Functional Brain Correlates of Social and Nonsocial Processes in Autism Spectrum Disorders: An Activation Likelihood Estimation Meta-Analysis

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Background: Functional neuroimaging studies of autism spectrum disorders (ASD) have examined social and nonsocial paradigms, although rarely in the same study. Here, we provide an objective, unbiased survey of functional brain abnormalities in ASD, related to both social and nonsocial processing.

Methods: We conducted two separate voxel-wise activation likelihood estimation meta-analyses of 39 functional neuroimaging studies consisting of 24 studies examining social processes (e.g., theory of mind, face perception) and 15 studies examining nonsocial processes (e.g., attention control, working memory). Voxel-wise significance threshold was $p < .05$, corrected by false discovery rate.

Results: Compared with neurotypical control (NC) subjects, ASD showed greater likelihood of hypoactivation in two medial wall regions: perigenual anterior cingulate cortex (ACC) in social tasks only and dorsal ACC in nonsocial studies. Further, right anterior insula, recently linked to social cognition, was more likely to be hypoactivated in ASD in the analyses of social studies. In nonsocial studies, group comparisons showed greater likelihood of activation for the ASD group in the rostral ACC region that is typically suppressed during attentionally demanding tasks.

Conclusions: Despite substantial heterogeneity of tasks, the rapidly increasing functional imaging literature showed ASD-related patterns of hypofunction and aberrant activation that depended on the specific cognitive domain, i.e., social versus nonsocial. These results provide a basis for targeted extensions of these findings with younger subjects and a range of paradigms, including analyses of default mode network regulation in ASD.

Key Words: Anterior cingulate cortex, autism, cognitive control, default mode network, functional magnetic resonance imaging (fMRI), insula, meta-analysis, pervasive developmental disorders (PDD), positron emission tomography (PET), social cognition

Recent functional neuroimaging studies focused on identifying the neural correlates of autism spectrum disorders (ASD) have generated several encouraging lines of investigation, albeit with varying degrees of replication. Since impairments in social and communicative skills are the hallmarks of ASD (1–3), most neuroimaging studies have used social cognition-based paradigms testing the ability to interpret and predict others' beliefs, intentions, and desires (i.e., theory of mind), as well as the perception of specific social stimuli such as human faces. Both processes have been found to be abnormal in early development of individuals with ASD and have been linked to the associated social and communicative impairments (3–5).

Based on models of the social brain (6–9), studies have focused on a priori regions of interest typically implicated in mentalizing, including medial prefrontal cortex/paracingulate cortex, temporoparietal junction, temporal pole, amygdala, and periamygdaloid cortices. Depending on the specific task employed, ASD-related abnormalities have been reported for each of these regions, with moderate degrees of agreement (10–12). For instance, hypoactivations of rostral anterior medial prefrontal cortex, adjacent anterior paracingulate cortex, and perigenual anterior cingulate cortex (ACC) have been found in some studies using theory of mind paradigms (13–15) but not in others (16). Likewise, some studies of emotional processing (e.g., 16,17) describe ASD-related amygdala hypoactivation but not others (18,19). An area of particular convergence is facial perception, with ASD-related hypoactivation of fusiform gyrus (FG) observed across both studies of facial form and facial expression perception (e.g., 20–23). However, negative reports (18,19,24) have raised questions regarding the nature and specificity of FG dysfunction in ASD. In sum, studies of ASD based on social cognitive models have identified candidate regions of dysfunction, albeit with only moderate convergence across studies.

Although deviant development of the ability to engage in appropriate social interactions is the central dysfunction in ASD, additional cognitive and sensorimotor impairments often co-occur (e.g., 1,25,26). For instance, working memory, planning, cognitive flexibility, inhibitory control, and action monitoring are impaired in both children and adults with autism (e.g., 27–34). Some authors hypothesize that such abnormalities underlie the pattern of restricted and stereotyped interests that complete the diagnostic triad of autism, along with social and communicative impairments (1). These observations have motivated parallel lines of investigation on the ASD-neuronal correlates of executive dysfunction. Brain correlates of other functions also found impaired in ASD, such as language, have been also examined (10).

Frontal cortical hypoactivation has emerged as one of the most consistent results across these studies. Specifically, reduced

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activation of dorsolateral prefrontal cortex (DLPFC) and dorsal ACC (dACC) have been described in individuals with ASD performing working memory, inhibitory control, visuospatial attention, and embedded figure tasks (e.g., 35–39). Hypofunction of other frontal regions has been reported depending on the specific task employed (for reviews, see 10,40). Accompanying hypoactivation in task-targeted regions, increased function in areas implicated in more basic sensory processing (e.g., in visual cortex) has been consistently described (10,12,41). Of note, such patterns of atypical recruitment have also been reported in studies examining social processes (e.g., 20,22).

Despite broadly convergent findings, the neuronal correlates of ASD remain underspecified. Reasons include the use of generally small samples with substantial heterogeneity with respect to age ranges, clinical presentation, tasks, and statistical methods. Most studies used fixed rather than random effects models, many lacked direct group comparisons, and most relied on region-of-interest analyses that limit generalizability and increase type I error rates. Overcoming these limitations definitively will require pooling larger samples and standardization of data collection methods across laboratories (42). Pending such a large-scale effort, a systematic assessment of current functional neuroimaging findings can inform the field and suggest priorities for future investigations.

Quantitative meta-analyses have emerged as useful methodological approaches to provide unbiased, objective measures of brain functioning in various clinical populations (43–46), but none have been conducted in ASD. In contrast to qualitative syntheses of the current literature (10,11,41,47,48), a quantitative meta-analysis can lead to the identification of regions that might otherwise be overlooked and is less likely to be driven by prominent theoretical models.

Here, we provide a voxel-wise quantitative meta-analysis using activation likelihood estimation (ALE) (49–51). The ALE meta-analysis produces voxel-wise formal estimates of probabilities of activation. Using the exact coordinates reported by each study instead of author-assigned anatomical labels, ALE provides better spatial resolution and reduces errors due to overly broad spatial designations or region mislabeling (52).

Given that ASD-related abnormalities extend across multiple cognitive domains, it is important to take into account the impact of domain specificity. In other words, the ability of meta-analytic techniques to detect consistent ASD-related abnormalities in a given region likely depends on the specific processing domain examined. For example, an extensive literature in neurotypical subjects supports the hypothesis that studies examining social cognition would show ASD-related hypoactivation in the perigenual ACC (pgACC)/rostral medial prefrontal cortex (3,6,7,9,53–58). As most studies of nonsocial cognition in ASD included components of executive functions, we anticipated ASD-related hypoactivation in dorsal ACC/presupplementary motor area (pre-SMA) and lateral prefrontal regions commonly identified in normative studies (e.g., 59–65). Fortunately, ALE allows comparing different task domains, even when not directly contrasted in the same studies. Accordingly, we conducted ALE meta-analyses of published functional neuroimaging studies of ASD in both social and nonsocial domains.

Methods and Materials

Article Selection

Using PubMed (http://www.pubmed.org), we searched for English-language, task-based, functional neuroimaging studies of ASD published between 1990 and January 2008 with the Keywords "autism;" "fMRI;" "PET;" "neuroimaging;" "PDD-NOS;" and "Asperger." Abstracts of initially identified articles were first reviewed as the basis for selecting papers for full-text review. References cited in the selected articles were also reviewed. We included studies where both ASD and neurotypical control (NC) groups were examined and within-group foci were available in standardized stereotaxic space (Talairach and Tournoux [66] or Montreal Neurological Institute [MNI] atlases). To preserve data interpretability, we included only task-based functional magnetic resonance imaging (fMRI) and blood flow positron emission tomography (PET) studies. Likewise, because few papers reported deactivations, only foci of significant activations were included. When more than one paper was based on the same sample we selected the first published study. Thirty-nine studies met inclusion criteria comprising 453 NC subjects and 479 subjects with ASD. Most (79%) studies focused on adults (group mean age >18 years) and the remaining focused on school-age children and adolescents (weighted mean ages 28.2 and 27.7 years for adults with ASD and NC subjects, respectively, and 12.7 years for youths in both groups). Of the 39 studies included, 24 tested paradigms related to social cognition such as theory of mind, face processing, and emotional processing; they were classified as the social study group. The remaining 15 studies mostly examined executive functions ranging from spatial attention, interference control, working memory, and motor control. They were grouped as nonsocial studies. This distinction provided a sufficient number of foci within each diagnostic group per domain to yield reliable ALE results (social: 290 and 220 foci; nonsocial: 189 and 139 foci; for NC and ASD subjects; respectively). See Figure 1 for study selection flow diagram and Table 1 for study characteristics.

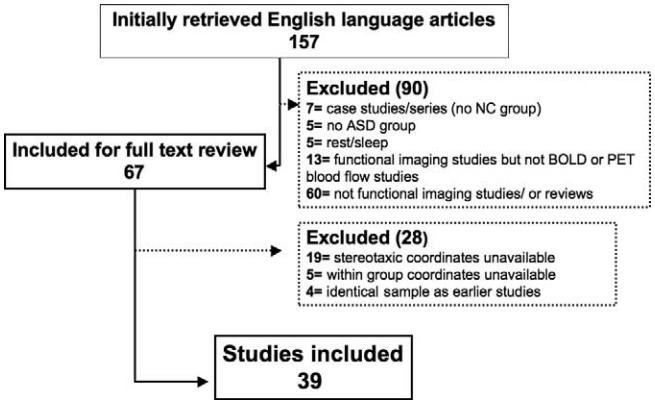

Figure 1. Article Selection Flow. Number of studies selected and reasons for exclusion.

Meta-Analyses

For each study, statistically significant foci of activation from one contrast were included (Table 1). When more than one contrast was reported (31% of studies), we selected the broadest comparison available to better detect common group differences across studies. Montreal Neurological Institute coordinates were converted to Talairach space using Brett's transformation (67). Meta-analyses were conducted using ALE (51) implemented in BrainMap (http://brainmap.org/; Research Imaging Center of the University of Texas Health Science Center, San Antonio, Texas) (50,52). We first conducted a meta-analysis within each group (i.e., NC, ASD). Then, to directly compare the groups, we ran a

subtraction meta-analysis. Specifically, for each group, ALE maps were generated by modeling each equally weighted activation peak using a three-dimensional (3-D) Gaussian probability density function centered at the given coordinates. For any given voxel, meta-analytic significance resulted from the degree of spatial overlap of independently produced 3-D Gaussian probability density functions. In agreement with other ALE meta-analyses (43–45,50,51,68), we set full-width at half maximum (FWHM) = 10 mm to account for spatial resolution limitations and interindividual differences in anatomic variability. Next, voxel-wise likelihoods of activation for the two ALE maps (ASD, NC) were calculated using permutation testing (5000 permutations) and corrected for multiple comparisons using false discovery rate ($p < .05$, corrected), with a cluster extent threshold of eight voxels. As these foci were generated randomly, no assumption was made as to their spatial location or separation within the brain. The group subtraction meta-analysis yielded an ALE map of the regions in which the two groups differed significantly (43,50). The difference ALE maps were then permuted and statistically corrected to generate voxel-wise statistical scores.

Task-Domain Analyses. Prior to conducting group analyses, we verified the presence of significant differences in neural activation for the two processing domains (social, nonsocial) by conducting a subtraction ALE meta-analysis between social and nonsocial study foci across both groups (NC, ASD) combined. We then examined ASD-related differences in activation for each processing domain by performing within- and between-group ALE comparisons (i.e., ASD > NC, NC > ASD) for the social and nonsocial domains separately. Given the prominence of studies examining face processing, we conducted post hoc analyses on ASD-related differences across the 16 studies employing faces, as well as subgroupings of face form perception (e.g., faces vs. scrambled faces; 8 studies) and facial emotional/intentional expression (e.g., emotion vs. gender; 9 studies). Finally, to examine a more homogeneous group of nonsocial studies, we conducted a secondary meta-analysis of those papers focusing on executive functions, thus excluding works on language processing and paced finger tapping (69–72) (Table 1).

Results

Social Versus Nonsocial Studies: Both Groups Combined

As shown in Supplement 1, direct comparisons between social and nonsocial studies resulted in a broad functional distinction of the ACC (here defined as anterior cingulate gyrus proper and paracingulate gyrus [73–76]). Specifically, consistent with the hypothesized linkages to mentalizing, person perception, joint attention, and self-knowledge (e.g., 7), a cluster centered at the pgACC (Brodmann area [BA] 32) and extending anteriorly toward the rostral medial prefrontal cortex (MPFC; BA 10) showed greater probability of activation in social studies compared with nonsocial studies. In contrast, nonsocial studies displayed significantly larger likelihood of activation in a cluster extending from dorsal ACC (BA 32) to neighboring pre-SMA (BA 6). Other regions typically implicated in different aspects of social cognition, such as the right amygdala, the posterior cingulate, and a region extending from the right superior temporal gyrus deep to the anterior insula, showed significantly larger likelihood of activation in the social studies. Bilateral mid-FG was also highlighted, as expected given the high proportion of face-processing studies.

Social Studies: NC Versus ASD

Between-group comparisons of the individual group ALE maps for the social studies (see Supplement 2 for within-group clusters of activation) showed that NC subjects had significantly higher probability of activation in those clusters consistently activated in the combined group analysis for social studies. These included pgACC, right amygdala, and left FG. Accompanying these areas that are classically involved in social cognition (e.g., 7,9,56,57) and that have also been implicated in ASD (2,3,77), NC subjects also showed greater probability of activation in the right anterior insula (AI), related to the attribution of emotions to others and oneself (78), and in the posterior cingulate, implicated in attribution of emotional salience, episodic memory, and self-referential processing (79–81) (Table 2, Figures 2 and 3). In contrast, the ASD group displayed greater probability of activation in somatosensory regions, such as postcentral gyrus, posterior portions of the superior temporal gyrus, inferior occipital gyrus, and posterior-lateral FG, but not in medial wall areas or in the sublobar regions specifically related to social processing that were revealed in the comparison between social and nonsocial studies (Table 2, Figure 2). Post hoc analyses limited to the 17 face-processing studies revealed ASD-related differences highly similar to those obtained in the primary social study analysis, with a notable difference in FG activation. When limited to face-processing studies, ASD hypoactivation of FG was noted bilaterally. In the primary meta-analysis including all social studies, FG hypoactivation in ASD reached significance only in the left hemisphere with subthreshold right-sided differences. When face-processing studies were further divided into those requiring perception of facial forms and those focusing on facial expressions, ASD-related abnormalities in the medial wall (pgACC, PCC) were only detectable in the facial expression studies. Fusiform gyrus hypoactivations in face form processing studies were limited to the right FG and were located more posteriorly than the loci resulting from the facial expression studies (Supplement 3).

Nonsocial Studies: NC Versus ASD

Neurotypical control subjects showed a greater likelihood of activation in a cluster extending from pre-SMA to dACC, which is typically implicated in cognitive control (e.g., 82) (Figure 2). Similar differences with the NC group showing greater likelihood of activation appeared in DLPFC (BA 9/10) and lateral parietal cortex such as supramarginal gyrus and inferior parietal lobule (BA 40). This group subtraction also revealed atypical regional recruitment in ASD compared with NC subjects. Specifically, in contrast to the pre-SMA/dACC region that was more likely to be activated in NC subjects, the ASD group showed a greater probability of activation in the more posterior supplementary motor area (SMA) proper, which is typically related to lower-order motor planning (83). Similarly, meta-analysis of nonsocial studies revealed a greater likelihood of ASD activation in the pgACC (BA32), which is typically implicated in social paradigms (Table 3 and Figure 2). Secondary analyses, limited to nonsocial studies focusing on executive function, revealed substantially unchanged ASD-related hypoactivations. By contrast, only hyperactivation of rostral ACC in ASD compared with NC subjects in rostral ACC remained in this more restricted analysis (Supplements 4 and 5).

Discussion

This quantitative meta-analysis revealed ASD-related abnormalities (both decreases and increases) in probabilities of acti-

Table 1. Characteristics of the Included Studies

Article/Reference Number	Imaging Modality	ASD *n*	ASD Age M (SD)[a]	NC *n*	NC Age M (SD)	Task	Contrast	Number Foci NC	Number Foci ASD
Social (24)									
Ashwin *et al.* 2007[b] (144)	fMRI	13	31.2 (9.1)	13	25.6 (5.1)	Facial processing	Faces vs. scrambled faces	5	1
Hubl *et al.* 2003[b] (145)	fMRI	10	27.7 (7.8)	10	25.3 (6.9)	Facial processing	Faces vs. scrambled faces	4	4
Schultz *et al.* 2000[b] (20)	fMRI	14	23.8 (12.4)	14	21.7 (7.2)	Facial processing	Faces vs. objects	1	1
Bird *et al.* 2006[b] (146)	fMRI	16	33.3 (12.1)	16	35.3	Facial processing	Faces vs. houses	5	5
Deeley *et al.* 2007[b] (147)	fMRI	9	34 (10)	9	27 (5)	Facial processing	Neutral faces vs. fixation	21	25
Kleinhans *et al.* 2007[b] (148)	fMRI	19	23.5 (7.8)	21	25.1 (7.6)	Facial processing one-back task	Neutral faces vs. houses	1	3
Koshino *et al.* 2008[b] (149)	fMRI	11	24.5 (10.2)	11	28.7 (10.9)	Facial processing n-back WM	N-back face task vs. fixation	15	9
Dichter and Belger 2007[b] (150)	fMRI	14	22.9 (5.2)	15	23.2 (5.7)	Flanker gaze task	Congruent vs. incongruent gaze	8	2
Dapretto *et al.* 2006[c] (151)	fMRI	10	12.05 (2.5)	10	12.38 (2.2)	Imitating facial expressions	Face imitation vs. rest	36	16
Wang *et al.* 2004[c] (152)	fMRI	12	12.2 (4.8)	12	11.8 (2.5)	Facial emotion processing	Faces (angry/fearful) vs. geometric forms	10	11
Hall *et al.* 2003[c] (153)	PET	8	20–33	8	NA	Facial emotion processing	Emotion vs. gender	6	7
Critchley *et al.* 2000[c] (22)	fMRI	9	37 (7)	9	27 (7)	Facial emotion processing	Emotional vs. neutral faces	6	3
Pelphrey *et al.* 2007[c] (154)	fMRI	8	24.5 (11.5)	8	24.1 (5.6)	Facial emotion processing	Dynamic vs. static emotional face	6	1
Pelphrey *et al.* 2005[c] (155)	fMRI	10	23.2 (9.9)	9	23.4 (5.8)	Intentional eye gaze processing	Congruent vs. incongruent eye gaze	7	4
Pierce *et al.* 2004[c] (156)	fMRI	7	27.1 (9.2)	9	(16–40)	Facial processing	Familiar vs. stranger faces	9	4
Pinkham *et al.* 2008[c] (157)	fMRI	10	24.08 (5.71)	12	27.08 (3.99)	Trustworthiness face task	Trustworthy faces vs. baseline	6	6
Baron-Cohen *et al.* 1999[c] (16)	fMRI	6	26.3 (2.1)	12	25.5 (2.8)	Inferring mental states/ eye	Emotion vs. gender	53	29
Castelli *et al.* 2002 (158)	PET	10	33 (7.6)	10	25 (4.8)	Inferring mental states/ animated shapes	Tom animation vs. random animation	10	10
Happe *et al.* 1996 (13)	PET	5	24	6	38	Story comprehension	Tom story vs. unconnected sentences	4	4
Gervais *et al.* 2004 (159)	fMRI	5	25.8 (5.9)	8	27.1 (2.9)	Voice processing	Vocal vs. nonvocal sounds	6	0
Wang *et al.* 2006 (160)	fMRI	18	11.9 (2.8)	18	11.9 (2.3)	Judging sentences sarcasm	Sarcastic sentences vs. rest	16	19
Wang *et al.* 2007 (15)	fMRI	18	12.5 (2.9)	18	11.8 (1.9)	Cartoon irony/sarcasm task	Ironic cartoons vs. nonironic cartoons	35	32
Mason *et al.* 2008 (161)	fMRI	18	26.5	18	27.4	Inference reading comprehension task	Intentional inference vs. fixation	13	20
Williams *et al.* 2006 (162)	fMRI	16	15.4 (2.24)	15	15.5 (1.6)	Action imitation task	Imitation vs. action execution	7	4
Nonsocial (15)									
Ring *et al.* 1999 (39)	fMRI	6	26.3 (2.1)	12	25.5 (2.8)	Embedded figure task	Task vs. fixation	10	10
Manjaly *et al.* 2007 (38)	fMRI	12	14.4 (2.7)	12	14.3 (2.7)	Embedded figure task	Embedded figure task vs. control task	2	4
Lee *et al.* 2007 (37)	fMRI	12	13.5 (1.6)	12	13.8 (1)	Embedded figure task	Embedded vs. matching task	11	3
Just *et al.* 2007 (131)	fMRI	18	27.1 (11.9)	18	24.5 (9.9)	Tower of London task	Hard vs. easy condition	13	19
Kennedy *et al.* 2006 (114)	fMRI	15	25.5 (9.6)	14	26.1 (8)	Stroop task	Number vs. rest	8	8
Koshino *et al.* 2005 (115)	fMRI	14	25.7	13	29.8	N-back working memory task	N-back task vs. fixation	24	24
Schmitz *et al.* 2006 (163)	fMRI	10	38 (8)	12	39 (9)	Go/No-Go	No-Go vs. Go	11	6

Table 1. (continued)

Article/Reference Number	Imaging Modality	ASD *n*	ASD Age M (SD)[a]	NC *n*	NC Age M (SD)	Task	Contrast	Number Foci NC	Number Foci ASD
Haist *et al.* 2005 (164)	fMRI	8	23.4 (11.4)	8	25.6 (3.8)	Spatial attention task	Spatial target vs. null	40	1
Belmonte and Yurgelun-Todd 2003 (165)	fMRI	6	32.7 (9.8)	6	27.2 (4.4)	Visual spatial attention task	Task vs. fixation	7	4
Schmitz *et al.* 2008 (116)	fMRI	10	37.8 (7)	10	38.2 (6)	CPT task with monetary incentive	Rewarded vs. nonrewarded stimuli	5	4
Gomot *et al.* 2006 (166)	fMRI	17	10.37 (1.52)	14	10.87 (1.47)	Auditory change detection	Novel vs. standard sound	17	17
Gaffrey *et al.* 2007 (72)[d]	fMRI	10	26.1 (10.5)	10	25.3 (9.8)	Semantic category	Semantic vs. perceptual task	14	13
Harris *et al.* 2006 (71) [d]	fMRI	14	36 (12)	22	31 (9)	Single word lexical semantic processing	Concrete vs. abstract words	8	4
Just *et al.* 2004 (70) [d]	fMRI	17	NA	17	NA	Sentence comprehension	Sentence vs. fixation	8	10
Muller *et al.* 2001 (167) [d]	fMRI	8	28.4 (8.9)	8	28.5	Paced finger tapping	Tapping vs. rest	11	12

The 39 studies included in the meta-analysis were subdivided into a social and nonsocial task class based on the paradigm used. Overall, a total of 359 and 479 foci were included for the ASD and the NC groups, respectively.

ASD, individuals with autism spectrum disorders; CPT, continuous performance task; fMRI, functional magnetic resonance imaging; NA, not available; NC, neurotypical control subjects; PET, positron emission tomography; Tom, Theory of Mind.

[a]M age (SD) = mean age of subjects ± standard deviation are reported if available in published article.

[b]Grouped as face form perception study.

[c]Grouped as facial emotional/intentional expression studies; these two study groups formed the face processing study group for post hoc analyses.

[d]These studies were excluded in the secondary analysis of nonsocial studies of executive processes only.

vation in distributed regions, which appeared largely domain-specific. The primary distinction is between studies focusing on social processing versus those examining nonsocial cognition, typically pertaining to executive function.

Social-Related Abnormalities

The findings emerging from the meta-analyses of tasks examining social functioning (e.g., mentalizing, emotional processing) not only revealed hypofunction in regions classically associated with social impairments in ASD (i.e., pgACC, anterior rostral MPFC, and amygdala) but also highlighted previously overlooked regions. In particular, the right anterior insula, a recent focus of attention in the social cognition literature (78,84–88), showed decreased likelihood of activation in ASD compared with NC subjects. Insights into AI function have emerged from recent attempts to differentiate the neuronal correlates of mentalizing (i.e., attribution of others' beliefs, desires, and intentions) and empathizing (i.e., understanding and sharing others' emotions) (78,87,89). Rather than being used interchangeably and/or simply being attributed to the MPFC, empathizing has been related to AI cortex, while mentalizing has been related to anterior rostral MPFC and adjacent ACC (7,78,87,89). Consistent patterns of hypofunction in right AI cortex support an expanded focus on AI and on efforts to disentangle the relative contributions of ventral MPFC/ACC and AI in studies of ASD (90).

Our meta-analysis also revealed ASD hypoactivation in PCC. Autism spectrum disorder related abnormalities in this region have been sporadically highlighted (e.g., 91), but its role in the pathophysiology of autism remains underelaborated. Given recent work suggesting broad impairments in self-referential cognition in ASD (92), a possible link between PCC and ASD stems from studies implicating the PCC in various aspects of self-referential processing (e.g., representing self-mental states) (53,81,93). This intriguing hypothesis remains provisional as ASD-related deficits in self-referential cognition have yet to be extensively examined (94). The mirror neuron system (95) has also been implicated in ASD (96) based on its role in action understanding (97–99) and awareness of the embodied self (100) and of self-intentions and self-emotions (93,101,102). We found ASD hypoactivation in a mirror neuron system area (the right pars opercularis) but in both social and nonsocial studies. Further behavioral and neurological investigations are needed to determine the relevance of the mirror neuron system for ASD symptomatology.

Consistent with the amygdala theory of autism (77), we found right amygdala hypoactivation. Amygdala dysfunction was initially linked to ASD due to the region's proposed role in evaluating facial expression and representing affective salience (57) and more recently, by work directly implicating it in the development of mentalizing (103). However, the nature of amygdala abnormalities in autistic-like behaviors remains unclear. While our meta-analysis suggests that ASD is characterized by amygdala hypofunction, a recent fMRI study demonstrated amygdala hyperactivity in ASD and related it to ASD-related phenomena such as diminished eye-gaze fixation (18). Similarly, amygdala lesions in monkeys produced increases in social interaction, not decreases (104). Such inconsistencies may reflect the functional and structural complexities of the amygdala or possible differences in specific paradigms employed for amygdala activation.

Finally, consistent with the neurotypical literature (105), post hoc analyses suggested that right hemisphere abnormalities in FG were limited to studies employing face-processing tasks. Furthermore, they suggest that localization of FG abnormalities may be sensitive to the specific task employed, with hypoactivation observed for tasks assessing facial expression extending more ventrally than those examining facial form perception. However, the direct role of FG hypoactivation in the pathophysiology of ASD remains unclear in light of recent findings of lack of ASD differences in FG after controlling for fixation or time of eye gaze or during processing of familiar faces (18,19,24).

Nonsocial-Related Abnormalities

The analyses of nonsocial studies revealed ASD-related hypoactivation in regions typically implicated in top-down cognitive control processes (60,62,63,82,106–108). Such findings agree with empirical evidence of executive dysfunction in ASD (28,32,36,109–111) and support the importance of examining broader cognitive functions beyond social cognition in ASD (32,112,113). Given the centrality of language abnormalities in autism, we examined whether findings for nonsocial studies depended on verbal paradigms. Only 6 of the 15 nonsocial studies employed verbal stimuli (70–72,114–116); removing them from the nonsocial meta-analysis did not change the pattern of results appreciably (data not shown).

Atypical Activations in ASD

We found ASD-related patterns of hypofunction accompanied by abnormal recruitment of activity in lower-order processing systems. For example, while NC subjects consistently activated mid-FG, commonly associated with face identity (117–120), the ASD group exhibited consistent patterns of activation in the posterior lateral portion of the FG, typically associated with physical aspects of face processing (117,119). Similarly, for nonsocial tasks, NC subjects consistently recruited activity in dACC/pre-SMA regions associated with attentional and motor control (60,62,63,81,106–108), while the ASD group recruited activity in the SMA proper, which is linked to more rote aspects of motor planning (83).

Finally, meta-analyses showed that the failure to activate dACC/pre-SMA regions during nonsocial tasks in the ASD group was accompanied by inappropriate recruitment of activity in the pgACC region activated during social tasks in NC subjects. This finding is intriguing given recent studies highlighting the default mode network (DMN) as a novel locus of dysfunction in autism (121,114). Motivated by reports that DMN deactivation facilitates performance of attentionally demanding tasks (122–125), failure to suppress DMN was found in adults with ASD during a Stroop task and was related to clinical measures of autism severity (social subscore of the Autism Diagnostic Interview-Revised) (114). Parallel lines of research have demonstrated ASD-related compromises in both structural and functional integrity of long-range connections within the DMN (126–128). Such findings support the disconnection model of autism (113,129–131), emphasizing the potential importance of abnormalities in functional

Table 2. Group Comparisons of Regions with Significantly Elevated Likelihood of Activation: Social Studies

			Talairach			
	BA	Volume (mm^3)	x	y	z	ALE (X 10^{-2})[a]
NC > ASD						
Precentral gyrus R & L	6	128	48	−2	38	1.10
	6	296	−44	−5	37	1.18
	44	248	54	11	8	1.22
Middle frontal gyrus L	9	168	−44	16	36	1.13
Inferior frontal gyrus R & L	46	872	49	20	23	1.61
	47	112	40	22	−13	1.03
	47	400	−43	27	1	1.35
Anterior cingulate	32	600	0	47	6	1.43
Subcallosal gyrus	34	176	−24	5	−14	1.19
Cingulate gyrus	24	184	5	4	42	1.24
Inferior parietal lobule /angular gyrus	7	392	−32	−55	43	1.46
Superior temporal gyrus R & L	22	248	51	−10	2	1.05
	22	816	−63	−27	2	2.03
Insula/superior temporal gyrus R	13/38	488	47	11	−6	1.54
Posterior cingulate	30	176	0	−49	18	1.19
Parahippocampal gyrus amygdala R		712	19	−7	−10	1.68
Fusifom gyrus (middle) L		208	−35	−57	−11	1.21
Lingual gyrus L		248	−17	−78	−13	1.30
Middle occipital gyrus L	19	200	−51	−68	8	1.15
Inferior occipital gyrus R	1	200	23	−88	−9	1.12
Thalamus R		448	28	−27	1	1.33
ASD > NC						
Precentral gyrus L	9	328	−43	6	31	1.21
Postcentral gyrus L	3	136	−37	−32	54	1.12
Middle temporal gyrus L	22	208	−48	−44	9	1.20
Superior temporal gyrus R	22	616	56	−28	5	1.42
Inferior temporal gyrus R	37	104	45	−64	−8	1.07
	37	240	49	−46	−14	1.25
Fusiform gyrus (posterior-lateral) L	37	504	−36	−70	−14	1.17
Inferior occipital gyrus L	18	224	−27	−86	−4	1.16

Brain regions labels and their corresponding Brodmann area (BA) and Talairach coordinates of the weighted center for each cluster showing greater probability of activation resulting from group subtraction using only the social study foci. Anatomical labels are based on the Talairach atlas.

ALE, activation likelihood estimates; ASD, autism spectrum disorders; BA, Brodmann area; L, left; NC, neurotypical control subjects; R, right.

[a]Each cluster was observed with a peak p value ≤.01, corrected; activation likelihood estimates (ALE) are reported.

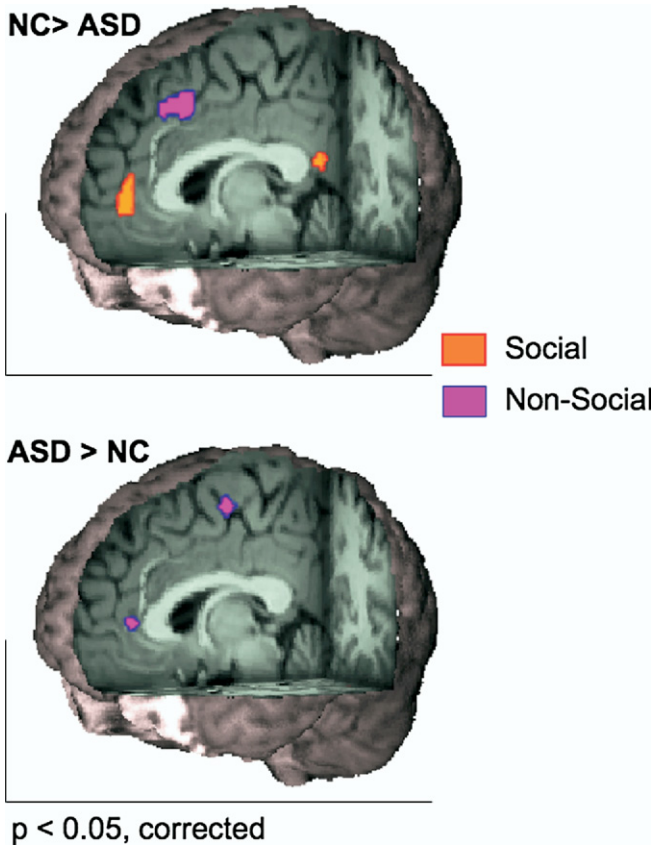

Figure 2. Medial-wall task-based group difference emerging from the separately conducted group subtractions including social studies only (orange) and nonsocial studies only (purple). The top panel shows greater probability of activation in neurotypical control (NC) subjects compared with autism spectrum disorders (ASD) in a cluster centered at the perigenual anterior cingulate cortex (ACC; x = 0, y = 47, z = 6) and posterior cingulate (x = 0, y = −49 , z = 18) for the analysis limited to social studies (light gray; red orange in the color version of the online Journal), while greater activation in a cluster centered at the presupplementary motor area (x = 0, y = 19, z = 46) resulted from the analysis limited to nonsocial studies (dark gray; blue-violet in the color version of the online Journal). The bottom panel shows ASD > NC activation likelihood estimate maps in a cluster centered in pgACC (x = 0, y = 40, z = 8) and in the supplementary motor area (x = 0, y = −10, z = 58) appearing only in the analysis of nonsocial studies. Images are displayed in neurological convention (right is right). ACC, anterior cingulate cortex; ASD, autism spectrum disorders; NC, neurotypical control.

and structural connections between regions rather than focal abnormalities alone. Future studies should characterize ASD-related abnormalities in both DMN integrity and the mechanisms by which the DMN and related networks (122,125,132) are regulated.

A Compelling Need for a Developmental Perspective

In discussing the neural basis of any childhood-onset disorder, an obvious concern is the degree to which group differences interact with development. This is especially true for ASD, where the nature of differences in gray and white matter volumes change during early development (133–136). The current functional literature is dominated by studies in adults who are better able to minimize movement during scanning and comply with task demands, which limited our ability to detect age-related changes in the neural correlates of autism. Given the protracted development of the neocortical mentalizing areas BA 10 and pgACC (137–140), as well as dACC and its related cognitive functions (141,142), it is likely that the pattern of ASD activation in the ACC regions emphasized in this study will differ in pediatric samples. Future investigations will need to both place greater focus on examining young children with autism and provide direct comparisons of children and adults to clarify this issue.

Limitations

The present work has several limitations common to efforts to synthesize the psychiatric neuroimaging literature (43,143). First, several studies did not report voxel-wise direct group comparisons. While ALE meta-analytic approaches allowed us to compare data provided by group, the paucity of direct between-group comparisons potentially limited our ability to detect more subtle group differences. Second, although the number of studies and the related number of foci included in the present work were substantial and comparable with other meta-analyses of clinical populations (43,143), many studies that did not report stereotaxic coordinates were excluded, also limiting our power to detect more subtle differences. A priori regions of interest used by several investigators also limited our ability to discern novel regional differences. As for any meta-analyses, type II errors due to publication bias cannot be ruled out. Despite these limitations, we were able to detect meaningful consistent results, which future work can confirm through direct experimentation with sufficiently large samples. Finally, 70% of the studies within each study class used block designs, which, though efficient, are potentially susceptible to the development of strategic processing and/or habituation that may differ between groups. Accordingly, event-related designs should be emphasized in future task-based approaches.

Multiple limitations with respect to ALE should also be noted. First, the current version of ALE weights all studies equally, regardless of potential differences in sample sizes. However, NC and ASD samples were comparable across studies, so that this simplification did not likely impact the groups differentially. Second, ALE does not allow covarying potential confounders such as IQ, which is strongly associated with ASD. Fortunately, most studies group-matched patient and control groups for IQ, and mean IQ for NC and ASD groups did not differ across studies. Finally, to attain a sufficiently large number of foci as

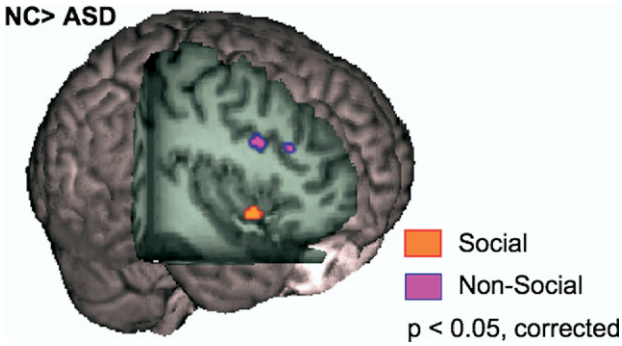

Figure 3. For social studies, neurotypical control (NC) subjects showed greater likelihood of activation in the right anterior insula when compared with participants with autism spectrum disorders (x = 47, y = 11, z = −6 light gray; orange in the color version of the online Journal). For nonsocial studies, NC subjects exhibited greater activation in the middle frontal gyrus (x = 40; y = 13; z = 27; x = 42; y = 27; z = 26 dark gray; purple in the color version of the online Journal). Image displayed in neurological convention. NC, neurotypical control; ASD, autism spectrum disorder.

Table 3. Group Comparisons of Regions with Significantly Elevated Likelihood of Activation: Nonsocial Studies

	BA	Volume (mm^3)	Talairach x	Talairach y	Talairach z	ALE (X 10^{-2})[a]
NC > ASD						
Medial frontal gyrus R	6	1856	1	19	46	1.54
Middle frontal gyrus R & L	9	656	40	13	27	1.37
	9	168	42	27	26	.92
	10	256	−33	57	7	1.04
Superior parietal lobule R	7	168	22	−67	46	.94
Inferior parietal lobule L	40	472	−49	−48	38	1.19
Supramarginal gyrus R	40	168	51	−51	33	.93
Claustrum/insula R	13	256	30	14	11	1.14
Superior temporal gyrus R	22	256	57	−47	13	1.08
Lingual gyrus L	17	104	−20	−93	0	.89
Thalamus L		336	−12	−1	10	1.27
ASD > NC						
Medial frontal gyrus	6	360	0	−10	58	1.24
Inferior frontal gyrus L	9	296	−51	20	20	1.19
Anterior cingulate	32	200	0	40	8	1.03
Superior temporal gyrus L	39	208	−52	−52	12	1.09
Middle occipital gyrus L	18	352	−23	−93	15	1.15
Lingual gyrus L		224	−14	−84	−8	1.17
Lateral geniculum body R & L		320	24	−25	−5	1.23
		136	−22	−27	−2	.96
Declive R		176	30	−78	−18	1.03

Brain regions labels and their corresponding Brodmann area (BA) and Talairach coordinates of the weighted center for each cluster showing greater probability of activation resulting from group subtraction using only the nonsocial study foci. Anatomical labels are based on the Talairach atlas.

ALE, activation likelihood estimates; ASD, autism spectrum disorders; BA, Brodmann area; L, left; NC, neurotypical control subjects; R, right.

[a]Each cluster was observed with a peak p value ≤.01, corrected; activation likelihood estimates (ALE) are reported.

recommended for ALE (≥100), we heuristically divided domains into those corresponding to social and nonsocial studies. The nonsocial domain in particular could be characterized as arbitrary, as it mostly included a heterogeneous set of executive functions. Nevertheless, the ability of ALE to demonstrate consistent findings that accorded with normative results suggests that this approach can be effective even in the face of such task heterogeneity. Future imaging studies of ASD may benefit from fractionating social and nonsocial domains into their major subcomponents.

Conclusions

Meta-analyses of the existent ASD neuroimaging literature provided evidence of 1) the dependence of ASD-related patterns of hypofunction on the specific cognitive domains examined (e.g., dACC/pre-SMA for nonsocial, pgACC for social); 2) ASD-related abnormalities in regions commonly highlighted in neurobiological models (e.g., pgACC/MPFC and amygdala), as well as regions only beginning to receive attention in relation to ASD (e.g., AI and PCC); 3) inappropriate recruitment of lower-order processing regions (e.g., SMA) in place of higher-order regions (e.g., dACC/pre-SMA); and 4) abnormalities in the default mode network (e.g., rostral ACC and PCC hypoactivation for social studies and abnormal activation in rostral ACC for nonsocial studies). Despite the limitations of the current neuroimaging literature on ASD, the remarkable overall coherence of these meta-analytical results appears to provide a solid basis for future work with even greater specificity.

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Supplementary material cited in this article is available online.

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