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Functional Neuroimaging of Social and Nonsocial Cognitive Control in Autism

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Abstract This study investigated cognitive control of social and nonsocial information in autism using functional magnetic resonance imaging. Individuals with autism spectrum disorders (ASDs) and a neurotypical control group completed an oddball target detection task where target stimuli were either faces or nonsocial objects previously shown to be related to circumscribed interests in autism. The ASD group demonstrated relatively increased activation to social targets in right insular cortex and in left superior frontal gyrus and relatively decreased activation to nonsocial targets related to circumscribed interests in multiple frontostriatal brain regions. Findings suggest that frontostriatal recruitment during cognitive control in ASD is contingent on stimulus type, with increased activation for social stimuli and decreased activation for nonsocial stimuli related to circumscribed interests.

Keywords Autism · Functional magnetic resonance imaging; cognitive control · Repetitive behaviors · Frontostriatal

Introduction

Functional magnetic resonance imaging (fMRI) studies of individuals with autism spectrum disorders (ASDs) have revealed anomalous patterns of frontostriatal brain activation during cognitive control tasks (for a review, see Dichter 2012), including hyperactivation in inferior and orbital frontal gyri during motor and cognitive interference-inhibition (Schmitz et al. 2006; Dichter and Belger 2007), hyperactivation in rostral anterior cingulate cortex during an antisaccade task (Thakkar et al. 2008), hypoactivation in anterior prefrontal cortex during a task requiring overcoming prepotent response tendencies (Solomon et al. 2009), and hyperactivation in dorsomedial prefrontal cortex during social target detection (Dichter et al. 2009).

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These findings have been interpreted to reflect deficits in behavioral inhibition and/or generation of adaptive behaviors linked to the expression of symptoms of restricted and repetitive behaviors and interests (e.g., South et al. 2007; Lopez et al. 2005). Although the direction of effects has varied across studies (i.e., frontostriatal hyperactivation vs. hypoactivation), likely due to differing task demands and analysis methods, anomalous frontostriatal activation during tasks requiring cognitive control has been a consistent finding.

In nonclinical contexts, detection of oddball target events evokes activity within frontostriatal regions, including the striatum, superior, middle, and inferior frontal gyri, and dorsal medial prefrontal cortex (Kirino et al. 2000; Huettel 2004). Oddball tasks measure specific aspects of cognitive control, a construct that subsumes working memory, inhibition, and mental flexibility abilities that share the purpose of engaging, disengaging, and reengaging with the environment to guide behavior (Lezak 1995). In the context of oddball tasks, prefrontal activation to target events is thought to reflect the context-dependent strategic control of behavior (Huettel et al. 2004; Casey et al. 2001), dynamic changes in behavioral response strategies (Huettel and McCarthy 2004), as well as set shifting and inhibitory control (Rubia et al. 2001; Konishi et al. 1999; Rogers et al. 2000), whereas striatal (i.e., caudate nucleus and putamen) activation has been implicated in planning and the execution of self-generated novel actions (Monchi et al. 2006).

Our research group has conducted a series of studies examining frontostriatal brain function during oddball tasks in individuals with ASDs. We demonstrated that individuals with ASDs were characterized by frontostriatal hypoactivation to geometric shape targets in a manner that predicted the severity of restricted and repetitive behaviors and interests (Shafritz et al. 2008). In a follow-up study, we reported dorsomedial prefrontal cortex hyperactivation in ASD to oddball targets that were images of faces, and that activation in dorsal anterior cingulate cortex was inversely correlated with social symptom severity (Dichter et al. 2009). We interpreted this pattern of frontostriatal hyperactivation to reflect compensatory mechanisms reflective of cortical inefficiency to respond flexibly to social targets in ASD (see also Schmitz et al. 2006). This account is consistent with patterns of increased brain activation in other forms of psychopathology during tasks requiring cognitive control (e.g., Wagner et al. 2006; Buchsbaum et al. 2007; Manoach 2003).

The purpose of the present study was to extend this line of research to examine frontostriatal responses in individuals with ASDs to oddball stimuli selected to be related to restricted and repetitive behaviors and interests. This symptom domain is not a unitary construct, and factor analytic studies have indicated three or more factors, where a factor related to circumscribed interests has consistently emerged (Lam and Aman 2007; Honey et al. 2006; Tadevosyan-Leyfer et al. 2003; Lam et al. 2008). This factor reflects the types of unusual and intense interests, preoccupations, and attachments commonly seen in individuals with ASD (Kanner 1943; Turner-Brown et al. 2011). To date, there has been very little mechanistic research on this unique aspect of autism, despite the fact that previous phenomenological studies have pointed out that parents report that this feature of autism is among the most difficult aspects of autism to manage on a day-today basis (South et al. 2005).

Our research group has created a set of 34 images conceptually and empirically related to circumscribed interests in ASDs. These images, which include trains, electronics, and vehicles, contain no social content, elicit greater visual attention from individuals with ASDs (Sasson et al. 2008, 2011), are more subjectively pleasing to individuals with ASDs relative to images of other objects and images of people (Sasson et al. 2012), and have been shown to differentially activate reward circuitry in individuals with ASDs (Dichter et al. 2012a). Taken together, these eyetracking, behavioral, and brain imaging data suggest that these images, referred to here as "High Autism Interest" (HAI) images, are disproportionately salient and rewarding for individuals with ASDs.

In the present study, we compared neural responses both to faces and HAI images within the context of an oddball target detection task. Based on our previous findings (Dichter et al. 2009), we hypothesized that the ASD group would be characterized by relative frontostriatal *hyper*activation to face targets, reflecting processing inefficiency while responding flexibly to these social stimuli. Conversely, because HAI images were selected to be salient and rewarding for individuals with ASDs, we hypothesized that the ASD group would be characterized by relative frontostriatal *hypo*activation to these non-social targets, reflecting relatively decreased "cognitive effort" to respond flexibly to these stimuli. Finally, we evaluated relations between neural responses to both classes of target stimuli and autism symptom severity, and predicted that the magnitude of frontostriatal activation to social and non-social targets would predict the severity of clinical manifestations of autism within the autism group.

Methods

Participants

Participants included fifteen individuals with ASDs (13 males; mean age (SD): 26.3 (9.4); range 16.9–45.3, 14 right handed) and seventeen neurotypical controls (12 males; mean age (SD): 24.3 (3.7); range 20.1–33.3, all right

handed). Groups did not differ in age, $t(30) = 0.80$; $p > .20$, or gender distribution, χ^2 (1) = 2.05, $p > .10$; however, groups did differ significantly on full-scale IQ as measured by the Wechsler Abbreviated Scale of Intelligence, t(30) = 3.59; $p < .01$, and thus full-scale IQ was included as a covariate in imaging analyses. The ASD group (two diagnosed with Asperger's syndrome and thirteen with high functioning autism) were recruited via the NC Autism Research Registry maintained through the Carolina Institute for Developmental Disabilities. Exclusion criteria included a prior history of gestational age <34 weeks, birth weight <2,000 g, intraventricular hemorrhage, history of known medical conditions associated with autism including Fragile X Syndrome, tuberous sclerosis, neurofibromatosis, phenylketonuria, epilepsy and gross brain injury, full scale intelligence score ≤75 or MRI contradictions (e.g., presence of metal in body) as assessed by MRI safety questionnaire. The control group was recruited from lists maintained by the Duke-UNC Brain Imaging and Analysis Center.

Nineteen participants with clinical diagnoses of an ASD were referred from the Autism Subject Registry. These participants were first phone screened to verify that they had no MRI contraindications (none did) and to assess repetitive behavior symptom severity using the Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders (CYBOCS-PDD, Scahill et al. 2006). Participants with a minimum CYBOCS-PDD total severity score of at least eight (16 out of 19 participants) were then invited for an in-person assessment with the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al. 2000) administered by a research reliable assessor using standard cutoffs as well as the Wechsler Abbreviated Scale of Intelligence (WASI, Weschler 1999) to ensure that full-scale IQ scores were 75 or above. Fifteen out of these sixteen participants met the autism spectrum cut-off on the ADOS and all met WASI inclusion criteria. These fifteen were then invited to complete other psychometric measures (i.e., the SRS-SR, RBS-R, and AQ) and the fMRI scan session. All participants consented to protocols approved by the Human Investigations Committees at both UNC-Chapel Hill and Duke University Medical Centers and were paid $40 for completing the imaging portion of the study. All participants had normal or corrected-to-normal vision and had either participated in fMRI studies in the past or completed a mock scan session prior to the fMRI session to acclimate to the scanner environment (Table 1).

fMRI Task

A visual oddball target detection task similar to that described previously (Dichter et al. 2009) was used and is illustrated in Fig. 1. Briefly, each of 8 runs contained 160 stimuli presented centrally for 500 ms with an interstimulus interval (ISI) that was jittered between 1,000 and 2,500, during which a fixation cross was presented. Each run lasted 5 min 4 s, and thus acquisition time for all eight runs was 40 min 32 s. There were three stimulus categories, circles of various colors and sizes, pictures of faces, and HAI images. At the start of each run, participants were instructed both verbally and via an instruction screen (e.g.,

Table 1 Means (SDs) of demographic data and symptom profiles

	Autism (n = 15)	Control (n = 17)	t(*p*)
Age	26.3 (9.4)	24.3 (3.7)	0.24 (.81)
ADOS			
Comm	5.8 (5.3)		
SI	8.7 (2.2)		
SBRI	2.25 (1.8)		
WASI[a]			
Verbal	108.1 (24.9)	128.5 (7.2)	−2.68 (.015)
Performance	109.1 (14.1)	122.2 (7.5)	−3.26 (.0039)
Full	109.9 (20.3)	127.0 (8.1)	−3.08 (.0066)
AQ	24.7 (13.1)	12.4 (5.3)	3.55 (.002)
RBS-R	20.8 (24.8)	3.6 (4.7)	4.44 (.0004)
SRS-SR (raw scores)	70.7 (34.3)	33.7 (18.5)	3.89 (.0008)

WASI Wechsler Abbreviated Scale of Intelligence (Weschler 1999), *ADOS* Autism Diagnostic Observation Scale (Lord et al. 2000), *Comm* Communication, *SI* Reciprocal Social Interaction, *SBRI* Stereotyped Behaviors and Restricted Interests, *AQ* Autism Spectrum Quotient (Baron-Cohen et al. 2001); a threshold of 32 or higher suggests cause for clinical concern in community samples, *RBS-R* Repetitive Behavior Scale-Revised (Bodfish et al. 1999)

[a] WASI missing from 1 autism participant with Leiter IQ score of 121

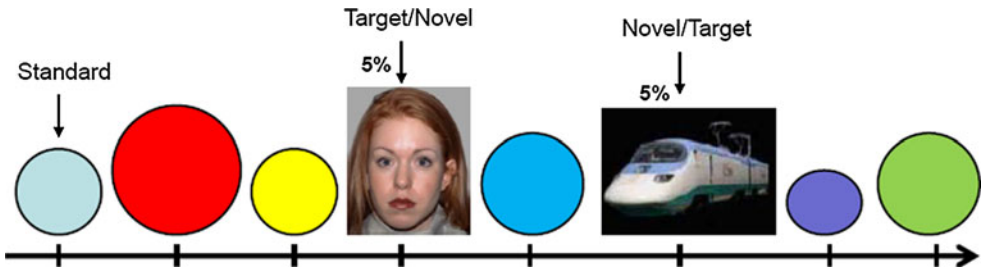

Fig. 1 The Target Detection Oddball task. Runs alternated between images of faces and High Autism Interest ("HAI") images as targets

"Targets = Faces") which stimulus category would be targets on that particular run. Each run included frequent 'standard' stimuli (circles) that occurred on 90 % of trials, infrequent 'novel' stimuli that occurred on 5 % of trials, and infrequent 'target' stimuli that occurred on 5 % of trials. On alternating runs, either face or HAI images were targets with the other category serving as novel stimuli. Participants responded via a right-hand button box to every stimulus as quickly and as accurately as possible and pressed one button for all non-target stimuli and an alternate button for all target stimuli. The run type presented first (i.e., face target or HAI target) was counterbalanced across participants. Stimuli were presented using CIGAL presentation software (Voyvodic 1999) and displayed in the scanner through magnet-compatible goggles (Resonance Technology, Inc., Northridge, CA, USA).

Face and High Autism Interest (HAI) Stimuli

Face stimuli were neutral closed-mouth images from the NimStim set of facial expressions (Tottenham et al. 2009). As described previously (Dichter et al. 2012a), the nonsocial images were systematically derived by our research group in the following manner. First, a large number of potential nonsocial images was selected based on response profiles from semi-structured parent-report interviews about circumscribed interests in ASDs (e.g., machines, mechanical systems, trains and electronic devices; Turner-Brown et al. 2011; South et al. 2005; Klin et al. 2007). Next, the visual salience of these images was evaluated via passive-viewing visual exploration eyetracking studies of individuals with and without ASDs (Sasson et al. 2008, 2011). These eyetracking studies identified 34 images without social content that garnered relatively greater visual attention (i.e., number of fixations and duration of fixations) in ASD samples. Finally, 56 adults with self-identified ASDs provided significantly higher valence ratings of these images relative to 213 adults without ASD (Sasson et al. 2012). These 34 nonsocial images were used in the present study and are depicted in the Appendix of Dichter et al. (2012a).

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). An eight-channel head coil was used for parallel imaging. Head movement was restricted using foam cushions and Velcro straps. 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 = $0.9375 \times 0.09375 \times 1.9$ mm^3) and used for coregistration 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 1,500 ms (TE = 27 ms; FOV: 25.6 cm; isotropic voxel size: 4.00; 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 4.1.4 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford University, UK). Preprocessing was applied in the following steps: (1) non-brain removal using BET (Smith et al. 2004), (2) motion correction using MCFLIRT (Smith 2002), (3) spatial smoothing using a Gaussian kernel of FWHM 5 mm, (4) mean-based intensity normalization of all volumes by the same factor, and (5) high-pass filtering (Jenkinson et al. 2002). Functional images of each participant were co-registered to structural images in native space, and structural images were normalized into a standard stereotaxic space (Montreal Neurological Institute) for intersubject 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 stimulus presentation 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 representing average signal change from baseline. Group-wise activation 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). Consistent with guidelines of Lieberman and Cunningham (2009) for clinical studies where a balance of Types I and II error probabilities is sought, clusters of ten or more voxels with Z-values >2.58 ($p < .005$) (FLAME 1 + 2, Beckmann et al. 2003) were classified as significant. We also report whether central findings were significant with a more conservative FWE-corrected $p < .05$ significance threshold by using a small volume correction consisting of the striatum (i.e., caudate nucleus, putamen, and nucleus accumbens), defined on the basis of the Harvard–Oxford subcortical probabilistic atlas (Desikan et al. 2006), and the frontal lobes, defined on the basis of the MNI structural probabilistic atlas (Mazziotta et al. 2001) thresholded at 25 %, binarized, and then combined via fslmaths. The cluster size for uncorrected statistical thresholds of $p < .005$ to reflect cluster-corrected $p < .05$ significance were determined by 1,000 Monte Carlo simulations using AlphaSim (Ward 2000) to be 38.5 voxels (308 mm^3) using this frontostriatal small volume correction.

Results

In-Scanner Participant Motion

In-scanner participant motion was extracted with MCFLIRT (FMRIB). Participants did not differ in deviation of center of mass (in mm), p's > .15: ASD means (SD): x: 0.024 (0.044); y: 0.019 (0.089); z: 0.050 (0.081); Control means (SD): x: 0.026 (0.016); y: 0.011 (0.026); z: 0.015 (0.046).

In-Scanner Behavior

A series of 2 (Group: ASD, Control) × 5 (Category: Face Target, HAI Target, Face Novel, Object Novel, Standard) repeated measures ANOVAs were conducted separately for accuracy (i.e., percent correct) and latency (i.e., reaction time) data, followed by within-group and within-condition t tests.

Accuracy analyses revealed a main effect of Category, multivariate $F(4, 120) = 25.25$, $p < .001$, a main effect of Group, $F(1, 30) = 10.55$, $p < .003$, and a Group × Category interaction, multivariate $F(4, 120) = 3.68$, $p < .007$ (see the top left of Fig. 2). Between-groups t tests revealed that the ASD group was relatively less accurate in response to all stimulus categories other than standard stimuli, p's < .05. Within the control group, paired t tests indicated greater accuracy to standard stimuli versus other categories, p's < .01, to face targets versus HAI targets, $p < .02$, and to both HAI novels and face novels versus HAI targets, p's < .04. Paired t tests within the ASD group indicated greater accuracy to standard stimuli versus other categories, p's < .005. The ASD group was more accurate to face targets versus HAI targets, $p < .005$, as well as HAI novels versus HAI targets, $p < .001$ and face novels, $p < .01$. We also compared groups on target discriminability via d', calculated as $|Z_{Hits} - Z_{False\ Alarms}|$, with hits reflecting correct responses to targets and the false alarms reflecting incorrect responses to standards or novels. The top right of Fig. 2 illustrates that the ASD group was characterized by poorer discriminability to face and HAI targets, p's < .0001. In summary, the ASD group was relatively less accurate overall and demonstrated decreased accuracy to both face and HAI stimuli.

Latency analyses revealed a main effect of Category, multivariate $F(4, 120) = 48.35$, $p < .0001$, but not of Group, multivariate $F(1, 30) = 3.53$, $p > .05$, or Group × Category interaction, $F(4, 120) = 2.43$, $p > .05$ (see the bottom of Fig. 2). Between-groups t tests revealed that groups did not differ in latency across all stimulus categories, p's > .05. The control group had shorter reaction times to standard stimuli versus all other categories, p's < .0001 and longer reaction times to face targets compared with all other categories, p's < . 01. The ASD group had shorter reaction times to standard stimuli versus all other categories, p's < .005. In summary, groups did not differ in reaction times across all stimulus categories, and both groups had quicker responses to standards than other categories.

Imaging Data

Analyses of functional imaging data included all trials and included accuracy, reaction times for condition-specific responses, and full-scale IQ as covariates. Analyses without these covariates yielded highly similar results (see Supplementary Figure 1). Primary analyses included models that directly compared groups (ASD > Control, Control > ASD) within each target type, followed by results of whole-brain Group (ASD, Control) × Target Type (Face Target, HAI Target) interaction analyses.

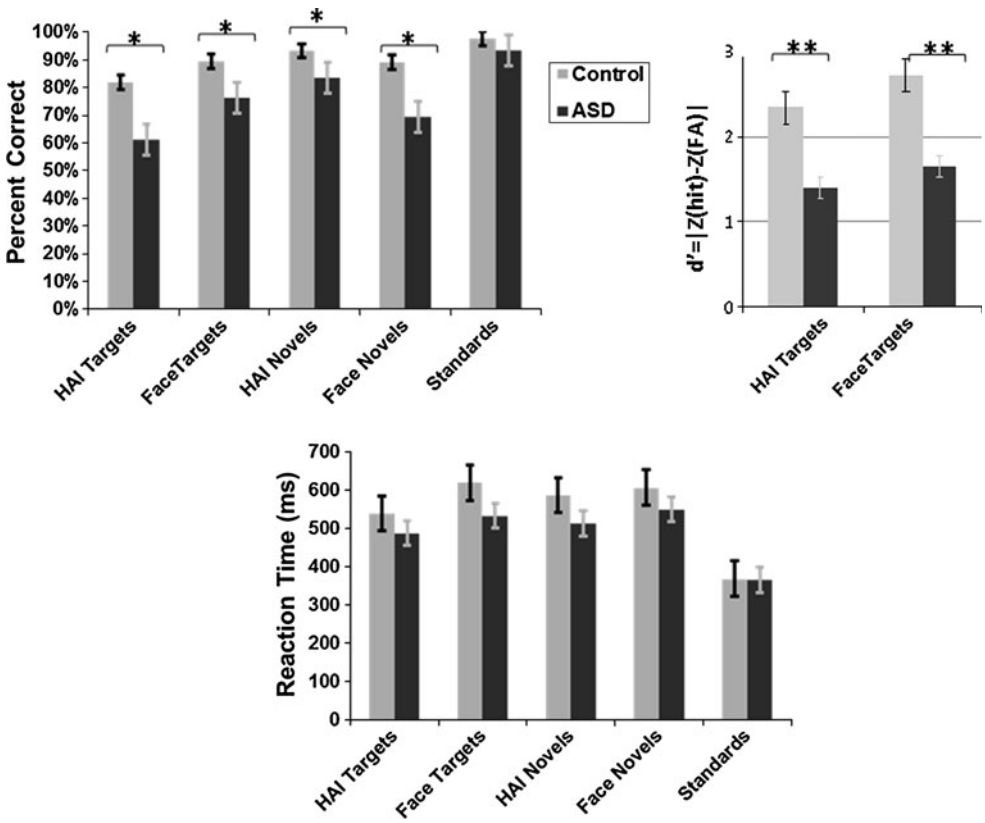

Fig. 2 In-scanner accuracy (*top left*), d' (*top right*), and reaction time (*bottom*). *Errors bars* represent group standard errors of the mean. $*p < .05$; $**p < .001$

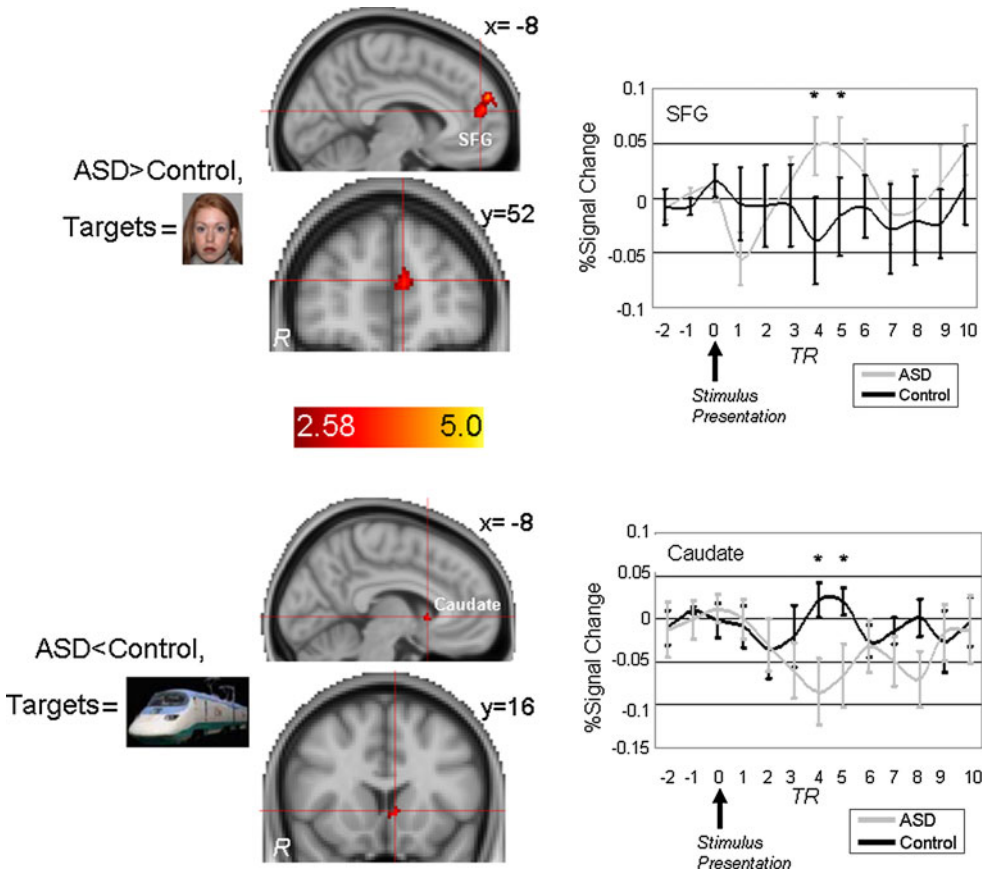

Fig. 3 *Top* Brain areas showing increased activation to face targets in ASD participants relative to controls included two superior frontal gyrus (SFG) clusters and a cluster within *right* insular cortex (not shown). *Bottom* Brain areas showing decreased activation to High Autism Interest ("HAI") targets in ASD participants relative to controls included the *left* caudate nucleus. $p < .05$; Coordinates are in MNI space

Table 2 Clusters showing significant group differences to Face and HAI targets

Region	Side	Brodmann area	Size (mm^3)	Z Max	MNI x	MNI y	MNI z
Face targets							
ASD > control							
Insular cortex	Right		112	3.31	40	8	−8
Superior frontal gyrus	Left	9	104	2.85	−6	52	18
Superior frontal gyrus	Left		128	3.23	−6	56	28
HAI targets							
ASD < control							
Amygdala	Left		96	2.94	−26	−2	−20
Caudate	Left		104	2.84	−6	14	0
Central opercular cortex	Left		160	3.03	−48	−10	8
Inferior frontal gyrus, pars opercularis	Left	44	192	3.42	−58	10	14
Lateral occipital cortex (superior)	Left		248	3.35	−34	−76	24
Anterior cingulate gyrus	Midline		96	2.82	2	6	30
Central opercular cortex	Right	42	248	3.23	62	−8	10
Lingual gyrus	Right	18	328	3.16	10	−82	−4
Middle frontal gyrus	Right		240	2.99	26	20	42
Occipital fusiform gyrus	Right		392	3.14	28	−66	−18
Precentral gyrus	Right		88	2.75	50	2	26
Temporal occipital fusiform	Right		344	3.23	30	−56	−12

Table 3 Clusters showing significant group (ASD, control) × target type (face target, HAI target) interactions

Region	Side	Size (mm^3)	Z Max	MNI x	MNI y	MNI z
Lingual gyrus	L	328	4.14	−16	−60	−6
Lingual gyrus	R	240	3.98	22	−50	−2
Posterior cingulate gyrus		1,880	3.96	0	−50	4
Caudate nucleus	B	648	3.41	0	0	−4
Precentral gyrus	R	104	3.18	26	−2	48

Group Contrasts to Face Targets

The top left of Fig. 3 and the top of Table 2 illustrate brain areas showing relatively greater activation in the ASD group than the control group to face targets (there were no brain areas with relatively decreased activation to face targets in the ASD group). Brain areas with relatively increased activation to face targets in the ASD group included clusters within left superior frontal gyrus and the right insular cortex. Average hemodynamic responses across subjects in the SFG are presented in the top right of Fig. 3 and indicate greater BOLD signal change in the ASD group 6 and 7.5 s after face target presentation. The sizes of these clusters (104–128 mm^3) were not large enough to survive more conservative cluster-correction (>308 mm^3) (Table 3).

Group Contrasts to HAI Targets

The bottom left of Fig. 3 and the bottom of Table 2 illustrate brain areas showing relatively decreased activation in the ASD group than the control group to HAI targets (there were no brain areas with relatively increased activation to HAI targets in the ASD group). Brain areas with relatively decreased activation to HAI targets in the ASD group included a cluster in the left caudate nucleus as well as clusters within left inferior frontal gyrus, anterior cingulate gyrus, right middle frontal gyrus, and the left amygdala. Average hemodynamic responses across subjects in the left caudate nucleus cluster are presented in the bottom right of Fig. 3 and indicate decreased BOLD signal change in the ASD group 6 and 7.5 s after HAI target presentation. The size of this caudate cluster (104 mm^3) was not large enough to survive more conservative cluster-correction (>308 mm^3)

Group × Target Type Interaction

Figure 4 illustrates results of a Group (ASD, Control) × Target Type (Face Target, HAI Target) fMRI model. This analysis yielded a midline caudate nucleus cluster which was further queried by analyzing subject- and condition-specific signal intensities via a mixed repeated measures ANOVA. This analysis revealed a significant Group x Target Type interaction, multivariate $F(1,30) = 4.41$, $p < .05$, but no significant effects of Target Type or Group, p's > .39.

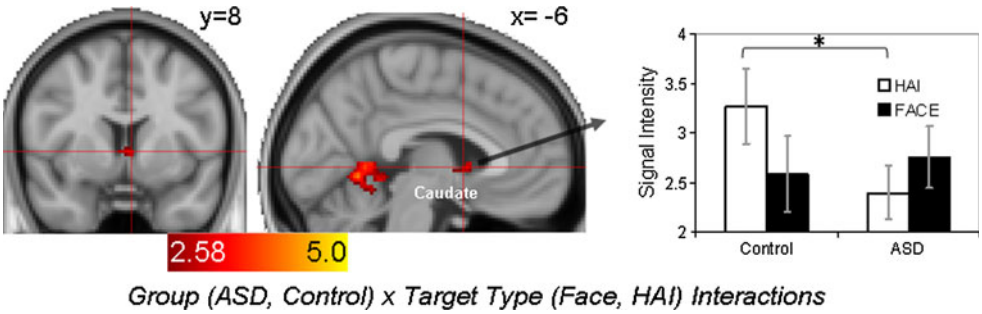

Fig. 4 Results of the group (ASD, neurotypical) × target type (face target, HAI Target) fMRI model (*left*) and subject- and condition-specific signal intensities extracted from the significant midline caudate nucleus cluster. $p < .05$; Coordinates are in MNI space

Consistent with findings above, a follow-up *t* test indicated that responses in this caudate cluster to HAI targets were significantly less in the ASD group, $p < .05$. The size of this caudate nucleus cluster (648 mm^3) was large to survive more conservative cluster-correction (>308 mm^3).

Relations to Symptoms

We evaluated whether the magnitude of brain activation in frontostriatal clusters that differentiated groups in response to social (i.e., left superior frontal gyrus and right insular cortex) and HAI (left caudate, left inferior frontal gyrus, anterior cingulate gyrus, and right middle frontal gyrus) targets as well as the caudate nucleus cluster yielded by the Group × Target Type Interaction model predicted symptom severity measured by the SRS-SR and the RBS-R within the ASD group. These analyses revealed that higher RBS-R scores were correlated with decreased left inferior frontal gyrus activation ($r = -0.53$, $p < .03$) and decreased right middle frontal gyrus activation ($r = -0.65$, $p < .007$) to social targets in the ASD group.

Discussion

Previous research has demonstrated that ASD is characterized by aberrant frontostriatal activation during tasks that require cognitive control. These findings represent a possible neural mechanism of restricted and repetitive behaviors and interests that are a core feature of the disorder (Dichter et al. 2009; Schmitz et al. 2006; Thakkar et al. 2008; Solomon et al. 2009; Shafritz et al. 2008). The aim of the present study was to extend this line of research to investigate neural correlates of cognitive control of both social stimuli and nonsocial stimuli related to circumscribed interests in ASD via an oddball target detection task. This task requires flexible responding and inhibition of prepotent responses and has been shown to recruit frontostriatal brain regions, including the striatum, superior, middle, and inferior frontal gyri, and dorsal medial prefrontal cortex (Huettel and McCarthy 2004; Kirino et al. 2000). Faces were used as social stimuli given their centrality to social functioning, and nonsocial images of objects related to circumscribed interests known to be salient and rewarding to individuals with ASDs were used as nonsocial targets (Dichter 2012a; Sasson et al. 2008, 2011).

We found that the ASD group was characterized by relatively increased prefrontal activation to social targets and by relatively decreased activation to HAI targets in the caudate nucleus and multiple prefrontal brain regions. Although the localization of these clusters at uncorrected thresholds suggested to be appropriate in smaller-scale clinical studies (Lieberman and Cunningham 2009) are consistent with hypotheses and previous fMRI research addressing the neural correlates of cognitive control in autism, only the caudate nucleus cluster yielded by the Group × Target Type interaction model was significant at a more conservative cluster-corrected threshold.

Findings in the present study of hyperactivation in a medial aspect of superior frontal gyrus in the ASD group to face targets are consistent with previous results given the central role the superior frontal gyrus plays in executive tasks (Fan et al. 2005; MacDonald et al. 2000). The insular cortex, and the inferior frontal gyrus more broadly, mediates strategic planning in oddball tasks (Huettel 2004; Kirino et al. 2000) and modulates arousal to facilitate selective attention, particularly in the context of conflict (Eckert et al. 2009). Thus, localization of hyperactivation in the superior frontal gyrus and insular cortex to face targets implicates prefrontal brain areas that mediate flexible patterns of behavioral responding. Because hyperactivation in prefrontal regions during tasks requiring cognitive control may reflect compensatory neural mechanisms (Dichter et al. 2009), the ASD group may have required greater neural resources to respond flexibly to social stimuli requiring cognitive control. This interpretation is consistent with studies in control samples indicating that dorsal prefrontal cortical regions play a key role in regulating response selection, goal maintenance and recall of task-relevant information (Milham et al. 2003; Woodward et al. 2008).

The novel finding in the present study was that the ASD group was characterized by relatively decreased activation

to HAI oddball targets in multiple frontostriatal brain regions that mediate cognitive control, including the caudate nucleus, left inferior frontal gyrus, anterior cingulate gyrus, and right middle frontal gyrus, (Fan et al. 2005; Kirino et al. 2000; Huettel 2004). We have demonstrated previously with multiple methodologies (i.e., behavioral ratings (Sasson et al. 2012), eye-tracking (Sasson et al. 2008, 2011), and functional brain imaging (Dichter et al. 2012a, b; Richey et al. 2013) that social and HAI stimuli have different motivational value for individuals with autism. Cognitive control is impacted by the motivational value of the information being processed (Padmala and Pessoa 2010, 2011; Krebs et al. 2013). Thus, we interpret the present findings to suggest that cognitive control is not a pervasive deficit in ASD, but rather that the degree of deficit is likely impacted by the nature of the information being processed, and that the increased motivational value associated with processing HAI information may diminish the cognitive control deficits in ASD.

In-scanner behavioral performance indicated that both diagnostic groups were slower and less accurate to target stimuli relative to novel and standard images, confirming that target responses required greater cognitive control. Additionally, the ASD group made slower and less accurate responses across stimulus categories and were slower and less accurate to both target categories. This domain-general pattern of impaired performance stands in contrast to functional brain imaging results indicating activation patterns that were moderated by target type in the ASD group. Individuals with ASDs have been consistently found to demonstrate slower reaction times in a range of cognitive control tasks (Geurts et al. 2009; Hill 2004). As reviewed above, the social and HAI stimulus categories hold differential motivational value for individuals with ASDs, and motivational properties would be expected to impact behavioral performance in a conflict paradigm. Thus, we interpret the present behavioral results to reflect general response slowing characteristic of ASD rather than the established motivational differences between these two stimulus categories. Of central importance, however, is that behavioral responses in the ASD group were apparently produced via differential patterns of neural activation within the cognitive control network. This differential pattern of behavioral versus neural results has been found previously in studies of cognitive control (Botvinick et al. 2001; Rushworth et al. 2004), and particularly in autism studies (Agam et al. 2010; Dichter et al. 2009). Conflict-related neural hyperactivation in the context of poorer behavioral performance has been interpreted to reflect neural inefficiency, differential strategies, and/or overactive performance monitoring, whereas conflict-related neural hypoactivation may be evident in contexts of relatively decreased conflict processing or task engagement (Melcher et al. 2008). Thus, it may be the case that the presence of social versus HAI conflict stimuli exposed different neural correlates of cognitive control deficits in ASD.

Analyses of relations between neural response and symptom profiles within the ASD group revealed that activation in two prefrontal clusters to social targets predicted the severity of repetitive behaviors and restricted interests in the ASD group. This finding provides further evidence that responses during cognitive control tasks are related to the severity of repetitive behavior symptoms (e.g., Agam et al. 2010), and in particular during a task that requires cognitive control of social information, the stimulus condition that would be most likely to tap cognitive deficits in autism (Ozonoff 1995).

Limitations of the present study should be addressed in future research. First, all participants viewed the same set of HAI images. Although this approach provided experimental internal validity, circumscribed interests in ASD are idiosyncratic and person-specific. In this regard, HAI images were not used as a proxy for person-specific interests but rather as a 'press' to investigate differences in activation patterns to social and salient non-social images across both groups. The use of standardized object images is likely a conservative estimate of patterns of brain activation to person-specific interests, but future research with person-specific images and other object images not associated with circumscribed interests will be necessary to address this. Additionally, given that social stimuli were faces with neutral expressions and that face expression moderates brain activation patterns in ASD (Kleinhans et al. 2010), future research should address the potential moderating effect of face expression on cognitive control in autism. We also note that social and nonsocial stimuli were not equated with respect to perceptual properties, and future research that parametrically varies these stimulus properties may evaluate to what extent these features effect brain activation.

Despite these limitations, the present study extends the extant literature on the neural mechanisms of cognitive control in ASD and suggests that functioning of cognitive control systems in ASD is critically dependent on the type of stimulus processed. Specifically, individuals with ASDs appear to be characterized by frontostriatal hyper- and hypoactivation to social and nonsocial stimuli related to circumscribed interest, respectively. The present findings indicate a potential novel neural correlate of circumscribed interests in individuals with ASDs.

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