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Social reward processing: A biomarker for predicting psychosis risk?

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ABSTRACT

The desire to obtain social rewards (e.g. positive feedback) features prominently in our lives and relationships, and is relevant to understanding psychopathology – where behavior is often impaired. Investigating social rewards within the psychosis-spectrum offers an especially useful opportunity, given the high rates of impaired social functioning and social isolation. The goal of this study was to investigate hedonic experience associated with social reward processing as a potential biomarker for psychosis risk. This study used a task-based functional magnetic resonance imaging (fMRI) paradigm in adolescents at clinical high-risk for the development of psychosis (CHR, $n = 19$) and healthy unaffected peers (healthy controls – HC, $n = 20$). Regional activation and connectivity of the ventromedial prefrontal cortex and ventral striatum were examined in response to receiving positive social feedback relative to an ambiguous feedback condition. Expectations of impaired hedonic processes in CHR youth were generally not supported, as there were no group differences in neural response or task-based connectivity. Although interesting relationships were found linking neural reward response and connectivity with social, anticipatory, and consummatory anhedonia in the CHR group, results are difficult to interpret in light of task limitations. We discuss potential implications for future study designs that seek to investigate social reward processing as a biomarker for psychosis risk.

1. Introduction

The discovery of "biomarkers" for various illnesses, including mental health diagnoses, is a prominent focus within research. The premise of this work is that through identifying characteristics in our biology (e.g. within brain, blood, hormones), we can generate indicators of normative processes or pathophysiology (Atkinson et al., 2001). Individuals meeting clinical criteria for the attenuated psychosis syndrome (e.g. recent onset or increasing subthreshold hallucinations, delusions, or disorganization that are present at least once per week in the past month) (American Psychiatric Association and American Psychiatric Association, 2013; McGlashan et al., 2001) represent an ideal opportunity to utilize the biomarker framework of research, as these individuals are at heightened risk for the development of psychotic disorders such as schizophrenia. Approximately 10–30% of these adolescents and young adults (also termed as being at clinical high-risk (CHR) for psychosis) will going on to develop frank psychotic illness (Fusar-Poli et al., 2012). The existing biomarker research within the CHR population highlights brain volume, connectivity, cortisol, inflammatory markers, and electroencephalography response to sensory stimuli (e.g. mismatch negativity – MMN) as potential markers of risk (Kambeitz-Ilankovic et al., 2016; Koutsouleris et al., 2012; Koutsouleris et al., 2015; Naatanen et al., 2016; Schmidt et al., 2017; Strobl et al., 2012). Although informative, there are still no standard biomarker "tests" to inform early identification and intervention efforts. One option to enhance this line of work is to expand into new, uninvestigated domains.

Social reward processing (e.g. how we take in, interpret, and output socially rewarding information, such as positive feedback from others) represents one area for novel investigation. Research into social reward processing is particularly relevant for understanding and treating psychotic disorder such as schizophrenia, given the hallmark features of impaired social functioning (Billeke and Aboitiz, 2013; Couture et al., 2006; Green et al., 2015), and evidence indicates that the decline in social functioning is already apparent during the CHR period (Addington et al., 2008; Ballon et al., 2007; Niendam et al., 2007). Understanding social reward and related behavior in CHR youth is important for clarifying

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biological mechanisms underlying illness, particularly during a developmental period where social functioning skills are of the utmost importance.

Our understanding of social reward in this CHR state is limited, and to date, there are no functional imaging studies examining this area, which is an important step for linking dynamic brain and behavior relationships. Imaging investigations into reward processing often utilize a task-based functional magnetic resonance (fMRI) paradigm, as it allows us to make inferences regarding links between behavior and the brain through evaluating the blood oxygen level dependent (BOLD) signal in conjunction with particular stimuli. Although research is mixed regarding whether social rewards are processed differently in the brain than non-social rewards (e.g. money) (Chan et al., 2016), the general consensus is that there is a "common" reward circuitry within the brain (Izuma et al., 2008; Ruff and Fehr, 2014). Key reward regions include the ventromedial prefrontal cortex (vmPFC), ventral striatum (VS), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC), among others (Haber and Knutson, 2010). There has been particular interest in the VS, given that it robustly responds to the anticipation and consumption of rewards (Haber, 2011). Relatedly, research often includes an additional focus on the vmPFC due to its role in assigning value to rewards, and the direct focal projection from the vmPFC to VS (specifically ending in the nucleus accumbens) (Diekhof et al., 2012; Dillon et al., 2008; Haber and Knutson, 2010).

Although social reward processing has not been investigated in CHR youth, there are numerous studies evaluating social anhedonia (i.e. diminished frequency and intensity of pleasure in response to social activity) and anhedonia more broadly (in response to school/work, recreation, and physical activities that are experienced with the senses). Anhedonia can be considered a behavioral representation of altered reward processing that is also a key negative symptom of psychosis (Kirkpatrick et al., 2006); it remains unclear what aspects of non-social hedonic experience are altered (if at all) in CHR youth given contradictory findings (Cressman et al., 2015; Juckel et al., 2012; Schlosser et al., 2014; Simon et al., 2010; Wotruba et al., 2014). Based on self-report, social anhedonia, and related social withdrawal, are significantly elevated in CHR youth and are critically linked to risk of transitioning to established psychotic illness (Corcoran et al., 2011; Kwapil, 1998; Piskulic et al., 2012; Velthorst et al., 2009). Commonly used anhedonia measures include self-report scales including the Revised Chapman Physical and Social Anhedonia Scales (Eckblad et al., 1983), the Temporal Experience of Pleasure Scale (TEPS), the Snaith-Hamilton Pleasure Scale (SHPS) (Snaith et al., 1995), and clinical interviews such as the Structured Interview for Psychosis-Risk Syndromes (SIPS), which includes an item that assesses broad social anhedonia and social withdrawal behavior (McGlashan et al., 2001).

Similarly, although no imaging studies of social reward in CHR youth exist, there are relevant social reward studies examining anhedonia in healthy adolescent/young adult populations. One such investigation showed that adolescents with greater anhedonia exhibited increased activation of the medial prefrontal cortex (including areas of the vmPFC) during positive social feedback in contrast to ambiguous social feedback (Healey et al., 2014). Further, they found elevated task-based functional connectivity between the VS and the medial prefrontal cortex in response to receiving positive social feedback (i.e. increased coactivation in BOLD signal among regions during receipt of social reward) (Healey et al., 2014).

The present study used a task-based fMRI investigation to assess social reward processing, and specifically hedonic experience during receipt of social reward in CHR youth. Social reward processing was examined by assessing participants' neural response during the receipt of positive social feedback relative to ambiguous social feedback. We assessed whether the hedonic social reward experience was altered at the neural level in CHR youth and tested this prediction in two primary ways: 1) examination of regional BOLD signal during the receipt of social reward and, 2) through the investigation of task-dependent connectivity analysis using generalized psychophysiological interaction models (gPPI). Based on previous CHR youth work using non-social rewards (Juckel et al., 2012; Wotruba et al., 2014) and earlier work using this task (Davey et al., 2010; Healey et al., 2014), we used a region-of-interest (ROI) analysis involving the vmPFC and the VS (specifically the nucleus accumbens). Behavioral studies evaluating anhedonia and reward in CHR youth (Cressman et al., 2015; Kwapil, 1998; Schlosser et al., 2014) and social reward imaging studies in related anhedonic samples (Healey et al., 2014), suggest that CHR youth should show evidence of disrupted hedonic processing through heightened vmPFC activation and decreased VS activation. Based on results in adolescents exhibiting anhedonia (Healey et al., 2014; Piskulic et al., 2012) it was expected that CHR would show a pattern of increased connectivity between the vmPFC and VS, more so than healthy controls, during the positive – ambiguous contrast of interest.

We also investigated relationships between the social reward fMRI response and relevant clinical symptomatology. Given that social reward has not been directly investigated in a CHR population, we focused our efforts on replicating earlier work and links with anhedonia as an initial starting point. Based on available evidence, it was expected that greater self-reported anhedonia would relate to the aberrant activation and connectivity patterns evident during the receipt of social reward (Dowd and Barch, 2012; Healey et al., 2014).

2. Method

2.1. Participants

The sample included 43 (21 CHR, 22 control) right-handed adolescents/young adults aged 16–21, who were recruited to the University of Colorado Boulder's Adolescent Development and Preventive Treatment (ADAPT) research program. The sample originally included an additional two healthy control participants (HC); however, they were excluded due to errors in data collection (e.g. incorrect stimuli, scanning errors). Exclusion criteria for both groups included history of head injury, neurological disorder, any contraindications to the magnetic resonance imaging (MRI) environment (e.g. current pregnancy or metal in the body), and having a DSM-IV-TR Axis I psychotic disorder. The presence of a psychotic disorder in a first-degree relative or meeting for a current Axis I disorder was an additional exclusionary criterion for HCs. Participants' consent was obtained according to the Declaration of Helsinki and the University of Colorado Boulder Institutional Review Board approved the protocol and written informed consent procedures for this investigation.

2.2. Materials and procedure

2.2.1. Clinical and cognitive assessment

Trained graduate students conducted all clinical assessments. The Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2001) was administered to detect the presence of a prodromal syndrome and to determine CHR status, which generates distinct categories of prodromal symptoms including positive and negative symptom dimensions (higher scores corresponding to greater symptomatology). Social anhedonia symptoms were assessed using the SAS-R (Eckblad et al., 1983). This self-report measure consists of 40 true/false questions, with higher scores indicating greater anhedonic experience. A portion of the current sample (CHR: $n = 15$, HC: $n = 11$) completed an additional self-report – the TEPS (Gard et al., 2006) – to assess for anticipatory (i.e. the anticipation of a reward) vs. consummatory anhedonia (i.e. in-the-moment pleasure experience). The TEPS assesses anhedonia more broadly across various domains with an emphasis on physical anhedonia such as, "The smell of freshly cut grass is enjoyable to me," with higher scores indicating less anhedonia. Race and current medication usage were also gathered from participant self-report.

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The Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1995) was administered to determine the presence of DSM-IV Axis I diagnoses, and specifically, to rule our the presence of psychosis in both samples, along with any current Axis I diagnosis within the HC group. Depression and anxiety were also specifically examined given evidence that 40% of CHR youth exhibit a co-occurring depression diagnosis, and 15% show symptoms indicative of an anxiety diagnosis (Fusar-Poli et al., 2014). As such, anxiety and depression were assessed using the self-report Beck Anxiety Inventory (BAI) (Beck et al., 1988) and the Beck Depression Inventory (BDI) (Beck et al., 1961).

Specific sub-tests of cognitive functioning were extracted from a larger cognitive battery to assess for 4 domains of interest: working memory, verbal fluency, motor control, and social cognition. These domains were selected based on their relevancy for the current fMRI task that involved some aspect of all of these processes. Working memory/executive functioning tests included the Hopkins Verbal Learning Test, the Wechsler Memory Spatial Span and Letter-Number Span, which were all taken from the Matrics Consensus Cognitive Battery (MCCB) (Nuechterlein and Green, 2006). For verbal fluency performance, animal naming – a verbal fluency sub-test of the MCCB was extracted. Motor control was examined with a measure of participant's postural sway, with higher sway area indicating less motor control (Bernard et al., 2014). Performance scores were extracted for each test and transformed into z-scores. For domains with more than one test, z-composite scores were created to optimize the ability to capture each cognitive domain fully.

2.2.2. FMRI social reward task

The social reward task utilized in the present study was originally developed by Davey and colleagues (Davey et al., 2010) and subsequently adapted (Healey et al., 2014). The adapted version was provided by the Healey et al. group and was used as provided (with minor alterations made due to the need to alter TR for the multiband MRI sequence). In brief, the fMRI social reward task had two parts: the pre-scanning session preparation and manipulation followed by the scanning session. First, participants were asked to rate 40 faces (50% female) of a similar aged peer group based on how much they think they'd like to meet them and spend time with the individuals in the photos (photos were acquired through the AR-face database) (Martinez and Benavente, 1998). Participants were told that these individuals were also participating in our study at different universities and that we needed to take a similar photo of them (headshot with neutral expression on white background) so that these peers of theirs can rate their picture in a similar manner over our secure online study website. As such, each participant consented to having his or her photo taken accordingly. This part of the task was a study manipulation designed to mimic an ecologically valid socially rewarding experience, as no one rated our participants' photos. Participants' ratings were used to generate the in-scanner feedback and were classified into separate feedback groups based on how high the participant rated the face (e.g. highest rated faces were grouped into a "positive" feedback group similar to Healey et al., 2014), with 32 of the 40 faces selected to represent positive and ambiguous social feedback (see Supplemental material for thorough description of task).

Participants were invited back for the scanning session (in order to allow time to convince participants that others had indeed rated their photo as part of the larger task), where they participated in a passive viewing task and saw the faces representing the positive and ambiguous social feedback. The task was a block design and consisted of 8 blocks (4 positive and 4 ambiguous), lasting approximately 12 min. Participants were told that faces with the green background (representing positive social feedback) were anyone who rated their photo as 5 or higher on the "likeability" scale, and faces with the white background (representing ambiguous social feedback) were people who did not get a chance to finish the study and rate their photo. Button presses were required to assess task engagement and participants were instructed to press a button every time they saw a face to let us know that they were awake, attending to task, and trying to remember who liked them and who did not get a chance to rate their photo. We also monitored participants via camera throughout the task to observe if they had their eyes closed. Post-scan behavioral ratings of reward (how good it felt to receive feedback on scale of 0–9) were assessed along with believability in task manipulation (given that no one actually rated participants' photos). On average, participants underwent the scanning procedure 2 weeks after this rating process took place (CHR M = 2.346 weeks, SD = 1.354, range 1–6; HC M = 1.950, SD = 0.708, range 1–3.8).

2.2.3. Image acquisition and preprocessing

Images were acquired with a Siemens Magnetom Tim Trio 3-T scanner with a 32-channel head coil. Structural images were acquired using a high-resolution structural 3D MPRAGE (0.8 mm isotropic resolution), and whole-brain functional images were acquired with a high-resolution multiband EPI sequence adapted from CMRR sequences (http://www.cmrr.umn.edu/multiband/) along with a short reverse phase-encoded EPI collected to allow for distortion correction. Data was processed using FSL (v.5.0.8; http://fsl.fmrib.ox.ac.uk/fsl). The preprocessing pipeline involved distortion correction, trimming of the first 6 volumes, brain extraction, motion correction, spatial smoothing (6 mm), intensity normalization, high-pass filtering, and registration to the MNI template. Additional imaging details are available in the Supplementary materials.

2.2.4. Imaging analysis

A priori ROI masks were created based on a previous meta-analysis examining 33 monetary reward processing studies since no social reward meta-analyses exist (Sescousse et al., 2013) (Fig. 1). The method of using a meta-analysis over a specific study (e.g. the previous study utilizing this task) allows for optimal ROI selection, as the peak ROI coordinates of a solitary study may be due, in part, to noise (Poldrack, 2007). ROI masks were generated using the Wake Forest University PickAtlas (Maldjian et al., 2004; Maldjian et al., 2003) using a 6 mm radius for the left and right VS and a 10 mm radius for the vmPFC.

2.2.4.1. Activation. Following completion of preprocessing, functional activation analyses were conducted using FSL (v.5.08; http://fsl.fmrib.ox.ac.uk/fsl). First level analysis examined the within-subject solitary run using a fixed effects analysis in FEAT (v. 6.00) and estimated single subject parameters for the contrast of social reward (positive – ambiguous feedback). Double-Gamma HRF convolution was selected along with

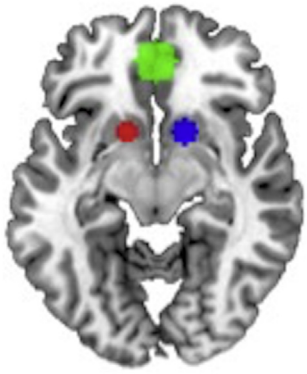

Fig. 1. Seed regions of interest. Axial slice (MNI coordinates: x = −14, y = 19, z = −9). Left (red) and right (blue) ventral striatum (MNI coordinates: −14, 10, −12; 14, 10, −8). The ventromedial prefrontal cortex (MNI coordinates 0, 44, −8). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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prewhitening. Percent signal change was extracted using *featquery* from the a priori ROIs in order to acquire a numerical value of change in activation for each participant to aid in interpretation of results. Percent signal change was also used to determine outliers, which included participants exhibiting ROI signal 3 SD away from the mean (in either direction) (Supplemental Fig. 2).

Group-level analyses utilized non-parametric permutation statistics using FSL's *randomise* (Winkler et al., 2014). Contrasts were defined to assess whether the bilateral VS signal was dampened in CHR relative to the HC group and whether the vmPFC activation was heightened in CHR in comparison with HCs. As such, a priori hypotheses totaled 3 *t*-tests. Group-level statistics were conducted using 5000 permutations with clusters defined with threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009). TFCE accurately detects both high signal (intensity) and large signal (size) activation patterns, allowing for increased sensitivity and output that is more interpretable than standard cluster-based thresholding such as using a cluster-extent approach with FWE or FDR (Smith and Nichols, 2009). Results were considered significant at $p < 0.05$ FWE.

2.2.4.2. Task-based functional connectivity analyses. Task-based connectivity was conducted using gPPI (McLaren et al., 2012) within FSL. The inference made from this analysis is that an increase in correlation between a source ROI and target ROIs within one condition/task versus the other suggests the increase in exchange of information based on task (O'Reilly et al., 2012). Two *t*-tests were conducted and results of the gPPI were calculated using permutation methods as described above.

2.2.4.3. Relationships with symptoms and cognition. Relationships between regional activation and connectivity with total anhedonia symptoms (3 sub-scales of anhedonia) were examined within FSL using the GLM within the CHR group alone. Given that only a subset of our CHR sample were administered the TEPS, the resulting smaller sample size made the analyses for the two subscales (anticipatory and consummatory) more exploratory in nature. Specific tests were conducted in hypothesized directions (i.e. 3 tests for each of the 3 ROIS for activation analyses and 3 tests for each of the 2 connectivity patterns (vmPFC – lvs and vmPFC – rvs). Permutation tests were performed as described above. We also conducted additional exploratory analyses involving total positive and negative symptoms (Supplemental Tables 2 and 3).

We examined the relationship between cognitive processes and BOLD data with the goal of determining task specificity around social reward process, as well as to aid in result interpretation. More specifically, we first extracted reverse inference BOLD signal maps from neurosynth meta-analyses (http://neurosynth.org/) for 4 cognitive domains of interest. Cognitive maps obtained included verbal fluency (75 studies), social cognition (166 studies), working memory (901 studies), and motor control (175 studies). This analysis included masking the BOLD signal in the positive – ambiguous contrast with cognitive-related ROIs, and then correlating the resulting cognitive signal with cognitive behavioral performance within the sample. Significant bivariate correlations would suggest that 1) the cognitive process of interest (i.e. verbal fluency, social cognition, working memory/executive functioning, and motor control) was likely active during the task, and 2) that this cognitive process might account for any results observed in the analyses. As an additional step, we tested the difference in the resulting correlations in order to determine whether a particular cognitive process was most active. We expected that the correlation involving social cognition would be significantly greater than the correlations involving the other cognitive domains given that the fMRI task highlighted social processing.

2.2.4.4. Analysis of sample characteristics and behavioral data. Regression models were used to evaluate group differences in demographic variables such as age and sex, along with attenuated psychosis symptoms, diagnoses, and anhedonia. Potential confounding medication, depression, and anxiety were also examined using regression. A two-way ANOVA was used to examine main effects of group and stimulus type (i.e. positive vs. ambiguous) on post-scan ratings.

3. Results

3.1. Sample characteristics

As expected, all measures of clinical symptomatology were significantly higher in CHR youth relative to HCs, consistent with prior studies (Fusar-Poli et al., 2014). The majority of the sample was white, and the mean age for both groups was 20.629 years (SD = 1.510). A small percentage of the CHR sample utilized psychotropic medication, and in particular, current mood stabilizer usage was significantly different between groups. In regard to DSM-IV Axis I diagnoses, 10 CHR youth met clinical criteria for the following mood and anxiety presentations: Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) (2 CHR participants), Panic Disorder (1 CHR participant), Bipolar Disorder (2 CHR participants), MDD and Posttraumatic Stress Disorder (2 CHR participants), Social Phobia (1 CHR participant), MDD and Panic Disorder (1 CHR participant), and Adjustment Disorder (1 CHR participant). In accordance with the study protocol, no healthy control participants met clinical criteria for current DSM diagnoses. Lifetime diagnostic presentations varied by group, with 15 CHR participants meeting criteria for various mood and anxiety disorders, and 2 HC participants met past diagnostic criteria for a major depressive episode. No other group differences in demographics were noted (Table 1).

3.2. fMRI task evaluation

3.2.1. Behavioral evaluation

Although we expected that the groups would rate the task stimuli differently in regard to how rewarding they found the feedback, a two-way ANOVA revealed no significant main effect of group ($F = 0.126$, $p = 0.724$), stimulus type (positive versus ambiguous; $F = 1.37$, $p = 0.246$), or interaction between the two ($F = 0.871$, $p = 0.354$) on post-scan ratings. As anticipated, both groups displayed a moderate belief in the task manipulation and the groups did not significantly differ in their ratings of task believability (Table 2).

Participants were excluded from analyses if they 1) did not press the button at all during the task and/or 2) had notes regarding eyes closing and/or sleeping during the task. Based on this review of the notes and data, 4 participants (2 HC and 2 CHR) were removed from the overall 43 person sample – 3 people had notes regarding eyes closing/sleeping and 1 individual did not press the button the entire task. Following this exclusionary procedure, data from 39 individuals (19 CHR and 20 HC) were retained and were included in the subsequent analyses. Both groups responded approximately 85% of the time during the task indicating that as a whole, participants were engaged and responding to the task accordingly. Importantly, responses did not significantly differ between groups; however, individual differences in button response were evident in both groups (Table 2). Given this significant variation in button presses, response percentage was included in all further analyses as a covariate.

3.2.2. Confounds

Prior to conducting the hypothesized analyses, relationships between BOLD data in the positive – ambiguous contrast and potential confounds including age, sex, antipsychotics, antidepressants, mood stabilizers, stimulants, and depression and anxiety (BAI/BDI) were examined in higher level models using the GLM within FSL. These results showed no significant relationships between potential confounds and the imaging data. As such, none of these variables were included as covariates in higher-level analyses investigating group differences or relationships with symptoms.

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Table 1
Sample characteristics.

Measure	CHR ($n = 19$)	HC ($n = 20$)	F	p
Sex (% male)	63.2%	50%	0.663	0.421
Age	20.629 (1.510)	20.987 (1.821)	0.442	0.510
Race (% white)	63.16%	60%	0.194	0.662
Medication	–	–	–	–
Current antipsychotic (% taking, #)	10.5% (2)	0%	2.232	0.144
Current antidepressant (% taking, #)	15.8% (3)	0%	3.558	0.067
Current stimulant (% taking, #)	15.8% (3)	0%	3.558	0.067
Current mood stabilizer (% taking, #)	26.3% (5)	0%	6.778	0.013*
Clinical Symptoms	–	–	–	–
Current SCID diagnosis (%, #)	52.63% (10)	0%	21.083	<0.001**
Lifetime SCID diagnosis (%, #)	78.95 (15)	7.5% (2)	34.567	<0.001**
Current depression (BDI)	17.526 (13.247)	2.500 (3.395)	24.099	< 0.001**
Current anxiety (BAI)	19.737 (13.584)	4.000 (4.304)	24.303	< 0.001**
Total positive symptoms (SIPS)	11.105 (5.227)	0.300 (0.657)	84.184	<0.001**
Total negative symptoms (SIPS)	12.105 (8.116)	0.300 (0.657)	42.080	<0.001**
Total social anhedonia (SAS-R)	16.316 (9.972)	5.200 (4.124)	21.078	<0.001**
Anticipatory anhedonia (TEPS)	3.547 (0.901)	4.500 (0.463)	10.240	0.004**
Consummatory anhedonia (TEPS)	4.687 (0.927)	4.776 (0.722)	0.070	0.794

Abbreviations: CHR – clinical high-risk; HC – healthy control. SCID – Structured Clinical Interview for DSM-IV; BDI – Beck Depression Inventory; BAI – Beck Anxiety Inventory; SIPS – Structured Interview for Psychosis-Risk Syndromes (positive symptom range 0–30, negative symptoms range 0–36, higher scores indicate greater severity); SAS-R – Social Anhedonia Scale – Revised (symptom range 0–40, higher scores indicate greater anhedonia); TEPS – Temporal Experience of Pleasure Scale (symptom range 1–6, higher scores indicate less anhedonia).
* $p < 0.05$.
** $p < 0.01$.

3.3. Group differences

3.3.1. Group differences in activation

It was expected that the bilateral VS would show decreased activation in CHR relative to HCs in the positive – ambiguous contrast, and that CHR youth would show increased activation in the vmPFC compared to the HC group in this same contrast of positive – ambiguous. However, no significant group differences in activation appeared in the bilateral striatum or vmPFC in the positive – ambiguous contrast, counter to predictions (Table 3, Supplemental Fig. 3).

3.3.2. 3.3.2 Group differences in task-based connectivity

We predicted that the relationship between the vmPFC to bilateral VS would increase in the positive – ambiguous contrast, and that this pattern would be stronger in CHR relative to HCs. This hypothesis was not supported, as there were no significant group differences the between-group gPPI analyses (Table 4). Percent signal change and change in parameter estimates (vmPFC – left VS ($\beta = 0.019$) and vmPFC – right VS ($\beta = 0.008$)) are depicted in Table 4 and Supplemental Figs. 4 and 5.

3.4. Relationships with symptoms and cognition

3.4.1. Signal activation and symptoms

We expected that lower ventral striatum activation in the positive – ambiguous contrast would be related to having higher anhedonia in CHR youth. Further, we predicted that higher vmPFC activation in the positive – ambiguous contrast would link with greater presence of symptoms within the CHR group. There was a significant relationship between higher vmPFC activation and greater reporting of social anhedonia as expected ($p = 0.047$). No other relationships with anhedonia were noted (Table 5).

3.4.2. Connectivity and symptoms

In support of hypotheses, higher connectivity between the vmPFC and right VS was associated with greater anticipatory and consummatory anhedonia in CHR youth. There were no other significant relationships, contrary to expectations (Table 6).

3.4.3. BOLD signal and cognition

Across groups, significant relationships emerged involving social cognition behavioral task performance and neural signal ($r = 0.432$, $p = 0.007$), as well as motor control ($r = 0.407$, $p = 0.012$), but no relationships involving working memory ($r = 0.173$, $p = 0.298$) or verbal fluency ($r = 0.306$, $p = 0.062$) were found. Within groups, we did not find any significant relationships involving working memory (CHR: $r = 0.366$, $p = 0.123$; HC: $r = 0.066$, $p = 0.788$) or verbal fluency (CHR: $r = 0.268$, $p = 0.267$; HC: $r = 0.369$, $p = 0.120$). The CHR group showed a significant association involving motor performance ($r = 0.544$, $p = 0.016$) that was not evident in the HC group ($r = 0.383$, $p = 0.116$). Finally, HC exhibited a significant link between social cognitive behavioral performance and neurological signal, while the CHR group's relationship was at a trend level (CHR $r = 0.445$, $p = 0.056$; HC $r = 0.517$, $p = 0.023$).

Table 2
Task evaluation.

Measure	CHR	HC	F	p
Positive faces rating	5.618(1.579)	5.233(1.486)	0.565	0.458
Ambiguous faces rating	5.208(1.526)	4.688(1.434)	0.894	0.353
Task believability	4.790(3.207)	5.526(3.151)	0.510	0.480
% button-box response	85.540(30.195)	87.374(25.171)	0.043	0.838

Values presented are mean (standard deviation). Positive and ambiguous faces rating values are on a scale of 0–9, with higher scores indicating a higher rating of social reward. Task believability was also rated on the same scale of 0–9, with higher scores indicating greater believability in task manipulation (i.e. that the stimuli represented actual people who provided the feedback for the present study). Button-box response represents the total time participants pressed a button in response to each individual stimuli as instructed.

Table 3
Group differences in BOLD signal activation.

Region	Contrast	% Signal Change	p
left VS	HC > CHR	0.088	0.148
right VS	HC > CHR	0.013	0.402
vmPFC	CHR > HC	0.030	0.513

All results presented involved testing group differences in the positive – ambiguous contrast. Abbreviations: VS – ventral striatum; vmPFC – ventromedial prefrontal cortex; CHR – clinical high-risk; HC – healthy controls. CHR youth did not exhibit significantly decreased bilateral VS response in comparison to HCs. CHR youth also did not show significantly elevated vmPFC activation relative to the HC group.

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Table 4
Group differences in task-based connectivity.

Source - Target	Contrast	% Signal Change	p
vmPFC – left vs	CHR > HC	0.18	0.533
vmPFC – right vs	CHR > HC	0.15	0.479

Abbreviations: VS – ventral striatum; vmPFC – ventromedial prefrontal cortex; CHR – clinical high-risk; HC – healthy controls. Clinical high-risk youth did not show a significantly greater pattern of increasing connectivity involving the vmPFC and bilateral VS as expected.

In examining the difference in these correlations across groups, the social cognition correlation was not significantly different from the working memory ($z = 1.397$, $p = 0.072$), motor control ($z = -0.138$, $p = 0.443$) or verbal fluency correlations ($z = 0.642$, $p = 0.252$). These results suggest that despite having a larger effect, social cognitive processes were not significantly active more so than other cognitive domains across the groups. Based on the between-group analysis of correlations, the CHR and HC groups did not significantly differ in their engagement of working memory ($z = 0.93$, $p = 0.176$), verbal fluency ($z = -0.33$, $p = 0.371$), motor control ($z = 0.600$, $p = 0.274$), or social cognition ($z = -0.27$, $p = 0.394$). These latter results suggest that the groups did not significantly differ in their recruitment of cognitive processes during the fMRI task.

4. Discussion

To our knowledge, this study is the first investigation into social reward processing in CHR youth using a task-based fMRI paradigm. The current findings represent initial steps toward determining whether social reward processing has utility as a biomarker for psychosis risk. Within the CHR group, we found associations between neural response to social reward and anhedonia. First, higher vmPFC activation during social reward receipt was associated with elevated symptoms of social anhedonia. In addition, increased vmPFC – right VS connectivity (when receiving positive social feedback) was related to increased anticipatory and consummatory anhedonia. Considering these findings alongside methodological limitations, results presented here highlight both the future potential and complications of studying social reward processing as a psychosis risk biomarker.

We found no group differences in the VS or vmPFC during receipt of social reward, which is in contrast to our expectations and the available literature. The lack of findings around VS signal in the present study is in opposition to the one previous imaging investigation into social reward processing in schizophrenia (Gromann et al., 2013), which showed dampening of VS activation during positive cooperative interactions with others. The present lack of group differences in vmPFC response also contradicts imaging research involving adolescents with anhedonic experience (Healey et al., 2014) and behavioral studies of CHR youth (Schlosser et al., 2014).

Table 5
Relationships between regional activation and clinical symptoms.

Test	Region	β	p
Social anhedonia	left vs	0.008	0.425
Anticipatory anhedonia	left vs	0.578	0.761
Consummatory anhedonia	left vs	1.651	0.431
Social anhedonia	right vs	0.011	0.168
Anticipatory anhedonia	right vs	−0.256	0.550
Consummatory anhedonia	right vs	1.739	0.291
Social anhedonia	vmPFC	**0.235**	**0.047**
Anticipatory anhedonia	vmPFC	−2.330	0.436
Consummatory anhedonia	vmPFC	−1.097	0.542

Abbreviations: VS – ventral striatum; vmPFC – ventromedial prefrontal cortex. Positive relationships were tested involving social anhedonia, given that higher social anhedonia scores (derived from the social anhedonia scale – SAS-R) equal greater impairment. Negative relationships were tested for anticipatory and consummatory anhedonia, given that higher anticipatory and consummatory anhedonia scores (derived from the temporal experience of pleasure scale – TEPS) equal less impairment. β values refer to the parameter estimates extracted from higher-level analyses using FSL's featquery.
Relationships were considered significant at $p < 0.05$ using Threshold-Free Cluster Enhancement (TFCE) in FSL's randomise function, and corrected for multiple comparisons using FWE.

Table 6
Relationships between task-based connectivity and clinical symptoms.

Test	Source - Target	β	p
Social anhedonia	vmPFC – left vs	0.001	0.732
Anticipatory anhedonia	vmPFC – left vs	−0.024	0.612
Consummatory anhedonia	vmPFC – left vs	−0.022	0.638
Social anhedonia	vmPFC – right vs	0.002	0.236
Anticipatory anhedonia	vmPFC – right vs	**−0.059**	**0.040**
Consummatory anhedonia	vmPFC – right vs	**−0.066**	**0.008**

Abbreviations: VS – ventral striatum; vmPFC – ventromedial prefrontal cortex. All relationships examined were based on a priori hypotheses. Tests examined positive relationships, other than those involving anticipatory and consummatory anhedonia, as higher ratings on these scales equaled less impairment and required testing negative relationships. β values refer to the parameter estimates extracted from higher-level analyses using FSL's featquery.
Relationships were considered significant at $p < 0.05$ using Threshold-Free Cluster Enhancement (TFCE) in FSL's randomise function, and corrected for multiple comparisons using FWE.

Within the CHR group, we found that the vmPFC activation and vmPFC – VS connectivity significantly related to self-reported anhedonia. Interestingly, hyperactivation of the vmPFC in response to pleasant stimuli is also associated with anhedonia in depressed samples (Keedwell et al., 2005b). Within healthy populations, greater vmPFC activation occurs in response to unpleasant stimuli relative to pleasant stimuli (Keedwell et al., 2005a). Evidence also shows that individuals diagnosed with schizophrenia assign greater negative emotions to positive stimuli (Strauss et al., 2017). Thus, one hypothesis for the current finding is that those CHR youth who experience the positive feedback as unpleasant/uncomfortable report a greater level of social anhedonia.

We also found that increased connectivity between the vmPFC and right VS was associated with higher self-report of anhedonia in a subset of the CHR youth sample. Previous work utilizing this fMRI task paradigm showed a sample of anhedonic adolescents also exhibiting increased connectivity between the ventral striatum and medial prefrontal cortex during social reward processing (Healey et al., 2014). Positive connectivity in the positive versus ambiguous condition could indicate different processes that might be occurring – the vmPFC could be signaling the striatum for more activation or that the vmPFC could be down-regulating the striatal reward response (Haber, 2011; Pujara et al., 2016). Notably, a recent optogenetic study showed that the hyperactivity of the vmPFC may function as an inhibitory mechanism on reward behavior through increased connections with, in part, the VS (Ferenczi et al., 2016). Thus, our data is in accordance with the theory that an increased exchange of information between the VS and vmPFC in our CHR group implies down-regulation of reward response behavior.

However, it is ultimately difficult to confidently interpret the brain – behavior associations found in the present study as meaningful psychosis risk biomarkers due to several limitations. First and foremost, within the HC group, there was no significant activation of the a priori ROIs as would be expected in a reward paradigm (see Supplemental material). Although the striatum did respond to task (response was not significant after multiple comparison corrections), it was definitively more dorsal than ventral striatum and included the caudate nucleus; the caudate nucleus is considered part of the reward circuit and receives information from reward-related PFC regions (e.g. OFC, vmPFC) (Haber and Knutson, 2010). Similarly, the CHR group exhibited striatal response to task, but it also did not meet statistical thresholding (even prior to correcting for multiple comparisons). Overall, both groups exhibited a

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neural response to reward that allows for some possibility that the task tapped into reward circuitry, just not at the level expected based off non-social and previous investigations (see whole-brain response to task in Supplemental Fig. 1).

The absence of a main effect of task may be due 1) discrepancy in sample and methodology in the present study compared to previous work and 2) limitations of the social reward paradigm. First, the racial makeup of our sample was notably different from previous studies that used this fMRI paradigm (earlier work reported sample as 80% white (Healey et al., 2014)), which could significantly impact between-group differences and within-group differences in reward, particularly in regard to how participants respond to the races of the visual stimuli used in the study. Further, the CHR group showed symptoms indicative of a wide range of mood, anxiety, and subthreshold psychosis diagnoses; in contrast Davey et al., 2010 examined participants who had never met clinical criteria for a DSM-IV diagnosis and Healey et al. allowed only depression and anxiety (not OCD) diagnoses in the study. Finally, a large portion of the current CHR sample was taking psychotropic medication during our study evaluation, while both previous investigations had psychotropic medication as an exclusionary criterion for all participants. These discrepancies in samples may account for some of the differences in main findings.

Importantly, the CHR group in the current investigation exhibited similar psychosis and anticipatory and social anhedonic symptoms relative to previous studies (SIPS, SAS-R, and TEPS scores) (Cressman et al., 2015; Schlosser et al., 2014). However, our CHR sample showed intact consummatory experience (i.e. ratings similar to our HC and other HC samples), which is contrary to earlier CHR work that showed significantly impaired reports of reward consumption (Schlosser et al., 2014). This discrepancy suggests it is likely that hedonic experience fluctuates over time in this at-risk group, which could impact findings.

For methodology, we evaluated button-box responses in the scanner as a means of determining task engagement. While earlier work reported doing the same process, they did not report on the number of individuals engaged in task, the specific percentage of button responses, nor did they use eyetracking monitors to ensure participants were awake, as was done in the present investigation (Healey et al., 2014). Furthermore, we investigated the believability of the task manipulation; previous work reported no such rating (Davey et al., 2010; Healey et al., 2014). In general, our data suggests that participants had significant variation in task engagement and believability in the paradigm, which likely confounds response to task. Earlier work also emphasized separating the task into various other fMRI contrasts (as opposed to the broad positive – ambiguous condition contrast) (Healey et al., 2014), although robust reward activation was still noted in the positive – ambiguous contrast (Healey et al., 2014). Further, previous research also used imaging methodology that was appropriate at the time of publication, but could be considered dated, including very large ROI delineation (i.e. 25 mm mPFC vs. the 10 mm used here), liberal initial or cluster thresholding, and parametric analyses (Eklund et al., 2016; Woo et al., 2014). CHR youth are also known to exhibit altered neural response and behavioral ratings of emotion in response to neutral faces (i.e. they attribute other emotions such as anger to otherwise neutral expressions) (Seiferth et al., 2008; van Rijn et al., 2010), which could influence and/or change the valence of the ambiguous condition in the present task. Indeed, social ambiguity as a task condition for fMRI may impact findings more broadly, given the inherent aversive nature of unpredictable social stimuli, and the possibility that both positive and negative valences can be attributed (Davis et al., 2016). In total, these sample and methodological factors could account for the null findings presented here.

Despite these considerations, it is still surprising that healthy controls did not exhibit a neural activation indicative of reward response. In a post hoc investigation, we examined the specificity of the task to various cognitive processes. We found evidence that the current task did not significantly tap into social reward related processes. Specifically, across groups, social cognition (which would be expected to be engaged in a socially rewarding task) was not significantly more active in comparison with working memory, verbal fluency, or motor control.

Within this context, future studies aiming to develop biomarkers would benefit from advancing social reward research in novel ways. Existing social reward designs include social interactions/decision making using game theory (Sanfey, 2007), changing social context (e.g. alone versus with others), positive evaluative feedback (from unknown others or friends/family), attractive faces, positive emotion expressions, social reputation, love, and social exclusion or rejection (Collip et al., 2014; Krach et al., 2010; Rademacher et al., 2010; Ruff and Fehr, 2014). However, there is push to shift toward explicitly emphasizing emotional engagement and ecologically valid social interaction, as opposed to observation or even more scripted/contrived social exchanges (Schilbach et al., 2013). Although the paradigm used in the present study attempted to incorporate this perspective, our data suggests that it was limited in emotional engagement (as indicated by post-scan reward ratings), and was overall a passive viewing fMRI task. Game theory designs (e.g. the ultimatum game, prisoner's dilemma, trust game) also incorporate an emotionally engaging and interactive component. However, a major focus of these paradigms is on the exchange of money (Sanfey, 2007). Although not inherently problematic, the emphasis on money does represent a very specific type of interaction. Expansion to include other forms of interaction could allow for attention to focus on socially relevant and rewarding factors including gesture, eye contact, facial expression, intonation, and matching social cues among dyads.

As reviewed elsewhere (Heerey, 2015), the field could significantly advance by studying interactions through virtual reality paradigms, and focus more on manipulating pre-interaction states (e.g. mood, affect) and less on manipulating the interaction itself. This would allow for a more ecologically valid investigation of social interactions and in turn, enhance the potential for social reward as a biomarker of psychosis risk. Future investigations would also benefit from looking across a wider range of psychopathology and including a "help-seeking" or clinical control group in order to more definitively understand the contribution of psychosis risk symptomatology to social reward. Other sample characteristics will also be important to consider in regard to influence on social reward processing such as race, age, and gender.

In sum, although the fMRI paradigm did not elicit as robust a reward signal as predicted, the study did yield information regarding biological mechanisms underlying social reward and anhedonia that may be useful in guiding future biomarker research with improved social reward paradigms. Further, the study of social reward remains an important area of investigation for understanding the social impairments in psychosis and psychosis risk. We believe that publishing null results is vitally important to prevent file drawer effects and improving future research design. Paradigms emphasizing social interaction through a virtual reality framework will be particularly useful in enhancing the study of social reward in psychosis risk.

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Contributors

Author Pelletier-Baldelli designed the study and authors Orr, Bernard, and Mittal contributed to the study design. All authors contributed to data collection and data analysis. Author Pelletier-Baldelli wrote the manuscript, and all other others contributed editorial remarks. All authors contributed to and have approved the final manuscript.

Conflict of interest

Author Mittal is a consultant for Takeda Pharmaceuticals. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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