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Autism is characterized by dorsal anterior cingulate hyperactivation during social target detection

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Though the functional neural correlates of impaired cognitive control and social dysfunction in autism spectrum disorders (ASD) have been delineated, brain regions implicated in poor cognitive control of social information is a novel area of autism research. We recently reported in a non-clinical sample that detection of 'social oddball' targets activated a portion of the dorsal anterior cingulate gyrus and the supracalcarine cortex (Dichter, Felder, Bodfish, Sikich, and Belger, 2009). In the present investigation, we report functional magnetic resonance imaging results from individuals with ASD who completed the same social oddball task. Between-group comparisons revealed generally greater activation in the ASD group to both social and non-social targets. When responses to social and non-social targets were contrasted, the ASD group showed relatively greater activation in the right and middle inferior frontal gyri and a region in dorsomedial prefrontal cortex that abuts the dorsal anterior cingulate (Brodmann's Area 32). Further, dorsal anterior cingulate activation to social targets predicted the severity of social impairments in a subset of the ASD sample. These data suggest that the dorsal anterior cingulate mediates social target detection in neurotypical individuals and is implicated in deficits of cognitive control of social information in ASD.

Keywords: autism; fMRI; target detection; face processing; cingulate gyrus

INTRODUCTION

The purpose of this study was to examine patterns of regional brain activation in individuals with autism spectrum disorders (ASD) during a target detection task that involved both social and non-social components. Whereas previous studies have demonstrated that individuals with ASD show anomalous brain activation during target detection tasks (Gomot *et al.*, 2008; Shafritz *et al.*, 2008), these studies used tasks that involved non-social information. However, the social cognitive deficits that are the *sine qua non* of autism should produce a unique pattern of responses during tasks that press for cognitive control of social information. Such tasks would represent a reasonable facsimile of everyday social situations wherein successful adaptation requires the identification of relevant and irrelevant social cues as well as the differential processing of social and non-social sources of information.

We recently reported the neural correlates of social target detection in a non-clinical sample via a novel 'social oddball' functional magnetic resonance imaging (fMRI) task that allows for the comparison of responses to infrequent social (i.e. faces) and non-social (i.e. geometric shapes) target events (Dichter *et al.*, 2009). As in classic oddball tasks, comparing responses to target and novel stimuli allows for the isolation of processes unique to events requiring a task-dependent shift in pre-potent behavioral responses (MacDonald *et al.*, 2000; Botvinick *et al.*, 2001; Barber and Carter, 2005). Unique to this task, however, is the prospect of comparing responses to social and non-social target events (both relative to novel events) to isolate brain regions that mediate cognitive control of social information. Results from this non-clinical sample indicated that shape and face targets activated the post-central gyrus, the anterior and posterior cingulate gyri and the right midfrontal gyrus, relative to non-target novel events. Face targets additionally activated the thalamus, fusiform and temporooccipital cortex, lingual gyrus and paracingulate gyrus. A direct comparison of face and shape targets, each relative to novel events, revealed that the supracalcarine cortex and a portion of the dorsal anterior cingulate gyrus

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(dACC; Brodmann's Area 32) were preferentially activated to face targets. We interpreted the greater activation of the supracalcarine cortex to be due to its role in face-processing networks rather than mediation of target detection *per se*. However, because the dACC is a component of a cognitive control brain network (e.g. MacDonald *et al*., 2000), we hypothesized that this region may critically mediate social target detection (Dichter *et al*., 2009).

The focus of the present investigation was to evaluate differential activation of cognitive control brain regions by social *vs* non-social stimuli in ASD via this same social target detection task. Primary hypotheses focused on differential functioning of cognitive control brain regions while processing social targets, rather than functioning of social brain regions *per se*. Of central interest was the contrast of responses to face and shape targets to evaluate whether autism is characterized by anomalous functioning of the dACC during social target detection.

One autism study to date has addressed cognitive control while processing social information, but utilized a task that required inhibition of social versus non-social interference (Dichter and Belger, 2007). Results suggested relatively decreased functioning of cognitive control brain regions in ASD in the presence of social stimuli. Briefly, participants indicated the direction of centrally-presented arrow (i.e. non-social) or gaze (i.e. social) stimuli in the presence of similar congruent or incongruent flanking stimuli. In the ASD group, incongruent social stimuli elicited hypoactivation in prefrontal structures that mediate cognitive control, namely the inferior and middle frontal gyri and the anterior cingulate, and the intraparietal sulcus. However, it was unclear whether results reflected differential processing of the central or peripheral stimuli in the task array. In other words, in the ASD group, activation differences may have been due to impaired processing of the central social stimuli, or the relative lack of interference from the peripheral social stimuli. The oddball target detection task employed in the present study overcomes this potential confound by presenting stimuli in isolation, allowing for a more direct test of differential responses to attended social and non-social target stimuli.

In the present study, we compared results from neurotypical participants reported in Dichter *et al*. (2009) to an ASD sample. Primary hypotheses concerned differential neural recruitment to target faces because (i) face perception has been called the 'lower-level subprocess of social cognition' (Brothers, 1990), (ii) face perception tasks have been widely employed in studies of social perception and social cognition in non-clinical contexts (e.g. Allison *et al*., 1994; Kanwisher, McDermott, and Chun, 1997) and in ASD samples (e.g. Aylward *et al*., 2004; Hadjikhani *et al*., 2004; Pierce *et al*., 2004; Dalton *et al*., 2005; Schultz, 2005) and (iii) previous findings indicate anomalous recruitment of cognitive control brain regions in social contexts in autism (Dichter and Belger, 2007).

Based on prior neuropsychological evidence of deficits in autism on tasks requiring cognitive control (see Hill, 2004, for a review), we hypothesized that the ASD group would demonstrate relatively less accuracy in response to target events than their neurotypical counterparts. Based on previous psychophysiological (Gomot *et al*., 2006) and neuroimaging (Shafritz *et al*., 2008) evidence, we hypothesized that we would observe diagnostic group differences in fMRI responses to both social and non-social target events in prefrontal regions that mediate cognitive control. We further hypothesized diagnostic group differences in response to social targets specifically would be localized to a region shown to mediate these responses in a nonclinical sample (Dichter *et al*., 2009), i.e. the dACC. Finally, we hypothesized linkages between recruitment of dACC in the ASD sample and the severity of autism symptoms.

METHODS

Participants

The participants for this study included 15 adults (1 female) with ASD and a control group matched on gender, age and IQ. The average age of the ASD group was 23.3 ± 11.1 years old, and 13 were right-handed. The control group included 19 (1 female; 18 right-handed) adults (28 ± 7.9 years old) recruited from the community and screened against clinically significant psychiatric symptoms with the Symptom Checklist-90-Revised (SCL-90; Derrogatis, 1977; Derogatis, 2000). Analyses of fMRI data from control participants have been previously reported (Dichter *et al*., 2009). Exclusion criteria included a prior history of gestational age <34 weeks, birth weight <2000 g, intraventricular hemorrhage, history of known medical condition associated with autism including Fragile X syndrome, tuberous sclerosis, neurofibromatosis, phenylketonuria, epilepsy and gross brain injury, full scale intelligence score ≥ 75 (with the exception of one participant with a full scale score of 68 who was included after demonstrating task proficiency during screening sessions) or MRI contraindications (e.g. presence of metal in body) as assessed by MRI safety questionnaire.

Autism diagnoses were based on a history of clinical diagnosis of autism informed by the Autism Diagnostic Interview-Revised (ADI-R, Lord, Rutter, and Le Couteur, 1994), a parent interview, or proband assessment via the Autism Diagnostic Observation Schedule (ADOS-G, Lord *et al*., 2000). Ten participants received the ADOS-G and five the ADI-R. Standard clinical ADOS-G and ADI-R algorithm cutoffs were employed. All participants consented to a protocol approved by the local Human Investigations Committees at both UNC-Chapel Hill and Duke University Medical Centers and were paid $50 for completing the imaging portion of the study. All participants had normal or corrected-to-normal vision and completed a mock scan session prior to fMRI sessions to become familiar with the fMRI task and acclimated to the scanner environment.

Table 1 Means (s.d.) for the Weschler Abbreviated Scale of Intelligence and the Wisconsin Card Sorting Test

	Control group ($n = 19$)	ASD group ($n = 9$ for the WASI, $n = 15$ for the WCST)	*P*-value
WASI			
Verbal	113 (7.7)	101.7 (26.6)	0.07
Performance	113 (14.5)	104 (19.5)	0.17
Full	114 (9.4)	102.8 (24.0)	0.08
WCST			
Persev. Errors	6.2 (3.2)	12.73 (11.0)	0.02
Non-Persev. Errors	7.1 (5.8)	16.0 (14.3)	0.02
Categories completed	5.9 (0.2)	5.1 (1.5)	0.02

WASI, Weschler Abbreviated Scale of Intelligence (Weschler, 1999); WCST, Wisconsin Card Sorting Test, computerized version (Heaton, 1981).
Six participants in the ASD group completed IQ tests other than the WASI: three completed the Leiter International Performance Scale-Revised (Roid and Miller, 1997) and received scores of 82, 105 and 121; one participant completed the Kaufman Brief Intelligence Test (K-BIT, Kaufman and Kaufman, 1990) and received a verbal score of 120 and a non-verbal score of 110; one participant completed the Reynolds Intellectual Assessment Scales (Reynolds and Kamphaus, 2003) and received a verbal score of 118 and a non-verbal score of 93; one participants completed the Wechsler Intelligence Scale for Children (WISC, Wechsler, 1991) and received a non-verbal score of 115 and a verbal score of 115.

Table 1 lists the sample characteristics on tests of intelligence and executive function, and illustrates that the control group and the sub-sample of autism participants who received the Weschler Abbreviated Scale of Intelligence (Weschler, 1999) did not differ significantly on verbal or performance measures of intelligence. Further, groups differed on measures of executive function as indexed by subscales of the Wisconsin Card Sorting Test (Heaton, 1981). Table 2 indicates the SCL-90-R (Derogatis, 2000) sub-scale scores of control participants and illustrates that, as a whole, the control group did not report significant symptoms of distress associated with psychopathology. It also indicates mean autism symptoms in the domains of repetitive behaviors and social responsiveness, as well as ADOS-G and ADI-R scores from ASD participants, and illustrates that this high-functioning sample demonstrated mild-to-moderate levels of autism symptomatology.

Table 2 Symptom Checklist-90-Revised (SCL-90-R, Derogatis, 2000) *t*-scores for neurotypical participants ($n = 19$) and symptom scores of ASD participants (n = 15)

Subscale	*t*-score (s.d.)
Scores for neurotypical participants	
Somatization	48.9 (9.9)
Obsessive–Compulsive	54.2 (11.7)
Interpersonal sensitivity	51.8 (11.0)
Depression	52 (14.2)
Anxiety	51.8 (12.8)
Anger–hostility	47.7 (9.8)
Phobic Anxiety	49.6 (6.9)
Paranoid thought	46.7 (10.9)
Psychotism	50.5 (9.8)
General Symptom Index	50.5 (12.7)
Subscale	
Scores of ASD participants	ASD, mean (s.d.)
RBS-R[a]	
Stereotyped	2.6 (2.2)
Self-injurious	1.4 (1.5)
Compulsive	4.9 (3.1)
Ritualistic	5.1 (3.6)
Sameness	8.1 (6.8)
Restricted	3.2 (2.1)
Total	26.0 (14.9)
SRS *t*-scores[a]	
Awareness	68.4 (13.4)
Cognition	77.9 (12.4)
Communication	77.5 (12.1)
Motivation	76.7 (13.7)
Autistic mannerisms	78.1 (17.5)
Total	80.4 (13.6)
ADOS ($n = 12$)	
Communication	3.7 (1.6)
Social interaction	6.9 (3.3)
Repetitive behavior	2.1 (1.5)
ADI-R ($n = 3$)	
Communication	15 (2.6)
Social interaction	22 (2.6)
Repetitive behavior	6.7 (2.1)

[a]Data are missing for one individual.
RBS-R, Repetitive Behavior Scale, Revised. (Bodfish *et al.*, 1999); SRS, Social Responsiveness Scale (Constantino *et al.*, 2003); ADOS, Autism Diagnostic Observation Schedule-Generic (Lord *et al.*, 2000); ADI-R, Autism Diagnostic Interview-Revised (Lord *et al.*, 1994).

fMRI Task

The fMRI task is identical to that described in Dichter *et al.* (2009). Briefly, a visual target-detection task that included nine task runs was used. Each run contained 160 stimuli, presented centrally for 500 ms with an interstimulus interval (ISI) that was jittered between 1000 ms and 2500 ms, during which a fixation cross was presented. There were four stimulus categories: squares, circles, and triangle of various colors and sizes and pictures of faces with neutral expressions drawn from the highly standardized set of pictures of Ekman and Friesen series (Ekman and Friesen, 1976). Pictures were cropped below the hairline and above the bottom of the chin. At the start of each imaging run, participants were instructed both verbally and via an instructional screen (e.g. 'Targets = ●') which stimulus category would be the 'target' category on that run. Each run included three conditions: (i) frequently occurring 'Standard' stimuli that occurred on 90% of trials and that required a right-hand button press; (ii) infrequently occurring 'Novel' stimuli that occurred on 5% of trials and that required the same button press as the Standard stimuli; and (3) infrequently occurring 'Target' stimuli that occurred on 5% of trials and that required an alternative button press. Infrequent events (i.e. target and novel stimuli) were separated by a minimum of 12 s to adequately observe the hemodynamic response for each event.

Participants were instructed to respond via right-hand button box to every stimulus as quickly and accurately as possible, and to press one button for all non-target stimuli (including standards) and an alternate button for target stimuli. Runs 1, 2, 4, 5, 7 and 8 included shapes as targets (two each of circles, squares and targets), and runs 3, 6 and 9 included face targets. Immediately prior to the scanning session, participants were trained on the task. All stimuli were presented using CIGAL presentation software (Voyvodic, 1996) and displayed to participants in the scanner through magnet-compatible goggles (Resonance Technology, Inc., Northridge, CA, USA).

Imaging methods

Scanning was performed on a General Electric Health Technologies, 3 Tesla Signa Excite HD scanner system with 50 mT/m gradients (General Electric, Waukesha, Wisconsin, USA). Head movement was restricted using foam cushions and Velcro straps. An eight-channel head coil was used for parallel imaging. Sixty-eight high-resolution images were acquired using a 3D fast SPGR pulse sequence (TR = 500 ms; TE = 20 ms; FOV = 24 cm; image matrix = 256^2; voxel size = $0.9375 \times 0.9375 \times 1.9\,mm^3$) and used for co-registration with the functional data. These structural images were aligned in the near axial plane defined by the anterior and posterior commissures. Whole-brain functional images consisted of 34 slices parallel to the AC–PC plane using a BOLD-sensitive gradient-echo sequence with spiral-in k-space sampling and SENSE encoding to take advantage of the 8-channel coil, at TR of 1500 ms (TE = 27 ms; FOV = 25.6 cm; isotropic voxel size = $4\,mm^3$; SENSE factor = 2). Runs began with 4 discarded RF excitations to allow for steady state equilibrium.

Imaging data analysis

Functional data were preprocessed using FSL version 4.0.4 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford University, UK]. Timing files were converted to FSL compatible format and NIFTI image data files were generated. Preprocessing was applied in the following steps: (i) brain extraction for non-brain removal (Smith *et al*., 2004), (ii) motion correction using MCFLIRT (Smith, 2002), (iii) spatial smoothing using a Gaussian kernel of FWHM 5 mm, (iv) mean-based intensity normalization of all volumes by the same factor, and (v) high-pass filtering (Jenkinson *et al*., 2002). Functional images of each subject were co-registered to structural images in native space, and structural images were normalized into a standard stereotaxic space (Montreal Neurological Institute) for inter-subject comparison. The same transformation matrices used for structural-to-standard transformations were then used for functional-to-standard space transformations of co-registered functional images. All registrations were carried out using an intermodal registration tool (Jenkinson *et al*., 2002; Smith *et al*., 2004). Voxel-wise temporal autocorrelation was estimated and corrected using FMRIB's Improved Linear Model (Jenkinson and Smith, 2001).

Onset times of events were used to model a signal response containing a regressor for each response type, which was convolved with a double-γ function to model the hemodynamic response. Model fitting generated whole-brain images of parameter estimates and variances, representing average signal change from baseline (activation; positive regressor) and below baseline (deactivation; negative regressor). Groupwise activation and deactivation images were calculated by a mixed effects higher-level analysis using Bayesian estimation techniques, FMRIB Local Analysis of Mixed Effects (FILM, Woolrich *et al*., 2001) with conservative cluster mean threshold of $Z > 2.3$ and a cluster-corrected significance threshold of $P < 0.05$ (FLAME 1 + 2, Beckmann, Jenkinson, and Smith, 2003).

To isolate brain activation in response to the inhibition of a prepotent response set from brain activation reflecting involuntary attention or orienting to infrequent events, of primary interest were analyses that isolated brain activation to the contrast of target stimuli >novel stimuli. In other words, the 'novel' condition controlled for stimulus infrequency and thus allowed for isolation of the psychological process of interest (i.e. inhibition of a prepotent response set to respond flexibly to task-relevant rare events). This approach is consistent with methods used in classic oddball papers in the neuroimaging and ERP literatures (Kirino *et al*., 2000; Yamasaki, LaBar, and McCarthy, 2002) and the approach used in analysis of neurotypical participants from the present study (Dichter *et al*., 2009).

RESULTS

In-scanner behavioral performance

Two (Group: Autism, Neurotypical) × Four (Category: Shape Targets, Face Targets, Novels, Standards) repeated measures ANOVAs were conducted separately for accuracy (i.e. percent correct) and latency (i.e. reaction time) data, and followed by within-group and within-condition *t-tests*, uncorrected for multiple comparisons to fully illustrate any evident trends (see Figure 1).

Accuracy analyses revealed a main effect of Category, multivariate $F(3,30) = 43.32$, $P < 0.0001$, a main effect of Group, $F(1,32) = 9.70$, $P < 0.004$, and a Group × Category interaction, multivariate $F(3,30) = 6.47$, $P < 0.002$. Between-groups *t-tests* revealed that the neurotypical group was more accurate to shape targets, $P < 0.001$, and face targets, $P < 0.0009$, but not to novel or standard stimuli, $P > 0.30$. In the neurotypical group, paired *t-tests* indicated accuracy differences between all four stimulus categories (P values range from 0.01 for standards *vs* novels to <0.0001 for standards *vs* shape targets). In the ASD group, paired *t-tests* indicated no accuracy difference for novels *vs* standards, $P > 0.25$, but significant accuracy differences

between all other possible pairs of stimulus categories (P <0.002 for shape *vs* face targets and <0.0001 for all the other comparisons).

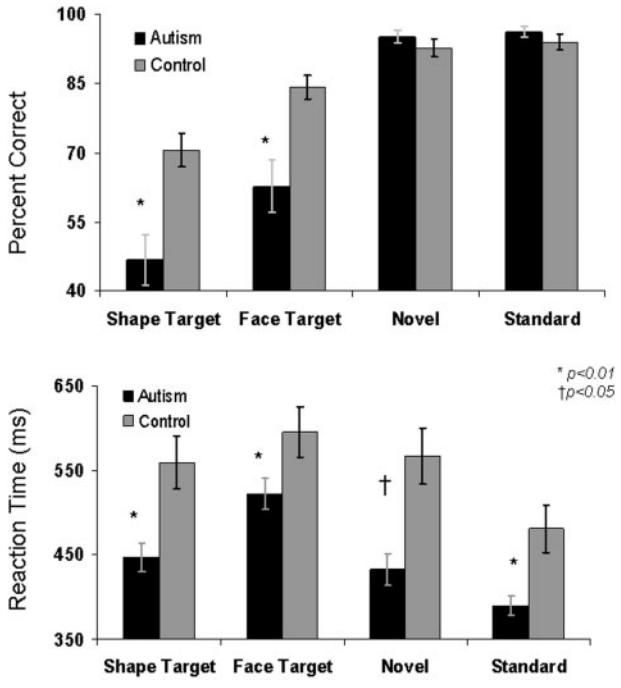

Fig. 1 Accuracy (top) and Reaction time (bottom) during the fMRI task. Errors bars represent group standard errors of the mean. Significance values are for within-condition between-groups *t*-tests.

Latency analyses revealed a main effect of Category, multivariate $F(3,30) = 14.51$, P <0.0001, a main effect of Group, $F(1,32) = 9.21$, P <0.005, but no Group X Category interaction, multivariate $F(3,30) = 0.48$, $P = 0.70$. Between-groups *t-tests* revealed that groups differed in latency to all categories (shape targets P <0.004, face targets P <0.006, novel P <0.008, and standard stimuli P <0.006).

Imaging data

Analyses of functional imaging data included accuracy and reaction time as covariates. Thus, despite the relatively lower accuracy of autism participants, all trials were included in fMRI analyses. Analyses without accuracy as a covariate but that include only epochs corresponding to correct responses yield highly similar results.

Figure 2 illustrates brain areas showing greater activation in the neurotypical group than the ASD group. The top of Figure 2 illustrates that there were no areas with relatively greater activation in the neurotypical group to the Target Shape >Novel contrast. The middle of Figure 2 illustrates that the right superior parietal lobule was the only region with relatively greater activation in the neurotypical group to the Target Faces >Novel contrast. The bottom of Figure 2 illustrates that the left frontal pole and the left superior lateral occipital cortex were the only two areas showing greater activation in the neurotypical group to the critical (Target Face–Novel) >(Target Shape–Novel) contrast.

Figure 3 depicts brain areas showing relatively greater activation in the ASD group than the neurotypical group. The top of Figure 3 illustrates that a number of brain

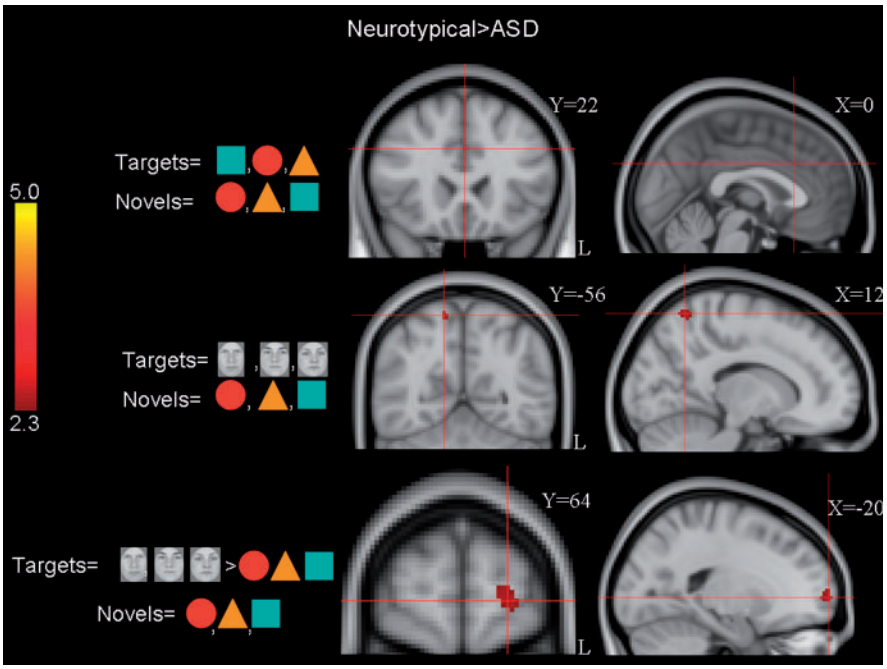

Fig. 2 Brain areas showing greater activation in neurotypical relative to ASD participants. Coordinates are in MNI space.

regions, including the anterior cingulate cortex (ACC), insula, and frontal pole showed relatively greater activation in the autism group to the Target Shape >Novel contrast. The middle of Figure 3 illustrates that a number of brain regions, including a region in dorsomedial prefrontal cortex (DMPFC) that abuts the dorsal ACC (Brodmann's Area 32), insula, and middle frontal gyrus showed relatively greater activation in the autism group to the Target Face >Novel contrast. Finally, of central interest were results of the (Target Face–Novel) >(Target Shape–Novel) contrast, which showed relatively greater activation in three brain regions in the autism group: the right middle and inferior frontal gyri and a region in DMPFC that abuts the dorsal ACC (Brodmann's Area 32) (see the bottom of Figure 3). Table 2 lists significant clusters of between-group activation differences for each contrast.

Exploratory covariate analyses assessed relations between patterns of brain activation to the central contrast of interest, namely (Target Face >Novel) >(Target Shape >Novel) in the ASD sample and algorithm scores from ADOS-G ($n = 10$). The classification of Autistic Disorder on the ADOS-G is based on algorithm scores in social and communication domains, and higher scores on each indicate relatively greater symptom severity. Figure 4 illustrates that signal intensity in the dACC (as well as another, more posterior ACC cluster and a cluster in the cuneal cortex) were significantly *inversely* related with symptoms of reciprocal social interaction as measured by the ADOS-G. In other words,

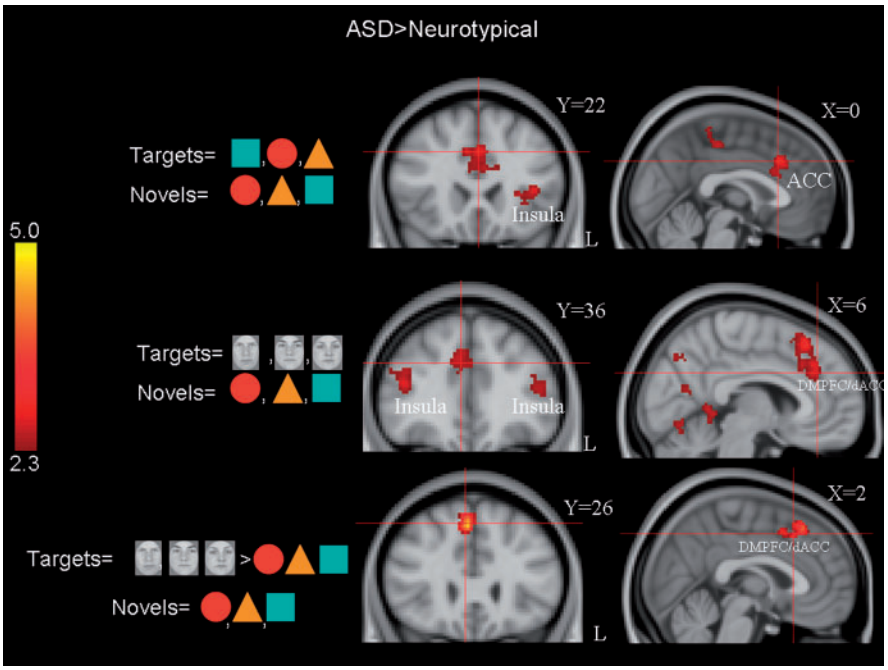

Fig. 3 Brain areas showing greater activation in ASD relative to neurotypical participants. Coordinates are in MNI space.

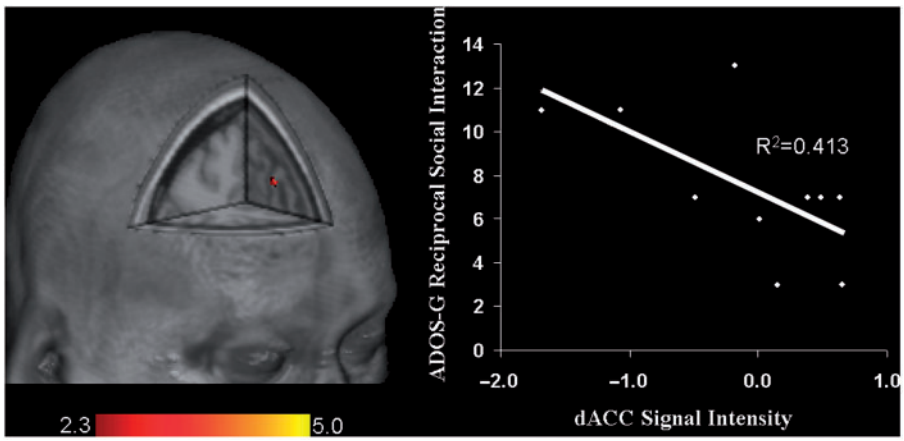

Fig. 4 Left: Relations between the magnitude of (Target Face > Novel)> (Target Shape > Novel) contrast activations in the 10 autism participants who received the ADOS-G and ADOS-G reciprocal social interaction algorithm scores. Right: Scatterplot showing individual participant signal intensity values in the dACC and ADOS-G algorithm scores.

Table 3 Regions of activation for experimental contrasts

Region	Size	Z_{max}	Coordinates		
			X	*Y*	*Z*
Neurotypical > Autism					
Target face > Novel					
Parietal lobule (superior, left)	25	2.94	−12	−56	62
(Target Shape > Novel) > (Target Face–Novel)					
Frontal gyrus (Inferior pars triangularis, left)	28	3.39	−54	32	18
Frontal gyrus (superior, left)	52	3.25	−6	26	48
Frontal orbital cortex (left)	22	2.78	−40	26	−10
(Target Face > Novel) > (Target Shape–Novel)					
Frontal pole (right)	48	2.78	18	64	4
Lateral occipital cortex (superior, right)	31	3.07	40	−76	14
Autism > Neurotypical					
Target Shape > Novel					
Amygdala (left)	30	3.01	−20	2	−18
Anterior cingulate (dorsal)	59	3.09	−4	24	28
Caudate					
Left	27	3.03	−10	4	2
Left	57	3.09	−16	−8	20
Central opercular cortex (left)	293	3.92	−56	−12	12
Cingulate gyrus					
Left	20	3.13	−12	−20	32
Left	133	3.89	−6	−24	46
Frontal gyrus (superior, left)	45	4.08	−14	4	70
Frontal orbital cortex (left)	82	3.21	−22	26	−16
Frontal pole (left)	632	4.68	−26	48	14
Heschl's gyrus (left)	70	3.27	−36	−26	4
Insular cortex (left)	879	4.8	−38	6	0
Lingual gyrusvision (right)	39	3.55	16	−46	−12
Paracingulate gyrus					
Right	35	3.79	10	52	0
Left	506	4.27	0	24	36
Precentral gyrus					
Right	47	3.38	50	2	38
Right	53	3.14	24	−18	60
Precuneous cortex					
Left	27	2.98	−48	44	10
Left	1705	4.22	−12	−56	10
Putamen (left)	36	3.21	−20	14	−4
Supplementary motor cortex	353	3.46	4	−12	50
Temporal gyrus (middle, temporooccipital, left)	192	3.73	−46	−50	10
Thalamus (left)	48	3.19	−12	−16	−4
Target Shape > Novel					
Amygdala (left)	25	2.76	−24	−8	−18
Central opercular cortex (right)	51	2.86	44	6	12
Dorsomedial prefrontal cortex (DMPFC)/anterior cingulate gyrus	27	2.88	−14	34	12
Frontal gyrus (middle)					
Right	22	2.64	44	22	28
Left	83	3.09	−44	16	36
Left	31	2.71	−36	6	48
Frontal gyrus (superior, left)	802	4.56	−4	26	54
Frontal medial cortex (left)	55	2.99	−10	56	−10
Frontal operculum cortex (left)	2169	4.69	−44	12	0
Frontal orbital cortex (right)	65	3.39	24	22	−8
Frontal pole (right)	120	3.06	40	44	12
Insular cortex (right)	132	3.28	28	14	10
Intracalcarine cortex (Right)	63	3.3	14	−68	12
Lingual gyrus					
Right	123	3.1	6	−78	−12
Right	87	3.68	20	−54	4

(continued)

Table 3 Continued

Region	Size	Z_{max}	Coordinates		
			X	*Y*	*Z*
Occipital fusiform gyrus (left)	42	2.87	−14	−78	−12
Paracingulate gyrus (left)	22	3.06	−10	46	20
Parietal lobule (superior, right)	70	2.98	34	−42	40
Post-central gyrus (left)	40	2.89	−52	−20	24
Pre-central gyrus (left)	36	2.89	−44	2	30
Precuneous cortex					
Right	250	3.95	12	−74	44
Left	347	3.66	−20	−60	14
Supramarginal gyrus (posterior)					
Left	35	3.04	−46	−46	52
Left	459	4.13	−50	−42	38
Temporal gyrus (middle, posterior, left)	193	3.48	−50	−24	−8
Thalamus (left)	223	3.51	−12	−16	0
(Target Shape > Novel) > (Target Face > Novel)					
Frontal pole (right)	48	2.78	18	64	4
Lateral occipital cortex (superior, right)	31	3.07	40	−76	14
(Target Shape > Novel) > (Target Face > Novel)					
Dorsomedial prefrontal cortex (DMPFC)/anterior cingulate gyrus (Dorsal)	52	3.25	−6	26	48
Frontal gyrus (inferior, left)	22	2.78	−40	26	−10
Frontal gyrus (middle, left)	28	3.39	−54	32	18

Note: The comparison of Neurotypical > Autism for the Target Shape > Novel contrast revealed no areas of groups differences in activation.

greater dACC activation predicted less autism symptoms in the social domain. No other relations emerged as significant.

DISCUSSION

The goal of the present investigation was to map differential recruitment of brain regions by individuals with ASD during a social target detection task. In-scanner behavioral results indicated that, within both diagnostic groups, accuracy and reaction times were decreased for both target categories, and that performance to shape targets was worse than to face targets. Further, the ASD group demonstrated faster but less accurate responses to both categories of targets than their neurotypical counterparts. Of central relevance in the present context, however, is that both groups demonstrated comparably slower and less accurate responses to target events, validating that this oddball target detection task required cognitive control in both diagnostic groups.

Imaging data from neurotypical participants in this study reported previously (Dichter *et al*., 2009) indicated that the dACC (Brodmann's Area 32) and supracalcarine cortex were preferentially activated to face relative to shape targets. Relatively greater supracalcarine cortex activation may be conceptualized within the role of this region more broadly in face processing. Preferential activation of dACC, a region that is typically implicated in standard oddball tasks, suggested that this region may play a critical role in processing cognitive control stimuli that contain social information, a finding that is consistent with conceptualizations of this region as an intermediary processing stream between ventral cortical and subcortical regions (Mayberg, 1997) and as a region that integrates the emotional and motivational relevance of stimuli with attentional functions (Mesulam, 1981; Papez, 1995).

Direct comparisons between brain activation in the neurotypical and autism groups revealed a number of interesting findings. First, as a whole, the autism group showed generally greater activation to target events of both categories than did the neurotypical group. In fact, no brain regions were relatively more active in the neurotypical group to shape targets, and the only regions showing relatively greater neurotypical activation to the face target condition were small localized clusters outside of the classic cognitive control network (i.e. the dACC, the midfrontal gyrus, the inferior frontal gyrus).

We interpret DMPFC/dACC hyperactivation to face targets to reflect the impaired cognitive control processes (specifically flexible responding to social information and the inhibition of prepotent response sets) that are generally reported to characterize individuals with autism (Hill, 2004; but see Geurts, Corbett, and Solomon, 2009 regarding inconsistencies in this literature). In other words, it may be the case that hyperactivation in ASD reflects a compensatory mechanism engaged to perform the target detection task (see also, Schmitz *et al*., 2006). Data from other disorders validate the possibility that psychopathological states may be associated with *hyper*activation of relevant

Table 4 fMRI studies that have investigated cognitive control in ASD.

Study	Sample	Medication status	Task	Post preprocessing analysis	Primary findings	Covariates in primary fMRI analyses	Task performance	Symptom covariates
Belmonte *et al*. (2003)	Six ASD (one female) six controls (one female)	All but one ASD subject were medication-free	Bilateral visual spatial attention task	GLM (SPM99)	ASD hypoactivation in left ventral occipital cortex; ASD hyperactivation in left intraparietal sulcus; variable in superior parietal lobe.	None	No group differences in accuracy or RT	None
Schmitz *et al*. (2006)	10 ASD (all male) 12 controls (all male)	All were medication-free	GO/NO-GO task (motor response inhibition and selective attention)	GLM (SPM99)	ASD hyperactivation in left inferior and orbital frontal gyrus during correct inhibition	None	No group differences in accuracy or RT for all tasks.	None
			STROOP task (interference inhibition)		ASD hyperactivation in left insula during correct responses	None		
			SWITCH task (cognitive set shifting)		ASD hyperactivation in parietal lobes during correct responses	None		
Dichter and Belger (2007)	17 ASD (1 female) 15 controls (1 female)	Not reported	Flanker task (interference inhibition)	Epochal	ASD hypoactivation in prefrontal and parietal regions during the incongruent social condition but not the incongruent non-social condition	None	No group differences in accuracy or three	Not significant
Just *et al*. (2007)	18 ASD (1 female) 18 controls (3 female)	Six ASD taking one SSRI, three taking 1 + psychotropic medication	Tower of London (planning and problem-solving)	GLM (SPM99)	Similar activation in dorsolateral prefrontal cortex	None	No group differences in accuracy or RT to easy condition. Control participants responded faster in hard condition.	None
Gilbert *et al*. (2008)	14 ASD (3 females) 18 controls (5 females)	Not reported	Random generation task (flexible switching and inhibition of prepotent responses)	GLM (SPM2)	ASD hypoactivation in cerebellum and left lateral temporal cortex during to baseline > random contrast	None	No group differences in response type	None
			Alphabet task (prospective memory and behavioral organization in unstructured circumstances)		ASD hyperactivation in medial rostral prefrontal cortex to stimulus-oriented > stimulus-independent contrast	None	No group differences in accuracy or RT	
Shafritz *et al*. (2008)	15 ASD (2 females) 14 controls (2 females)	All but one ASD subject were medication-free	Oddball target detection task (cognitive and behavioral set shifting)	Epochal	ASD hypoactivation in frontal, striatal, and parietal regions.	None	ASD showed lower accuracy but similar RT to oddball target events	Repetitive behaviors negatively correlated with ACC and posterior parietal activation.
Gomot *et al*. (2008)	12 ASD (all male) 12 controls (all male)	All were medication-free	Auditory novelty detection	GLM (SPM2)	ASD hyperactivation in right prefrontal-premotor and left inferior parietal regions	None	ASD showed quicker RTs but similar accuracy to novel targets	ASQ (Baron-Cohen, *et al*., 2001) correlated with prefrontal activation.
Thakkar *et al*. (2008)	12 ASD (2 females) and 14 contols (6 females)	4 ASD taking psychotropic medication (fluoxetine and lithium; buproprion and clonazepam; citalopram and sertraline and methylphenidate	Antisaccade Paradigm	GLM (FreeSurfer)	ASD hyperactivation to correct responses in bilateral rACC	ADI-R restricted and repetitive behaviors algorithm scores; Age	ASD group made significantly more antisaccade errors	Increased activation in the ACC was related to more repetitive behaviors.

brain regions. Explanations proposed for this pattern of findings include cortical 'inefficiency' (e.g. Wagner *et al*., 2006; Buchsbaum *et al*., 2007) as well as a critical dependence between brain activation magnitude and task performance (Karlsgodt *et al*., 2007). Indeed, as suggested by Manoach (2003) in a review of an analogous issue in the schizophrenia literature, it may well be that variability in behavior and brain activation may best be regarded as intrinsic to heterogeneous disorders. Thus, we interpret the present pattern of findings within the framework of dysregulated and inefficient frontostriatal recruitment in ASD during cognitive control tasks.

A pattern of hyperactivation during cognitive control of both social and nonsocial stimuli in autism is broadly consistent with findings of other groups: (i) Schmitz and colleagues (2006) reported greater frontal activation during go/no-go and spatial Stroop tasks and greater parietal activation during a set-shifting task, and (ii) Gilbert and colleagues (2008) reported greater cerebellar activation during a random response generation task. However, our research group has reported *hypo*activation in autism during a standard oddball task (Shafritz *et al*., 2008) and a social flanker task (Dichter and Belger, 2007), whereas Belmonte and Yurgelun-Todd (2003) reported a pattern of mixed results using a bilateral visual spatial attention task (i.e. decreased activity in the left ventral occipital cortex, increased activity in the left intraparietal sulcus and variable patterns in the superior parietal lobe in the autism group). Finally, others have reported comparable activation in autism using a Tower of London task (Just *et al*., 2007) and to a standard flanker task (Dichter and Belger, 2007).

These seemingly contradictory patterns of findings in the literature are summarized in Table 4. Though the precise reasons for the disparities are presently unclear, the heterogeneity with respect to fMRI tasks and analyses methods do not allow for a direct comparison between studies. Additionally, heterogeneity of patient samples and matching strategies likely contribute to the inconsistent findings. Despite these limitations, a generally consistent pattern emerges of aberrant recruitment of frontostriatal systems during cognitive control in autism, though the direction of effects is inconsistent. It may be that neurofunctional compensatory mechanisms result in hyperactivation of relevant brain regions [i.e. cortical 'inefficiency' (Wagner *et al*., 2006; Buchsbaum *et al*., 2007)], whereas differential task performance may result in reduced activation (Shafritz *et al*., 2008) during tasks of cognitive control.

We also note that one motivating factor for the present study was to disambiguate a potential confound of the findings of Dichter and Belger (2007) that indicated decreased functioning of cognitive control brain regions in ASD during a social flanker task. The design of the flanker task left unresolved whether results reflected differential processing of the central or peripheral stimuli in the task array. The social oddball task utilized herein presents a single stimulus in isolation, and thus results may be linked more directly to anomalous brain activation during processing of the attended social versus nonsocial stimuli.

Exploratory covariate analyses revealed an *indirect* association between dACC (Target Face >Novel) >(Target Shape >Novel) activation in the 10 autism participants who received the ADOS-G and ADOS-G reciprocal social interaction scores. This inverse relation, where greater activation of the dACC was associated with less symptom severity, may appear initially to contradict the primary findings of the present study, since hyperactivity of this region was observed in the ASD relative to the control group. However, given our conceptualization described earlier that dACC hyperactivation in the ASD group reflected a compensatory mechanism, we interpret these correlational findings to indicate that ASD participants with less severe symptoms were capable of engaging such compensatory mechanisms to a relatively greater degree than those with more severe symptoms. Stated another way, it may be that brain function in less severe autism does not necessarily mimic brain function observed in neurotypical individuals, but rather reflects relatively greater compensatory brain activation to cope with environmental demands.

We note a number of limitations of the present study. First, as noted in Dichter *et al*. (2009), the social oddball task did not include non-face target events that differed in stimulus features from the novel and standard events (i.e. that were not geometric shapes themselves), a design feature of future studies that would be needed to confirm that the present findings are due to the social nature of face targets rather than differential saliency. Additionally, the inclusion of faces as novel stimuli would be necessary to establish that aberrant responses to face targets in the ASD group was not indicative of aberrant responses to faces *per se*, although we note that the high overlap of frontostriatal activation to face targets, shape targets, and the contrast of these two conditions suggests that results reflect primarily activation during target detection of these classes of stimuli. Despite these limitations, the present study expands our knowledge of brain areas mediating cognitive control of social information in ASD, and may ultimately serve as a useful benchmark of ASD treatments designed to improve social cognitive functioning.

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