Title
Reduced Neural Sensitivity to Social vs Nonsocial Reward in Schizophrenia.

Journal
Schizophrenia Bulletin, 45(3)

ISSN
0586-7614

Authors
Lee, Junghee
Jimenez, Amy M
Reavis, Eric A
et al.

Publication Date
2019-04-25

DOI
10.1093/schbul/sby109

Peer reviewed

Schizophrenia Bulletin vol. 45 no. 3 pp. 620–628, 2019
doi:10.1093/schbul/sby109
Advance Access publication 5 September 2018

Reduced Neural Sensitivity to Social vs Nonsocial Reward in Schizophrenia

Junghee Lee*[,1,2], Amy M. Jimenez[1,2], Eric A. Reavis[1,2], William P. Horan[1,2], Jonathan K. Wynn[1,2], and Michael F. Green[1,2]

[1]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA; [2]Desert Pacific Mental Illness Research, Education and Clinical Center, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA

*To whom correspondence should be addressed; Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, 760 Westwood Plaza, Room 27-460, Los Angeles, CA 90211, USA; tel: 310-794-9010, fax: 310-268-4056, e-mail: jungheelee@g.ucla.edu

Background: **Human beings find social stimuli rewarding, which is thought to facilitate efficient social functioning. Although reward processing has been extensively studied in schizophrenia, a few studies have examined neural processes specifically involved in social reward processing. This study examined neural sensitivity to social and nonsocial rewards in schizophrenia.** ***Methods:*** **Twenty-seven patients with schizophrenia and 25 community controls completed a One-Armed Bandit Task, an implicit reinforcement learning task, in the scanner. There were 2 conditions with an identical trial structure, one with social rewards and the other with nonsocial rewards. The data were analyzed using a region of interest (ROI) approach, focusing on the ventral striatum, ventromedial prefrontal cortex, and anterior cingulate cortex.** ***Results:*** **Across all 3 ROIs, patients showed reduced activation for social rewards compared to controls. However, the 2 groups showed comparable levels of activation for nonsocial rewards. Within the patient group, levels of neural activation in these ROIs during the social reward condition were associated with better performance.** ***Conclusions:*** **This study found reduced neural sensitivity in patients with schizophrenia in key reward-processing regions for social but not for nonsocial rewards. These findings suggest a relatively specific social reward-processing deficit in schizophrenia during an implicit reinforcement learning task.**

Key words: social reward/ventral striatum/ventromedial prefrontal cortex/anterior cingulate cortex/schizophrenia/social preference/social motivation

Introduction

Human beings are intrinsically tuned for social stimuli, and the way individuals process social information in everyday life shapes their social behaviors. For example, people tend to find social stimuli rewarding, which encourages interaction with others in complex social environments (ie, social approach motivation) and provides a foundation for efficient social functioning.[1] Conversely, abnormal social reward processing likely contributes to social dysfunction. Although reduced social motivation may be crucial for understanding social dysfunction, a hallmark of schizophrenia,[2,3] little is known about sensitivity to social rewards in this disorder. This study aimed to examine neural sensitivity to social and nonsocial rewards in schizophrenia using functional magnetic resonance imaging (fMRI) during an implicit reinforcement learning task.

Considerable work has been done on the substrates involved in processing nonsocial rewards. The ventral striatum (VS) and ventromedial prefrontal cortex (vmPFC) have emerged as key areas involved in nonsocial reward processing.[4] Only recently, it has become clear that social stimuli (eg, happy faces) can also engage these regions as rewarding stimuli. Both the VS and vmPFC have shown similar levels of activation for social and nonsocial rewards.[5,6] Further, the levels of activation in these areas varied as a function of social reward magnitudes.[6,7] These findings suggest that certain social stimuli are processed as rewarding stimuli at the neural level, engaging reward-processing regions in the brain much like primary rewards (eg, food) do.

Many studies have examined reward valuation in schizophrenia using various reinforcement learning paradigms. Most of these studies focused on nonsocial rewards and the extent to which patients showed impairment seems to have depended on specific task requirements. For example, compared with controls, patients showed impairment on explicit reward learning tasks, but largely spared performance during implicit reward learning tasks ([8–10], but see Reddy et al[11]). Similar to performance-based studies,

fMRI studies of implicit reinforcement learning also found intact neural responses to reward outcomes in the VS[12–14] and vmPFC.[14] In addition to these 2 core reward-processing areas, studies in schizophrenia have shown that anterior cingulate cortex (ACC) responses are closely related to value representation of rewarding stimuli.[15–17] Notably, because a few studies have examined sensitivity to social reward using reinforcement learning paradigms in schizophrenia, it remains unclear whether patients process social and nonsocial rewards in a similar way.

Although few studies have directly examined both social and nonsocial rewards in schizophrenia, several recent studies suggest that patients with schizophrenia experience more difficulty processing social vs nonsocial stimuli in general. For example, compared with healthy controls, patients direct less attention to social stimuli.[18,19] When remembering social and nonsocial stimuli,[20] controls showed better memory for social than nonsocial stimuli, but patients showed equivalent memory for both types of stimuli, failing to benefit from social information. These findings raise a question about whether patients with schizophrenia may have reduced sensitivity to social but not to nonsocial rewards on an implicit reinforcement learning task.

This study aimed to address this unanswered question. To do so, we used the One-Armed Bandit Task, an implicit reinforcement learning task, in the scanner. The task consists of 2 conditions with an identical trial structure but different reward types: social rewards and nonsocial rewards. This design allowed us to directly compare neural sensitivity with social and nonsocial reward in schizophrenia, focusing on 3 a priori regions of interest (ROIs): VS, vmPFC, and ACC. On the basis of emerging evidence suggesting that patients with schizophrenia do not prioritize social information as much as controls,[2] we hypothesized that patients with schizophrenia would show reduced neural sensitivity to social rewards, but not to nonsocial rewards.

Method

Participants

Twenty-seven clinically stable, chronic outpatients with a *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) diagnosis of schizophrenia and 26 community controls participated in this study. Patients were recruited from outpatient clinics at University of California Los Angeles (UCLA) and the Veterans Affairs Greater Los Angeles Healthcare System (VAGLAHS) and from local board and care facilities in Los Angeles. Community controls were recruited through website postings. The diagnostic eligibility was confirmed with the Structural Clinical Interview for *DSM-5* Disorders (SCID)[21] for all participants.

Exclusion criteria for all participants were as follows: clinically significant neurological diseases (eg, epilepsy), a lifetime history of serious head injury or loss of consciousness more than 15 min, severe or moderate substance or alcohol use disorder in the past 3 months, insufficient fluency in English to understand the procedure (based on judgment of the clinical interviewers), sedatives or anxiolytics on the day of assessment, and pregnancy based on a urine pregnancy test for women. Additional exclusion criteria for patients were as follows: evidence of intelligence quotient < 70 or development disability based on chart review, first-generation antipsychotic medication, inpatient hospitalization for 3 months before testing, and change in antipsychotic medication in a month before testing. We excluded patients taking first-generation antipsychotics from this study because these antipsychotic medications may have a larger effect on reward processing[22] and changes in neural structure in schizophrenia.[23] Additional exclusion criteria for controls were as follows: a lifetime psychiatric history of schizophrenia, other psychotic disorders, bipolar disorders or recurrent major depressive disorder; no family history of psychotic disorder based on self-report; and any of avoidant, paranoid, schizoid, schizotypal, or borderline personality disorder.[24] All participants had normal or corrected to normal vision of at least 20/30.

Clinical characteristics for patients were assessed with the Expanded 24-item version of the Brief Psychiatric Rating Scale (BPRS)[25] and Clinical Assessment Interview for Negative Symptoms (CAINS).[26] CAINS consists of 2 subscales: Motivation and Pleasure (MAP), reflecting diminished motivation and pleasure associated with negative symptoms (ie, anhedonia, avolition, asociality), and Expressivity, reflecting diminished expressivity (ie, blunted affect, alogia). We also assessed neurocognitive ability and social cognition using the MATRICS Cognitive Consensus Battery (MCCB).[27] The MCCB includes 6 neurocognitive domains and 1 social cognitive domain (ie, emotion management).

All interviewers were trained through the Treatment Unit of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center. SCID interviewers were trained to a minimum kappa of 0.75 for key psychotic and mood items, and symptom raters were trained to a minimum intraclass correlation of 0.80. All participants were evaluated for the capacity to give informed consent and provided written informed consents after procedures were fully explained, as approved by the institutional review boards at UCLA and VAGLAHS.

fMRI Data Acquisition

All scanning was conducted on a 3T Trio scanner (Siemens) located at the UCLA Staglin IMHRO Center for Cognitive Neuroscience with a 32-channel head coil. For anatomical reference, a short 3-plane localizer and a high-resolution T1-weighted scan

(magnetization-prepared rapid acquisition gradient-echo [MPRAGE]; image matrix = 256 × 256, repetition time (TR) = 1900 ms, echo time (TE) = 2.26 ms, inversion time (TI) = 900 ms, flip angle = 9 degrees, field of view (FoV) = 250 mm, voxel size = 1 × 1 × 1 mm) were acquired. To measure blood oxygen level-dependent (BOLD) signal during the One-Armed Bandit Task, a simultaneous multislice echo planar imaging sequence was used, acquiring 72 slices parallel to the anterior–posterior commissure plane (matrix = 104 × 104, TR = 2000 ms, TE = 34 ms, FoV = 208 mm, flip angle = 75 degrees, voxel size = 2 × 2 × 2 mm, multiband factor = 4). All visual stimuli were back-projected onto a screen at the head end of the scanner using a Sharp LCD projector and behavioral responses were recorded using an MR-compatible 4-button response box (Resonance Technology).

One-Armed Bandit Task

To assess neural sensitivity to social and nonsocial reward, all participants completed the One-Armed Bandit Task[5,28] in the MRI scanner, programmed with E-Prime software (Psychology Software Tools, Inc.).

As an implicit reinforcement learning task, this version of the One-Armed Bandit Task has 2 conditions with identical trial structures except for the type of reward (ie, social or nonsocial) (figure 1). The 2 conditions were counterbalanced across participants. For the social reward condition, color photographs of 6 unfamiliar male faces from the NimStim collection[29] were used showing happy (positive outcome), angry (negative outcome), or neutral (neutral outcome) expressions. For the nonsocial reward condition, the stimuli included an image of a dollar bill (positive outcome), an image of a dollar bill crossed out (negative outcome), or an image of an empty rectangle (neutral outcome).

Each trial began with the display of 2 slot machines: a "good" slot machine paired with a "neutral" slot machine (ie, high-payout trials) or a "bad" slot machine paired with a neutral slot machine (ie, low-payout trials). A "good" slot machine had an 80% probability of a positive outcome and a 20% probability of neutral outcome; a "bad" slot machine had an 80% probability of negative outcome and a 20% probability of neutral outcome; and a "neutral" slot machine had one-third probability of each positive, neutral, and negative outcomes. Participants had up to 2.5 s to choose the slot machine that would give them the best outcome by pressing a left or right button. Then, the reward outcome was presented for 1.5 s. There were 100 trials: 50 high-payout trials and 50 low-payout trials. Importantly, participants were not

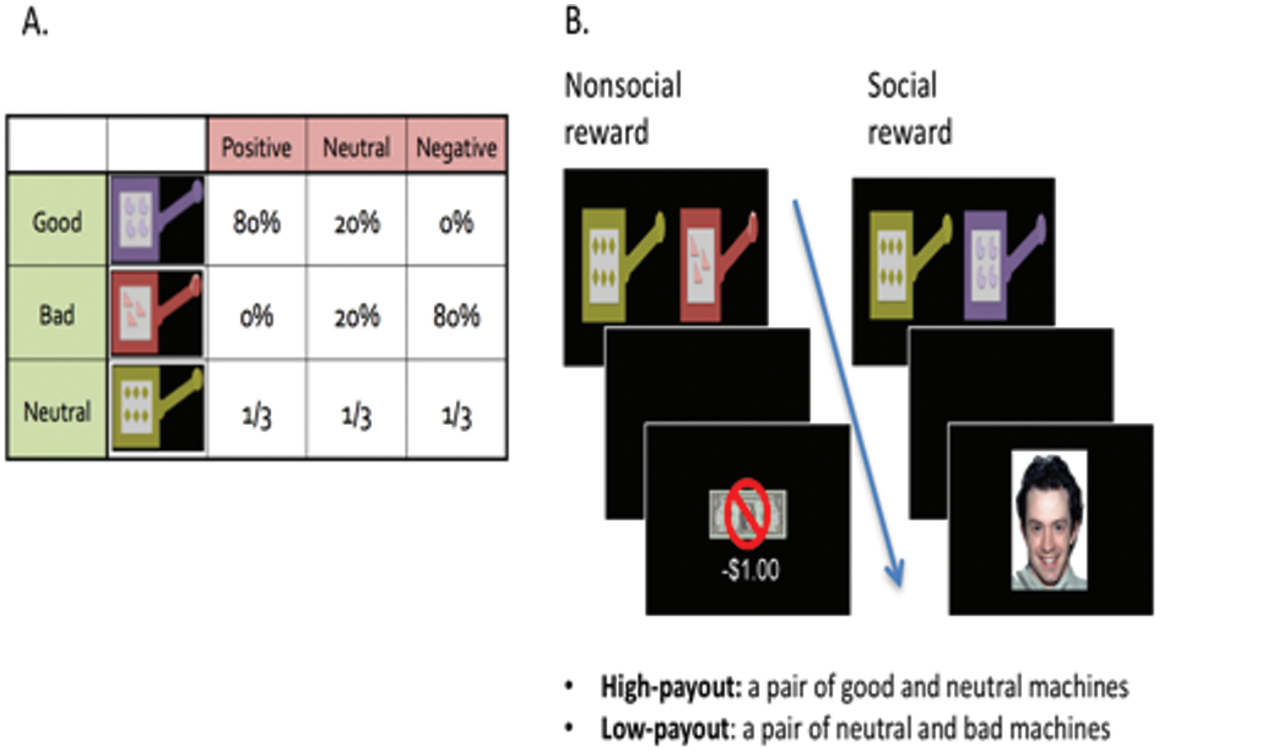

Fig. 1. A schematic diagram of the One-Armed Bandit Task. (A) There are 3 types of slot machines. A "good" slot machine had an 80% probability of a positive outcome and a 20% probability of neutral outcome; a "bad" slot machine had an 80% probability of negative outcome and a 20% probability of neutral outcome; and a "neutral" slot machine had a one-third probability of each positive, neutral, and negative outcomes. (B) Each reward condition with an identical trial structure consisted of 2 trial types: a high-payout trial and a low-payout trial. For the high-payout trial, a good slot machine was paired with a neutral slot machine. For the low-payout trial, a bad slot machine was paired with a neutral slot machine. The key contrast for sensitivity to reward for functional magnetic resonance imaging (fMRI) data was the contrast of high-payout vs low-payout trials for social and nonsocial reward conditions.

told of the reward probabilities associated with each slot machine and had to learn them over the course of the task. In addition, each condition also had 48 nonchoice trials in which 2 identical slot machines were presented (eg, 2 good machines, 2 bad machines, or 2 neutral machines) and participants pressed any button to proceed. These nonchoice trials were included to control for potential confounders (eg, choice behavior) and included as nuisance variables in the fMRI data analysis.

The dependent variable for behavioral performance was the percentage of trials with optimal outcome (ie, choosing a good machine over a neural machine or choosing a neutral machine over a bad machine). The key contrast for sensitivity to reward for fMRI data was the contrast of [high-payout > low-payout trials] during reward outcome for social and nonsocial reward conditions.

fMRI Data Analyses

All fMRI data analyses were carried out using the FMRIB Software Library (FSL, version 5.0.9; Analysis Group, Oxford, UK). The preprocessing steps include the following: brain extraction using optiBET[30], spatial smoothing using a Gaussian kernel of full width at half maximum 4 mm, and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s) and motion correction using MCFLIRT.[31] Potential motion-related artifacts were addressed as follows: First, we excluded participants whose fMRI data had absolute head movement greater than 2 mm. Second, to further control for head motion-related artifacts beyond what linear motion parameters can fix, we conducted motion scrubbing using the FSL Motion Outlier tool. Finally, motion parameters from MCFLIRT (ie, summed volume to volume translation and rotation) and DVARS (ie, the root mean square [RMS] change in BOLD signal from volume to volume) from the FSL Motion Outlier tool[32] were included as nuisance variables in the general linear model to remove any motion-related artifacts. To facilitate multisubject analyses, statistical images created for each subject were normalized into a standard space using Montreal Neurological Institute coordinates.

The primary analysis was an ROI-based approach using a priori regions: VS, vmPFC, and ACC. Specifically, spherical ROIs (diameter = 10 mm) were centered around peak coordinates of these 2 regions (VS, x = ±12, y = 12, z = −10; vmPFC, x = 2, y = 46, z = −8; and ACC, x = 0, y = 44, z = 6) based on previous neuroimaging studies of reward processing.[15,16,33,34] The hemodynamic response function (HRF) for reward outcome of high-payout trials and low-payout trials for social and nonsocial conditions was modeled using a canonical double-gamma HRF, along with motion parameters, DVARS, and nonchoice trials as nuisance variables. Then, for each ROI, beta weights for the key contrast of [high-payout > low payout] were extracted and analyzed using a repeated-measures ANOVA with group as between-subject factor and ROI and reward type as within-subject factor.

In addition to the primary ROI analysis, we conducted an exploratory whole-brain analysis to examine whether any brain regions other than a priori ROIs were associated with sensitivity to social and nonsocial rewards. The whole-brain analysis was conducted using a mixed-effect model (FLAME 1).[35,36] The resulting statistical images were thresholded using the cluster threshold of $z > 3.2$ and $P < .05$, corrected for multiple comparison using Gaussian random field theory.[37]

Results

One control was excluded from data analyses due to excessive head motion (ie, absolute estimated mean displacement greater than 2 mm). Hence, table 1 shows the demographic and clinical characteristics of 27 patients and 25 controls. Patients and controls were comparable on age, parental education, personal education, and gender distribution. Patients showed a significant impairment on the MCCB social cognitive domain score and MCCB neurocognitive composite. Psychiatric symptoms and negative symptoms of patients assessed using the 24-item BPRS and CAINS were comparable to those of chronic, stable schizophrenia patients that we have reported previously.[38,39] Two groups did not differ in terms of head motion during the One-Armed Bandit Task (see supplementary table S1).

Behavioral performance (percent optimal responses; see table 1) during the One-Armed Bandit Task was analyzed using a 2 × 2 repeated-measures ANOVA with reward type (social and nonsocial rewards) as the within-subject factor and group as the between-subject factor. There was a significant main effect of reward type ($F_{1,47} = 6.46$, $P < .05$, $\eta_p^2 = .12$). Both groups showed a higher percentage of trials with optimal outcomes in the nonsocial reward condition. No other effects were significant.

Figure 2 shows beta weights for sensitivity to reward (ie, contrast of high-payout > low-payout trials) in 3 ROIs: VS, vmPFC, and ACC. A 3 × 2 × 2 repeated-measures ANOVA with ROI and reward type (social and nonsocial rewards) as within-subject factors and group as the between-subject factor showed a significant reward type by group interaction ($F_{1,50} = 4.14$, $P < .05$, $\eta_p^2 = .07$). No other effects were significant. Across ROIs, patients with schizophrenia showed significantly less activity for social than nonsocial reward ($P < .05$), but controls showed comparable levels of neural activation for social and nonsocial rewards ($P = .56$). This indicates that patients and controls showed comparable levels of neural sensitivity to nonsocial reward, but patients showed blunted neural sensitivity to social rewards compared with controls.

We performed several follow-up control analyses to evaluate the influence of other factors that might have

Table 1. Demographic and Clinical Characteristics[†]

	Patients	Controls	Statistics
Age	45.8 (10.3)	47.2 (9.2)	$F_{1,50} = .27$, $P = .60$
Personal education (y)	13.4 (2.3)	14.5 (1.7)	$F_{1,50} = 3.85$, $P = .056$
Parental education (y)	14.0 (4.3)	15.2 (2.7)	$F_{1,50} = 1.35$, $P = .25$
Gender (% female)	42%	32%	$\chi^2 = .57$, $P = .44$
Age of onset	22.1 (9.2)		
BPRS total	41.4 (10.6)		
CAINS Expressivity	1.0 (0.9)		
CAINS MAP	1.5 (0.6)		
MCCB			
Social cognitive domain	39.2 (11.6)	48.6 (8.8)	$F_{1,50} = 10.33$, $P < .01$
Neurocognitive composite	43.6 (8.9)	50.3 (9.1)	$F_{1,50} = 6.99$, $P < .05$
A One-Armed Bandit Task[a]			
Social reward	0.57 (0.13)	0.61 (0.15)	$F_{1,50} = 1.19$, $P = .27$
Nonsocial reward	0.63 (0.13)	0.68 (0.17)	$F_{1,50} = 1.29$, $P = .26$

Note: BPRS, the Brief Psychiatric Rating Scale; CAINS, Clinical Assessment Interview for Negative Symptoms; MAP, Motivation and Pleasure subscale of CAINS; MCCB, MATRICS Consensus Cognitive Battery.
[†]Values are presented as mean (standard deviation).
[a]Percent of optimal responses (ie, choosing a good machine over a neutral machine for high-payout trials or choosing a neutral machine over a bad machine for low-payout trials).

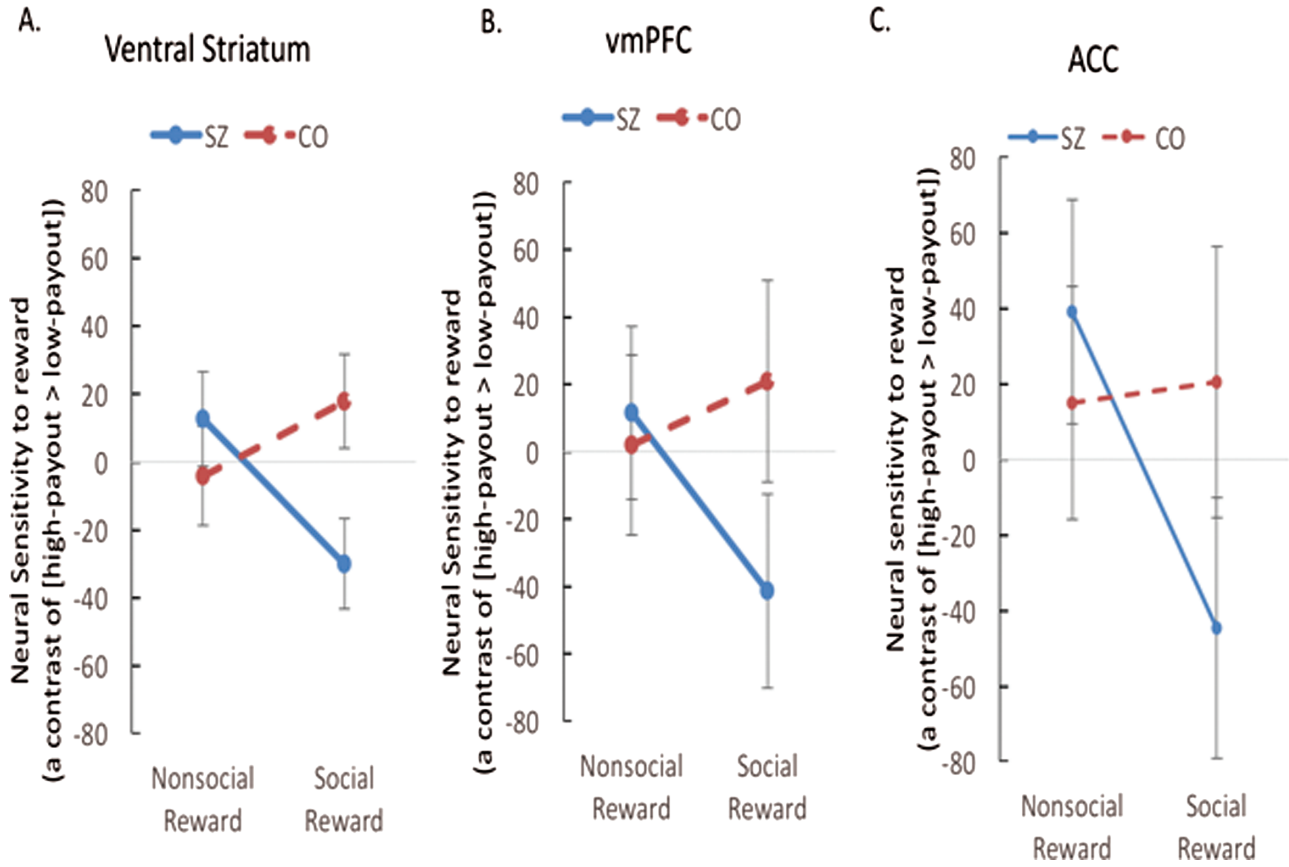

Fig. 2. Neural sensitivity to social and nonsocial reward of patients with schizophrenia (SZ) and controls (CO) during the One-Armed Bandit Task in the ventral striatum (A), ventromedial prefrontal cortex (vmPFC, B), and anterior cingulate cortex (ACC, C). The y-axis represents neural sensitivity to social reward (ie, a contrast of high-payout trials vs low-payout trials).

contributed to this finding. To investigate the possible influence of condition order, we performed a repeated-measures ANOVA with the order of reward conditions as an additional factor. However, there was no significant main effect of order, and there were no interaction effects involving condition order while the reward type by group interaction remained significant. Hence, condition order effects do not explain the findings. To explore whether general cognitive ability and social cognition might contribute to reduced neural sensitivity to social rewards in schizophrenia, we conducted 2 additional $3 \times 2 \times 2$ repeated-measures ANOVAs using the MCCB neurocognitive composite score and MCCB social cognitive domain score as covariates. In both analyses, the reward type by group interaction remained significant, indicating that the pattern of findings was not explained by differences in general neurocognitive factors or social cognition.

Next, we examined associations between ROI beta weights, task performance, and clinical symptoms using Spearman's rho. Controls did not show any association between performance and beta weights for any ROI, in either the nonsocial or social reward conditions. Similarly, patients did not show any significant association between performance and beta weights for nonsocial rewards. However, in the social reward condition, patients with schizophrenia showed a significant correlation between percent optimal response and neural sensitivity to reward across all 3 ROIs: $\rho = .48$, $P < .05$ in vmPFC ($\rho = .52$, $P < .01$); $\rho = .60$, $P < .01$ in VS; and $\rho = .56$, $P < .01$ in ACC. Regarding clinical symptoms (ie, BPRS total, MAP, and Expressivity subscales of CAINS), there were no significant associations with neural sensitivity to reward for any ROI.

Finally, we conducted an exploratory whole-brain analysis for social and nonsocial stimuli separately to determine whether any brain regions outside of the ROIs might be involved in processing these types of rewards. We did not find any brain regions that were significantly activated above a predetermined threshold (ie, $z > 3.2$ and $P < .05$, corrected for multiple comparisons) when each group was examined separately, or when both groups were directly compared with each other.

Discussion

In this study, we examined neural sensitivity to social vs nonsocial rewards in schizophrenia using an implicit reinforcement learning task. At the behavioral level, we observed a similar pattern of performance across 2 groups: Both patients with schizophrenia and controls showed more optimal responses in the nonsocial reward condition than the social reward condition. At the neural level, an ROI-based analysis revealed a significant group by reward condition interaction, reflecting reduced sensitivity in patients to social reward, but not nonsocial reward. We also found that the findings were not explained by differences in general cognitive ability or social cognitive performance. Further, neural sensitivity to social reward in these ROIs was positively associated with individuals' percentage of optimal responses during the social reward condition in patients.

In this study, reduced neural sensitivity to social rewards in patients with schizophrenia was observed across 3 key reward-processing regions. Notably, patients with schizophrenia did not show blunted neural sensitivity to nonsocial rewards, consistent with previous studies showing similar responses to nonsocial rewards in schizophrenia during implicit reinforcement learning.[12,13] Thus, reduced neural activation to social rewards does not appear to be attributable to an overall dysfunction of these reward-processing regions. Rather, the relatively specific social reward-processing deficit in schizophrenia found in this study suggests that reward type may be an important factor for understanding implicit reinforcement learning in schizophrenia. It remains to be determined whether a similar effect of reward type might also be present in schizophrenia during explicit reinforcement learning.

The reduced neural sensitivity to social rewards in schizophrenia that we observed was assessed by comparing high-payout and low-payout conditions on the implicit reinforcement learning task. In other words, patients showed greater activity in the low-payout condition (ie, neutral vs bad machines) than in the high-payout condition (neutral vs good machines), resulting in reduced neural sensitivity to social rewards. This pattern suggests that the reduced sensitivity to social rewards might relate to abnormal processing during choices between positive and neutral social stimuli. This possibility is consistent with previous findings in schizophrenia of impaired discrimination between positive and neutral affective stimuli but not between neutral vs negative stimuli, which have been examined in the context of reduced social approach motivation, part of negative symptoms.[40–42] Thus, this study provides additional evidence of reduced social approach motivation in schizophrenia. This study failed to find the association between reduced neural sensitivity to social rewards and negative symptoms. Although the lack of relationship in this study could be due to a small sample of clinically stable patients, it should be noted that previous studies have not always found associations between impaired reward processing and negative symptoms in schizophrenia.[8,12,17,43,44] The lack of congruency across studies suggests a rather complex relationship between social motivation measured in the laboratory and negative symptoms assessed with clinical interviews.[45,46]

Patients in this study showed numerically but not statistically lower optimal choice rates on the One-Armed Bandit Task, compared with controls. In other words, we found neural differences in reward processing in the absence of performance differences between patients and controls. It is possible that neural measures may be more

sensitive to subtle reward-processing abnormalities in patients, which would be detected in studies with a small sample size. It is also possible that patients may recruit compensatory brain regions other than ROIs to perform the task at adequate levels. If compensatory brain regions were involved and were varied across patients, studies with a small sample size could miss such brain regions.

Our finding of reduced neural sensitivity to social rewards in schizophrenia can be viewed in the context of a recently proposed model of disrupted social preference or social motivation in the disorder.[2] This model posits that patients with schizophrenia do not preferentially process social over nonsocial information, resulting in impaired social processing. Empirical support for this model comes mainly from behavioral studies. Our current findings provide additional evidence of disrupted social preference in schizophrenia at the neural level. Further, in this model, impaired glutamatergic function, specifically *N*-methyl-$_D$-aspartate (NMDA) receptor hypofunction, was proposed as a neurobiological mechanism underlying disrupted social preference. A recent study showed that the NMDA receptor antagonist memantine reduced neural activation for rewarding social stimuli in the VS of healthy adults.[47] It needs to be determined whether reduced sensitivity to social reward in schizophrenia is associated with NMDA receptor hypofunction using a multimodal neuroimaging approach (eg, magnetic resonance spectroscopy and fMRI). This model proposes that disrupted social preference in schizophrenia can lead to diminished social interaction and then to less effective development of social cognitive skills. The assumption is that the influences are bidirectional, with social competence having a reciprocal influence on social preference. Because our study used a cross-sectional design of patients with chronic schizophrenia, it was not possible to determine how reduced neural sensitivity to social reward arises over the course of illness. A longitudinal study with individuals during their early course of illness could address the question of how changes in social preference emerge over time.

The findings of this study should be interpreted in the context of several limitations. All patients were taking second-generation antipsychotic medication at the time of testing. Although we cannot completely rule out any confounding effect of antipsychotic medication, it is unlikely that the current findings can be explained this way considering that we observed reduced neural sensitivity only to social rewards in patients. This study used emotional faces as socially rewarding stimuli and patients have difficulty recognizing emotional expression of faces.[48,49] Although we showed that impaired social cognition (ie, emotion management) could not explain the current pattern of findings, associations between other types of social cognition (eg, facial affect recognition) and sensitivity to social reward remain to be examined. This study used static images of faces and dollar bills as social and nonsocial rewarding stimuli and did not ask participants to rate how rewarding they found each stimulus to be. Thus, it needs to be determined whether a similar pattern of findings would be observed with different types of reward (eg, dynamic video stimuli, social touch, and food) or could be explained by differences in the subjective value of rewards.

Conclusion

In summary, this study found a reduced neural sensitivity to social, but not to nonsocial reward, in chronic schizophrenia patients during an implicit reinforcement learning task. These findings provide an empirical evidence of disrupted social preference and aberrant social approach motivation in schizophrenia at the neural level.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

Funding

This work is supported by the National Institute of Mental Health (MH102567 to J.L.) and Brain & Behavior Research Foundation NARSAD Young Investigator Award to J.L.

Acknowledgments

We would like to thank Ana Ceci Myers and Julio Iglesias for their assistance in data collection and Michelle J. Dolinsky for the recruitment of participants. These data were presented at the 16th International Congress on Schizophrenia Research.

Conflict of Interest

M.F.G. has been a consultant for AiCure, Takeda, and Lundbeck, a member of the Scientific Board of Cadent, and has received research funds from Forum. J.L. and W.P.H. have worked as a consultant for Takeda. The rest of the authors do not have any conflict of interest to report.

References

1. Heerey EA. Learning from social rewards predicts individual differences in self-reported social ability. *J Exp Psychol Gen*. 2014;143(1):332–339.
2. Lee J, Green MF. Social preference and glutamatergic dysfunction: underappreciated prerequisites for social dysfunction in schizophrenia. *Trends Neurosci*. 2016;39(9):587–596.
3. Green MF, Horan WP, Lee J, McCleery A, Reddy LF, Wynn JK. Social disconnection in schizophrenia and the general community. *Schizophr Bull*. 2018;44(2):242–249.
4. Wang KS, Smith DV, Delgado MR. Using fMRI to study reward processing in humans: past, present, and future. *J Neurophysiol*. 2016;115(3):1664–1678.

5. Lin A, Adolphs R, Rangel A. Social and monetary reward learning engage overlapping neural substrates. *Soc Cogn Affect Neurosci*. 2012;7(3):274–281.
6. Izuma K, Saito DN, Sadato N. Processing of social and monetary rewards in the human striatum. *Neuron*. 2008;58(2):284–294.
7. Spreckelmeyer KN, Krach S, Kohls G, et al. Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. *Soc Cogn Affect Neurosci*. 2009;4(2):158–165.
8. Barch DM, Carter CS, Gold JM, et al. Explicit and implicit reinforcement learning across the psychosis spectrum. *J Abnorm Psychol*. 2017;126(1):694–711.
9. Heerey EA, Bell-Warren KR, Gold JM. Decision-making impairments in the context of intact reward sensitivity in schizophrenia. *Biol Psychiatry*. 2008;64(1):62–69.
10. Waltz JA, Gold JM. Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. *Schizophr Res*. 2007;93(1–3):296–303.
11. Reddy LF, Waltz JA, Green MF, Wynn JK, Horan WP. Probabilistic reversal learning in schizophrenia: stability of deficits and potential causal mechanisms. *Schizophr Bull*. 2016;42(4):942–951.
12. Dowd EC, Frank MJ, Collins A, Gold JM, Barch DM. Probabilistic reinforcement learning in patients with schizophrenia: relationships to anhedonia and avolition. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2016;1(5):460–473.
13. Culbreth AJ, Westbrook A, Xu Z, Barch DM, Waltz JA. Intact ventral striatal prediction error signaling in medicated schizophrenia patients. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2016;1(5):474–483.
14. Wolf DH, Satterthwaite TD, Kantrowitz JJ, et al. Amotivation in schizophrenia: integrated assessment with behavioral, clinical, and imaging measures. *Schizophr Bull*. 2014;40(6):1328–1337.
15. Waltz JA, Schweitzer JB, Ross TJ, et al. Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. *Neuropsychopharmacology*. 2010;35(12):2427–2439.
16. Strauss GP, Waltz JA, Gold JM. A review of reward processing and motivational impairment in schizophrenia. *Schizophr Bull*. 2014;40 (suppl 2):S107–S116.
17. Waltz JA, Xu Z, Brown EC, Ruiz RR, Frank MJ, Gold JM. Motivational deficits in schizophrenia are associated with reduced differentiation between gain and loss-avoidance feedback in the striatum. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(3):239–247.
18. Walsh-Messinger J, Ramirez PM, Wong P, et al. Impairment in emotional modulation of attention and memory in schizophrenia. *Schizophr Res*. 2014;157(1–3):63–69.
19. Zivotofsky AZ, Oron L, Hibsher-Jacobson L, Weintraub Y, Strous RD. Finding the hidden faces: schizophrenic patients fare worse than healthy subjects. *Neuropsychologia*. 2008;46(8):2140–2144.
20. Harvey PO, Lepage M. Neural correlates of recognition memory of social information in people with schizophrenia. *J Psychiatry Neurosci*. 2013;38(5):130007.
21. First MB, Williams JBW, Karg RS, Spitzer RL. *Structural Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV)*. Arlington, VA: American Psychiatric Association Publishing; 2015.
22. Kirsch P, Ronshausen S, Mier D, Gallhofer B. The influence of antipsychotic treatment on brain reward system reactivity in schizophrenia patients. *Pharmacopsychiatry*. 2007;40(5):196–198.
23. Vita A, De Peri L, Deste G, Barlati S, Sacchetti E. The effect of antipsychotic treatment on cortical gray matter changes in schizophrenia: does the class matter? A meta-analysis and meta-regression of longitudinal magnetic resonance imaging studies. *Biol Psychiatry*. 2015;78(6):403–412.
24. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin L. Structured Clinical Interview for DSM-IV Axis II Personality Disorders. Washington DC: American Psychiatric Association Publishing; 1997.
25. Ventura J, Lukoff D, Nuechterlein KH, Liberman RP, Green MF, Shaner A. Brief Psychiatric Rating Scale (BPRS) expanded version 4: scales, anchor points, and administration manual. *Int J Methods Psychiatr Res*. 1993;3:227–243.
26. Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. *Am J Psychiatry*. 2013;170(2):165–172.
27. Nuechterlein KH, Green MF. *MATRICS Consensus Cognitive Battery Manual*. Los Angeles, CA: MATRICS Assessment, Inc.; 2006.
28. Lin A, Rangel A, Adolphs R. Impaired learning of social compared to monetary rewards in autism. *Front Neurosci*. 2012;6:143.
29. Tottenham N, Tanaka JW, Leon AC, et al. The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res*. 2009;168(3):242–249.
30. Lutkenhoff ES, Rosenberg M, Chiang J, et al. Optimized brain extraction for pathological brains (optiBET). *PLoS One*. 2014;9(12):e115551.
31. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimisation for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17(2):825–841.
32. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage*. 2012;59(3):2142–2154.
33. Lockwood PL, Apps MA, Valton V, Viding E, Roiser JP. Neurocomputational mechanisms of prosocial learning and links to empathy. *Proc Natl Acad Sci U S A*. 2016;113(35):9763–9768.
34. Bartra O, McGuire JT, Kable JW. The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. *Neuroimage*. 2013;76:412–427.
35. Beckmann CF, Jenkinson M, Smith SM. General multilevel linear modeling for group analysis in FMRI. *Neuroimage*. 2003;20:1052–1063.
36. Woolrich MW, Behrens TE, Beckmann CF, Jenkinson M, Smith SM. Multilevel linear modelling for FMRI group analysis using Bayesian inference. *Neuroimage*. 2004;21:1732–1747.
37. Worsley KJ. Statistical analysis of activation images. In: Jezzard S, Matthews PM, Smith SM, eds. *Functional MRI: An Introduction to Methods*. Oxford: Oxford University Press; 2001: 251–270.
38. Kern RS, Penn DL, Lee J, et al. Adapting social neuroscience measures for schizophrenia clinical trials, Part 2:

trolling the depths of psychometric properties. *Schizophr Bull*. 2013;39(6):1201–1210.

39. Reddy LF, Horan WP, Barch DM, et al. Understanding the association between negative symptoms and performance on effort-based decision-making tasks: the importance of defeatist performance beliefs. *Schizophr Bull*. In press.
40. Horan WP, Wynn JK, Kring AM, Simons RF, Green MF. Electrophysiological correlates of emotional responding in schizophrenia. *J Abnorm Psychol*. 2010;119(1):18–30.
41. Reinen JM, Van Snellenberg JX, Horga G, Abi-Dargham A, Daw ND, Shohamy D. Motivational context modulates prediction error response in schizophrenia. *Schizophr Bull*. 2016;42(6):1467–1475.
42. Kirschner M, Hager OM, Bischof M, et al. Deficits in context-dependent adaptive coding of reward in schizophrenia. *NPJ Schizophr*. 2016;2:16020.
43. Waltz JA, Kasanova Z, Ross TJ, et al. The roles of reward, default, and executive control networks in set-shifting impairments in schizophrenia. *PLoS One*. 2013;8(2):e57257.
44. Waltz JA, Frank MJ, Robinson BM, Gold JM. Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. *Biol Psychiatry*. 2007;62(7):756–764.
45. Radua J, Schmidt A, Borgwardt S, et al. Ventral striatal activation during reward processing in psychosis: a neurofunctional meta-analysis. *JAMA Psychiatry*. 2015;72(12):1243–1251.
46. Fulford D, Campellone T, Gard DE. Social motivation in schizophrenia: how research on basic reward processes informs and limits our understanding. *Clin Psychol Rev*. 2018;63:12–24.
47. Jocham G, Klein TA, Ullsperger M. Differential modulation of reinforcement learning by D2 dopamine and NMDA glutamate receptor antagonism. *J Neurosci*. 2014;34(39):13151–13162.
48. Spilka MJ, Goghari VM. Similar patterns of brain activation abnormalities during emotional and non-emotional judgments of faces in a schizophrenia family study. *Neuropsychologia*. 2017;96:164–174.
49. Bortolon C, Capdevielle D, Raffard S. Face recognition in schizophrenia disorder: a comprehensive review of behavioral, neuroimaging and neurophysiological studies. *Neurosci Biobehav Rev*. 2015;53:79–107.