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Neuroimaging of social motivation during winning and losing: Associations with social anhedonia across the psychosis spectrum

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Abstract

Background: Individuals with psychosis spectrum disorders (PSD) have difficulty developing social relationships. This difficulty may reflect reduced response to social feedback involving functional alterations in brain regions that support the social motivation system: ventral striatum, orbital frontal cortex, insula, dorsal anterior cingulate cortex, and amygdala. Whether these alterations span PSD is unknown.

Methods: 71 individuals with PSD, 27 unaffected siblings, and 37 control participants completed a team-based fMRI task. After each trial, participants received performance feedback paired with the expressive face of a teammate or opponent. A 2×2 (win versus loss outcome x teammate versus opponent) repeated measures ANOVA by group was performed on activation in the five key regions of interest during receipt of feedback.

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Results: Across groups, three social motivation regions, ventral striatum, orbital frontal cortex, and amygdala, showed sensitivity to feedback (significant main effect of outcome), with greater activation during win versus loss trials, regardless of whether the feedback was from a teammate or opponent. In PSD, ventral striatum and orbital frontal cortex activation to win feedback was negatively correlated with social anhedonia scores.

Conclusions: Patterns of neural activation during social feedback were similar in PSD, their unaffected siblings, and healthy controls. Across the psychosis spectrum, activity in key social motivation regions during social feedback was associated with individual differences in social anhedonia.

Keywords

schizophrenia; psychotic disorders; sibling study; social motivation; social reward; social anhedonia; team task; functional magnetic resonance imaging (fMRI)

1. Introduction

Humans are inherently social beings, with powerful internal motivation to seek out and maintain interpersonal relationships (1). These relationships are among the most important sources of life satisfaction and mental and physical wellbeing (2–5). However, for individuals with psychosis spectrum disorders (PSD), including schizophrenia, schizoaffective disorder, and mood disorders with psychotic features, developing and maintaining social relationships is often difficult. These individuals have fewer, poorer quality, and more stressful social connections throughout the course of illness than healthy individuals (6,7). Social impairments are particularly debilitating because social interactions are such an inherent part of role functioning, including successful work/school performance, interpersonal relationships, and independent living. Beyond evidence for social impairment as a core feature of psychotic illness, a growing body of literature suggests that such dysfunction also constitutes a risk factor for psychosis (8,9).

Social dysfunction in PSD has most often been studied in terms of social processing deficits, and we know from extensive research that social cognition in schizophrenia and other PSD is impaired (10–14). Another, less studied domain that may impact social functioning in PSD is social motivation. In general, motivation refers not to what patients *can* do, but what they are *willing* to do, and includes the direction, intensity, and persistence of goal-directed behavior (15). Deficits in social motivation are reflected clinically as social anhedonia, which refers to a disinterest in social contact and a lack of pleasure in social situations and is typically assessed in PSD with interview or self-report scales (16,17). However, our understanding of the neurobehavioral mechanisms underlying dysfunctional social motivation in PSD is much less than we know about the ability factors.

According to prominent social neuroscience models, social behavior is evident across humans and non-human animals, including the tendency to seek out, engage in, and maintain close bonds with conspecifics (18–20). Such models posit that a social motivation system promotes social engagement, bonding, and attachment (21,22). This system primarily involves brain regions implicated in reward and emotion processing, including the ventral

striatum (VS), orbital frontal cortex (OFC), insula, dorsal anterior cingulate cortex (dACC), and amygdala (23–26). Brain reward circuitry, particularly VS and OFC, is strongly linked to dopaminergic and opioid pathways (27–29). Limbic and midbrain nuclei are likewise rich in oxytocin receptors. Although findings related to the role of oxytocin in social processes are mixed (30,31), some research suggests that oxytocin enhances the salience of social cues (32–34),. These pathways are thus thought to promote expectation of positive social outcomes and enhance approach-related social behaviors.

Studies in humans show that traits associated with social behaviors that promote bonding and attachment, including extraversion, gregariousness, and sociability, are at least moderately heritable in the general population (35) and individual differences in attachment involve a complex combination of genetic and environmental influences (36–40). Social anhedonia and withdrawal are strongly associated with vulnerability to psychosis (41–43) and are elevated in unaffected family members (9,44). However, the neural correlates of social motivation, including social anhedonia, have not been examined in unaffected siblings of individuals with PSD.

The aims of the current study were to identify potential abnormalities in the social motivation system in a transdiagnostic sample of individuals with several types of psychotic illness and to determine whether these potential abnormalities extend to their unaffected siblings. Our primary focus was to understand social motivation deficits across the psychosis spectrum, and this project was supported by the NIMH Research Domain Criteria (RDoC) Initiative, which has a transdiagnostic focus. To do so, we utilized a functional magnetic resonance imaging (fMRI) paradigm designed to engage the participant in a task as a cooperative team member. In this paradigm, participants received feedback based on their task performance: win/loss outcome along with a happy or angry facial expression from a teammate or opponent. Importantly, the social context of the task was designed to examine in-group versus out-group effects, something that has rarely been investigated in PSD. In-group/out group classification is an important element of social identity and relationship dynamics (45), and can result in preferential inclusion, attachment, and affiliation with fellow in-group members and, conversely, exclusion, animosity, and bias against out-group members (46). In-group attachment and out-group bias may be altered in schizophrenia and other psychotic disorders (47,48). The paradigm used in the current study (49) requires participants to perform as part of a team, potentially generating social affiliation toward fellow in-group members (teammates). Performance feedback is provided by teammates and opponents, implicating both rewarding and aversive aspects of social feedback. Although the paradigm was not designed to remove the influence of social processing ability per se (i.e., social cognition), it did allow for assessment of responsivity to social reward (i.e., social motivation).

In previous studies with healthy participants, this task generated a blood oxygen level dependent (BOLD) response in brain regions linked to social motivation, including VS, amygdala, dACC, OFC, and AI (20,49). More specifically, these regions showed sensitivity to positive versus negative social feedback, and this activity varied depending on whether the feedback was given by a teammate or an opponent. Based on these prior findings, we selected *a priori* these five areas as key regions of interest (ROIs) for the current study.

We predicted reduced BOLD responses in the ROIs for the PSD compared with the control group, particularly when given rewarding (win) feedback from a teammate, and that siblings would be intermediate between the two. Further, we predicted associations between activity in ROIs and self-reported social anhedonia across groups.

2. Methods and Materials

2.1. Participants

This study was part of a larger transdiagnostic project designed to examine social affiliation in individuals with psychosis and their unaffected full biological siblings ("Social Affiliation in Psychosis: Mechanisms and Vulnerability Factors", MH107422, PI: William Horan). In this paper we present data from the fMRI portion of the study that included 80 individuals with diagnoses in the psychosis spectrum (PSD), 28 unaffected siblings, and 39 healthy control subjects. Of those, 3 PSD and 2 controls did not complete the scan, data from 4 PSD and 1 sibling could not be analyzed due to technical issues, and 2 PSD were excluded for excessive motion (see Section 2.4 for details regarding motion correction and data quality assurance). In total, data from 71 PSD, 27 siblings, and 37 controls were included in the current analysis.

PSD were recruited from VA Greater Los Angeles Healthcare System (GLA) and University of California, Los Angeles (UCLA) outpatient clinics, community clinics, and local board and care facilities. Controls were recruited primarily from internet postings. Sibling participants were recruited by phone or letter if the PSD proband agreed to release their sibling's name to us. All study procedures were approved by the Institutional Review Boards of GLA and UCLA. All participants had the capacity to give informed consent and provided written informed consent prior to participation after all procedures were fully explained. All participants were provided monetary compensation for their time.

Inclusion criteria for all participants were: a) age 18 – 65; b) sufficient English language proficiency to understand testing procedures; c) normal or corrected vision; and d) expressed willingness to participate in neuroimaging. Exclusion criteria were: a) clinically significant neurological disease as determined by medical history (e.g., epilepsy); b) history of serious head injury (i.e., loss of consciousness longer than 15 min, neuropsychological sequelae, cognitive rehabilitation treatment post head injury); c) substance or alcohol abuse in the last month; d) sedative or benzodiazepine use within 12 hours of testing; e) positive urine toxicology screen at the time of assessment; f) IQ < 70 based on WRAT-4 or developmental disability based on self-report and observation; and g) current mood episode (within the last 2 months).

Additional inclusion criteria for PSD were: a) a diagnosis in the psychosis spectrum, which included schizophrenia (n = 32), schizoaffective disorder (n = 6), delusional disorder (n = 0), brief psychotic disorder (n = 0), schizophreniform disorder (n = 1), psychotic disorder not otherwise specified (n = 11), bipolar disorder with psychotic features (n = 19), or major depressive disorder with psychotic features (n = 2); and b) clinical stability (i.e., no inpatient hospitalizations within three months, and no psychoactive medication changes within four weeks, prior to enrollment). An additional exclusion criterion for siblings was

history of primary psychotic symptoms. Additional exclusion criteria for controls were: a) history of primary psychotic symptoms, bipolar disorder, or recurrent major depression; b) the following personality disorders: avoidant, paranoid, schizotypal, schizoid, or borderline; and c) psychotic disorder in first-degree relatives, based on participant report.

All participants completed the Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID-I/P, (50) to establish psychiatric diagnoses. Controls and siblings were also interviewed with portions of the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (51). Interviewers were trained through the Treatment Unit of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center (MIRECC) to a minimum kappa of .75 for key psychotic and mood items. To supplement self-report information when necessary for PSD, collateral information was obtained from medical records and clinician reports if available.

2.2. Clinical assessment

Psychiatric symptoms were evaluated for all participants using the 24-item version of the Brief Psychiatric Rating Scale (BPRS) (52) and the Clinical Assessment Interview for Negative Symptoms (CAINS) (53). For the BPRS we report mean score for the positive symptom factor (54). For the CAINS we report the motivation and pleasure (MAP) and expressive negative symptoms (EXP) subscales (53).

Social anhedonia was measured via the Social Anhedonia Scale — Brief (SAS) (55). The SAS is a 24-item (dichotomously scored) self-report measure for assessing decreased social pleasure, including lack of interest in social connections, aversion from social interactions, and preference for solitude and solo activities.

2.3. fMRI Task

Participants completed a simple dot perception task in a social game context (49). See Figure 1 for an illustration of the task design. Before the MRI scan, participants were informed that they would play a game as a member of the HOME team, playing against the AWAY team. To introduce the participant to the teams they were shown a set of four faces (2 female, 2 male), each paired with a name, labeled as their teammates on the HOME team, and four named faces (2 female, 2 male) labeled as opponents on the AWAY team. Sufficient time was devoted to each participant to ensure they understood the team-based aspects of the game and the introductions took as long as necessary to ensure that they were familiar with the faces of their own teammates as well as opponent team members.

The game involved selecting which side of the computer screen displayed more dots (left/right using a button box). A correct response resulted in winning a point for the participant’s team, whereas an incorrect response resulted in losing a point for their team. The participant’s goal was to win as many points as possible for his/her team. Each trial sequence comprised a central fixation cross (jittered duration: range: 3000 ms – 7000 ms), a screen divided by a vertical line with a variable number of dots (10 – 15) randomly appearing on each side of the screen (500 ms), response selection (left/right using a button box; up to 4000 ms), and response feedback (1500 ms). The number of dots on the two display sides adjusted adaptively on a trial-by-trial basis to increase or decrease level

of difficulty (by decreasing or increasing the difference in the number of dots per side, respectively) based on the participant's performance to ensure approximately equal numbers of correct and incorrect trials (actual mean correct = 57%). Specifically, after each trial if the percent correct fell below a threshold of 47.5% the difference in number of dots per side increased in increments of 1 until the difference was 5. If the difference between the two sides was already 5, then it stayed at 5. If the percent correct reached above a threshold of 52.5% the difference in number of dots per side would decrease in increments of 1 until the difference was only 1. If the difference between the two sides was already only one, then it stayed at 1.

After each primary test trial (n = 100), the participant received feedback on the computer monitor on the outcome of their performance paired with the expressive face of a teammate (n = 50) or an opponent (n = 50). The faces of teammates were happy/smiling for win outcomes (won a point) and angry/scowling for loss outcomes (lost a point) (i.e., congruent with outcome); the faces of opponents were angry for win outcomes and happy for loss outcomes (i.e., incongruent with outcome). Thus, the social feedback that participants received on a trial-by-trial basis reinforced the team status of each other player during the duration of the task.

The task was modified from the original version to simplify the instructions for use with patients with psychosis and to include a neutral control condition which consisted of a scrambled face with the word "REDO" instead of feedback on 25 randomly intermixed trials. For these control trials, participants were told that neither the HOME team nor the AWAY team won a point. In total, participants completed 125 randomized trials with four built-in rest periods for a total scanning time of approximately 25 minutes.

2.4. MRI acquisition and pre-processing

All scanning was performed using identical 3T Siemens Magnetom Prisma^{fit} scanners running identical software at the UCLA Ahmanson-Lovelace Brain Mapping Center and the UCLA Staglin Center for Cognitive Neuroscience. Each scanner utilized the same quality assurance protocols daily to assess scanner performance. See Supplementary Materials (Table S1) for detailed comparisons by scanner and a description of the scanning protocol. A high-resolution T1-weighted magnetization prepared rapid-acquisition gradient echo image (MPRAGE) was acquired from each subject for anatomical localization and registration of functional data [TR = 2300 ms; TE = 2.32 ms; flip angle = 8°; 192 sagittal slices; slice thickness = 0.9 mm; matrix = 256×256; FOV = 240 mm; voxel size = 0.9×0.9×0.9 mm]. Four functional runs were acquired with T2*-weighted blood oxygen level-dependent (BOLD) gradient echo planar imaging (EPI) sequences for each activation task (TR = 2000 ms, TE = 24 ms, flip angle = 90°, 36 interleaved slices, slice thickness = 3.0 mm; matrix = 64 × 64; FOV = 200 mm; voxel size = 3.1 × 3.1 × 3 mm).

Image preprocessing was carried out using the FMRIB Software Library (FSL v5.0.9; Analysis Group, Oxford, UK). Preprocessing steps included motion correction (described in detail below), skull stripping using BET (56), spatial smoothing using a Gaussian kernel of FWHM 5mm, high-pass filtering (100 s cut-off), and registration. Registration was carried out using FSL's FLIRT (FMRIB's Linear Image Registration Tool v6.0) (57). Each

run of individual EPI data was registered to the T1-weighted MPRAGE (Boundary-Based Registration, BBR) (58) then to Montreal Neurological Institute (MNI) standard space (affine transformation, 12 degrees of freedom).

We addressed potential motion artifacts in several ways. First, motion estimates from raw data were inspected to ensure that relative mean displacement did not exceed 0.5mm for any participant. In addition, all images were realigned to the middle volume using MCFLIRT and movement parameters calculated by MCFLIRT were modeled as nuisance covariates (57,59). Finally, the FSL motion outliers tool was used to remove the effects of any time-points corrupted by motion beyond what realignment and linear motion parameter regression methods can fix.

2.5. fMRI data analysis

Analysis of fMRI data was performed using a general linear model (GLM) approach with FEAT (FMRI Expert Analysis Tool v6.0), and a timing model based on a double-gamma hemodynamic response function. In the first-level analysis, linear contrasts of trials by condition were created for each subject (see Supplementary Materials Table S4 for a complete list of contrasts included in the GLM). We conducted a 2 × 2 analysis by group: outcome (win versus loss) × team (same versus other), with each experimental condition contrasted against the neutral control condition.

The primary analytic approach was to use region of interest (ROI) analysis to focus on areas associated with social motivation (VS, OFC, insula, dACC, and amygdala). Bilateral cortical ROIs (OFC, insula, dACC) were drawn from a well-validated cortical parcellation map (60). We used the 400 parcel parcellation, projected to FSL MNI space and matched to a corresponding network in the 7 network parcellation by Yeo et al (61). Bilateral subcortical ROIs (VS and amygdala) were created in individual native space based on the HarvardOxford subcortical probability atlas at a 25% probability threshold. See Figure 2 for ROI locations. Mean beta values extracted from the five key ROIs during performance feedback receipt on test versus control trials were analyzed using repeated measures ANOVA to compare within- and between-group activation across the task conditions. A two-tailed Bonferroni adjusted significance threshold for each test was applied, corresponding to $p < .01$ for the five ROIs (.05/5).

After the ROI analyses, we also conducted a secondary voxel-wise whole-brain analysis with FSL. The four runs per task for each participant were averaged together in a fixed effects model. These averages were then entered into a random-effects model for group analysis, using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 module (62). Variance estimates were calculated for each group separately. Clusters exceeding a height threshold of $Z>2.3$ and a cluster probability of $p<.05$, corrected for whole-brain multiple comparisons are reported (63,64).

We used hierarchical regression to examine the association between condition effects related to social motivation (i.e., wins and losses) and social anhedonia ratings (SAS total scores) in ROIs that showed sensitivity to task manipulations (VS, OFC, amygdala). Further, we tested whether the strength of these associations varied by group. SAS total scores were entered as

the dependent variable, and ROI activity, group (dummy coded with PSD as the reference level), and the interaction between ROI activity and group were entered as independent variables in a series of three blocks (see Table 2). This approach allowed us to test for a main effect of group and an interaction effect of group by ROI activity. Data were analyzed using SPSS Version 28.0.0 for Windows (SPSS Inc., Chicago, IL, USA). A two-tailed Bonferroni adjusted significance threshold for each test was applied, corresponding to $p < .017$ for the three ROIs (.05/3).

3. Results

3.1. Demographic, Clinical, and Behavioral Data

Table 1 provides group demographic, clinical, and behavioral data. Across the three groups there was a significant difference in terms of sex and level of personal education. Although the ratio of males to females was matched between PSD and controls, there were more females in the unaffected sibling group. In addition, PSD had fewer years of education. There were no differences between groups in terms of age, race, ethnicity, or parental education. PSD were typically chronically ill, exhibited mild to moderate symptoms, and most were receiving clinically determined doses of medication. Seven PSD reported not receiving any psychiatric mediation at the time of the assessment and psychiatric medication information was missing for two PSD. Group differences for symptom ratings were not observed between controls and siblings. Groups did not differ in mean accuracy on the task.

3.2. ROI analyses

For VS, OFC, and amygdala, we saw a significant effect of outcome (wins > loss) after Bonferroni correction for multiple comparisons, and no significant main or interaction effect involving group or team status. In all three regions there was significantly greater activation for wins compared to losses (VS: $F_{1,132} = 95.07$, $p < .001$, $\eta_p^2 = .42$, Figure 3A; OFC: $F_{1,132} = 7.26$, $p = .008$, $\eta_p^2 = .05$, Figure 4A; amygdala: $F_{1,132} = 6.79$, p = .01, $\eta_p^2 = .05$; Supplementary Materials Figure S1).

Unexpectedly, there were no significant main or interaction effects involving team status or group in any of the ROIs. Furthermore, the insula ROI did not show any significant within-group condition effects or between-group effects of the task (Supplementary Materials Figure S1). For dACC there was a trend level outcome by group interaction ($F_{2,132} = 2.71$, $p = .07$, $\eta_p^2 = .04$). Given our interest in group and subgroup comparisons, we examined this trend further and found that PSD ($p = .004$), but not siblings or controls, showed greater activity in dACC to *loss* compared to win feedback regardless of team status (Supplementary Materials Figure S1).

To explore potential effects of PSD subgroups, we re-ran the ROI analyses in those with affective versus non-affective subtypes. See Supplementary Materials (Table S2) for a comparison of demographic and clinical variables by subgroup. None of the ROIs showed any significant main or interaction effects involving patient subtype.

3.3. Whole-brain analyses

Full results of exploratory whole brain analyses are listed in Supplementary Materials Table S3 and Figure S2. For the main effect of outcome, all groups showed significantly greater BOLD activity in response to win compared to loss feedback (win > loss contrast) in several expected social processing regions bilaterally, including VS, amygdala, ventral ACC, medial prefrontal cortex, posterior cingulate cortex, precuneus, and fusiform gyrus. Direct group comparisons revealed that controls showed significantly greater activation compared to PSD in several right hemisphere frontal regions including middle and superior frontal gyrus and frontal pole, and in left superior parietal lobule. There were no significant differences between PSD versus siblings and siblings versus controls. For the loss > win contrast, only a few regions showed significant activation, including bilateral superior frontal gyrus and left inferior frontal gyrus, with no significant between-group differences.

For the main effect of team, there were no significant within- or between-group effects for the same > other team contrast. For the other > same team contrast PSD showed significant BOLD response in bilateral inferior and middle frontal gyri, right superior frontal gyrus, and bilateral fusiform gyri. No significant activation was observed for this contrast in the sibling or control groups; however, no group differences were significant after correction for multiple comparisons.

3.4. Neural correlates of social anhedonia

We examined associations between win and loss condition effects and SAS total scores in VS, OFC, and amygdala. Activity in VS and OFC during win feedback was significantly associated with SAS total scores after Bonferroni correction for multiple comparisons, whereas activity in these regions during loss feedback was not. No significant relationships with SAS total scores were observed for amygdala activity.

For VS, the overall relationship (i.e., across groups) between VS activity during win feedback and SAS total scores was not significant in the first block ($F_{1,133} = 3.74$, $p = .06$, $R^2 = 0.03$). Including group status in Block 2 resulted in a significant change in R^2 ($R^2 = 0.10$, $\Delta R^2 = 0.07$, $p = .008$), and including the group × VS activity interaction in Block 3 resulted in a significant change in R^2 compared to Block 2 ($F_{2,129} = 3.54$, $p = .03$, $\Delta R2 = 0.05$). The overall model in Block 3 was significant ($F_{5,129} = 4.32$, $p = .001$, $R^2 = 0.14$). Therefore, the model from Block 3 was the focus of interpretation.

There was a significant group x VS activity interaction such that PSD showed a significant relationship between VS activity and SAS total scores ($\beta = -0.34$, $p = .002$), and this relationship was stronger in PSD than in siblings ($\beta = .06$, $p = .01$) but not controls ($\beta = .03$, $p = .24$). The relationship between VS activity and SAS total scores was not significant in siblings ($\beta = .03$, $p = .20$) or controls ($\beta = -.01$, $p = .61$), and this relationship was not significantly different between siblings and controls ($\beta = -.04$, $p = .19$) (Figure 3B). See Table 2 for the model summary and coefficients of all variables.

For OFC, the overall relationship between activity during win feedback and SAS total scores was not significant in the first block ($F_{1,133} = 3.29$, $p = .067$ $R^2 = 0.02$). Including group status in Block 2 resulted in a significant change in R^2 ($R^2 = 0.08$, $\Delta R^2 = 0.06$, $p = .02$), and

including the group x OFC activity interaction in Block 3 resulted in a significant change in R^2 compared to Block 2 ($F_{2,129}$ = 3.74, p = .03, $\Delta R2$ = 0.05). The overall model in Block 3 was significant ($F_{5,129}$ = 3.99, p = .002, R^2 = 0.13). Therefore, the model from Block 3 was the focus of interpretation.

There was a significant group x OFC activity interaction such that PSD showed a significant relationship between OFC activity and SAS total scores (β = −0.06, p = .002), and this relationship was stronger in PSD than in controls (β = .09, p = .01) but not siblings (β = .07, p = .14). The relationship between OFC activity and SAS total scores was not significant in siblings (β = .01, p = .78) or controls (β = .03, p = .31), and this relationship was not significantly different between siblings and controls (β = .02, p = .74) (Figure 4B). See Table 2 for the model summary and coefficients of all variables.

In *post hoc* analyses we also explored the relationship between win and loss condition effects and psychiatric symptoms (i.e., BPRS positive symptom factor score, CAINS MAP and EXP subscale scores) in patients for VS, OFC, and amygdala using bivariate correlation. After Bonferroni correction for multiple comparisons, only one observed correlation was significant. Patients showed a significant negative relationship between VS activity during win feedback and the CAINS MAP subscale score (Pearson's r = −.312, p = .009).

4. Discussion

The current study investigated potential neural abnormalities in the social motivation system in PSD, unaffected siblings, and control participants. In an effort to closely model the experience of social group dynamics using fMRI, we selected a relatively complex team-based paradigm designed to approximate the interaction between winning vs. losing in the contexts of teammates (i.e., in-group members) vs. opponents (i.e., out-group members). The paradigm was somewhat successful in accomplishing these goals, in that there were strong effects related to outcome in VS, OFC, and amygdala. However, it was not fully successful in that there were no main or interaction effects related to team status. In addition, there were no group differences in any of the ROIs that were sensitive to task outcome. This suggests relatively normal overall reward processing in PSD (within what this paradigm could assess). Although there were no group or sub-group differences in mean activation levels, activation in two of these ROIs (VS and OFC) was significantly associated with individual differences in social anhedonia among those with PSDs. This finding is consistent with a transdiagnostic approach that focuses on links with traits rather than diagnostic categories.

The paradigm was successful in eliciting strong task effects related to outcome in VS, OFC, and amygdala in all three groups. These three regions were sensitive to reward, with greater BOLD response to win compared to loss feedback, regardless of whether the feedback was provided by a teammate or an opponent. The effect was particularly strong in VS, resulting in a very large effect size for task outcome ($\eta_p^2 = .42$) We did not find any significant task-related effects for insula or dACC.

Whole-brain analyses revealed additional regions associated with overall win versus loss feedback across all three groups. These included regions typically associated with social information processing (i.e., social cognition) as well as the default mode network, such as the fusiform gyrus, medial prefrontal cortex, and posterior cingulate/precuneus (65,66). PSD showed reduced effects for this contrast compared to controls, but not siblings, and there were no differences between controls and siblings. Specifically, PSD showed reduced activation in frontal and parietal regions associated with higher order associative processing, the organization and control of goal-directed behavior (66,67), conflict resolution (Egner 2011; Schreiter et al., 2018), as well as cooperation among players engaged in collaborative tasks (68). These reductions in PSD may thus reflect alterations at the intersection of social motivation and social cognition.

It is notable that we did not find significant main or interaction effects of group across the ROIs. Activity in the three ROI's that showed significant overall reward sensitivity did not vary by group; thus, there was no evidence of impairment in general reward processing in PSD. These findings are in line with some previous fMRI studies showing a lack of significant differences during reward processing in schizophrenia compared to controls (69), particularly during reward feedback (70). However, previous findings are mixed, with other studies showing group differences in regional brain activation during nonsocial (e.g., monetary) reward processing, in contrast to our findings (71,72) In addition, we did not find an intermediate pattern of activation in the ROIs in siblings (i.e., between PSD and controls). This was also contrary to our expectations. Prior research findings in siblings are also mixed, with some studies showing intact activation of the reward network in healthy siblings of patient with schizophrenia for nonsocial (e.g., monetary) rewards (73), whereas others using similar paradigms show reduced activation in these regions in siblings (74). Finally, Within the PSD group, there was no significant difference in the pattern of results in those with nonaffective compared to affective psychosis. Although no significant between group differences in mean activation levels were identified, the groups did differ in terms of the association between activation levels and individual differences in social anhedonia.

In PSD, social anhedonia was significantly negatively correlated with activation in VS and OFC for win feedback, whereas the association was not significant in siblings and controls. That is, lower VS and OFC activation in patients was associated with higher self-reported social anhedonia. This finding is in line with previous work in major depression that showed greater severity of anhedonia is associated with altered activity in these regions (75,76). We found a similar relationship in patients between VS activity for win feedback and the MAP subscale score of the CAINS, such that lower VS activation was associated with higher clinician-rated severity of experiential negative symptoms. Findings suggest that reduced VS and OFC responsivity to reward is an important component of the neural substrates of anhedonia. The lack of significant social anhedonia associations in siblings and controls in the current study could be due to several factors, including the larger sample size of the PSD group and resulting higher statistical power to detect an effect, as well as range-restriction of SAS scores in the sibling and control groups compared to the PSD group. However, it is also possible that variability in VS and OFC activity in PSD is more meaningfully associated with social anhedonia in PSD due to qualitative differences in reward processing in this group that lead to a more direct link to social functioning.

We did not find significant task effects related to team status across the ROIs. This could be due to limitations to the paradigm. First, although we used an extensive training session to ensure that participants clearly understood the team aspect of the task and remembered which faces represented teammates versus opponents, we did not have them perform a memory test after the scan to verify their retention. Thus, it is possible that the team-based elements of the task were not sufficiently grasped and thus not reflected in the patterns of activation. However, we also note that the facial expression from teammates providing feedback was always congruent with the trial outcome (i.e., smiling face for win trials, scowling face for loss trials) whereas the facial expression from opponents was always incongruent (i.e., scowling face for win trials, smiling face for loss trials). Thus, the social feedback that participants received on a trial-by-trial basis reinforced the team status of each other player during the duration of the task. Still, future iterations of this type of task could include a memory test to verify that participants remember team status of the other players, as well as a team-building exercise before scanning to improve participant's sense of belonging to their team and thus more effectively establishing the in/out group effect of team status.

In addition, the outcome feedback (win/loss) occurred simultaneously with the facial expression (happy/angry). Thus, it could be that the outcome effect was inherently more salient for the participants, and effectively overrode the weaker team (in-group/out-group) manipulation. Future studies should consider ways to parse reward processing from the social context when designing studies to experimentally manipulate social motivation in individuals with PSD.

Finally, the current task design focused on the feedback period of test trials, during which participants received information about trial outcome. This period most closely approximates reward receipt, and results are described in those terms. Our findings of robust VS activity during positive (win) feedback replicates prior findings using this task paradigm in adults (49) and adolescents (77). Prior literature using nonsocial reward paradigms, such as the Monetary Incentive Delay task (70,71) have found that activation in VS is particularly driven by reward anticipation, rather than reward receipt. The design and timing of the current task did not allow for meaningful separation of signal relating to other stages of reward processing (e.g., reward anticipation). Future iterations of the task could be revised to include adequate modeling of the anticipation period to answer this question.

Another limitation of the study is that we did not evaluate social anxiety disorder in the sample. Thus, we cannot evaluate the role of clinically significant social anxiety in our findings. A strength of the study was the inclusion of a patient sample that spanned a spectrum of psychosis-related diagnoses. There is considerable value in examining social motivation deficits transdiagnostically because it allows us to expand on findings in schizophrenia only and to examine subgroups, such as affective versus nonaffective psychosis subtypes. The two subgroups in the current sample were comparable on basic demographic variables. The nonaffective group had higher levels of positive and negative symptoms, consistent with prior literature suggesting that those with nonaffective psychosis often exhibit a more severe symptom profile (78). Still, we found no effect of group in the subgroup analyses in any ROI. Thus, the lack of group differences in neural activation of

the social motivation system appears to extend beyond schizophrenia to other schizophrenia spectrum and affective psychotic disorders.

In conclusion, the current study found no differences in neural activation of the social motivation system in PSD and their unaffected siblings during general reward processing within a social context. Social motivation is an understudied area of critical importance for understanding of social deficits across the spectrum of psychotic illness. In a task designed to manipulate social motivation within an in-group versus out-group context, we did not find strong neural effects associated with team status across key ROIs associated with the social motivation system. Rather, we found strong effects of outcome across groups regardless of team status, likely reflective of general, rather than social, reward processing. This activation showed no evidence of abnormality in our sample of PSD probands as well as their unaffected siblings. However, PSD probands did show reduced activation in frontal and parietal regions, which may reflect difficulties with higher order associative processing required for complex social interactions and cooperative collaborations. Within the PSD group, activation among key social motivation regions, including VS and OFC, was associated with self-reported levels of social anhedonia. Taken together, the findings suggest that activation within the social motivation system in response to complex social feedback as well as disruptions beyond that system play a role in social functioning deficits in psychotic spectrum disorders and are related to real-world social behaviors and aspects of social motivation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

J.L. has served as a consultant for Takeda. M.F.G. has been a consultant for AiCure, Biogen, Takeda, and Lundbeck, a member of the Scientific Board of Cadent, and has received unrelated research support from Forum. W.P.H. is Vice President of Clinical Science at VeraSci. The rest of the authors report no biomedical financial interests or potential conflicts of interest.

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Highlights

- Individuals with psychotic illness demonstrate low social motivation
- Alterations within the social motivation system of the brain in patients is unknown
- Whether these alterations are present in unaffected siblings is also unknown
- We used a team-based social reward task during fMRI
- Patients and siblings did not show differences in key regions-of-interest
- Ventral striatum activity negatively associated with social anhedonia in patients

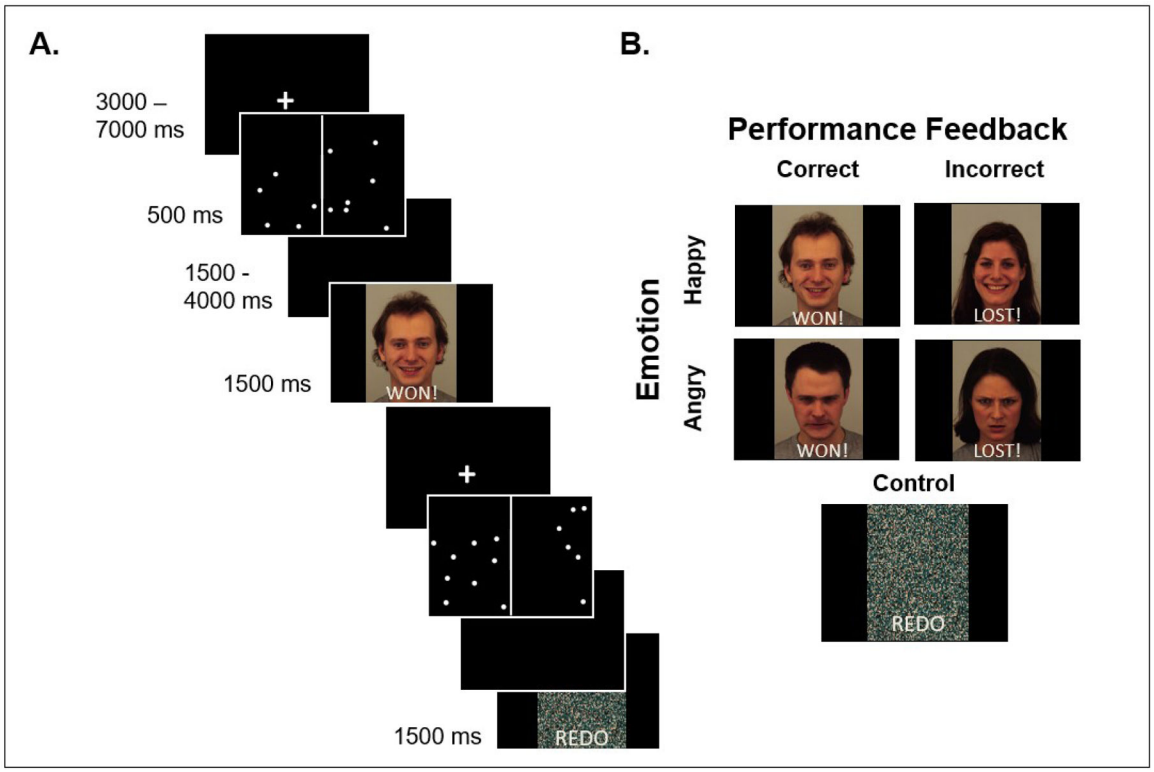

Figure 1.
Illustration of the team-based dot counting task. A) Sample stimuli and trial schematic. B) Feedback conditions.

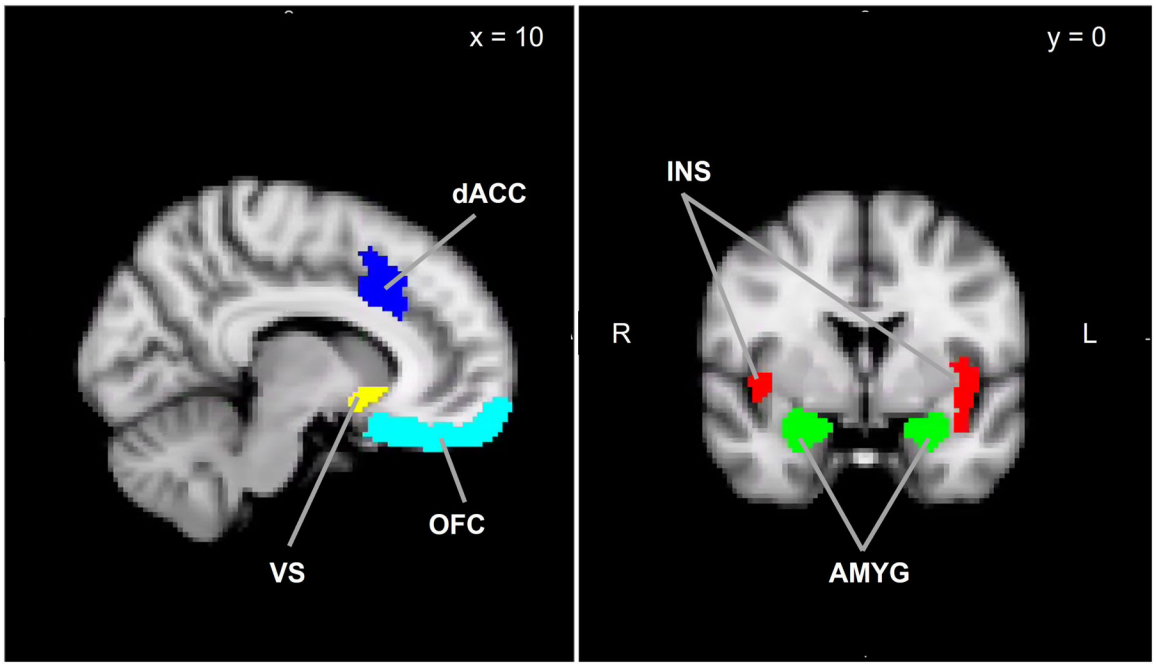

Figure 2.

Location of regions-of-interest (ROI). Bilateral cortical ROI: orbital frontal cortex (OFC, light blue), dorsal anterior cingulate cortex (dACC, dark blue), and insula (INS, red), were drawn from a standardized parcellation map. Bilateral sub-cortical ROI: ventral striatum (VS, yellow) and amygdala (AMYG, green) were based on the 25% probability HarvardOxford subcortical atlas. Slice location provided in Montreal Neurological Institute (MNI) space. R = Right, L = Left.

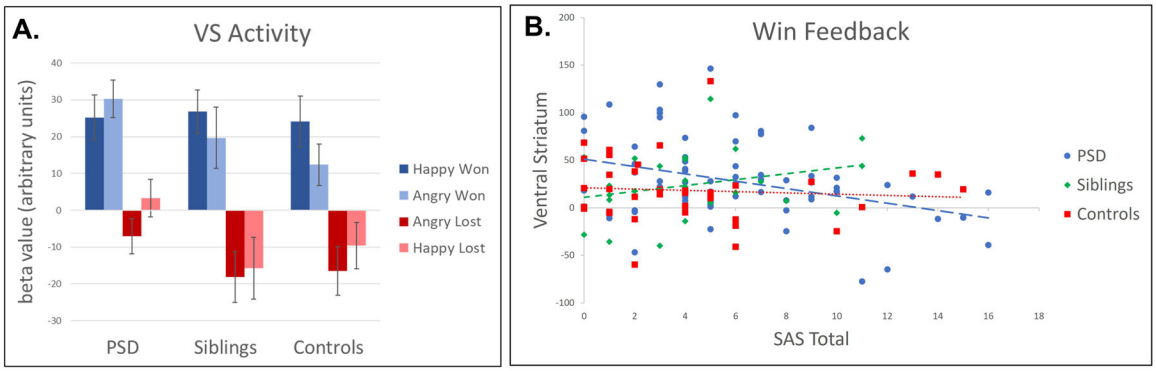

Figure 3.

Ventral striatum activity and associations with social anhedonia.. A.) Bilateral ventral striatum activity plotted across all conditions (mean beta values ± inter-subject standard error) by group, showing significantly greater activation to win feedback when paired with either a teammate (smiling face) or opponent (angry face), compared to loss feedback when paired with either a teammate (angry face) or opponent (smiling face). B.) Associations by group between social anhedonia scale (SAS) scores and activity in ventral striatum for win feedback versus control contrast. Only the negative association among PSD was significant. For visualization purposes, simple Pearson correlations are displayed. VS = ventral striatum, ROI = region of interest, PSD = psychosis spectrum disorders.

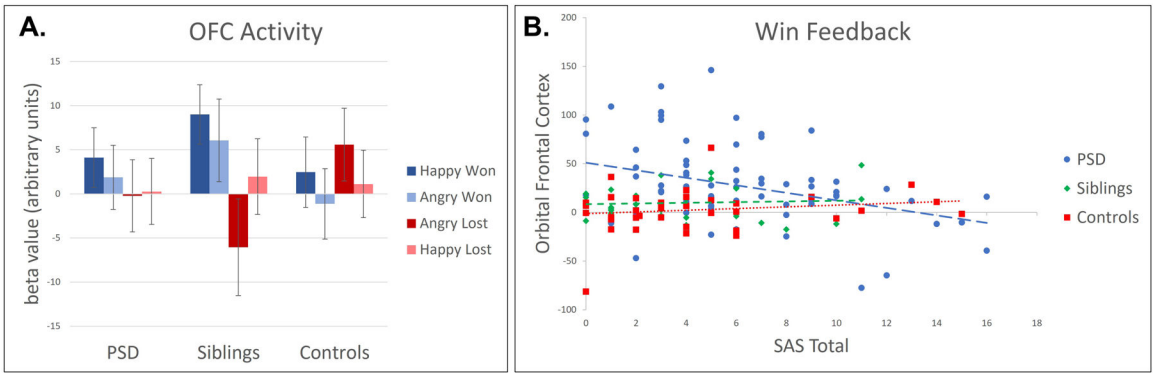

Figure 4.

Orbital frontal cortex activity and associations with social anhedonia. A.) Bilateral orbital frontal cortex activity plotted across all conditions (mean beta values ± inter-subject standard error) by group, showing greater activity to win versus loss feedback when paired with either a teammate (smiling face) or opponent (angry face). B.) Associations by group between social anhedonia scale (SAS) scores and activity in orbital frontal cortex for win feedback versus control contrast. Only the negative association among PSD was significant. For visualization purposes, simple Pearson correlations are displayed. OFC = orbital frontal cortex, ROI = region of interest, PSD = psychosis spectrum disorders.

Table 1.

Demographic and Clinical Data by Group

	PSD n = 71	Siblings n = 27	Controls n = 37	Group Comparison
Sex	48M 23F	10M 17F	25M 12F	X2 (2) = 8.52, p = .01 siblings ≠ PSD, controls PSD = controls
Ethnicity[1]				X2 (2) = 0.79, p = .67
Hispanic/Latino	10	6	6	
Not Hispanic/Latino	57	21	25	
Race[2]				X2 (10) = 11.52, p = .32
American Indian/Alaskan Native	1	0	0	
Asian	4	0	4	
Black/African American	25	4	7	
Hawaiian/Pacific Islander	1	1	1	
More than one race	4	2	1	
White/Caucasian	32	19	18	
Mean (SD)				
Age	46.69 (12.5)	42.56 (15.1)	48.16 (9.9)	F(2,132) = 1.67, p = .19
Personal Education	13.63 (2.1)	14.41 (2.4)	14.65 (1.8)	F(2,132) = 3.38, p = .04 PSD < controls
Parental Education[3]	13.63 (3.1)	14.92 (3.2)	14.12 (3.0)	F(2,124) = 1.64, p = .20
SAS-Brief Total Scores	6.05 (4.01)	3.96 (3.24)	4.22 (4.03)	F(2,132) = 4.27, p = .02 PSD > siblings PSD > controls
Clinical Symptom Ratings				
BPRS Positive	1.76 (.86)	1.11 (.21)	1.05 (.13)	F(2,132) = 19.74, p < .001
CAINS MAP[4]	1.47 (.83)	0.67 (.43)	0.84 (.73)	F(2,128) = 15.13, p < .001
CAINS Expressive[5]	0.82 (.84)	0.20 (.37)	0.16 (.26)	F(2,131) = 16.20, p < .001
Team Task Performance				
Accuracy	.56 (.06)	.58 (.03)	.56 (.06)	F(2,132) = 1.82, p = .17

Note:

[1] Information is missing for six controls and four PSD.

[2] Information is missing for one sibling.

[3] Information is missing for three controls, one sibling, and four PSD.

[4] Information is missing for one control, one sibling, and two PSD.

[5] Information is missing for one PSD.

PSD = psychosis spectrum disorders; BPRS = Brief Psychiatric Rating Scale; CAINS = Clinical Assessment Interview for Negative Symptoms; MAP = Motivation and Pleasure; SAS-Brief = Social Anhedonia Scale-Brief

Table 2.

Hierarchical regression analyses of predictors of social anhedonia scale ratings. Separate analyses were conducted for A.) ventral striatum, and B.) 0rbital frontal cortex. No significant associations were found for amygdala (not shown).

A. Predictor Variables	**Step 1**	**Step 2**	**Step 3**
Ventral striatum activity during win feedback	−0.017	−0.019 *	−0.034 **
Group			
Sibling		−2.180 *	−3.680 ***
Control		−2.019 *	−2.606 **
Interaction			
Ventral striatum activity x Sibling group			0.062 *
Ventral striatum activity x Control group			0.025
R^2	0.027	0.096	0.143
ΔR^2		0.069	0.047
F	3.736	4.657 **	4.318 ***
ΔF		5.005 **	3.538 *
B. Predictor Variables	**Step 1**	**Step 2**	**Step 3**
Orbital frontal cortex activity during win feedback	−0.027	−0.027	−0.057 ***
Group			
Sibling		−1.966 *	−2.511 **
Control		−1.911 *	−2.205 **
Interaction			
Orbital frontal cortex activity x Sibling group			0.069
Orbital frontal cortex activity x Control group			0.086 *
R^2	0.024	0.084	0.134
ΔR^2		0.060	0.050
F	3.287	3.994 **	3.992 **
ΔF		4.266 *	3.739 *

* $p < .05$;

** $p < .01$;

*** $p < .001$