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Evidence of reward system dysfunction in youth at clinical high-risk for psychosis from two event-related fMRI paradigms

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ABSTRACT

Abnormal reward processing is thought to play an important role in the development of psychosis, but relatively few studies have examined reward prediction errors, reinforcement learning (RL), and the reward circuitry that subserves these interconnected processes among individuals at clinical high-risk (CHR) for the disorder. Here, we present behavioral and functional neuroimaging results of two experimental tasks designed to measure overlapping aspects of reward processing among individuals at CHR ($n = 22$) and healthy controls ($n = 19$). We found no group differences in response times to positive, negative, or neutral outcome-signaling cues, and no significant differences in brain activation during reward anticipation or receipt. Youth at CHR, however, displayed clear RL impairments, as well as attenuated responses to rewards and blunted prediction error signals in the ventral striatum, dorsal anterior cingulate cortex (dACC), and ventromedial prefrontal cortex (vmPFC). Greater contrasts for cue valence (gain-loss) and outcome magnitude (large-small) in the vmPFC were associated with more severe negative symptoms, and deficits in dACC signaling during RL were associated with more depressive symptoms. Our results provide evidence for RL deficits and abnormal prediction error signaling in the brain's reward circuitry among individuals at CHR, while also suggesting that reward motivation may be relatively preserved at this stage in development. Longitudinal studies, medication-free participants, and comparison of neurobehavioral measures against both healthy and clinical controls are needed to better understand the role of reward system abnormalities in the development of psychosis.

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1. Introduction

Psychotic disorders are often characterized by both positive and negative symptoms, but whether these two dimensions share a common neurobiology remains poorly understood. A neurobehavioral system that may play a role in the development and maintenance of both positive and negative symptomatology is the reward system. In the typically developing brain, dopamine release transiently increases in the midbrain and basal ganglia in response to better than expected outcomes, whereas dopamine release in these areas transiently decreases in response to worse than expected outcomes (Schultz, 2016). This mismatch between expectation and outcome, known as a reward prediction error (RPE), is considered a core mechanism of reinforcement learning (RL). Reward prediction errors serve as teaching signals to guide updating of expectations and beliefs about the world (Fletcher

and Frith, 2009). Dopamine hypotheses of psychosis suggest that tonic dysregulation of dopaminergic activity disrupts normal prediction error signaling, directing attention and motivation toward innocuous aspects of the environment (generating aberrant salience attributions and leading ultimately to positive symptoms), and reducing motivation toward relevant aspects of the environment (leading to negative symptoms; Heinz et al., 2018; Howes and Kapur, 2009).

There is considerable empirical support for the dopamine hypothesis of psychosis. Experimental evidence indicates that aberrant or deficient patterns of dopamine-driven salience attribution may be responsible for several of the core cognitive, motivational, and functional deficits seen among affected individuals, including abnormal neural responses to reward anticipation or feedback (Radua et al., 2015), impaired RL (Gold et al., 2008), and delusions (Corlett et al., 2010). Reinforcement learning depends on normal functioning of the ventral striatum (VS), dorsal anterior cingulate cortex (dACC), and ventromedial prefrontal cortex (vmPFC) — regions that show abnormal patterns of activity among people with psychosis both at rest (Kühn and Gallinat, 2011; McCutcheon

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et al., 2017) and while engaged in a range of cognitive, emotional, and motivational tasks, including reward processing (Suk Lee et al., 2015). Furthermore, RL and its neural correlates have been linked to positive and negative symptom severity in numerous studies of people with psychosis (Deserno et al., 2013).

Despite compelling evidence of reward system impairments in psychosis, relatively few studies have examined these processes among individuals at “clinical high-risk,” who experience attenuated but impairing or distressing psychotic symptoms and high rates of progression to formal psychosis. Studies measuring monetarily-incentivized responses to task-relevant versus task-irrelevant stimulus dimensions (e.g., color, object type) have found that individuals at CHR are more likely to attend to irrelevant stimulus features, interpreted as an impaired ability to make adaptive salience attributions (Roiser et al., 2012; Schmidt et al., 2017). Similarly, using tasks that require participants to make win/lose predictions about probabilistically reinforced stimuli (e.g., shapes, household objects), other studies have found that decision-making among youth with attenuated psychosis is less subject to reinforcement than it is among healthy controls, regardless of whether contingencies are relatively simple (Rausch et al., 2015; Waltz et al., 2015) or complex (Karcher et al., 2015). These impairments have been associated with abnormal striatal activity during task performance (Karcher et al., 2018; Rausch et al., 2015) which, like positive RL deficits (Karcher et al., 2015; Waltz et al., 2015), have themselves been related to CHR symptom severity (Roiser et al., 2012; Schmidt et al., 2017).

Nonetheless, several limitations to the CHR literature suggest more studies are needed that combine neurofunctional and behavioral measures of reward processing in this population. First, the few available CHR studies assessing neural responses to reward anticipation versus receipt – components of reward processing that may be differentially affected in the psychosis spectrum (Radua et al., 2015) – have produced mixed findings, despite using the same experimental task (i.e., the Monetary Incentive Delay task; Juckel et al., 2012; Wotruba et al., 2014). Second, the role of other reward-related brain regions such as the vmPFC and dACC in signaling reward anticipation, feedback, and RPEs remains unclear. Third, few studies have examined the relation of neural reward processing signals to symptoms of depression among those at CHR, despite the high rates of mood disorders in this population (Fusar-Poli et al., 2014) and the potential for negative and depressive symptomatology to stem from distinct abnormalities in the neurobehavioral systems associated with motivation, learning, and salience signaling (Whitton et al., 2015).

The purpose of this study was to investigate the behavioral, neural, and clinical aspects of reward processing in a sample of youth at CHR for psychosis relative to a group of healthy, same-aged peers. To improve confidence in our findings, we analyzed fMRI and behavioral data from two separate reward learning tasks designed to elicit RPEs: One task designed to separate neural correlates of reward anticipation/incentive value signaling from those of reward receipt, and another designed to measure probabilistic RL and its neural substrates. In supplementary analyses, we considered a number of other factors that could influence reward-related signals, including age (given developmental influences on reward processing; Steinberg, 2005), attention deficit/hyperactivity disorder diagnosis (ADHD; as reward-related behavior and neural signals are altered in this disorder; Plichta and Scheres, 2014), and treatment with psychostimulant or antipsychotic medications (given that dopamine agonists and antagonists influence reward signals; Hengartner and Moncrieff, 2018; Knutson et al., 2004).

Drawing from the basic reward literature and from studies of people with first episode or chronic psychosis, we hypothesized that youth at

CHR would exhibit attenuated reward anticipation signals in the VS and dACC and reduced vmPFC responses to reward receipt. We also hypothesized that youth at CHR would exhibit impaired RL and attenuated neural responses to reward prediction errors. Finally, we expected that the strengths of these reward-related signals would correlate with symptom dimensions related to reward processing – that is, negative and depressive symptoms.

2. Methods

2.1. Participants

Individuals at CHR ($n = 22$) were referred by community clinicians, hospital clinics, and schools; some self-referred following exposure to outreach efforts. Healthy controls (HCs; $n = 19$) were recruited using flyers and advertisements in the community. Enrollment for all participants required an age of 12–25, a willingness to provide written consent/assent, and no contraindication to the scanning environment. To date, we have administered follow-up assessments to 12 of the 22 CHR participants. Nineteen participants at CHR were already receiving mental health services, whereas 3 were not. Healthy control status required participants to have no current psychiatric disorder or history of psychosis, bipolar disorder, or major depressive disorder; no current mental health treatment; and no first-degree relative with psychosis. The study was approved by Institutional Review Boards.

2.2. Measures

2.2.1. Clinical measures

The Structured Interview for Psychosis-risk Syndromes (SIPS) was used to determine CHR status and negative symptom severity (Miller et al., 2003). To meet criteria for CHR, an individual must report (1) attenuated positive symptoms of psychosis at a frequency of at least once per week; (2) positive symptoms of psychotic-level intensity that are too brief to meet criteria for a formal psychotic disorder; or (3) a $\geq 30\%$ functional decline in the past year, plus schizotypal personality disorder or a first-degree relative with psychosis. The six negative symptoms are rated on a 0–6 (absent-extreme) scale. All interviewers were certified by formal SIPS trainers and attended weekly diagnostic conferences. Inter-rater reliability was $ICC = 0.84$ for total symptoms and $\kappa = 1.0$ for diagnosis across 10 recorded interviews.

The Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS; Kaufman et al., 1997), a semi-structured interview commonly used in developmental psychopathology research, was used to establish DSM diagnoses. Consensus diagnoses are made on the basis of separate interviews with youth and, when available, parents. Interviewers trained via supervised KSADS administration and were considered reliable when their diagnostic conclusions were consistent with trained supervisors' on ≥ 3 participants.

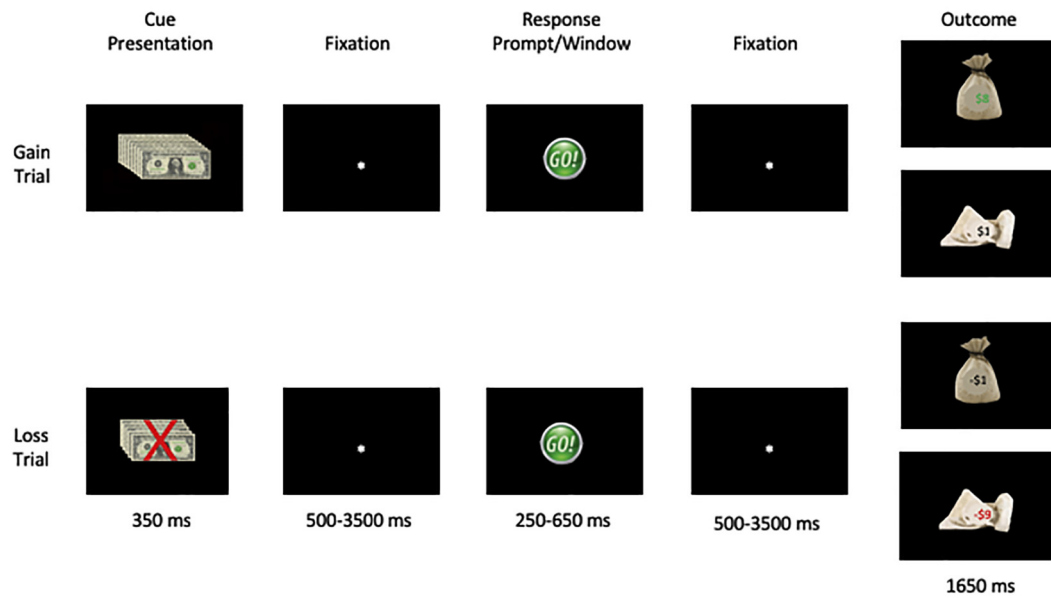
The Behavior Assessment System for Children, 2nd Edition (BASC-2) is a widely-used self-report measure of clinical, behavioral, and personality domains (Reynolds, 2004). Items are answered on a 4-point scale or as true or false. The depression scale consists of 12 items and is closely related to other popular depression scales (Children's Depression Inventory). Raw scores are converted to standardized values with a population average of 50 and a standard deviation of 10.

2.2.2. Behavioral paradigms

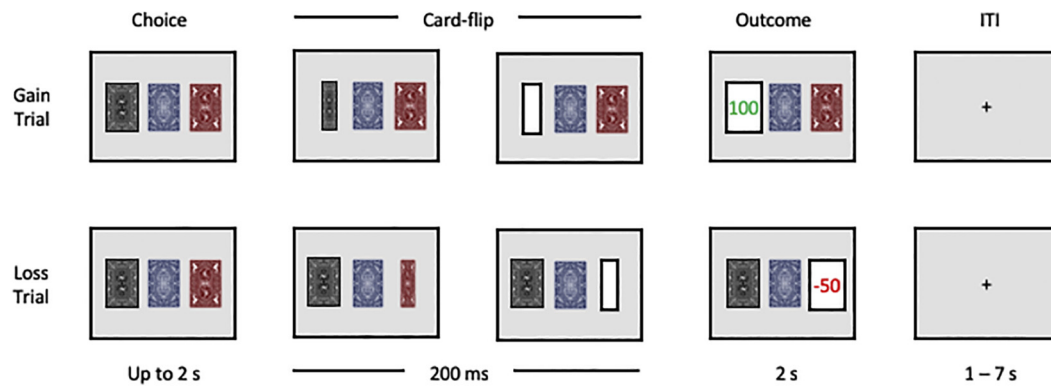
In order to distinguish neural signals evoked by reward anticipation from those associated with reward feedback, we used a modified Monetary Incentive Delay (MID) task (Knutson et al., 2001; see Fig. 1A for

Fig. 1. A. Schematic of the Modified Monetary Incentive Delay (MID) task. Participants were presented with Gain Trials, Loss Trials, and Neutral Trials (not shown). On neutral trials, participants were shown a rectangle the size and color of a monetary cue and received a neutral outcome regardless of their response time. B. Schematic of the Card Betting Reinforcement Learning (RL) Task. Participants chose from one of 3 decks, each of which was rewarded probabilistically. In order to maximize their winnings, participants needed to identify the optimal deck, in a given run, and choose it as often as possible. C. Performance on the RL task in people at clinical high-risk (CHR) and healthy controls (HC).

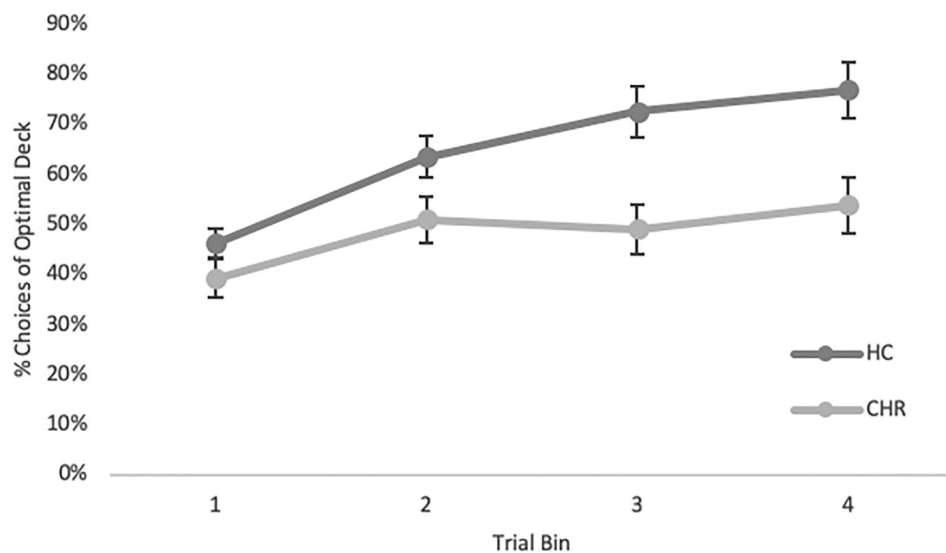
A



B



C



sample trials). Participants saw cues that signaled they could either expect to gain money, lose money, or experience a neutral outcome. Responding within an acceptable time window on a given trial resulted in either a large gain (\$8 or \$15) or a nominal loss (\$1). Failing to respond within this window on a given trial resulted in either a nominal gain (\$1) or a large loss (\$5 or \$9). On neutral trials, participants always received \$0. Each of the 4 runs included 14 gain trials, 14 loss trials, and 7 neutral trials, together taking ~19 min. In our study, participants did not actually receive additional money based on their performance; thus, outcomes for this task were akin to points, which have been shown in several foundational schizophrenia, Parkinson's, and general population studies to effectively engage reward, learning, and decision-making neurobehavioral systems (e.g., Corlett et al., 2007; Frank et al., 2004; Holroyd et al., 2008).

In order to distinguish neural signals evoked by surprising and unsurprising gains and losses, participants performed a version of the Card Betting Task (CBT; Fig. 1B; Friedland, 1998), a simple probabilistic RL paradigm. Participants selected one out of three card decks, identified by color (black, red, and blue) using their right hand. Choices were rewarded probabilistically, with a choice of the "optimal deck" (the one with the highest expected value) leading to a 100-point gain on 70% of trials (and a loss of 50 points on 30% of trials). Choices of two non-optimal decks led to 100-point gains on 50% and 30% of trials (and losses of 50 points on 50% and 70% of trials, respectively). Positions of the three decks (left, right, middle) changed randomly by trial, and participants were instructed to try to identify the optimal deck as quickly as possible. After each run of 40 trials, a new deck (color) would become the optimal one. The task included 160 trials, subdivided into 4 runs. The behavioral paradigms are described further in the Supplement.

2.3. Statistical analyses of behavioral outcome measures

Data from the MID task were analyzed for the proportion of trials on which participants made "in-time" responses, sorted by the five levels of cue (\$9 loss, \$5 loss, neutral, \$8 gain, \$15 gain). These values were subjected to analyses of variance (ANOVAs), with factors of diagnosis and cue condition. Data from the Card Betting Task were analyzed for the proportion of trials on which the participant chose the more frequently reinforced deck in each run, as well as whether participants repeated their choice ("stayed") or switched to another deck ("shifted") after feedback. These values were subjected to ANOVA, with factors of diagnosis, trial bin, and their interaction. Finally, we used a computational model to estimate action values and prediction errors on a trial-wise basis. Because fits to patient data were generally poor (due to their poor performance), we did not perform further analyses on these parameters.

2.4. MRI data acquisition and analysis

Whole-brain functional EPI images (for measurement of T2*-weighted BOLD effects) were acquired simultaneous with task performance, using 3-T Siemens scanners (Erlangen, Germany; 28 participants were scanned on a Trio magnetom; 13 were scanned on a PRISMA Fit). Functional images were acquired using the following parameters: 81 2-mm axial slices; 128×128 matrix; FOV = 22×22 cm; TR = 2 s. For the MID task, 480 images were acquired across 4 runs (16 min 0 s). For the RL task, 620 images were acquired across 4 runs (20 min 40 s). In each session, we acquired a whole-brain T1-weighted structural image (MPRAGE) for anatomical reference (1-mm³ isotropic voxels; TR = 8.6 s; TE = 4 ms; FA = 20°).

2.4.1. Single-subject analyses: MID task

For the purpose of modeling blood-oxygen-level-dependent (BOLD) MRI signals acquired during the MID task, we constructed binary regressors based on the time-stamps of the three types of cue events

(expected gains, losses, or neutral outcomes) and the five types of outcome events (large gains, small gains, large losses, small losses, and neutral outcomes). Regressor functions for single-subject voxel-wise time series (general linear models; GLMs) included head-motion vectors (L-R, A-P, I-S, pitch, roll, yaw) as nuisance regressors. We also modeled condition contrasts ([Expected Gains – Expected Losses], [Large Received Gains – Small Gains], and [Large Received Losses – Small Losses]) as general linear trends. Because small gains and large losses were received when participants failed to respond within the allowable time window, these outcomes served as de facto negative RPEs.

2.4.2. Single-subject analyses: RL task

We constructed binary regressors based on the time-stamps of four types of feedback events: valid wins (rewarded for choosing the optimal deck); valid losses (negative feedback for choosing a suboptimal deck); invalid wins (probabilistic positive feedback, despite choosing a suboptimal deck); and invalid losses (probabilistic negative feedback, despite choosing the optimal deck). Regressor functions for single-subject voxel-wise time series GLMs included feedback for nonresponses and head-motion vectors as nuisance regressors. We also modeled contrasts (e.g., [Valid Wins – Valid Losses]), as general linear trends. Because Valid Wins and Valid Losses were informative feedback, when subjects chose the optimal and suboptimal decks, respectively, these contrasts were used to assess neural sensitivity to outcome valence. Because an Invalid Loss meant that the subject was being punished despite choosing the optimal deck, this outcome represented a violation of expectations. Thus, in modeling data from both experiments, we set up contrasts to test for neural sensitivity to both outcome valence, and whether the outcome represented an RPE. For both tasks, binary regressors were 1-second stick functions, locked to the onset of cues/outcomes and convolved with a model hemodynamic response function.

2.4.3. Whole-brain group-level analyses

To test for significant activations and contrasts within groups and for significant between-group differences in BOLD signal activations and contrasts, we used whole-brain *t*-tests (AFNI 3dttest++ command). For whole-brain analyses, we used a voxel-wise threshold of $p = 0.001$ and a cluster-size threshold of 180 voxels, determined by Monte Carlo simulations.

2.4.4. Analyses of event-related neural activations and contrasts in regions-of-interest (ROIs)

We looked for effects of expected value magnitude, RPE valence and magnitude, and outcome valence and magnitude in VS (bilaterally), vmPFC, and dACC (Supplementary Materials include specific coordinates with justification). For the VS, we formed a single, bilateral ROI. Both ROIs in PFC consisted of 10-mm radius spheres.

For the MID task, our primary focus was on the effect of diagnostic group on BOLD signals of cue- and outcome-valence and magnitude. For the RL task, our primary focus was on interactions between diagnostic group and RPE valence and magnitude in modulating neural responses. We performed *t*-tests on contrasts between parameter estimates for regressors of interest, averaging all of the voxels within an ROI; where data violated normality assumptions, we performed Mann-Whitney *U* tests.

We examined relations between BOLD signal activations and contrasts in ROIs (from both tasks) and clinical variables (SIPS total negative symptoms and BASC-2 depression) in the CHR group using Pearson or Spearman correlations (when data were not distributed normally). In supplementary analyses, we considered effects of age, mood/ADHD diagnosis, and medication use (Tables S3-S10).

3. Results

Table 1 indicates there were no significant demographic differences between the groups. As expected, negative and depressive symptoms

Table 1
Demographic and clinical characteristics of the present sample.

	CHR (n = 22)	HC (n = 19)	Test statistic (t or χ^2)	p
	Mean or frequency (SD or %)			
Age	17.26 (3.29)	18.03 (4.44)	0.64	0.53
Female	12 (54.5)	7 (36.8)	1.29	0.26
Family income			0.03	0.86
<20k	7 (31.8)	5 (26.3)		
20k–59.9k	3 (13.6)	5 (26.3)		
60k–99.9k	2 (9.1)	3 (15.8)		
≥100 k	6 (27.3)	6 (31.6)		
Race			0.83	0.36
Black or African American	10 (45.5)	6 (31.6)		
White	6 (27.3)	11 (57.9)		
Asian	3 (13.6)	0		
More than 1 race	3 (13.6)	2 (10.5)		
Medication			–	–
Antipsychotic	5 (22.7)	–		
Antidepressant	10 (45.5)	–		
Mood stabilizer	2 (9.1)	–		
Stimulant	8 (36.4)	–		
DSM diagnoses			–	–
Mood disorder	14 (66.7)	–		
Anxiety disorder	15 (71.4)	–		
PTSD	6 (28.6)	–		
ADHD	11 (52.4)	–		
Substance use disorder	1 (4.8)	–		
SIPS negative symptoms	15.48 (6.42)	2.53 (2.06)	–8.75	< 0.001
BASC-2 depressive symptoms	62.12 (14.86)	42.78 (5.58)	–4.78	<0.001

Note. One (CHR) participant was missing DSM diagnostic data; percentages therefore reflect the valid percent. Three (CHR) participants were missing BASC-2 data. For age, $df = 39$; for the clinical variables, Levine's test indicated unequal population variances, thus $df = 32.38$ for positive symptoms, $df = 24.47$ for negative symptoms, and $df = 20.21$ for depressive symptoms; for all other comparisons, $df = 1$. CHR, clinical high-risk; HC, healthy control; PTSD, posttraumatic stress disorder; ADHD, attention deficit/hyperactivity disorder; SIPS, structured interview for psychosis-risk syndromes; BASC-2, Behavioral Assessment System for Children, Second Edition.

were more severe in the CHR group. Two of the 12 CHR individuals with follow-up assessments transitioned to a diagnosable psychotic illness.

3.1. Behavioral performance

3.1.1. Performance on the MID task

Analysis of in-time responses during the MID indicated a main effect of cue condition ($F_{2,36} = 29.52, p < 0.001$), but no main effect of group ($F_{1,37} = 0.96, p = 0.33$) and no group \times cue interaction ($F_{1,36} = 0.50, p = 0.61$; Fig. S1). Overall, participants made more in-time responses to cues predicting monetary gains (67%; $t = 7.713; p < 0.001$) and losses (63%; $t = 5.691; p < 0.001$) than to neutral cues (45%). Relative to loss cues, the number of in-time responses to gain cues was significantly greater ($t = 2.308; p = 0.027$). Participants' subjective ratings (see Supplementary Results) indicated that they felt better when winning money than losing money, with no differences between groups ($t_{36} = -0.71, p = 0.48$).

3.1.2. Performance on the Card Betting RL Task

As shown in Fig. 1C, when we examined overall accuracy in RL (rates of choosing the optimal deck), we observed significant main effects of block ($F_{3,111} = 34.601, p < 0.001$) and group ($F_{1,37} = 7.495, p = 0.009$), as well as a significant block \times group interaction ($F_{3,111} = 5.99, p = 0.001$). While both controls ($F_{3,51} = 34.01, p < 0.001$) and individuals at CHR ($F_{3,60} = 7.35, p < 0.001$) showed improved performance throughout the task, those at CHR learned at a significantly slower rate. We also found that participants at CHR were less likely to select cards that had just been rewarded than were HCs ($t_{33,12} = 2.57,$

$p = 0.015$), and marginally more likely to repeat card choices that had just been punished ($t_{35,2} = -2.00, p = 0.053$).

3.2. Whole-brain analyses of the MID and Card Betting RL Task

The results of whole-brain analyses of the MID and RL task are presented in Figs. 2 and S2, and in Tables S1 and S2. The MID was effective in eliciting responses in the brain's reward and salience circuits (e.g., VS, caudate, dACC, insula) during reward anticipation and outcome, but there were no significant group differences in these effects (despite some medium effect sizes). Whole-brain analysis of the RL task revealed that the task was effective in eliciting reward processing signals, including RPEs in canonical regions (e.g., VS, dorsolateral PFC), with several significant between-group differences in activation contrasts.

3.3. ROI analyses of neural signals from the MID task

In ROIs (Fig. 3A), we observed no significant [Expected Gain – Loss] contrasts (differences from 0) in the entire sample and no between-group differences (Fig. 3B). We observed significant contrasts within the entire sample for [Received Large – Small Gain] contrasts in the VS ($t_{37} = 7.862, p < 0.001$), vmPFC ($t_{37} = 2.798, p = 0.008$), and dACC ($t_{38} = 2.250, p < 0.030$; Fig. 3C) and for [Received Large – Small Loss] contrasts in the VS ($t_{37} = 3.703, p = 0.001$; Fig. 3D). There were no statistically significant between-group differences in these contrasts for any ROI. Nonetheless, effect sizes for several of these contrasts were in the medium range: VS [Expected Gain – Loss], $d = 0.549$; vmPFC [Expected Gain – Loss], $d = 0.523$; vmPFC [Received Large – Small Gain], $d = 0.545$; VS [Received Large – Small Loss], $d = 0.614$; vmPFC [Received Large – Small Loss], $d = 0.501$.

3.4. ROI analyses of neural signals from the Card Betting RL Task

Fig. 4A shows there were no group differences in contrasts between evoked responses to valid rewards and invalid losses from the RL task in the VS, vmPFC, or dACC. As shown in Fig. 4B, however, we observed significant between-group differences in the [Valid Win – Invalid Loss] contrast in the VS (Z of $U = 2.530, p = 0.010$) and vmPFC (Z of $U = 2.192, p = 0.027$). Individuals at CHR showed less differentiation in the VS and vmPFC between positive RPEs (wins) and negative RPEs (surprising losses). Group comparison of the [Valid Win – Invalid Loss] contrast in dACC was not significant (Z of $U = 1.441, p = 0.156$).

3.5. Relations between neural signals in ROIs and clinical measures

Given the medium effect size estimates for between-group differences on MID contrasts, we examined relations of these contrasts to symptomatology. We found that more severe negative symptoms were associated with both greater [Expected Gain – Loss] contrasts ($p = 0.619, p = 0.005$; Fig. 3E) and greater [Received Large – Small Gain] contrasts in the vmPFC ($p = 0.470, p = 0.042$; Fig. 3F). These associations were driven by greater *deactivations* (relative to baseline activity) among CHR participants to expected losses and to received small gains (negative prediction errors; Table 2). For the RL task, we observed no significant correlations between negative symptom scores and contrasts in neural signals from (Table 3). Depression symptoms, however, were correlated with both the [Valid Win – Valid Loss] ($p = -0.608, p = 0.014$) and [Valid Win – Invalid Loss] ($p = -0.688, p = 0.005$) contrasts in dACC, such that CHR individuals reporting the most severe depressive symptoms showed the least differentiation between valid wins and losses (Fig. 4C–D).

3.6. Supplementary analyses

We then considered several factors that could influence our results, including age, comorbid diagnosis (e.g., ADHD) and use of

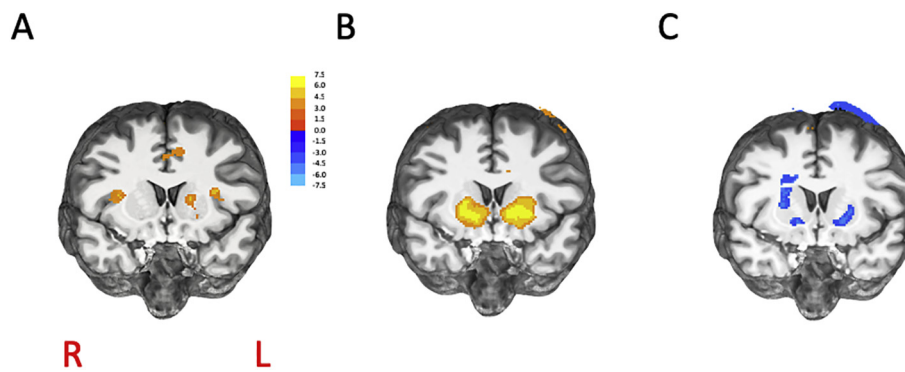


Fig. 2. MID task. A. Significant effects of cue condition (Expected Gain vs. Expected Loss) in the entire sample, from the whole-brain analysis. B. Significant effects of outcome magnitude (Large vs. Small) on trials resulting in gains in the entire sample, from the whole-brain analysis. C. Significant effects of outcome magnitude (Large vs. Small) on trials resulting in losses in the entire sample, from the whole-brain analysis. In all panels, images cut at $y = 13$. Radiological convention was used (left is right; right is left). No significant between-group differences were observed in any of these regions. Color scale indicates voxel-wise t -value for each parameter estimate/contrast.

psychostimulants or antipsychotic drugs. These analyses are detailed in the Supplement (Tables S3–S10; Figs. S3, S4). We observed effects of age on both behavioral and neuroimaging measures from RL task, but these effects did not account for the effects of risk status or symptom severity that we observed. Stimulant use increased proportions of in-time responses on the MID task, but there were no effects of comorbid diagnosis or medication on any other experimental measures.

4. Discussion

The purpose of this study was to better understand reward processing in adolescents and young adults at CHR for psychosis by analyzing multiple behavioral and neurobiological measures of these processes and evaluating their relationships to theoretically-relevant symptom dimensions. We found that some aspects of reward processing were impaired in those at CHR, whereas others appeared relatively intact. The results have implications for the roles of motivation, salience attribution, RL, and dopamine function in individuals at risk for developing a psychotic disorder.

4.1. Behavioral findings

At the behavioral level, we found that participants at CHR exhibited substantially impaired RL relative to HCs. While controls showed a mean performance improvement of $>30\%$ from Block 1 to Block 4 of the RL task, CHR participants improved by approximately 15%. These findings are consistent with a large body of literature reporting on RL deficits in people with chronic schizophrenia (Strauss et al., 2013), first episode psychosis (Murray et al., 2008), unaffected first-degree relatives (Wagshal et al., 2012), and several other studies of individuals with attenuated psychosis (Karcher et al., 2018; Karcher et al., 2015; Waltz et al., 2015). Although not all studies assessing RL in CHR have reported between-group differences (Ermakova et al., 2018), our results add to a growing literature suggesting that RL deficits in CHR can be measured using a range of experimental tasks and may play an important role in the early stages of psychosis.

Despite the RL impairments among individuals at CHR for psychosis, these participants rated losses and rewards on the MID as equally pleasurable relative to HCs, and were equally as proficient as HCs when challenged to respond quickly to cues, regardless of whether these cues signaled positive, negative, or neutral outcomes. Although caution is warranted when interpreting findings suggesting similarities across small sample groups, our observation that CHR youth exhibited reduced win-stay rates relative to controls, but similar (numerically higher) lose-shift rates suggests that some individuals at CHR may exhibit a behavioral profile seen in people with multi-episode schizophrenia: A deficit in learning from positive outcomes alongside intact learning from negative outcomes.

4.2. Neuroimaging findings

We found that both cues and outcomes from the MID task were successful in eliciting a response in the brain's reward and salience circuits, as indicated by significantly increased VS, dACC, and insula responses to cues predicting gains relative to losses, as well as in response to large versus small gains across groups. We also observed significantly reduced VS and dACC activity in response to large relative to small losses. Despite the lack of statistically significant group differences in activation contrasts, several MRI signal contrasts from the MID showed medium effect sizes and strong correlations with negative symptoms in the CHR group. Individuals with greater negative symptoms showed greater gain-loss cue contrasts and greater received gain magnitude contrasts in the vmPFC, indicating that CHR youth with more severe negative symptoms were especially sensitive to disappointing outcomes (i.e., small gains, which were negative prediction errors). As negative symptoms are associated with social functioning difficulties (Corcoran et al., 2011) and transition to psychosis (Piskulic et al., 2012), our results suggest that reward processing in the vmPFC deserves further attention as a possible biomarker of CHR-related psychiatric concerns.

Results of the RL task revealed that youth at CHR displayed blunted BOLD responses to rewards and blunted prediction error signaling in the VS and vmPFC during RL. Contrasts between valid wins and valid losses and between valid wins and invalid losses in the vmPFC were especially reduced among individuals higher in depressive symptoms, although they did not correlate significantly with negative symptoms. Considered against the high rates of mood disorders in our sample and in the broader CHR population (Fusar-Poli et al., 2014), these results raise questions about which illness processes are primarily operating among individuals at CHR. Affective disorders are characterized by similar reward processing impairments as those seen in formal or attenuated psychosis (Whitton et al., 2015), as are numerous other disorders that commonly co-occur with CHR states, including attention, anxiety, and trauma-related psychopathologies. Reduced striatal activity during reward anticipation or receipt (Benson et al., 2015; Elman et al., 2009; Plichta and Scheres, 2014), impaired RL (Sailer et al., 2008; White et al., 2016), and RL-related deficits in functioning of the salience network (Sailer et al., 2008; White et al., 2016) have been observed in these disorders. Although our supplementary analyses revealed no effect of comorbidities, larger studies powered to comprehensively examine the multidimensional nature of psychopathology associated with CHR syndromes will be important for determining whether findings such as ours reflect psychosis-risk specifically or more generalized expressions of psychopathology. Use of clinical controls without attenuated psychosis will be critical to achieving this goal (Millman et al., in resubmission).

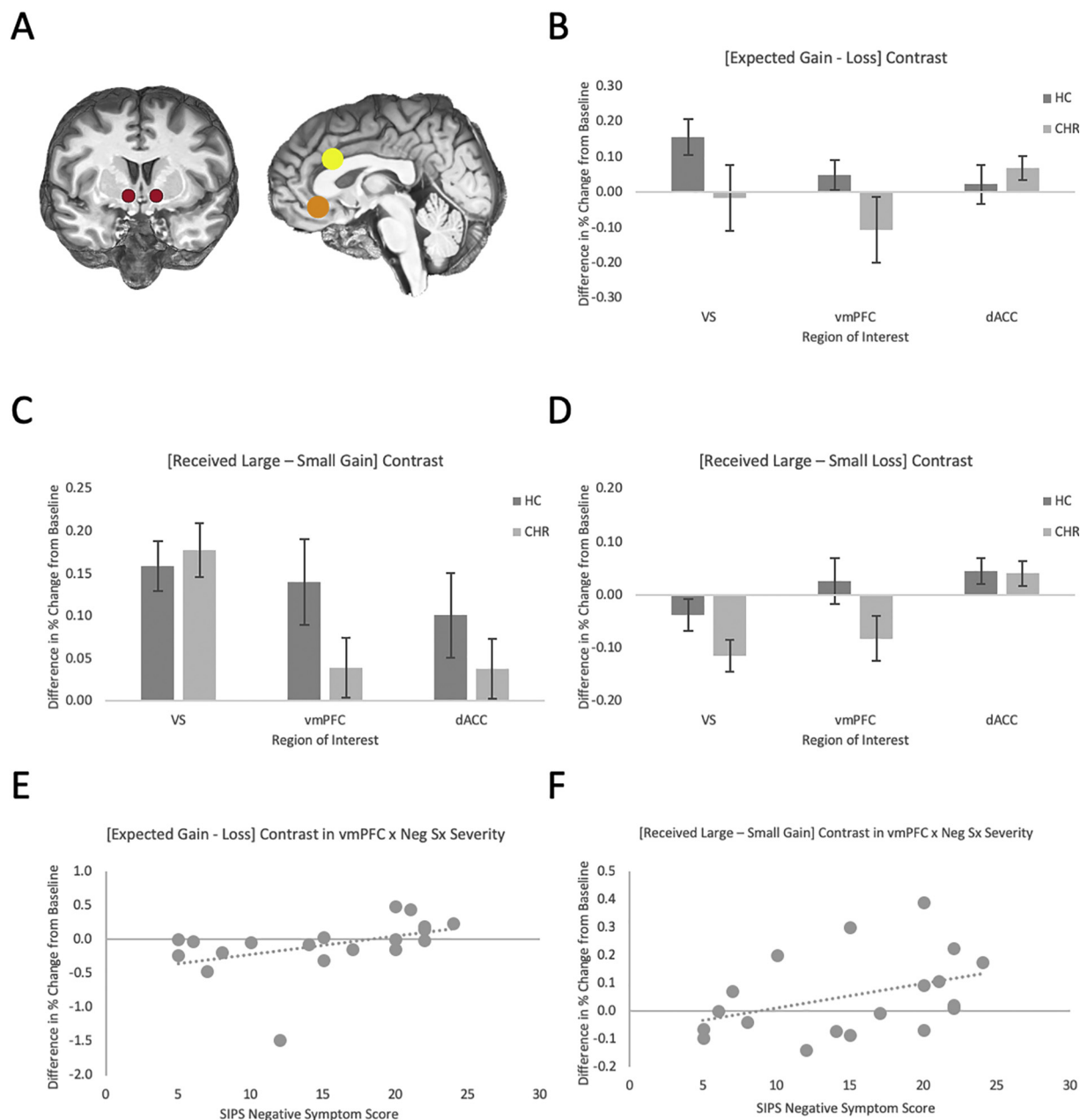


Fig. 3. MID task. Regions-of-interest (ROI) analyses of effects of obtained outcome valence on positive RPE signals. A. The ventral striatum (VS) ROI consisted of two spheres of 5-mm radius, centered on $(\pm 10, 8, -4)$. Cut at $y = 8$. The ventromedial prefrontal cortex (vmPFC) ROI consisted of a sphere of 10-mm radius, centered on $(3, 32, -7)$, while the dorsal anterior cingulate (dACC) ROI consisted of a sphere of 10-mm radius, centered on $(5, 22, 27)$. Brain image cut at $x = 4$. B. We observed no significant [Expected Gain - Loss] contrasts (differences from 0) in the entire sample and no between-group differences. C. We observed significant contrasts within the entire sample for [Received Large - Small Gain] contrasts in the VS, vmPFC, and dorsal anterior cingulate cortex (dACC), and for D. [Received Large - Small Loss] contrasts in the VS. E. More severe negative symptoms were associated with both greater [Expected Gain - Loss] contrasts and F. greater [Received Large - Small Gain] contrasts in the vmPFC among individuals at CHR. MID, Monetary Incentive Delay task; CHR, clinical high-risk; HC, healthy control.

4.3. Limitations and future directions

In addition to sample size limitations noted above, our study lacked a measure of general cognitive ability as well as longitudinal follow-up of participants. Neurocognitive and reward systems undergo maturation during adolescence (Steinberg, 2005), and our finding that neural and behavioral measures of RL differed among younger versus older participants underscores the importance of tracking variability on such measures over time. Additionally, the majority of our CHR participants were either on stimulants or antipsychotics, which can influence corticostriatal signaling and RL (Evers et al., 2017; Hengartner and Moncrieff, 2018). Acute psychostimulant exposure, for example, has been shown to

temporarily “equalize” the degree of VS signaling during anticipation of gain versus loss (Knutson et al., 2004). Our finding that participants taking stimulants showed a greater proportion of in-time responses to the MID task is consistent with this literature; studies of unmedicated individuals at CHR will be important in future work.

Despite these considerations, our results provide evidence of reward system abnormalities in individuals at CHR for psychosis. Our observations of abnormal prediction error signals complement our finding of impaired RL learning in this group, supporting the hypothesis that disruptions in striatal salience signaling contribute to motivational deficits and aberrant salience attributions early in the course of psychosis. In general, these results are consistent with the psychosis literature and support the hypothesis that abnormal dopamine signaling associated

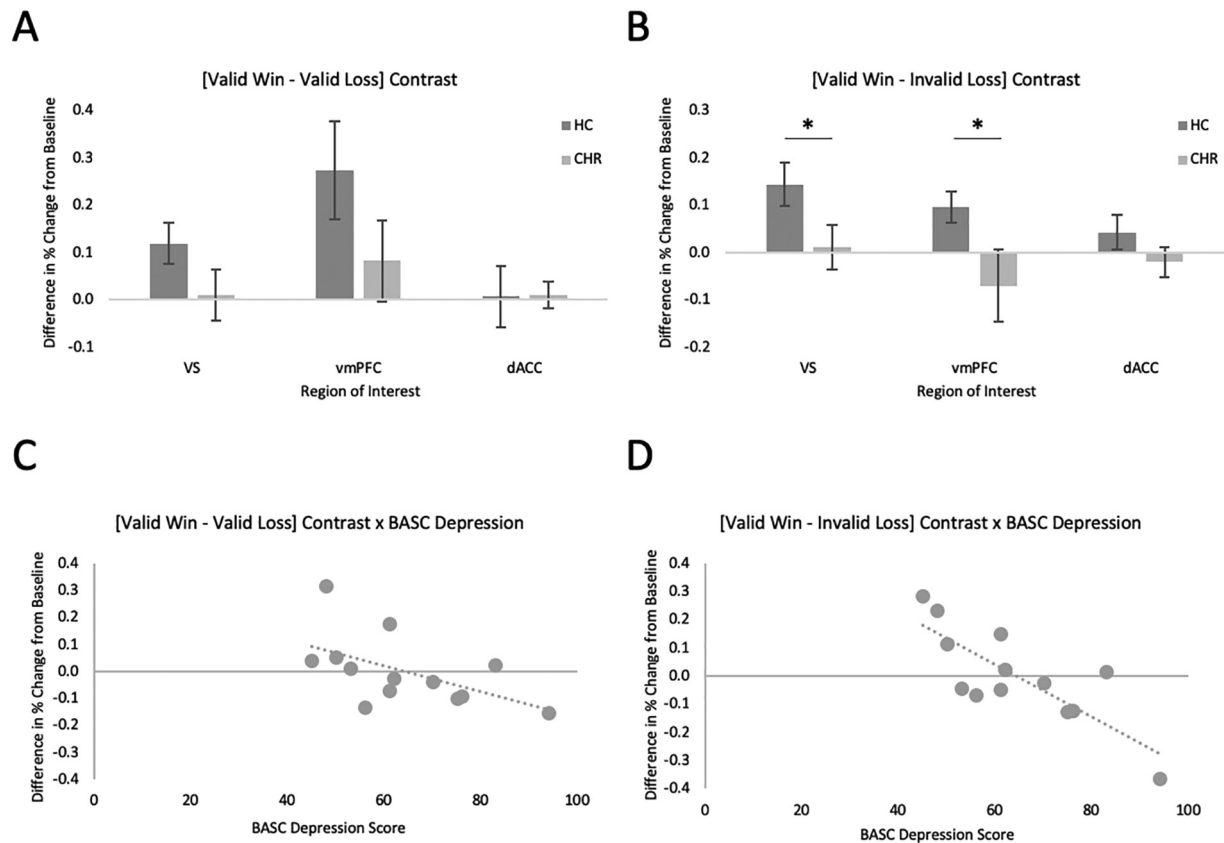


Fig. 4. Card Betting Task condition contrasts in youth at CHR and controls. A. We observed no significant between-group differences in the [Valid Win – Valid Loss] contrast in any of the a priori regions of interest (ROIs). B. We observed significant between-group differences in the [Valid Win – Invalid Loss] contrast in ventral striatum (VS) and ventromedial prefrontal cortex (vmPFC). C. Both the [Valid Win – Valid Loss] and D. [Valid Win – Invalid Loss] contrasts in the dorsal anterior cingulate cortex (dACC) correlated with depression scores from the BASC among youth at CHR. CHR, clinical high-risk; HC, healthy controls; BASC, Behavior Assessment System for Children, Second Edition.

with reward processing and RL may play a role in the early stages of the disorder.

Conflicts of interest

All authors declare they have no conflicts of interest.

Table 2

Spearman correlations between BOLD signal contrasts in ROIs from the MID task and negative and depressive symptoms.

BOLD signal contrast ROI	Spearman's ρ	
	SIPS negative symptoms	BASC depression
[Expected Gain – Loss]		
VS	0.235	0.022
vmPFC	0.619***	0.283
dACC	–0.019	–0.204
[Received Large – Small Gain]		
VS	0.130	–0.393
vmPFC	0.470**	–0.158
dACC	–0.094	0.222
[Received Large – Small Loss]		
VS	0.096	0.437
vmPFC	0.145	0.427
dACC	0.093	0.054

Note. BOLD, blood oxygen level dependent; ROI, region of interest; MID, monetary incentive delay task; SIPS, structured interview for psychosis-risk syndromes; BASC, Behavioral Assessment System for Children, Second Edition; VS, ventral striatum; vmPFC, ventromedial prefrontal cortex; dACC, dorsal anterior cingulate cortex.

** $p < 0.05$.

*** $p < 0.01$.

Contributors

Authors Waltz, Schiffman, Reeves, Gold, Demro, and Millman designed and ran the study. Authors Millman, Waltz, and Gallagher managed literature reviews and undertook data analyses. Authors Millman and Waltz wrote the manuscript with conceptual and written assistance from Authors Gallagher, Rakhshan Rouhakhtar, Andorko, Fitzgerald, Redman, Rowland, Hong, Buchanan, and Schiffman.

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Table 3

Correlations between BOLD signal contrasts in ROIs from the RL task and negative and depressive symptoms.

BOLD signal contrast ROI	Spearman's ρ	
	SIPS negative symptoms	BASC depression
[Valid Win – Valid Loss]		
VS	–0.353	–0.303
vmPFC	0.009	0.113
dACC	0.051	–0.608***
[Valid Win – Invalid Loss]		
VS	–0.270	–0.369
vmPFC	–0.182	–0.239
dACC	0.042	–0.688***

Note. BOLD, blood oxygen level dependent; ROI, region of interest; RL, reinforcement learning; SIPS, structured interview for psychosis-risk syndromes; BASC, Behavioral Assessment System for Children, Second Edition; VS, ventral striatum; vmPFC, ventromedial prefrontal cortex; dACC, dorsal anterior cingulate cortex.

*** $p < 0.01$.

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Appendix A. Supplementary materials

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2019.03.017>.

References

- Benson, B.E., Guyer, A.E., Nelson, E.E., Pine, D.S., Ernst, M., 2015. Role of contingency in striatal response to incentive in adolescents with anxiety. *Cogn. Affect. Behav. Neurosci.* 15 (1), 155–168.
- Corcoran, C., Kimhy, D., Parrilla-Escobar, M., Cressman, V., Stanford, A., Thompson, J., David, S.B., Crumblay, A., Schobel, S., Moore, H., 2011. The relationship of social function to depressive and negative symptoms in individuals at clinical high risk for psychosis. *Psychol. Med.* 41 (2), 251–261.
- Corlett, P.R., Murray, G.K., Honey, G.D., Aitken, M.R., Shanks, D.R., Robbins, T.W., Bullmore, E.T., Dickinson, A., Fletcher, P.C., 2007. Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. *Brain* 130 (9), 2387–2400.
- Corlett, P.R., Taylor, J., Wang, X.-J., Fletcher, P., Krystal, J., 2010. Toward a neurobiology of delusions. *Prog. Neurobiol.* 92 (3), 345–369.
- Deserno, L., Boehme, R., Heinz, A., Schlagenhauf, F., 2013. Reinforcement learning and dopamine in schizophrenia: dimensions of symptoms or specific features of a disease group? *Front. Psych.* 4, 172.
- Elman, I., Lowen, S., Frederick, B.B., Chi, W., Becerra, L., Pitman, R.K., 2009. Functional neuroimaging of reward circuitry responsivity to monetary gains and losses in posttraumatic stress disorder. *Biol. Psychiatry* 66 (12), 1083–1090.
- Ermakova, A.O., Knolle, F., Justicia, A., Bullmore, E.T., Jones, P.B., Robbins, T.W., Fletcher, P.C., Murray, G.K., 2018. Abnormal reward prediction-error signalling in antipsychotic naive individuals with first-episode psychosis or clinical risk for psychosis. *Neuropsychopharmacology* 43 (8), 1691.
- Evers, E., Stiers, P., Ramaekers, J., 2017. High reward expectancy during methylphenidate depresses the dopaminergic response to gain and loss. *Soc. Cogn. Affect. Neurosci.* 12 (2), 311–318.
- Fletcher, P.C., Frith, C.D., 2009. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nat. Rev. Neurosci.* 10 (1), 48.
- Frank, M.J., Seeberger, L.C., O'Reilly, R.C., 2004. By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science* 306 (5703), 1940–1943.
- Friedland, N., 1998. Games of luck and games of chance: the effect of luck-versus chance-orientation on gambling decisions. *J. Behav. Decis. Mak.* 11 (3), 161–179.
- Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A.R., McGuire, P.K., 2014. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. *Schizophr. Bull.* 40 (1), 120–131.
- Gold, J.M., Waltz, J.A., Prentice, K.J., Morris, S.E., Heerey, E.A., 2008. Reward processing in schizophrenia: a deficit in the representation of value. *Schizophr. Bull.* 34 (5), 835–847.
- Heinz, A., Murray, G.K., Schlagenhauf, F., Sterzer, P., Grace, A.A., Waltz, J.A., 2018. Towards a unifying cognitive, neurophysiological, and computational neuroscience account of schizophrenia. *Schizophr. Bull.* <https://doi.org/10.1093/schbul/sby154> (in press).
- Hengartner, M.P., Moncrieff, J., 2018. Inconclusive evidence in support of the dopamine hypothesis of psychosis: why neurobiological research must consider medication use, adjust for important confounders, choose stringent comparators, and use larger samples. *Front. Psych.* 9, 174.
- Holroyd, C.B., Pakzad-Vaezi, K.L., Krigolson, O.E., 2008. The feedback correct-related positivity: sensitivity of the event-related brain potential to unexpected positive feedback. *Psychophysiology* 45 (5), 688–697.
- Howes, O.D., Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr. Bull.* 35 (3), 549–562.
- Juckel, G., Friedel, E., Koslowski, M., Witthaus, H., Özgürdal, S., Gudlowski, Y., Knutson, B., Wrase, J., Brüne, M., Heinz, A., 2012. Ventral striatal activation during reward processing in subjects with ultra-high risk for schizophrenia. *Neuropsychobiology* 66 (1), 50–56.
- Karcher, N.R., Martin, E.A., Kerns, J.G., 2015. Examining associations between psychosis risk, social anhedonia, and performance of striatum-related behavioral tasks. *J. Abnorm. Psychol.* 124 (3), 507.
- Karcher, N.R., Hua, J.P., Kerns, J.G., 2018. Probabilistic category learning and striatal functional activation in psychosis risk. *Schizophr. Bull.* 45 (2), 396–404.
- Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Schedule for affective disorders and schizophrenia for school-age children—present and lifetime version (K-SADS-PL): initial reliability and validity data. *J. Am. Acad. Child Adolesc. Psychiatry* 36 (7), 980–988.
- Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J. Neurosci.* 21 (16), RC159.
- Knutson, B., Bjork, J.M., Fong, G.W., Hommer, D., Mattay, V.S., Weinberger, D.R., 2004. Amphetamine modulates human incentive processing. *Neuron* 43 (2), 261–269.
- Kühn, S., Gallinat, J., 2011. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. *Schizophr. Bull.* 39 (2), 358–365.
- McCutcheon, R., Beck, K., Jauhar, S., Howes, O.D., 2017. Defining the locus of dopaminergic dysfunction in schizophrenia: a meta-analysis and test of the mesolimbic hypothesis. *Schizophr. Bull.* 44 (6), 1301–1311.
- Miller, T.J., McGlashan, T.H., Rosen, J.L., Cadenhead, K., Cannon, T., Ventura, J., McFarlane, W., Perkins, D.O., Pearlson, G.D., Woods, S.W., 2003. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr. Bull.* 29 (4), 703–715.
- Murray, G., Corlett, P., Clark, L., Pessiglione, M., Blackwell, A., Honey, G., Jones, P., Bullmore, E., Robbins, T., Fletcher, P., 2008. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol. Psychiatry* 13 (3), 267.
- Piskulic, D., Addington, J., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Heinssen, R., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., 2012. Negative symptoms in individuals at clinical high risk of psychosis. *Psychiatry Res.* 196 (2–3), 220–224.
- Plichta, M.M., Scheres, A., 2014. Ventral-striatal responsiveness during reward anticipation in ADHD and its relation to trait impulsivity in the healthy population: a meta-analytic review of the fMRI literature. *Neurosci. Biobehav. Rev.* 38, 125–134.
- Radua, J., Schmidt, A., Borgwardt, S., Heinz, A., Schlagenhauf, F., McGuire, P., Fusar-Poli, P., 2015. Ventral striatal activation during reward processing in psychosis: a neurofunctional meta-analysis. *JAMA Psychiat.* 72 (12), 1243–1251.
- Rausch, F., Mier, D., Eifler, S., Fenske, S., Schirmbeck, F., Englisch, S., Schilling, C., Meyer-Lindenberg, A., Kirsch, P., Zink, M., 2015. Reduced activation in the ventral striatum during probabilistic decision-making in patients in an at-risk mental state. *J. Psychiatry Neurosci.* 40 (3), 163.
- Reynolds, C.R., 2004. Behavior Assessment System for Children. Wiley Online Library.
- Roiser, J.P., Howes, O.D., Chaddock, C.A., Joyce, E.M., McGuire, P., 2012. Neural and behavioral correlates of aberrant salience in individuals at risk for psychosis. *Schizophr. Bull.* 39 (6), 1328–1336.
- Sailer, U., Robinson, S., Fischmeister, F.P.S., König, D., Oppenauer, C., Lueger-Schuster, B., Moser, E., Kryspin-Exner, I., Bauer, H., 2008. Altered reward processing in the nucleus accumbens and mesial prefrontal cortex of patients with posttraumatic stress disorder. *Neuropsychologia* 46 (11), 2836–2844.
- Schmidt, A., Antoniadis, M., Allen, P., Egerton, A., Chaddock, C.A., Borgwardt, S., Fusar-Poli, P., Roiser, J.P., Howes, O., McGuire, P., 2017. Longitudinal alterations in motivational salience processing in ultra-high-risk subjects for psychosis. *Psychol. Med.* 47 (2), 243–254.
- Schultz, W., 2016. Dopamine reward prediction-error signalling: a two-component response. *Nat. Rev. Neurosci.* 17 (3), 183.
- Steinberg, L., 2005. Cognitive and affective development in adolescence. *Trends Cogn. Sci.* 9 (2), 69–74.
- Strauss, G.P., Waltz, J.A., Gold, J.M., 2013. A review of reward processing and motivational impairment in schizophrenia. *Schizophr. Bull.* 40 (Suppl.2), S107–S116.
- Suk Lee, J., Jung, S., Park, I.H., Kim, J.-J., 2015. Neural basis of anhedonia and motivation in patients with schizophrenia: the role of reward system. *Curr. Neuropharmacol.* 13 (6), 750–759.
- Wagshal, D., Knowlton, B.J., Cohen, J.R., Poldrack, R.A., Bookheimer, S.Y., Bilder, R.M., Fernandez, V.G., Asarnow, R.F., 2012. Deficits in probabilistic classification learning and liability for schizophrenia. *Psychiatry Res.* 200 (2–3), 167–172.
- Waltz, J.A., Demro, C., Schifman, J., Thompson, E., Kline, E., Reeves, G., Xu, Z., Gold, J., 2015. Reinforcement learning performance and risk for psychosis in youth. *J. Nerv. Ment. Dis.* 203 (12), 919–926.
- White, S.F., Geraci, M., Lewis, E., Leshin, J., Teng, C., Averbach, B., Meffert, H., Ernst, M., Blair, J.R., Grillon, C., 2016. Prediction error representation in individuals with generalized anxiety disorder during passive avoidance. *Am. J. Psychiatr.* 174 (2), 110–117.
- Whitton, A.E., Treadway, M.T., Pizzagalli, D.A., 2015. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Curr. Opin. Psychiatry* 28 (1), 7.
- Wotruba, D., Heekeren, K., Michels, L., Buechler, R., Simon, J.J., Theodoridou, A., Kollias, S., Rössler, W., Kaiser, S., 2014. Symptom dimensions are associated with reward processing in unmedicated persons at risk for psychosis. *Front. Behav. Neurosci.* 8, 382.