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Common and distinct neural features of social and non-social reward processing in autism and social anxiety disorder

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Autism spectrum disorders (ASDs) and social anxiety disorder (SAD) are both characterized by social dysfunction, but no study to date has compared neural responses to social rewards in ASDs and SAD. Neural responses during social and non-social reward anticipation and outcomes were examined in individuals with ASD ($n = 16$), SAD ($n = 15$) and a control group ($n = 19$) via functional magnetic resonance imaging. Analyses modeling all three groups revealed increased nucleus accumbens (NAc) activation in SAD relative to ASD during monetary reward anticipation, whereas both the SAD and ASD group demonstrated decreased bilateral NAc activation relative to the control group during social reward anticipation. During reward outcomes, the SAD group did not differ significantly from the other two groups in ventromedial prefrontal cortex activation to either reward type. Analyses comparing only the ASD and SAD groups revealed greater bilateral amygdala activation to social rewards in SAD relative to ASD during both anticipation and outcome phases, and the magnitude of left amygdala hyperactivation in the SAD group during social reward anticipation was significantly correlated with the severity of trait anxiety symptoms. Results suggest reward network dysfunction to both monetary and social rewards in SAD and ASD during reward anticipation and outcomes, but that NAc hypoactivation during monetary reward anticipation differentiates ASD from SAD.

Keywords: autism; social anxiety disorder; nucleus accumbens; ventromedial prefrontal cortex; functional magnetic resonance imaging; reward

INTRODUCTION

Given that a number of psychiatric disorders are characterized by social deficits that contribute significantly to morbidity, deficits in social processing represent a promising candidate for mechanistic research that may elucidate the etiology of multiple forms of psychopathology. Social anxiety disorder (SAD) and autism spectrum disorders (ASDs) are two such disorders, and studies contrasting these disorders may provide a means for identifying processes that drive phenotypic specificity. Consistent with the objectives of NIMHs Research Domain Criteria project ('RDoC', see http://www.nimh.nih.gov/research-funding/rdoc.shtml) to identify endophenotypes that potentially cut across traditional diagnostic boundaries (Insel and Cuthbert, 2009; Miller, 2010), in the present study we addressed common and unique patterns of brain activity during different aspects of social and non-social reward processing in SAD and ASD, with the ultimate long-term goal to help refine classification and aid in the development of empirically derived approaches to treatment for these conditions (Hasler *et al.*, 2004; Carter, 2005; Jacob *et al.*, 2009).

There is emerging consensus that ASDs are characterized by altered function of frontostriatal brain circuitry in response to rewards (Scott-Van Zeeland *et al.*, 2010; Demurie *et al.*, 2011; Kohls *et al.*, 2011; Larson *et al.*, 2011; Dichter *et al.*, 2012b). A number of studies have further suggested that such deficits encompass responses to social rewards, a pattern hypothesized to reflect diminished interest in and pleasure from social activity in ASDs (Scott-Van Zeeland *et al.*, 2010; Kohls *et al.*, 2011; Dichter *et al.*, 2012c). Recent reviews of this topic have highlighted that disrupted neural mechanisms mediating social motivation may be causally linked to social deficits in ASDs (Kohls *et al.*, 2012), may provide a mechanistic account of disrupted social attention in ASDs (Dawson *et al.*, 2012) and may provide etiologic insights into the poor development of social skills and social cognition in ASDs (Chevallier *et al.*, 2012). However, it is not clear whether reward circuitry dysfunction to social stimuli is specific to ASDs or whether this pattern of dysfunction is present in other disorders characterized by social impairments.

Reward processing is mediated in large part by dense dopaminergic projections originating from the ventral tegmental area (VTA) that project to the striatum, orbitofrontal cortex, ventromedial prefrontal cortex (vmPFC) and the anterior cingulate cortex, forming a mesolimbic dopamine pathway sensitive to the magnitude and probability of reward (Swerdlow and Koob, 1987; Berridge and Robinson, 1998, 2003; Schultz, 1998, 2000; Ikemoto and Panksepp, 1999; Berridge and Kringelbach, 2008; Berridge *et al.*, 2009). Reward-predictive dopamine bursts originating in VTA send signals to the striatum, including the nucleus accumbens (NAc), that code incentive motivation thought to underlie approach behaviors to salient goals (Knutson *et al.*, 2001; Knutson and Cooper, 2005; Kim *et al.*, 2006; Bjork and Hommer, 2007; Forbes *et al.*, 2009), and emerging evidence suggests that the neural circuits that mediate reward processing may have

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evolved, at least in part, to facilitate social attachment (Insel, 2003; Douglas *et al.*, 2004; Trezza *et al.*, 2011). Consistent with this conceptualization, social interaction mobilizes the same mesolimbic network that is active while processing non-social rewards such as food, money, sex and drugs of addiction (Koob and Le Moal, 1997; Schultz, 1997; Zink *et al.*, 2004; McClure *et al.*, 2007; Spreckelmeyer *et al.*, 2009). Furthermore, functioning of the mesolimbic circuit in the context of positive stimuli is associated with high subjective valuation, incentive salience and motivation (Smith *et al.*, 2011). Therefore, reward mechanisms may serve to encode and consolidate positive memories of social experiences, facilitating social functioning abilities hypothesized to be impaired in ASD (Dawson *et al.*, 1998, 2005; Schultz, 2005).

The primary goal of the current study was to compare the neural correlates of social and non-social reward processing in ASD and SAD, a psychiatric disorder also characterized by impaired social functioning though specifically with respect to fear of negative social evaluation (American Psychiatric Association, 1994). A pathognomonic feature of SAD, relative to other anxiety disorders, is the specificity of symptoms of anxious arousal in response to social interactions (Brown *et al.*, 1998; Kashdan, 2004; Etkin and Wager, 2007; Goldin *et al.*, 2009). Functional neuroimaging studies of SAD indicate the centrality of amygdala dysfunction in this disorder (Freitas-Ferrari *et al.*, 2010; Shin and Liberzon, 2010). However, it is not known whether impaired social functioning in SAD potentially reflects aberrant reward network engagement in response to social rewards or whether such responses may more generally reflect a pattern of dysfunctional activation to non-social and social rewards. Additionally, despite potential similarities with respect to reward processing deficits in SAD and ASD, no neuroimaging study to date has examined reward circuitry function in SAD in comparison to ASD.

We recently reported that ASD is characterized by aberrant frontostriatal responses while processing both non-social and social rewards. Specifically, we found decreased NAc activation during monetary reward anticipation and decreased vmPFC activation during monetary reward outcomes in ASD, increased amygdala activation during social reward anticipation in ASD and increased vmPFC activation while processing non-social rewards linked to circumscribed interests in ASD (Dichter *et al.*, 2012b, 2012c). These findings dovetail with other ASD studies reporting decreased left anterior cingulate gyrus and left midfrontal gyrus activation to rewards during sustained attention (Schmitz *et al.*, 2008), ventral striatal hypoactivation during social and non-social learning (Scott-Van Zeeland *et al.*, 2010), ventral striatal hypoactivation to monetary rewards and amygdala and anterior cingulate cortex hypoactivation to monetary and social rewards (Kohls *et al.*, 2013) and increased bilateral insula and anterior cingulate cortex activation to images of food (Cascio *et al.*, 2012) in ASDs. In the present study, we extend this line of research by comparing neural responses during social and monetary reward anticipation and outcomes in individuals with SAD to individuals with ASD and control participants.

Primary regions of interest included the NAc during the anticipation phase of the task and the vmPFC during the outcome phase of the task because of the centrality of these regions to reward anticipation and outcomes, respectively (Knutson *et al.*, 2003; Haber and Knutson, 2010). Additionally, the amygdala was a region of interest given that: (i) amygdala dysfunction has been linked to social impairments in SAD in response to emotional (Freitas-Ferrari *et al.*, 2010; Shin and Liberzon, 2010) and neutral (Birbaumer *et al.*, 1998; Cooney *et al.*, 2006) faces, (ii) the amygdala responds to rewarding input in certain contexts (Gottfried *et al.*, 2003; Shabel and Janak, *et al.*, 2009) and (iii) ASD is characterized by amygdala hyperactivation during social reward anticipation (Dichter *et al.*, 2012c).

Given our previous findings of reward circuitry dysfunction in ASD to monetary and social rewards (Dichter *et al.*, 2012b, 2012c) and research indicating that SAD is characterized by specific deficits in social functioning (Brown *et al.*, 1998; Kashdan, 2004; Goldin *et al.*, 2009), our central hypothesis was that the SAD group would be characterized by reward circuitry dysfunction to social, but not monetary, rewards relative to controls and would be differentiated from ASD on the basis of unimpaired reward circuitry dysfunction in response to monetary reward. Finally, given the framework of the present study that reward network dysfunction to social rewards may be mechanistically linked to the expression of social deficits in SAD, we predicted that neural responses to social rewards would predict the degree of social deficits in the SAD group.

METHODS

Participants

Inclusion/exclusion criteria for neurotypical control participants and participants with ASD as well as functional magnetic resonance imaging (fMRI) results comparing these two groups have been reported previously (Dichter *et al.*, 2012c). All participants had normal or corrected to normal vision and no history of neurological problems. Nineteen right-handed control participants [six female; mean (s.d.) age: 25.3 (7.0)] 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. The high-functioning ASD group included 16 right-handed participants [2 female; mean (s.d.) age: 26.0 (9.1); 2 diagnosed with Asperger's Disorder and 14 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. 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. Diagnoses of ASD were based on a history of clinical diagnosis confirmed by proband assessment by a research reliable assessor via the Autism Diagnostic Observation Schedule (ADOS-G) (Lord *et al.*, 2000) with standard clinical algorithm cutoffs.

The SAD group was recruited via online ads in Chapel Hill and Durham and included 15 participants [6 female; mean (s.d.): 26.9 (5.3)]. Individuals with SAD were required to meet DSM-IV criteria for current SAD based on the Anxiety Disorders Interview Schedule for DSM-IV (Di Nardo *et al.*, 1994), administered by a doctoral level interviewer reliable with other interviewers at Kappa = 0.80 or above. SAD participants had Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987) scores ≥60 on the social fear subscale. Thirteen SAD participants were not taking psychotropic medication; one was taking Prozac and one was taking Celexa. 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 between $35 and $45 for the imaging portion of the study. Participants completed a mock scan prior to imaging.

Participants completed: (i) The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) [one ASD participant completed the Leiter-R (Roid and Miller, 1997) instead of the WASI]; (ii) the Autism Quotient (Baron-Cohen *et al.*, 2001), to assess the overall severity of autism symptoms as well as to verify that the neurotypical and SAD groups did not have significant autistic symptoms and (iii) the

Table 1 Mean (s.d.) age and symptom profiles

	Autism ($n = 16$)	SAD ($n = 15$)	Control ($n = 19$)	Group comparison *P*-values		
				Control-ASD	ASD-SAD	Control-SAD
Age	26.0 (9.1)	26.9 (5.3)	25.3 (7.0)	0.95	0.89	0.80
No. of female	2	6	6	0.10	0.02	0.18
ADOS Comm	6.1 (5.5)	0.6 (0.9)	–	–	<0.001	–
ADOS SI	8.7 (2.2)	1.5 (1.7)	–	–	<0.0001	–
ADOS SBRI	2.25 (1.8)	0.2 (0.4)	–	–	<0.001	–
WASI*	109.9 (19.6)	116.4 (9.38)	127.0 (7.9)	<0.01	0.28	<0.01
AQ total score	24.8 (12.7)	22.9 (5.85)	12.4 (5.1)	<0.0001	0.61	<0.0001
RBS-R total score	28.3 (25.7)	13.5 (10.94)	3.6 (4.6)	<0.001	0.06	<0.01
SRS total score	79.4 (22.0)	147.0 (16.5)	57.1 (13.7)	<0.01	<0.01	<0.0001
LSAS total	–	133.0 (13.24)	–			
LSAS fear subscale	–	67.1 (6.89)	–			
LSAS avoidance subscale	–	66.3 (7.55)	–			
STAI-T	–	46.53 (3.44)	–			

*One ASD participant completed the Leiter-R (Roid and Miller, 1997) instead of the WASI and is not included in this average.
WASI, Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999); RBS-R, The Repetitive Behavior Scale-Revised (Bodfish *et al.*, 1999; Lam and Aman, 2007); AQ, the Autism Quotient (Baron-Cohen *et al.*, 2001); SRS, Social Responsiveness Scale (Constantino *et al.*, 2003); LSAS, Liebowitz Social Anxiety Scale (Liebowitz, 1987); STAI-T: State-Trait Anxiety Inventory (Knight *et al.*, 1983); ADOS: Autism Diagnostic Observation Schedule.

Social Responsiveness Scale, a continuous measure of autism symptom severity (Constantino *et al.*, 2003) (see Table 1). The SAD group, but not the other two groups, completed the trait scale of the State-Trait Anxiety Inventory (STAI-T) (Knight *et al.*, 1983) and the LSAS, which are not validated for use with ASD populations. Groups did not differ in age, $F(48) = 0.24$; $P > 0.80$, or gender distribution, $\chi^2(1) = 1.58$, $P > 0.21$.

fMRI task

The fMRI task was an incentive delay task (Knutson *et al.*, 2000) modified such that on alternating runs money and pictures of neutral faces were presented as rewards. All runs were 'win versions' (i.e. money or faces could be won or not won, but could not be lost). Three runs were modified such that 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 order and the run type presented first was counter-balanced across participants. Runs began with a 10 s instructional screen indicating the forthcoming run type. The two reward types (i.e. money and faces) 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 the following: (i) a 2000 ms cue indicating whether adequately quick responses to the bulls-eye would result in a 'win' (a triangle) or not (a circle); (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 not, with wins accompanied by either an image of money or of a face 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 no potential win) were aperiodic and pseudorandomly ordered. Each 8 min run contained 40 trials, of which 20 were potential win trials.

During money runs, participants won $1 per trial if bulls-eye responses were adequately quick. During face runs, participants viewed a face image if bulls-eye responses were adequately quick. Coincident with feedback, cumulative win totals were presented. Participants were instructed to respond to all target bulls-eyes as quickly as possible to win on as many trials as possible, and win or non-win outcomes were contingent on reaction times (RTs). The task was adaptive such that participants were successful on two-thirds of trials, regardless of individual differences in RTs (confirmed via inspection of behavioral data collected during scanning).

Standard administration of incentive delay tasks involves showing participants rewards that may be won prior to scanning (Knutson *et al.*, 2001). Consistent with this procedure, participants were shown the money they could win based on scanner task performance and were informed that they would receive the total amount of money won during the scan. Prior to scanning, participants rated face stimuli on the dimensions of valence and arousal. Stimuli were presented using E-Prime presentation software version 1.1 (Psychology Software Tools Inc., Pittsburgh, PA, USA) and displayed through magnet-compatible goggles (Resonance Technology, Inc., Northridge, CA, USA).

Imaging methods

Scanning was performed on a General Electric Health Technologies, 3 T 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 = 7.33 ms; TE = 3.03 ms; FOV = 22 cm; image matrix = 256^2; voxel size = 0.85 mm × 0.85 mm × 3.80 mm) and used for co-registration with the functional data. These structural images were aligned in the near axial plane defined by the anterior and posterior commissures. Whole-brain functional images consisted of 30 slices parallel to the AC–PC plane using a BOLD-sensitive gradient-echo EPI sequence with higher order shimming, at TR of 2000 ms (TE: 30 ms; FOV: 22 cm; isotropic voxel size: 3.43 × 3.43 × 4.00; flip angle 77°). Runs began with four 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: (i) brain extraction (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

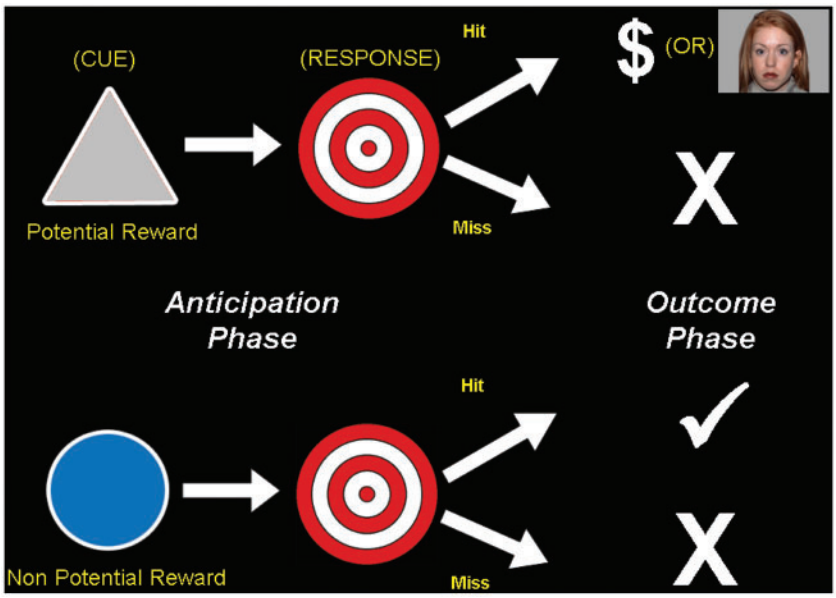

Fig. 1 Incentive delay task. Participants alternated 'money' and 'face' reward runs, denoted by an instructional screen at the start of each run. Each trial consisted of a cue (i.e. a triangle indicated an incentive trial, a circle indicated a non-incentive trial), an anticipatory delay, a target and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

(Jenkinson *et al.*, 2002). Functional images 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 events were used to model a signal response containing a regressor for each response type, which was convolved with a double-γ function to model the hemodynamic response of the entire duration of the anticipation and outcome phases of the task. Model fitting generated whole-brain images of parameter estimates and variances, representing average signal change from baseline. Group-wise activation and deactivation images were calculated by a mixed effects higher level analysis using Bayesian estimation techniques, FMRIB Local Analysis of Mixed Effects (Woolrich *et al.*, 2001) with cluster mean threshold of at least $Z > 2.3$ and a cluster-corrected significance threshold of $P < 0.05$ (FLAME 1 + 2) (Beckmann *et al.*, 2003).

Imaging data analytic strategy

The primary omnibus method of fMRI data analysis was a 3 (Group: ASD, SAD, Control) × 2 (Reward type: Money, Faces) mixed analysis of variance (ANOVA) model applied separately for the anticipatory and outcome phases of the task, each modeled against an implicit baseline (the anticipatory phase modeled only 'potential win' trials and the outcome phase modeled only successful 'potential win' trials). Significant clusters were further evaluated by extracting subject- and condition-specific signal intensity coefficients to evaluate simple effects. This approach allowed us to identify activations that potentially overlapped between groups (i.e. common variation). Supplementary analyses excluded controls and modeled SAD *vs* ASD only to highlight activations that were specific to SAD relative to ASD.

Activation localizations were based on Harvard–Oxford cortical and subcortical structural probabilistic atlases as implemented in FSLView version 3.0. Because groups differed in estimated intelligence, models were evaluated that included full-scale estimated intelligence as a covariate. These analyses yielded highly similar results, and thus results without these covariates are presented for comparison with other studies of reward network function in ASD that did not covary these variables (Schmitz *et al.*, 2008; Scott-Van Zeeland *et al.*, 2010).

Finally, relations between neural responses to rewards and social anxiety symptoms from the LSAS and STAI-T were assessed in the SAD group alone (associations between neural responses to rewards and autism symptoms in the ASD group have been reported previously (Dichter *et al.*, 2012c)) by using group-level activation maps to extract mean subject-specific parameter estimates that were then analyzed in SAS 9.2 (Cary, NC, USA). For these exploratory correlational analyses, we did not correct for multiple comparisons.

RESULTS

Behavioral results

In-scanner RTs to task bulls-eyes are depicted in Figure 2 and were compared via a 3 (Group: ASD, SAD, Control) × 2 (Trial Type: Money potential win, Money non-potential win, Faces potential win, Faces non-potential win) mixed ANOVA, followed by two Group × Trial Type mixed ANOVAs comparing the SAD group to both other groups. The ANOVA including all three groups yielded no Group × Stimulus Type interaction, $F(2,48) = 0.40$, $P > 0.85$, no main effect of Group, $F(2,48) = 0.44$, $P > 0.60$, but a main effect for Reward Type, $F(1,48) = 6.67$, $P < 0.02$, reflecting faster RTs overall on money trials relative to face trials. There was no main effect of Group for SAD *vs* controls, $F(1,33) = 0.48$, $P > 0.45$, or SAD *vs* ASD, $F(1,34) = 0.04$, $P > 0.80$. Exploratory between-groups *t*-tests comparing groups on all trial types revealed no significant group differences, $Ps > 20$.

Valence and arousal ratings of faces were examined by separate 3 (Group: ASD, SAD, Control) ANOVAs as well as *t*-tests comparing the SAD group to the two other groups. Analysis of valence ratings yielded no main effect of Group, $F(1,48) = 0.243$, $P = 0.78$, or significant differences between the SAD group and the two other groups, $Ps > 0.30$. Analysis of arousal ratings yielded no main effect of group,

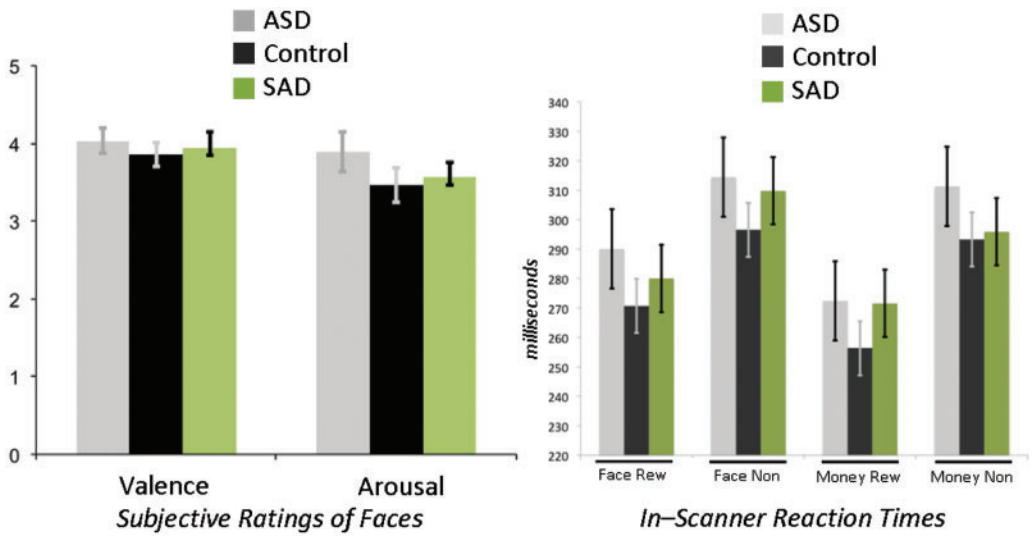

Fig. 2 Left: Average valence and arousal ratings of faces. Valence = 0 (extremely unpleasant) to + 8 (extremely pleasant); Arousal = 0 (not at all aroused) to + 8 (extremely aroused). Right: Average reaction times during face and money conditions for both potential reward ('Rew') and non potential reward ('Non') trials. Error bars represent standard errors of the mean.

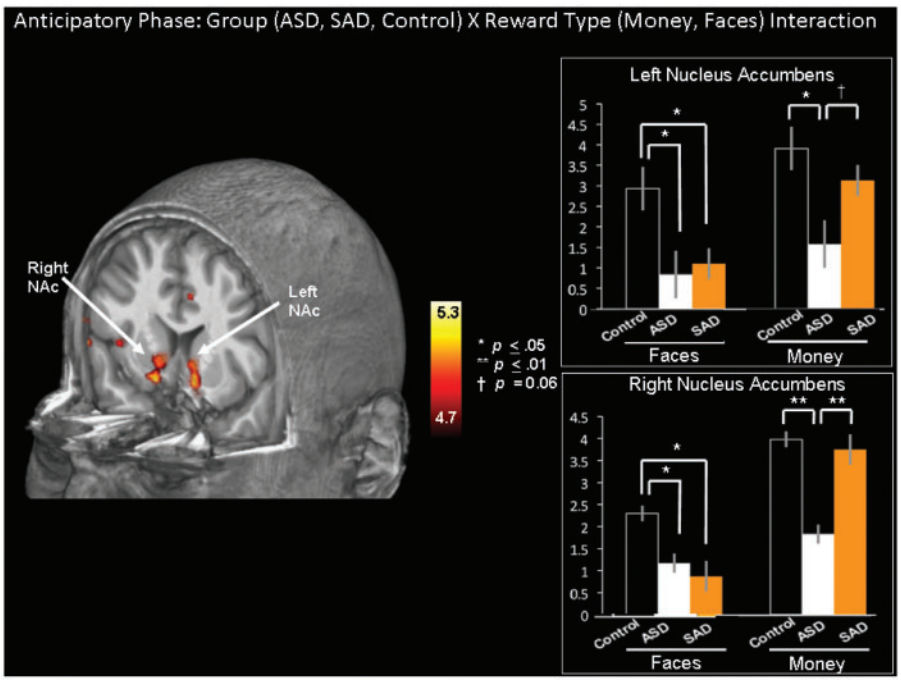

Fig. 3 Brain areas showing significant Group (ASD, SAD, Control) × Reward Type (Money, Faces) interactions during the anticipatory phase of the task. The bar graphs depict parameter estimates by group and trial type in the significant NAc clusters.

$F(1,48) = 1.20$, $P = 0.31$, or significant differences between the SAD group and the two other groups, $Ps > 0.20$.

fMRI results

Three-group analysis, anticipatory phase

During the anticipatory phase of the task, a whole-brain 3 (Group: ASD, SAD, Control) × 2 (Reward Type: Money, Faces) analysis revealed significant interactions in bilateral NAc [Right: $F(50) = 5.35$, $P < 0.001$; Left: $F(50) = 5.35$ $P < 0.001$, see Figure 3]. To assess the nature of these interactions, subject- and condition-specific signal intensity values were extracted from these two NAc clusters to assess simple effects. This revealed that during anticipation of monetary rewards, SAD did not differ from controls in NAc activation (Right: > 0.90; Left: $P > 0.60$), but did activate NAc more than the ASD group (Right: $P < 0.01$; Left: $P = 0.06$), although the difference between ASD and SAD in left NAc was at the level of a trend. During anticipation of social rewards, the NAc showed significantly less activation in both SAD (Right: $P < 0.05$; Left: $P = 0.05$) and ASD (Right: $P = 0.05$; Left: $P < 0.05$), relative to controls. Within-group comparisons revealed no significant differences in NAc activation between face and monetary conditions for any group. Results of all pairwise comparisons for anticipatory phase data are presented in Table 2, as well as activation patterns and coordinates of all significant clusters.

Supplementary analyses examined the 3 (Group: ASD, SAD, Control) × 2 (Reward Type: Money, Faces) interaction term during the anticipatory phase of the task for the contrast of potential win *vs* non-potential win trials. As depicted in Supplementary Figure S1, this approach also yielded significant interaction clusters in bilateral NAc. However, subject- and condition-specific signal intensity values extracted from these NAc cluster did not yield any significant between-groups or between-conditions differences other than larger responses in controls to money than face rewards.

Our previous article directly comparing these ASD and control sample reported findings at a corrected threshold of $Z > 2.3$ (Dichter *et al.*, 2012c). Supplementary Figure S2 depicts results of the 3 (Group: ASD, SAD, Control) × 2 (Reward Type: Money, Faces) interaction term in an axial slice through bilateral NAc at this same corrected threshold of $Z > 2.3$. As is evident from this figure, the resulting cluster that subsumes bilateral NAc is so large that meaningful interpretation of group- and condition-specific signal intensities from this cluster is not possible.

Three-group analysis, outcome phase

During the outcome phase of the task, a Group × Reward Type model revealed a significant interaction in vmPFC (see Figure 4; denoted Subcallosal Cortex [*x*,*y*,*z* = 0.91, 15.97, −4.20] in Table 3). Once again, subject- and condition-specific signal intensity values were extracted from this cluster to assess simple effects, which revealed no significant difference between SAD and ASD or control groups during social ($Ps > 0.38$) or monetary ($Ps > 0.54$) reward outcomes (see Table 3). However, the SAD group demonstrated relatively decreased vmPFC activation to face reward outcomes than monetary reward outcomes, $t(14) = 4.09$, $P < 0.001$. No other within-group comparisons were significant ($Ps > 0.05$).

Supplementary analyses considered responses during the outcome phase of the task for successful *vs* non-successful trials. As depicted in Supplementary Figure S3, this approach yielded a significant interaction cluster spanning a larger area of medial prefrontal cortex. Subject- and condition-specific signal intensity values extracted from this cluster did not yield any significant between-groups or between-conditions differences other than larger responses in controls to money than face rewards.

Supplementary analyses: ASD *vs* SAD

To isolate the neural mechanisms of reward processing that may be specific to SAD relative to ASD, we analyzed models comparing SAD and ASD only (i.e. without modeling responses in the control group) via a 2 (Group: SAD, ASD) × 2 (Reward type: Money, Faces) mixed ANOVA applied separately for the anticipatory and outcome phases of

Table 2 Clusters reflecting Group (ASD, SAD, Control) × Reward Type (money, faces) interactions during the anticipatory phase of the task and follow-up pairwise *t*-tests

Region	MNI coordinates			*Z* mean	*P*-values Face rewards			Between-groups *P*-values Money rewards		
	x	*y*	*z*		C-A	A-S	C-S	C-A	A-S	C-S
Left accumbens	−10.41	15	−8.07	5.21	0.03	0.85	0.05	0.02	0.06	0.64
Subcallosal cortex	9.55	18.27	−11.92	5.14	0.55	0.57	0.30	0.009	0.02	0.54
Right temporal occipital fusiform	26.67	−58.93	−12.67	5.13	0.44	0.62	0.78	0.93	0.59	0.76
Left lingual gyrus	−18.69	−55.34	−10.93	5.13	0.64	0.99	0.60	0.46	0.18	0.76
Right accumbens	11	8.33	−8.50	5.13	0.05	0.74	0.04	0.008	0.01	0.94
Left thalamus	−11.43	−26.2	0.05	5.17	0.56	0.63	0.91	0.43	0.54	0.76
Right insular cortex	39.2	7.6	−0.4	5.07	0.95	0.80	0.84	0.13	0.81	0.12
Right insular cortex	37.73	15.07	−0.13	5.12	0.99	0.91	0.92	0.22	0.58	0.51
Right thalamus	9.11	−28.67	2	5.13	0.58	0.28	0.12	0.04	0.05	0.79
Left intracalcarine cortex	−16.04	−69.89	11.37	5.23	0.93	0.98	0.92	0.62	0.51	0.94
Left precentral gyrus	−57.20	7.2	7.6	5.15	0.77	0.30	0.42	0.25	0.53	0.73

C-A, controls *vs* ASD; A-S, ASD *vs* SAD; C-S, controls *vs* SAD.

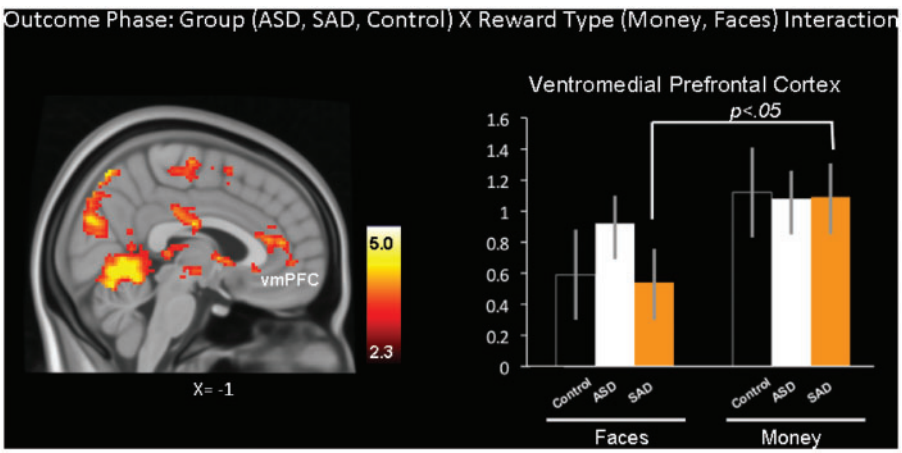

Fig. 4 Brain areas showing significant Group (ASD, SAD, Control) × Reward Type (Money, Faces) interactions during the outcome phase of the task. The bar graph depicts parameter estimates by group and trial type in the significant vmPFC cluster.

Table 3 Clusters reflecting Group (ASD, SAD, Control) × Reward Type (money, faces) interactions during the outcome phase of the task and follow-up *t*-tests

Region	MNI coordinates			*Z* mean	*P*-values			Between-groups *P*-values		
					Face rewards			Money rewards		
	x	*y*	*z*		C-A	A-S	C-S	C-A	A-S	C-S
Right lingual gyrus	1.29	−65.49	5.37	3.29	0.77	0.86	0.90	0.94	0.37	0.54
Right parahippocampal gyrus	24.75	4.4	−14.36	2.96	0.16	0.14	0.89	0.12	0.19	0.68
Right fusiform gyrus	41.91	−57.49	−16.68	3.52	0.88	0.62	0.63	0.75	0.65	0.99
Left amygdala	−24.30	−3.25	−14.63	2.89	0.12	0.25	0.87	0.65	0.21	0.10
Left inferior temporal gyrus	−42.27	−49.23	−17.92	3.72	0.32	0.31	0.83	0.70	0.86	0.61
Right temporal pole	35	18	−24.5	2.83	0.10	0.34	0.74	0.20	0.76	0.48
Right temporal fusiform	41	−20.5	−19	2.6	0.62	0.75	0.79	0.70	0.90	0.65
Left frontal pole	−27	59	−14	2.82	0.66	0.65	0.96	0.67	0.19	0.16
Left frontal orbital cortex	−32.68	30.08	−3.56	2.74	0.97	0.51	0.55	0.49	0.67	0.41
Subcallosal cortex	5.07	25.73	−4.93	2.66	0.98	0.52	0.59	0.85	0.82	0.98
Right lateral occipital cortex	47	−76	−4	2.60	0.89	0.27	0.29	0.99	0.58	0.65
Right thalamus	2	−20.1	−4	2.56	0.81	0.89	0.89	0.85	0.72	0.63
Right cerebral cortex	37.25	−60	1.25	2.65	0.39	0.42	0.15	0.62	0.46	0.91
Subcallosal cortex	0.1	19	−2	2.6	0.33	0.39	0.86	0.17	0.87	0.12
Right frontal orbital cortex	34.29	29.71	−0.86	2.6	0.66	0.08	0.16	0.31	0.88	0.28
Cingulate cortex	3.7	40.32	9.8	2.9	0.57	0.25	0.68	0.62	0.44	0.93
Left precentral gyrus	−44.75	6.62	31.33	3.03	0.78	0.55	0.81	0.32	0.68	0.25
Left frontal cortex	−44.56	28	2.33	2.63	0.24	0.39	0.80	0.31	0.85	0.43
Left occipital pole	−20.67	−95.47	3.67	3.31	0.37	0.35	0.99	0.85	0.90	0.93
Right occipital pole	12	−96.2	5	2.67	0.27	0.72	0.56	0.70	0.55	0.91
Right middle temporal gyrus	49.7	−57.8	8.75	2.77	0.09	0.61	0.41	0.03	0.78	0.10
Left putamen	−21.5	5	4	2.55	0.25	0.68	0.49	0.71	0.24	0.50
Left supracalcerine cortex	−4.59	−86.24	9.18	2.73	0.40	0.53	0.70	0.64	0.17	0.19
Right frontal pole	21.5	26.5	8.5	2.59	0.05	0.06	0.98	0.48	0.52	0.81

C-A, controls *vs* ASD; A-S, ASD *vs* SAD; C-S, controls *vs* SAD.

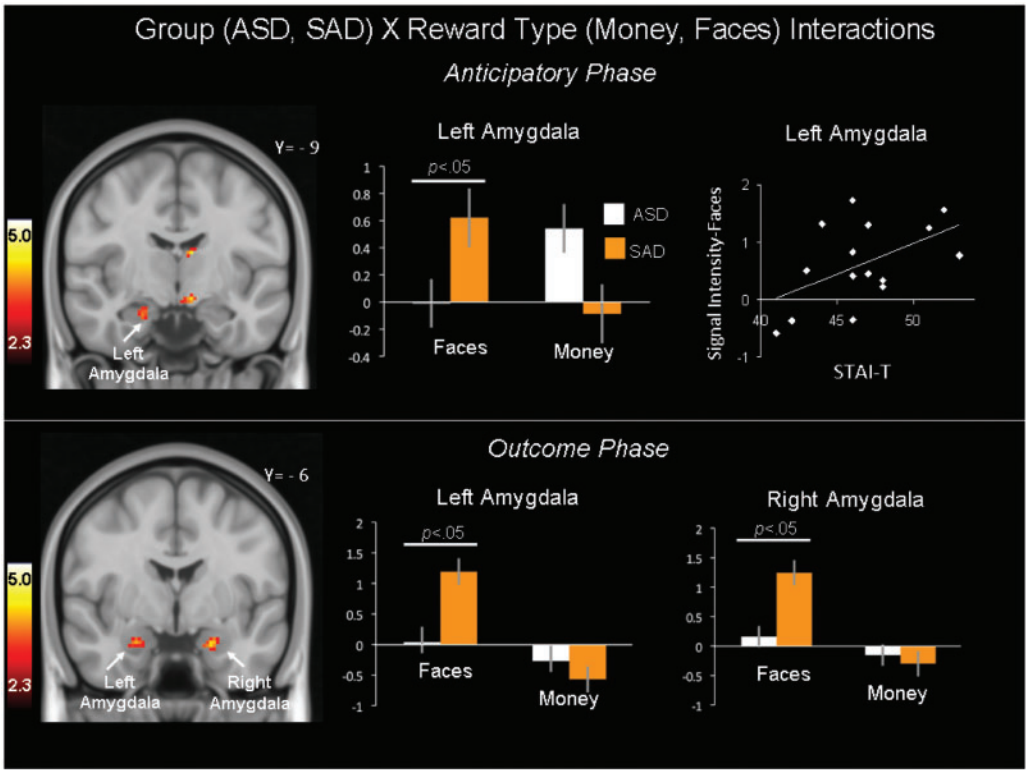

Fig. 5 Brain areas showing significant Group (ASD, SAD) × Reward Type (Money, Faces) interactions during anticipatory (upper panel) and outcome (lower panel) phases of the task. The bar graphs depict parameter estimates by group and trial type in the significant amygdala clusters. The scatterplot illustrates the significant correlation ($r = 0.65$, $P < 0.01$) between trait anxiety measured by the STAI-T and signal intensity during anticipation of social rewards in the left amygdala cluster that differentiated ASD and SAD during face reward anticipation.

Table 4 Clusters reflecting Group (ASD, SAD) × Reward Type (money, face) interactions and between-groups *t*-tests

Region	MNI coordinates			*Z* mean	*P*-value	
	x	*y*	*z*		Faces	Money
Anticipatory phase						
Brain stem	−0.97	−11.74	−24.39	2.61	0.02	0.78
Left hippocampus	21.1	−11	−19.1	2.38	0.07	0.33
Left fusiform cortex	−37.2	−43.2	−21.6	2.5	0.04	0.84
Right frontal pole	38.67	35.93	−17.82	2.7	0.007	0.20
Right middle temporal gyrus	56.86	−4.86	−18.29	2.5	0.15	0.07
Subcallosal cortex	2.4	6.4	−19.2	2.34	0.07	0.06
Right insula	34.43	4.71	−16	2.45	0.06	0.55
No label	−6.78	−10.61	−12.78	2.59	0.04	0.48
Left amygdala	−24.33	−7.39	−17.5	2.52	0.02	0.11
Left middle temporal gyrus	−45.67	−34	−4.33	2.38	0.0001	0.12
Posterior cingulated	11.65	−32.71	4.59	2.52	0.07	0.96
Right putamen	24.75	9.25	0.5	2.44	0.05	0.32
Right putamen	30.67	0.67	3.56	2.43	0.17	0.66
Right frontal pole	34.31	51.03	16.99	2.81	0.55	0.11
Left frontal pole	−25	63.5	7	2.54	0.01	0.13
Right Heschl's gyrus	42.57	−19.71	9.14	2.34	0.25	0.95
Left lateral occipital cortex	−47.75	−61.75	14.25	2.45	0.07	0.25
Left thalamus	−8.06	−7.02	16.15	2.61	0.02	0.72
Outcome phase						
Left hippocampus	−22.31	−6.14	−22.45	3.58	0.94	0.15
Right fusiform cortex	41.9	−51.73	−19.13	3.69	0.50	0.31
Brain stem	1.18	−14.12	−23.76	3.47	0.59	0.02
Left fusiform cortex	−40.87	−48.53	−20.6	3.7	0.50	0.23
Right amygdala	24.7	−3.81	−22.70	3.5	0.03	0.84
Left amygdala	−18.1	−6	−24.4	3.64	0.04	0.91
Right lingual gyrus	16.24	−64.96	−8.42	3.63	0.46	0.15
Left lingual gyrus	−9.38	−58.63	−6.25	3.56	0.93	0.66
Brain stem	2.75	−33.75	0.5	3.38	0.71	0.31
Right thalamus	2.12	1.53	3.06	3.6	0.24	0.06
Right thalamus	0.69	−18.62	8.62	3.51	0.85	0.18
Cingulate gyrus	2.12	37.72	16.4	3.44	0.63	0.16
Right inferior frontal gyrus	48.1	20.75	18.59	3.64	0.01	0.21
Left cuneal cortex	−7.81	−71.62	21.24	3.4	0.58	0.66
Right cuneal cortex	7.67	−80.33	21.33	3.36	0.18	0.08
Posterior cingulate	1.37	−20.04	27.45	3.78	0.34	0.29
Right cuneal cortex	1.74	−80.52	31.65	3.44	0.28	0.82
Left cuneal cortex	−6.17	−84.83	35.83	3.58	0.31	0.48
Left precuneus	−4.64	−77.52	43.36	3.58	0.03	0.40
Right precentral gyrus	46.44	−1.11	44.67	3.45	0.12	0.73
Right angular gyrus	53.2	−50.8	48.4	3.36	0.35	0.95
Left angular gyrus	−51.14	−52.29	48.57	3.40	0.72	0.50
Right precentral gyrus	8.5	−29.17	60.33	3.41	0.97	0.10
Left fusiform cortex	−22	−55.1	−15.35	3.56	0.23	0.92

the task, followed up by *t*-tests on significant clusters. During the anticipation phase, these analyses revealed no significant interaction clusters in NAc, but significant interaction clusters in bilateral amygdala. Follow-up tests on extracted signal intensity values within these amygdala clusters revealed that during anticipation of social rewards, SAD subjects activated bilateral amygdala (right: $t[29] = 2.11$ $P < 0.05$; left: $t[29] = 2.09$, $P < 0.05$) significantly more than the ASD group (see Figure 5 and Table 4). During the outcome phase, a Group × Reward Type analysis revealed no significant interaction clusters in vmPFC, but once again significant interaction clusters in bilateral amygdala. Follow-up tests on these amygdala clusters revealed greater amygdala activation in the SAD group, relative to the ASD group, to social reward outcomes for both the right ($t[29] = 2.18$, $P < 0.05$) and left ($t[29] = 2.58$, $P < 0.05$) amygdala.

Relations to anxiety symptom in the SAD group

To examine relations between neural responses to rewards and LSAS and STAI-T scores in the SAD group, we extracted parameter estimates from the following: (i) the significant bilateral NAc interaction clusters yielded by the three-group analysis during the anticipation phase of the task, (ii) the significant vmPFC interaction cluster yielded by the three-group comparison during the outcome phase of the task and (iii) the bilateral amygdala interaction clusters yielded by the two-group comparison for both anticipatory and outcome phases of the task. A significant correlation was found between the STAI-T and activation in the left ($r = 0.65$, $P < 0.01$) amygdala cluster that differentiated SAD and ASD groups during anticipation of social rewards (see Figure 5). This relation was not found for the amygdala cluster that differentiated SAD from ASD during monetary anticipation, suggesting that the correlation between amygdala activity and trait anxiety in the SAD group was specific to anticipating social rewards. No other correlations were significant.

COMMENT

Emerging research suggests that dysfunctional reward processing characterizes a range of psychiatric and neurodevelopmental disorders suggesting that altered mesolimbic responses to rewards may be an

endophenotype that cuts across diagnostic boundaries (Hyman, 2007). However, research to date has not focused on comparing disorders characterized by reward circuitry dysfunction to identify common and unique patterns of the brain activity. The present findings represent the first study of social and non-social reward processing in SAD and the first to directly compare reward responses in SAD and ASD. More broadly, these results suggest that distinct temporal phases of reward responses (i.e. reward anticipation and outcomes) may drive unique behavioral phenotypes among disorders with reward processing deficits.

The present results indicate reward network dysfunction in both ASD and SAD, but that the nature of this dysfunction is related to the type of reward processed. During reward anticipation, the ASD group was characterized by NAc hypoactivation during both social and monetary reward anticipation, whereas SAD was characterized by NAc hypoactivaton only during social reward anticipation. We also found that the SAD group demonstrated greater vmPFC activation to monetary relative to social rewards outcomes and no such effect of reward type for the ASD group. Thus, for both temporal phases of reward processing examined, we found that SAD was characterized by deficits during social reward processing specifically, whereas ASD was characterized by a more generalized pattern of reward processing deficits.

Models that compared only SAD and ASD were analyzed to highlight brain activation that differentiated SAD from ASD specifically. These analyses revealed no group differences in NAc and vmPFC during reward anticipation or outcomes. However, there was evidence of bilateral amygdala hyperactivity in SAD relative to ASD during social and non-social reward anticipation, and activity in amygdala clusters that differentiated groups during social reward anticipation was significantly correlated with trait levels of anxiety within the SAD group. The amygdala is a central structure for social cognition (Adolphs, 2010) and is critically involved in reward learning (Shabel and Janak, 2009) and coding social reward value (Gottfried *et al.*, 2003). There is a rich literature on the relevance of amygdala dysfunction to social processing deficits in SAD mainly in the context of threat (Freitas-Ferrari *et al.*, 2010; Shin and Liberzon, 2010), but this is the first study to link amygdala dysfunction in SAD to deficits in reward processing.

The linkage between trait anxiety levels in the SAD group and amygdala activation during anticipation of social rewards suggests that amygdala function to social rewards may be mechanistically linked to the expression of anxiety symptoms in SAD. In this regard, we note that multiple studies have reported anomalous amygdala activation during face processing in ASD that has been interpreted to contribute to social deficits in ASDs (Pierce *et al.*, 2004; Dalton *et al.*, 2005; Corbett *et al.*, 2009; Kleinhans *et al.*, 2009). The present findings of amygdala hyperactivity in SAD relative to ASD suggest that amygdala dysfunction in social contexts may not be specific to ASD and may even be less pronounced in ASD than in SAD. Given high rates of comorbid anxiety disorders in ASD (White *et al.*, 2009) and given partial phenotypic overlap of social impairments in ASD and SAD, it is possible that amygdala deficits observed in ASD are a reflection of certain aspects of social impairments that are common across disorders. If this is the case, comparing multiple groups on different aspects of social processing may help uncover deficits specific to different disorders and thus driving specific impairments. It is noteworthy that amygdala response during social reward anticipation predicted levels of anxiety symptoms in the SAD group despite the lack of group differences with respect to subjective responses to face stimuli. This likely reflects that amygdala responses predictive of anxiety symptoms were evident during face anticipation, whereas subjective ratings were collected during faces viewing.

The finding that NAc hypoactivation to social rewards was a common feature of both ASD and SAD suggests that the social deficits that are pathognomonic in ASD and SAD may be linked to alterations in approach-driven motivational processes. If replicated, this may indicate a novel target for mechanistic and treatment research, particularly given that social deficits in SAD are commonly viewed as manifestations of heightened avoidance motivation rather that deficient approach motivation (Ouimet *et al.*, 2009). When conceptualized within a developmental experience-dependent perspective, a failure to experience social stimuli as rewarding at a young age may contribute to the development of social avoidance. Alternatively, anxiety elicited by social stimuli may interfere with the processing of social rewards. This latter explanation seems most plausible for the SAD group where processing social rewards was associated with heightened amygdala activation.

Although the ASD and SAD groups both showed decreased NAc activation to social rewards, the groups were differentiated on the basis of NAc responsivity to monetary rewards, suggesting the possibility of a more domain-general pattern of reward network dysfunction during reward anticipation in ASD relative to SAD. As we have discussed previously, a pattern of domain-general reward network dysfunction in ASD is a novel conceptualization of social deficits in ASD (Dichter *et al.*, 2012c) that may provide a potentially parsimonious account of even non-social deficits (e.g. restricted and repetitive behaviors) that characterize the disorder (Dichter *et al.*, 2012b).

This three-group study contains data from individuals with ASDs and controls previous reported by our research group (Dichter *et al.*, 2012c). The analytic approaches presented here (i.e. omnibus three-group models and models comparing only the ASD and SAD groups) were selected to highlight patterns of similarities and differences across all three groups and not to repeat ASD-control comparisons presented previously. However, these models also result in activation clusters that differed in extent and localization from clusters previously reported when comparing only the ASD and control groups. Specifically, in Dichter *et al.* (2012c) we reported that the ASD group was characterized by hypoactivation during monetary but not social reward anticipation. In the present analysis (see the bar graphs in Figure 3), the NAc clusters identified by the omnibus three-group anticipatory analysis indicate significant differences between ASD and control groups for both monetary and social reward conditions. We note that the NAc clusters in Figure 3 are ventral (*z*-coordinates: Left:−8.07; Right: −8.50) to the right NAc cluster presented in Figure 3 of Dichter *et al.* (2012c) (*z*-coordinates: −4), suggesting that the ventral striatum may possibly show relatively greater sensitivity to social reward anticipation deficits in ASD than the dorsal striatum.

Results from the current study should be evaluated in light of methodological limitations. First, some patients in both clinical groups were taking psychotropic medications, and future studies with medication-free samples will be needed. Additionally, we used neutral faces as social rewards because individuals with ASD show impairments at emotional expressions detection impairments (Sasson, 2006), and there is evidence that individuals with SAD may rate neutral faces as negative (Yoon and Zinbarg, 2008) and may show increased amygdala activity to neutral faces (Birbaumer *et al.*, 1998; Cooney *et al.*, 2006). We note that valence and arousal ratings of neutral faces were equivalent across groups, but future studies may compare reward system function in SAD and ASD to face rewards with a range of expressions. We also note that the uneven gender distribution across groups may have influenced results. Additionally, anxiety symptoms were not assessed in the ASD group, raising the possibility that shared neurofunctional features in both clinical groups may be influenced by the presence of anxiety symptoms in the ASD group. Additionally, depressive symptoms were not assessed in either clinical group, and

depression status (Pizzagalli *et al.*, 2009) is known to influence neural processing of rewards. Given that both ASD (Simonoff *et al.*, 2012) and SAD (Kessler *et al.*, 1999) have high rates of comorbidities with mood disorders, this will be an important consideration for future research.

It will also be important in future studies to examine reward-based brain activation in individuals with comorbid SAD and ASD. A growing literature supports that anxiety is common in the context of ASD (White *et al.*, 2009, 2010) and that ASD and SAD may be highly comorbid, with ~29% of children with ASD also meeting criteria for SAD (Simonoff *et al.*, 2008). The present findings of similarities in aspects of reward circuitry response to social and non-social rewards in ASD and SAD may shed light on apparent comorbidity of these disorders. However, we caution against interpreting the current results as evidence for ASD-like features in SAD or anxiety-like features in ASD; rather, these finding appear to reflect shared and distinct neurofunctional markers of social dysfunction in these two disorders.

In summary, this study reports on neural mechanisms of reward processing deficits in SAD and ASD. Results indicate that both ASD and SAD are characterized by reward network dysfunction, but that deficits in ASD may be domain general whereas deficits in SAD may be specific to social incentives. Although future research will be needed to assess the clinical and diagnostic utility of these brain activation patterns in patients characterized by social dysfunction, linkages reported here between neural response to social reward anticipation and anxiety symptoms in SAD suggest the clinical relevance of addressing SAD within the context of a social reward processing deficit framework that highlights the failure to assign reward value to social stimuli. When considered in light of recent models of ASD pathophysiology that emphasize reward network dysfunction in response to social and non-social rewards (Scott-Van Zeeland *et al.*, 2010; Kohls *et al.*, 2011; Dichter *et al.*, 2012b, 2012c), as well as empirical findings of dysfunctional reward circuitry in a number of psychiatric conditions, including substance use disorders (Kalivas and Volkow, 2005), schizophrenia (Waltz *et al.*, 2009), affective disorders (Hasler and Northoff, 2011) and attention deficit/hyperactivity disorder (Cubillo *et al.*, 2012), mesolimbic responses to rewards appear to be a common endophenotype that cuts across diagnostic boundaries and thus an important intervention target (Hyman, 2007; Insel *et al.*, 2010; Dichter *et al.*, 2012a).

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

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