.8)	'non-retarded'	Autism, AS, PDD-NOS	DSM-IV, ADI	Gender, handedness, task performance	Attend to one location and switch attention when target stimuli observed; fixation baseline.	Control > ASD: bilateral superior parietal lobe and medial frontal gyrus, left medial temporal gyrus, postcentral gyrus and inferior frontal gyrus, right premotor cortex and medial frontal gyrus.
Dichter and Belger (2007)	16:1	22.9 (5.2)	105 (18.6)	14 HFA, 3 AS	DSM-IV, ADI, ADOS	Age, IQ, gender, handedness, education, task performance	1. Indicate via button press direction of central arrow that was congruent (condition1) or incongruent (condition2) with direction of flanker arrows.	1. No significant group difference.
							2. Indicated via button press direction of eye gaze in central face that was congruent (condition1) or incongruent (condition2) with direction of eye gaze in flanker faces.	2. Control > ASD: bilateral dorsolateral prefrontal cortex, right inferior frontal/anterior insula cortex, anterior cingulate and bilateral intraparietal sulcus. (ROI analysis)
Gilbert et al. (2008)	12:3	38 (13)	119 (14)	ASD	ADOS	Age, IQ, task performance	1. Sequenced button press; randomly generated button press as baseline.	1. Control > ASD: left cerebellum and left lateral temporal cortex.
							2. Press in response to curved letters as progress through alphabet; same task with only start letter presented and thereafter task was stimulus independent.	2. Control > ASD: medial parietal and occipital cortex. ASD > control: medial prefrontal cortex, amygdala, cerebellum and other temporal and parietal regions.
Haist et al. (2005)*	8:0	23.4 (11.4)	101.0 (9.3)	6 HFA, 2 AS	DSM-IV, ADI, ADOS	Age, gender, IQ	Spatial attention task: two boxes and central fixation cross on the screen, initially attend to cross then attention cued to one box followed by variable interval (short or long ISI) before letter E appears in one of the boxes – congruent to cue in 75% of trials, incongruent in 25%; participants asked to shift attention to letter and note the orientation	Short ISI Control > ASD: bilateral precentral and frontal gyri, right middle frontal gyrus, left parietal lobe and right insula

Table 6 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
								Long ISI Control > ASD: right middle frontal gyrus and left precentral gyrus
Just et al. (2007)	17:1	27.1 (11.9)	109.3 (17.7)	Autism	ADI, ADOS	Age, IQ, gender, socioeconomic status, task performance	Indicate via button press required number of moves to complete Tower of London task displayed, Easy condition and hard condition; fixation baseline.	Controls > ASD: bilateral inferior and superior parietal area, angular gyri, superior, and middle occipital areas, middle frontal gyri, and the right precentral gyrus, superior frontal and the left inferior frontal gyri. Autism > Controls: bilateral hippocampus, thalamus and left lingual gyrus. Autism > Controls in right middle occipital gyrus for hard vs easy contrast. Functional connectivity analysis See Table 8
Kana et al. (2007)*	11:1	26.8 (7.7)	110.1 (12.6)	HFA	ADI, ADOS	Age, IQ, gender, handedness, socioeconomic status	Go/no go task with increasing working memory load: 1 – simple response inhibition, 2 – response inhibition with working memory component; fixation baseline.	1. Controls > ASD: left inferior temporal gyrus, right parahippocampal gyrus, right calcarine sulcus, right premotor cortex, right middle cingulate gyrus, bilateral postcentral gyrus, right insula/right inferior frontal gyrus and left lingual gyrus 2. Controls > ASD: left anterior cingulate gyrus, left middle occipital gyrus, bilateral calcarine sulcus, right angular gyrus and left precuneus 3. ASD > Controls: bilateral premotor area
Kennedy et al. (2006)*	12:0	26.5 (12.8)	101.6 (15.2)	6 autism, 6 AS	ADI-R, ADOS	Age	Counting Stroop task with emotional, neutral and number words. Participants asked to count number of words on the screen. Baseline fixation cross	Number vs rest ASD > Control: right supramarginal gyrus, right precuneus, bilateral inferior parietal lobule, right superior frontal gyrus, left medial frontal/anterior cingulate Emotional vs neutral Control > ASD: right medial orbitofrontal cortex, right middle occipital gyrus Functional connectivity analysis See Table 8

Table 6 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Koshino et al. (2005)*	13:1	25.7	100.1	HFA	ADI, ADOS	Age, IQ, gender, socioeconomic status, task performance	n-back task (0,1,2); fixation baseline.	Control > ASD: left dorsolateral prefrontal cortex, inferior frontal gyrus, posterior precentral sulcus and inferior parietal lobe. ASD > control: right inferior frontal gyrus, inferior parietal lobe and bilateral temporal lobe. (ROI analysis and no spatial normalisation) Functional connectivity analysis See Table 8
Koshino et al. (2008)*	11:0	24.5 (10.2)	104.5 (13.1)	HFA	ADI-R, ADOS	Age, IQ, gender, socioeconomic status, task performance	0, 1 and 2-back working memory task with face identity; fixation baseline.	Control > ASD: left inferior prefrontal and right posterior temporal cortex. *Different location of the Fusiform Face Area within the fusiform gyrus in ASD group compared to controls.* Functional connectivity analysis See Table 8
Lee et al. (2009)	9:3	10.2 (1.6)	113.3 (17.3)	ASD	DSM-IV, ADI-R, ADOS	Age, gender. IQ	Go/NoGo task	ASD > Control: right cingulate cortex Functional connectivity analysis See Table 8
Schmitz et al. (2006)*	10:0	38 (9)	105 (14)	2 HFA, 8 AS	ICD-10, ADI	Age, IQ, gender, handedness, task performance	1. Motor inhibition; motor response. (GO/NO-GO task) 2. Spatial STROOP task. Incongruent events; congruent events. 3. SWITCH task. Events where the rule switched; events where the rule was repeated.	1. ASD > control: left middle/inferior and orbitofrontal gyrus. 2. ASD > control: left insula. 3. ASD > control: right inferior and left mesial parietal cortex.
Schmitz et al. (2008)*	10:0	37.8 (7)	107 (9)	3 HFA, 7 AS	ICD-10, ADI	Age, IQ, gender, handedness, socioeconomic status, education, task performance	Continuous performance task with target identification events. Targets associated with monetary reward; targets with no associated monetary reward.	ASD > control: left anterior cingulate gyrus.
Shafritz et al. (2008)*	16:2	22.3 (8.7)	102.5 (17.6)	Autism	DSM-IV, ADI, ADOS	Age, IQ	Button press in response to targets; non-targets as baseline. Targets were maintained or shifted between runs.	Control > ASD: dorsolateral prefrontal cortex, basal ganglia and insula. (Stats uncorrected)

* Study included in meta-analysis.

Table 7
Group comparisons of regions with significantly elevated likelihood of activation in executive function tasks. Brain areas activated from the ALE analysis ($p_{FDR} < 0.05$ and a minimum cluster size of 200 voxels).

Comparison – age group	Brain region	BA	Volume (mm^3)	Talairach			ALE (10^{-2})
				x	*y*	*z*	
ASD > C; Adults	Middle Frontal Gyrus L	11	312	−28	42	−8	0.86
C > ASD; Adults	Insula L	13	984	−40	−12	12	2.40
	Lentiform Nucleus L		912	−20	10	2	1.97
	Inferior Parietal Lobule L	40	704	−34	−48	46	1.39
	Middle Frontal Gyrus R	6	264	40	4	50	1.39
	Middle Frontal Gyrus R	9	256	48	20	28	1.34
	Posterior Cingulate R	29	224	14	−48	8	1.34

The ratio of male to female participants in the fMRI literature in ASD is unrepresentative of the ASD population as a whole. Commonly reported gender ratios in autism are 4:1 or 3:1 and in Asperger Syndrome are 8:1 (Fombonne, 2003; Newschaffer et al., 2007; Holtmann et al., 2007). The overall ratio of male to female study participants in fMRI studies of 15:1 is therefore unrepresentative of the ASD population. This is likely to be driven by the relatively small sample sizes investigated within each study which means researchers opt to exclude female participants to reduce additional variation in their sample. With the increasing numbers of participants in fMRI studies generally and perhaps also the rise of multi-centre imaging (Belmonte et al., 2008), the recruitment of larger samples that are more representative of the ASD population should be possible.

There is a general bias in the fMRI literature of autism towards imaging adults. Whilst this is unsurprising given the demanding nature of participating in fMRI experiments, studying younger cohorts and carrying out longitudinal studies of a developmental disorder which manifests in early childhood is imperative if we are to gain an understanding of the aetiology of autism. Both behavioural and imaging data suggest that people with ASD develop alternative and compensatory processing styles and strategies which will likely confound findings in adult populations. The results from our meta-analysis support the idea that results may differ between different age groups. Case studies have been published using young children (Grelotti et al., 2005) suggesting that with enough preparation and the careful design of simple experimental paradigms the imaging of younger cohorts may be possible. Mock scanners can also help in acclimatizing people to the scanner environment.

Due to the demanding nature of fMRI it is not surprising that there is a bias in the fMRI literature to investigate high-functioning individuals. However, given reports that the majority of individuals with autism have a comorbid learning disability (Steffenburg et al., 2003) this is another imbalance in the literature that needs addressed. In addition to the practical difficulties of scanning an autistic group with additional learning disability, recruiting an appropriate comparison group is also a challenge. Due to the complex behavioural profile of autism which might present with both enhanced ability in some aspects of cognition in addition to broad ranging impairments, IQ may not be the most appropriate measure with which to ability match people with autism to a comparison group. Perhaps more stringent matching based on factors which indicate background and environmental influences (such as education and socioeconomic status) combined with age (and possible even pubertal status when investigating children and adolescents) and gender would provide a better method than IQ measures which can be an intrinsic element of the condition. Also, it is imperative that tasks continue to be designed in such a way that groups can be performance matched. Resting state fMRI is an increasingly popular approach which may be more acceptable to individuals of low cognitive ability.

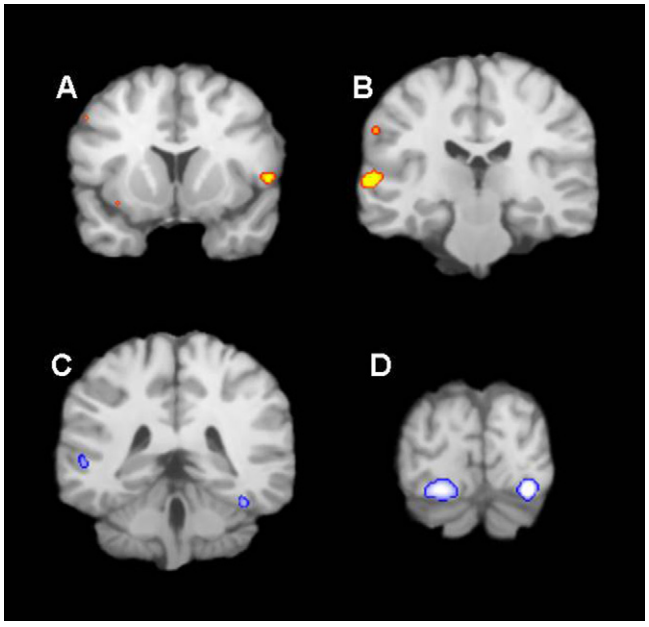

Fig. 5. Basic social tasks. Whole group analysis. ALE maps ($p_{FDR} < 0.05$) are superimposed on slices from grey matter template in Talairach space. The top panel illustrates areas of greater probability of activation in ASD subjects compared to controls in a cluster centred at (a) right superior temporal gyrus ($x = 54, y = 8, z = 4$); (b) left superior temporal gyrus ($x = -60, y = -28, z = 4$). The bottom panel shows C > ASD activation likelihood estimate maps in clusters centred at (c) right culmen ($x = 40, y = -42, z = -22$) and left middle temporal gyrus ($x = -52, y = -40, z = 0$); (d) right inferior occipital gyrus ($x = 30, y = -84, z = -14$) and left fusiform gyrus ($x = -20, y = -88, z = -14$).

4.1.2. Image analysis

The methodology applied in the analysis of fMRI data varied throughout the literature and it was not always possible to know the exact details of the contrast that was carried out or the exact image analysis methods used which led to the reported results. The use of different statistical thresholds, including those that were uncorrected for multiple comparisons, makes it difficult to directly contrast findings between studies. Similarly, whilst the use of ROI approaches was generally justified within each study, this adds further to the difficulty of synthesising data. Many studies also reported apparent differences on within group activation maps which were not statistically significant in between group contrasts. Other differences in imaging methodology also limit comparison between studies: the use of random effects analyses and fixed effects analyses may lead to different results, as does the use of different templates between studies, for example standard MNI templates versus ones derived from the participants scans. The choice of template is a particularly important factor which may influence results in populations in whom neuroanatomy is known to differ from typical populations.

Table 8
Auditory and language tasks. Abbreviations as in Table 2.

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Gaffrey et al. (2007)*	10:0	26.1 (10.5)	101.5 (11.9)	8 autism, 2 AS	DSM-IV, ADI, ADOS	Age, gender, handedness, Non-verbal IQ	Word categorisation (colours, tools and feelings) via button press; letter recognition in strings of non-word letters as baseline condition.	ASD > control: left medial frontal gyrus, middle temporal gyrus, lingual gyrus and cuneus, right lingual gyrus, middle occipital gyrus, post central gyrus, posterior cingulate and precuneus.
Gervais et al. (2004)*	5:0	25.8 (5.9)	81 (18.8)	Autism	DSM-IV, ADI	Age, gender	1. Passive listening to vocal sounds; silence as baseline. 2. Passive listening to vocal sounds; environmental sounds as baseline.	1. Control > ASD: right superior temporal sulcus region and bilateral superior temporal gyrus. 2. Control > ASD: right middle temporal gyrus and bilateral superior temporal sulcus region.
Gomot et al. (2006)*	12:0	13.5 (1.6)	116 (18)	HFA	DSM-IV, ADI	Age, IQ, gender, handedness	Passive auditory stimulation whilst participants watched a video. 1. Novel sounds; standard sounds as baseline. 2. Deviant sounds; standard sounds as baseline.	1. Control > ASD: bilateral inferior parietal lobe and posterior superior temporal gyrus, right inferior and middle frontal gyrus, left anterior cingulate gyrus and right anterior cerebellum. 2. Control > ASD: left anterior cingulate gyrus, left medial orbitofrontal region and left inferior frontal gyrus. (uncorrected stats)
Gomot et al. (2008)*	12:0	13.5 (1.6)	116 (18)	9 HFA, 3 AS	DSM-IV, ADI, AQ-adol	Age, IQ, gender, in scanner accuracy (but not RT)	Auditory oddball paradigm with 3 conditions; standard, deviant and novel. Button press to novel stimuli. Periods of rest i.e. no sound, interspersed.	Novel vs standard sounds ASD > control: right middle frontal gyrus, superior frontal gyrus, precentral gyrus, postcentral gyrus and inferior frontal gyrus, left inferior parietal lobule and middle frontal gyrus. Control > ASD: right caudate *$p < 0.001$ uncorrected* *Direct group comparison not performed. ASD group appeared to have greater activation of Wernicke's area and less Broca's area during semantic processing. Control group activation was modulated by word type – an effect not seen in the ASD group.*
Harris et al. (2006)	14:0	36 (12)	116 (8)	7 autism, 5 AS, 2 PDD-NOS	DSM-IV, ADI, ADOS	Age, gender, handedness, verbal IQ, task performance	Viewing concrete and abstract words. Perceptual task; upper/lower case discrimination. Semantic task; positive/negative discrimination.	
Just et al. (2004)	17	Not reported	>80	HFA	ADI, ADOS	Age, IQ, gender, socioeconomic status	Sentence comprehension (identifying the agent or recipient of the action); fixation baseline.	ASD > control: left superior temporal gyrus Control > ASD: left inferior frontal gyrus *ROI analysis restricted to left superior temporal gyrus and left inferior frontal gyrus* Functional connectivity analysis See Table 8

Table 8 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Kana et al. (2006)*	11:1	22.5 (8.8)	110.7 (9.2)	Autism	ADI, ADOS	Age, IQ, gender, socioeconomic status, task performance	1. Indicate via button press whether a low-imagery sentence is true or false; fixation baseline. 2. Indicate via button press whether a high-imagery sentence is true or false; fixation baseline.	1. ASD > control: left intraparietal sulcus, right superior parietal lobe, bilateral cuneus, precuneus and lingual gyrus. 2. Control > ASD: left inferior frontal gyrus, left angular gyrus and left middle frontal gyrus. Functional connectivity analysis See Table 8
Kleinhans et al. (2008a)*	14:0	24.1 (9.58)	98.14 (11.84)	8 autism disorder, 3 AS, 3PDD-NOS	DSM-IV, ADI, ADOS	age	2 tasks of verbal fluency. 1. Letter fluency: Participants generate as many words as possible beginning with the letter presented on screen; self-paced repetition of the word 'nothing' is response to seeing the word on screen (high level baseline); 'rest' condition (low level baseline). 2. Category fluency: Participants generate as many items as possible from the category presented on screen. High and low level baseline conditions as task 1.	1. Letter fluency vs high level baseline ASD > control: right inferior frontal lobe 2. Category fluency vs high level baseline Control > ASD: left middle frontal lobe
Knaus et al. (2008)*	12:0	15.46 (2.8)	105.42 (19.35)	ASD	DSM-IV, ADI, ADOS (but not all met cut off)	Age, gender, handedness	Language task with two conditions; Response naming condition – participants were shown a 3 word description and had to indicate the item described out of a choice of two presented options via button press; Letter judgement condition – three letters presented and participants indicated via button press if they were in upper or lower case. Cross hair presented for 4 seconds as the beginning of each block.	Response naming vs letter judgement Control > ASD: near the posterior corpus callosum/cingulate. ASD > control: right inferior frontal gyrus, middle frontal gyrus, middle temporal gyrus, pre-central gyrus, orbito-frontal gyrus and superior parietal gyrus. Left inferior frontal gyrus, inferior temproal gyrus, fusiform gyrus, pre-central gyrus, posterior superior temporal gyrus, medial superior/middle frontal gyrus, and medial pars triangularis/pars opercularis.

Table 8 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Mason et al. (2008)	17:1	26.5	101.9	HFA	ADI, ADOS	Age, IQ, gender, socioeconomic status, race	Read short scenarios and answered yes/no comprehension questions via button press. Intentional, emotional and physical sentences; fixation baseline.	ASD > control: right middle temporal gyrus, superior temporal gyrus, angular gyrus and supramarginal gyrus. *Whilst the recruitment of these regions was modulated by sentence type in the control group (greater activation when making mentalistic inferences) the ASD group recruited these regions for all sentence types.* Functional connectivity analysis See Table 8
Oktem et al. (2000)	9	12 (3.1)	76.78	AS	DSM-IV	Age, handedness	Instructed to think over general comprehension questions; rest as baseline.	Control > ASD: frontal lobe.
Redcay and Courchesne (2008)*	12:0	2.9 (0.6)		11 autism disorder, 1 ASD	ADI-R, CARS	Mental age matched group (MA) and chronological age matched group (CA)	Speech processing task. 3 conditions; simple forward speech, complex forward speech, backward speech and 'rest' i.e. no auditory stimulation	Response to forward speech vs 'rest' MA control > ASD: regions of bilateral frontal, temporal, parietal and occipital lobes, cerebellar cortex and right caudate. ASD > MA control: bilateral postcentral gyri CA control > ASD: left anterior cingulate, middle frontal gyrus, superior temporal gyrus, middle temporal gyrus and fusiform gyrus. Posterior regions of bilateral parietal, extrastriate and cerebellar cortices. ASD > CA control: right middle and inferior frontal gyri, insula and post central gyrus.
Takeuchi et al. (2004)	8:2	11.2 (2.6)	110.4 (14.8)	Autism	DSM-III	Age, IQ, handedness	Reading task involving attribution of complex mental states	ASD > Control: right prefrontal cortex *p < 0.01 (uncorrected)*
Wang et al. (2006)*	18:0	11.9 (2.8)	102 (18)	Autism, AS	ADI, ADOS	Age, IQ, gender, handedness, social responsiveness scale	Participants listen to scenarios and indicate via button press if the speaker means what they say. 1. Event knowledge and prosodic cues; resting baseline. 2. Event knowledge only; resting baseline. 3. Prosodic cues only; resting baseline.	1. ASD > control: left pre-central gyrus and bilateral inferior frontal gyrus. 2. Control > ASD: left superior frontal gyrus ASD > control: left pre and post-central gyrus, superior temporal gyrus, superior temporal sulcus region and medial temporal gyrus and right inferior frontal gyrus. 3. ASD > control: left superior temporal sulcus region and right temporal pole.
Wang et al. (2007)*	18:0	12.4 (2.9)	98 (17)	ASD	DSM-IV, ADI, ADOS	Age, IQ, gender, handedness, social responsiveness scale, task performance	Indicate via button press if the speaker is sincere or not. Storyboards and speech stimuli. 1. Participants asked to pay attention; resting baseline. 2. Participants asked to pay attention to facial expression or tone of voice; resting baseline. 3. All ironic scenarios; non-ironic scenarios.	1. Control > ASD: bilateral medial prefrontal cortex, superior temporal gyrus and cerebellum. 2. Control > ASD: superior temporal gyrus, cerebellum and visual cortex. 3. Control > ASD: bilateral temporal regions and medial prefrontal cortex.

* Study included in meta-analysis.

Table 9
Group comparisons of regions with significantly elevated likelihood of activation in auditory and language tasks. Brain areas activated from the ALE analysis ($p_{FDR} < 0.05$ and a minimum cluster size of 200 voxels). C/A: children/adolescents.

Comparison – age group	Brain region	BA	Volume (mm^3)	Talairach			ALE (10^{-2})
				x	*y*	*z*	
ASD > C: All	Precentral Gyrus R	6	1704	36	−10	54	1.13
	Declive L		720	−18	−78	−18	1.50
	Frontal Sub-Gyral L	6	392	−20	2	52	1.20
	Posterior Cingulate L	30	264	0	−50	14	1.07
ASD > C; C/A	Precentral Gyrus R	6	816	34	−8	54	0.99
ASD > C; Adults	Declive L		896	−18	−78	−18	1.50
	Posterior Cingulate L	30	384	0	−50	14	1.07
	Declive R		336	20	−70	−14	0.90
	Precuneus R	19	336	12	−78	38	0.82
C > ASD; All	Superior Temporal Gyrus R	22	1344	56	−8	−2	1.90
	Superior Temporal Gyrus L	41	1144	−52	−20	10	1.60
	Pyramis R		224	10	−78	−24	1.21
	Cingulate Gyrus L	32	224	−14	18	24	1.31
C > ASD; C/A	Superior Temporal Gyrus L	41	1048	−52	−20	10	1.59
	Superior Temporal Gyrus R	22	608	56	−8	−2	1.66
	Pyramis R		224	10	−78	−24	1.20
	Cingulate Gyrus L	32	224	−14	18	24	1.30
C > ASD; Adults	Cingulate Gyrus L	32	536	−4	22	34	1.23

4.1.3. *In-scanner behavioural performance*

Individuals with ASD and controls were generally well matched in terms of behavioural performance in the scanner, giving strength to the idea that differences seen in activation are not simply related to performance differences. It is somewhat unusual that so few studies report performance differences between the groups, given that many of the domains under examination are ones in which performance differences in a non-scanning environment have been noted. Tasks used in a scanner may be simpler than those used elsewhere, as they need to be able to be conducted in such an unusual environment. It is notable that tasks of complex social cognition were not behaviourally matched, possibly due to the inherent need for complexity within these tasks.

4.2. *Task related activation differences*

4.2.1. *Motor tasks*

Motor coordination impairments were included in Asperger's early descriptions of autistic psychopathy (Asperger, 1944) and, although not part of the diagnostic criteria, are regarded as a major feature of ASD (Fournier et al., 2010). Both hypo- and hyperactivation were seen in the meta-analysis, including in 'traditional' motor regions such as the anterior cerebellum, the precentral gyrus

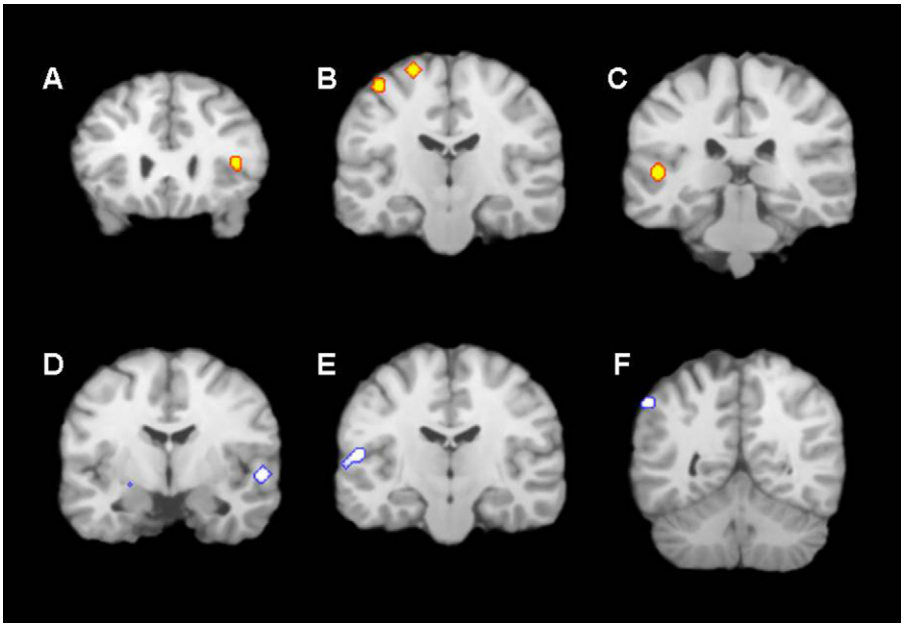

Fig. 6. Complex social tasks. Whole group analysis. ALE maps ($p_{FDR} < 0.05$) are superimposed on slices from grey matter template in Talairach space. The top panel illustrates areas of greater probability of activation in ASD subjects compared to controls in a cluster centred at (a) right inferior frontal gyrus ($x = 40$, $y = 22$, $z = 10$); (b) left precentral gyrus ($x = -20$, $y = -22$, $z = 64$) and left postcentral gyrus ($x = -40$, $y = -22$, $z = 54$); (c) left superior temporal gyrus ($x = -48$, $y = -32$, $z = 4$). The bottom panel shows C > ASD activation likelihood estimate maps in clusters centred at (d) right superior temporal gyrus ($x = 56$, $y = -8$, $z = -2$); (e) left superior temporal gyrus ($x = -52$, $y = -20$, $z = 10$); (f) left inferior parietal lobe ($x = -54$, $y = -56$, $z = 40$).

Table 10
Basic social tasks. Abbreviations as in Table 2.

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Ashwin et al. (2007)*	13:0	31.2 (9.1)	108.6 (17.1)	1 HFA, 12 AS	Clinical diagnosis, AQ	Age, IQ, gender, handedness, task performance	Button press in response to stimuli. Face condition (including high fear, low fear and neutral faces); scrambled face stimuli as baseline.	Control > ASD: left amygdala and orbitofrontal cortex. ASD > control: right anterior cingulate cortex and bilateral superior temporal cortex. *In controls, intensity of fear modulated activity in bilateral amygdala, fusifrom gyrus, right medial prefrontal cortex and superior temporal sulcus region, an effect not seen in the ASD group.*
Bird et al. (2006)*	14:2	33.3 (11.5)	119 (14)	1 autism, 15 AS	DSM-IV, ADOS, AQ	Age, IQ, gender, task performance	1. Localiser task: passive viewing of neutral faces; passive viewing of houses; fixation baseline. (fixation cross over 'eye region') 2. Same/different discrimination in horizontal or vertical plane via button press; pairs of faces and houses presented.	1. No between group differences in any contrast. 2. Attend to houses vs not attend No between group differences. Attend to faces vs not attend Control > ASD group: left fusiform gyrus. Connectivity analysis See Table 8
Bookheimer et al. (2008)	12:0	11.3 (4)	Not reported	8 autism, 2 AS, 2PDD-NOS	ADI-R, ADOS, SCQ	Age, gender	Matching task with three conditions; neutral faces, all upright; neutral faces, target inverted; shape matching task as a high level baseline condition.	Upright condition vs baseline Control > ASD: Left prefrontal cortex Inverted condition vs baseline Control > ASD: left prefrontal cortex ASD > control: bilateral precuneus *Functionally selected ROI analysis. No direct group comparison at whole brain level reported. Precuneus ROI applied post hoc.*
Corbett et al. (2009)*	12:0	9.01 (1.6)	90.71 (13.82)	12 HFA	DSM-IV, ADI and ADOS where possible	Age, performance in scanner	Participants indicate via button press; 1. Face emotion match 2. Face identity match 3. Object category match – not reported on 4. Pattern match – baseline	Emotion > pattern match Control > ASD: Right fusiform ASD > control: Left superior parietal lobe, precentral gyrus, middle frontal gyrus No significant between group differences in identity match condition *Fusiform and amygdala volume of interest analysis* *Identity > pattern match* *Control > ASD: left amygdala and right fusiform*

Table 10 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Critchley et al. (2000)*	9:0	37 (7)	102 (15)	Autism, AS	ICD-10, ADI	Age, IQ	Explicit emotion task: indicate via button press if face stimuli are happy/angry or neutral Implicit emotion task: indicate gender via button press (same stimuli).	Emotion vs neutral stimuli ASD > control: left superior temporal gyrus and peristriate visual cortex. Control > ASD: right fusiform cortex. *Significant group x condition interaction in cerebellar vermis, left lateral cerebellum, striatum, insula and amygdalohippocampal junction, and middle temporal gyrus.*
Dalton et al. (2005)*	1. 11:0	1. 15.9 (4.7)	1. 94 (19.5)	1. Autism, AS	1. DSM-IV, ADI	1. Age, gender	1. Indicate via button press if stimuli emotional or neutral. Happy, fear, anger and neutral face stimuli presented (half quarter turned, half facing ahead); resting baseline.	1. Control > ASD: bilateral fusiform, occipital gyrus and middle frontal gyrus. ASD > control: left amygdala and orbitofrontal gyrus. *Differences did not relate to orientation or emotional content.* *Fixation on eyes correlated with level of activity in left amygdala and right anterior fusiform gyrus in ASD group, effect not seen in controls.*
	2. 16:0	2. 14.5 (4.6)	2. 92.1 (27.7)	2. Autism, AS	2. DSM-IV, ADI	2. Age, gender	2. Discriminate familiar and unfamiliar faces via button press; resting baseline.	2. Control > ASD: bilateral fusiform, left anterior medial cortex, left posterior lateral cortex, right occipital cortex. *Greater activation in right occipital and fusiform gryus in control group in response to familiarity, effect not seen in ASD group. Fixation on eyes correlated with level of activity in right amygdala and right anterior fusiform gyrus in ASD group, effect not seen in controls.*
Deeley et al. (2007)*	9:0	34 (10)	114 (12)	AS	DSM-IV, ICD-10, ADI, ADOS	IQ, gender, handedness, task performance	Gender discrimination via button press. Neutral faces; emotional faces (high and low intensity); fixation baseline. 1. Fear vs baseline 2. Disgust vs baseline 3. Happy vs baseline 4. Sad vs baseline 5. Neutral faces (from each emotion condition) vs baseline	1. Control > ASD: right fusiform gyrus and cerebellum and left pre and postcentral gyrus. 2. Control > ASD: left fusiform gyrus, lingual gyrus and cerebellum. 3. Control > ASD: left fusiform gyrus, lingual gyrus and cerebellum. 4. Control > ASD: bilateral fusiform gyrus, lingual gyrus and cerebellum and left inferior occipital gyrus. 5. Control > ASD: fusiform, lingual, occipital cortices and cerebellum. *Intensity of emotion had an effect on brain activation at a trend level in both groups which varied with each emotion.*

Table 10 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Dichter and Belger (2007)	16:1	22.9 (5.2)	105 (18.6)	14 HFA, 3 AS	DSM-IV, ADI, ADOS	Age, IQ, gender, handedness, education, task performance	1. Indicate via button press direction of central arrow that was congruent (condition1) or incongruent (condition2) with direction of flanker arrows.	1. No significant group difference.
							2. Indicated via button press direction of eye gaze in central face that was congruent (condition1) or incongruent (condition2) with direction of eye gaze in flanker faces.	2. Control > ASD: bilateral dorsolateral prefrontal cortex, right inferior frontal/anterior insula cortex, anterior cingulate and bilateral intraparietal sulcus. (ROI analysis)
Dichter and Belger (2008)	12:0	23.2 (5.8)	106.9 (19.2)	HFA/AS	DSM-IV, ADOS, ADI	Age, IQ, in scanner accuracy (but not RT)	Participants completed a 2AFC task, indicating arrow direction via button press. 3 conditions were presented; neutral arrows, congruent and incongruent trails. Each trail was preceded with a high or low arousal image presented for 200 ms.	No significant between group differences were reported. *Within group maps were similar in the ASD and control groups when the incongruent trails were preceded by low arousal images. When preceded by high arousal images the ASD group did not modulate activity in right lateral midfrontal cortex as seen in the control group.*
Freitag et al. (2008)*	13:2	17.5 (3.5)	101.2 (21.2)	ASD	DSM-IV, ADI, ADOS	Age, IQ, gender, handedness	Indicate via button press if stimulus is biological motion or scrambled. Point-light walkers; scrambled version; fixation baseline.	1. All motion stimuli vs fixation: no group differences. 2. Biological motion vs scrambled Control > ASD: right middle temporal gyrus, medial and middle frontal gyrus and left anterior superior temporal gyrus, fusiform gyrus, and bilateral post central gyrus and inferior parietal lobule. (uncorrected stats.)
Greimel et al. (2009)*	15:0	14.9 (1.6)	109.9 (17.3)	12 AS, 3 HFA	DSM-IV, ICD-10, ADOS, ADI-R, SCQ	Age, IQ, gender, handedness	Participants are presented with face stimuli and indicate their response via button press in 3 conditions. Other condition; judge face stimuli as happy, sad or neutral. Self condition; judge own response to face as happy, sad or neutral. High level baseline; judge neutral faces as thin, average or wide.	Other condition vs high level baseline Control > ASD: left superior occipital gyrus, left cuneus, right anterior fusiform gyrus. Self condition vs high level baseline Control > ASD: left inferior frontal gyrus. *IFG and FG results were part of an ROI analysis.*

Table 10 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Grèzes et al. (2009)*	10:2	26.6 (10.4)	102 (20.6)	10 AS, 2 HFA	DSM-IV	Age, IQ, behavioural performance in scanner	Oddball paradigm; button press to upside down stimuli. Blank screen baseline. 1. Fearful dynamic body stimuli 2. Neutral dynamic body stimuli 3. Fearful static body stimuli 4. Neutral static body stimuli	Dynamic > static (1 + 2 > 3 + 4) Control > ASD: Right temporo-parietal junction, STG, middle STS, inferior temporal gyrus, medial superior frontal gyrus, precentral gyrus, precuneus, fusiform gyrus/cerebellum. Left inferior temporal gyrus and inferior frontal gyrus. Fear > neutral (1 + 3 > 2 + 4) Control > ASD: Right inferior frontal gyrus, precentral gyrus, inferior temporal gyrus, amygdala. ASD > controls: Left medial anterior superior frontal gyrus Interaction between fearful body expression and dynamic information (1–3 > 2–4) Controls > ASD: Right precuneus, STS, IFG, middle cingulate cortex, lingual gyrus ASD > controls: Right temporal gyrus. Left temporal pole/insula and temporo-parietal junction *A threshold of $p < 0.001$ (uncorrected) was applied.*
Hadjikhani et al. (2004a)	11:0	36 (12)	119 (8)	Autism, AS, PDD-NOS	DSM-IV, ADI-R, ADOS,	IQ, gender	Passive viewing of neutral faces with fixation cross over eye region; scrambled faces as baseline.	No significant differences between ASD and control group when activation within ROI's compared.
Hadjikhani et al. (2007)	8:2	34 (11)	124 (10)	6 autism, 3 AS, 1 PDD-NOS	ADI-R, ADOS	Age	Passive viewing of neutral faces with fixation cross over eye region; scrambled faces as baseline.	Control > ASD: right superior temporal sulcus region, somatosensory and premotor cortex, inferior frontal cortex and amygdala. (ROI analysis) *Fusiform Face Area activation in ASD group not significantly different from controls.*
Hadjikhani et al. (2009)*	9:3	30 (11)	126 (10)	8 autism, 3 AS, 1PDD-NOS *three excluded due to movement*	ADI, ADOS		Passive viewing of static body images (faces blurred) presented in blocks expressing fearful and neutral emotion	Processing fearful body images Control > ASD: bilateral colliculus, pulvinar, amygdala, extrastriate cortex, ventral temporal-occipital cortex, nucleus accumbens, anterior insula, putamen, motor and premotor cortex and inferior frontal cortex. No between group differences apparent in the neutral condition.

Table 10 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Herrington et al. (2007)*	10:0	27.6 (7.1)	109	AS	DSM-IV, ICD-10	Age, IQ, gender, handedness, task performance	Button press to indicate direction of movement. Point-light walkers; scrambled version; fixation baseline.	1. Scrambled movement vs fixation Control > ASD: right superior temporal gyrus and angular gyrus. 2. Walkers vs fixation Control > ASD: bilateral cerebellum, fusiform gyrus, middle temporal gyrus, middle occipital gyrus, cuneus, right inferior temporal gyrus and inferior occipital gyrus, and left superior temporal gyrus, inferior parietal lobe, angular gyrus, precuneus and precentral gyrus.
Hubl et al. (2003)	7:0	27.7 (7.8)	98 (17)	Autism	ICD-10, ADI, ADOS	Age, IQ, gender, task performance accuracy (not RT)	1. Indetify target via button press. Happy, sad, angry and neutral faces presented. Target happy (explicit emotion condition); target female (implicit emotion condition); scrambled faces as baseline condition. 2. Colour counting; shape counting within a mosaic; and a rest condition.	*Values from ROIs were extracted from each condition and investigated in an ANOVA for interactions with diagnosis, task, region and hemisphere.* *Activations for each task were different between ASD and controls.* *Different tasks activated different regions.* *The ASD and control groups differ with respect to the difference in activations caused by each task in different regions.*
Humphreys et al. (2008)*	13:0	27 (10)	VIQ 103 PIQ 106	Autism	ADI-R, ADOS	Age, gender	1. Blocks of line drawings of faces, buildings, objects and patterns presented. Press button when repetition occurs 2. Passive viewing of blocks of movies of faces, buildings, open fields and objects presented.	1. Control > Autism: bilateral fusiform face area for faces and right fusiform face area for objects. Selectivity for faces in the left fusiform face area. 2. Control > Autism: bilateral fusiform face area for faces. Selectivty for faces in bilateral fusiform face area Autism > Control Bilateral fusiform face area for scenes. In experiment 2 greater inter-individual variability was seen in the fusiform face area in the autism group than the controls. This effect was not seen in other ROIs – lateral occipital cortex and collateral sulcus *ROI analysis*
Kennedy et al. (2006)*	12:0	26.5 (12.8)	101.6 (15.2)	6 autism, 6 AS	ADI-R, ADOS	Age	Counting Stroop task with emotional, neutral and number words. Participants asked to count number of words on the screen. Baseline fixation cross	Number vs rest ASD > Control: right supramarginal gyrus, right precuneus, bilateral inferior parietal lobule, right superior frontal gyrus, left medial frontal/anterior cingulate Emotional vs neutral Control > ASD: right medial orbitofrontal cortex, right middle occipital gyrus Functional connectivity analysis See Table 8

Table 10 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Kleinhans et al. (2008b)*	19:0	23.5 (7.8)	106.7 (15.7)	8 autism, 9 AS, 2 PDD-NOS	DSM-IV, ADI-R, ADOS	Age, IQ, task performance	1-back with neutral faces; 1-back with houses as baseline.	No significant group differences. Functional connectivity analysis See Table 8
Kleinhans et al. (2009)*	19	21.9 (5.9)	107 (13.8)	ASD	DSM-IV, ADOS, ADI	Age, IQ, in scanner accuracy (but not RT)	Participants complete a 1 back working memory task with blocks of stimuli; upright neutral faces, inverted faces, houses and fixation baseline condition. Two runs of the task were completed, each with different stimuli.	Upright neutral faces vs fixation Run 1 No significant group differences Upright neutral faces vs fixation Run 2 ASD > control, left amygdala and right fusiform gyrus Faces vs fixation Run1 > Run2 Control > ASD: bilateral amygdala *Small volume corrections applied.*
Koshino et al. (2008)*	11:0	24.5 (10.2)	104.5 (13.1)	HFA	ADI-R, ADOS	Age, IQ, gender, socioeconomic status, task performance	0, 1 and 2-back working memory task with face identity; fixation baseline.	Control > ASD: left inferior prefrontal and right posterior temporal cortex. *Different location of the Fusiform Face Area within the fusiform gyrus in ASD group compared to controls.* Functional connectivity analysis See Table 8
Loveland et al. (2008)	4:1	18.25 (15.9)	112.6 (15.3)	Autism	DSM-IV, ADI-R, ADOS	Age, handedness	Emotional faces and voices presented in congruent and incongruent pairs. Participants asked to judge emotional congruence (condition of interest) or gender congruence (baseline).	Control > ASD: bilateral lingual gyrus, bilateral cuneus, right middle frontal gyrus, left parahippocampal gyrus, left fusiform.
Ogai et al. (2003)	5	21.8 (5.9)	112.4 (10.5)	HFA	DSM-IV	Age, IQ, socioeconomic status, education, emotion label task performance	Instructed to think about the emotion being expressed. 1. Happy faces; neutral faces 2. Fear faces; neutral faces 3. Disgust faces; neutral faces	1. No significant difference between groups. 2. Control > ASD: left middle frontal gyrus. 3. Control > ASD: left insula, left inferior frontal gyrus and left putamen.
Pelphrey et al. (2007)*	6:2	24.5 (11.5)	120 (9)	Autism	ADI, ADOS	Age, IQ, task performance	Button press in response to face stimuli. Static neutral; static emotional (anger and fear); dynamic neutral (identity morph); dynamic emotional (emotion morph) events. Fixation baseline.	1. Dynamic emotional condition vs fixation baseline Control > ASD: right amygdala and superior frontal gyrus, left fusiform gyrus and medial frontal gyrus and bilateral middle temporal gyrus.

Table 10 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
								2. Dynamic emotional condition vs static emotion *Group x condition contrast: control group modulate activity in amygdala, superior temporal sulcus region and fusiform gyrus, an effect not seen in ASD group.* 3. Dynamic neutral condition vs static neutral No group differences. 4. Static emotion condition vs fixation baseline ASD > control: superior temporal sulcus region. (No amygdala or fusiform gyrus differences) (ROI analysis)
Pelphrey et al. (2005)	9:1	23.2 (9.9)	107 (16)	Autism	ADI, ADOS	Age, IQ, task performance	Button press in response to shifts in eye gaze that were congruent with the location of a visual stimulus; incongruent trials.	*Group x condition contrast: posterior superior temporal sulcus region activity modulated by congruence in control group but not in ASD group. Inferior frontal gyrus and insular cortex modulated by congruence in ASD group but not control group.*
Pierce et al. (2001)	7:0	29.5 (8)	83.7 (10.9)	Autism	DSM-IV, ADI-R, ADOS, CARS	Age, gender, handedness, task performance	Button press in response to target. Neutral face perception; shape perception.	Control > ASD: bilateral fusiform and left amygdala. (ROI analysis, but findings supported by whole brain within group maps.)
Pierce et al. (2004)	8:0	27.1 (9.2)	80.3 (17.7)	Autism	DSM-IV, ADI, ADOS	Age, gender, handedness, task performance	Gender discrimination via button press with familiar and stranger faces; fixation baseline.	No significant between group differences.
Pierce and Redcay (2008)	9:2	9.9 (2.1)	108.5 (12.6)	9 autism, 1 AS, 1 PDD-NOS	ADI, ADOS	Age, gender, handedness, task performance	1-back task. Button press if stimuli repeated. Familiar adult; stranger adult; familiar child; stranger child; objects; fixation baseline.	No between group differences reported in whole brain analysis. Stranger faces vs baseline Control > ASD: left fusifrom. Familiar children vs baseline Control > ASD: posterior cingulate. (ROI analysis)
Piggot et al. (2004)	14:0	13.1 (2.5)	112 (15.9)	7 autism, 7 AS	DSM-IV, ADI, ADOS	Age, IQ, handedness, socioeconomic status, task performance accuracy (but not RT)	1. Match target by emotion to one of two response options. Fearful, surprised and angry face stimuli; shape matching as baseline.	1. Control > ASD: average fusiform gyrus. (ROI analysis.)
							2. Label emotion given two text choices. Fearful, surprised and angry face stimuli; shape matching as baseline.	2. No significant group differences.

Table 10 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Schultz et al. (2000)	14:0	23.8 (12.4)	109.1 (19.5)	8 HFA, 6 AS	ICD-10, ADI-R, ADOS, Vineland	Age, IQ, task performance	Same/different discrimination via button press. Neutral faces, objects; patterns.	Faces vs patterns Control > ASD: right fusiform gyrus ASD > control: bilateral inferior temporal gyrus activation. No differences between groups in object task. (ROI analysis)
Wang et al. (2004)*	12:0	12.2 (4.8)	Not reported	Autism, AS, PDD-NOS	ADI, ADOS	Age, gender, handedness, nonverbal language age, task performance	1. Match target by emotion to one of two response options. Fearful and angry face stimuli; shape matching as baseline.	1. Control > ASD: bilateral fusiform gyrus. ASD > control: precuneus.
							2. Label emotion given two text choices. Fearful and angry face stimuli; shape matching as baseline.	2. No significant group differences. (ROI analysis)
Wicker et al. (2008)*	11:1	27 (11)	81.3	8 autism, 4 AS	DSM-IV	Age	Explicit angry – happy face emotion judgements; baseline explicit gender judgement. Actors gaze either direct or averted	Control > ASD right temporal-parietal junction, right inferior frontal gyrus and medial superior frontal gyrus Effective connecitivity analysisSee Table 8

* Study included in meta-analysis.

and the basal ganglia, as well as other regions, such as the superior and inferior parietal lobules which may relate to attentional systems. Cerebellar abnormalities tended to be found in studies of simple motor tasks (Allen and Courchesne, 2003; Allen et al., 2004), whereas more complex sequence learning tasks tend to show differences in cortical-subcortical networks as opposed to the cerebellum (Muller et al., 2003, 2001, 2004).

It is important to consider these findings when interpreting results from other functional imaging studies in this population, where in most cases, a motor response via button press is the method used to gather behavioural performance data. Tasks requiring a motor response could disrupt cortico-cerebellar networks and alter connectivity patterns as a consequence of the response required rather than the task.

4.2.2. Visual processing tasks

The ALE meta-analysis revealed greater activation in control subjects than in individuals with ASD in visual areas, such as the lingual and occipital gyri, which, given the lack of a behavioural difference between the groups, may reflect more efficient processing of visual stimuli in these regions in individuals with ASD. This is consistent with the idea that individuals with ASD show enhanced perceptual systems (Samson et al., 2011; Soulieres et al., 2011).

Table 11
Group comparisons of regions with significantly elevated likelihood of activation in basic social tasks. Brain areas activated from the ALE analysis ($p_{FDR} < 0.05$ and a minimum cluster size of 200 voxels). C/A: children/adolescents.

Comparison – age group	Brain region	BA	Volume (mm^3)	Talairach			ALE (10^{-2})
				x	*y*	*z*	
ASD > C; All	Superior Temporal Gyrus L	22	984	−60	−28	4	1.14
	Superior Temporal Gyrus R	22	360	54	8	4	0.89
ASD > C; C/A	No clusters found.						
ASD > C; Adults	Superior Temporal Gyrus L	41	392	−54	−24	6	0.92
	Superior Temporal Gyrus R	22	320	54	8	4	0.89
C > ASD: All	Fusiform Gyrus L	18	2424	−20	−88	−14	2.73
	Inferior Occipital Gyrus R	18	1080	30	−84	−14	3.14
	Culmen R		248	40	−42	−22	1.99
	Middle Temporal Gyrus L	22	248	−52	−40	0	1.85
C > ASD; C/A	Cuneus R	17	336	14	−82	8	0.91
	Parahippocampal Gyrus R	36	304	26	−36	−14	0.85
C > ASD; Adults	Fusiform Gyrus L	18	2112	−20	−88	−14	2.73
	Inferior Occipital Gyrus R	18	944	30	−84	−14	3.14

Table 12
'Complex' social cognition tasks. Abbreviations as in Table 2.

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Baron-Cohen et al. (1999)*	4:2	26.3 (2.1)	108.5 (10.5)	Autism, AS	DSM-IV, ICD-10	Age, IQ, handedness, socioeconomic status, education	Two alternate forced choice decision via button press on the mental state portrayed in eye stimuli; gender discrimination of same stimuli as baseline.	Control > ASD: left insula, inferior frontal gyus and right insula. ASD > control: bilateral superior temporal gyrus.
Chiu et al. (2008)	12:0	16.5 (3.3)	103 (18)	Autism, AS, PDD-NOS	DSM-IV, ADI, ADOS	Age, IQ, gender, task performance	Multiround trust game – investor (control subject) is given an amount of money and chooses to send a proportion of this to trustee (ASD subject). This is tripled and trustee then repays a proportion of the tripled amount. 1. 'other' condition; at the time of controls investment. 2. 'self' condition; when ASD subject returns proportion of the money.	1. no significant difference 2. Control > ASD: middle cingulate. *Reduced cingulate response in ASD group correlates with total, social and communication ADI scores. Controls activate cingulate in both 'self' and 'other' conditions, unless they were playing with a computer in which case they activate in a similar fashion to that seen in ASD subjects here – suggesting dysfunction in self-referential processing in ASD.* (ROI analysis)
Dapretto et al. (2006)*	9:1	12.05 (2.5)	96.4 (18.3)	HFA	ADOS, ADI	Age, IQ	Imitation of emotional expressions; observation of emotional expressions; fixation baseline.	Imitation vs rest Control > ASD: bilateral inferior frontal gyrus, insula, periamygdaloid regions, ventral striatum and thalamus. ASD > control: left anterior parietal and right visual association areas. Observation vs rest Control > ASD: bilateral inferior frontal gyrus.
Gilbert et al. (2009)	14:2	32 (7.7)	VIQ 117 (13.7) PIQ 115 (14.3)	ASD	Clinical dx and ADOS (but not all met criteria)	Age, handedness, IQ	Spatial task – participants follow outline of shape via button press. Alphabet task – participants indicate if letters were made up of only straight lines or included curves Both tasks have two conditions: stimulus orientated responses – where shapes or letters are visible; stimulus independent responses – where the task is continued without visual cues Also the pace of stimuli presentation varied and the participants were asked a) if the person controlling the pace of the presentation was being helpful or not (a mentalizing condition) or b) if the presentation was fast or slow (non-mentalizing condition) Same-function comparisons – mentalizing vs mentalizing and non-mentalizing vs non-mentalizing Cross function comparisons – mentalizing vs non-mentalizing	Multi-voxel similarity analysis within medial rostral prefrontal cortex: Control group show different distribution of activation when same function comparisons were compared to cross function comparisons whereas ASD group do not. Controls showed similar distributions of activation during mentalizing condition regardless of task format (spatial or alphabet) and during non-mentalizing condition regardless of task format. ASD group did not show this pattern indicating greater functional specialization in controls.

Table 12 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Greimel et al. (2009)*	15:0	14.9 (1.6)	109.9 (17.3)	12 AS, 3 HFA	DSM-IV, ICD-10, ADOS, ADI-R, SCQ	Age, IQ, gender, handedness	Participants are presented with face stimuli and indicate their response via button press in 3 conditions. Other condition; judge face stimuli as happy, sad or neutral. Self condition; judge own response to face as happy, sad or neutral. High level baseline; judge neutral faces as thin, average or wide.	Other condition vs high level baseline Control > ASD: left superior occipital gyrus, left cuneus, right anterior fusiform gyrus. Self condition vs high level baseline Control > ASD: left inferior frontal gyrus. *IFG and FG results were part of an ROI analysis.*
Kana et al. (2009)*	10:2	24.6 (6.9)	104.3 (14.4)	Autism	ADOS, ADI	Age, IQ, socioeconomic status, race and behavioural performance in scanner	4AFC of text to describe an animation of geometric shapes. Event related design with 3 conditions and fixation baseline. ToM interaction Goal Directed movement Random movement	ToM > Random Control > ASD: left superior medial frontal cortex, anterior paracingulate cortex and inferior orbital frontal gyrus. Bilateral anterior cingulate gyrus. ASD > control: right anterior superior temporal gyrus *p < 0.005 uncorrected*
Kennedy and Courchesne (2008)	13:0	26.9 (12.3)	101.7 (14.6)	6 autism, 6 AS, 1PDD-NOS	ADI-R, ADOS	Age, IQ, gender, handedness	Participants were provided with statements on which they make true/false judgments. Mental condition: Statements were about themselves (SELF condition) or a close other person (OTHER condition) and referred to psychological personality traits (INTERNAL condition) or observable external characteristics or behaviours (EXTERNAL condition). High level baseline condition: participants presented with maths equations and indicated whether the answer was true or false for that sum. Low level baseline; visual fixation.	All mental judgement conditions vs high level baseline: Control > ASD: ventral medial prefrontal cortex/ventral anterior cingulate cortex. All mental judgements vs low level baseline: Control > ASD: dorsomedial prefrontal cortex, retrosplenial/posterior cingulate cortex and left angular gyrus High level baseline vs low level baseline Control > ASD: ventral medial prefrontal cortex/ventral anterior cingulate cortex. *ROI analysis of default network.*
Mason et al. (2008)	17:1	26.5	101.9	HFA	ADI, ADOS	Age, IQ, gender, socioeconomic status, race	Read short scenarios and answered yes/no comprehension questions via button press. Intentional, emotional and physical sentences; fixation baseline.	ASD > control: right middle temporal gyrus, superior temporal gyrus, angular gyrus and supramarginal gyrus. *Whilst the recruitment of these regions was modulated by sentence type in the control group (greater activation when making mentalistic inferences) the ASD group recruited these regions for all sentence types.* Functional connectivity analysis See Table 8

Table 12 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Pinkham et al. (2008)*	12:0	24.08 (5.71)	110 (10.91)	HFA	DSM-IV, ADI, ADOS	Age, gender, handedness, verbal IQ	Indicate judgement of face stimuli via button press. Trustworthiness; age; fixation baseline.	1. Trust vs baseline Control > ASD: right amygdala and Fusiform Face Area and left venterolateral prefrontal cortex. 2. Age vs baseline ASD > control: left superior temporal sulcus region, right venterolateral prefrontal cortex. 3. Trust vs age *Comparison of within group maps: amygdala, superior temporal sulcus region and venterolateral prefrontal cortex activity modulated in control group, effect not seen in ASD group.* (ROI analysis.)
Silani et al. (2008)*	13:2	36.6 (11.7)	117.6 (13.5)	HFA/AS	DSM-IV, ADOS	Age, IQ, gender and behavioural performance in scanner	Internal task; participants rated pictures (unpleasant, neutral and pleasant) on the emotion invoked by the picture (positive to negative) External task; participants rated pictures (unpleasant, neutral and pleasant) on colour balance in the picture (black to white)	Internal task > external task Control > ASD: medial prefrontal cortex, ACC, precuneus, left temporal lobe and cerebellum ASD > control: parietal and occipital cortex Unpleasant > pleasant stimuli Controls > ASD: Right cerebellum. Left inferior orbitofrontal cortex ASD > controls: Right middle occipital cortex and calcarine Internal (unpleasant – neutral) > external (unpleasant – neutral) Control > ASD: Right corpus callosum *p < 0.001 uncorrected*
Takeuchi et al. (2004)	8:2	11.2 (2.6)	110.4 (14.8)	Autism	DSM-III	Age, IQ, handedness	Reading task involving attribution of complex mental states	ASD > Control: right prefrontal cortex *p < 0.01 (uncorrected)*
Uddin et al. (2008)	12:0	13.19 (2.61)	116 (14)	HFA	ADI, ADOS (except one partici-pant)	Age, IQ, gender, handedness, in scanner performance	Faces presented morphing from 100% self to 100% other plus a scrambled image, plus fixation baseline. Participants indicated via button press whether the face was self or other.	No significant between group differences in WBA. *Whilst both groups activated right inferior frontal gyrus when viewing 'self' images, only the control group activated this region when viewing 'other' images. This finding reached statistical significance when a functionally derived ROI was applied to the right frontal cortex.*

Table 12 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Wang et al. (2006)*	18:0	11.9 (2.8)	102 (18)	Autism, AS	ADI, ADOS	Age, IQ, gender, handedness, social responsiveness scale	Participants listen to scenarios and indicate via button press if the speaker means what they say. 1. Event knowledge and prosodic cues; resting baseline. 2. Event knowledge only; resting baseline. 3. Prosodic cues only; resting baseline.	1. ASD > control: left pre-central gyrus and bilateral inferior frontal gyrus. 2. Control > ASD: left superior frontal gyrus ASD > control: left pre and post-central gyrus, superior temporal gyrus, superior temporal sulcus region and medial temporal gyrus and right inferior frontal gyrus. 3. ASD > control: left superior temporal sulcus region and right temporal pole.
Wang et al. (2007)*	18:0	12.4 (2.9)	98 (17)	ASD	DSM-IV, ADI, ADOS	Age, IQ, gender, handedness, social responsiveness scale, task performance	Indicate via button press if the speaker is sincere or not. Storyboards and speech stimuli. 1. Participants asked to pay attention; resting baseline. 2. Participants asked to pay attention to facial expression or tone of voice; resting baseline. 3. All ironic scenarios; non-ironic scenarios.	1. Control > ASD: bilateral medial prefrontal cortex, superior temporal gyrus and cerebellum. 2. Control > ASD: superior temporal gyrus, cerebellum and visual cortex. 3. Control > ASD: bilateral temporal regions and medial prefrontal cortex.
Williams et al. (2006)*	16:0	15.4 (2.24)	100.4 (21.7)	ASD	ADI, ADOS	Age, IQ, gender	Passive viewing task. Hand with index or middle finger raised; hand stimuli with cross on middle or index finger; cross on left or right side of screen; resting baseline. Hand with index or middle finger raised (imitation); hand stimuli with cross on middle or index finger (execution); cross on left or right side of screen (execution); resting baseline.	Imitation vs rest Control > ASD; right fusiform gyrus, middle occipital gyrus, lingual gyrus, middle temporal gyrus and bilateral inferior parietal lobe, and greater activation in right parahippocampal gyrus and cingulate gyrus, left uncus, precentral gyrus, claustrum, middle frontal gyrus, middle occipital gyrus and bilateral superior temporal gyrus. Imitation vs execution Control > ASD group had less activation in right precuneus, left anterior cingulate and inferior parietal lobe. ASD > control; left superior parietal lobe and bilateral precentral gyrus and middle frontal gyrus. *ROI of Mirror Neuron System; ASD group activated anterior parietal lobe and somatosensory cortex less than the control group in response to both imitation and action execution. Left amygdala activity was modulated in the control group by task conditions; activity in this region was significantly less variable in the ASD group.*

* Study included in meta-analysis.

Table 13
Group comparisons of regions with significantly elevated likelihood of activation in complex social cognition tasks. Brain areas activated from the ALE analysis ($p_{FDR} < 0.05$ and a minimum cluster size of 200 voxels). C/A: children/adolescents.

Comparison – age group	Brain region	BA	Volume (mm^3)	Talairach			ALE (10^{-2})
				x	*y*	*z*	
ASD > C; All	Superior Temporal Gyrus L	22	536	−48	−32	4	1.59
	Precentral Gyrus L	4	264	−20	−22	64	1.58
	Postcentral Gyrus L	3	256	−40	−22	54	1.37
	Inferior Frontal Gyrus R	13	232	40	22	10	1.36
ASD > C; C/A	Superior Temporal Gyrus L	22	472	−48	−32	4	1.58
	Precentral Gyrus L	4	248	−20	−22	64	1.58
	Postcentral Gyrus L	3	224	−40	−22	54	1.37
	Inferior Frontal Gyrus R	13	208	40	22	10	1.36
ASD > C; Adults	No clusters found.						
C > ASD; All	Superior Temporal Gyrus L	41	864	−52	−20	10	1.60
	Superior Temporal Gyrus R	22	320	56	−8	−2	1.66
	Inferior Parietal Lobule L	40	208	−54	−56	40	1.52
C > ASD; C/A	Superior Frontal Gyrus L	41	832	−52	−20	10	1.60
	Superior Temporal Gyrus R	22	228	56	−8	−2	1.66
	Inferior Parietal Lobule L	40	208	−54	−56	40	1.52
C > ASD; Adults	Claustrum R		368	32	−16	16	1.02

Examining tasks of visual processing in more detail suggests they can be considered in three main sub-groups: sensorimotor control, visual search and object processing paradigms. Sensorimotor paradigms encompass saccadic and pursuit eye movement tasks (Takarae et al., 2007; Luna et al., 2002) and investigation of antisaccades (Thakkar et al., 2008) and report seemingly contradictory results with both increased and decreased activation in the cingulate cortex. Studies employing visual search tasks report findings which tend to show less activation in prefrontal regions in ASD compared to control subjects and a greater activation of the occipitotemporal regions in participants with ASD, supporting a more visually based processing strategy (Ring et al., 1999; Keehn et al., 2008; Bölte et al., 2008). Object processing paradigms are often carried out as comparison or high level control tasks during other visual or face processing tasks and as such results often go unreported. In addition, the choice of task and stimuli varies dramatically between studies, presumably because they are chosen to match properties of the main task under examination. This hetereogeneity is reflected in the results from those papers which have reported them, which include areas of increased (Keehn et al., 2008) and decreased (Bölte et al., 2008; Hubl et al., 2003; Humphreys et al., 2008) activations in individuals with ASD, as well as no differences in activation between the groups (Bird et al., 2006; Pierce and Redcay, 2008; Schultz et al., 2000).

4.2.3. *Executive function tasks*

Executive dysfunction is well established as an important feature in ASD (Hill, 2004). When all executive function tasks were considered together in the ALE meta-analysis, greater activation in individuals with ASD was seen in the orbitofrontal cortex, which has been associated with learning and planning through the monitoring of reward and punishment (Kringelbach and Rolls, 2003, 2004). Reduced activation was seen in the dorsolateral prefrontal cortex, inferior parietal lobe, the insula, posterior cingulate gyrus and lentiform nucleus. One possible explanation for these findings is that in individuals with ASD, executive dysfunction is associated with disruptions to the automatic attentional systems involving the prefrontal-striatal network and the inferior parietal lobe (Haist et al., 2005), as well as the insula (Kana et al., 2007) which has been associated with executive control of attention. However, executive function is an umbrella term which encompasses a variety of different sub-domains, discussed below.

Spatial attention has been examined in several studies, with findings converging on hypoactivation in prefrontal and parietal regions in individuals with ASD relative to controls (Belmonte and Yurgelun-Todd, 2003; Haist et al., 2005; Shafritz et al., 2008). It has been suggested that reduced parietal activity may result in difficulty with automatically shifting spatial attention in individuals with ASD (Haist et al., 2005). Reductions in prefrontal and parietal activity in ASD have also been seen in a study of planning (Just et al., 2007).

Cognitive control tasks are mainly associated with hypoactivity of prefrontal cortical brain regions in ASD study participants, primarily the DLPFC (Dichter and Belger, 2008) and the anterior cingulate cortex (Koshino et al., 2005, 2008; Kana et al., 2007). The role of the DLPFC in many executive functions including working memory is well established in typically developing subjects (Wang et al., 2010; Brazdil et al., 2007), whereas the anterior cingulate cortex is known to be involved in response inhibition. Further evidence for anterior cingulate dysfunction comes from Schmitz et al. (2008) who found greater activation in the anterior cingulate cortex during a continuous performance task with associated reward. Several authors have chosen to modulate load during cognitive control tasks. Kana et al. (2007) introduced a working memory component to a response inhibition task and found that, in addition to underactivity in the anterior cingulate cortex, individuals with ASD also showed increased premotor cortex activation and reduced synchrony of the frontal inhibition network with inferior parietal regions and the inferior frontal gyrus. In a different approach Dichter and Belger (2007) incorporated social stimuli into their task which led to greater levels of hypoactivation being elicited in the ASD group than were seen when non-social stimuli were used. Thus it appears that greater differences in neural response are seen as tasks become more complex. There is also some suggestion from the literature, that as well as underactivating prefrontal regions during cognitive control tasks, individuals with ASD show greater activation in visuo-spatial regions (Belmonte and Yurgelun-Todd, 2003; Dichter and Belger, 2007; Gilbert et al., 2008; Koshino et al., 2005; Schmitz et al., 2006) suggesting that they use more visual imagery.

In summary, evidence from a variety of task types suggests that areas of the prefrontal cortex generally recruited for executive functions are activated to a lesser extent in ASD. These seem to particularly include regions which are involved in the control of attention.

Table 14
Connectivity analysis of fMRI data. Abbreviations as in Table 2.

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Bird et al. (2006)	14:2	33.3 (11.5)	119 (14)	1 autism, 15 AS	DSM-IV, ADOS, AQ	Age, IQ, gender, task performance	1. Localiser task: passive viewing of neutral faces; passive viewing of houses; fixation baseline. (fixation cross over 'eye region') 2. Same/different discrimination in horizontal or vertical plane via button press; pairs of faces and houses presented.	*ASD group shows a lack of attentional modulation of V1-parahippocampal and V1-fusiform connectivity.*
Cherkassky et al. (2006)	53:4	24 (10.6)	106 (16.2)	Autism	DSM-IV, ADOS	Age, IQ, gender	Resting state	Compared to controls ASD group show reduced functional connectivity in the left hemisphere generally, between anterior and posterior cingulate, and between the left parahippocampal region and all other ROIs
Grèzes et al. (2009)	10:2	26.6 (10.4)	102 (20.6)	10 AS, 2 HFA	DSM-IV	Age, IQ, behavioural performance in scanner	Oddball paradigm; button press to upside down stimuli. Blank screen baseline. 1. Fearful dynamic body stimuli 2. Neutral dynamic body stimuli 3. Fearful static body stimuli 4. Neutral static body stimuli	Effective connectivity analysis Control > ASD: amygdala with superior temporal sulcus, premotor area and inferior frontal gyrus; premotor area with superior temporal sulcus; inferior frontal gyrus with premotor area
Just et al. (2004)	17	Not reported	>80	HFA	ADI, ADOS	Age, IQ, gender, socioeconomic status	Sentence comprehension (identifying the agent or recipient of the action); fixation baseline.	Control > ASD: left inferior extrastriate with left inferior parietal lobe and left inferior temporal lobe; left pars triangularis with superior medial frontal paracingulate; left inferior temporal lobe with left frontal eye field; right dorsolateral prefrontal cortex left intraparietal sulcus, left inferior frontal gyrus, left inferior parietal lobe, left inferior extrastriate and occipital pole; left inferior frontal gyrus with calcarine fissure
Just et al. (2006)	17:1	27.1 (11.9)	109.3 (17.7)	Autism	ADI, ADOS	Age, IQ, gender, socioeconomic status, task performance	Indicate via button press required number of moves to complete Tower of London task displayed; fixation baseline.	Control > ASD: fronto-parietal connectivity

Table 14 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Just et al. (2007)	17:1	27.1 (11.9)	109.3 (17.7)	Autism	ADI, ADOS	Age, IQ, gender, socioeconomic status, task performance	Indicate via button press required number of moves to complete Tower of London task displayed, Easy condition and hard condition; fixation baseline.	Controls > ASD: bilateral inferior and superior parietal area, angular gyri, superior, and middle occipital areas, middle frontal gyri, and the right precentral gyrus, superior frontal and the left inferior frontal gyri Autism > Controls: bilateral hippocampus, thalamus and left lingual gyrus. Autism > Controls in right middle occipital gyrus for hard vs easy contrast Functional connectivity analysis See Table 12
Kana et al. (2006)	11:1	22.5 (8.8)	110.7 (9.2)	Autism	ADI, ADOS	Age, IQ, gender, socioeconomic status, task performance	1. Indicate via button press whether a low-imagery sentence is true or false; fixation baseline. 2. Indicate via button press whether a high-imagery sentence is true or false; fixation baseline.	*ASD group showed generally lower connectivity between lobes than controls but differences were non-significant*
Kana et al. (2007)	11:1	26.8 (7.7)	110.1 (12.6)	HFA	ADI, ADOS	Age, IQ, gender, handedness, socioeconomic status	Go/no go task with increasing working memory load: 1 – simple response inhibition, 2 – response inhibition with working memory component; fixation baseline.	Control > ASD: Inhibition network (cingulate cortex, cingulate gyri and insula) with right inferior parietal areas and right inferior frontal gyrus
Kennedy and Courchesne (2008)	12:0	26.5 (12.8)	101.6 (15.2)	6 autism, 6 AS	ADI-R, ADOS	Age	Counting Stroop task with emotional, neutral and number words. Participants asked to count number of words on the screen. Baseline fixation cross	Functional connectivity analysis of task positive network and task negative network ASD individuals showed reduced connectivity within the task negative network, localised to the medial prefrontal cortex and the left angular gyrus No between group differences with respect to task positive network
Kleinhans et al. (2008b)	19:0	23.5 (7.8)	106.7 (15.7)	8 autism, 9 AS, 2 PDD-NOS	DSM-IV, ADI-R, ADOS	Age, IQ, task performance	1-back with neutral faces; 1-back with houses as baseline.	Control > ASD: right fusiform face area with left amygdala, bilateral posterior cingulate and left cuneus *Social impairment correlated with reduced connectivity between right fusiform face area and left amygdala, and with increased connectivity between right fusiform face area and left inferior frontal gyrus*

Table 14 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Koshino et al. (2005)	13:1	25.7	100.1	HFA	ADI, ADOS	Age, IQ, gender, socioeconomic status, task performance	n-back task (0,1,2); fixation baseline.	Control > ASD: left inferior parietal lobe with right dorsolateral prefrontal cortex, right frontal eye fields, right posterior precentral sulcus, left intraparietal sulcus, right intraparietal sulcus and right superior parietal lobe; left intraparietal sulcus with superior medial frontal paracingulate
Koshino et al. (2008)	11:0	24.5 (10.2)	104.5 (13.1)	HFA	ADI-R, ADOS	Age, IQ, gender, socioeconomic status, task performance	0, 1 and 2-back working memory task with face identity; fixation baseline.	Control > ASD: left frontal-fusiform connectivity
Lee et al. (2009)	9:3	10.2 (1.6)	113.3 (17.3)	ASD	DSM-IV, ADI-R, ADOS	Age, gender. IQ	Go/NoGo task	Functional connectivity analysis of inferior frontal gyrus No group differences but ASD group showed a negative relationship between age and right inferior frontal gyrus connectivity with bilateral supplementary motor area and right caudate which was not seen in controls
Mason et al. (2008)	17:1	26.5	101.9	HFA	ADI, ADOS	Age, IQ, gender, socioeconomic status, race	Read short scenarios and answered yes/no comprehension questions via button press. Intentional, emotional and physical sentences; fixation baseline.	Control > ASD: Left medial frontal cortex with left temporal-parietal junction (emotional); left medial frontal cortex with left inferior frontal and middle temporal gyri and right temporo-parietal junction (intentional)
Mizuno et al. (2006)	8:0	28.4 (8.9)	86.5 (11.4)	Autism	DSM-IV, ADI-R, CARS	Age, gender, handedness, task performance	Image of hand with dot indicating appropriate button press for a 6-digit repeated sequence; single-digit stimuli as baseline.	Functional connectivity analysis of thalamus: Control > ASD: Right thalamus with bilateral superior frontal gyri, left paracentral gyrus, right precuneus, left medial temporal lobe, right superior temporal lobe and right parahippocampal gyrus Left thalamus with bilateral parahippocampal gyrus and right superior temporal gyrus ASD > Control: Right and left thalamus with bilateral insula, middle frontal gyrus, medial frontal region, precentral and postcentral gyri and left inferior parietal lobe. Left thalamus with left cuneus and superior temporal gyrus

Table 14 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Noonan et al. (2009)	10:0	23.0 (9.9)	96.7 (16.1)	6 autism, 4 AS	DSM-IV, ADI-R, ADOS	Age, gender, IQ	Source memory task: Participants given lists of words to remember in visual and auditory domains then presented with more lists of words and asked to judge whether they were new, previously presented in the visual domain or previously presented in the auditory domain; blank screen baseline. Analysis performed only on visual recognition runs	ROIs chosen because they showed distinct patterns of activation between groups ASD > Control: Left middle frontal gyrus with bilateral precentral gyrus and supplementary motor area, bilateral superior temporal, left middle temporal, right parahippocampal, left supramarginal and left postcentral gyri and left precuneus Left superior parietal lobe with bilateral supplementary motor area and left precentral gyrus, right inferior frontal, bilateral superior and middle temporal gyri, left superior and inferior parietal lobules, left fusiform and left lingual gyri and left cerebellum Left middle occipital gyrus with bilateral inferior frontal and superior temporal gyri
Turner et al. (2006)	8:0	28.4 (8.9)	86.5 (11.4)	Autism	DSM-IV, ADI-R, CARS	Age, gender, handedness, task performance	Image of hand with dot indicating appropriate button press for a 6-digit repeated sequence; single-digit stimuli as baseline.	Functional connectivity analysis of caudate nucleus: Control > ASD Bilateral caudate with right superior frontal gyrus. Right caudate with left middle temporal gyrus, right parahippocampal gyrus and bilateral occipital cortex ASD > Control Bilateral caudate with right middle frontal gryus, bilateral precentral gyrus, left medial frontal gyrus, right postcentral gyrus, bilateral cingulate gyrus, and left cuneus.
Villalobos et al. (2005)	8:0	28.4 (8.9)	86.5 (11.4)	Autism	DSM-IV, ADI-R, CARS	Age, gender, handedness, task performance	Image of hand with dot indicating appropriate button press for a 6-digit repeated sequence; single-digit stimuli as baseline.	Functional connectivity analysis of visual cortex: Control > ASD: Bilateral inferior frontal area, right superior frontal gyrus and paracentral lobule, bilateral thalamus, right basal ganglia and cerebellar vermis

Table 14 (*Continued*)

Study (year)	Autism group					Control matching criteria	Task design	Main findings
	N (M:F)	Mean age (sd)	Mean IQ (sd)	Diagnosis	Diagnostic measures			
Welchew et al. (2005)	13:0	31.2 (9.1)	108.6 (17.1)	Asperger syndrome	DSM-IV, AQ	age, IQ, gender, handedness	Implicit emotional face processing paradigm. Participants viewed fearful faces, non-fearful faces, neutral faces and scrambled faces. Asked to press a button when stimulus appeared	Reduced functional distance between medial temporal structures (bilateral parahippocampal gyrus and left amygdala) and rest of brain
Wicker et al. (2008)	11:1	27 (11)	81.3	8 autism, 4 AS	DSM-IV	Age	Explicit angry – happy face emotion judgements; baseline explicit gender judgement. Actors gaze either direct or averted	Effective connectivity analysis Control > ASD Dorsomedial prefrontal cortex with dorsolateral prefrontal cortex, occipital cortex with fusiform gyrus, dorsolateral prefrontal cortex with ventrolateral prefrontal cortex ASD > Control Dorsolateral prefrontal cortex with fusiform gyrus

4.2.4. Auditory and language tasks

Given the relative primacy of communication dysfunction in the diagnostic triad, there have been surprisingly few fMRI studies which have directly examined language function in individuals with ASD, although a much greater number of studies rely on language processing for successful task completion.

The ALE meta-analysis revealed clusters of reduced activation in individuals with ASD in the bilateral superior temporal gyri, a region which is well known to be associated with receptive language. Reduced activation in this region in individuals with ASD in response to spoken language (Gervais et al., 2004; Wang et al., 2007) may underlie some of the verbal communication difficulties in ASD. Less activation was also seen in individuals with ASD in the right pyramis of the cerebellar vermis and the left middle cingulate gyrus. Increased activations were found in individuals with ASD compared to controls in the motor cortex, the cerebellar declive and the posterior cingulate. The role of the cerebellum in language function is increasingly recognised (Stoodley, 2011) and the cerebellar declive has been previously associated with dyslexia (Pernet et al., 2009). It is not necessarily clear why the motor cortex or the cingulate cortex should be activated differently in individuals with ASD during language tasks. Some studies have identified motor cortex activation during language tasks (Hauk et al., 2004; Floel et al., 2003) and it is possible that this occurs to a greater degree in individuals with ASD due to the use of atypical language processing strategies. Alternatively it may be that the differences are task related with studies involving forced choice and target detection tasks differentially recruiting the premotor and anterior cingulate cortices in ASD.

In keeping with the idea that language processing in ASD occurs outwith 'traditional' language regions, reductions in the laterality of language regions have been identified in a number of studies. During a response naming task Knaus et al. (2008) identified greater activations in frontal and temporal regions in individuals with ASD. These included Broca's area which was also significantly less lateralised in individuals with ASD. Takeuchi et al. (2004) also found reduced left lateralisation of language functions due to an increase in right sided activation during a reading task. Similarly Kleinhans et al. (2008a) showed that individuals with ASD had reduced left laterality in a verbal fluency task. These findings are consistent with a study using structural MRI by De Fossé et al. (2004) which found reversal of asymmetry in frontal language regions in individuals with autism.

4.2.5. Basic social processing

As social deficits are a core feature of ASD and much social information during everyday communication is conveyed within faces, it is unsurprising that face processing has attracted a lot of attention in the fMRI investigation of ASD (Williams, 2006; Itier and Batty, 2009). The main body of fMRI research in ASD concentrates on the investigation of networks underlying face perception and interpretation of facial expressions and emotions.

The processing of faces in individuals with ASD appears to be atypically organized in comparison to the network seen in control subjects. Activations in the fusiform face area (FFA – Haxby et al., 2002), and the occipital face area are commonly reported as reduced in individuals with ASD (Humphreys et al., 2008; Hadjikhani et al., 2007; Pierce et al., 2001; Bookheimer et al., 2008; Kleinhans et al., 2008a,b) and this is reflected in the results of our meta-analysis. In the meta-analysis by Di Martino et al. (2009) of social tasks in ASD, a relative hypoactivation was also reported in the left fusiform and bilateral occipital lobe.

Schultz et al. (2000) hypothesized that ASD participants lacking expertise in processing faces so that they would therefore process face stimuli in a manner similar to object processing which is "typically reliant on the detection of individual features" and therefore less susceptible to the inversion effect of faces. Their fMRI findings support the hypothesis that in ASD the neural network recruited to process faces is more akin to that used for object processing. Pierce et al. (2001) confirmed FFA hypoactivation in ASD and also found that individuals with ASD showed maximal activation during face processing in a wide variety of other areas, including the cerebellum and frontal lobe. In combination with other studies suggesting that the FFA may respond not only to faces but also to stimuli for

which specialization has occurred in response to experiential factors (Gauthier et al., 2000), this suggests that individuals with ASD use an object processing style due to a lack of developed expertise for faces.

Differences in eye scan path when examining faces has been reported in the behavioural literature leading to the suggestion that reports of hypoactivation in typical face processing brain regions in ASD result from ASD participants processing faces using a different method rather than being reflective of a difference in the functional neuroanatomy of people with autism. In keeping with this idea, studies which have directed participants eye gaze towards the eye region have reported a lack of difference in fusiform activation (Hadjikhani et al., 2004a, 2007; Bird et al., 2006). Similarly Dalton et al. (2005) reported hypoactivation of the fusiform gyrus in individuals with ASD when viewing faces but this was associated with spending less time fixating on the eyes of the faces.

We also found aberrant activity in the superior temporal sulcus region in individuals with ASD compared to controls (increased in the superior temporal gyrus and reduced in the middle temporal gyrus) in line with the STG over and under-activation reported in the meta-analysis by Di Martino et al. (2009). In addition to the well established role of this superior temporal sulcus region in auditory perception, increasing evidence also points to an important role of this region in the interpretation of social stimuli (Zilbovicius et al., 2006).

Although it was not identified in our meta-analysis, aberrant activation of the amygdala has been reported in a number of studies of face processing. Dalton et al. (2005) reported amygdala hyperactivation which was related to time spent fixating on the eyes and suggested this may be because individuals with ASD find eye gaze to be an anxiety provoking stimulus. Kleinhans et al. (2009) reported that repeated exposure to face stimuli led to *apparent* amygdala hyperactivation in the ASD group due to a lack of amygdala habituation to neutral faces typically seen in controls. In contrast, other groups report reduced amygdala activation in individuals with ASD (Hadjikhani et al., 2007; Bookheimer et al., 2008; Corbett et al., 2009). Differences in the stimuli used and instructions given may possibly account for these inconsistencies e.g. emotional versus non-emotional faces, passive viewing versus active response.

Studies of emotional faces are complicated by the joint investigation of face processing and emotional processing in the same experiment. Several studies have reported modulation of social brain areas in response to the intensity of emotion presented (Ashwin et al., 2007; Critchley et al., 2000; Deeley et al., 2007). Critchley et al. (2000) also manipulated task demands to explore differences between groups if the emotional content was explicitly attended to by participants (emotion label) or not (gender label). This resulted in a significant group by condition interaction in the cerebellum, striatum, insula, amygdalohippocampal junction and middle temporal gyrus. Further evidence of the importance of the stimuli presented comes from Pelphrey et al. (2007) who found no difference between individuals with ASD and controls when static emotion stimuli were used but greater activation of the superior temporal sulcus region in the ASD group when dynamic stimuli were employed. This led the authors to suggest that aberrant activation of social brain regions in ASD is specific to dynamic emotion. Whilst this is in contrast with some previous reports of hypoactivation in ASD cohorts in response to static displays of faces, it may be that in this study group differences were sub-threshold with neutral and static face stimuli and the effect is more robust using these more salient and environmentally valid stimuli like dynamic emotion morphs.

The two fMRI studies which analysed effective connectivity in face-selective networks in ASD present advanced explanatory approaches of the differently activated networks in ASD and control subjects. For a mechanistic understanding of a network, effective connectivity measures provide causal influences between neurons and neuronal population, which can be interpreted as connection strengths between regional neuronal populations within a network. Both effective connectivity studies provide evidence for significant alterations in face-selective processing in ASD participants (Wicker et al., 2008; Bird et al., 2006). Connection strengths for facial emotion processing are greater in control groups in two main aspects: firstly, controls show a greater connection strength between the V1 and the FFA than individuals with ASD. Secondly, prefrontal brain regions, the amygdala and the STS are involved in the network to a greater extent in control individuals than those with ASD (Wicker et al., 2008; Bird et al., 2006). Not only do both studies on effective connectivity support findings on reduced activations in face-selective regions but they also suggest that this is modulated by underconnectivity with prefrontal and occipital regions.

There is emerging behavioural evidence that social deficits in ASD may not be limited to facial stimuli or indeed the visual domain (Philip et al., 2010). Several studies have also been designed to specifically address the processing of movement from social stimuli i.e. biological motion (Freitag et al., 2008; Grèzes et al., 2009; Herrington et al., 2007). These provide evidence that in ASD, the brain processes movement in a different way but particularly when the movement conveys information that is socially relevant. To determine the effect of emotional content in biological motion Grèzes et al. (2009) conducted a study examining brain activation in individuals with ASD in response to fearful and neutral emotional body movements. They found that when the BOLD response to fearful gestures was compared to that for neutral gestures individuals with ASD showed hypoactivation of the right inferior frontal gyrus, precentral gyrus, inferior temporal gyrus and the amygdala; they also showed overactivation of the left medial anterior superior frontal gyrus. The authors suggest that whilst the systems which underlie the detection and representation of action are intact in people with ASD, the brain regions involved in emotion processing are not and that this relates to reduced connectivity between the amygdala and prefrontal cortex.

4.2.6. Complex social cognition tasks

Social cognition deficits in ASD are most frequently discussed in terms of a mentalizing deficit or Theory of Mind dysfunction (Baron-Cohen et al., 1999). The theory states that individuals with ASD have difficulty attributing mental states to others and this may stem from difficulties in processing social information and cues from others. These cues may be in the form of facial expression but also extend to body posture, tone of voice and the more general context of the situation.

The meta-analysis of complex social cognition tasks revealed evidence of aberrant activation in the superior temporal gyri (both increased and decreased activations were apparent in people with ASD). As discussed above, there is increasing evidence for the role of superior temporal sulcal regions in social cognition and our findings and others (Di Martino et al., 2009) suggest that this region is affected in ASD.

Aberrant activations were also seen in the right inferior frontal gyrus (increased in ASD) and left inferior parietal lobule (decreased in ASD). Both of these are regions have been previously shown to activate differently within social tasks in ASD (Di Martino et al., 2009) and are thought to form part of the mirror neuron system (MNS) in humans. The MNS comprises populations of neurons which have been shown in animal studies to activate to both the execution of a particular motor action and in response to observing that same motor act performed by another (Gallese et al., 1996). It has been proposed that for successful complex mentalizing to take place, another's cognitive perspective must be assessed and re-represented following the observation of their actions (Uddin

et al., 2008). The MNS has thus been proposed as a system enabling emotion understanding via action representation. On a neural level it is thought that whilst the inferior frontal gyrus and parietal cortex code the observed action (Freitag et al., 2008), in the case of socially relevant and emotional stimuli the limbic system is also recruited via the insula, allowing internally felt emotional significance (Carr et al., 2003; Schulte-Rüther et al., 2007). By understanding and coding the function of others actions, intention can be attributed and an understanding of another's mental state can be achieved. Together with these studies our meta-analysis provides evidence for mirror neuron dysfunction in ASD.

In neither our analysis of basic or complex social tasks did we observe aberrant activity of the anterior cingulate cortex, reported by Di Martino et al. (2009) in their meta-analysis of social tasks. This discrepancy may be accounted for by differences in subdivision of tasks as well as differences in approach taken to carry out the meta-analysis; Di Martino et al. extracted within group data and contrasted this whereas we extracted significant results from between group contrasts and calculated activation likelihood estimations from this.

4.3. Emerging themes across task domains

4.3.1. The influence of specific task/stimuli demands

Not only the stimulus type but also the task demands are critical factors when designing tasks to elucidate brain function differences in ASD. Whilst some studies suggest task independent dysfunction (Kennedy and Courchesne, 2008), many apparent contradictions in fMRI data using tasks and stimuli of a similar nature with comparable study populations could be accounted for by the specific task instructions given. For example, Critchley et al. (2000) report a significant group x task interaction suggesting that the ASD group and control group responded differently to whether the task required them to explicitly attend to the emotional content of face stimuli or not. Differences in fusiform gyrus activity in response to face processing has been reported when participants carried out a perceptual emotion match task, but not a more linguistic emotion label task even though both tasks employed the same stimuli (Piggot et al., 2004; Wang et al., 2004). Further, when investigating the effect of face familiarity on brain activation in autism, an implicit task where the condition of familiarity did not have to be attended to for successful task completion failed to reveal any differences between groups (Pierce et al., 2004); whereas when the task employed required participants to discriminate on the basis of familiarity, fusiform hypoactivation was reported in the ASD group (Dalton et al., 2005). It is therefore important to carefully consider the question to be answered when designing tasks and also when interpreting data.

4.3.2. Lack of preference for social stimuli

Although we identified fusiform gyrus hypoactivation in ASD in the meta-analysis, there are multiple reports of typical fusiform gyrus function in autism. In studies which show typical fusiform activation tasks have been designed to incorporate cues to ensure participants engage with the face stimuli and attend to the salient features of faces such as eyes. This suggests that face processing differences in individuals with ASD may result from a lack of motivation to attend to, or a preference for not attending to, the socially salient features of faces, as opposed to a deficit in the fusiform face area per se.

Interestingly, there are several examples in the literature of tasks which identify no between group differences in brain activation, yet when social stimuli are incorporated into the task a deficit in the ASD group becomes evident. For instance, when investigating brain responses to congruence, hypoactivation in the ASD group was not found in the task employing arrow stimuli but only was when face stimuli were used (Dichter and Belger, 2007). Similarly, when attention modulation was investigated, brain responses when house stimuli were used did not differ between the ASD group and the control group. However, the same task involving face stimuli revealed a hypoactivation in the ASD group (Bird et al., 2006). In the auditory domain this pattern has been repeated. No differences were reported in response to environmental sounds, however vocal sounds resulted in less activation in the ASD group relative to the control group, with 3 of the 5 individuals with autism tested showing no superior temporal sulcus activation (Gervais et al., 2004). Both tasks that investigated biological motion reported hypoactivation in response to biological motion in the ASD group that was either not present or far less extensive than in response to motion derived from a non-biological source (Freitag et al., 2008; Herrington et al., 2007). These studies suggest that typically developing individuals show an increase in brain activation in response to social stimuli, possibly due to increased attention to them, which is not seen in ASD.

In each of the aforementioned studies, although participants were asked to attend to the stimuli, they were not required to make a social judgement based upon them. Studies which have incorporated explicit social judgements, in contrast to the above, tend to show hyperactivation of the social brain network (Baron-Cohen et al., 1999; Wang et al., 2006), perhaps reflecting less efficient, or increased effortful, processing.

4.3.3. Lack of modulation in response to task/stimuli demands

Another repeated finding in tasks of various types, using a range of stimuli, is that whilst between group contrasts fail to identify any differences between ASD and control samples, suggesting that the typical neural circuitry is recruited in both groups, subtle modulation of this activation in response to task demands or intensity of stimuli is observed in the control group but not in the ASD group. Whilst the appropriate brain network is crudely recruited, finer and more subtle control of activity in these brain regions is lacking.

In tasks of facial emotion processing where the intensity of stimuli modulated brain responses in the control group, this additional level of responsiveness to the stimuli was not observed in the ASD group (Ashwin et al., 2007; Deeley et al., 2007). In another face processing task, this time of neutral stimuli, whilst there were no differences between groups in response to task stimuli the control group modulated brain activity in response to attention demands, an effect not seen in the ASD group (Bird et al., 2006). Dalton et al. (2005) reported a modulatory effect on the fusiform gyrus with regard to the familiarity of the face stimuli presented in the control group but this effect was not present in the ASD group. Motion has been shown to modulate facial emotion processing in controls but not participants with ASD (Pelphrey et al., 2007). In both studies investigating the neural response to the congruence of stimuli, similar circuitry was recruited by both the ASD and control groups in response to processing information from eye gaze. However whether eye gaze was congruent or not with the appearance of a target, modulated the activity in this system in the control group but not the ASD group (Dichter and Belger, 2007; Pelphrey et al., 2005). A lack of modulation in ASD has also been reported in lexical tasks. Again, broadly, the control and ASD participants were reported to recruit typical neural circuitry for the task but the control group modulated this in accordance with the type of word (Harris et al., 2006) or sentence (Mason et al., 2008) presented whereas the ASD group did not. During an imitation task, specific task conditions were found to affect the levels of activity in the mirror neuron system and amygdala in the control group and whilst these brain regions did activate in the ASD group the variability in response to conditions was not observed (Williams et al., 2006). Also in tasks involving understanding the intentions of others, whilst control group activation varied in relation to the

judgement they were making (Pinkham et al., 2008) or the ironic content of stimuli (Wang et al., 2007), these features of the task failed to modulate brain activation in the ASD group.

4.3.4. Visuo-spatial processing style

Cumulatively, there are findings from a variety of task types to suggest that areas of the prefrontal cortex generally recruited for executive functions are activated to a lesser extent in ASD. More weight is however generally given to visual and perceptual systems. It is not obvious how a visually predisposed cognitive style relates to the core clinical features of autism but it is interesting to note that the evidence based and most commonly adopted approaches used to teach children with autism rely heavily on the use of visual supports. In establishing basic requesting skills in non-verbal children with autism, the Picture Exchange Communication Systems has been found to be effective (Bondy and Frost, 2001) and is commonly implemented by Speech and Language Therapists in schools across the UK. In classrooms, the TEACCH approach (Treatment and Education of Autistic and related Communication handicapped Children) has been found to be an effective method for working with children with autism (Probst and Leppert, 2008) and relies on a range of visual measures (visual timetables, start/finish boxes, timers) to support children with autism through their school day. It may be that the effectiveness of these strategies at least in part is due to the fact that they capitalize on the naturally visual cognitive style of people with autism.

4.3.5. Dysconnectivity

In recent years increasing interest has focused on the idea that many of the deficits in ASD result from changes to brain connectivity. Evidence from electroencephalography (Hughes, 2007) and diffusion tensor imaging (Barnea-Goraly et al., 2004; Lee et al., 2007a) as well as structural MRI studies of white matter (Herbert et al., 2003) all support this idea. The majority of fMRI studies have concentrated on single brain regions which, whilst interesting, is somewhat artificial and does not take into account the influence that distributed networks may have on brain activity.

Findings from the review suggest that reductions in brain connectivity are widespread and not task specific. Some studies have suggested that decreases are primarily confined to cortico-cortical connectivity with increases occurring in subcortico-cortical connections (Mizuno et al., 2006; Turner et al., 2006). This increase in subcortico-cortical connectivity might be explained by compensation for reduced cortico-cortical connectivity or compensation for greater arousal modulation in ASD subjects than in healthy subjects (Belmonte et al., 2004). Future research should hopefully clarify the exact nature and distribution of connectivity differences in ASD.

4.3.6. Age-related changes

The age group comparisons revealed different activated clusters in the different age groups compared with the clusters found in the whole-group analysis. Both age groups showed different activated clusters within the same network and different activations in different networks. In addition, the individual age group analyses compared with the main analyses in the same task domains revealed substantial differences in the amount of significant clusters in the networks, the probability of activations in the same clusters and the probability of activations in different clusters in the network.

The age-separated meta-analyses in auditory and language tasks, social tasks and complex cognition tasks reveal different findings in child and adolescent populations than in adults, suggesting that different developmental changes in brain activation occur in individuals with ASD than in typically developing individuals. Different patterns of brain development have been reported in structural MRI studies of ASD (Stanfield et al., 2008; Redcay and Courchesne, 2005); our findings suggest that this may also be the case for brain function. This may relate to innate neurobiological differences which affect brain development but may also be secondary to experiential factors and learnt compensatory mechanisms in individuals with ASD. One caveat to our findings is that the separate meta-analyses conducted for the different age groups relied upon small numbers of studies and at present these findings must be regarded as preliminary in nature.

4.4. Limitations of the current review

The results of the meta-analysis will obviously depend upon which tasks are allocated to which domain and previously studies have taken a different approach to ours (Di Martino et al., 2009). Combining dissimilar tasks risks increasing heterogeneity, whereas overenthusiastic subdivision leads to a lack of power. We have tried to strike a balance between these opposing strategies but acknowledge the somewhat arbitrary decisions that this entails. For example, many of the tasks which we considered to be visual in nature also contained components of executive function. This is particularly true for visual search or embedded figures tasks where the consideration of context is paramount. It is not clear at what point a task becomes more visual and less executive in nature or vice versa and this is further complicated by the fact that individuals with ASD seem to recruit visual regions more than controls do to accomplish executive tasks. Decisions regarding the sub-division of social tasks into simple and complex were also difficult to make but we feel that the distinct areas of activation identified for each of these domains to some extent validates this approach. Participants appeared to overlap between studies, although different tasks were used in each. Thus findings from the meta-analyses may be more heavily weighted towards differences in the populations that have been published on most frequently, particularly if they examined tasks from the same domain. Finally, we excluded studies which were not published in English which may bias the results somewhat.

5. Future directions

It is clear that for pragmatic reasons the majority of the ASD cohorts studied using fMRI are not entirely representative of the ASD population as a whole. Whilst findings from these samples do add a valuable contribution to the understanding of autistic neurophysiology the interpretation of findings should be extremely cautious. Effort is therefore required to address the sample selection issues in this field and careful design of simple tasks may allow the study of lower IQ and younger cohorts. The use of simple tasks may also shed light on more basic cognitive processes which may underlie some of the more complex deficits seen in ASD. Greater investigation of children and adolescents will allow developmental changes in brain function to be examined and also shed light on whether differences identified in adult populations are related to the expression of ASD or represent mechanisms developed to compensate for impairment. High-risk studies of very young infants, although ethically challenging, would provide vital information regarding brain development prior to the onset of observable features of ASD and may facilitate the development of predictive tools and preventative interventions.

The small sample size investigated in many studies along with the use of liberal statistical thresholds also make it difficult to draw firm conclusions from the research to date. It is increasingly acknowledged that ASD, or even autism itself, does not represent a single disorder but is likely to be the result of multiple underlying causes leading to similar clinical features – the 'autisms' (Baumann, 2010; Geschwind and Levitt, 2007). It is not surprising

therefore that heterogeneity exists in the current neuroimaging literature. To reduce this, future studies could examine subgroups based on clinical phenotypes; this would maximize the power of studies to identify significant differences between groups and examine the effect of putative aetiological mechanisms. The converse approach may also be useful, i.e. using functional imaging to derive subgroups based upon patterns of activation and then examining the clinical features associated with these. Subdividing samples on the basis of putative genetic or environmental risk factors and examining the brain activation associated with these is also likely to be a fruitful approach. All of these approaches will require large samples and detailed clinical characterisation of research participants. The progression of multicentre imaging as proposed by Belmonte et al. (2008) will allow for larger samples to be investigated.

Using meta-analysis, as we have, to look for replicated findings between studies is one way of attempting to overcome the limitations inherent in the literature due to small sample sizes. However, as we have discussed, heterogeneity may also result from the use of even subtly different stimuli or task designs between studies, adding further statistical noise to the meta-analysis. Replication studies are given relatively low priority by investigators, funders and journal editors alike; we would politely suggest that this policy is revisited.

Task design in general, including the selection of baseline conditions, requires careful consideration as both task demands and features of stimuli appear to have differential effects in ASD. The broad range of tasks used to investigate ASD which report atypical brain activation also require investigators to be aware that even when designing a task with a specific element of interest, assumptions made about other aspects of the task may not be the same as those that could be made about a typical population. Parametric designs may be particularly informative when studying this population due to the consistent reports of aberrant modulation of activation in ASD.

There are a number of more specific areas identified by this review that would benefit from greater investigation. It is clear that there has been an emphasis on the processing of social stimuli in the ASD literature, in particular faces. This is not surprising given that social communication difficulties form a core basis of the autistic phenotype. However, impairment is not limited to face processing or the visual domain; investigating the neural response of individuals with ASD when processing other kinds of social stimuli, such as voice tone and movement, particularly in relation to emotion may illuminate regions of the brain which are common to socio-emotional processing, regardless of the form in which it is presented. Other areas which appear to have been underinvestigated to date include communication, motor function and, especially, sensory hypersensitivity.

6. Conclusion

Despite the difficulties identified during this review it is clear that fMRI has added greatly to our understanding of ASD and there are a number of consistent themes running through the literature. Improvements in paradigm design, data acquisition and analysis technology are likely to further refine our understanding of ASD in the future.

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