

Reward circuitry function in autism spectrum disorders

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Social interaction deficits and restricted repetitive behaviors and interests that characterize autism spectrum disorders (ASDs) may both reflect aberrant functioning of brain reward circuits. However, no neuroimaging study to date has investigated the integrity of reward circuits using an incentive delay paradigm in individuals with ASDs. In the present study, we used functional magnetic resonance imaging to assess blood-oxygen level-dependent activation during reward anticipation and outcomes in 15 participants with an ASD and 16 matched control participants. Brain activation was assessed during anticipation of and in response to monetary incentives and object image incentives previously shown to be visually salient for individuals with ASDs (e.g. trains, electronics). Participants with ASDs showed decreased nucleus accumbens activation during monetary anticipation and outcomes, but not during object anticipation or outcomes. Group \times reward-type-interaction tests revealed robust interaction effects in bilateral nucleus accumbens during reward anticipation and in ventromedial prefrontal cortex during reward outcomes, indicating differential responses contingent on reward type in these regions. Results suggest that ASDs are characterized by reward-circuitry hypoactivation in response to monetary incentives but not in response to autism-relevant object images. The clinical implications of the double dissociation of reward type and temporal phase in reward circuitry function in ASD are discussed.

Keywords: autism; reward; nucleus accumbens; anticipation; functional magnetic resonance imaging

INTRODUCTION

Social interaction deficits and restricted repetitive behaviors and interests are core features of autism spectrum disorders (ASDs; American Psychiatric Association, 1994). A novel approach to understanding the pathophysiology of these core autism symptoms is to assess the functional integrity of brain reward circuits. It may be the case that hypo-responsivity to social stimuli in ASD reflects a failure to assign reward value to social interactions (Mundy and Neal, 2001; Dawson *et al.*, 2004, 2005), a conceptualization supported by data demonstrating a disturbance in the motivational mechanisms that normally draw an infant's attention to social information (Rochat and Striano, 1999). Similarly, it may be the case that restricted repetitive

behaviors and interests reflect hyper-reactive reward brain-circuitry responses to certain classes of stimuli in individuals with ASD, a model that may help to explain symptoms of circumscribed interests that are highly prevalent in ASDs (Klin *et al.*, 2007; Lam *et al.*, 2008).

In non-clinical contexts, anticipation of rewarding stimuli recruits the nucleus accumbens (NAc) as well as other limbic structures including the caudate, thalamus and putamen, markers of incentive motivation underlying approach behaviors to salient goals. The experience of pleasure, on the other hand, activates the NAc as well as the caudate, putamen, amygdala, and, perhaps most robustly, the ventromedial prefrontal cortex (VMPFC; Knutson *et al.*, 2001; Ernst *et al.*, 2004; Wacker *et al.*, 2009). Although most studies of reward processing have used monetary incentives, reactivity of these brain circuits has been demonstrated in response to a range of stimuli, including pleasant pictures (Canli *et al.*, 2001), appetizing foods (Stice *et al.*), juice (Kim *et al.*, 2010) and pictures of attractive faces (Hayden *et al.*, 2007; Winston *et al.*, 2007).

Neurobiological responses to rewards have been shown to be aberrant in a number of psychiatric disorders, including major depressive disorder (Knutson *et al.*, 2008), schizophrenia (Juckel *et al.*, 2006), substance dependence (Wrase *et al.*,

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2007) and attention-deficit/hyperactivity disorder (Strohle *et al.*, 2008). However, despite the potential centrality of reward-circuitry function to core autism symptoms, no brain imaging study to date has examined responses to the anticipation and receipt of rewarding stimuli in ASDs. Although one ASD study examined responses to a task that involved monetary rewards (Schmitz *et al.*, 2008), the effects of reward feedback were assessed during a sustained attention task, rather than responses to rewards *per se*. Additionally, Scott-Van Zeelan *et al.* (2010) investigated rewarded implicit learning in children with ASDs using social and monetary rewards, and found diminished ventral striatal response during social, but not monetary, rewarded learning. However, this study did not assess responses during reward anticipation.

In the present study, we used a monetary incentive delay (MID; Knutson *et al.*, 2001) task to assess brain responses during reward anticipation and outcomes in individuals with ASDs via functional magnetic resonance imaging (fMRI). Additionally, to test whether reward circuitry function in ASDs is moderated by different classes of reward stimuli, brain function was assessed in response to both monetary incentives and object images known to be visually salient for individuals with ASDs (Sasson *et al.*, 2008, 2010), conceptualized as a proxy for circumscribed interests that are highly prevalent in ASDs (South *et al.*, 2005; Klin *et al.*, 2007; Lam *et al.*, 2008).

Primary hypotheses concerned responses to monetary incentives and were based on theories postulating that social amotivation in ASDs may reflect broader hypo-responsivity of neurobiological systems that respond to rewards (Dawson *et al.*, 2004, 2005). We hypothesized that participants with ASDs would demonstrate decreased activation in the striatum, and in the NAc in particular, during monetary anticipation, and decreased striatal and VMPFC activation during monetary outcomes. Secondary hypotheses concerned responses to object images and were based on previous studies of circumscribed interests in ASDs that have shown bias towards these categories of stimuli (Turner, 1999; South *et al.*, 2005; Klin *et al.*, 2007; Sasson *et al.*, 2008; Sasson *et al.*, 2010; Turner-Brown *et al.*, 2010). We hypothesized that group differences in NAc and VMPFC activation during the anticipation and outcome phases of the task, respectively, would be moderated by reward type (i.e. monetary incentives *vs* object images), reflecting relatively greater reward circuitry activation within the ASD group in response to object images relative to monetary incentives. Exploratory analyses evaluated potential linkages between the severity of autism symptoms and brain activation magnitudes to both types of incentives.

MATERIALS AND METHOD

Participants

Sixteen right-handed adult male control participants (27.5 ± 7.5 -years old) were recruited from lists of control

samples maintained by the Duke-UNC Brain Imaging and Analysis Center. Control participants were not taking any psychotropic medications at the time of scanning. Fifteen adult males with ASDs identified as high-functioning comprised the ASD group (30.1 ± 11.6 -years old; 14 right-handed; two diagnosed with Asperger's Disorder and 13 with High Functioning Autism) and were recruited via the Autism Subject Registry maintained through the UNC Carolina Institute for Developmental Disabilities. Exclusion criteria for the ASD group included a history of medical conditions associated with autism, including Fragile X syndrome, tuberous sclerosis, neurofibromatosis, phenylketouria, epilepsy and gross brain injury, full-scale intelligence < 80 or MRI contraindications. Six ASD participants were not taking any psychotropics; three were taking citalopram, one was taking prozac, one was taking risperidol and the remaining four were taking multiple psychotropic medications (i.e. combinations of prozac, lorazepam, clonidine, zyprexa, zoloft and abilify).

Diagnoses of ASDs were based on a history of clinical diagnosis confirmed by proband assessment by a research reliable assessor via the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord *et al.*, 2000) with standard clinical algorithm cutoffs. Participants consented to a protocol approved by the local Human Investigations Committees at both UNC-Chapel Hill and Duke University Medical Center and were paid at least \$35 for scanning. Participants had normal or corrected-to-normal vision and completed a mock scan session prior to imaging.

Clinical testing

Participants completed: (i) the Weschler Abbreviated Scale of Intelligence (WASI) (Weschler, 1999) [one ASD participant completed the Leiter-R (Roid and Miller, 1997) instead of the WASI]; (ii) the Repetitive Behavior Scale-Revised (RBS-R) (Bodfish *et al.*, 1999; Lam and Aman, 2007), a measure designed to assess multiple RRB factors; and (iii) the Autism Quotient (Baron-Cohen *et al.*, 2001), administered to assess the overall severity of autism symptoms as well as to verify that the control group did not have significant autistic symptoms. When possible, intelligence testing records of ASD participants were accessed, with permission of participants, from records of past studies conducted at UNC-Chapel Hill ($n = 6$). All other assessments were conducted on the day of the fMRI scan.

fMRI task

The fMRI task was modified from the MID task as implemented in Knutson *et al.* (2000). Participants completed six functional imaging runs. Three runs were the standard 'win version' of the MID task during which money could be won or not won, but could not be lost. Three runs were modified so that participants could 'win' the opportunity to view a salient object image rather than money (the procedure for deriving these images is described below). Run types

(i.e. ‘money runs’ or ‘object runs’) were presented in alternating and counter-balanced order. Runs began with a 10-s instructional screen indicating the forthcoming run type. The two reward types were segregated by run to minimize the number of cues to be memorized.

Task conditions and trial timings are summarized in Figure 1. Each trial consisted of: (i) a 2000-ms cue (either a triangle or a circle) that indicated whether adequately quick responses to a forthcoming bulls-eye would result in a win or a non-win; (ii) a 2000–2500 ms crosshair fixation; (iii) a target bulls-eye, presented for up to 500 ms, that required a speeded button press; (iv) 3000 ms of feedback that indicated whether that trial was a win or a non-win; and (v) a variable length ITI crosshair presented such that the total duration of each trial was 12 s. Trial types (i.e. potential win or non-win) were aperiodic and pseudorandomly ordered. Each 8-min run contained 40 trials: 20 were potential win trials, 20 were potential non-win trials.

During money runs, participants won \$1 per trial for an adequately quick response to the forthcoming bulls-eye. During object image runs, participants ‘won’ one image per trial for an adequately quick response to the forthcoming bulls-eye. Feedback was given to indicate whether each trial was a ‘win’ or not as well as cumulative win totals. Participants were instructed to respond to all target bulls-eyes as quickly as possible, that win or non-win outcomes were contingent on reaction times (RTs), and that the amount of money they would receive for participating in the imaging portion of the study was contingent on their monetary win totals during the scanner task. They were also told that adequately quick responses on object trials would enable them to view an object on those trials and that they would receive a high-quality print-out of the object images ‘won’. The task was adaptive such that participants were successful on two-thirds of trials, regardless of individual differences in RTs.

Participants viewed a booklet of all object images prior to the scanning session. Stimuli were presented using E-Prime presentation software v. 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA) and displayed through magnet-compatible goggles (Resonance Technology Inc., Northridge CA, USA).

Object incentives

An ASD-relevant set of object images has been systematically derived by our research group in the following manner. First, a large number of potential object images was selected based on profiles of responses from semi-structured parent-report interviews about circumscribed interests in ASDs (e.g. trains and electronic devices; South *et al.*, 2005; Klin *et al.*, 2007). The validity of the content of these object images was confirmed by recent findings that, among 50 children with ASDs and 50 children without ASDs, parents reported that the content of interests within the ASD group was significantly more likely to involve machines, mechanical systems, vehicles, building, computers, physics and object motions (Turner-Brown *et al.*, in press). Next, the set of object images was evaluated via a passive-viewing visual exploration eyetracking study of 29 children with and 24 children without ASDs (Sasson *et al.*, 2008; see also Sasson *et al.*, 2010). This eye-tracking study-identified object images that garnered relatively greater visual attention (i.e. numbers of fixations) in the ASD sample. The 40 object images that demonstrated the highest number of visual fixations were used in this study (Appendix Fig. A1). Object images were subsequently modified to a resolution of 300 pixels per inch, a width of 500 pixels, a height of 400 pixels and superimposed on a black background.

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, WI, USA). Head movement was restricted using foam cushions. An eight-channel head coil was used for parallel imaging. Thirty high-resolution images were acquired using a 3D fast SPGR pulse sequence (TR = 7.332 ms; TE = 3.032 ms; FOV = 22 cm; image matrix = 256²; voxel size = 0.859384 × 0.859375 × 3.800000 mm) 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 30 slices parallel to the AC-PC plane using a BOLD-sensitive gradient-echo EPI sequence, at TR of 2000 ms (TE: 30 ms; FOV: 22 cm; isotropic voxel size: 3.4375 × 3.4375 × 4.0000). Runs began with four 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

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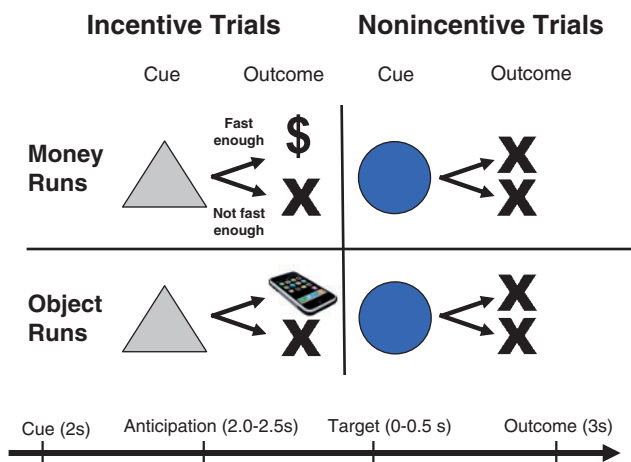


Fig. 1 Modified MID task. ‘Money’ and ‘Object’ runs were presented in alternating order. Each trial consisted of a cue (i.e. a triangle indicated an incentive trial, a circle indicated a non-incentive trial), an anticipatory delay, a target and feedback.

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 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).

Event onset times 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). 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). Following the guidelines of Lieberman and Cunningham (2009) for clinical studies where a balance of Types I and II error probabilities are sought, clusters of ten or more voxels with minimum Z -values of >2.50 ($P < 0.005$) were identified using customized MATLAB scripts.

Imaging data analytic strategy

Anticipation and outcome phases were analyzed separately. For both phases, the primary method of analysis was to evaluate clusters that revealed a significant effect of diagnostic status on the contrast of potential win versus non-win trials during the anticipation phase and for wins *vs* non-wins during the outcome phase. This approach was carried out separately for monetary and object incentive runs. Next, a higher order 2 (Group: ASD, control) \times 2 (Reward Type: money, object images) interaction model was tested to evaluate group differences with respect to reward type during both phases. Activation localizations were based on Harvard–Oxford cortical and subcortical structural probabilistic atlases as implemented in FSLView v3.0.

RESULTS

Sample characteristics

Table 1 illustrates that diagnostic groups did not differ on the full scale or verbal measures of IQ but differed with respect to performance IQ. Results of analyses that included performance IQ as a covariate were nearly identical. Groups differed in the 'sameness behavior' and 'circumscribed interests' subscales of the RBS-R, as well as in overall autism symptoms as measured by the AQ.

MID RTs

Average RTs to bulls-eyes presented within the MID task were compared via a 2 (Group: ASD, neurotypical) \times 2 (Reward Type: Money, object image) rMANOVA that revealed a main effect of Reward Type, multivariate $F(1, 29) = 9.14$, $P < 0.006$, reflecting that RTs overall were faster to money (average = 201 ± 37 ms) than image (average = 212 ± 39 ms) bulls-eyes, and a main effect of Group, $F(1, 29) = 4.34$, $P < 0.05$, reflecting that the neurotypical group (average = 193 ± 29 ms) was faster overall than the ASD group (average = 219 ± 39 ms), but no Group \times Reward Type interaction, multivariate $F(1, 29) = 1.30$, $P > 0.26$.

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

	Autism ($n = 15$)	Control ($n = 16$)	$t(P)$
Age	30.1 (11.6)	27.5 (7.5)	0.75 (0.46)
WASI ^a			
Verbal	109.9 (26.2)	117.9 (13.4)	1.08 (0.29)
Performance	111.0 (15.9)	121.8 (7.7)	2.41 (0.023)
Full	111.9 (22.7)	122.2 (10.7)	1.57 (0.13)
AQ ^b	26.1 (10.2)	14.8 (6.4)	3.90 (0.00064)
ADOS			
Comm	5.1 (4.5)		
SI	8.3 (2.6)		
SBRI	2.2 (1.6)		
RBS-R			
Stereo	2.9 (2.9)	2.4 (2.5)	0.55 (0.59)
SIB	1.9 (0.9)	0.9 (1.2)	1.24 (0.23)
Comp	5.5 (2.9)	2.9 (4.3)	1.52 (0.14)
RIT	5.2 (2.2)	2.2 (3.5)	1.95 (0.061)
Same	7.9 (3.8)	3.8 (3.8)	2.20 (0.036)
CI	2.8 (1.1)	1.1 (1.1)	2.45 (0.021)
Total	25.8 (19.6)	13.8 (13.3)	1.94 (0.062)

^aWASI missing from one autism participant with Leiter IQ score of 121. ^bAQ missing from two autism and two control participants. WASI, Wechsler Abbreviated Scale of Intelligence (Wechsler, 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; Lam and Aman, 2007); Stereo, stereotyped behavior; SIB, self-injurious behavior; Comp, compulsive behavior; Rit, ritualistic behavior; Same, sameness behavior; CI, circumscribed interests.

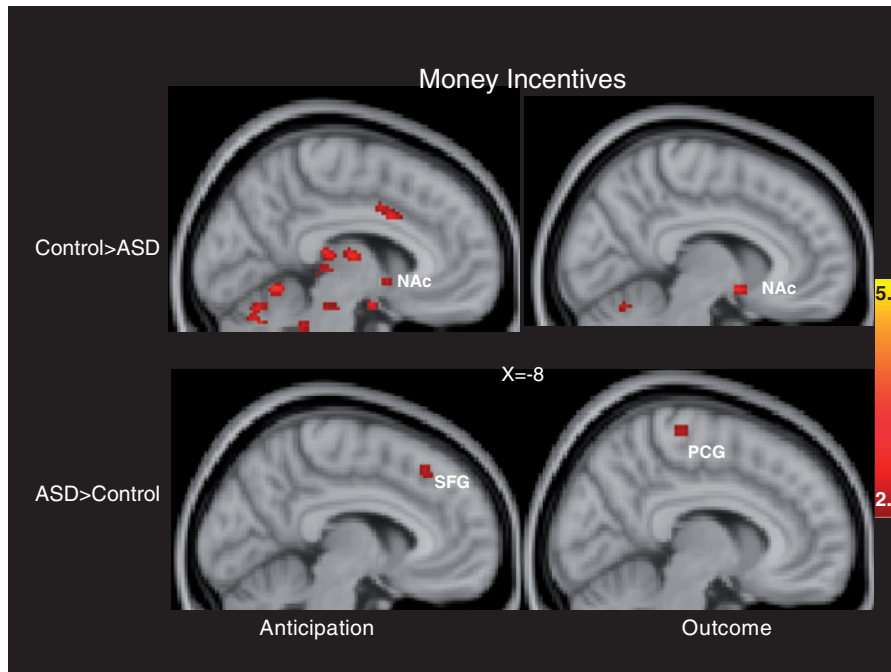


Fig. 2 Brain areas showing significant group differences in response to monetary incentives. Anticipatory responses are on the left and outcome responses are on the right; clusters with relatively greater activation in the control group are in the top panels, clusters with relatively greater activation in the ASD group are in the bottom panels. SFG: superior frontal gyrus; PCG: precentral gyrus.

Monetary incentive fMRI results

Anticipation phase

The left side of Figure 2 and the top of Table 2 depict whole-brain results during monetary anticipation. The figure illustrates that striatal reward regions, including the left NAc and right putamen, were less active in the ASD relative to the control group. In contrast, there were no striatal regions that showed relatively greater activation in the ASD group relative to the control group.

Outcome phase

The right side of Figure 2 and the bottom of Table 2 depict whole-brain results during monetary outcomes. The figure illustrates that the ASD group demonstrated relatively less activation in the left NAc, as well as the right frontal pole and right insular cortex, but not in VMPFC. In contrast, the ASD group did not demonstrate relatively increased activation in the VMPFC or in any striatal regions, although the ASD group demonstrated relatively greater activation in a number of cortical regions outside of classic reward circuits.

Object incentive fMRI results

Anticipation phase

The left side of Figure 3 and the top of Table 3 depict whole-brain results during anticipation of object incentives. In this context, the ASD group did not show decreased

activation in striatal regions, but rather demonstrated decreased activation in the dorsal anterior cingulate cortex only, relative to the control group. The ASD group demonstrated relatively increased activation in clusters of bilateral paracingulate gyrus as well other frontal lobe regions.

Outcome phase

The right side of Figure 3 and the bottom of Table 3 depict whole-brain results while viewing salient object incentives. The ASD group did not show decreased activation in any striatal regions or ventromedial prefrontal regions, relative to the control group. The ASD did demonstrate, however, relatively increased activation in VMPFC (Brodmann's area 10) as well as other frontal lobe regions relative to the control group.

Group \times reward type fMRI results

Anticipation phase

Figure 4 and the top of Table 4 depict whole-brain 2 (Group: ASD, control) \times 2 (Reward Type: money, objects) interaction terms for anticipatory phase data. This analysis revealed clusters in bilateral NAc, as well as the left caudate nucleus, cerebellum, left-frontal orbital cortex, left lingual gyrus, right occipital pole, left planum temporale, left temporal pole and left thalamus. To further examine the patterns of data within the left and right NAc clusters identified by significant interaction terms, average signal intensities were

Table 2 Clusters showing significant group differences in response to monetary incentives

Region	Side	Size (mm ³)	Z (maximum)	MNI coordinates		
				X	Y	Z
Anticipation						
Control > autism						
Accumbens	Left	104	2.72	-6	6	-4
Anterior cingulate gyrus	Left	1424	3.15	-4	18	26
Cerebellum ^a	Left	360	2.87	-36	-60	-26
Cerebellum ^a	Right	472	3.05	8	-44	-28
Frontal operculum cortex	Right	152	2.79	40	20	4
Frontal orbital cortex	Left	104	2.68	-22	8	-20
Insular cortex	Left	1848	3.76	-38	14	-12
Insular cortex	Right	280	2.95	40	6	-2
Lingual gyrus	Left	4640	3.32	-8	-58	-8
Occipital pole	Right	600	3.14	14	-92	-6
Planum polare	Right	136	2.82	44	-14	-6
Precentral gyrus	Left	104	2.85	-30	-16	70
Putamen	Right	464	2.99	30	-14	-10
Temporal pole ^a	Right	272	3.07	38	18	-24
Autism > control						
Angular gyrus	Left	3768	3.61	-50	-52	24
Frontal pole	Left	80	2.83	-20	56	30
Hippocampus	Right	144	2.89	26	-14	-26
Middle-frontal gyrus	Left	480	3.04	-36	22	44
Middle-temporal gyrus (temporooccipital)	Left	88	2.60	-64	-50	0
Postcentral gyrus	Right	528	4.06	50	-20	60
Precuneous cortex	Left	112	2.75	-4	-60	46
Superior frontal gyrus	Left	1016	3.52	-12	26	52
Superior temporal gyrus (posterior)	Left	88	2.79	-58	-30	-2
Superior temporal gyrus (posterior)	Right	136	3.15	66	-16	-4
Outcome						
Control > autism						
Accumbens	Left	88	2.96	-8	8	-10
Frontal pole	Right	280	3.58	48	34	-12
Insular cortex	Right	88	2.74	44	6	-10
Autism > control						
Frontal pole	Left	752	3.45	-44	46	12
Hippocampus	Right	520	3.18	26	-10	-26
Inferior frontal gyrus (pars opercularis) ^a	Left	536	3	-44	28	6
Juxtapositional lobule cortex	Left	80	2.63	0	6	62
Lateral occipital cortex (inferior)	Right	112	2.73	40	-64	0
Lateral occipital cortex (superior) ^a	Left	1312	4	-32	-76	48
Lateral occipital cortex (superior)	Right	216	2.99	30	-66	28
Middle-frontal gyrus	Left	2272	4.06	-36	38	38
Middle-temporal gyrus (posterior)	Left	176	2.81	-64	-24	-10
Middle-temporal gyrus (temporooccipital)	Left	128	2.8	-64	-50	-4
Postcentral gyrus	Left	592	2.84	-44	-26	54
Postcentral gyrus	Right	520	3.38	42	-24	52
Precentral gyrus ^b	Left	2488	3.22	-34	-4	56
Precentral gyrus ^c	Right	136	3.51	30	-16	58
Superior frontal gyrus ^a	Left	2024	4.59	-14	28	58
Superior frontal gyrus	Right	264	2.96	4	20	58
Superior parietal lobule	Left	256	3.12	-36	-52	64
Superior temporal gyrus (posterior)	Left	88	2.78	-68	-36	8

^aTwo clusters within same region, coordinates and peak activation reported for highest peak activation. ^bFour clusters within same region, coordinates and peak activation reported for highest peak activation. ^cThree clusters within same region, coordinates and peak activation reported for highest peak activation.

extracted from these two clusters, grouped by diagnosis and reward type (see the lower right of Figure 4). Mixed 2 (Group: ASD, control) × 2 (Reward Type: money, objects) MANOVAs performed separately on signal intensity Z-values in the right and left NAc revealed significant Group × Reward Type interactions in both left and right NAc, multivariate F 's (1, 29) > 18.73, P 's < 0.0002, significant main effects of Reward Type, multivariate F 's (1, 29) > 11.14, P 's < 0.003 and trends towards a main effects of Group, F 's (1, 29) < 13.56, P 's < 0.07. Follow-up within-groups t -tests revealed a significantly greater response to money than objects in the control group, P < 0.0002 (right NAc) and P < 0.0001 (left NAc), but no reward type difference in the ASD group, P 's > 0.40. Between-groups t -tests revealed significantly greater responses to money in the control relative to the ASD group, P < 0.004 (right NAc) and P < 0.01 (left NAc), but no significant difference between groups in responses to objects, P 's > 0.45. These results suggest that in both the left and right NAc, difference between groups with respect to anticipatory responses to rewards were contingent on reward type, and that responses to monetary rewards in the control group were larger than in the other conditions.

Outcome phase

Figure 5 and the bottom of Table 4 depict whole-brain 2 (Group: ASD, control) × 2 (Reward Type: money, objects) interaction terms for outcome data. This analysis revealed a significant cluster in VMPFC, as well as the right NAc and a number of other prefrontal regions. A mixed 2 (Group: ASD, control) × 2 (Reward Type: money, objects) MANOVA performed on signal intensity Z-values within the VMPFC cluster identified by the interaction term above revealed a significant Group × Reward Type interaction, multivariate $F(1, 29) = 8.32$, P < 0.008, but no significant main effects, P 's > 0.10. Follow-up within-groups t -tests revealed a significantly greater response to money than to object image rewards in the control group, P < 0.02, but a significantly greater response to object image rewards than to money in the ASD group, P < 0.05. Between-groups t -tests revealed significantly less response to money in the ASD relative to the control group, P < 0.005, and significantly greater response to objects in the ASD relative to the control group, P < 0.008. These results suggest that in the VMPFC, difference between groups with respect to anticipatory responses to rewards was contingent on reward type; however, this interaction term was driven by both greater activity in controls to money than objects, but the opposite pattern in the ASD group (i.e., greater activity to objects than money).

Brain-symptom correlations

Correlations were evaluated between symptom severity scores (i.e. total and subscale scores of the RBS-R, the AQ and ADOS algorithms) and in-scanner RTs from

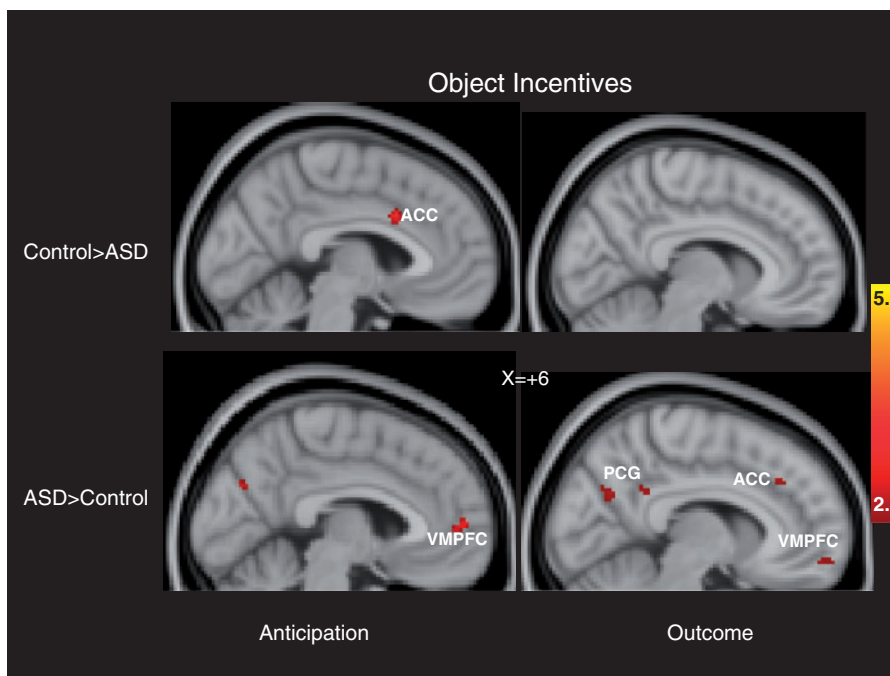


Fig. 3 Brain areas showing significant group differences in response to object incentives. Anticipatory responses are on the left and outcome responses are on the right; clusters with relatively greater activation in the control group are in the top panels, clusters with relatively greater activation in the ASD group are in the bottom panels. ACC: anterior cingulate cortex; PCG: posterior cingulate gyrus.

participants in the ASD group with signal intensities within the right and left NAc clusters that predicted Group \times Reward Type interactions during the anticipatory phase and within the VMPFC cluster that predicted Group \times Reward Type interactions during the outcome phase. No significant relations were found.

DISCUSSION

Despite the potential relevance of reward system dysfunction to core autism symptoms, no studies to date have assessed neural responses during reward anticipation and outcomes in ASD. We employed a monetary incentive delay task that has been extensively used in the nonclinical literature (Knutson and Greer, 2008) and in multiple contexts in the clinical literature (Juckel *et al.*, 2006; Wrase *et al.*, 2007; Knutson *et al.*, 2008; Strohle *et al.*, 2008). In non-clinical contexts, the anticipation of monetary incentives recruits activation in NAc, as well as other basal ganglia structures, including the thalamus, putamen and caudate, whereas monetary outcomes recruit activation in medial and VMPFC, as well as basal ganglia structures, including the NAc, amygdala, caudate and putamen (Delgado *et al.*, 2000; Knutson and Greer, 2008; Wacker *et al.*, 2009; Pizzagalli *et al.*, 2009; Forbes *et al.*, 2009).

Responses during the monetary portion of the fMRI task in the present study revealed that the ASD group was characterized by relative NAc hypoactivation during monetary

anticipation and outcomes, suggesting reward system dysfunction in ASDs in response to monetary incentives. Responses to object incentives, conceptually derived from reports of stimuli that are the focus of restricted interests in ASDs (e.g. trains, electronic devices; South *et al.*, 2005; Klin *et al.*, 2007) and that capture visual attention in ASDs (Sasson *et al.*, 2008, 2010), revealed a different pattern of data. The ASD group was not characterized by decreased reward circuitry activation during either anticipatory or outcome phases of the task in response to object incentives. Rather, the dorsal anterior cingulate cortex, a region more typically associated with deficits in cognitive control in ASDs (Dichter *et al.*, 2009a), showed decreased activation in the ASD group during object image anticipation, whereas the VMPFC showed relatively greater activation in the ASD group.

To more fully understand the pattern of responses to both types of rewards, Group \times Reward Type interactions were evaluated for both temporal phases of the MID task. This approach yielded a more focused and constrained pattern of results. During anticipation, groups differed in responses to the two types of rewards in bilateral NAc and the left-caudate nucleus, reflecting that the ASD group was characterized by blunted anticipatory responses to both types of rewards relative to response of control participants to monetary incentives. During the outcome phase of the task, groups differed in responses to the two types of rewards in a VMPFC cluster, reflecting relative VMPFC hyperactivation

Table 3 Clusters showing significant group differences in response to object incentives

Region	Side	Size (mm ³)	Z (maximum)	MNI coordinates		
				X	Y	Z
Anticipation						
Control > autism						
Anterior cingulate gyrus	Left	152	2.86	-4	12	32
Autism > control						
Angular gyrus	Right	480	3.28	54	-56	20
Frontal pole	Left	456	3.08	-46	36	-2
Frontal pole	Right	88	2.72	26	40	44
Lateral occipital cortex (inferior)	Left	552	3.63	-40	-64	14
Middle-frontal gyrus	Left	552	3.35	-26	36	36
Middle-temporal gyrus (posterior)	Right	88	2.83	62	-22	-6
Paracingulate gyrus	Left	160	2.84	-4	54	8
Paracingulate gyrus (VMPFC)	Right	216	3.07	6	54	6
Postcentral gyrus	Left	80	2.85	-34	-34	42
Postcentral gyrus ^a	Right	808	3.55	44	-30	56
Precuneus gyrus ^b	Right	560	3.15	48	-10	56
Precuneus cortex ^c	Left	200	2.81	-6	-72	30
Superior temporal gyrus (posterior)	Right	128	2.95	60	-22	2
Outcome						
Control > autism						
Inferior frontal gyrus (pars opercularis)	Left	144	3.1	-40	16	22
Lateral occipital cortex (superior)	Left	152	3.09	-36	-84	24
Occipital fusiform gyrus ^c	Left	608	3.01	-18	-80	-6
Occipital pole	Left	88	2.78	-24	-94	2
Superior parietal lobule	Right	96	2.81	18	-52	72
Temporal occipital fusiform cortex	Left	128	2.81	-26	-52	-12
Autism > control						
Angular gyrus	Left	640	3.18	-58	-56	12
Cingulate gyrus (posterior)	Right	152	2.98	10	-44	28
Frontal orbital cortex	Left	408	3.65	-26	16	-26
Frontal pole (VMPFC)	Right	152	2.73	6	56	-10
Frontal pole	Right	320	3.19	28	38	42
Frontal pole	Left	104	2.76	-24	62	-8
Lateral occipital cortex (superior)	Left	336	2.96	-38	-64	16
Middle-temporal gyrus (posterior)	Left	80	2.96	-58	-14	-14
Middle-temporal gyrus (temporooccipital)	Right	528	3.08	66	-46	2
Planum temporale	Left	80	2.89	-62	-24	10
Precuneus cortex	Right	1040	3.21	10	-66	28
Paracingulate gyrus	Right	128	3.03	6	30	36

^aThree clusters within same region, coordinates and peak activation reported for highest peak activation. ^bFour clusters within same region, coordinates and peak activation reported for highest peak activation. ^cTwo clusters within same region, coordinates and peak activation reported for highest peak activation.

to object incentives, relative to money incentives, in the ASD group.

Localization of differential anticipatory activation to the NAc and caudate implicates core brain regions mediating reward-based motivational salience (Berridge, 1996). The caudate nucleus mediates neurobiological processes that serve to link rewards to behavior, reward-related decision-making and encoding motivational feedback (Balleine *et al.*, 2007; Lau and Glimcher, 2007). Blunted striatal anticipatory reward responses have been observed in other psychiatric disorders, such as major depressive disorder (Smoski *et al.*, 2009) and schizophrenia (Juckel *et al.*, 2006), suggesting potential shared neurobiology between ASD and other disorders with regards to reward-based anticipatory processes.

Dawson *et al.* (2004, 2005) hypothesized that ASDs are characterized by a social motivation deficit such that social information is not rewarding and thus does not serve to guide and shape social behavior. The present results suggest that social motivation deficits may reflect blunted anticipatory response to rewards more broadly. We thus place this pattern of findings within a broader *Social Cognitive and Affective Neuroscience* perspective of ASDs, suggesting that the disorder may be categorized within a broader framework of dysregulated motivational processes. Though the present study did not measure responses to social stimuli *per se*, the pattern of findings is consistent with an anticipatory pleasure deficit in response to a classic laboratory reward in individuals with ASDs.

The patterns of responses during the outcome phase of the task suggest relative hyperactivation in response to object incentives in ASDs. The VMPFC has been implicated in processing monetary outcomes in nonclinical samples (Knutson *et al.*, 2000, 2001, 2003), and the NAc, a region implicated in reward outcomes as well (Delgado *et al.*, 2000; Forbes *et al.*, 2009). This finding is consistent with a model that circumscribed interests in ASDs may reflect hyperreactive reward brain circuitry in response to certain classes of stimuli and helps explain the circumscribed interests that are highly prevalent in autism (Klin *et al.*, 2007; Lam *et al.*, 2008) and clinical reports of the intense sense of pleasure reported by individuals with ASD about their circumscribed interests (Mercier *et al.*, 2000). In this regard, the VMPFC cluster that showed ASD hyperactivity in response to object incentives was localized to the paracingulate gyrus, a region that mediates representations of others' mental states (Gobbini *et al.*, 2007) and that has shown decreased synchrony in autism during mentalizing tasks (Kana *et al.*, 2009).

RT data revealed that the neurotypical group was faster at responding during the imaging task, a pattern that is consistent with reports of non-specific RT delays in individuals with ASDs in a variety of contexts (South *et al.*, 2008). Both groups responded more quickly on trials with potential monetary rewards relative to potential image rewards, but there was no differential effect of diagnostic

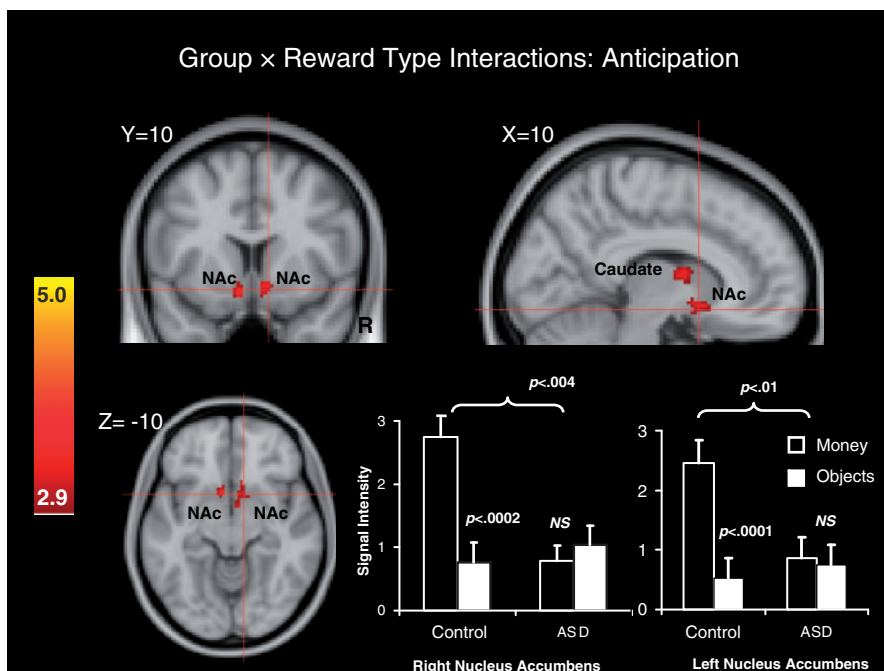


Fig. 4 Brain areas showing significant Group x Reward Type interactions during anticipation and bar graphs depicting Z-score intensity values in the right and left NAc clusters identified by significant interaction effects. Error bars represent standard errors of the mean.

status on RTs to both trial types. Thus, fMRI patterns did not recapitulate behavioral responses, highlighting the unique information conveyed by the functional neuroimaging data.

Correlations between activation magnitudes in *a priori* regions of interests, in-scanner behavioral responses and severity of autism symptoms were not significant. Power to detect correlations was likely attenuated by the low scores on measure of ASD symptoms in this high-functioning sample, particularly the AQ, on which a substantial number of ASD participants did not score above the recommended autism cutoff (Baron-Cohen *et al.*, 2001). Additionally, participants with ASDs were not selected based on the presence of high levels of RRBs or circumscribed interests in light of the diagnostic criteria for high-functioning autism (American Psychiatric Association, 1994).

Although the monetary condition in the present study was included as a standard laboratory reward that is ubiquitously used as a proxy for primary rewards, we acknowledge that there may be social influences on perceived monetary value. In other words, the value of money may be contingent on an exchange with another person, and thus the social deficits that are a defining feature of autism may influence neural responses to money. Additionally, because participants were adults, it is not possible to discern the extent to which altered responses to social and object rewards may have influenced the maturation of experience-dependent and experience-expectant portions of reward

circuits during development (Meredith *et al.*, 2008). Future pediatric studies of reward system function in autism will be necessary to more fully understand the effects of reward system function on the emergence of autism symptoms.¹

Interpretation of brain-activation patterns to salient objects in the present study warrants caution for a number of reasons. First, a standard set of object images rather than images of participant-specific interests was used to allow for a direct comparison of responses between participants with and without ASDs and to allow for follow-up and replication studies using the same stimulus set. In this regard, the object image set was used not as a proxy for person-specific interests but rather as a ‘press’ to recruit brain reward networks in the context of the fMRI task. Similar approaches have been used to investigate not only other areas of deficits in ASDs, such as responses to standard face stimuli (Pelphrey *et al.*, 2002; Corbett *et al.*, 2009), but also to investigate a host of deficits in other forms of psychopathology, including investigations of emotional processing in schizophrenia (Fahim *et al.*, 2004), unipolar depression (Dichter *et al.*, 2009b, c), mania (Bermphohl *et al.*, 2009) and posttraumatic stress disorder (Morey *et al.*, 2008). The use of a standardized object image set likely provides a conservative estimate of the effects that may be observed with person-specific interests, and a next logical step in

¹ We thank an anonymous reviewer for raising these points.

Table 4 Clusters showing significant Group (Control, ASD) \times Reward Type (Money, Object) interactions

Region	Side	Size (mm ³)	Z (maximum)	MNI Coordinates		
				X	Y	Z
Anticipation						
Accumbens	Left	624	3.61	-6	18	-14
Accumbens	Left	992	3.71	0	2	-6
Caudate nucleus	Left	40	3.06	-18	22	10
Caudate nucleus	Left	160	3.20	-16	12	16
Cerebellum	Right	64	3.12	28	-52	-30
Cerebellum ^a	Right	744	3.5	4	-66	-14
Frontal orbital cortex	Left	72	3.3	-32	24	-22
Lingual gyrus	Left	96	3.5	-2	-84	-18
Occipital pole	Right	40	3.05	12	-92	-6
Planum temporale	Left	128	3.33	-42	-40	12
Temporal pole	Left	120	3.57	-534	12	-12
Thalamus	Left	5656	3.89	-14	-8	10
Outcome						
Accumbens	Right	448	2.71	8	8	-8
Angular gyrus	Right	400	2.42	56	-42	38
Cerebellum ^b	Right	1320	2.53	4	-60	-20
Cerebellum ^a	Left	360	2.73	-14	-66	-28
Cuneal cortex	Right	400	2.57	12	-68	22
Frontal orbital cortex	Right	104	2.53	36	28	4
Frontal orbital cortex	Right	704	3.04	50	34	-12
Frontal pole	Left	40	2.29	-28	-60	12
Frontal pole	Right	256	2.68	8	56	-14
Frontal pole	Right	320	2.70	26	38	42
Heschl's gyrus	Left	288	2.45	-40	-22	6
Insular cortex	Left	144	2.26	-36	16	-10
Insular cortex	Right	48	2.11	42	16	-8
Lingual gyrus	Right	360	2.88	2	-82	-24
Middle-frontal gyrus	Right	136	2.48	34	18	54
Middle-temporal gyrus, temporooccipital ^a	Right	328	2.55	62	-52	4
Paracingulate gyrus	Right	120	2.42	8	30	40
Paracingulate gyrus (VMPFC)	Right	1544	2.70	0	42	-6
Planum polare	Left	360	2.62	-44	8	-20
Precuneous cortex	Left	72	2.49	-16	-68	24
Precuneous cortex	Right	40	2.31	6	-80	46
Supramarginal gyrus (posterior)	Right	88	2.24	60	-36	18
Temporal pole	Right	48	2.18	42	18	-20
Thalamus	Right	184	2.35	2	-16	10

^aTwo clusters within same region, coordinates and peak activation reported for highest peak activation.

this line of research would be to extend this paradigm to include person-specific interests.

Additionally, although we cannot definitely conclude that viewing these object images was rewarding for individuals with ASDs, the eyetracking validation studies that were the basis for selecting these images indicated relatively greater visual saliency of these images in individuals with ASDs

(Sasson *et al.*, 2008, 2010). These eye-tracking results, combined with non-clinical brain imaging data suggesting inherent linkages between striatal activation magnitude, stimulus reward value, and stimulus saliency (Zink *et al.*, 2004, 2006), suggest that these images were coded as having reward value in individuals with ASDs. We also note that the Sasson and colleagues (2008, 2010) eye-tracking validation studies were based on data from children, whereas the present sample was comprised of adults. Future eyetracking studies will be necessary to establish that adults with ASDs demonstrate similar patterns of visual attention to these stimuli. In this regard, however, we note that lifespan developmental studies have shown that the severity of repetitive behaviors can maintain with advancing age (Piven *et al.*, 1996; Esbensen *et al.*, 2008).

Another interpretive caution relates to the use of the WASI as an estimate of intelligence. This shortened form of a full intelligence test such as the WAIS (Wechsler, 1981) may accentuate the effects of the peaks and troughs known to occur on specific subtests in individuals with ASDs (Lockyer and Rutter, 1970). Additionally, although brain-imaging results were nearly identical when performance IQ was entered as a covariate, a group of control participants well matched on intelligence would improve the internal validity of findings (Mervis and Klein-Tasman, 2004). Finally, we did not assess for comorbid psychiatric conditions in our ASD sample, a design feature of future studies that will be necessary to conclusively link the patterns of brain imaging responses to symptoms of autism *per se*. This is particularly noteworthy given the high rates of comorbid psychiatric disorders in ASDs that are also characterized by reward system dysfunction (Leyfer *et al.*, 2006; Cederlund *et al.*, 2010).

The present data suggest a possible neurobiological mechanism for the social deficits and restricted interests that are commonly reported in ASDs (American Psychiatric Association, 1994; Klin *et al.*, 2007; Lam *et al.*, 2008). Aberrant functioning of reward pathways to standard laboratory rewards is a novel conceptualization of the pathophysiology of ASDs. Much is known about the role of dysregulated reward circuitry in other neuropsychiatric disorders (Kalivas and Volkow, 2005; Juckel *et al.*, 2006; Kienast and Heinz, 2006; Dunlop and Nemeroff, 2007; Kirsch *et al.*, 2007; Dichter *et al.*, 2009b, c), and we speculate that reward-circuitry dysfunction in various neuropsychiatric disorders may be contingent on different classes of rewarding stimuli, a speculation that may account for the disparate symptom profiles across disorders that share this pathophysiological trait. An increased understanding of reward processes in these disorders has provided a direction for the development of both psychosocial and psychopharmacological treatments (Nestler and Carlezon, 2006; Petry *et al.*, 2005; Roll *et al.*, 2004). If reward circuitry dysfunction plays a causal role in the development and expression of autism symptoms, then reward processes and their

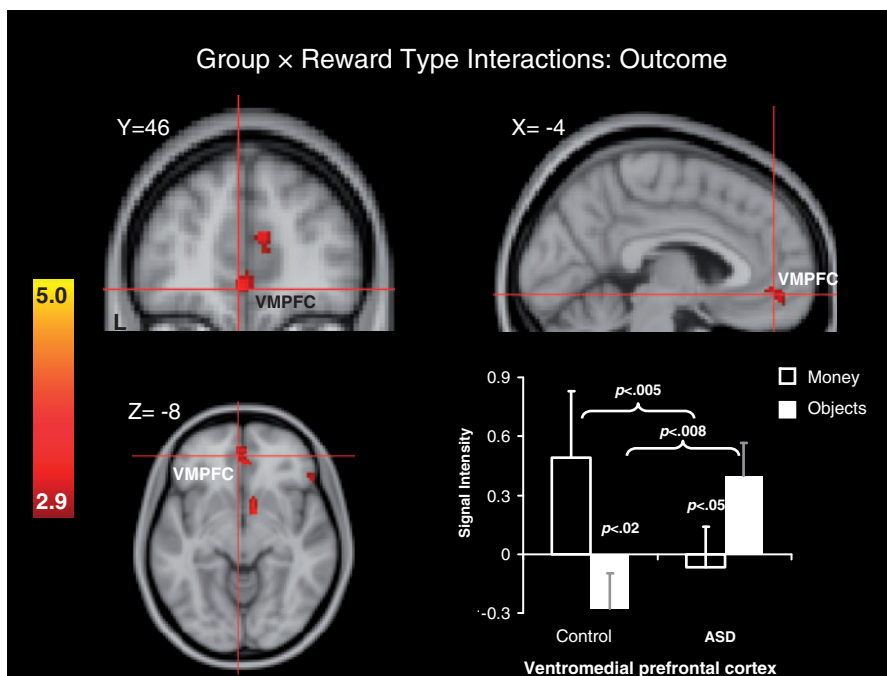


Fig. 5 Brain areas showing significant Group × Reward Type interaction effects during outcomes and a bar graph depicting Z-score intensity values in the VMPFC cluster identified by significant interaction effects. Error bars represent standard errors of the mean.

underlying neural circuitry may provide reasonable targets for the development of novel therapeutic approaches in autism.

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APPENDIX 1

Appendix: Object Images

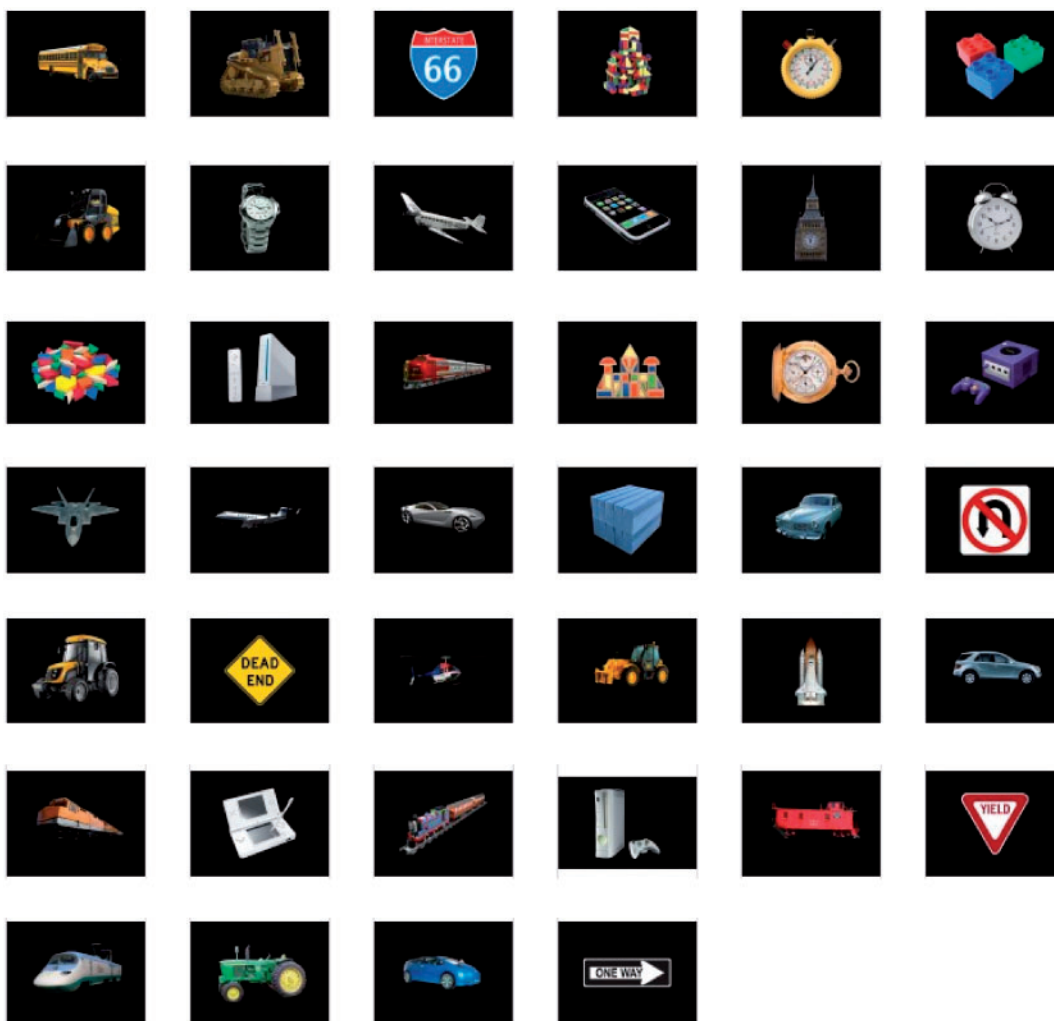


Fig. A1 Object images.