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Reward Processing in Autism

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Abstract

The social motivation hypothesis of autism posits that infants with autism do not experience social stimuli as rewarding, thereby leading to a cascade of potentially negative consequences for later development. While possible downstream effects of this hypothesis such as altered face and voice processing have been examined, there has not been a direct investigation of social reward processing in autism. Here we use functional magnetic resonance imaging to examine social and monetary rewarded implicit learning in children with and without autism spectrum disorders (ASD). Sixteen males with ASD and sixteen age- and IQ-matched typically developing (TD) males were scanned while performing two versions of a rewarded implicit learning task. In addition to examining responses to reward, we investigated the neural circuitry supporting rewarded learning and the relationship between these factors and social development. We found diminished neural responses to both social and monetary rewards in ASD, with a pronounced reduction in response to social rewards (SR). Children with ASD also demonstrated a further deficit in frontostriatal response during social, but not monetary, rewarded learning. Moreover, we show a relationship between ventral striatum activity and social reciprocity in TD children. Together, these data support the hypothesis that children with ASD have diminished neural responses to SR, and that this deficit relates to social learning impairments.

Keywords

functional MRI (fMRI); social cognition; reward; learning

Introduction

Autism is a pervasive neurodevelopmental disorder with hallmark deficits in social communication and reciprocity. Whereas typically developing (TD) infants show a preference for social over non-social stimuli [Legerstee, Anderson, & Schaffer, 1998], retrospective studies of videotaped birthday parties indicate that children who develop autism show decreased motivation to attend to social stimuli, as evidenced by reduced attention to faces of others, decreased pointing and showing, and failing to orient to their

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name, as early as the child's first birthday [Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998b; Osterling & Dawson, 1994]. These observations led to the development of the social motivation hypothesis of autism [Dawson et al., 1998b; Dawson, Webb, & McPartland, 2005; Schultz, 2005], which posits that reduced time spent attending to faces, speech, and other social stimuli leads to a cascade of negative consequences for the development of social cognition and language such as decreased expertise in human face [Grelotti, Gauthier, & Schultz, 2002; Pelphrey, Adolphs, & Morris, 2004; Schultz et al., 2000] and speech [Klin, 1991; Kuhl, Coffey-Corina, Padden, & Dawson, 2005; Pelphrey et al., 2004] processing. This lack of social motivation has been attributed to a decreased reward value for social stimuli. Although it has been established that infants with autism spend less time orienting to social events, it is difficult to directly test whether this is due to a primary dysfunction of the reward system per se using behavioral measures alone. Functional magnetic resonance imaging (fMRI) allows a more direct investigation into the neural correlates of reward processing in humans, including response to social rewards (SR). A number of fMRI studies have highlighted a reward network—comprised primarily of anterior cingulate (ACC), orbitofrontal cortex (OFC), and ventral striatum (VS)—which responds to primary rewards such as food [O'Doherty, Deichmann, Critchley, & Dolan, 2002], as well as to secondary rewards such as money [O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Thut et al., 1997; see also Knutson & Cooper, 2005 for a review]. Studies of SR in humans support involvement of these same reward networks while viewing pictures of faces [Bartels & Zeki, 2004; Phillips et al., 1998; Spreckelmeyer et al., 2009].

Surprisingly, only one study thus far has examined the neural correlates of reward processing in adults with autism, using fMRI to examine responses to monetary rewards [MR; Schmitz et al., 2008]. Here, we used both MR and SR to investigate reward processing in children with autism spectrum disorder (ASD). Importantly, we examined the social motivation hypothesis by investigating reward processing in the context of socially rewarded learning, that is, learning reinforced by positive social stimuli such as a smiling face. The social rules of engagement are rarely taught explicitly and are likely acquired through observation, imitation, and implicit learning of stimulus–outcome associations [see Frith, 2008 for review]. For example, individuals can acquire fear of a novel object simply by watching another being conditioned to fear that object (i.e., paring the object with a painful shock), even when the object is masked and the observer is unable to report when the stimulus occurs [Olsson & Phelps, 2004]. It is likely that this learning occurs via mirroring of the fearful expression in the observer, thereby creating a subliminal, implicitly acquired, stimulus–outcome association between the novel object and fear. Impairment in the ability to implicitly acquire stimulus–outcome associations could have clear repercussions for social learning. In fact, computational modeling work suggests the development of certain social behaviors such as gaze following and joint attention may rely on probabilistic reward-related learning [Triesch, Teuscher, Deak, & Carlson, 2006].

In this study, we examined the behavioral and neural correlates of rewarded implicit learning in children with ASD, given conventional rewards (i.e., monetary gain) and SR (i.e., smiling faces). Specifically, we focused on three hypotheses regarding reward-related brain activity in children with and without ASD. First, we examined neural responsiveness of brain areas known to be involved in reward processing (e.g., VS) to both social and non-social rewards to examine whether ASD children would demonstrate an overall reduced neural response to rewards, or a more specific deficit for SR. second, we examined the neural correlates of reward-related learning to test the hypothesis that children with ASD would show decreased activity in brain regions known to support implicit learning and reward processing (i.e., frontostriatal networks). Finally, we investigated whether activity in the reward system is related to the level of social functioning by correlating neural reward response to behavioral measures of social responsiveness.

Methods

Participants

Participants were recruited through referrals from the UCLA Autism Evaluation Clinic and through flyers posted around the UCLA campus and the greater Los Angeles area. Sixteen high-functioning boys with autism spectrum disorder with normal IQ and 16 age- and IQ-matched TD boys (see Table I) underwent fMRI scans. The groups did not significantly differ in age or FSIQ as assessed by the Wechsler Abbreviated Scales of Intelligence—Revised [Wechsler, 1999] or Wechsler Intelligence Scale for Children—Third Edition [Wechsler, 1991]. Receptive language skills were assessed with the Peabody Picture Vocabulary Test—Third Edition to verify the ability to understand the verbal instructions. Additionally, the ASD children had a VIQ well within the normal range (108.8±14.9), further indicating a sufficient level of verbal comprehension. For the ASD group, prior clinical autism diagnosis was confirmed by the Autism Diagnostic Observation Scale—General [ADOS-G; Lord et al., 2000] and Autism Diagnostic Interview—Revised [ADI-R; Lord, Rutter, & Le Couteur, 1994]. All children met criteria for autism as defined by the ADI-R (cutoff=22; mean=44.4, range=28–64). Six participants met criteria for Autism Spectrum (cutoff=7; mean=9.2; range=7–11) and ten met autism criteria (cutoff=10, mean=13.3, range= 10–19) as defined by the ADOS-G. Seven participants were not currently taking any medications. Out of the remaining children, two were taking psychostimulants only, two were taking atypical antipsychotics only, three were taking both antipsychotic and psychostimulant medication, one was taking a selective serotonin reuptake inhibitor, one was taking an atypical antidepressant, and medication status was unknown for one child. We would expect the effects due to medication to reduce the between-group differences in the blood oxygenation level dependent (BOLD) response. By report, none of the participants had any known loss of consciousness longer than 5 min, or any neurological (e.g. epilepsy), genetic (e.g., Fragile X) or major psychiatric (e.g., schizophrenia) disorder other than autism. Written informed consent was obtained from participants and their parents according to the specifications of the UCLA Institutional Review Board.

Experimental Design

Two rapid event-related mixed-trial rewarded learning tasks were designed by adapting the weather prediction task [Knowlton, Squire, & Gluck, 1994] for use in this population. The task requires participants to classify abstract fractal-like images (created using Art Matic Pro, U&I Software LLC) into “Group 1” and “Group 2” pictures by responding with a simple button press (“1” or “2”), with feedback presented after each classification trial (see Fig. 1). Children were asked to press a button every time they saw a picture, and encouraged to win as many rewards as possible. Simple “Group 1” and “Group 2” classifications were used rather than the traditional “Rain” or “Sunshine” to avoid idiosyncratic responses associated with concrete semantic interpretations in children with ASD (e.g., a child might use the presence of blue in the picture to always predict rain or yellow to always predict sunshine). To discourage memorization of the pairs, children were also told that the computer occasionally “messes up” and sometimes a correct answer would result in the wrong feedback, and vice versa.

The task was designed to be easy enough to allow improvement in accuracy within one 6 min run, but challenging enough to maintain a reliance on implicit learning of the associations; this was done by limiting the probabilities to either 0, 50 or 100% predictive of one of two outcomes. The presence of randomly (50%) associated pairs in 1/3 of the trials further discouraged a memorization strategy. Each stimulus was associated with either reward or neutral feedback. Therefore, six different abstract stimuli were used for each run, one for each probability and feedback condition (rewarded or neutral). A total of 12 abstract

images were used, 6 for the monetary feedback version and 6 for the social feedback version. To prevent item effects, stimuli were counterbalanced across children such that each was equally associated with “1” or “2” as well as with reward or neutral feedback. Each run consisted of 72 interspersed trials optimized for detection of trial-related reward activity [Wager & Nichols, 2003]. Each trial lasted an average of 5 sec, and inter-stimulus intervals were randomly jittered between 1,250 and 2,500 msec. Each stimulus was displayed approximately 2,000 msec, and feedback was displayed for 1,250 msec after each stimulus presentation.

The monetary task provided either MR or monetary neutral (MN) feedback to guide learning of stimulus–response associations and the social version used either SR or social neutral (SN) feedback. Correct MR feedback consisted of a picture of three gold coins, and incorrect MR feedback was presented as the same image with three red X’s through the coins. MN feedback was presented as the words “Correct!” in green or “Incorrect” in red to provide feedback. The SR feedback consisted of a picture of a smiling woman with the words “That’s Right!” in green text for correct trials and a picture of the same woman with a sad face along with the words “That’s Wrong” in red text for incorrect trials. SN feedback consisted of the same woman with a neutral expression and the same text in black. The chosen reward stimuli, faces and coins, are consistent with those used in previous studies of reward processing [e.g., Bray & O’doherty, 2007; Galvan et al., 2006; Izuma, Saito, & Sadato, 2008].

Before the scans, all participants were told that they were going to play two games; during one of them they could earn an extra $5, and for the other they would receive a different kind of “reward” but it was not specifically stated what it would be. To verify that the participants had an equal and realistic idea of the value of money, prior to the scan the experimenter coached the participants to think about what they would buy if they earned the full amount, compared to what they could buy if they did not earn the extra money. All children seemed to fully grasp the concept of potentially gaining more money. Participants received the full $5 bonus regardless of performance at the end of the scanning session. Participants completed both versions of the task, and the presentation order of the two runs was counterbalanced across children.

Data Acquisition

Scans were acquired in a single session on a Siemens Allegra 3 Tesla head-only MRI scanner at the Ahmanson-Lovelace Brain Mapping Center at the University of California, Los Angeles. A pre-scan session in a mock scanner was available to participants to familiarize them with the scanning procedures and sounds. For each participant, a high-resolution structural T2-weighted echo-planar imaging volume (spin-echo, TR=5,000 msec, TE=33 msec, matrix size=128 by 128, FOV=20 cm, 36 slices, 1.56 mm in-plane resolution, 3 mm thick) was acquired coplanar with the functional scans to allow for spatial registration of each participant’s data into a standard coordinate system. For each run 180 functional images were acquired using an echo-planar (EPI) gradient-echo acquisition lasting 6 min and covering the whole cerebral volume (TR=2,000 msec, TE=30 msec, flip angle=90, matrix size 64×64, FOV=20 cm, 33 slices, 3.125 mm in-plane resolution, 4 mm thick). Two volumes at the beginning of each functional run were used to allow equilibration to steady state and were subsequently excluded from the analysis.

Visual stimuli were presented to the subject using 512×512 resolution magnet-compatible 3-D goggles and headphones under computer control (Resonance Technologies, Inc., Northridge, CA). The stimuli were presented using Matlab 7.0.4 psychological experimentation software (The MathWorks Inc., Natick, MA), ran on a Macintosh G4 Powerbook computer. Key press and RTs were recorded for behavioral analysis.

Statistical Analysis

RTs and stimulus classification accuracy for the deterministic trials were collapsed into eight successive trial bins and resulted in three measures each for each trial type (rewarded or neutral) across the duration of the task. Repeated measures analysis of variance analyses were conducted to investigate learning. Two-tailed *t*-tests were used for group comparisons on demographic variables including age and IQ.

fMRI Data Analysis

fMRI analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.63, part of FSL version 3.3 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Functional volumes were motion corrected to the median volume with MCFLIRT [Jenkinson, Bannister, Brady, & Smith, 2002], using a normalized correlation ratio cost function and linear interpolation. Brains were skull stripped using BET (brain extraction tool) [Smith, 2002]. Images were spatially smoothed using a Gaussian kernel of FWHM 5 mm, intensity normalized, and temporally high-pass filtered. Time-series statistical analysis was carried out using FILM with local autocorrelation correction [Woolrich, Ripley, Brady, & Smith, 2001]. Regressors of interest were created by convolving a delta function representing trial onset times with a canonical (double-gamma) hemodynamic response function, along with their temporal derivative. Motion parameters for each subject were entered as covariates of no interest. Groups were equivalent in the amount of head motion during the runs (monetary: TD=0.31 mm (0.27); ASD= 0.33 mm (0.22); $t(30)=0.163$, $P=0.87$; social: TD= 0.28 mm (0.11); ASD=0.39 mm (0.25); $t(30)=1.68$, $P=0.103$). Functional images were aligned using FMRIB's Linear Image Registration Tool to high-resolution coplanar images via an affine transformation with six degrees of freedom. The high-resolution coplanar images were then aligned to the standard Montreal Neurological Institute (MNI) average of 152 brains using an affine transformation with 12 degrees of freedom.

Fixed-effect models were run separately for each subject for each run. The fixed-effect models were taken into a higher-level mixed effects model to investigate within- and between-groups effects. An index of learning (AccSlope) was calculated as the difference between the percent correct during the last eight stimulus presentations and the first eight presentations; as there was a significant difference in accuracy between the TD and ASD groups, this index was used as a covariate in all between-group analyses. First, within-group mixed effects models were run for each condition to identify main effects. Next, two separate two-sample *t*-tests were run to investigate between-group differences for the Monetary and Social reward runs. All contrasts were cluster corrected at $Z>1.96$ and $P<0.05$. Our a priori region of interest, the VS, was corrected for multiple comparisons with an α of 0.005 and a cluster threshold of at least 20 voxels, corresponding to a false-positive probability of less than 0.00001 [Forman et al., 1995]. Correlation analyses with the Social Responsiveness Scale [SRS; Constantino et al., 2003] were masked by a combined mask of areas of activation for TD and ASD groups for correct SR>incorrect SR and confirmed with a Kendall's rank correlation on extracted parameter estimates from significant clusters in a priori regions of interest (i.e., VS).

Results

Behavioral Results

Overall accuracy, as measured by the percent correct in eight-trial bins for neutral and rewarded trials, increased over time in the TD children for both themonetary (Fig. 2A) and social (Fig. 2B) runs, whereas the ASD children's performance remained near chance. This suggests a deficit in implicit learning in ASD, regardless of feedback type (i.e., monetary or social feedback). Additionally, within-group analyses showed there were no differences in

accuracy between rewarded and neutral trials for either the TD or ASD children, nor were there significant differences in accuracy between the social and monetary runs in either group. These findings indicate that children with ASD demonstrate a general deficit in implicit learning, regardless of reward or feedback type. Overall, RTs were not significantly different between groups ($F(1,30) = 3.834$, $P = 0.60$), indicating that all children attended and responded to the task. RTs for both groups of children significantly decreased over the course of both monetary and social tasks ($F(2,29) = 17.68$, $P < 0.001$). After scanning, subjects were explicitly asked to identify the stimulus–outcome relationships. Analysis of post-test data revealed that both groups performed at chance when asked to identify the outcome ("1" or "2") for each stimulus (see Table II), indicating that subjects had not gained explicit knowledge about the stimulus–outcome associations. These data suggest that both groups of children were equally engaged during the task, despite the poor learning in the ASD group.

fMRI Results

Stimulus and feedback responses were modeled separately for each trial type (i.e., random/deterministic, neutral/rewarded) for all analyses. The inclusion of random trials in the experimental design curtailed potential confounds by providing sufficient numbers of positive and negative feedback events for all participants although accuracy differed (see Table II). We ran an overall analysis of *all events* (i.e., positive and negative feedback for rewarded and neutral trials) compared to inter-trial rest (implicit baseline) to verify that both groups attended to and processed sensory aspects of the test similarly (see Table III). To further confirm that both TD and ASD children processed the facial features during the social feedback events, a region of interest analysis was conducted in the fusiform gyrus (FG). Using a face localizer contrast (all facial feedback>all stimulus events) to functionally define the FG ROI in TD children (216 voxels at 42, −48, −18), the percent signal change during social feedback was extracted for each child and compared across groups. Percent signal change was computed from average parameter estimates using the height of an isolated event as the scaling factor, and was relative to the voxel mean. There were no significant differences in the amount of FG activity between groups (TD=3.08 (2.27); ASD=2.29 (2.09); $t(30) = 1.03$, $P = 0.310$). While FG activation in response to facial stimuli is a reliable indicator of attention to the face, we cannot conclude however that face processing in the children with ASD is unimpaired.

Due to the significant differences in accuracy between groups, the slope of each participant's learning curve was used as a covariate in the between-group analyses to insure that any observed differences did not merely reflect a difference in the rate of learning. This index of learning (AccSlope) was calculated as the difference in percent accuracy between the first eight and last eight deterministic trials. The AccSlope measure, rather than overall accuracy, was chosen in order to capture the individual differences in the rate of learning.

Children With ASD Show Pronounced Deficits in VS Response to SR

Monetary Reward Response

Within-group analyses—Within-group analyses for the response to positive MR feedback (i.e., coins) as compared to negative MR feedback (i.e., crossed-out coins) revealed a large cluster of activity in regions restricted to the VS (see Fig. 3, Table IV) in TD children only. Neither group demonstrated VS activity in response to correct vs. incorrect neutral feedback, suggesting a specific and robust response to MR in the VS for the TD group only.

Between-Group Analyses

Although there were qualitative differences between the TD and ASD children in the VS response to MR, the between-group comparison (TD>ASD) was not significant (Z=1.84, P=0.66). The converse contrast (ASD>TD) revealed a significant difference in paracingulate cortex and OFC (Table IV). These results suggest increased activity in prefrontal cortex may compensate for a blunted VS response to MR in children with ASD.

Social Reward Response

Within-group analyses—The social feedback run was analyzed in an identical manner to the monetary feedback run. As seen in Figure 3, the contrast between positive SR (i.e., smiling face) and negative SR (i.e., sad face) revealed a significant cluster of activity in VS in the TD group only. In addition to the VS response, there were additional clusters in regions associated with processing socially relevant information including medial prefrontal cortex and superior temporal gyrus. Additional regions are listed in Table IV. Neither group showed significant activation in the contrast of correct vs. incorrect SN feedback. A contrast between positive SR and positive SN expression feedback revealed a significant cluster in pregenual cingulate cortex (Z=3.19, P<0.05 cluster corrected, MNI coordinates: 8, 38, 8) in the TD group only (Fig. 4), consistent with an increased subjective value for social reward feedback in this group.

Between-group analyses—Between-group comparisons on the positive SR compared to negative SR (i.e., smiling vs. frowning face) revealed significantly greater activity in bilateral VS in TD compared to ASD children (right VS magnitude=P<0.005, 75 voxels; left VS magnitude=P<0.005, 41 voxels). There were no regions of activation for the converse contrast (ASD>TD). This indicates a significantly reduced neural response to SR, such as smiling faces, in the VS in children with ASD.

Children With ASD Show Decreased Frontostriatal Activity During Social Rewarded Learning

We then investigated the neural correlates of reward-guided learning. Feedback for trials that were 100% predictive (deterministic) and trials that predicted an outcome 50% of the time (random) were analyzed separately. This allowed us to investigate the effect of instructive feedback processing (i.e., feedback which can guide learning of stimulus–outcome associations) via correct deterministic trials, as opposed to random positive feedback. See Table V for a list of significant activation clusters.

Monetary Reward-Related Learning

Within-group analyses—Within-group analysis of positive MR feedback for deterministic trials compared to inter-trial rest revealed activity in regions involved in both reward processing, such as VS and OFC, as well as regions involved in learning and memory, including right hippocampus and putamen in TD children. For the same contrast, the ASD group also showed significant clusters in the right hippocampus, frontal regions including IFG and MFG, and the inferior parietal lobule. Despite the apparent differences in activity across groups as revealed by the within-group comparisons, direct statistical contrasts between the two groups indicated no significant between-group differences in the neural response to positive monetary rewarded feedback for deterministic trials.

Social Reward-Related Learning

Within-group analyses—Analysis of positive SR feedback for deterministic trials within the TD group revealed involvement of bilateral anterior caudate head, rostral ACC and FG,

supporting recruitment of implicit learning and reward-processing networks. Conversely, for the same contrast the ASD group demonstrated only FG and lateral occipital cortex activity, suggesting only basic processing of the stimulus features for this type of feedback. These results may point to a reliance on different processing strategies between TD and ASD children, such that TD children show activity in canonical implicit learning and reward regions such as VS, dorsal striatum, and PFC, whereas ASD children primarily utilize visual processing regions without showing activity in reward-related regions such as the VS.

Between-group analyses—A between-group comparison demonstrated significantly greater activity in ACC, ventral PFC and striatum for TD as compared to ASD children. There were no significant regions of activation for the converse contrast (ASD>TD). The between-group comparisons are consistent with the hypothesis that the TD, but not ASD, children engage frontostriatal networks during socially rewarded learning (see Fig. 5), without evidence of compensatory activity in the ASD children outside of canonical rewarded-learning networks.

VS Response to SR Relates to the Level of Social Functioning

To test the hypothesis that response to positive social feedback relates to the development of social reciprocity, we examined the relationship between neural responses in the VS to different reward types and level of social functioning as measured by the SRS [Constantino et al., 2003]. We hypothesized that poorer social reciprocity would predict lower VS response to SR. The SRS is a continuous measure of social behaviors for use in typical and atypical populations. Poorer social functioning is reflected in a higher score. In our sample, the mean TD score was 12.4±8.7 and the mean ASD score was 103±26.4. A regression masked by the combined TD and ASD mean activation to positive SR>negative SR was conducted within the TD and ASD groups on the response to positive deterministic rewards as compared to rest for each run. A significant negative correlation between the SRS score and the response to positive deterministic SR was seen only in the TD group in dorsal striatum (Z=3.14; MNI coordinates=14, 8, 4), VS (Z=2.69; MNI coordinates=14, 22, −4), precuneus (Z=2.99; MNI coordinates=4, −56, 14), and the right temporal–parietal junction (Z=2.65; MNI coordinates=50, −30, 28). No significant correlations were observed for positive deterministic MR for TD children, nor for ASD children for either feedback condition, suggesting a specific relationship between VS responsiveness to SR and levels of social reciprocity in TD children (see Fig. 6). Though the absence of a relationship between SRS and VS response to SR in children with ASD could also be due to the lack of significant activation in the VS in these subjects, the Bartlett test of homogeneity of variances between the TD and ASD children on the amount of VS activity was non-significant (P=0.257).

Discussion

In this study, we found that children with ASD show both a behavioral impairment in implicit learning, as well as a reduced neural response to SR and socially rewarded learning in canonical reward-processing brain regions. First we examined whether TD and ASD children were able to implicitly learn the stimulus–outcome associations. TD children demonstrated significant learning over the course of the paradigm for both neutral and rewarded trials within both the social and monetary tasks. However, classification accuracy within the ASD group remained near chance for rewarded and neutral trials for the duration of both social and monetary tasks. These findings indicate impaired implicit learning in ASD, independent from reward processing. Next, we examined the neural response to rewards, independent of learning, by examining responses to both random and deterministic rewards. Although significant VS activity for both monetary and SR was observed in TD,

but not ASD, children, significant between-group differences were found only for SR, indicating reduced neural responses to SR in children with ASD. We then investigated whether there were differences in the networks associated with rewarded learning between ASD and TD children. Again, we found that children with ASD showed significantly reduced activation of frontostriatal networks relative to TD children during socially rewarded learning. Finally, we examined the degree to which the neural response to reward was related to measures of social functioning and found a positive correlation in the VS in TD children only, such that better social functioning was related to greater activity in the VS in response to positive social feedback.

Our goal was to test the social motivation hypothesis by examining rewarded learning within monetary and social contexts in children with ASD. Using traditional behavioral measures, such as looking preferences, the reward response to social stimuli in autism is difficult to assess. With fMRI we were able to investigate both the behavioral and neural correlates of rewarded learning in autism. Our findings are consistent with the prediction that children with ASD do not find social stimuli rewarding, as evidenced by reduced neural responses to SR in regions associated with reward processing. When we examined the general neural response to monetary and social reward events, we discovered that only TD children showed VS activity for both reward types, whereas ASD children did not demonstrate a significant response to either monetary or SR. However, significant between-group differences were shown only for SR, suggesting that children with ASD may be specifically impaired on processing SR. These findings are consistent with the behavioral evidence that children with autism do not find social stimuli rewarding. Furthermore, comparisons between positive reward feedback and positive neutral feedback indicate a strong valuation signal in pregenual cingulate cortex in TD children specifically in response to SR. This suggests that during typical development, positive social feedback may be particularly salient and have a high intrinsic reward value [de Araujo, Kringelbach, Rolls, & McGlone, 2003; Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008; Plassmann, O'Doherty, Shiv, & Rangel, 2008]. This signal was not seen for either reward type in ASD children, nor for MR in TD children, thus further supporting the hypothesis of abnormal social reward processing in children with ASD.

As there is a demonstrated relationship between learning and reward, we also examined the neural correlates of instructive feedback processing (i.e., feedback which can guide learning of stimulus–outcome associations) via correct deterministic reward trials (i.e. trials in which the stimulus–outcome association are constant). At the behavioral level, TD children were able to learn the stimulus–outcome associations for both reward types, whereas the children with ASD were unable to learn the associations during the task and overall accuracy remained near chance. Post-test data confirmed that neither group explicitly memorized the stimulus–outcome associations. These behavioral results indicate impaired implicit learning in children with ASD, though this is largely an unexplored area in the field. To control for this difference in learning between the ASD and TD children, an estimate of each child's learning rate was included as a covariate in all between-group analyses. At the neural level, TD children demonstrated activity in networks involved in reward processing and implicit learning, including dorsal and VS, frontal cortices, and hippocampus for both monetary and social tasks. Children with ASD demonstrated activity in these regions during the monetary-rewarded learning task but not during the social condition. Between-group comparisons revealed greater frontostriatal activity for TD than ASD children for social reward learning trials. Together, the between-group differences in basic reward processing and rewarded learning specifically within the social context supports impaired socially rewarded learning in children with ASD. Thus, this finding provides empirical support for the social motivation hypothesis of autism [Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998a; Dawson et

al., 2004, 2005; Schultz, 2005] which posits that decreased reward value of social stimuli in children with ASD can negatively impact the development of social behaviors.

Finally, we investigated whether activity in the reward system, particularly the response to SR, related to the children's level of social functioning. We found a relationship between a previously validated measure of reciprocal social behaviors [SRS; Constantino et al., 2003] and the amount of VS activity for SR that guide learning in TD children only. This correlation was not seen in children with ASD, supporting the hypothesis that appropriate response to SR, especially those that inform learning, are related to the development of social skills in children. The lack of a correlation in the ASD group may also reflect decreased variance in the percent signal change due to the overall small amount of activity observed in the VS. Notably, however, our findings are not likely due to a failure on the part of the children with ASD to attend to the task, as there was activation of similar neural networks for all events (as compared to rest) across groups, as well as comparable RT data. Furthermore, equivalent amounts of activity in fusiform cortices during trials involving the presentation of facial expressions suggest that differences between groups during processing of social feedback are not likely due to a failure of ASD children to attend to or process the faces.

One previous fMRI study examined reward responsiveness in adults with ASD using MR and did not find between-group differences in reward-related areas such as VS or OFC [Schmitz et al., 2008]. By also examining responses to SR, we were able to reveal significant reduction in reward circuitry activity during processing of SR in children with ASD. Our findings are also consistent with previous structural [Haznedar et al., 2006; Hollander et al., 2005; Kates et al., 1998; Langen, Durston, Staal, Palmen, & van Engeland, 2007; Sears et al., 1999] and functional [Haznedar et al., 2006; Takarae, Minshew, Luna, & Sweeney, 2007] MRI studies demonstrating abnormalities in the striatum in individuals with autism. However, it is unclear to what extent these functional and structural differences are primary or secondary to social abnormalities. While the current study is limited in the ability to draw conclusions about causality, the evidence supporting early differences in social motivation and response to rewarding social stimuli in children with autism are suggestive of abnormal function and structure early in life contributing to the development of abnormal social behaviors. This hypothesis will need to be addressed in younger cohorts in future studies. An additional limitation of our study is the potential confound due to the medication status of nine of our participants with ASD. However, when we examined activity in our primary region of interest, the VS, we did not find evidence for an association between medication status and activity in this region. In fact, unmedicated children demonstrated some of the lowest VS responses. The children in this study were primarily taking psychostimulants, which have demonstrated no effects on the hemodynamic response [Rao et al., 2000] and antipsychotics, which have been shown to normalize BOLD responses [Lencz et al., 2000; Schlosser et al., 2003; Snitz et al., 2005]. Thus, the use of medication in several ASD participants may have actually decreased group differences between ASD and TD children. However, both stimulants and antipsychotics act on the dopamine system, albeit in opposite directions, which is one of the neurotransmitters involved in reward signaling. As such, the presence of these medications may alter the neural response to reward. Future studies on reward processing controlling for the effects of medication should be pursued.

By placing rewards within an implicit learning paradigm, we were able to examine the relationship between reward processing and implicit learning, functions which have been shown to rely on neighboring frontostriatal networks [Shohamy, Myers, Kalanithi, & Gluck, 2008]. As suggested by computational models, impaired implicit learning may have repercussions for the development of social behaviors such as joint attention [Triesch et al.,

2006]. A previous investigation by Mostofsky et al. [2000] found impaired procedural learning—a type of implicit learning—in individuals with ASD which the authors interpreted as reflective of cerebellar dysfunction. Our behavioral findings show an implicit learning deficit in children with ASD, providing additional evidence of impaired implicit learning in this population. However, future studies should be pursued to better characterize the nature of this impairment. Behaviors that arise from rewarded learning trials are often conceptualized in terms of classical conditioning [Pavlov, 1927] and modeled as a function of a prediction error, that is, the difference between expected rewards and actual reward receipt. For instance, the Rescorla–Wagner learning model [Rescorla & Wagner, 1972] presumes that prediction error estimates will converge towards 0 irrespective of accuracy in a deterministic context, effectively assuming that subject accuracy is not dependent on the prediction error. Currently, there are no data that investigate the applicability of this model for learning impaired subjects, and for this reason we did not employ that prediction error model. Future studies should further examine implicit learning and prediction error in individuals with ASD.

Our investigation into the neural correlates of rewarded learning in ASD is a direct test of the social motivation hypothesis of autism. In at least some animals, it appears that social stimuli serve as important primary rewards that influence behaviors important for survival. For example, the same neural networks involved in other forms of reward processing (e.g., food, drugs, etc.), underlie social processes such as pair-bonding [Young, Murphy Young, & Hammock, 2005; Young & Wang, 2004] and mother–offspring bonding [Levy, Kendrick, Goode, Guevara-Guzman, & Keverne, 1995] in small rodents [Febo, Numan, & Ferris, 2005] and voles [Young et al., 2005]. Impaired reward processing and learning may be the underlying factor for the abnormal development of some social behaviors in children with ASD, and targeting brain regions involved in social rewarded learning for possible therapeutic intervention in this population may prove to be a valuable early treatment approach. For example, oxytocin, a neurohypophyseal hormone linked to pro-social behaviors, has a high density of receptors within the nucleus accumbens. Administration of this neurohormone to individuals with ASD has been shown to decrease repetitive behaviors [Hollander et al., 2003] and increase affective speech comprehension [Hollander et al., 2007]. Furthermore, oxytocin administration has been shown to modulate BOLD activity in regions associated with social cognition and reward in human [Kirsch et al., 2005] and rodent [Febo et al., 2005]. Conversely, our results may reflect differences in the structural integrity of a distributed reward processing and learning network, in which case future studies should examine the developmental trajectory of these structures and their connectivity. Our data would suggest that increasing reward responsiveness in ASD, perhaps through pharmacotherapy, might augment social learning. Future studies may investigate the degree to which manipulating VS activity affects social responsiveness, and ultimately autistic symptomatology, in children with autism spectrum disorders.

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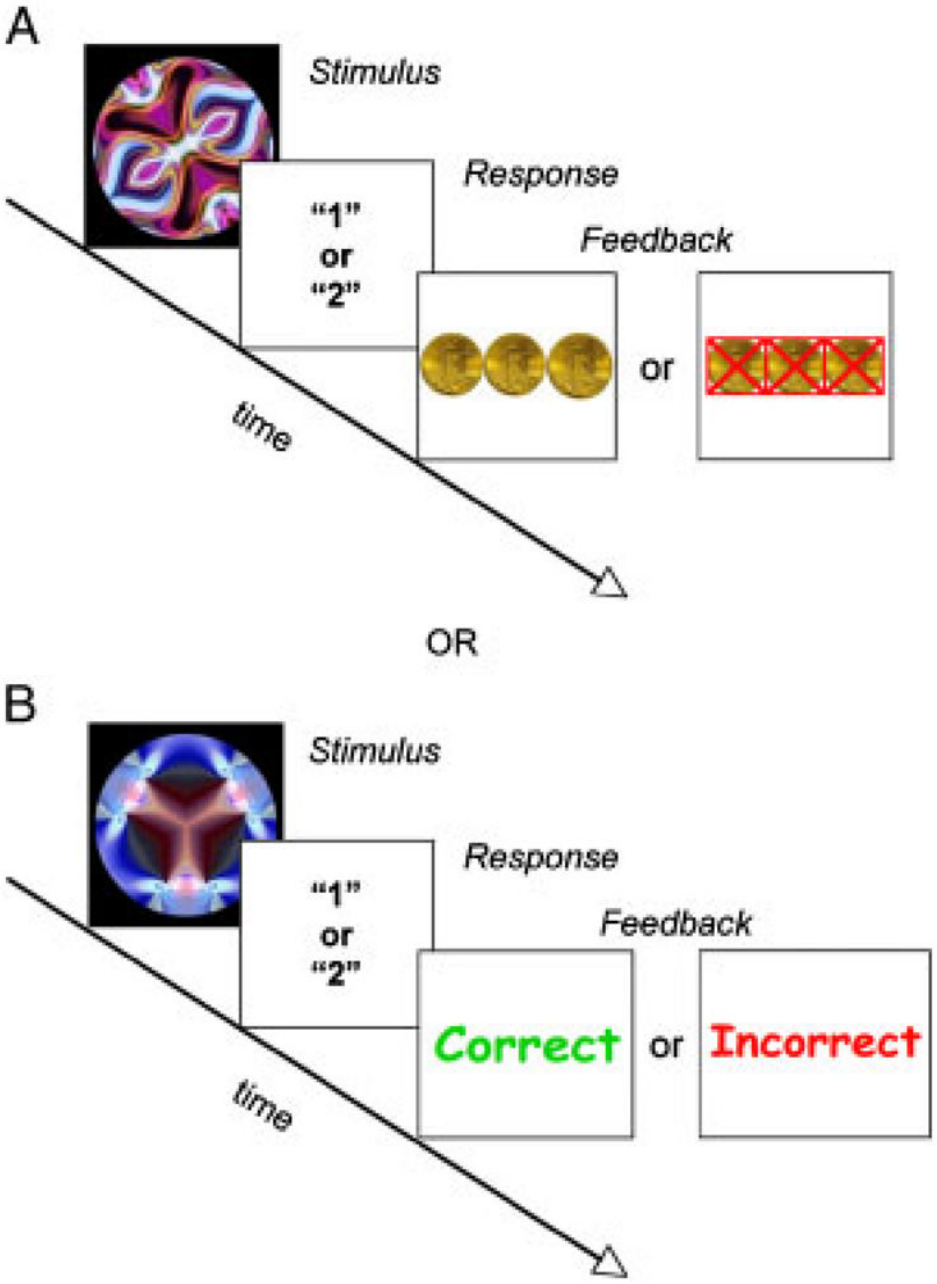

Figure 1.
Paradigm design. 4/6 trials were associated with "1" or "2" 100%, 2/6 were random (50%). Panel **A** depicts an example of a rewarded trial. Panel **B** is an example of a neutral trial. During the Social version, the coins were replaced with a picture of a woman either smiling, for positive feedback, or frowning, for negative feedback. Neutral trials were replaced with a picture of the same woman with a neutral expression. Trials lasted an average of 5 sec, inter-trial intervals were randomly jittered between 1,250 and 2,500 msec, feedback display was jittered between 1,000 and 1,250 msec after stimulus presentation.

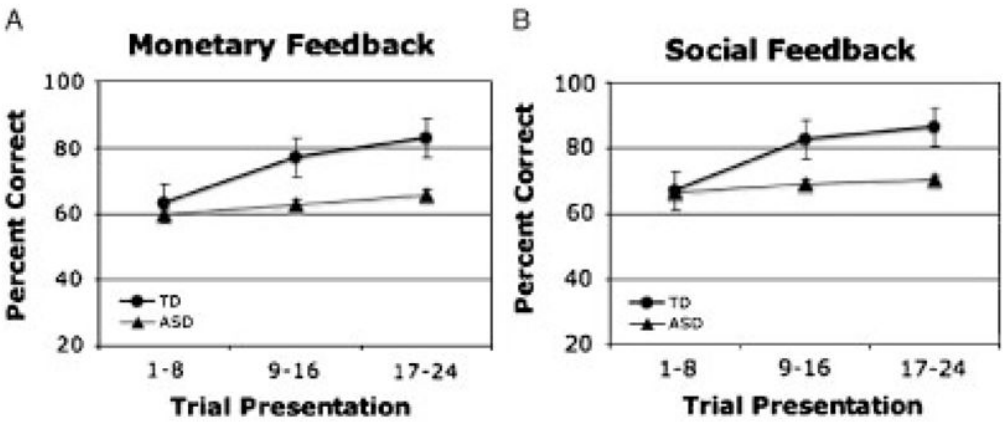

Figure 2.
Behavioral performance. Accuracy during Monetary (**A**) and Social (**B**) tasks. Error bars represent standard error of the mean (SEM).

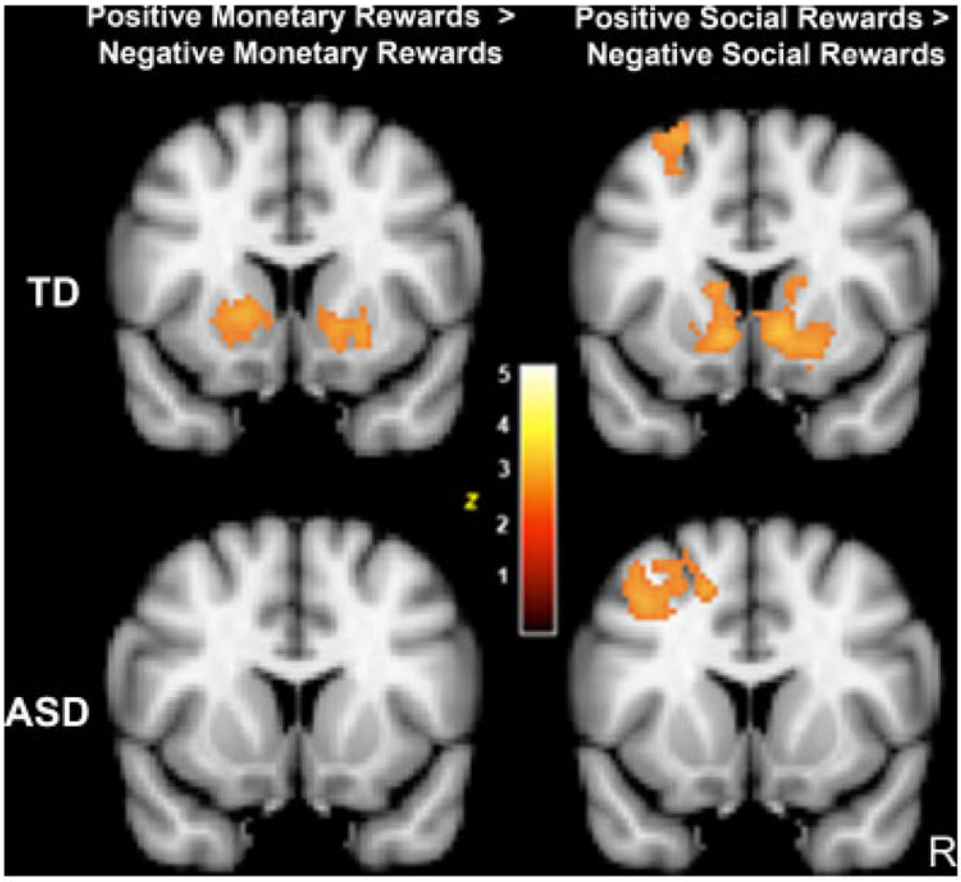

Figure 3.
Reward response within groups for positive vs. negative reward feedback. MNI coordinates, y=12, Z>1.96, P<0.05 cluster corrected.

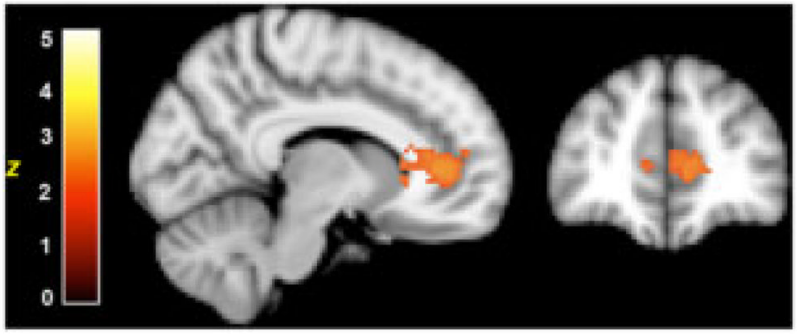

Figure 4.
Outcome valuation signal in TD children for social rewards. MNI maximum coordinates 8, 38, 8; Z=3.19, P<0.05 cluster corrected.

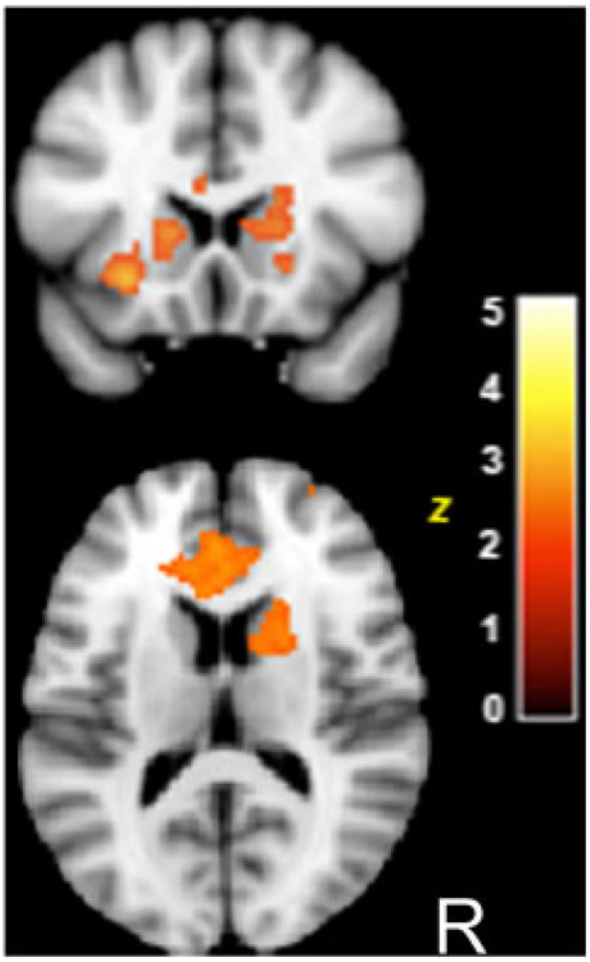

Figure 5.
Between-group differences in response to socially rewarded learning trials. TD>ASD deterministic social rewards vs. rest. MNI coordinates, z=14. Z>1.96, P<0.05 cluster corrected.

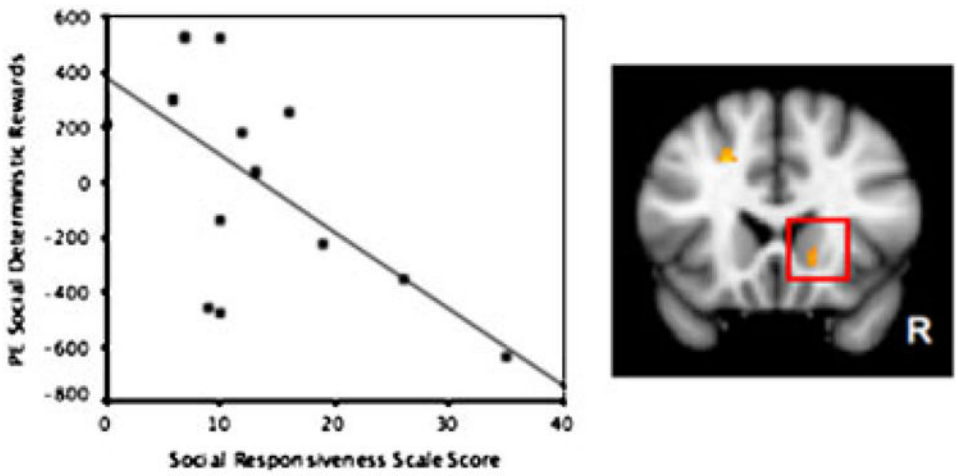

Figure 6.

Ventral striatum response to positive social feedback relates to a measure of social responsiveness in TD children. Negative correlation between SRS and parameter estimates (PE) in ventral striatum adjacent to nucleus accumbens for deterministic social rewards in TD children. $Z = 2.68$, $P<0.005$; Kendall's rank correlation PE_{social}, $\tau = -0.53$, $P = 0.007$; PE_{money}, $\tau = -0.31$, $P = 0.11$.

Table I

Mean and Standard Deviation of Sample Descriptives

	AGE	FSIQ	VIQ*	PIQ	PPVT-III
TD	12.3 (1.76)	119.0 (8.4)	119.4 (12.6)	111.50 (8.1)	121.6 (14.4)
ASD	12.4 (2.14)	112.3 (13.6)	108.8 (14.9)	114.13 (13.1)	116.2 (16.0)

* *P*=0.037.

Table II

Behavioral Results: Task Performance for TD and ASD Groups

	TD *M* (SD)	ASD *M* (SD)
Total percent correct		
Monetary	74.39 (20.2)	62.90 (16.0)
Social	79.03 (12.2)	68.8 (15.5)
Post-test number correct (out of 4)		
Monetary	2.25 (1.2)	1.63 (1.2)
Social	2.13 (1.5)	1.88 (1.4)
No. of positive rewarded events		
Monetary	22.43 (5.9)	19.07 (4.9)
Social	23.0 (4.1)	22.2 (4.9)
No. of negative rewarded events		
Monetary	15.33 (4.8)	12.38 (5.1)
Social	11.25 (3.8)	12.73 (4.7)

Task accuracy is calculated as the total percent correct over the run for deterministic trials, post-test accuracy is described as the correct number of associations identified out of four possible. The mean number of positive and negative events (i.e., deterministic and random combined) within groups is also reported.

Table III

General Task Effects: MNI Anatomical Coordinates for All Events as Compared to Rest for Monetary and Social Runs by Group

		Monetary: all events—Rest										Social: all events—Rest									
		TD					ASD					TD					ASD				
Anatomical region		**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**
Caudate	L																				
	R		12	10	6	2.94		14	12	6	3.19		16	4	14	2.72					
Putamen	L																				
	R												18	4	6	2.87					
Globus Pallidus	L																				
	R												20	4	−2	2.38					
Orbitofrontal	L	11	−40	38	−10	3.04															
	R	11 47	24 28	42 18	−14 −18	2.75 3.26															
Inferior frontal gyrus	L						46	−40	36	8	3.78	45 47	−46 −26	24 14	20 −20	3.68 2.50					
	R	46	42	38	18	3.98	46	48	32	16	4.14										
Middle frontal gyrus	L						8	−40	12	40	3.53	9	−48	24	34	2.94					
	R						6/8	50	8	40	4.26	9	44	26	32	3.33	9	52	26	34	3.36
Precentral gyrus	L	6	−44	4	32	3.71	4	−44	4	32	3.30	6	−40	2	34	2.87					
	R						4	48	6	32	4.14	6	46	4	34	3.12	6	52	0	48	3.47
Frontal Pole	L						10	−28	58	−6	4.02	10	−42	52	−6	3.14					
	R	10	42	50	4	3.60	10	28	54	−2	4.27										
Hippocampus/Parahippocampal gyrus	L	30	−16	−36	−4	3.98						35	−18	−32	−6	3.46					
	R	30	18	−32	−8	3.61	28	22	−30	−4	3.57										
Cingulate																					
Anterior		24	8	30	20	3.96															
Paracingulate							6/8	4	24	44	3.50										
Posterior																					
Insula	L		−28	18	−8	3.50		−32	16	4	3.42		−30	16	−8	2.81					
	R		34	20	2	4.06		36	16	−4	4.05										
Fusiform gyrus	L	37	−32	−76	−20	5.85	37	−30	−68	−16	5.61	37	−28	−70	−18	5.42	37	−40	−70	−18	5.45

		Monetary: all events—Rest										Social: all events—Rest									
		TD					ASD					TD					ASD				
Anatomical region		**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**
	R	37	22	−72	−16	5.71	37	40	−60	−14	5.15	37	32	−60	−20	5.01	37	30	−80	−20	5.36
Occipital cortex	L																				
	R						18	10	−98	16	5.70	18	32	−90	−6	5.47	18	12	−100	16	5.70
Superior parietal lobule	L																				
	R	7	28	−60	52	3.96											7	34	−60	54	3.37
Inferior parietal lobule	L	40	−38	−52	48	3.85															
	R																40	40	−52	42	3.37
Supramarginal gyrus	L						40	−48	−52	50	4.30										
	R						40	48	−44	54	3.94										

BA refers to putative Brodmann's Area; L and R refer to left and right hemispheres; *x*, *y*, and *z* refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; *Z* refers to the *Z*-score at those coordinates (local maxima or submaxima). Cluster corrected for multiple comparisons, $Z>1.96$, $P<0.05$.

Table IV

Neural Responses to Rewards: MNI Anatomical Coordinates for the Contrasts Positive Reward–Negative Reward Feedback for Monetary and Social Runs by Group

		Monetary: positive reward>negative reward feedback															Social: positive reward>negative reward feedback									
		TD					ASD					ASD>TD					TD					ASD				
Anatomical region		**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**
Caudate	L																	−12	14	10	3.18		−10	22	0	2.97
	R																	16	14	14	2.46					
Putamen	L		−16	10	−2	3.32												−20	4	−2	2.55					
	R																	26	6	2	2.36					
Nucleus accumbens	L		−12	4	−10	3.22												−10	14	−4	3.44					
	R		12	6	−8	3.19												6	14	−4	3.37					
Medial Prefrontal	L																10	0	60	2	3.02					
	R																									
Orbitofrontal	L																					11	−26	24	−18	2.99
	R											11	14	52	−14	3.15										
Inferior frontal gyrus	L																									
	R																47	32	32	−14	2.72					
Middle frontal gyrus	L																8	−28	26	46	3.01	6/8	−30	8	42	3.21
	R																									
Precentral gyrus	L																4	−40	−8	60	3.08	6	−38	0	30	3.47
	R																									
Frontal Pole	L																									
	R											10/11	14	50	−14	3.03	10	30	64	6	2.99	10	28	54	−12	2.79
Cingulate																										
Anterior																						32/24	2	42	−4	3.12
Paracingulate												32	−6	38	−16	2.98										
Posterior																	31	0	−48	46	3.26	31	−2	−34	34	3.44
Subcallosal	L											25/11	−2	26	−18	3.10						32	−8	36	−12	3.03
	R																									
Occipital cortex																						19	30	−72	38	2.84
Superior parietal lobule	L																7	24	−56	64	3.40					

		Monetary: positive reward>negative reward feedback															Social: positive reward>negative reward feedback									
		TD					ASD					ASD>TD					TD					ASD				
Anatomical region		**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**	**BA**	***x***	***y***	***z***	**Z**
Superior temporal gyrus	R																7	36	−46	60	3.26					
	L																									
	R																41	58	−32	20	3.10					

BA refers to putative Brodmann's Area; L and R refer to left and right hemispheres; *x*, *y*, and *z* refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; *Z* refers to the *Z*-score at those coordinates (local maxima or submaxima). Cluster corrected for multiple comparisons, $Z>1.96$, $P<0.05$.

Table V

Neural Responses to Reward-Based Learning: MNI Anatomical Coordinates for Instructive Feedback (Deterministic Positive Rewards as Compared to Rest) for Monetary and Social Runs by Group

		Monetary positive deterministic rewards>rest										Social positive deterministic rewards>rest													
		TD					ASD					TD					ASD					TD>ASD				
Anatomical region		**BA**	***x***	***y***	***z***	***Z***	**BA**	***x***	***y***	***z***	***Z***	**BA**	***x***	***y***	***z***	***Z***	**BA**	***x***	***y***	***z***	***Z***	**BA**	***x***	***y***	***z***	***Z***
Caudate	L												−8	16	0	2.52							−14	18	6	2.97
	R												8	18	0	2.53							16	4	12	2.75
Putamen	L																						−26	14	0	2.60
	R		32	−16	2	3.67																	20	10	−2	2.29
Nucleus accumbens	L		−8	10	−8	2.23																				
	R																									
Orbitofrontal	L	47	−24	10	−18	3.19																				
	R	47	38	24	−18	3.18																				
Inferior frontal gyrus	L																									
	R						45	52	26	14	2.91															
Middle frontal gyrus	L						9	−42	16	36	3.13															
	R																									
Precentral gyrus	L						4	−44	8	34	3.03															
	R	4	34	−24	42	3.06	4	48	2	30	3.48															
Frontal Pole	L											10	−16	66	20	2.29										
	R						10/11	44	50	2	3.33											10	30	50	−6	3.32
Hippocampus/Parahippocampal gyrus	L																									
	R	35	24	−6	−26	2.35		30	−20	−14	2.44															
Cingulate																										
Anterior												24	−2	38	6	3.39						24	−4	36	12	3.23
Paracingulate		32	6	44	24	3.09																				
Posterior		31	2	−22	46	3.08																				
Subcallosal	L																									
	R											32	−2	24	−12	2.41										
Insula	L																									
	R																									

		Monetary positive deterministic rewards>rest										Social positive deterministic rewards>rest														
		TD					ASD					TD					ASD					TD>ASD				
Anatomical region		**BA**	***x***	***y***	***z***	***Z***	**BA**	***x***	***y***	***z***	***Z***	**BA**	***x***	***y***	***z***	***Z***	**BA**	***x***	***y***	***z***	***Z***	**BA**	***x***	***y***	***z***	***Z***
Fusiform gyrus	L	37	−20	−74	−10	4.03	37	−38	−68	−18	3.94	37	−42	−50	−20	3.46	37	−32	−76	−12	3.99		−26	18	−10	3.45
	R	37	34	−68	−14	4.16	37	26	−70	−16	3.84	37	42	−52	−18	3.61	37	20	−12	−12	3.74					
Occipital cortex	L	17	2	−92	6	4.18											18	−22	−96	−8	3.59					
	R							34	−66	46	3.68						18	8	−94	16	3.57					
Inferior parietal lobule	L						7	−46	−52	50	3.44															
	R																									
Supramarginal gyrus	L						40	−44	−52	50	3.09															
	R						40	50	−46	50	2.91															

BA refers to putative Brodmann's Area; L and R refer to left and right hemispheres; *x*, *y*, and *z* refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; *Z* refers to the *Z*-score at those coordinates (local maxima or submaxima). Cluster corrected for multiple comparisons, $Z>1.96$, $P<0.05$.