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Reward Circuitry Function in Autism During Face Anticipation and Outcomes

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Abstract The aim of this study was to investigate reward circuitry responses in autism during reward anticipation and outcomes for monetary and social rewards. During monetary anticipation, participants with autism spectrum disorders (ASDs) showed hypoactivation in right nucleus accumbens and hyperactivation in right hippocampus, whereas during monetary outcomes, participants with ASDs showed hyperactivation in left midfrontal and anterior cingulate gyrus. Groups did not differ in nucleus accumbens responses to faces. The ASD group demonstrated hyperactivation in bilateral amygdala during face anticipation that predicted social symptom severity and in bilateral insular cortex during face outcomes. These results add to the growing body of evidence that autism is characterized by altered functioning of reward circuitry. Additionally, atypical amygdala activation during the processing of social rewards may contribute to the development or expression of autistic features.

Keywords Autism · Nucleus accumbens · Anticipation · Functional magnetic resonance imaging · Social cognition · Reward

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Introduction

Orientation to social stimuli in typical development begins during early infancy (Farroni et al. 2002) and is critical for optimal social development (Brooks and Meltzoff 2002) and social adaptation through the lifespan (Emery 2000). It is believed that attention towards social stimuli, even in infancy, is accompanied with feelings of pleasure and reward (Dawson et al. 2004, 2005). Such reward mechanisms, in turn, may serve to encode and consolidate positive memories of social experiences (Labar 2007) that, in turn, ultimately influence future responses to social stimuli. Thus, in typical development, reward brain circuitry may be shaped to guide responses to social sources of information through a complex integrative process.

A number of theorists have suggested that autism is characterized by social motivational deficits centered on the detection, decoding, and interpretation of social signals conveyed through the face (Dawson et al. 1998, 2005; Schultz 2005). Decreased motivation to engage in

reciprocal social behaviors may result in fewer experiences with social sources of information. This relatively impoverished social environment may negatively impact the development of social cognition and language skills, perhaps due to lack of motivation to participate in activities where such skills are typically forged (Schultz et al. 2000; Kuhl et al. 2005). Consistent with this model, very young children with autism demonstrate decreased orienting to social stimuli (Dawson et al. 1998; Klin et al. 2009) that is predictive of decreased social competence (Klin et al. 2002).

Despite the potential causal linkages between social motivational deficits and decreased social competence, only two published studies have assessed the neural bases of social reward processing in autism. Schmitz et al. (2008) investigated the neural substrates of reward feedback in the context of a sustained attention task and reported increased activation in left anterior cingulate gyrus and left midfrontal gyrus on rewarded trials in autism. Scott-Van Zeeland et al. (2010) investigated the neural correlates of rewarded implicit learning in children with autism using both social and monetary rewards. They found diminished ventral striatal response during social, but not monetary, rewarded learning, and reported that activity within the ventral striatum predicted social reciprocity within the control group, but not the autism group.

The goal of the present study was to extend this line of autism research to address reward network responses to social stimuli during both anticipatory and outcome phases of the reward response. This was accomplished via a modified incentive delay task to probe responses to both monetary rewards and to pictures of faces. A strength of this task is the ability to probe responses during both anticipatory and outcome phases. This is critical, given that the anticipation and experience of reward are mediated by distinct neurobiological systems (Wise 2008; Berridge 1996; Aberman et al. 1998) the dysregulation of which may be treated via independent mechanisms (Willner 1983; Xi and Gardner 2008; Howes and Kapur 2009).

Animal and human nonclinical research has identified a neural network sensitive to rewards that receives dense dopaminergic projections from the ventral tegmental area and is comprised of both dorsal and ventral aspects of the striatum, orbitofrontal cortex (OFC), ventromedial prefrontal cortex (VMPFC), and anterior cingulate cortex (ACC) (Schultz 1998, 2000; Ikemoto and Panksepp 1999; Berridge and Robinson 1998). Anticipation of pleasurable stimuli recruits the nucleus accumbens (NAc), a marker of incentive motivation underlying approach behaviors to salient goals, whereas the experience of pleasure activates VMPFC (Knutson et al. 2001; Knutson and Cooper 2005). There is also evidence that some brain regions, including the medial OFC, ACC, and, in certain contexts, the NAc, are active during both the anticipatory and consummatory phase of the reward response (Kim et al. 2006; Bjork and Hommer 2007; Forbes et al. 2009).

Although the majority of reward studies have employed monetary incentives, reactivity of reward brain circuits has been demonstrated in response to a range of stimuli, including pleasant pictures (Canli et al. 2001) and appetizing foods (Stice et al. 2010). Additionally, there is a growing body of literature describing reward network responses to social stimuli during both anticipatory and outcome periods (Hayden et al. 2007; Winston et al. 2007; Rademacher et al. 2010), suggesting that social stimuli may be used in the context of reward tasks to assay responses of the reward system.

We recently reported results of a functional magnetic resonance imaging (fMRI) study wherein individuals with autism completed an incentive delay task modified such that participants could win money or the opportunity to view nonsocial objects (Dichter et al. 2011). Participants with autism showed decreased NAc activation during monetary anticipation and outcomes but VMPFC hyperactivation during object outcomes. This result indicates that reward network function in autism is contingent on both the temporal phase of the response and the type of reward processed, suggesting that it is critical to assess the temporal chronometry of responses in a study of reward processing in autism.

In the present study, we probed brain activation during anticipation and outcome phases of an incentive delay task that presented both monetary and social rewards to individuals with autism spectrum disorders (ASDs). In the monetary conditions we hypothesized NAc hypoactivation during anticipation and outcomes (Dichter et al. 2011) and ACC hyperactivation during outcomes (Schmitz et al. 2008) in the ASD group. Based on a prevailing model of social-motivation deficit in autism (Dawson et al. 1998, 2005; Schultz 2005) and the findings of Scott-Van Zeeland et al. (2010), we further predicted reward system dysfunction to social rewards in the ASD group. Though no study has assessed anticipatory response to social rewards in autism, we hypothesized NAc hypoactivation during this condition based on the premise that social stimuli have decreased salience (Sasson et al. 2007, 2008) and thus possibly decreased motivational properties in ASD. Finally, relations between reward system dysfunction to social stimuli and the severity of autism symptoms were examined in an exploratory manner.

Method

Participants

Twenty neurotypical right-handed control participants (fourteen male; mean (SD) age: 25.3 (7.0); age range:

18.9–49.0) were recruited from lists of control samples maintained by the Duke-UNC Brain Imaging and Analysis Center. Control participants were not taking psychotropic medications. The ASD group was comprised of sixteen right-handed participants (two female; mean (SD) age: 26.0 (9.1); age range: 16.9–45.3; two diagnosed with Asperger's Disorder and fourteen with high functioning autism) and were recruited via the Autism Subject Registry maintained through the 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, and MRI contraindications. Groups did not differ in age, $t(34) = .24$; $p > .80$, or gender distribution, χ^2 (1) = 1.58, $p > 0.21$. Seven ASD participants were not taking psychotropic medications; of the remaining nine, four were taking Abilify, one was taking Adderall, one was taking Celexa, one was taking Prozac, one was taking Risperdal, and one was taking both Adderall and Prozac. The present study was conducted as a companion study to Dichter et al. (2011), and nine participants with ASDs and three control participants participated in both studies.

Diagnoses 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 Centers and were paid between $35 and $45 for the imaging portion of the study. Participants had normal or corrected-to-normal vision and completed a mock scan session prior to imaging. Table 1 illustrates symptom profiles of both diagnostic groups.

Table 1 Mean (SDs) age and symptom profiles

Age	Autism (n = 16) 26.0 (9.1)	Control (n = 20) 25.4 (7.0)	t (p) 0.24 (.8)
ADOS comm	6.1 (5.5)		
ADOS SI	8.7 (2.2)		
ADOS SBRI	2.25 (1.8)		
WASI (full-scale)	109.9 (20.3)	127.0 (8.1)	3.1 (.007)
WASI (performance)	109.1 (14.1)	122.2 (7.5)	3.3 (.004)
WASI (verbal)	108.1 (24.0)	125.6 (9.5)	2.7 (.02)
AQ total score	24.7 (13.1)	12.4 (5.3)	3.55 (.002)
RBS-R total score	20.8 (24.8)	3.6 (4.7)	4.44 (.0004)
SRS-SR total scores	70.7 (34.3)	33.7 (18.5)	3.89 (0.0008)

Both groups completed: (1) The Weschler Abbreviated Scale of Intelligence (WASI) (Weschler 1999) (one ASD participant completed the Leiter-R (Roid and Miller 1997); (2) The Repetitive Behavior Scale-Revised (RBS-R) (Bodfish et al. 1999; Lam and Aman 2007), a measure designed to assess multiple RRB factors; (3) the Autism Quotient (AQ) (Baron-Cohen et al. 2001), administered to assess the overall severity of autism symptom as well as to verify that the neurotypical group did not have significant autistic symptoms, and (4) the Social Responsiveness Scale (SRS), a continuous measure of autism symptom severity (Constantino et al. 2003)

fMRI Task

The fMRI task was modified from the Monetary Incentive Delay (MID) task as implemented in Knutson et al. (2000). On three runs, money could be won or not won, but money could not be lost; on the other three runs, trial "wins" resulted in the presentation of a static image of a face rather than monetary gain. Face stimuli were neutral expression, closed mouth images selected from the NimStim set of facial expressions (Tottenham et al. 2009). Run types (i.e., "money runs" or "face runs") were presented in alternating and counterbalanced order. Runs began with a 10-s instructional screen indicating the run type. Money and faces rewards were segregated by run to minimize the number of cues to be memorized.

Task conditions and trial timings are summarized in Fig. 1. Each trial consisted of: (1) a 2,000 ms cue indicating whether adequately quick responses to the bulls-eye would result in a "win" (a triangle) or not (a circle); (2) a 2,000–2,500 ms crosshair fixation; (3) a target bulls-eye presented for up to 500 ms that required a speeded button press; (4) 3,000 ms of feedback that indicated whether that trial was a "win" or not, with wins accompanied by either an image of money or a face; and (5) a variable length ITI crosshair resulting in a total trail duration of 12 s. Potential win and non-win trials were aperiodic and pseudorandomly ordered. Each 8-min run contained 40 trials, of which half were potential win trials.

During money runs, potential win trials resulted in $1 won if bulls-eye responses were adequately quick. During face runs, potential win trials resulted in presentation of a face image if bulls-eye responses were adequately quick. Coincident with feedback, cumulative win totals were presented. Participants were instructed to try to win on as many trials as possible, and win or non-win outcomes were contingent on reaction times. The task was adaptive such that participants were successful on two-thirds of trials, regardless of individual differences in reaction times.

Standard administration of the MID task involves showing participants, prior to scanning, rewards that may be won (Knutson et al. 2001). Consistent with this procedure, participants were shown the money they could win and were informed they would receive the amount of money won.

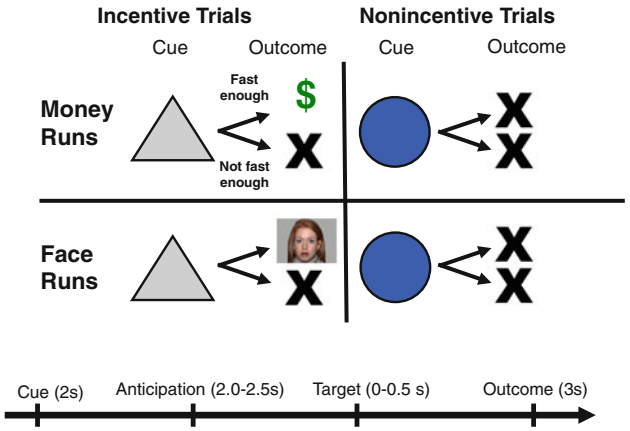

Fig. 1 Modified MID task. Participants alternated completing "money" and "face" runs, denoted by a 10-s instructional screen at the start of each run. Each trial consisted of a cue (i.e., a *triangle* indicated an incentive trial, a *circle* indicated a non-incentive trial), an anticipatory delay, a target, and outcome feedback

Prior to scanning, participants rated face stimuli on the dimensions of valence and arousal. Stimuli were presented using E-Prime v. 1.1 (Psychology Software Tools Inc., Pittsburgh, PA) and displayed through magnet-compatible goggles (Resonance Technology, Inc., Northridge CA).

Imaging Methods

Scanning was performed on a GE Health Technologies, 3 Tesla Signa Excite HD scanner with 50-mT/m gradients (General Electric, Waukesha, Wisconsin, 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 = 256^2; voxel size = 0.86 × 0.86 × 3.80 mm) and used for coregistration with the functional data. 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 with higher-order shimming, at TR of 2,000 ms (TE: 30 ms; FOV: 22 cm; isotropic voxel size: 3.4375 × 3.4375 × 4.0000). 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, U.K.). Preprocessing was applied as follows: (1) brain extraction (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, (5) high-pass filtering (Jenkinson et al. 2002), and (6) resampled to 2 × 2 × 2 cm. Functional and structural images were co-registered in native space and normalized to a standard stereotaxic space (Montreal Neurological Institute). Registrations used an intermodal registration tool (Jenkinson et al. 2002; Smith et al. 2004), and 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 signal responses containing a regressor for each response type 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 changes 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) with cluster mean threshold of $Z > 2.3$ and a cluster-corrected significance threshold of $p < 0.05$ (FLAME 1 + 2, Beckmann et al. 2003).

Imaging Data Analytic Strategy

Anticipation and outcome phases were analyzed separately; within each, group differences with respect to responses to money and faces were modeled. Next, 2 (Group: ASD, control) × 2 (Reward Type: money, faces) interaction models were tested during both anticipation and outcome phases to evaluate group differences with respect to reward types.

Localizations were based on Harvard-Oxford cortical and subcortical structural probabilistic atlases as implemented in FSLView v3.0. Cortical activations were visualized with Freesurfer (Fischl et al. 1999a, b) and displayed on a partially inflated cortical surface. Because groups differed in estimated intelligence, models were evaluated that included this covariate. These analyses yielded highly similar results (see Supplementary Figures 5 and 6), and results without this covariate are presented for comparison with other studies of reward network function in autism (Schmitz et al. 2008; Scott-Van Zeeland et al. 2010; Dichter et al. 2011) that did not covary intelligence. Additionally, we note that results of only males participants (14 control and 14 ASD participants) also yielded highly similar results (see Supplementary Figures 7 and 8).

Results

Head motion, measured as average amount of movement in six planes of motion, did not differ between groups (ASD

mean absolute displacement = 0.9 mm (SD = 0.8); control mean absolute displacement = 0.4 mm (SD = 0.2), $p > .05$).

Image Ratings

Groups did not differ in ratings of faces on the dimensions of Valence ($p > .75$) and Arousal ($p > .90$) (see Fig. 2).

MID Reaction Times

Reaction times (RTs) to MID bulls-eyes are depicted in Fig. 2 and were compared via a 2 (Group: ASD, Control) × 2 (Stimulus Type: Money, Faces) mixed ANOVA. There was no Group X Stimulus Type interaction, $F(1,34) = 0.11$, $p > .70$, or main effect of Group, $F(1,34) = 1.68$, $p = .20$. There was a main effect for Stimulus Type, $F(1,34) = 11.18$, $p < .002$ reflecting faster RTs overall on money trials relative to face trials.

fMRI Responses to Monetary Incentives

Figure 3 and Table 2 depict responses to monetary incentives. Responses of the control group alone replicated patterns observed in the nonclinical literature (Knutson and Greer 2008), including NAc activation during monetary anticipation and medial prefrontal activation during monetary outcomes (see Supplementary Materials Figure 2). Replicating our previous findings (Dichter et al. 2011), individuals with ASDs demonstrated hypoactivation in right NAc during monetary anticipation. Decreased activation was also observed in right OFC, the ACC, as well as a number of regions outside of the reward network. The ASD group demonstrated greater activation during monetary anticipation in a ventral cluster that included the hippocampus and entorhinal cortex, as well as precentral gyrus and right temporal pole. During monetary outcomes, there were no clusters with decreased activation in the ASD group. There were, however, a number of prefrontal regions that demonstrated relatively greater activation in the ASD group, including bilateral inferior frontal gyrus, the left midfrontal gyrus (MFG), right superior frontal gyrus, right insular cortex, and left frontal pole.

fMRI Responses to Faces

Figure 4 and Table 3 depict response to faces. There were no clusters with relatively decreased activation in the ASD group. However, there were a number of regions with relatively greater responses in the ASD group: during face anticipation, greater activation in the ASD group was observed in bilateral amygdala as well as the left frontal pole, whereas during face outcomes, relatively greater activation in the ASD group was observed in a number of prefrontal regions, including right middle frontal gyrus, bilateral superior frontal gyrus, and bilateral insular cortex.

Group × Reward Type fMRI Results

2 (Group: ASD, control) × 2 (Reward Type: money, faces) interaction tests during reward anticipation revealed a

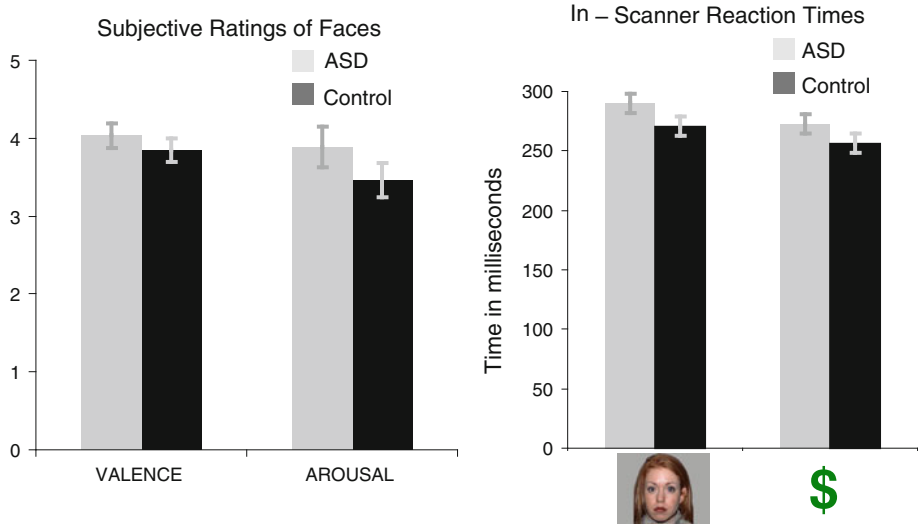

Fig. 2 *Left:* Average valence and arousal ratings of faces. Valence = 0 (extremely unpleasant) to +8 (extremely pleasant); Arousal = 0 (not at all aroused) to +8 (extremely aroused). *Right*: Average reaction times during face and money conditions. The main effect of Stimulus Type reflected faster RTs on money trials relative to face trials in both the control group (money mean (SD): 256 (31) ms; face mean (SD): 270 (41) ms; $t(1,19) = 2.21$, $p < .001$) and the ASD group (money mean (SD): 270 (42) ms; face mean (SD): 290 (53) ms; $t(1,15) = 2.54$, $p < .05$). *Error bars* represent standard errors of the mean

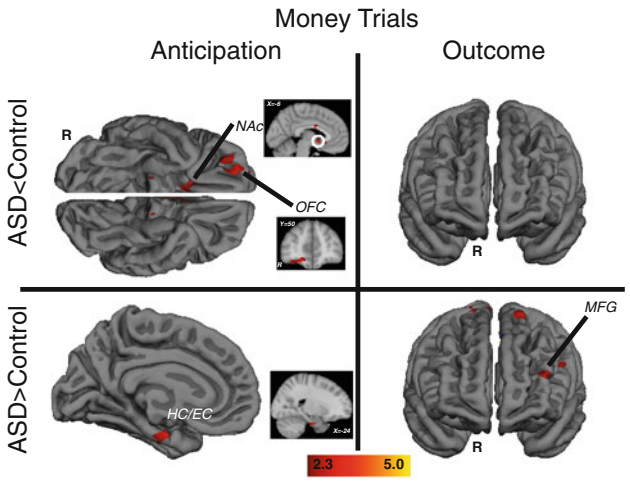

Fig. 3 Brain areas showing significant group differences in response to monetary incentives. Anticipatory responses are on the *left* and outcome responses are on the *right*; clusters with relatively less activation in the ASD group are in the *top panels*, clusters with relatively greater activation in the ASD group are in the *bottom panels*. Outcome panels depict the anterior view of the brain. *OFC* orbital frontal cortex, *NAc* nucleus accumbens, *HC/EC* hippocampus/entorhinal cortex, *MFG* midfrontal gyrus

significant interaction cluster in right NAc (see Supplementary Materials Figure 3). Simple effects tests revealed that this interaction term reflected relatively greater response to money than faces in the control group ($p < .05$) but not in the ASD group. A similar analysis conducted during reward outcomes revealed no interaction effects in NAc or VMPFC, but a significant interaction cluster in anterior cingulate cortex (see Supplementary Materials Figure 4). Simple effects tests revealed that this interaction term reflected relatively greater response to money than faces in the control group ($p < .05$) but not in the ASD group.

Brain-Symptom Correlations

To test whether responses to social rewards predicted social symptom severity within the ASD group, relations between neural responses to social rewards and social functioning were evaluated. Significant correlations were found between the social interaction subdomain algorithm scores of the ADOS-G (Lord et al. 2000) and both the left ($r = .74$, $p = .0011$) and right ($r = .58$, $p = .018$) amygdala clusters that differentiated groups during face anticipation. Signal strengths in these clusters were derived by extracting signal strength values for each participant for the clusters defined by the between-groups analysis. These direct associations indicate that more severe social deficits predicted greater bilateral amygdala activation during face anticipation.

Discussion

Social-motivation deficits in ASDs have long been theorized to mediate difficulties with social information processing by decreasing the saliency of social information (Dawson et al. 1998, 2004, 2005; Schultz 2005). The objective of the present study was to evaluate responses to money and faces presented within the context of an incentive delay task. This approach was informed by the wealth of infrahuman and human data indicating that reward anticipation outcomes recruit distinct neurobiological systems (e.g., Berridge and Robinson 1998; Knutson et al. 2001) and that various neuropsychiatric disorders are characterized by anomalous patterns of brain function during different temporal phases of the reward response (Smoski et al. 2009; Juckel et al. 2006b; Abler et al. 2007).

Responses to Monetary Rewards

Brain activation during monetary anticipation revealed decreased NAc activation in the ASD group, replicating our previous findings (Dichter et al. 2011) and suggestive of reward system dysfunction in ASD during anticipation of a standard laboratory incentive. The NAc receives dense dopaminergic projections from the ventral tegmental area and mediates incentive motivation salience in a number of contexts (for a review, see Knutson and Greer 2008). Responses during monetary anticipation also revealed the novel but complimentary finding of OFC hypoactivation in the ASD group. Nonclinical investigations of neural responses during incentive delay tasks have not consistently observed OFC activation (Knutson et al. 2001; Dillon et al. 2008), possibly due to the potential for fMRI artifact just above the sinus cavities. In the present study, the use of higher-order shimming improved BOLD signal coverage within the OFC, increasing power to detect effects in this ventral brain region (see Supplementary Materials Figure 1).

The OFC codes the magnitude and affective value of positive and negative rewards and primary reinforcers (Bechara et al. 2000), tracks the subjective utility of delayed rewards (Kable and Glimcher 2007), and facilitates decision-making based on cost-benefit gradients (de Lafuente and Romo 2006), particularly in ambiguous contexts (Hsu et al. 2005). As such, the OFC codes hedonic value and abstract representations of positive and negative outcomes and responds similarly to obtained rewards and avoided losses (Rolls 1996; Kim et al. 2006). Thus, the OFC aids in forming associations between unconditioned stimuli and primary reinforcers to adaptively guide behavior. Lesions of the OFC result in impaired reward learning and impaired adaptive behavior in the face of changing reinforcement contingencies (Rolls and

Table 2 Clusters showing significant group differences during money trials (minimum cluster size = 8 voxels)

Region	Brodmann Area	Size (mm^3)	Z Max	MNI coordinates		
				X	Y	Z
Anticipation						
Control > Autism						
Accumbens (left)		256	3.21	−4	6	−4
Amygdala (right)	34	96	2.7	24	4	−20
Cingulate gyrus (Anterior, right)		1,168	4	0	−2	24
Frontal orbital cortex (left)		1,240	2.66	−30	38	−2
Frontal pole						
Right	10	168	2.71	30	58	16
Left		128	2.59	−26	38	−14
Occipital frontal cortex (right)		1,848	3.36	20	50	−16
Occipital cortex (superior, lateral, right)		224	2.75	40	−68	24
Planum porale (right)	41	352	2.92	54	−30	16
Precentral gyrus (right)	6	88	2.58	38	2	40
Subcallosal cortex (right)		224	2.65	10	12	−14
Subcallosal cortex (left)	24	144	2.58	−4	22	−8
Supramarginal gyrus (anterior, right)		288	3.2	64	−28	40
Supramarginal gyrus (posterior)						
Right		464	2.83	58	−42	32
Left	40	520	3.44	−62	−44	40
Temporal gyrus (posterior, middle)						
Right		144	2.61	46	−22	−14
Left		112	3.15	−48	−36	−6
Autism > Control						
Hippocampus (right)	35	512	3.12	24	−12	−30
Precentral gyrus (left)	6	104	2.7	−8	−20	54
Temporal pole (right)		408	3.22	46	6	−28
Outcome						
Autism > Control						
Frontal gyrus (inferior)						
Right[a]		368	2.7	54	12	4
Left		232	2.8	−48	14	6
Frontal gyrus (middle, left)		1,880	3.3	−24	2	52
Frontal gyrus (superior)						
Right[a]		1,512	3.2	14	−10	72
Frontal pole (left)		336	2.9	−40	46	18
Insular cortex (right)		160	2.7	44	10	−6
Intracalcarine cortex						
Right		200	2.7	26	−62	4
Left		224	3.1	−10	−76	4
Lingual gyrus (right)		1,064	3.3	8	−62	4
Occipital cortex (lateral, superoir)						
Right	39	80	3.5	50	−76	30
Right	7	272	2.9	26	−64	34
Right		200	3	18	−80	42
Opercular cortex (central, Right)		112	2.6	46	−8	12
Operculum cortex (frontal)						
Left		160	2.7	−46	16	−4

Table 2 continued

Region	Brodmann Area	Size (mm^3)	Z Max	MNI coordinates		
				X	Y	Z
Right		104	2.6	40	22	2
Precentral gyrus						
Right[a]		304	3.4	56	2	44
Putamen						
Right		272	2.5	24	10	−6

[a] Two clusters within same region, coordinates and peak activation reported for highest peak activation

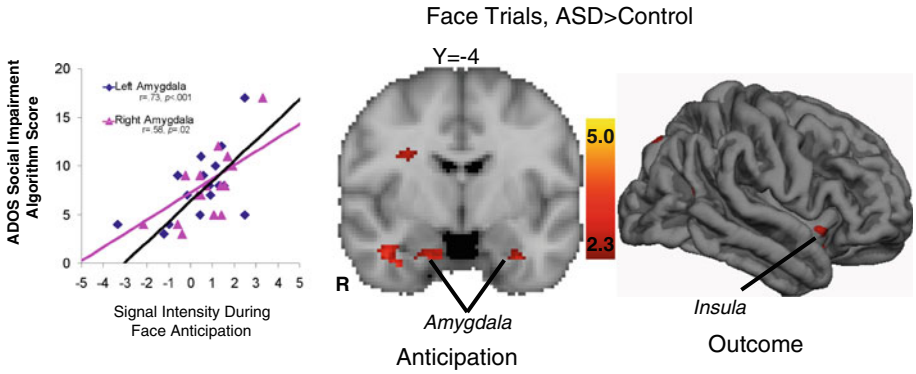

Fig. 4 Brain areas showing significantly greater activation in ASD participants relative to control participants in response to face incentives. Anticipatory responses are on the left and outcome responses are on the *right*

Grabenhorst 2008). These lines of evidence suggest that in incentive tasks the OFC functions to code for the hedonic value of incentives with respect to optimizing behavioral choices (Kim et al. 2006). Thus, decreased OFC activation in the ASD group during monetary anticipation may reflect diminished tagging of this reward stimulus with affective value. Because a major function of the OFC in incentive contexts is to influence future decision making (Deco and Rolls 2006), this has implications for the downstream effects of decreased OFC activation on goal-oriented behaviors.

Findings during monetary anticipation overlapped with those of Scott-Van Zeeland et al. (2010), who examined responses to rewards presented within the context of an implicit learning task and found decreased NAc and OFC activation to monetary rewards. Though the disparity with respect to the temporal phases of these responses (i.e., during anticipation in the present study and rewarded feedback in Scott-Van Zeeland et al. (2010)), such convergence suggests that NAc and OFC hypoactivation to rewards may reflect a replicable effect in autism.

Our finding of ACC hyperactivation during monetary anticipation in the ASD group overlaps with findings of Schmitz et al. (2008) who reported ACC hyperactivation in ASD during a rewarded continuous performance task. ACC activity is associated with reward anticipation (Dillon et al. 2008) and numerous theories of ACC function suggest that this structure maximizes adaptive responses by mediating cognitive control in ambiguous contexts (Brown and Braver 2005; Magno et al. 2006) and evaluations about whether to expend effort for rewards (Walton et al. 2002, 2003). This finding may thus suggest increased allocation of resources in what may be interpreted as an ambiguous context.

An unexpected finding during monetary anticipation was *greater* ASD activation in a ventral cluster that included the hippocampus and entorhinal cortex. The hippocampus mediates declarative memory consolidation (Eichenbaum 2000) and has dense projections to the ventral striatum (Friedman et al. 2002). Animal studies have identified "hippocampal ripples" that covary with ventral striatal activation to contribute to reward-related memory consolidation (Le Van Quyen et al. 2008), and human studies have demonstrated complex associations between hippocampus, entorhinal cortex, and NAc activations in motivated learning tasks (Adcock et al. 2006). Greater hippocampus/entorhinal cortex activation may signal increased allocation of resources towards reward-related memory formation, perhaps as a compensatory mechanism engaged coincident with decreased NAc activation during the same task period.

The ASD group also demonstrated greater left mid-frontal gyrus activation during monetary outcomes. This is somewhat surprising given that outcome reward responses are typically localized to medial ventral aspects of the prefrontal cortex. Dorsal lateral prefrontal cortex is

Table 3 Clusters showing significant group differences during face trials (minimum cluster size = 8 voxels)

Region	Brodmann Area	Size (mm^3)	Z Max	MNI coordinates		
				X	Y	Z
Anticipation						
Autism > Control						
Amygdala (right)		1,344	4.54	22	−4	−32
Amygdala (left)		544	3.46	−26	−4	−30
Cingulate gyrus (posterior, right)		168	2.71	4	−36	4
Frontal pole (left)	9	88	2.8	−20	54	28
Hippocampus (left)		216	2.74	−14	−40	4
Intracalcarine cortex (right)		712	3.07	32	−66	8
Occipital cortex (inferior, lateral, left)		304	3.32	−36	−66	8
Occipital fusiform gyrus (right)		264	2.78	36	−58	−6
Opercular cortex (central, left)		152	2.95	−34	−2	18
Parietal operculum cortex (left)		416	3.35	−36	−32	28
Planum temporale (left)		104	2.69	−34	−38	10
Precuneous cortex						
Right		288	3.03	24	−52	24
Left		88	2.79	−28	−62	14
Temporal gyrus (inferior, temporooccipital, left)		208	3.21	−56	−54	−14
Outcome						
Autism > Control						
Angular gyrus (right)	19	776	3.34	42	−58	16
Frontal gyrus (middle, right)		160	3.08	44	6	52
Frontal gyrus (superior)						
Right		120	3.03	0	18	60
Left		136	2.78	−26	4	60
Insular cortex						
Right		4,160	3.36	38	14	−6
Left		144	2.72	−30	12	−12
Left	13	584	3.13	−42	14	−4
Intracalcarine cortex (left)	18	248	2.89	−8	−76	4
Lingual gyrus (right)		944	2.97	10	−56	−2
Occipital cortex (superoir, lateral, right)	19	584	3.59	18	−82	42
Pallidum (left)		272	2.71	−20	2	−4
Parahippocampal gyrus (posterior, left)		152	2.83	−10	−34	−16
Precuneous cortex (left)		104	2.52	−18	−62	16
Putamen						
Right		352	2.67	32	−2	4
Left[a]		792	2.81	−28	−4	8
Temporal gyrus (middle, temporooccipital, left)		104	2.54	−46	−58	8
Temporal pole (right)		80	2.43	52	6	−20

[a] Two clusters within same region, coordinates and peak activation reported for highest peak activation

typically engaged in contexts that require working memory (Fletcher and Henson 2001; MacDonald et al. 2000; for a review, see Haber and Knutson 2010), when multiple value options must be compared and held in memory (Haber and Knutson 2010; Ridderinkhof et al. 2004; Knutson et al. 2007). It may be the case that reward value is more uncertain in the ASD group, thus prompting greater mid-frontal gyrus activation. It is noteworthy that, despite task differences, this finding is also consistent with those of Schmitz et al. (2008) who found left middle frontal gyrus hyperactivation in autism during a rewarded continuous performance task.

Responses to Social Rewards

Responses to social rewards revealed strikingly different patterns of activations. Contrary to hypotheses, groups did not differ with respect to NAc or VMPFC activation during face anticipation or outcomes, suggesting that faces held motivational relevance for both groups. It is noteworthy that this pattern of data stands in stark contrast to the findings of Scott-Van Zeeland et al. (2010), who reported decreased ACC, ventral PFC, and NAc activation in ASD to social rewards in an implicit learning task and highlights the likely context-dependent nature of reward circuitry function in autism.

The ASD group, however, demonstrated increased bilateral amygdala activation during anticipation of faces. Although the functions of the amygdala are varied and multifaceted, it is a critical structure for face processing specifically and social cognition more generally (for a review, see Adolphs 2010). There a rich literature linking the amygdala to social dysfunction in autism: structural MRI studies have documented abnormal amygdala growth trajectories linked to the severity of anxiety and social communication skills (Juranek et al. 2006; Munson et al. 2006), and fMRI studies have found both decreased (Pierce et al. 2001; Bookheimer et al. 2008) and increased (Dalton et al. 2005b; Monk et al. 2010) amygdala activation to faces, as well as decreased amygdala habituation to faces in autism (Lombardo et al. 2009; Kleinhans et al. 2009).

Though the amygdala is critical for fear conditioning, amygdala neurons also code for both rewarding and punishing stimuli and their predictors and thus play a critical role in reward learning (Shabel and Janak 2009). Thus, the amygdala appears to code social value, and, more specifically, mediates the flexible updating of representations of stimulus value (Gottfried et al. 2003). Although heightened amygdala activation during face anticipation may reflect increased arousal in the autism group (cf. Dalton et al. 2005a), alternatively it may more specifically reflect increased resource allocation to coding value from an ambiguous, uncertain, or abstract stimulus (Hsu et al. 2005). Of particular interest is the finding that the magnitude of amygdala activation to social rewards correlated with the degree of social impairments in the ASD sample, suggesting that amygdala activation during the processing of social rewards may contribute to the development or expression of autistic features. However, we note that the literature on amygdala activation to faces in autism is inconsistent: some studies have documented increased amygdala activation to faces in ASD (Dalton et al. 2005a; Kleinhans et al. 2009; Monk et al. 2010; Weng et al. 2010), whereas others have documented decreased amygdala activation to faces in ASD (Ashwin et al. 2007; Critchley et al. 2000; Dapretto et al. 2006; Grelotti et al. 2005; Hadjikhani et al. 2007; Pinkham et al. 2008). Thus, the implications of direct associations between amygdala activation to social rewards and clinical symptom severity are contingent on a better understanding of the nature of amygdala activation to faces in ASD.

The ASD group also demonstrated relatively increased bilateral insular cortex activation during face outcomes. In nonclinical studies, anticipation of monetary loss is accompanied by activation within insular cortex (Knutson et al. 2007), suggesting the possibility that faces outcomes were coded as a "loss" relative to expectations. An alternative function of the insular cortex is its role in the mirror neuron system engaged during empathy tasks (Singer et al. 2004; de Vignemont and Singer 2006; Wicker et al. 2003). The mirror neuron system plays a critical part in theory-of-mind functions (Gallese et al. 1996) and acts as an interface between frontal and limbic components of the mirror neuron system, facilitating the translation of an observed facial expression to its experienced significance (Carr et al. 2003). A number of studies have indicated mirror neuron dysfunction in autism, though not all have implicated the insular cortex (Nishitani et al. 2004; Dapretto et al. 2006; Oberman et al. 2005; Williams 2008), suggesting that theory-of-mind deficits in autism may be mediated by mirror neuron dysfunction. In this regard, aberrant insular cortex activation during face outcomes may reflect dysfunction of the mirror neuron system, although the direction of this effect bears replication.

Faces with neutral expression, rather than with happy expression, were used in the social reward condition to eliminate the potential confound of facial attractiveness or "approachablilty" with the "socialness" of this condition. Although the clear majority of nonclinical studies examining reward circuit reactivity to faces has investigated responses to attractive faces (e.g., Aharon et al. 2001; Cloutier et al. 2008; Liang et al. 2010) or positively valenced faces (e.g., O'Doherty et al. 2003; Chakrabarti et al. 2006). However, we note that the NAc is responsive to a broad range of socio-emotional stimuli (Phillips et al. 2003) as well as to unattractive faces (Liang et al. 2010), particularly in males (Cloutier et al. 2008). Additionally, we highlight a recent neuroimaging study that reported differential nucleus accumbens activation in autism to faces broadly, irrespective of emotional expression (Weng et al. 2010). Future studies that parametrically manipulate face attractiveness and face expression will be needed to define the boundary conditions of differential reward circuitry responses to faces in autism. Finally, we note that data suggesting differential brain activation responses to familiar versus unfamiliar faces in autism (Dalton et al. 2005b), as well as data suggesting that circumscribed interests may improve social behavior in children with

autism (Boyd et al. 2007) underscore potential mechanisms by which responses to faces in ASD may be modulated.

Reaction times and subjective ratings revealed no group differences, highlighting the unique information conveyed by fMRI data and the utility of brain imaging to reflect neurobiological processes not accessible to conscious awareness or evaluation. Divergence between self-report, behavioral, and neurobiological data is consistent with findings in other domains of clinical neurobiological research (Dichter and Tomarken 2008; Hempel et al. 2005; Rehme et al. 2009). Divergence between fMRI and self-report data in autism is also not surprising given that autism is characterized by poor insight into feeling states and manifest symptomatology (Johnson et al. 2009).

One limitation of the present study is that a significant portion of participants in the ASD group were taking psychotropic medications. Because these agents have disparate (Juckel et al. 2006a; McCabe et al. 2010) or unknown effects on neural response to rewards, particularly in contexts where more than one agent is taken simultaneously, the present study does not have a sufficient sample to conduct a systematic analysis of medication effects in the ASD group or to conduct an analyses restricted to only ASD participants not taking any medications. Such studies will be the focus of future research.

In sum, results suggest that the processing of reward-related information in autism is characterized by (a) diminished reward-circuitry (i.e., NAc OFC) activation in response to monetary incentives, (b) comparable activation of reward-circuitry (i.e., NAc, OFC, VMPFC) in response to social incentives, and (c) increased activation of multiple brain areas during reward processing (i.e., ACC and HC to monetary incentives; amygdala and insular cortex to social incentives). These results both replicate our previous findings with respect to monetary incentives (Dichter et al. 2011) and extend our model of atypical reward circuitry function in ASD to include the domain of social rewards. Taken together, these results suggest that a possible "bias" in reward processing may exist in ASD that favors nonsocial rewards at the expenses of social rewards. Such a bias could influence experience-dependent development such that nonsocial events acquire salience over social events in a manner consistent with the expression of the autism phenotype.

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