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Reward anticipation-related neural activation following cued reinforcement in adults with psychotic psychopathology and biological relatives

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Abstract

Background. Schizophrenia is associated with hypoactivation of reward sensitive brain areas during reward anticipation. However, it is unclear whether these neural functions are similarly impaired in other disorders with psychotic symptomatology or individuals with genetic liability for psychosis. If abnormalities in reward sensitive brain areas are shared across individuals with psychotic psychopathology and people with heightened genetic liability for psychosis, there may be a common neural basis for symptoms of diminished pleasure and motivation.
Methods. We compared performance and neural activity in 123 people with a history of psychosis (PwP), 81 of their first-degree biological relatives, and 49 controls during a modified Monetary Incentive Delay task during fMRI.
Results. PwP exhibited hypoactivation of the striatum and anterior insula (AI) during cueing of potential future rewards with each diagnostic group showing hypoactivations during reward anticipation compared to controls. Despite normative task performance, relatives demonstrated caudate activation intermediate between controls and PwP, nucleus accumbens activation more similar to PwP than controls, but putamen activation on par with controls. Across diagnostic groups of PwP there was less functional connectivity between bilateral caudate and several regions of the salience network (medial frontal gyrus, anterior cingulate, AI) during reward anticipation.
Conclusions. Findings implicate less activation and connectivity in reward processing brain regions across a spectrum of disorders involving psychotic psychopathology. Specifically, aberrations in striatal and insular activity during reward anticipation seen in schizophrenia are partially shared with other forms of psychotic psychopathology and associated with genetic liability for psychosis.

Introduction

Schizophrenia (SZ) is characterized by diminished motivation and pleasure which implicate poor engagement with rewarding experiences. A limited drive for rewards may lead to reduced abilities to pursue goals of daily living (Kring & Elis, 2013). A likely result is that many individuals with schizophrenia present as disengaged and behaviorally inactive. While similar difficulties are observed in other forms of psychotic psychopathology, the underlying neural dysfunction of reduced reward engagement that may be evident across disorders remains under-investigated. Studies of neural activation during reward anticipation that rely on conventional diagnostic boundaries demonstrate mixed results, suggesting that an approach that spans diagnostic boundaries (i.e. transdiagnostic, Cuthbert, 2014) may resolve the heterogeneity within diagnostic categories. For example, whereas SZ is generally associated with less neural activation during reward expectation, the literature for bipolar disorder is mixed. Studies have revealed increased striatal (Whitton, Treadway, & Pizzagalli, 2015) and anterior cingulate cortex activation in bipolar disorder (Kollmann, Scholz, Linke, Kirsch, & Wessa, 2017) and psychotic bipolar disorder (Smucny et al., 2021). However, others have found blunted activation in nucleus accumbens (NAcc) in bipolar disorder (Johnson, Mehta, Ketter, Gotlib, & Knutson, 2019), similarly blunted activation across SZ and bipolar disorder (Schwarz et al., 2020), and no differences relative to controls (Kirschner et al., 2020). Thus, it is not a given for people with bipolar disorder to show increased activation during reward anticipation. Expanding on the call for transdiagnostic investigations to identify common mechanisms, researchers have pointed to the importance of considering equifinality, such that similar

symptoms or behavioral phenotypes can emerge via distinct pathophysiological mechanisms (Nusslock & Alloy, 2017). However, few prior studies include a transdiagnostic sample. To clarify the role of reward system abnormalities in severe mental disorders where psychosis can be present, it is critical to directly compare diagnostic groups in their neural activations during potential reward and loss situations. In the present study we used a parametrically-adjusted odd-one-out reaction time task to examine neural reward system responses in individuals with schizophrenia, schizoaffective disorder, or bipolar disorder with a history of psychosis, as well as their first-degree biological relatives. We sought to clarify the diagnostic specificity of reward system aberrations and determine their relevance to genetic liability for psychotic psychopathology.

Researchers have typically used Monetary Incentive Delay (MID) tasks, in which rewards are cued and dependent on response speed, to investigate the neural correlates of reward anticipation in people with a history of psychosis (PwP; Knutson, Adams, Fong, & Hommer, 2001). Various instantiations of MID tasks have revealed striatal hypoactivation during reward anticipation in SZ, first-episode psychosis, and relatives of PwP (Li et al., 2018; Radua et al., 2015). In studies of reward processing in non-psychiatric samples, ventral striatum responses have been associated with incentivization, expectancy formation, and potential pleasure while dorsal striatal activity has been associated with attributing value to novel actions or stimuli through reinforcement (Klawonn & Malenka, 2018; Tricomi, Delgado, & Fiez, 2004). More specifically, studies have revealed associations between apathy severity and ventral striatal hypoactivation to reward in SZ (Simon et al., 2015; Stepien et al., 2018) as well as anhedonia severity and dorsal striatal activation to reward in non-psychiatric participants (Chung & Barch, 2015), thereby suggesting that associations between brain activation and impaired behavioral functioning extend beyond SZ. Also, the anterior insula (AI), a cortical region associated with reward processing, is consistently activated during both gain and loss anticipation (Liu, Hairston, Schrier, & Fan, 2011; Oldham et al., 2018), potentially in relation to the cognitive processing of uncertain rewards (Mohr, Biele, & Heekeren, 2010; Purcell et al., 2023).

Investigating reward system function in biological first-degree relatives of PwP (hereafter Relatives) allows one to determine whether abnormal neural responses during reward anticipation are related to genetic liability for psychotic psychopathology in the absence of symptoms and antipsychotic medication. Inclusion of relatives also addresses the possible equifinality of reward processing aberration through allowing a test of whether individuals without psychotic symptomatology who are at heightened genetic liability show similar reward anticipation brain responses. It remains unclear whether reward system dysfunction in SZ extends to groups with heightened genetic liability for psychosis.

Deviations in reward-related activation across brain regions may be indicative of a broader abnormality in reward circuitry that might involve salience, central executive, and default networks (Wilson et al., 2018). For example, evidence of less connectivity between NAcc and insula while receiving reward, and between ACC and insula during uncertain reward anticipation and pursuit (Gradin et al., 2013; Purcell et al., 2023; Schmidt et al., 2016), suggest aberrations in salience network regions in psychosis possibly contributing to expectancy formation during reward processing. Resting-state striatal abnormalities are evident in SZ and, albeit milder, in bipolar disorder (Li et al., 2020). While striatal functional connectivity has been explored across diagnostic categories, it remains underexplored in a psychosis-spectrum sample (Schwarz et al., 2020, 2022).

The purpose of the current study was to use the Cued Reinforcement Reaction Time (CRRT) task (a modified MID task) during fMRI to test whether abnormalities in neural activation during reward anticipation are shared across disorders of psychotic psychopathology and genetic risk for psychosis. The CRRT task required cognitive resources to resolve response uncertainty related to an odd-one-out target. We used fMRI to examine neural activation and connectivity during gain/loss anticipation cues in PwP and Relatives to test several hypotheses: (1) PwP, but not Relatives, would demonstrate impaired task behavior (e.g. higher error rates); (2) PwP and Relatives would demonstrate reduced brain activation in the NAcc, caudate, and AI during gain anticipation and caudate and AI during loss anticipation; (3) functional connectivity between the caudate and salience regions (e.g. AI, ACC) would be lower only in PwP; and (4) lower behavioral task performance and striatal hypoactivation would be associated with more negative symptoms in PwP.

Methods

Participants

The study was completed by 253 participants between the ages of 18 and 69 (see Table 1, online Supplementary Materials, and Table S1 for sample description), including participants with psychotic psychopathology (schizophrenia [SZ], schizoaffective disorder [SZA], bipolar disorder with psychotic features [BPp]), their first-degree biological relatives [Rel], and control [Ctrl] participants according to DSM-IV-TR criteria. Study procedures, recruitment, and inclusion criteria are further documented elsewhere (Demro et al., 2021). Relatives were enrolled regardless of psychopathology, though presence of a psychotic disorder was exclusionary. Control participants had no personal or family history of psychotic symptoms or psychiatric hospitalization for affective disorder. Procedures were approved by the University of Minnesota Institutional Review Board (#1607M90781).

Clinical and behavioral assessment

Participant diagnoses were assessed using the Structured Clinical Interview for DSM-IV-TR (SCID; First, Spitzer, Gibbon, & Williams, 2002). Within the PwP group, psychosis-related symptomatology across the previous 30 days was assessed using the Scales for the Assessment of Negative/Positive Symptoms (SANS/SAPS; Andreasen, 1984, 1989), with sums of global ratings (excluding attention; Blanchard & Cohen, 2006) reflecting the total negative and positive symptoms and sums of item ratings reflecting the negative symptom dimensions of Diminished Expressivity (e.g. blunted affect, alogia) and Motivation and Pleasure (e.g. anhedonia, avolition) identified by confirmatory factor analysis in the literature (Strauss et al., 2018).

Cued reinforcement reaction time (CRRT) task

In traditional MID tasks, trial performance depends on responding using a single, known button-press and monetary outcomes are binary (an amount is either earned or not). The CRRT (Simon et al., 2015), a MID variant, requires additional recruitment of cognitive resources during reward anticipation, as each trial requires the identification of an odd-one-out stimulus rather than merely

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Table 1. Sample demographics and characteristics

	Ctrl ($n = 49$)	REL ($n = 81$)	PwP ($n = 123$)	Comparison	Tukey post-hoc
Mean age (s.d.)	39.0 (13.1)	44.8 (15.2)	37.9 (12.2)	$F_{(2,250)} = 6.82$, $p = 0.001$	PwP *v.* Ctrl: $p = 0.880$ PwP *v.* REL: $p = 0.001$ REL *v.* Ctrl: $p = 0.045$
Female sex	51% (25)	62% (50)	43% (53)	χ^2 (2, $N = 253$) = 6.79, $p = 0.034$	
Race: AI/A/AA/HL/Mult/W	0/1/3/ 1/1/43	0/1/4/ 3/2/71	1/5/19/ 5/5/88	χ^2 (10, $N = 253$) = 11.97, $p = 0.287$	–
Diagnosis or relation SZ/SZA/BPp	–	50/8/23	75/14/34	–	–
WAIS-IV IQ	106.8 (11.2)	102.5 (10.7)	97.6 (11.2)	$F_{(2,250)} = 13.26$, $p < 0.001$	PwP *v.* Ctrl: $p = 0.001$ PwP *v.* REL: $p = 0.006$ REL *v.* Ctrl: $p = 0.089$
Years of education	16.1 (2.5)	15.2 (2.2)	14.1 (2.1)	$F_{(2,250)} = 15.7$, $p < 0.001$	PwP *v.* Ctrl: $p < 0.001$ PwP *v.* REL: $p = 0.001$ REL *v.* Ctrl: $p = 0.077$
Cued reinforcement reaction time task performance					
Total task winnings	$29.59 ($5.92)	$29.33 ($6.73)	$24.99 ($6.64)	$F_{(2,250)} = 14.58$, $p < 0.001$	PwP *v.* Ctrl: $p < 0.001$ PwP *v.* REL: $p < 0.001$ REL *v.* Ctrl: $p = 0.974$
Total task errors	12.70 (7.78)	12.9 (7.3)	19.3 (11.5)	$F_{(2,250)} = 14.48$, $p < 0.001$	PwP *v.* Ctrl: $p < 0.001$ PwP *v.* REL: $p < 0.001$ REL*vs.* Ctrl: $p = 0.992$
Reward speeding (+$2 *v.* +$0)	−0.047 (0.053)	−0.037 (0.049)	−0.033 (0.051)	χ^2 (2, $N = 253$) = 2.61, $p = 0.272$	–
Reward speeding (+$2 *v.* +$0.40)	−0.015 (0.037)	−0.016 (0.042)	−0.012 (0.36)	χ^2 (2, $N = 253$) = 0.56, $p = 0.754$	–
Loss avoidance speeding (−$1 *vs.* −$0)	−0.043 (0.049)	−0.040 (0.042)	−0.029 (0.051)	χ^2 (2, $N = 253$) = 4.56, $p = 0.102$	–
Loss avoidance speeding (−$1 *v.* −$0.20)	−0.011 (0.035)	−0.008 (0.034)	0.001 (0.037)	χ^2 (2, $N = 253$) = 4.47, $p = 0.107$	–

Note: Ctrl, controls; REL, relatives; PwP, people with psychosis; SZ, schizophrenia; SZA, schizoaffective disorder; BPp, bipolar disorder with psychosis; AI, American Indian; A, Asian; AA, African American; HL, Hispanic/Latino; Mult, multiracial; W, White. Reward/loss speeding comparisons used Kruskal–Wallis test.

a speeded motor response (Fig. 1). Monetary outcome amounts also modulate according to relative, within-subject reaction time (RT), establishing a reinforcement contingency that incentivizes the active process of mustering flexible, executive control co-occurring with reward anticipation. Thus, the CRRT task strives to mimic the real-world, preemptive allocation of cognitive resources to concerted reward attainment. The CRRT task accounts for individual differences in RT using a staircase function to adjust the payment structure according to each participant's practice trial RTs. Thus, it evaluates performance within-subject, above and beyond the confound of differing between-subject processing speeds.

Participants completed the CRRT variant during fMRI scanning at the University of Minnesota Center for Magnetic Resonance Research. Prior to fMRI data collection, all

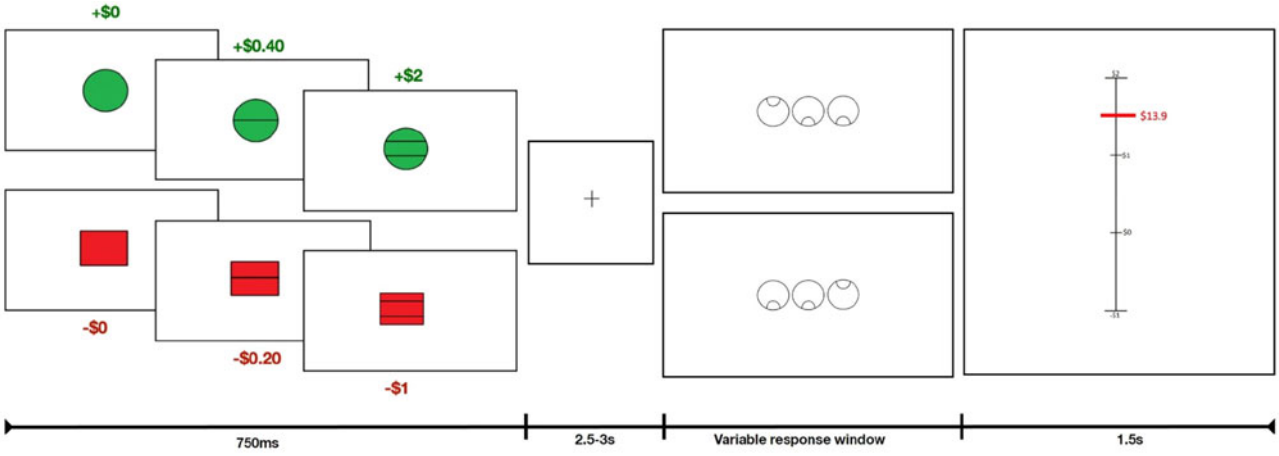

Figure 1. Cued Reinforcement Reaction Time (CRRT) task: Either a green circle or red square was presented to cue a potential gain or loss trial, respectively; null, low, and high trials were differentiated by the number of horizontal lines (0 lines = ±$0, 1 line = +$0.40/−$0.20, 2 lines = +$2.00/−$1.00). Each of the three circles for the target stimulus contained an arch within the top or bottom. Via right/left button press, participants indicated whether the arch location within the circle on the right or left did not match the other two. The right-most panel shows the two types of feedback that were given simultaneously: (1) current trial reward amount indicated by a red line along a −$1 to $2 spectrum; (2) across-trial running total in Arabic numerals (i.e. $13.9).

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participants completed practice trials until there were two instances where 20 of 25 trials received correct responses. Task performance was evaluated based on number of errors and RTs to high gain *v.* both neutral stimuli (i.e. reward-related speeding) and to high loss *v.* both neutral stimuli (i.e. loss avoidance speeding; Table 1) relative to the mean for all conditions. Whereas error trials (on which the participant chose the incorrect option or omitted a response) were removed, correct responses outside of the within-subject RT response window (i.e. late responses) were included in analyses.

Neuroimaging data acquisition

Imaging data were acquired with a 3T Siemens Prisma scanner using a standard 32-channel Siemens head coil. A T1-weighted structural image (MP-RAGE: 0.8 mm isotropic voxels, 256 × 240 mm FOV, 8° flip angle, TR/TE/TI = 2500/1.81/1000 ms) was used for anatomical reference. Two 13-min task-based event-related fMRI scans were administered during the CRRT task, preceded by two spin-echo scans acquired with opposite phase encoding directions to compensate for distortion due to B_0 inhomogeneity. Functional scans were acquired with a gradient echo EPI sequence (2 mm isotropic voxels, TR/TE = 800/37 ms, flip angle = 52°, number of slices = 72, echo spacing = 0.58 ms, multi-band acceleration factor = 8).

Neuroimaging data processing

Data quality of fMRI scans was evaluated using modified function Biomedical Informatics Research Network (fBIRN) scripts that include advanced quality assurance metrics (see Greve et al., 2011). For quality control, participants with more than 20% of volumes removed due to significant displacement were excluded from analysis ($n = 5$, online Supplementary Materials; Caballero-Gaudes & Reynolds, 2017; Jones et al., 2010) yielding a final analysis sample of 253 participants. Additional information on task completion rates and data quality can be found in the online Supplementary Materials under 'Excluded participants'. fMRI data were analyzed using Analysis of Functional NeuroImages (AFNI v2018.02.04; online Supplementary Materials). A non-parametric permutation test was implemented to mitigate risk of false positive results (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Eklund, Nichols, & Knutsson, 2016).

Statistical analysis

Behavioral and ROI analyses were performed using SPSS (v22) and Rstudio. Group differences in sample characteristics, behavioral task performance, and fMRI activation patterns were tested using chi-square and ANOVA. For non-normally distributed data such as RT Kruskal–Wallis/Mann–Whitney *U* test were used. Stimulus condition valence (gain/loss relative to neutral) and amount (based on RT) were entered as within-subject factors, and group (Ctrl, PwP, or Rel) was entered as the between-subjects factor. Pearson correlations were used to examine the association between neural activation and clinical variables.

Whole-brain fMRI analyses

A whole-brain analysis was conducted to identify activation differences during gain, loss, and neutral anticipation trials without bias to any particular regions. The whole-brain cluster-level family-wise error rate was used to correct for multiple comparisons and the cluster-defining voxel-level threshold was $p < 0.001$. Minimum cluster sizes ($p < 0.05$) were determined using AFNI's 3dClustSim, implemented as a non-parametric permutation test within AFNI's 3dttest++ (Cox et al., 2017).

An event-related design was used to model anticipation during the six monetary cue onsets. Consistent with the literature, our primary contrasts of interest were *HighGain-NullAnticipation* and *HighLoss-NullAnticipation* as lesser gains/losses typically yield lesser neural activation that weakens signal when combined with higher gains/losses (Kirschner et al., 2020; Knutson et al., 2001; Simon et al., 2015).

Region of interest (ROI) fMRI analyses

Based on previous studies using the CRRT task, our whole-brain analysis results, and regions implicated in reward anticipation literature, the NAcc, caudate, and AI were selected as ROIs. The putamen was additionally included to ensure full coverage of all three reward-related striatal subregions, and to test which are implicated in psychotic psychopathology (online Supplementary Fig. S2). Given disagreement on its subdivisions (Centanni, Janes, Haggerty, Atwood, & Hopf, 2021), the 10 mm spherical bilateral AI ROI was defined using peak coordinates provided in the reward-anticipation literature (Oldham et al., 2018). All other ROIs were defined in AFNI using Montreal Neurological Institute (MNI) coordinates provided by a publicly available atlas (MNI_avg152; Mazziotta et al., 2001a, 2001b) to ensure no overlap between striatal subregions. Mean percent signal change within ROI masks was extracted using AFNI and between-group ANOVAS were run in SPSS (v22). ROI results were further confirmed by exploratory analyses covarying for antipsychotic medication (via chlorpromazine equivalents; Leucht, Samara, Heres, & Davis, 2016) and tobacco use (lifetime pack years), which have been related to neural activation during reward anticipation (Juckel, 2016; Rose et al., 2012).

Functional connectivity analyses

A beta-series correlation method was used for connectivity analyses (Cisler, Bush, & Steele, 2014; Rissman, Gazzaley, & D'Esposito, 2004). The beta series were averaged across bilateral caudate voxels. This served as the seed ROI (online Supplementary Fig. S3). This region was chosen due to its association with processing gains/losses, its role in reinforcement contingency learning (Elliott, Friston, & Dolan, 2000; Knutson et al., 2001; Tricomi et al., 2004; Wilson et al., 2018), its implication in previous work using the CRRT (Kirschner et al., 2020), as well as our between-group activation differences (Fig. 2). The correlation between the seed and all voxels in the brain were computed for each condition and then Fisher-z transformed. We contrasted the anticipation of high gain and loss conditions relative to the neutral condition (*AnticipateHighGain-NullAnticipation*; *AnticipateHighLoss-NullAnticipation*) and compared between groups.

Minimum significant ($p < 0.05$) cluster size was determined to be 24 voxels using AFNI, as above, with cluster-defining threshold set to $p < 0.005$ (uncorrected) for each voxel. This threshold was selected because connectivity analyses contain more noise than ROI or whole-brain analyses.

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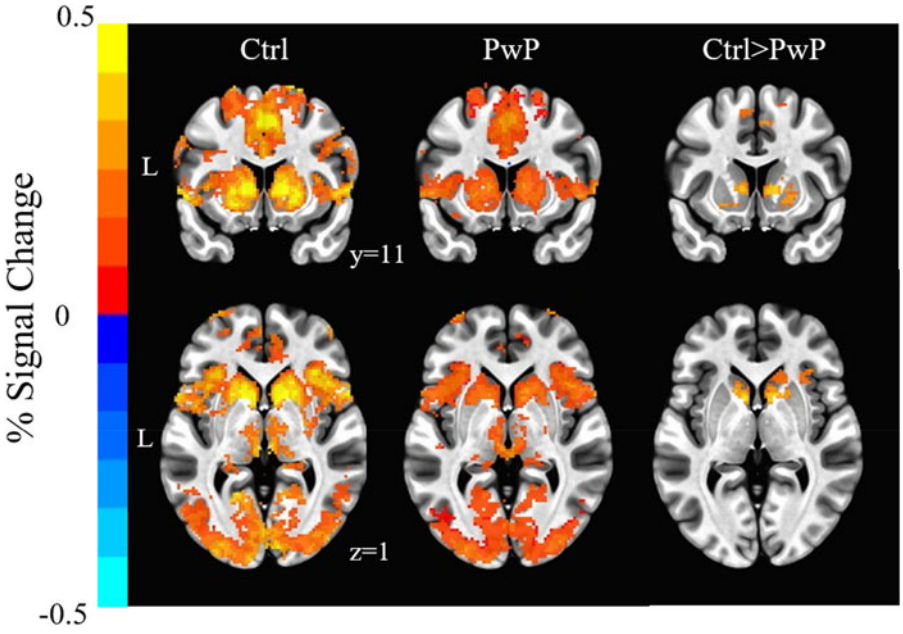

Figure 2. Whole-brain activation patterns across groups during anticipation of reward (+$2 *v.* $0). Thresholded at $p < 0.001$.

Results

Behavioral

Full-sample RT across all conditions ranged from 145.60 to 742.20 ms (mean = 436.84 s.d. = 85.16) after removal of outliers (Hoaglin & Iglewicz, 1987) and were not normally distributed (Kolmogorov-Smirnov test $p < 0.001$). RT data were analyzed using Kruskal–Wallis and Mann–Whitney *U* tests. PwP made more errors and earned less money overall on the task compared to Relatives and Controls (Table 1). However, Relatives performed similarly to controls, indicating that individuals with genetic liability for psychosis exhibit normative cognitive-task performance on the CRRT. All participants demonstrated within-group reward-related speeding such that RTs on high gain trials were faster than null outcome trials, but no between group differences emerged. The same was true for high loss compared to neutral trials. Further, when comparing large gains (+$2) to small gains (+$0.40) and large losses (−$1) to small losses (−$0.20), participant groups did not differ (see Table 1). Thus, our study demonstrates intact reward-related and loss-avoidance speeding among PwP and Relatives.

Task-related neural activation

Whole-brain analyses revealed hypoactivation in the bilateral caudate, bilateral prefrontal cortex, and right AI (among other regions) in PwP compared to controls during anticipation of high reward relative to neutral trials (i.e. $0) (Fig. 2, online Supplementary Table S2). PwP had lower right putamen activation compared to Relatives during the reward condition (online Supplementary Fig. S1). An exploratory analysis comparing diagnostic subgroups confirmed hypoactivation in the bilateral caudate among SZ compared to controls, whereas SZA and BPp did not show differences from controls.

In bilateral caudate, ROI analyses showed an effect of group for both anticipation of reward ($F_{(2,250)} = 16.02$, $p < 0.001$, $\eta^2 = 0.11$; Fig. 3) and anticipation of loss ($F_{(2,250)} = 6.04$, $p = 0.003$, $\eta^2 = 0.05$; online Supplementary Fig. S4). Both results survive Bonferroni correction for multiple comparisons. Post-hoc analyses indicate that, for both conditions, PwP had lower caudal activation than Controls (reward: $p < 0.001$; loss: $p = 0.006$) and Relatives (reward: $p = 0.004$; loss: $p = 0.037$) and Relatives had lower caudal activation than controls during reward anticipation ($p = 0.029$). Exploratory analyses comparing diagnostic groups provide further evidence for consistent effects across psychotic disorders. During reward anticipation all psychotic disorder subgroups demonstrated lower bilateral caudate activation compared to controls (SZ $p < 0.001$, SZA $p = 0.005$, BPp $p = 0.005$) and SZ differed from Relatives ($p = 0.018$). Diagnostic comparisons for the loss condition (−$1) showed that SZ had lower caudal activation than Ctrl during loss anticipation ($p = 0.046$; online Supplementary Fig. S4).

ROI analyses further revealed an effect of group in putamen ($F_{(2,250)} = 12.56$, $p < 0.001$, $\eta^2 = 0.09$), NAcc ($F_{(2,250)} = 5.32$, $p = 0.005$, $\eta^2 = 0.04$), and AI ($F_{(2,250)} = 9.66$, $p < 0.001$, $\eta^2 = 0.07$) activation during reward anticipation, all surviving Bonferroni correction. Specifically, PwP had lower activation of NAcc ($p = 0.006$), putamen ($p < 0.001$), and AI ($p < 0.001$) compared to Ctrl and lower activation of putamen ($p = 0.008$) and AI ($p = 0.005$) compared to Relatives, whereas Relatives had lower NAcc activation than controls during reward anticipation ($p = 0.013$). Diagnostic comparisons indicate that diagnostic subgroups had lower activation than controls in putamen (SZ $p < 0.001$, SZA $p = 0.011$, BPp $p = 0.010$), NAcc (SZ $p = 0.018$), and AI (SZ $p = 0.003$, BPp $p = 0.023$) during reward anticipation. Thus, hypoactivation in these regions was present across diagnoses, and SZ showed the strongest hypoactivation compared to the other PwP. There was no group difference during loss anticipation in these regions.

Since PwP diagnostic groups differed in antipsychotic medication exposure in our sample (online Supplementary Table S1) and other factors such as nicotine exposure are known to affect reward processing, ROI analyses were repeated with these covariates. All ROI results remain consistent when controlling for antipsychotic medication and tobacco use (online Supplementary Materials).

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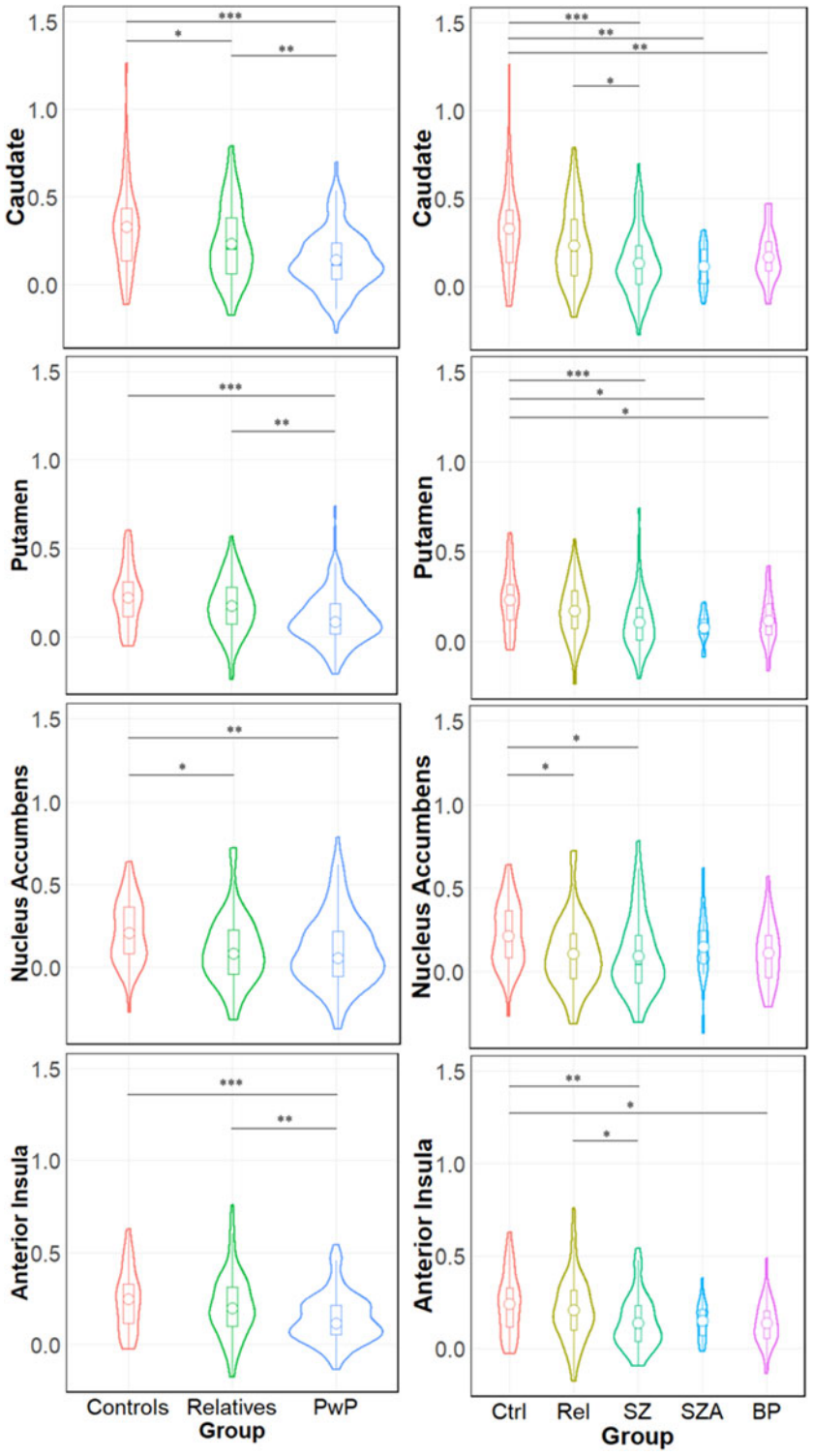

Figure 3. Density plots showing group differences in activation in 4 regions of interest during anticipation of reward (+$2 *v.* $0). Participants with psychotic disorders (PwP) generally had lower activation of the bilateral caudate, putamen, NAcc, and AI compared to Controls (Ctrl) and Relatives (Rel) during anticipation of reward. Schizophrenia (SZ) showed the strongest hypoactivation in these regions compared to the other PwP. Relatives had lower activation compared to controls in caudate and NAcc. *Y*-axis represents percent BOLD signal change bilaterally within the named region during anticipation of reward (+$2) relative to the neutral condition. Boxplots inside the violin density plots show group means. BP, bipolar disorder with psychosis.

Symptom and behavioral correlations

Among PwP, bilateral caudate activation during *HighGain-NullAnticipation* correlated with the negative symptom dimension of Diminished Expressivity ($r = -0.23$, $p = 0.011$) but not Motivation and Pleasure ($r = -0.14$, $p = 0.115$) indicating that less increase in caudate activity during reward anticipation was related to interviewer ratings of reduced emotional expression. This association survived FDR correction for multiple comparisons and was driven by the SZ group (Expressivity: $r = -0.24$, $p = 0.037$); the smaller SZA group showed a similar pattern (online Supplementary Fig. S5). However, diagnostic comparisons did not survive FDR. Among PwP, higher total negative symptom item ratings correlated with less connectivity between the caudate seed and anterior cingulate cortex ($r = -0.18$, $p = 0.048$), but this weak association did not survive FDR.

In the full sample, larger amounts of money earned was related to greater activation during anticipation of high reward relative

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to neutral trials in caudate ($r = 0.23$, $p < 0.001$), putamen ($r = 0.23$, $p < 0.001$), and AI ($r = 0.26$, $p < 0.001$) but not NAcc ($r = 0.07$, $p = 0.263$). Interestingly, PwP and Relatives showed a similar pattern of association in AI (PwP $r = 0.19$, $p = 0.038$; Relatives $r = 0.26$, $p = 0.018$) but only Relatives showed a trend towards significance in the other regions (caudate: $r = 0.22$, $p = 0.050$; putamen: $r = 0.22$ $p = 0.052$) and controls showed no significant associations. All other comparisons were not significant.

Functional connectivity

Participants with psychotic disorders showed less connectivity between bilateral caudate and bilateral medial frontal gyrus, left anterior cingulate, right AI, and bilateral putamen compared to Ctrl during *HighGain-NullAnticipation* (Fig. 4 and online Supplementary Table S3). Each diagnostic category within PwP similarly showed less caudate connectivity to several of these regions compared to controls. Specifically, SZ, SZA, and BPp showed less connectivity between bilateral caudate and left anterior cingulate, and right AI/putamen compared to Ctrl. Additionally, SZ and BPp had less connectivity between caudate and left putamen, SZ with left superior frontal gyrus, BPp with right medial frontal gyrus, and SZA with right precuneus compared to controls. Thus, hypoconnectivity between caudate and regions of the salience network was evident in all diagnostic subcategories of PwP but strongest in SZ. Relatives had less connectivity in parietal and temporal lobes compared to controls (online Supplementary Table S3). No differences in caudate connectivity were found between groups or subgroups during *HighLoss-NullAnticipation*.

Discussion

We used the CRRT task with fMRI to examine neural activation during reward anticipation in people with psychotic psychopathology, their first-degree biological relatives, and controls. Behaviorally, people with psychosis and their relatives responded faster to cues indicating larger reward than smaller reward, but PwP made more errors on the task than controls and relatives. These results suggest intact reward-motivated behavior but impairment in allocating cognitive resources necessary to exploit potential rewards. Neuroimaging results showed that people with psychosis had hypoactivation of the dorsal and ventral striatum as well as reduced connectivity between bilateral caudate and key salience network regions during cued reward anticipation. These findings are consistent with the literature, which shows striatal hypoactivation during reward anticipation in SZ, first-episode psychosis, and relatives of PwP (Li et al., 2018; Radua et al., 2015) as well as bilateral AI activation during reward anticipation in people with SZ, bipolar disorder, and non-psychiatric controls (Kirschner et al., 2020). Results from reward anticipation tasks other than MID indicate that there is less AI activation in SZ, first-degree relatives of SZ, and participants with first-episode schizophrenia and schizoaffective, but not psychotic bipolar disorder (de Leeuw, Kahn, & Vink, 2015; Moran, Culbreth, Kandala, & Barch, 2019; Smucny et al., 2021). Taken together, our study demonstrated aberrations in striatal and insular activity during reward anticipation across a spectrum of disorders involving psychotic psychopathology and genetic liability for psychosis.

Given mixed findings in the literature regarding reinforcement-related speeding (Kirschner et al., 2020; Murray et al., 2008; Simon et al., 2015; Stepien et al., 2018), we tested whether participants with psychotic psychopathology failed to respond faster to cues indicating larger reward. We found evidence for intact reward-speeding among people with psychosis and relatives. This suggests that PwP normatively modulate their response speed to varying reward values. However, PwP made more errors on the task than controls and relatives. This is consistent with our hypothesis and suggests that PwP have difficulties rallying cognitive resources required for responding to the odd-one-out target while maintaining reward cue information. Such difficulties are likely related to phenotypic deficits in executive control and reward processing in this population.

Our imaging results show that people with psychosis had hypoactivation of the dorsal and ventral striatum during cued reward anticipation. Results do not indicate regional specificity within the striatum, as all striatal regions of interest that were examined demonstrated this effect. This medium-sized effect is consistent with investigations that show less activation of striatal circuits subserving reward prediction in disorders that make up a spectrum of psychotic psychopathology (Frost & Strauss, 2016; Kieslich, Valton, & Roiser, 2022; Li et al., 2018; Radua et al., 2015; Wang et al., 2023). The current study expands on this literature by using the same task to investigate reward-processing brain activation across individuals with varying forms of psychotic psychopathology as well as their biological first-degree relatives. Relatives, some of whom had psychopathology but not with psychosis, had hypoactivation of NAcc compared to controls and intermediate caudal activation compared to controls and PwP during cued reward anticipation. This is consistent with previous studies showing that the propensity to activate the striatum during reward and loss anticipation is partly heritable (Li et al., 2019), and that the striatum is less active in non-psychotic first-degree relatives of SZ (Grimm et al., 2014) and relatives free of all psychiatric disorders (Li et al., 2018; Vink, Ramsey, Raemaekers, & Kahn, 2006). Lower insular activation during reward anticipation is also apparent in relatives (de Leeuw, Kahn, & Vink, 2015) but one study revealed less deactivation in the region in relatives (Hanssen et al., 2015). We found that relatives did not differ from controls on putamen or insula activation, a level of granularity that prior studies have not reached when investigating striatal and salience network dysfunction in relatives of people with psychosis. Interestingly, despite reduced striatal activation during the task, biological first-degree relatives performed equally well (on all indices of behavioral performance: total errors, reaction time, and reward speeding) as controls. Among PwP, we found a link between less caudal activation during reward anticipation and more severe interviewer ratings of blunted emotional expression. This suggests a potentially distinct mechanism underlying this symptom domain. The link between brain activation and task behavior across the entire sample suggests that greater anticipatory brain activation was associated with greater success at earning rewards. This may relate to higher-performing participants being more incentivized, or perhaps more confident, during anticipation in their success at earning rewards upon the subsequent odd-one-out task. Even though relatives earned as much as controls on average, there is variability among relatives in neural signal which is associated with behavioral task performance. This is possibly related to some relatives carrying a heavier genetic load that predisposes them to neural activation that is more similar to PwP than controls. In sum, our results suggest that striatal dysfunction is present in psychotic disorders, not only in schizophrenia, and

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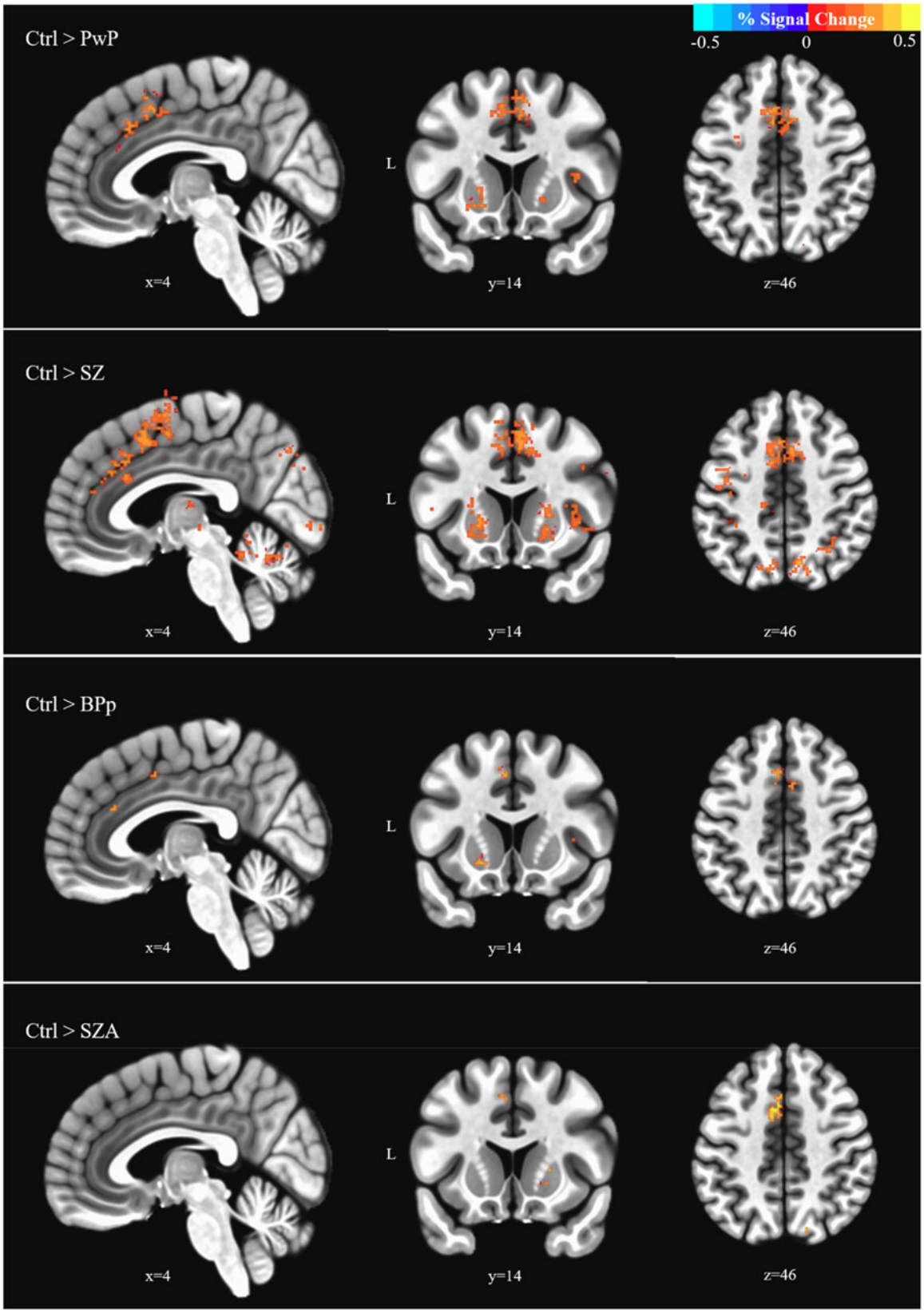

Figure 4. Functional connectivity. Participants with psychotic disorders (PwP; top panel) showed less connectivity between bilateral caudate and bilateral medial frontal gyrus, left anterior cingulate, right anterior insula, and bilateral putamen compared to controls (Ctrl). Each diagnostic category (SZ, schizophrenia; BPp, bipolar disorder with psychosis; SZA, schizoaffective disorder) similarly showed less connectivity in these regions compared to Ctrl. Results suggest impaired connectivity of the salience network in psychosis. Thresholded at $p < 0.005$.

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associated with genetic liability and symptom severity. It is important to note that relatives will vary in the genetic liability they carry and thus the intermediate findings may reflect differing levels of genetic propensity toward reward system abnormalities. Further, a proportion of relatives endorsed psychiatric symptoms (other than psychosis) which may have also influenced task-related striatal activation (see Nielsen et al., 2023).

Participants with psychosis, regardless of diagnosis, also showed reduced connectivity between bilateral caudate and key salience network regions (e.g. AI, anterior cingulate) implicated in reward processing. Further, our results indicate comparable AI activation across all study groups during loss anticipation, but decreased activation in SZ and BP groups compared to controls during reward anticipation. This activation and connectivity pattern may relate to deficits in recruiting executive control during gain-anticipation (Dowd, Frank, Collins, Gold, & Barch, 2016), given the AI's role as a core network node contributing to processing and filtering of information and its specific contributions to prediction error signaling and salience processing in SZ (Palaniyappan & Liddle, 2012).

Consistent with the literature (Chung & Barch, 2015; Mucci et al., 2015; Simon et al., 2015; Stepien et al., 2018), hypoactivation of the bilateral caudate during reward anticipation among individuals with schizophrenia was correlated with more severe negative symptoms, providing support for a potential treatment target for this symptom domain. Negative symptoms of schizophrenia such as amotivation and anhedonia disrupt occupational and social engagement (Green, Hellemann, Horan, Lee, & Wynn, 2012), are largely unaddressed by antipsychotic medication (Mäkinen, Miettunen, Isohanni, & Koponen, 2008), and comprise a subset of reward processing impairments (Fuentes-Claramonte et al., 2023). The current study identified a weak link between task-related neural activation and severity of negative symptoms in individuals with schizophrenia but not bipolar disorder or schizoaffective disorder consistent with negative symptomatology being most prevalent in schizophrenia. Future studies could build on the current findings by using biologically-based classification to identify subgroups of people with psychosis based on neural response patterns to potential gains and losses (Clementz et al., 2016).

Limitations

The limitations of the current study included limited coverage of orbito-frontal cortex activation due to the field-of-view alignment that prioritized superior frontal regions. Further, even though multi-band sequences may yield attenuated effect sizes for reward anticipation in subcortical regions like NAcc (Srirangarajan, Mortazavi, Bortolini, Moll, & Knutson, 2021), we had sufficient striatal signal to detect group effects. Additionally, all participants with psychosis were recruited from outpatient or community settings and most were receiving antipsychotic treatment. Thus, emerging or acute psychotic episodes are not reflected in the current sample potentially limiting generalizability to this population. Despite this limitation, PwP demonstrated variability in symptom severity, allowing for examination of covariance with neural activation and medication load, and analyses demonstrated that findings were likely not attributable to medication. Additionally, relatives showed intermediate performance and striatal activation, implicating factors other than medicine, such as genetic liability for psychosis or personal psychiatric history. Finally, participant groups differed on task performance (e.g. errors, money earned) which was correlated with activation in one of the four ROIs. Despite this, all participants seemed to be sufficiently engaged and motivated in the task (e.g. based on overall performance and reward speeding). Future studies could implement a task paradigm that ensures a certain success rate.

Conclusion

Our study demonstrated a transdiagnostic dysfunction of striatal regions in anticipation of reward that extends beyond schizophrenia to the broader spectrum of psychotic psychopathology, and may be associated with unexpressed genetic liability for psychosis.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003343

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Competing interests. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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