Neuroanatomical and Neurofunctional Markers of Social Cognition in Autism Spectrum Disorder

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Abstract: Social impairments in autism spectrum disorder (ASD), a hallmark feature of its diagnosis, may underlie specific neural signatures that can aid in differentiating between those with and without ASD. To assess common and consistent patterns of differences in brain responses underlying social cognition in ASD, this study applied an activation likelihood estimation (ALE) meta-analysis to results from 50 neuroimaging studies of social cognition in children and adults with ASD. In addition, the group ALE clusters of activation obtained from this was used as a social brain mask to perform surface-based cortical morphometry (SBM) in an empirical structural MRI dataset collected from 55 ASD and 60 typically developing (TD) control participants. Overall, the ALE meta-analysis revealed consistent differences in activation in the posterior superior temporal sulcus at the temporoparietal junction, middle frontal gyrus, fusiform face area (FFA), inferior frontal gyrus (IFG), amygdala, insula, and cingulate cortex between ASD and TD individuals. SBM analysis showed alterations in the thickness, volume, and surface area in individuals with ASD in STS, insula, and FFA. Increased cortical thickness was found in individuals with ASD, the IFG. The results of this study provide functional and anatomical bases of social cognition abnormalities in ASD by identifying common signatures from a large pool of neuroimaging studies. These findings provide new insights into the quest for a neuroimaging-based marker for ASD. *Hum Brain Mapp 00:000–000, 2016.*

Key words: activation likelihood estimation; social cognition; social brain; meta-analysis; autism; neuroimaging; brain

INTRODUCTION

Social cognition has been defined as the way in which people make sense of other people and themselves [Fiske and Taylor, 1991] and the ability to construct representations of the relation between oneself and others and to use those representations flexibly to guide social behavior [Adolphs, 2001]. Limited ability in social cognition in

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individuals with autism spectrum disorder (ASD) often result in poor social interaction. Recent neurobiological investigations involving human neuroimaging techniques have suggested several potential neural markers for ASD, primarily involving brain areas underlying social cognition. For example, atypical functional activation of the fusiform face area (FFA) [Spencer et al., 2011], superior temporal sulcus (STS) [Kaiser et al., 2010], amygdala [Baron-Cohen et al., 2000], and disrupted connectivity of the theory-of-mind (ToM) network [Deshpande et al., 2013; Kana et al., 2014] have been implicated as markers of ASD. These areas are considered part of the *social brain*, which comprises a network of regions that include the medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), amygdala (AMY), temporoparietal junction (TPJ), inferior frontal gyrus (IFG), Extrastriate Body Area (EBA), STS, and FFA [Blakemore et al., 2007; Brothers, 1990; Easton and Emery, 2004; Frith and Frith, 2008; Kennedy and Adolphs, 2012; Pelphrey and Carter, 2008]. The social brain areas mediate different social functions, such as joint attention, reading intentions, detecting agency, perceiving emotions, and processing faces which are all critical in navigating the social world. There is emerging evidence that the anatomy, functional activation, and connectivity of the social brain areas are altered in individuals with autism [Gotts et al., 2012; Kennedy and Adolphs, 2012; Pelphrey et al., 2011].

Among the relatively large number of functional neuroimaging studies of autism, many have focused primarily on individual social processes (e.g., face processing, biological motion, or theory-of-mind). Prior literature has suggested brain areas underlying social cognition to be potential candidates for a neuroendophenotype of ASD [Chiu et al., 2008; Kaiser et al., 2010; Spencer et al., 2011]. Chiu et al. [2008] found that cingulate response during a neuroeconomic social exchange task was related to ASD symptom severity. Kaiser et al. [2010] proposed the STS as a potential neuroendophenotype of autism based on their findings of differential state- and trait-related activation in STS during biological motion perception across children with ASD, their unaffected siblings, and TD children. In a similar study, Spencer et al. [2011] found that unaffected siblings and individuals with ASD demonstrated similar activity in FFA during a facial expression task, suggesting it to be a neuroendophenotype that captures both autism and the broader autism phenotype. In a recent study from our group, Deshpande et al. [2013] found that effective connectivity of the ToM network was able to successfully classify the participants into ASD and TD groups with about 95% accuracy. Further, studies using voxel-based morphology (VBM) and diffusion tensor imaging (DTI) have provided support for alterations in cortical anatomy in social brain areas [Cauda et al., 2011a, 2014]. Thus, emerging evidence from diverse neuroimaging studies point to several social brain areas as potential candidates for neural markers of ASD. Nevertheless, within the social brain, there has not been an overwhelming consensus on a specific region or network that may serve as the "best" candidate. Identifying neural signatures is critical to understanding the biological differences between individuals with and without ASD. Such markers can lead to better, more accurate, and early diagnosis of ASD, and can help design targeted intervention for individuals with ASD. As difficulties with social cognition and social behavior are pervasive throughout the autism spectrum, integrating inferences from numerous studies of social cognition in ASD gives the ideal vantage point to probe valid, common, and consistent neural signatures.

While there are several meta-analyses of social cognition in healthy individuals [Schilbach et al., 2012], there have been fewer attempts to consolidate the widespread and growing body of neuroimaging literature on social brain in autism. Using ALE meta-analysis on 24 studies of social cognition, DiMartino et al. [2009] found that the ASD participants demonstrated a greater likelihood of hypoactivation in the ACC and anterior insula. A more recent meta-analysis conducted by Sugranyes et al. [2011] analyzed 12 papers that compared ASD and control groups on standardized facial emotion recognition ($n = 5$) or ToM ($n = 7$) paradigms. For these two paradigms, the meta-analysis indicated hypoactivation of MPFC, amygdala and STS in ASD group primarily during ToM tasks. Developmental approaches to ALE have also been effectively utilized to identify social and nonsocial functional difference (i.e., fronto-temporal structures in particular) in children with ASD, relative to adults [Dickstein et al., 2013]. Notably, the number of papers, subjects, and foci used for the meta-analysis were significantly less in these studies by only including two social cognition paradigms. However, despite these limitations, similar findings have emerged across these studies both in terms of hypoactivation of ASD in ACC, anterior insula [Dimartino et al., 2009], MPFC, amygdala, and STS [Sugranyes et al., 2011]. The consistent presence of some of these regions highlight dysfunction within regions of the social brain in individuals

Abbreviations

ACC	anterior cingulate cortex
FFA	fusiform face area
IPL	inferior parietal lobule
ITG	inferior temporal gyrus
IFG	inferior frontal gyrus
MPFC	medial prefrontal cortex
MFG	middle frontal gyrus
MTG	middle temporal gyrus
MNS	mirror neuron system
OFC	orbitofrontal cortex
PCC	posterior cingulate cortex
pSTS	posterior superior temporal sulcus
STG/STS	superior temporal gyrus/sulcus
TPJ	temporoparietal junction
vmPFC	ventromedial prefrontal cortex

with ASD [Cauda et al., 2011b, 2014; DeRamus and Kana, 2014; Libero et al., 2014]. It is important to consider, however, that there have been a large number of studies suggesting that individuals with ASD differentially process, or at the very least have different BOLD activity in response to human faces in tasks involving face processing [Dalton et al., 2005b; Kleinhans et al., 2008; Pierce et al., 2001]. The number of face-processing studies of autism outweighs that of other topics of social cognition, perhaps underscoring the importance of this construct. The goal of this study is to comprehensively characterize the social brain abnormalities in autism at functional and anatomical levels by examining the emerging patterns across a large number of neuroimaging studies of social cognition in ASD. As such, this study of activation likelihood estimation (ALE) meta-analysis includes 50 peer-reviewed publications consisting of 675 participants with ASD, 695 TD individuals, and used a total of 1,843 foci of brain activity.

While dysfunction of the social brain in ASD has been demonstrated by many fMRI studies, a few studies have also examined the anatomical bases of such abnormalities. VBM data have suggested that structural alterations are within social brain areas in individuals with ASD, including the prefrontal cortex, amygdala, insula, and cingulate [Cauda et al., 2011a, 2014; DeRamus and Kana, 2014]. Meta-analyses of VBM studies reported smaller grey matter (GM) volumes in ASD in the temporal lobe, MPFC, amygdala/hippocampus, and precuneus [Duerden et al., 2012; Nickl-Jockschat et al., 2012; Stanfield et al., 2008]. Same studies have also found larger GM volumes in the lateral prefrontal cortex and temporo-occipital regions. A recent study reported smaller local GM volumes in ASD compared to TD participants in the bilateral amygdala, left anterior insula and MPFC [Radeloff et al., 2014]. Considering these anatomical abnormalities in autism, the present study applied the social brain regions (found from meta-analysis) to test anatomical integrity (cortical thickness, volume, and surface area) in an empirical dataset of 115 participants (55 ASD and 60 TD). This provides a valuable and novel dimension, of relating function to structure, to the present ALE-based meta-analysis. Thus, the findings of this study will provide important insights into the function and anatomy of the social brain in autism.

METHODS

Meta-Analysis

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines (http://www.prisma-statement.org/). The search method for published studies and inclusion criteria were specified in advance. Studies included in this meta-analysis investigated social cognition in participants with ASD and in TD control participants. Paradigms related to social cognition in this study are any neuroimaging experiments involving tasks that focus on processing information about the faces, bodies, feelings, thoughts, motions, and emotions of other humans (e.g., viewing stimuli made up of human faces or bodies, asking to make a judgment about another person's thoughts; see Fig. 1 for examples). Peer-reviewed and published scientific papers were identified through a computerized literature search using *Google Scholar* (http://scholar.google.com/), *Sleuth* (http://brainmap.org/sleuth/readme.html), *PubMed* (http://www.ncbi.nlm.nih.gov/pubmed), and *ScienceDirect* (http://www.sciencedirect.com/). We reviewed all functional neuroimaging papers published in English through the year 2014. The publications ranged from year 1992 to 2014. The following key words were used for search: "autism," "social," "cognition," "fMRI," "brain," "face," "emotion," "theory of mind," "empathy," "biological motion," "agency," "close other," "self-reference," their combinations and differing terminations. The data included in the meta-analysis was conducted on prior published studies from other research groups, and necessary data (i.e., foci of brain activation) were publicly available, IRB approval from our institution was not obtained. Instead, it is assumed that each individual study abided by high ethical standards and obtained IRB approval prior to conducting data collection at their institutions.

To meet our inclusion criteria, studies were required to (1) have both ASD and TD participants, (2) utilize fMRI or PET imaging, (3) use whole-brain image subtraction to identify clusters of significant task-related brain activations across groups and conditions, and (4) report results in standard stereotactic coordinates. Studies that did not meet these criteria were excluded from the analysis. Seventy-five functional imaging articles on autism were retrieved initially, 50 of which met our inclusion criteria. Notably, authors who did not report stereotactic coordinates in their paper were contacted by email, and coordinates were included when provided by the author. We also acknowledge that there may be coordinates that were not included due to publication bias. See Table I for an exclusive list of studies. The number of participants totaled 675 (53 female) ASD subjects and 695 (56 female) TD subjects. Papers included child, adolescent, and adult participants with ASD (overall mean age: 21.7 years) and their TD peers (overall mean age: 21.3 years).

In addition to the number of participants and task descriptions, the local maxima of task-related neural activity from each study were extracted and catalogued for the analysis. Task-related neural activity from each study encompasses any statistically significant clusters of brain activation derived from social cognitive tasks reported in each of the included manuscripts. Foci resulting from the meta-analysis were organized into tables for the various comparisons conducted. These comparisons were: (1) ASD + TD (within group), (2) TD (within-group), (3) ASD (within-group), (4) ASD > TD (between-group), (5) TD > ASD (between-group), (6) ASD-TD (between-group),

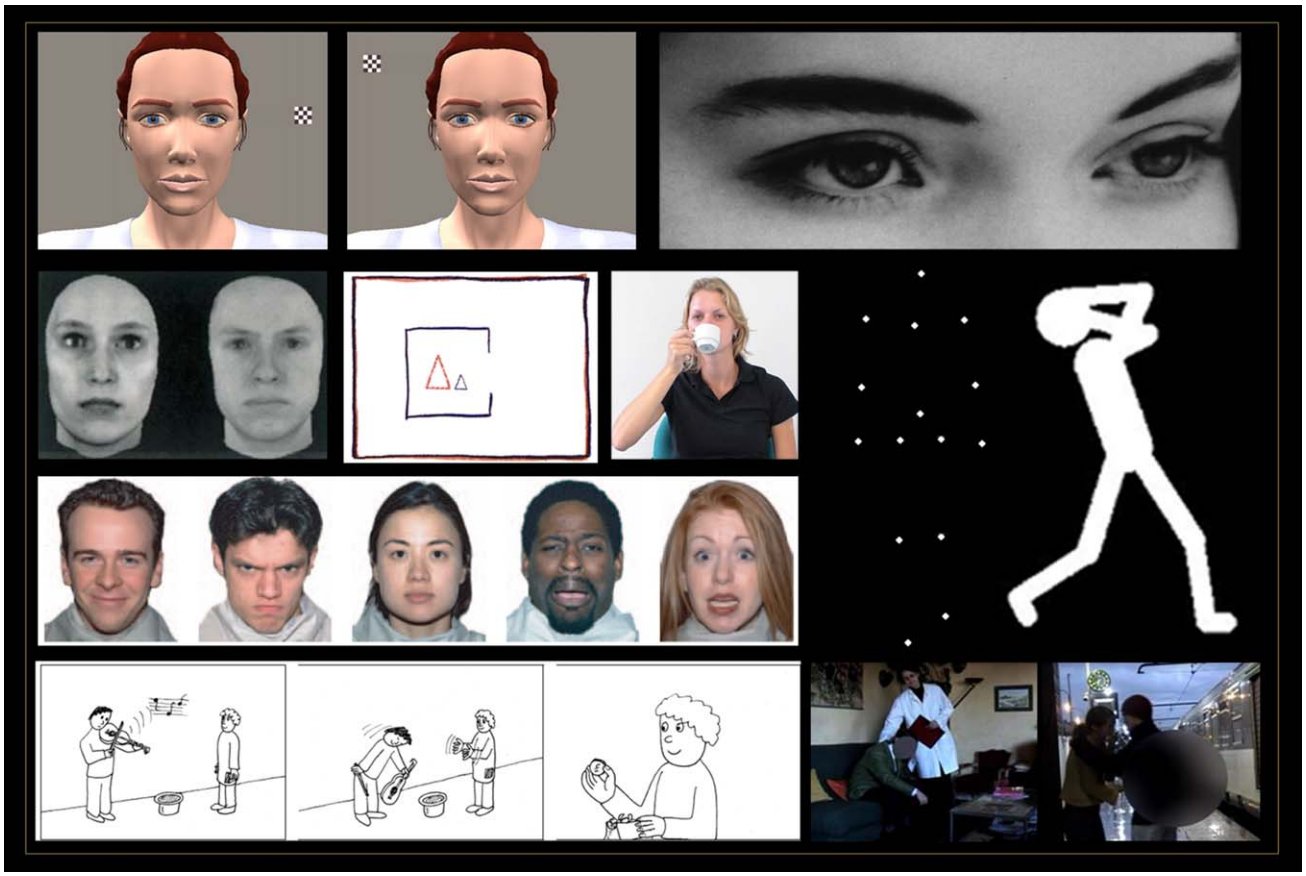

Figure 1.
Examples of social cognition tasks used in studies included in the meta-analysis. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

and (7) TD-ASD (between-group). Foci included the ASD + TD, TD, and ASD analyses came from within-group cluster tables for the social cognition task conditions reported in each included study. The foci included for the ASD > TD and TD > ASD between-group comparisons came from between-group cluster tables for the social cognition task conditions reported in each included study. Thus, the findings reported here emerged from within-group foci as well as between-group foci from 50 studies. In addition, since there is a relatively large number of face-processing studies in autism, subanalyses were conducted on social tasks involving face processing and those that do not. Analyses of activation peaks were performed using activation likelihood estimation via GingerALE software developed by the *Human Brain Mapping* Project (ALE) [Eickhoff et al., 2009, 2011, 2012; Turkeltaub et al., 2012]. Social cognition task contrasts from individual studies were comprised of contrasts between social (e.g., faces, direct gaze) and nonsocial (e.g., fixation, neutral) conditions and within social conditions (e.g., ToM, emotional faces).

All coordinates were entered into *GingerALE* in Montreal Neurological Institute (MNI) space. Coordinates of activation foci from studies that were not originally in MNI format were transformed to MNI from Talairach space using the Lancaster transform (tal2icbm tool) in GingerALE [Laird et al., 2010]. ALE values were computed for every voxel in the brain, testing the null distribution (calculated from 1000 repetitions using a permutation analysis) of the ALE statistic for each voxel. For each study, peaks were selected based on subject grouping. For each group, the centroid of the significant cluster uses the foci with the shortest Euclidian distance from the center of the distribution in each group. ALE scores from the convergent MA maps were then calculated on a voxel-by-voxel basis to test for convergent (random-effects) rather than study specific foci (fixed-effects). Subject information (*n* subjects per study group) was used to calculate Full-width Half-maximum of the Gaussian function. We conducted meta-analyses within-group (using separate within ASD group and within TD group coordinates) and between-group (using TD > ASD and ASD > TD cluster coordinates reported in each study). The Cluster-level Inference Thresholding value for the ASD, TD, ASD > TD, and TD > ASD were .05 with a False Discovery Rate (FDR)

TABLE I. Characteristics of the studies included in the meta-analysis

	Imaging	ASD			TD				
Article	Modality	*n*	*n* M/F	Mean age	*n*	*n* M/F	Mean age	Type of Task	Contrast(s)/task(s)
Ashwin et al. [2007]	fMRI	13	13/0	31.2	13	13/0	25.6	Face processing	Faces > scrambled
Baron-Cohen et al. [1999]	fMRI	6	4/2	26.3	12	6/6	25.5	Theory-of-mind	ToM
Bastiaansen et al. [2011]	fMRI	21	21/0	30.6	21	21/0	30.5	Face processing	Emotional faces
Bird et al. [2006]	fMRI	16	14/2	33.3	16	14/2	35.3	Face processing	Faces > houses; attended faces > unattended faces
Bookheimer et al. [2008]	fMRI	12	12/0	11.3	12	12/0	11.9	Face processing	Upright faces > forms
Brandenburg-Goddard et al. [2014]	fMRI	17	17/0	12.4	19	19/0	12.0	Face processing	Face matching > object matching; face labeling > face matching
Carter et al. [2012]	fMRI	12	9/3	13.8	13	11/2	11.46	Social judgment	Social > fixation; social > physical
Castelli et al. [2002]	PET	10	10/0	33	10	10/0	25	Theory-of-mind	ToM animations > Rd animations
Chiu et al. [2008]	fMRI	12	12/0	16.5	18	18/0	14.9	Self-response	Self-response in exchange game
Colich et al. [2012]	fMRI	16	14/2	14.27	16	14/2	13.15	Social orienting	Sincere > rest; ironic > rest
Corbett et al. [2009]	fMRI	12	12/0	9.01	15	13/2	9.17	Emotion processing	Emotion > control; person > control
Critchley et al. [2000]	fMRI	9	9/0	37	9	9/0	27	Face processing	Faces
Dalton et al. [2007]	fMRI	12	8/4	14.4	12	10/2	14.16	Face processing	Faces
Dalton et al. [2005]	fMRI	14	14/0	15.9	12	12/0	17.1	Emotion processing	Emotional faces
Dapretto et al. [2006]	fMRI	10	9/1	12.05	10	9/1	12.38	Imitation	Imitation of emotional expressions; observation of emotional expressions
Davies et al. [2011]	fMRI	14	12/2	11.69	14	12/2	12.3	Gaze processing	Direct gaze > null; averted gaze > null
Deeley et al. [2007]	fMRI	9	9/0	34	9	9/0	27	Emotion processing	Intense sadness > fixation; neutral faces > fixation; intense fear > fixation; intense disgust > fixation; intense happiness > fixation
Dichter et al. [2007]	fMRI	17	16/1	22.9	15	14/1	24.6	Gaze processing	Gaze
Freitag et al. [2008]	fMRI	15	13/2	17.5	15	13/2	18.6	Biological motion	Biological motion > scrambled motion;
Gebauer et al. [2014]	fMRI	19	17/2	26.2	20	18/2	24.5	Emotional music	Happy music > sad music
Gervais et al. [2004]	fMRI	5	5/0	25.8	8	8/0	27.1	Voice processing	Voice > nonvoice; voice > silence
Greimel et al. [2010]	fMRI	15	15/0	14.9	15	15/0	15	Self/other	Other > baseline; self > baseline
Hadjikhani et al. [2009]	fMRI	12	9/3	30	7	4/3	34	Emotion processing	Fear > neutral
Hall et al. [2003]	PET	8	8/0	20-33	8	8/0	20-33	Emotion processing	Emotions; emotion processing
Happe et al. [1996]	PET	5	5/0	24	6	6/0	38	Theory-of-mind	ToM
Hubl et al. [2003]	fMRI	10	10/0	27.7	10	10/0	25.3	Face processing	Face processing
Kana et al. [2012]	fMRI	15	15/0	21.14	15	15/0	22.28	Theory-of-mind	Intention causality > physical
Kana et al. [2009]	fMRI	12	10/2	24.6	12	12/0	24.4	Theory-of-mind	ToM > random
Kennedy et al. [2008]	fMRI	13	13/0	26.9	12	12/0	27.5	Theory-of-mind	ToM; internal > external; external-> internal; mental > math; other > self
Kleinhans [2009]	fMRI	19	18/1	21.9	20	20/0	24.7	Face processing	Faces > fixation 1; faces > fixation 2; faces > fixation time 1 > 2
Knaus et al. [2008]	fMRI	12	12/0	15.46	12	12/0	14.94	Response naming	Response naming vs visual processing

TABLE I. (continued).

	Imaging	ASD			TD				
Article	Modality	*n*	*n* M/F	Mean age	*n*	*n* M/F	Mean age	Type of Task	Contrast(s)/task(s)
Koshino et al. [2008]	fMRI	11	11/0	24.5	11	10/1	28.7	Face processing	Faces memory; working memory vs baseline
Lombardo et al. [2010]	fMRI	29	29/0	26.59	33	33/0	27.97	Self/other	Self vs other; self-mentalizing vs self-physical > other-mentalizing vs other-physical
Martineau et al. [2010]	fMRI	7	7/0	23	8	8/0	23.25	Imitation	Execution > rest; observation > rest
Morita et al. [2012]	fMRI	15	14/1	23.7	14	12/2	23.3	Self/other	Self vs other
Pelphrey et al. [2005]	fMRI	10	9/1	23.2	9	8/1	23.4	Gaze processing	Incongruent > congruent;
Pelphrey et al. [2007]	fMRI	8	6/2	24.5	8	6/2	24.1	Emotion processing	Emotion faces; dynamic emotions
Pfeifer et al. [2012]	fMRI	18	17/1	14.9	18	17/1	13.3	Self/other	Self > other
Pierce et al. [2004]	fMRI	8	8/0	27.1	10	10/0	16-40	Face processing	Familiar faces; familiar face > stranger face; stranger face
Pinkham et al. [2008]	fMRI	12	12/0	24.08	12	12/0	27.08	Face/social judgment	Trustworthiness; trust judgment of faces; age judgment of faces
Pitskel et al. [2011]	fMRI	15	15/0	23.4	14	13/1	24.2	Gaze processing	Direct > averted gaze; averted > direct gaze
Redcay et al. [2012]	fMRI	16	13/3	28.3	16	13/3	22.1	Joint attention	Joint attention; response to joint attention > solo attention
Schneider et al. [2012]	fMRI	28	16/12	31.39	28	16/12	31.29	Morality	Moral vs baseline; social-ethical dilemma vs baseline; individual gain moral dilemma; individual gain vs social-ethical dilemma
Silani et al. [2008]	fMRI	15	13/2	36.6	15	13/2	33.7	Emotion processing	Emotional vs neutral; internally vs externally oriented; emotional (unpleasant) > neutral stimuli; internal > external
Uddin et al. [2008]	fMRI	12	12/0	13.19	12	12/0	12.23	Self/other	Self > rest; other > rest
Vaidya et al. [2011]	fMRI	15	11/4	10.78	18	14/4	10.96	Gaze processing	Incongruent > congruent; congruent > neutral
Wang et al. [2004]	fMRI	12	12/0	12.2	12	12/0	11.8	Emotion processing	Matched emotions vs control; label emotions vs control
Wang et al. [2006]	fMRI	18	18/0	11.9	18	18/0	11.9	Irony	Irony vs no irony; event knowledge only + prosodic cue vs rest; event knowledge only; prosody only
Wang et al. [2007]	fMRI	18	18/0	12.4	18	18/0	11.8	Irony	Irony vs no irony
Williams et al. [2006]	fMRI	16	16/0	15.4	15	15/0	15.5	Imitation	Imitation vs rest; imitation vs cue execution; imitation vs observation; imitation vs rest; imitation vs cue execution

Note. ToM = theory of mind; Rd animations = animations of randomly moving shapes.

pN-based (no assumptions of correlations between data) cluster-forming threshold of $p < 0.05$. The total number of permutations for each analysis was 1000. No other information (e.g., effect size, autism diagnosis, age, MRI field strength) was used in the calculation of the ALE statistic, and none of this information can be used in the algorithm.

Cortical Surface-Based Morphology

Structural MRI data collected from 115 participants with ASD ($n = 55$; 49males/6 females; mean age = 18.2) and without ASD ($n = 60$; 55 males/5 females; mean age = 18.5-years) were entered into a general linear model (GLM) assessing surface-based cortical morphometry. Participants were aged 8–40 years ($M = 18.43$, SD = 6.80) and had IQs > 70. Anatomical scans were collected on a 3 T Siemens Allegra head-only scanner (Siemens Medical Inc., Erlangen, Germany) using high-resolution T1-weighted images using a 160 slice 3D MPRAGE volume scan with a repetition time (TR) = 200 ms, echo time (TE) = 3.34 ms, flip angle = 12°, field of view (FOV) = 25.6, 256 × 256 matrix size, and 1 mm slice thickness. The included 3D volumes were the remaining images following visual examination by three researchers independently to confirm data quality, and exclude images with significant distortion due to head motion or scanner artifact [Libero et al., 2014]. Scans were segmented using the standard *Freesurfer*™ [Fischl, 2012] pipeline, using a combination of Casual Markov-Field modeling and probabilistic calculations based on image intensity to a hand-labeled training set described in detail in Fischl [2004]. Statistically significant clusters (excluding the amygdala) from the modeled-activation map of the ASD + TD condition from all of the included studies (Fig. 3) were mapped from volumetric space to the cortical surface of the *fsaverage* brain template in *Freesurfer*™ using the *bbregister* function to form a social brain mask. The masks were then mapped to each subject's native space, and a Monte-Carlo null-*z* distribution was computed for the mask on the *fsaverage* brain template. Each participant's cortical surface maps for thickness, surface area, and volume for each hemisphere were then normalized to the *fsaverage* template and smoothed to a full-width half-maximum (FWHM) of 10 mm for group comparisons.

GLMs assessing TD versus ASD structural differences across the ALE mask included age, diagnosis, total-brain measures (estimated total intracranial volume for volume, cubed-root squared transform of total intracranial volume for surface area, and mean thickness of the left and right hemispheres for thickness), and the interaction terms for age and diagnosis, diagnosis and total-brain measure, age and total-brain measure, and the three-way interaction between age, diagnosis, and total-brain measure of interest. Each continuous variable (age, total-brain-measure) was centered along the group mean for the participant sample to reduce multicolinearity and increase power [Dalal and Zickar, 2012; Enders and Tofighi, 2007; Robinson and Schumacker, 2009]. GLMs for each metric of interest were performed individually on the left and right hemisphere, with the appropriate statistical correction for multiple hemispheres. Results were vertex-level corrected across the mask using a "cluster" threshold of 0.01 based on the null-*z* distribution computed across the mask for the group template.

RESULTS

The main results of this multilayered meta-analysis study are (1) combined fMRI meta-analysis of all participant groups (ASD + TD) revealed increased activity in several regions considered part of the social brain; (2) within-group activation maps (within-ASD, within-TD) showed overlapping activation in many social brain areas across ASD and TD groups; (3) meta-analysis of fMRI group differences as well as direct subtraction of within-group activation indicated reduced activity in ASD in fusiform gyrus and cingulate cortex; (4) A sub analysis of studies involving only face processing tasks revealed reduced activity in ASD in fusiform, insula, cingulate, and amygdala; and (5) a social brain mask created based on fMRI results to examine cortical morphology, in an empirical structural MRI dataset, revealed significantly decreased cortical matter in the STS, insula, FFA, and left IFG for the ASD group.

Brain Areas Associated With Social Cognition

To characterize the functional profile of the social brain, we investigated the entire sample (ASD + TD) as one group. This combined group meta-analysis ($N_{ASD+TD} = 89$, $N_{foci} = 1{,}109$] revealed significantly increased activation in the right insula, bilateral FFA, IFG, STG, MTG, precuneus, and amygdala, STG, left medial prefrontal cortex, left postcentral gyrus, left lingual gyrus during social cognition. Most of these regions have been considered to be part of the social brain. The results of this analysis provided a profile of the regions that are active in participants during social cognitive tasks. The corresponding anatomical regions and peak ALE maxima are shown in Table II and Figure 3.

Within-Group Brain Activity

When activation likelihood during social cognition was estimated separately for each group of participants (within-ASD, within-TD), both ASD and TD group showed several overlapping ALE clusters of activation. These include FFA, IFG, MPFC, and STS. There were also a few regions that showed unique activation in each group. For example, insula activation was only seen in ASD group, whereas the TD group showed unique activity in TPJ,

TABLE II. ALE cluster values for combined ASD and TD analysis depicting regions recruited for social cognition tasks

Brain Region	Gyrus	BA	Laterality	Site of maximum ALE			Volume[a] (mm^3)	Maximum ALE value	Contributing studies
				x	*y*	*z*			
TD+ASD									
Occipital	Fusiform	19	Right	42	−72	−10	17480	0.05412651	Kleinhans, 2009; Lombardo, 2010; Martineau, 2010; Morita, 2012; Pelphrey, 2005; Redcay, 2012; Schneider, 2012; Silani, 2007; Ashwin, 2007; Bastiaansen, 2011; Bird, 2006; Kana, 2009; Gervais, 2004; Hall, 2003; Deeley, 2007; Baron-Cohen, 1999; Uddin, 2008; Carter, 2012; Wang, 2006; Wang, 2007; Corbett, 2009; Dapretto, 2006; Davies, 2011
Temporal	Fusiform	37	Right	42	−50	−20	17480	0.053792123	
Temporal	Fusiform	37	Right	48	−56	−-8	17480	0.03487473	
Cerebellum	Declive		Right	32	−84	−14	17480	0.032379657	
Occipital	Lingual	18	Right	20	−86	−10	17480	0.03123553	
Occipital	Lingual	18	Right	14	−88	−8	17480	0.029813562	
Cerebellum	Pyramis		Right	28	−82	−28	17480	0.025772704	
Frontal	IFG	9	Right	50	6	26	16760	0.045581292	Martineau, 2010; Morita, 2012; Pelphrey, 2005; Redcay, 2012 In; Schneider, 2012; Silani, 2007; Bastiaansen, 2011; Kana, 2009; Pinkham, 2008; Baron-Cohen, 1999; Hall, 2003; Deeley, 2007; Carter, 2012; Colich, 2012; Wang, 2006; Davies, 2011; Dapretto, 2006
Frontal	IFG	13	Right	44	32	8	16760	0.039703425	
Frontal	IFG	13	Right	50	28	2	16760	0.037399296	
	Insula		Right	32	22	0	16760	0.035746727	
Temporal	STG	38	Right	46	12	−20	16760	0.031449612	
Frontal	IFG	44	Right	54	8	16	16760	0.030147722	
Temporal	Insula	38	Right	48	12	−10	16760	0.029856449	
Frontal	MTG	6	Right	48	4	40	16760	0.023461588	
Frontal	MFG	6	Right	40	6	38	16760	0.021827674	
Temporal	Fusiform	37	Left	−42	−52	−20	15608	0.055118725	Morita, 2012; Pelphrey, 2005; Redcay, 2012; Silani, 2007; Bastiaansen, 2011; Kana, 2009; Pinkham, 2008; Baron-Cohen, 1999; Deeley, 2007; Hall, 2003; Uddin, 2008; Carter, 2012; Colich, 2012; Wang, 2006; Corbett, 2009; Dapretto, 2006; Davies, 2011
Cerebellum	Declive		Left	−18	−82	−16	15608	0.040249955	
Occipital	Fusiform	19	Left	−40	−80	−12	15608	0.03462337	
Cerebellum	Declive		Left	−30	−86	−14	15608	0.031770688	
Occipital	MOG	18	Left	−30	−84	−2	15608	0.030657215	
Occipital	MOG	18	Left	−22	−90	−4	15608	0.025647033	
Occipital	Lingual	18	Left	−10	−84	−4	15608	0.01790161	
Temporal	STG	41	Right	46	−24	10	11736	0.0459998	Redcay, 2012; Schneider, 2012; Silani, 2007; Bastiaansen, 2011; Kana, 2009; Pinkham, 2008; Baron-Cohen, 1999; Gervais, 2004; Deeley, 2007; Carter, 2012; Colich, 2012; Wang, 2006; Wang, 2007; Corbett, 2009
Temporal	STG	39	Right	52	−52	10	11736	0.042618394	
Temporal	Insula	13	Right	50	−16	4	11736	0.03803319	
Temporal	MTG/STG	21	Right	48	−12	−12	11736	0.032998633	
Temporal	STG	22	Right	58	−12	2	11736	0.029443722	
Temporal	STG	41	Right	64	−22	8	11736	0.022896701	
Occipital	MTG	37	Right	46	−64	12	11736	0.021273583	
Temporal	STG	41	Left	−58	−24	6	7552	0.043187886	Morita, 2012; Pelphrey, 2005; Redcay, 2012; Silani, 2007; Bastiaansen, 2011; Baron-Cohen, 1999; Deeley, 2007; Carter, 2012; Colich, 2012; Wang, 2006; Dapretto, 2006
Temporal	MTG	22	Left	−62	−32	4	7552	0.036335785	
Temporal	MTG	21	Left	−64	−32	4	7552	0.034959424	
Temporal	STG	22	Left	−58	−44	8	7552	0.031985525	
Temporal	STG	41	Left	−46	−32	12	7552	0.028247612	
Temporal	STG	38	Left	−48	14	−22	5264	0.037705697	Morita, 2012; Redcay, 2012; Schneider, 2012; Silani, 2007; Ashwin, 2007; Kana, 2009; Baron-Cohen, 1999; Deeley, 2007; Carter, 2012; Colich, 2012; Wang, 2006; Wang, 2007
Frontal	IFG	13	Left	−36	26	2	5264	0.032419857	
Frontal	Insula	47	Left	−30	20	−6	5264	0.023984835	
Limbic	Cingulate	24	Right	4	2	46	5264	0.034800988	
Frontal	MPFC	6	Left	−2	6	56	5264	0.033842657	
Frontal	MPFC	6	Left	2	−4	56	5264	0.030689176	
Frontal	IFG	45	Left	−56	22	16	4408	0.032034855	

TABLE II. (continued).

Brain Region	Gyrus	BA	Laterality	Site of maximum ALE			Volume[a] (mm^3)	Maximum ALE value	Contributing studies
				x	*y*	*z*			
Frontal	Precentral	6	Left	−48	4	32	4408	0.03180007	Kleinhans, 2009; Silani, 2007; Bastiaansen, 2011; Pinkham, 2008; Baron-Cohen, 1999; Carter, 2012; Corbett, 2009; Dapretto, 2006; Davies, 2011; Dapretto, 2006;
Frontal	IFG	13	Left	−50	8	4	4408	0.023599483	
Frontal	IFG	13	Left	−40	18	16	4408	0.02340784	
Frontal	IFG	9	Left	−52	14	24	4408	0.02178787	
Limbic	Amygdala	13	Left	−20	−10	−12	2880	0.049200706	Martineau, 2010; Morita, 2012; Silani, 2007; Hall, 2003; Deeley, 2007; Uddin, 2008; Carter, 2012; Davies, 2011
Limbic	Amygdala	9	Left	−24	−2	−24	2880	0.030887658	
Frontal	MPFC	9	Left	0	52	24	2480	0.03270933	
Frontal	SFG	9	Left	−6	62	20	2480	0.021746332	
Frontal	Postcentral	3	Left	−34	−30	54	2112	0.029163424	Kleinhans, 2009; Ashwin, 2007; Bastiaansen, 2011; Baron-Cohen, 1999; Carter, 2012; Corbett, 2009; Dapretto, 2006; Davies, 2011
Frontal	Postcentral	2	Left	−46	−22	40	2112	0.022138184	
Limbic	Amygdala		Right	20	−6	−14	1720	0.047734328	Morita, 2012; Baron-Cohen, 1999; Gervais, 2004; Deeley, 2007
Temporal	MFG	39	Left	−46	−62	24	1104	0.03217082	Morita, 2012; Baron-Cohen, 1999; Deeley, 2007; Carter, 2012
Temporal	MFG	39	Left	−48	−58	16	1104	0.02153084	
Parietal	Precuneus	31	Right	28	−76	30	880	0.025590919	Schneider, 2012; Silani, 2007; Kana, 2009; Baron-Cohen, 1999
Occipital	Precuneus	31	Right	32	−66	30	880	0.02122378	
Parietal	Precuneus	31	Left	−2	−54	34	720	0.034940273	Bastiaansen, 2011; Carter, 2012; Davies, 2011

Note. Minimum cluster size based on FDR correction = 576; permutation equilibrium = 16. MFG = middle frontal gyrus, MPFC = medial prefrontal cortex, MTG = middle temporal gyrus, IFG = inferior frontal gyrus, SFG = superior frontal gyrus, STG = superior temporal gyrus, MOG = middle occipital gyrus.
[a]Repetition of same cluster volumes indicates that these peaks were all within the same cluster.

TABLE III. ALE cluster values within ASD group only

Brain Region	Gyrus/sulcus	BA	Laterality	Site of maximum ALE			Volume[a] (mm^3)	Maximum ALE value
				x	*y*	*z*		
ASD								
Temporal	Fusiform	37	Right	44	−66	−12	9264	0.030331947
Anterior	Culmen		Right	40	−54	−20	9264	0.030075628
Posterior	Declive		Right	36	−66	−18	9264	0.022844706
Occipital	Lingual	18	Right	16	−86	−8	9264	0.020278946
Occipital	Lingual	18	Right	6	−84	−6	9264	0.018359212
Posterior	Uvula		Right	30	−82	−26	9264	0.017297413
Posterior	Declive		Right	30	−82	−14	9264	0.015294376
Temporal	Fusiform	37	Left	−42	−52	−20	8848	0.025839185
Occipital	Fusiform	19	Left	−40	−74	−12	8848	0.022013115
Occipital	Inferior Occipital	18	Left	−32	−84	−2	8848	0.019835446
Occipital	Lingual	19	Left	−30	−80	4	8848	0.01900635
Posterior	Declive		Left	−18	−82	−12	8848	0.017046362
Occipital	Middle Occipital	18	Left	−22	−90	−6	8848	0.016933754
Sub-lobar	Insula	13	Right	34	24	−2	3240	0.024693143
Frontal	Middle Frontal	46	Right	46	30	10	3240	0.018757155
Temporal	Transverse Temporal	41	Right	46	−24	10	3216	0.028715182
Temporal	Superior Temporal	13	Right	50	−22	4	3216	0.024662865
Temporal	Superior Temporal	41	Right	58	−28	8	3216	0.012479794
Temporal	Middle Temporal	22	Left	−62	−36	4	2928	0.02310238
Temporal	Superior Temporal	41	Left	−58	−26	10	2928	0.020005718
Temporal	Superior Temporal	22	Left	−52	−28	2	2928	0.019399282
Temporal	Superior Temporal	41	Left	−48	−32	12	2928	0.016045671
Frontal	Inferior Frontal	9	Right	46	12	24	2160	0.020109536
Frontal	Inferior Frontal	9	Right	54	8	18	2160	0.018232806
Frontal	Inferior Frontal	47	Left	−44	18	−16	2024	0.020636568
Temporal	Superior Temporal	38	Left	−44	14	−28	2024	0.017843021
Sub-lobar	Insula	13	Left	−42	18	−2	2024	0.013671238
Frontal	Inferior Frontal	44	Left	−52	18	10	1560	0.020568147
Frontal	Inferior Frontal	45	Left	−54	22	16	1560	0.018506812
Frontal	Inferior Frontal	9	Left	−52	16	22	1560	0.01628338
Parietal	Postcentral	40	Left	−44	−28	60	1312	0.017873524
Parietal	Inferior Parietal	40	Left	−34	−40	54	1312	0.012122758
Sub-lobar	Lentiform Nucleus		Left	−24	−8	−12	1248	0.019479897
Limbic	Parahippocampal		Left	−18	−6	−16	1248	0.018269729
Temporal	Superior Temporal	22	Right	56	−50	8	1120	0.019661412
Limbic	Parahippocampal		Right	20	−6	−16	760	0.02188986
Temporal	Superior Temporal	38	Right	46	10	−20	664	0.0152831
Temporal	Middle Temporal	39	Left	−44	−60	24	496	0.020626092
Frontal	Inferior Frontal	6	Left	−48	6	32	496	0.018233394
Frontal	Paracentral Lobule	31	Left	2	−8	50	464	0.015399425

Note. Minimum cluster size based on FDR correction = 464; permutation equilibrium = 22.
[a]Repetition of same cluster volumes indicates that these peaks were all within the same cluster.

cingulate cortex, inferior temporal gyrus (ITG), precentral gyrus, and postcentral gyrus. Several of these regions showing statistically significant clusters in ASD and TD groups, including the STS, FFA, MPFC, IFG, and TPJ, have been implicated in previous studies of social cognition [Pelphrey and Carter, 2008]. Although ITG, precentral gyrus, and postcentral gyrus do not appear to be as commonly activated during social cognition tasks, some studies associate them with social cognition [Baron-Cohen et al., 1999; Chiu et al., 2008]. See Tables III and IV and Figure 2 for results.

Group Differences in Social Brain Activity: ASD > TD vs TD > ASD

The ASD group demonstrated significantly greater activation in the STG, insula, amygdala, IFG, MFG, precentral gyrus, and postcentral gyrus, compared to their TD counterparts ($N_{\text{ASD}>\text{TD contrast}} = 23$; $N_{\text{foci}} = 99$; Table V and Fig. 3). The ASD group showed significantly lower activity, when compared to TD participants ($N_{\text{TD}>\text{ASD contrast}} = 55$; $N_{\text{foci}} = 279$), in amygdala, hippocampus, FFA, STG, cingulate, and IFG. See Table VI and Figure 3 for

TABLE IV. ALE cluster values within TD group only

Brain region	Gyrus/sulcus	BA	Laterality	Site of maximum ALE			Volume[a] (mm^3)	Maximum ALE value
				x	y	z		
TD								
Anterior	Culmen		Right	42	−48	−22	7672	0.038141
Occipital	Fusiform	19	Right	40	−72	−10	7672	0.033462
Temporal	Subgyral	37	Right	50	−54	−8	7672	0.028119
Posterior	Declive		Right	34	−84	−14	7672	0.019529
Occipital	Lingual	18	Right	22	−88	−12	7672	0.018287027
Temporal	Fusiform	37	Left	−42	−52	−18	5008	0.031164583
Occipital	Inferior Temporal		Left	−48	−70	2	5008	0.017410288
Temporal	Fusiform	37	Left	−46	−68	−6	5008	0.0170422
Frontal	Inferior Frontal	45	Right	52	26	2	4656	0.027324826
Frontal	Middle Frontal	46	Right	42	34	10	4656	0.02456526
Sublobar	Insula	13	Right	48	12	−8	4656	0.022327906
Sublobar	Claustrum		Right	30	18	0	4656	0.02062103
Sublobar	Insula	13	Right	34	26	4	4656	0.015006449
Frontal	Inferior Frontal	9	Right	50	8	28	3912	0.032349057
Frontal	Precentral	44	Right	52	8	10	3912	0.01981003
Sublobar	Insula	13	Right	44	12	18	3912	0.01948477
Temporal	Subgyral	21	Right	48	−12	−12	3688	0.02865497
Sublobar	Insula	13	Right	50	−14	4	3688	0.025107788
Temporal	Superior Temporal	41	Right	40	−30	14	3688	0.022448573
Temporal	Superior Temporal	41	Right	60	−14	4	3688	0.02047863
Limbic	Cingulate	24	Right	4	2	46	2976	0.028651956
Frontal	Medial Frontal	6	Left	0	8	56	2976	0.022982934
Frontal	Medial Frontal	6	Left	2	2	58	2976	0.022076836
Temporal	Superior Temporal	39	Right	50	−52	12	2848	0.029311212
Temporal	Superior Temporal	41	Right	52	−40	6	2848	0.019602012
Occipital	Middle Temporal	37	Right	46	−64	12	2848	0.019062284
Temporal	Superior Temporal	41	Left	−58	−22	4	2776	0.032378495
Frontal	Medial Frontal	9	Left	0	52	24	2352	0.025336599
Frontal	Superior Frontal	9	Left	−6	64	18	2352	0.014481918
Posterior	Declive		Left	−18	−82	−16	2088	0.026589418
Posterior	Declive		Left	−32	−86	−14	2088	0.021471513
Occipital	Fusiform	19	Left	−40	−82	−12	2088	0.01831894
Sublobar	Lentiform Nucleus		Right	18	−8	−10	1272	0.03259568
Sublobar	Lentiform Nucleus		Left	−20	−10	−10	1216	0.03406375
Temporal	Superior Temporal	38	Left	−48	14	−22	1016	0.027216656
Frontal	Inferior Frontal	45	Left	−36	28	2	1016	0.022899399
Parietal	Postcentral	3	Left	−32	−30	52	848	0.017779186
Parietal	Postcentral	2	Left	−42	−22	40	848	0.01583136
Posterior	Pyramis		Right	26	−80	−32	736	0.01774826
Temporal	Superior Temporal	22	Left	−58	−44	10	704	0.023801552
Frontal	Precentral	44	Left	−52	6	4	576	0.018190052
Frontal	Precentral	44	Left	−50	6	8	576	0.01727778

Note. Minimum cluster size based on FDR correction = 528; permutation equilibrium = 11.
[a]Repetition of same cluster volumes indicates that these peaks were all within the same cluster.

results. Although several of these regions are common across these comparisons (ASD > TD and TD > ASD), the peak of activation coordinates differ in some cases. Nevertheless, it should be noted that the main regions of group difference, where ASD group had lower activity than TD, were FFA, hippocampus, and cingulate cortex.

Comparing Face-Processing Tasks vs Non-Face-Processing Tasks

Sub analyses of social cognition tasks involving only *face versus nonface stimuli* revealed several clusters of significantly reduced activation in ASD, compared to TD, individuals centered on right parahippocampal gyrus, left FFA,

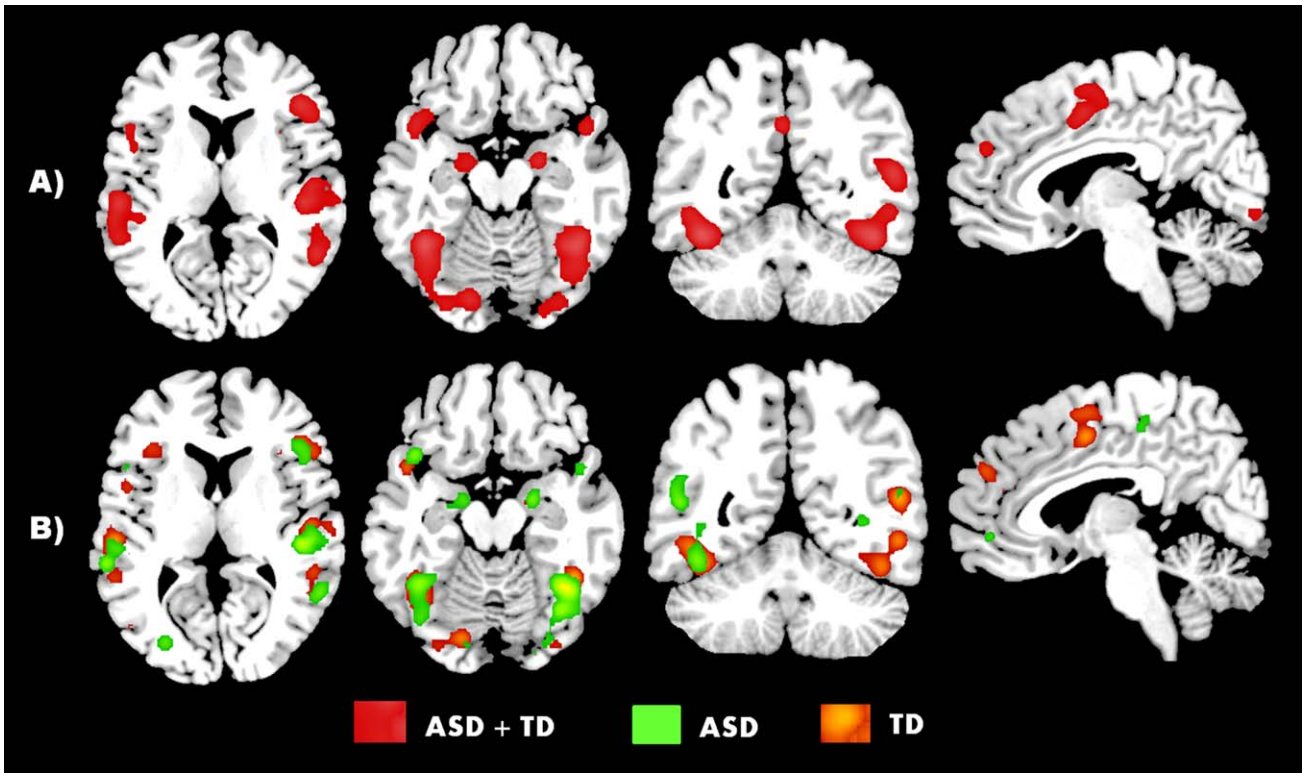

Figure 2.
ALE estimation of social brain activity across ASD, TD, and ASD and TD participants combined ($p < 0.05$, FDR cluster-forming threshold). Activity is seen in regions, such as the MPFC, bilateral STG, posterior cingulate/precuneus, fusiform gyrus, and bilateral inferior frontal gyrus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

cerebellum, left insula, left anterior cingulate, thalamus, bilateral cingulate, right MFG, and left IFG, during face-processing social tasks. Nonface social tasks, on the other hand, elicited reduced activity in ASD centered within the left precentral gyrus, STG, IFG, MTG, angular gyrus, cerebellum, IPL, right IFG, lingual gyrus, and MTG. The ASD participants showed greater activity, relative to TD, in the left parahippocampal gyrus during face processing, and greater activity in the following regions during non-face-processing tasks: left IFG, STG, postcentral gyrus, precentral gyrus, MPFC, MTG, ITG, right insula, IFG, and MFG tasks. These results are summarized in Table VII and Figure 4.

Surface-Based Morphometry Using Social Brain Mask

Application of the social brain mask, derived from ALE meta-analysis of fMRI studies, to empirical structural MRI data collected from 115 participants revealed significant morphological changes (cortical surface area, and thickness) in several social brain areas. Cortical surface area was found to be decreased in ASD participants in the superior temporal cortex and right insula relative to total-intracranial volume (Fig. 5). The effect within the superior temporal cortex was strongly influenced, but not fully explained by age. Analyses of cortical thickness revealed significant increases in thickness in individuals with ASD in the left pars opercularis aspect of the IFG relative to age, and to mean thickness of the left hemisphere. Interactions examining all 3 terms together revealed that the thickness of the left pars opercularis decreases in individuals with ASD as a function of age and as a function of the mean-thickness of the right hemisphere combined. A similar effect was also noticed in the right fusiform gyrus, with group differences heavily influenced by the interactions between age and mean thickness of the right hemisphere. Finally, qualitative examination of previous results from surface-based [Libero et al., 2014] and voxel-based [DeRamus and Kana, 2014] morphometry studies of ASD found several regions that overlap as well as differ with the findings of the current study.

DISCUSSION

This study attempted to consolidate the anatomy and function of the social brain in ASD using a comprehensive

TABLE V. ALE cluster values for ASD > TD between-group analysis

Brain region	Gyrus/sulcus	BA	Hem	Site of maximum ALE			Volume[a] (mm^3)	Maximum ALE value
				x	*y*	*z*		
ASD>TD								
Frontal	Inferior frontal	9	Left	−54	20	18	1232	0.02323516
Parietal	Postcentral	3	Left	−40	−26	58	968	0.013614106
Parietal	Inferior parietal	40	Left	−50	−26	50	968	0.011815298
Temporal	Superior temporal	22	Left	−48	−32	2	856	0.015697075
Limbic	Amygdala		Left	−22	−4	−26	752	0.014984485
Frontal	Precentral	4	Left	−30	−14	66	592	0.01119461
Frontal	Inferior frontal	9	Right	38	14	24	496	0.013928136
Sublobar	Insula	13	Right	40	22	12	488	0.013267966
Frontal	Middle frontal	47	Right	38	40	−14	480	0.013834674
Frontal	Precentral	6	Left	−34	4	34	480	0.013832372
Frontal	Medial frontal	6	Left	−2	5	60	480	0.013830137

Note. Minimum cluster size based on FDR correction = 312; permutation equilibrium = 11.
[a]Repetition of same cluster volumes indicates that these peaks were all within the same cluster.

meta-analysis of fMRI studies coupled with cortical morphology data from an empirical structural MRI study. The main findings point to several, but not all, regions of the social brain showing anatomical and functional alterations in ASD participants. Meta-analysis of ASD and TD groups combined resulted in an ALE map consisting of ROIs that highly overlap with areas of the social brain. These regions are the right cingulate cortex, left MFG, left postcentral gyrus, and bilateral: insula, FFA, amygdala, middle temporal gyrus, and precuneus. Specific social processes including ToM (TPJ, MPFC, PCC), emotional and moral processing (insula, vmPFC, amygdala), processing human faces and actions (FFA, STG, TPJ, premotor/mirror neurons), and social reasoning and self-reflection (MPFC,

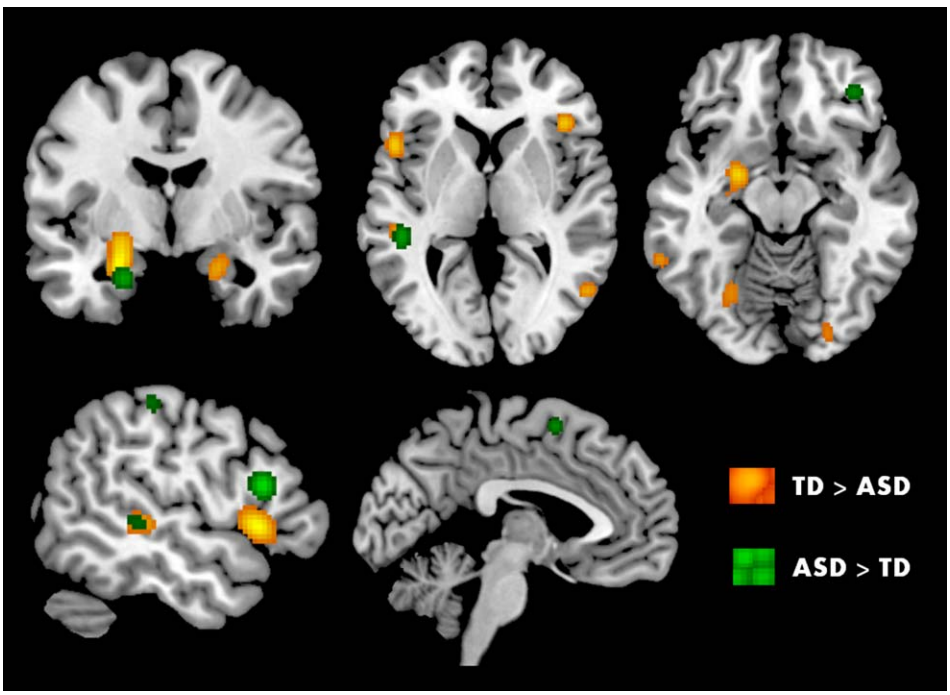

Figure 3.
ALE analysis for TD > ASD (orange) and ASD > TD (green) group differences across studies: ($p < 0.05$, FDR cluster-forming threshold). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE VI. ALE cluster values for TD>ASD between-group analysis

Brain region	Gyrus	BA	Hem	Site of maximum ALE			Volume[a] (mm^3)	Maximum ALE value
				x	*y*	*z*		
TD>ASD								
Limbic	Amygdala		Left	−24	−4	−20	2656	0.02320312
Limbic	Hippocampus		Left	−30	−14	−16	2656	0.013125481
Frontal	Precentral	44	Left	−52	18	0	1640	0.023291802
Posterior	Declive		Left	−26	−70	−16	1464	0.017044175
Occipital	Fusiform	19	Left	−26	−64	−8	1464	0.013665032
Limbic	Parahippocampal		Right	22	−4	−22	1096	0.014839961
Temporal	Superior temporal	22	Left	−52	−30	2	832	0.015007527
Frontal	Inferior frontal	13	Right	42	28	4	816	0.018335775
Occipital	Fusiform	19	Right	24	−88	−8	784	0.013432466
Posterior	Declive		Right	26	−88	−18	784	0.01089274
Limbic	Cingulate	31	Left	−24	−42	34	664	0.015882928
Parietal	Inferior parietal	40	Left	−32	−46	40	664	0.014318956
Temporal	Middle temporal	37	Right	54	−64	6	496	0.01714673
Temporal	Middle temporal	37	Left	−64	−48	−10	424	0.014566092
Frontal	Inferior frontal	47	Left	−32	14	−22	408	0.015064342

Note. Minimum cluster size based on FDR correction = 376; permutation equilibrium = 16.
[a]Repetition of same cluster volumes indicates that these peaks were all within the same cluster.

precuneus/PCC) are found to be mediated by activity in these regions [Adolphs, 2009; Fletcher et al., 1995; Gallagher and Frith, 2003; Iacoboni and Dapretto, 2006; Oberman and Ramachandran, 2007; Pelphrey and Carter, 2008; Ruby and Decety, 2003; Saxe and Kanwisher, 2003; Vogeley et al., 2001]. Notably, some moderate patterns emerged regarding the clusters identified and their contributing studies (Table II). Broadly, the largest clusters (e.g., first) are less differentiated and appear to be related to more general social cognition as these experimental paradigms involve face processing, theory-of-mind, self vs other, and imitation. However, smaller clusters, such as the last cluster in the table, appear more function specific. For example, the smallest cluster in the left parietal (precuneus) is related to social processing or social judgment (e.g., gaze and face processing).

When the meta-analysis was applied to each group (ASD, TD) separately, significant clusters of activity were seen common to both groups in left FFA, right insula, right MPFC, bilateral IFG, and STG. Within-group activation patterns suggest similar recruitment of social brain areas in ASD and TD groups. It should also be noted that there were some social brain area activity unique to each group; right FFA and left insula in ASD group, and MPFC, right cingulate, and precentral gyrus in TD group.

Group difference results indicate underactivity in ASD participants in several social brain areas, such as the amygdala, STG, FFA, and cingulate cortex. It should be noted that dysfunction of all these regions have been proposed by previous neuroimaging studies as potential neural markers of autism. For instance, lower level of amygdala activation has been found to play a significant role in social and emotional processing in autism [Baron-Cohen et al., 2000; Dalton et al., 2005a; Kliemann et al., 2013; Zalla and Sperduti, 2013]. Reduced cingulate activation during one's own decision (self-response) while playing a social exchange game has been found to predict ASD symptom severity [Chiu et al., 2008]. It has been suggested that developmental differences in the amygdala, and possibly other limbic areas such as the cingulate, could have a cascading effect on cortical areas that mediate areas related to social perception (e.g., FFA) [Baron-Cohen et al., 2000; Schultz, 2005]. Dysfunction of regions, such as the STG [Kaiser et al., 2010] and FFA [Spencer et al., 2011] has been proposed by recent neuroimaging studies as potential neuroendophenotypes of autism. The IFG, especially BA44 (pars opercularis aspect of IFG) was another area of underactivation found in ASD participants. Several functional [Dapretto et al., 2006; Oberman et al., 2005] and anatomical [Hadjikhani et al., 2009] abnormalities have been reported in the IFG in autism by previous studies. Thus, the group difference findings from this study revealed reduced activity in important nodes of the social brain in ASD participants.

It is possible that the alterations in brain response to different social cognition tasks in ASD individuals may underlie anatomical differences. An important and novel aspect of this study involves relating the functional MRI results from the meta-analysis to neuroanatomy in a relatively large empirical dataset. Surface-based Morphometry analysis of structural MRI data using the social brain mask (created based on the results of our ALE meta-analysis) showed reduced cortical surface area in right insula, left STG, and FFA in ASD participants, relative to TD controls.

TABLE VII. ALE clusters of between-group comparisons for face-processing vs non-face-processing tasks

Brain region	Gyrus/sulcus	BA	Hem	Site of maximum ALE			Volume[a] (mm^3)	Maximum ALE value
				x	*y*	*z*		
Face tasks:								
TD>ASD[b]								
Limbic	Inferior frontal	34	Left	−22	−2	−16	2096	0.020085309
Limbic	PHG		Right	22	−4	−22	1888	0.014839509
Occipital	Fusiform	19	Left	−26	−64	−8	1056	0.013205927
Cerebellum	Declive		Left	−34	−66	−18	1056	0.009973204
Cerebellum	Anterior lobe		Left	−36	−56	−30	696	0.011946438
Frontal	Insula	13	Left	−28	−34	28	480	0.015424337
Frontal	ACC	25	Left	2	18	−16	456	0.015806857
Frontal	ACC	24	Left	−8	26	−12	456	0.015807344
Limbic	Cingulate	31	Right	4	−38	32	456	0.015403693
Limbic	Cingulate	31	Left	−24	−42	34	456	0.015403725
Thalamic	Thalamus		Left	−4	−22	10	424	0.011637608
Limbic	Cingulate	24	Left	0	30	16	408	0.013570925
Frontal	IFG	45	Left	−58	20	18	392	0.012095158
Frontal	MFG	32	Right	2	44	−10	360	0.011654614
ASD>TD[c]								
Limbic	PHG	34	Left	−20	0	−26	384	0.008797275
Nonface tasks:								
TD > ASD[d]								
Frontal	Precentral	44	Left	−52	16	2	1544	0.018760668
Temporal	STG	22	Left	−52	−30	2	1472	0.015001407
Frontal	IFG	47	Left	−32	14	−22	736	0.014999792
Temporal	MTG	37	Left	−64	−48	−10	736	0.01456575
Limbic	Hippocampus		Left	−30	−14	−16	488	0.012515563
Parietal	Angular gyrus	39	Left	−54	−60	40	488	0.015507407
Frontal	IFG	13	Right	30	12	−18	480	0.013494215
Cerebellum	Declive		Left	−26	−70	−17	480	0.014803587
Occipital	Lingual gyrus	18	Right	24	−90	−8	480	0.011711578
Temporal	STG	38	Left	−44	10	−24	448	0.01222351
Temporal	MTG	37	Right	52	−64	6	440	0.014093696
Frontal	IFG	13	Right	42	26	4	408	0.012589583
Parietal	IPL	40	Left	−32	−46	40	392	0.013886107
ASD>TD[e]								
Frontal	IFG	44	Left	−54	20	16	912	0.019449683
Temporal	STG	22	Left	−48	−32	2	856	0.015597242
Frontal	IFG	13	Right	40	22	12	504	0.013254493
Parietal	Postcentral	3	Left	−40	−26	58	504	0.013563364
Frontal	IFG	9	Right	38	14	24	496	0.013926981
Frontal	MFG	47	Right	38	40	−14	480	0.013834672
Frontal	Precentral	6	Left	−34	3	34	480	0.013830137
Frontal	MPFC	6	Left	−2	5	60	480	0.013830137
Temporal	MTG	37	Left	−58	−69	12	384	0.013830137
Temporal	ITG	37	Left	−62	−65	−8	344	0.013830137

[a]Repetition of same cluster volumes indicates that these peaks were all within the same cluster
[b]Minimum cluster size based on FDR correction = 360; permutation equilibrium = 20.
[c]Minimum cluster size based on FDR correction = 200; permutation equilibrium = 19.
[d]Minimum cluster size based on FDR correction = 384; permutation equilibrium = 41.
[e]Minimum cluster size based on FDR correction = 288; permutation equilibrium = 11.
MFG = middle frontal gyrus, MPFC = medial prefrontal cortex, MTG = middle temporal gyrus, IFG = inferior frontal gyrus, SFG = superior frontal gyrus, STG = superior temporal gyrus, ITG = inferior temporal gyrus, MOG = middle occipital gyrus, IPL = inferior parietal lobule, PHG = parahippocampal gyrus.

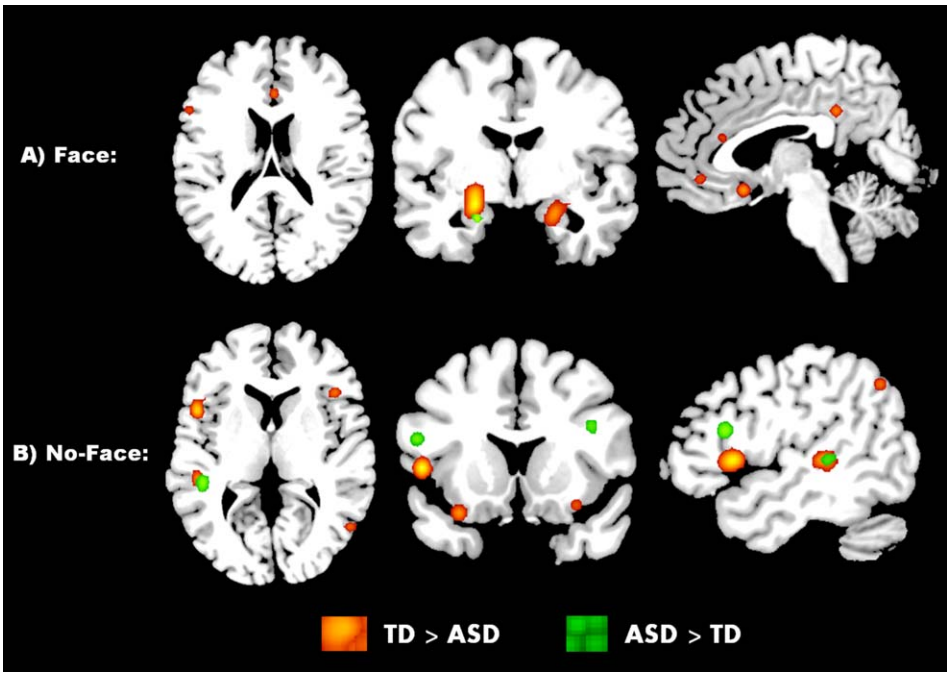

Figure 4.

Between-group differences in social task requiring face processing (A), and social tasks that do not require face processing (B). TD > ASD (orange), ASD > TD (green). All areas $p < 0.05$, FDR cluster-forming threshold. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

It should be noted that these regions were also found to show hypoactivity in ASD participants in the meta-analysis, suggesting an anatomical basis to some of the functional differences. Reduced sulcal depth [Dierker et al., 2013], cortical volume [Kosaka et al., 2010], and functional activation [Dimartino et al., 2009], as well as connectivity [Ebisch et al., 2011; Kana et al., 2007; Paakki et al., 2010] in the insula have been reported previously in the ASD literature. The insula is also considered as the hub of the "salience network," integrating external stimuli with self-perceptions and emotional states, dysfunction of which could relate to many of the behavioral symptoms of ASD [Silani et al., 2008; Uddin and Menon, 2009]. Alterations in cortical morphological features have also been reported in the STG and FFA in individuals with ASD [Boddaert et al., 2004; Dziobek et al., 2010; Ecker et al., 2010; Gervais et al., 2004; Hadjikhani et al., 2006; Jiao et al., 2010; McAlonan et al., 2005]. The frequency and consistency of functional and morphological abnormalities found in STG and FFA suggest a strong role of these regions in the pathobiology of ASD.

One region where we found an increase in cortical thickness in ASD was the IFG. While this finding is consistent with a recent meta-analysis of gray matter abnormalities in ASD [Via et al., 2011], it is in contrast with some previous findings of smaller gray matter volume in ASD [Dierker et al., 2013; Hadjikhani et al., 2006; Kosaka et al., 2010; Yamasaki et al., 2010]. It is possible that such differences in findings may reflect methodological differences, such as not including age and total intracranial metrics as factors in the analysis model, or the focus of studies on a specific developmental window (i.e., 18–30 years). Considering the developmental differences in total intracranial volume in ASD [Courchesne et al., 2010; Schumann et al., 2009], age can play a significant factor in determining cortical differences. In this context, it should also be noted that the folding patterns within the IFG and insula may be altered in ASD [Nordahl et al., 2007], which could potentially affect the way morphometric data are interpreted in autism.

Qualitative examination of previous results from voxel-based ALE meta-data [DeRamus & Kana, 2014; see Fig. 6) and whole-brain surface-based morphometry study of ASD [Libero et al., 2014] found overlap with the social brain ALE analysis results in the LIFG region reported in Libero et al. [2014], but also different results in the left middle temporal, and right fusiform and insula. There was little apparent overlap with the VBM meta-meta data (Supporting Information, Fig. 1). This divergence could be due to a number of factors, most of which are likely related to methodology and developmental level of the participants. Methodologically, Libero et al. [2014] used a whole-brain Monte Carlo correction for reporting the

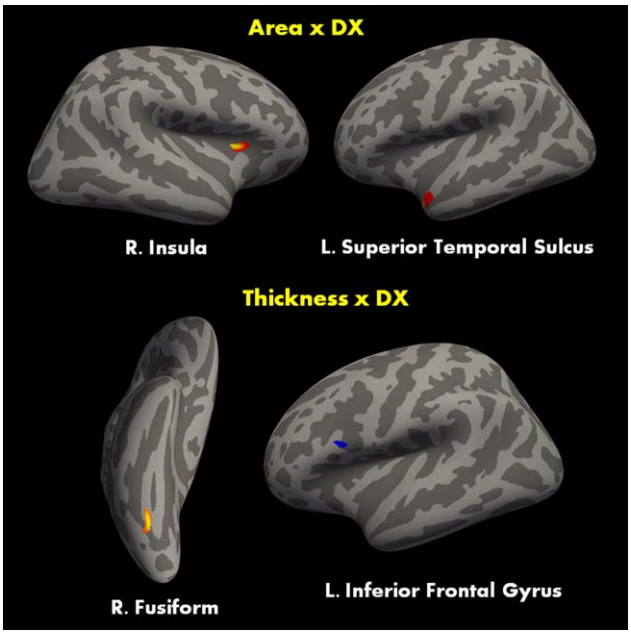

Figure 5.

Group differences in surface area (top) and cortical thickness (bottom) between a sample of T1 images of ASD and TD participants within social brain ROIs computed from the ALE mask. Red denotes decrease ASD and blue denotes increases in ASD. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

results. In contrast, the ALE social brain mask analysis is Monte Carlo corrected at the level of the mask (red regions in Fig. 2 and yellow regions in Fig. 6), and metrics of age and total intracranial volume (TICV) are centered at the mean. Voxel-based morphometry (VBM) can be used to measure grey or white matter concentration (proportion of matter type within a region) or volume (weighting voxel intensity by the Jacobian determinant) [Mechelli et al., 2005], both of which calculate measures differently compared to surface-based approaches (see Greve [2011] for a brief review of both techniques). With regard to development, there is a large amount of literature describing the effects of age on cortical metrics [Giedd et al., 1999] and how these developmental trajectories may be altered in ASD during development [Schumann et al., 2010; Wallace et al., 2010]. However, the cross-sectional nature and relatively large age-range in ALE studies like the current one limits the ability to pinpoint and interpret what stages of development are associated with significant morphological changes in the cortex.

One of the most widely studied areas of social cognition in autism is face processing, with evidence supporting abnormalities emerging from behavioral, neuroimaging, and eye-tracking studies [e.g., Corbett et al., 2014; Sasson and Touchstone, 2014; Yucel et al., 2014]. ALE maps for face processing tasks suggest that ASD participants, relative to TD, showed reduced activity in FFA, cingulate cortex, insula, and parahippocampus. In contrast, the ASD participants showed increased activity only in the left parahippocampal gyrus. These results underscore altered recruitment of core areas during face processing in individuals with ASD, as evidenced from numerous fMRI studies. Activation of FFA along with other social brain areas (cingulate, insula) in TD participants may suggest richer and more meaningful face processing in them. Understanding the effects of face versus non-face processing is important, particularly in the context of how faces are perceived in ASD: configural or featural. A number of studies of face processing in ASD suggest differences in activation and gaze/fixation preferences between TD and ASD individuals. Preference in eye fixation significantly affects the former, and some studies controlling for fixation [Hadjikhani et al., 2004] or manipulating familiarity [Pierce and Redcay, 2008] suggest that a difference in perceptual strategy in ASD. Studies of social cognition, especially neuroimaging studies, should control for perceptual preferences in order to improve the reliability of findings.

Notably, meta-analyses have the inherent publication bias and suffer the "file drawer" effect such that only studies with significant findings and thus published, not those with null findings, are included in the meta-analysis. Although the present ALE is also victim of the file drawer effect, it is more difficult to estimate the effect of publication bias since ALE is a function-location meta-analysis, but not effect size meta-analysis. Prior effect size meta-analyses of neuroimaging studies have estimated publication bias [Jennings and Van Horn, 2012]; however, further investigation is needed to determine the scientific method for estimating the bias in ALE. Additionally, although the areas identified herein appear to be related to social cognition, it should be noted that the function of these areas may not be exclusive to social cognition. For example, the FFA also responds to many visual stimuli not only social stimuli such as faces [Zachariou et al., 2015]. Further, it is possible that areas such as the motor, visual, or auditory cortex could play no role in social cognition but still be active in studies of social cognition due to requirements of tasks or presentation of stimuli that are inadequately controlled (e.g., button presses, on/off visual or auditory stimuli). Last, there were a few similar areas found in both the ASD > TD and TD >ASD analyses (e.g., left STG), which appears counterintuitive. It is important to highlight that the coordinates found with ALE analyses may be slightly different because studies entered for the analyses differ. For example, a study reports ASD > TD results and did not have any TD > ASD results; in such case, only the ASD > TD coordinates will be entered in the ALE. In this case, however, it appears that the greater activity (ASD > TD) in ASD participants in the STG is related to more general, even positive, emotional processing of faces [Dalton et al., 2005a; Williams et al., 2006]; whereas, less activity in ASD participants in the STG is related to

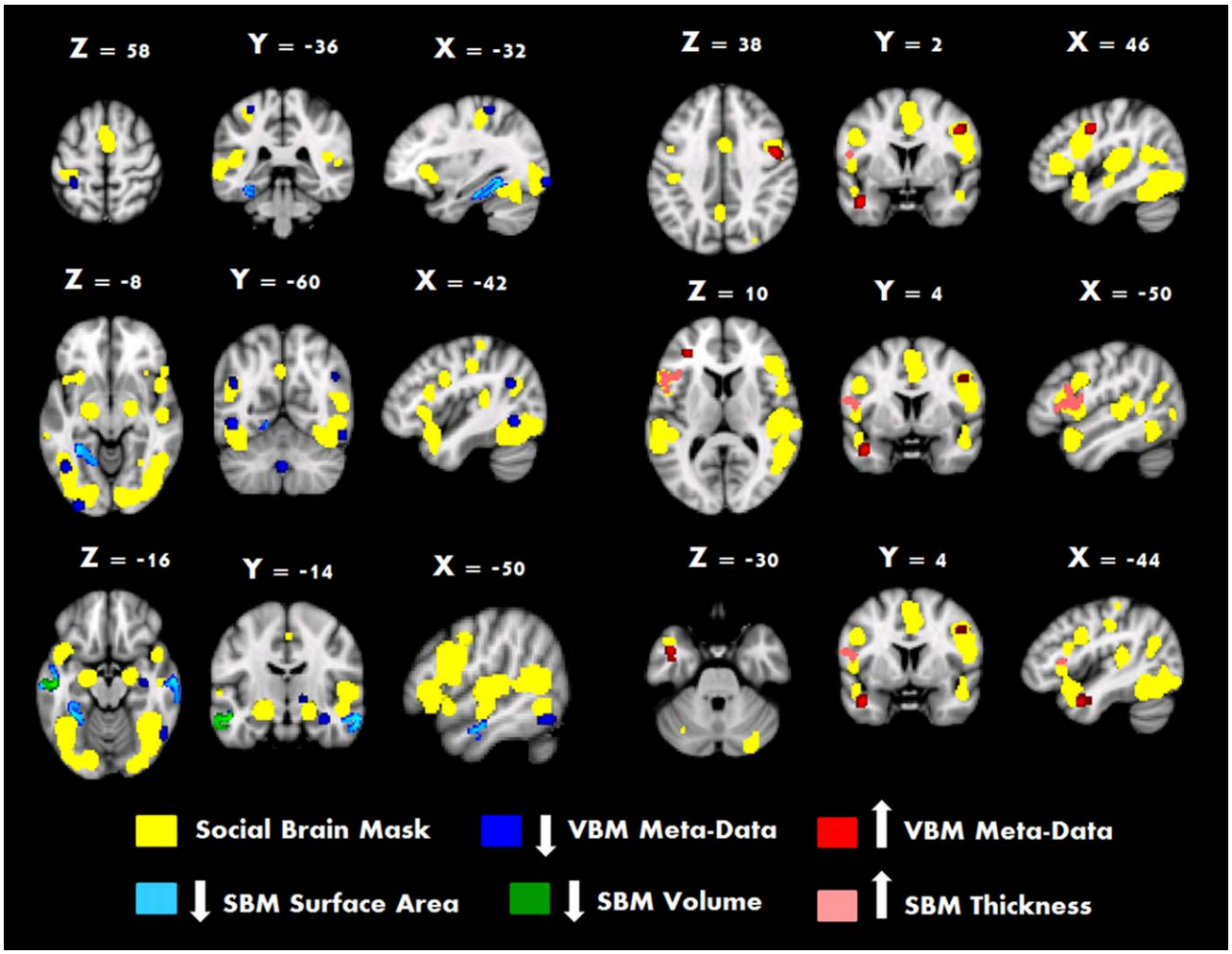

Figure 6.

The social brain mask produced across theory of mind task type across both TD and ASD participants is displayed as a yellow overlay. Results of the surface based analysis on the mask found regions of decreased surface area (dark blue), volume (green) and increased thickness (pink). This is displayed in conjunction with ALE computed VBM meta-data displaying decreased (dark blue) and increased (red) volume in ASD. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

processing of threatening (the "other" vs self, fear, trustworthiness) face processing [Hadjikhani et al., 2009; Pinkham et al., 2008].

In summary, the results of this ALE meta-analysis and cortical morphometry study validate the findings of many previous studies on activation, connectivity, and morphology in the social brain in individuals with ASD. Among the different social brain areas, insula, FFA, STG, and IFG seem to differentiate autism from control participants at functional and anatomical levels, suggesting alterations in these regions as potential neural markers of ASD. It is important to note that this fMRI meta-analysis and empirical structural MRI data provide a somewhat converging picture of multilevel abnormality in social cognition in autism. With continuing efforts toward data-sharing and classification analyses within the field of ASD research, meta-data approaches could be very useful in developing targets for multilevel neuroimaging models to assist in refining biomarkers for ASD, and develop relationships among function, structure, and connectivity.

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