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Increased ventral striatal functional connectivity in patients with schizophrenia during reward anticipation

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ABSTRACT

Background: Growing evidence points towards dysfunction of the ventral striatum as a neural substrate of motivational impairments in schizophrenia. Ventral striatal activity during reward anticipation is generally reduced in patients with schizophrenia and specifically correlates with apathy. However, little is known about the cortico-striatal functional connectivity in patients with schizophrenia during reward anticipation and its relation to negative symptoms.

Objectives: The aim of this study was to identify categorical group differences in ventral striatal functional connectivity during reward anticipation between patients with schizophrenia and healthy controls, and dimensional associations between cortico-striatal functional connectivity and negative symptom severity.

Method: A total of 40 patients with schizophrenia (10 females) and 33 healthy controls (8 females) were included from two previously published studies. All participants performed a variant of the Monetary Incentive Delay Task while undergoing event-related fMRI. Functional connectivity was assessed using psychophysical interactions (PPI) with the left and right ventral striatum as seeds and the contrast [High Reward Anticipation – No Reward Anticipation]. Negative symptoms were assessed using the Brief Negative Symptom Scale.

Results: Compared to controls, patients with schizophrenia showed increased functional connectivity between the left ventral striatum and the left precuneus and right parahippocampal gyrus, two hubs of the default mode network (cluster-level threshold: FWE, $p < .05$). In addition, we found a negative association between apathy scores on the BNSS and increased functional connectivity between the left ventral striatum and the left ventral anterior insula / putamen and the left inferior frontal gyrus / dorsal anterior insula (cluster-level threshold: FWE, $p < .05$).

Conclusions: Our results indicate that the patterns of increased functional connectivity between the ventral striatum and the dorsal default mode network during reward anticipation could act as a compensatory mechanism to regulate the activity of the ventral striatum. Our results also showed that functional connectivity patterns from the ventral striatum, much like its local activity, is specifically related to apathy, and not diminished expression.

1. Introduction

Motivational impairments are a core dimension of schizophrenia that appear early in the course of the disorder and often fail to respond to treatments (Foussias & Remington, 2010; Sabe et al., 2019; Schlosser et al., 2014). Within the different processes underlying motivation, reward anticipation has been shown to be particularly affected in people with schizophrenia (e.g., Kirschner et al., 2016; Radua et al., 2015; Strauss et al., 2013). The most frequently employed task for investigating reward anticipation using functional magnetic resonance imaging (fMRI) is the monetary incentive delay (MID) task (Knutson et al., 2000). The MID is a simple detection task where participants have to

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react as fast as possible when presented with a pre-specified target-cue. Task difficulty is calibrated to participants' mean reaction time to achieve a similar success rate (e.g., 60%) in all participants. Reward anticipation is elicited by presenting a cue indicating whether a high, low or no reward is at stake. This procedure allows for the mapping of brain regions sensitive to reward anticipation.

Two meta-analyses using the MID task with healthy controls found robust patterns of activation in mesocorticolimbic brain regions (Oldham et al., 2018; Wilson et al., 2018). Compared to healthy controls, patients with schizophrenia show decreased bilateral ventral striatal activity during reward anticipation in the MID task (Juckel et al., 2006; Nielsen et al., 2012b). This pattern of hypoactivity has been confirmed in meta-analyses (Leroy et al., 2020; Radua et al., 2015), but some studies do not show group differences (Kirschner et al., 2016; Stepien et al., 2018). Other regions activated during reward anticipation include the anterior cingulate cortex and the insula (Diekhof et al., 2012), which typically show lower activation in patients with schizophrenia (Cadena, White, Kraguljac, Reid, & Lahti, 2018; Leroy et al., 2020; Moran et al., 2019; Smucny et al., 2021). It should be noted that deficits in reward anticipation are present in other disorders, such as bipolar disorder, although a recent study showed that they may rely on different patterns of activation than in schizophrenia (Smucny et al., 2021).

In addition, ventral striatal activity during reward anticipation in patients with schizophrenia correlates with negative symptoms (Radua et al., 2015), in particular with apathy (Kirschner et al., 2016; Simon et al., 2010, 2015; Stepien et al., 2018; Wolf et al., 2014). However, this relationship might not be specific to the ventral striatum as it has been shown to extend to the dorsal striatum (Mucci et al., 2015a). Overall, there is clear evidence for categorical differences in ventral striatal activation during reward anticipation between patients with schizophrenia and healthy controls, as well as a dimensional association between ventral striatal activity during reward anticipation and negative symptoms.

In contrast to this extensive literature on local activation abnormalities during reward anticipation in patients with schizophrenia, the evidence for altered functional connectivity is surprisingly limited. One previous study (Simon et al. (2015) found reduced functional connectivity between the ventral striatum and orbitofrontal cortex, the thalamus and the dorsal striatum in patients with schizophrenia compared to a stratified sample of healthy controls. In this study, no dimensional association between connectivity and negative symptoms was found. To our knowledge, no other study has investigated corticostriatal functional connectivity during reward anticipation in patients with schizophrenia.

However, previous studies assessing functional connectivity in schizophrenia with resting state functional magnetic resonance imaging (rs-fMRI) found that cortico-striatal pathways are affected in patients with schizophrenia when compared with healthy controls (Fornito et al., 2013; Tu et al., 2012). The fronto-striatal network is particularly affected, as shown by functional dysconnectivities from seeds such as the insula (Sheffield et al., 2020; Tian et al., 2019) and the anterior cingular cortex (Cadena, White, Kraguljac, & Reid et al., 2019). In addition, several studies found an association between cortico-striatal dysconnectivity and negative symptoms (Brakowski et al., 2020; Shukla et al., 2018a; Tian et al., 2019; Tu et al., 2012; Wang et al., 2016). Taken together, these studies point towards categorical differences in cortico-striatal connectivity between patients with schizophrenia and healthy controls, as well as an association between dysconnectivity patterns and negative symptoms in schizophrenia. However, it is unclear whether these categorical and dimensional connectivity patterns extend to task-based functional connectivity during reward anticipation.

The present study aimed at investigating categorical group differences in ventral striatal functional connectivity during reward anticipation between healthy controls and patients with schizophrenia. Based on the study of Simon and colleagues (2015), we expected to find reduced cortico-striatal connectivity in patients, especially with regard to the medial orbitofrontal cortex, the thalamus and the dorsal striatum. Furthermore, we investigated dimensional relationships between ventral striatal connectivity during reward anticipation and negative symptoms in patients with schizophrenia. Based on our previous results showing a link between ventral striatal hypoactivation and apathy (Kirschner et al., 2016; Stepien et al., 2018), we hypothesized that cortico-striatal dysconnectivity would be specifically associated with symptoms of apathy. We also performed exploratory functional connectivity analyses on the insula and the anterior cingulate cortex, as patients with schizophrenia also show patterns of dysconnectivity from these regions.

2. Methods and materials

2.1. Participants

Participants came from two published fMRI studies (Kirschner et al., 2016; Stepien et al., 2018). Participants with schizophrenia (SZ; n = 43) were recruited from inpatient and outpatient units of the Psychiatric Hospital of the University of Zurich or from affiliated institutions. All patients were clinically stable and had no comorbid Axis I disorder. Healthy controls (HC; n = 48) were recruited from the general population. Both studies were approved by the local ethics committees and participants provided written informed consent.

Two duplicated patients were removed because they took part in both studies. Five healthy controls and one patient were removed because of missing data. Moreover, ten healthy female controls were removed in order to match groups regarding age and gender. This selection was performed blind to the results. In total, we analyzed the data of 74 participants, 40 (10 females) patients with schizophrenia and 33 (8 females) healthy controls (Table 1).

2.2. Clinical assessment

The Brief Negative Symptom Scale (Kirkpatrick et al., 2011; Strauss et al., 2012) was used to assess negative symptom severity. The two negative symptom dimensions apathy and diminished expression were calculated as proposed in previous studies (Bischof et al., 2016; Mucci et al., 2015b). The Positive and Negative Syndrome Scale (Kay et al., 1987) was used to assess the whole spectrum of symptoms in patients with schizophrenia. Daily chlorpromazine (CPZ) dose-equivalents based

Table 1
Summary of Demographic, Psychopathological and Clinical Variables.

Characteristic	Group (mean ± SD)		Statistical test	*p* value
	Schizophrenia	Control		
Age (year)	32.23 ± 8.01	31.94 ± 8.20	t = −0.15	0.88
Sex (female/total)	10/40	8/33	t = 0.07	0.94
Education (year)	12.08 ± 2.63	13.94 ± 3.30	t = 2.57	0.01*
Chlorpromazine equivalents, mg/d	416.38 ± 327.89	—	—	—
BNSS scores				
Apathy	14.40 ± 7.91	—	—	—
Diminished expression	8.93 ± 7.42	—	—	—
Total Negative Symptoms	23,93 ± 12,89			
PANSS scores				
Positive	9.23 ± 6.04	—	—	—
Negative	10.53 ± 6.06	—	—	—
Disorganized	4.53 ± 2.05	—	—	—
Excited	5.48 ± 1.96	—	—	—
Depressed	7.00 ± 3.98	—	—	—
Total	49.73 ± 13.67	—	—	—

Abbreviations: BNSS = Brief Negative Symptom Scale, PANSS = Positive And Negative Syndrome Scale. **p < .001,*p < .05.

on their daily or monthly medication intake were calculated with the procedure of Leucht et al. (2020).

Before being included in the study, patients were screened for the main causes of secondary negative symptoms, including depression, acute psychotic symptoms, extrapyramidal side-effects and substance abuse and excluded according to the following criteria (Kirschner et al., 2017). Exclusion criteria included any DSM-IV Axis I disorder other than schizophrenia (e.g., substance abuse and major depressive disorder) as assessed by the Mini-International Neuropsychiatric Interview (MINI), positive symptom expression above 4 on the PANSS positive scale, depressive symptoms above 8 on the Calgary Depression Scale for Schizophrenia (CDSS), benzodiazepine use (i.e. above 1 mg of lorazepam dose equivalence) and the presence of extrapyramidal symptoms (i.e. any score above 2 on the Modified Simpson-Angus Scale).

2.3. Experimental design and task

A modified version of the Monetary Incentive Delay (MID) task (MID; Knutson et al., 2000) developed by Simon and colleagues (2015) was employed to study reward anticipation. Each trial started with a cue (0.75 s) at the center of the screen indicating the maximum amount participants could win for this trial (0 CHF, 0.40 CHF, 2 CHF). After a short delay (2.5 to 3 s), participants had to identify the incongruence-based target within an array of three circles (1 s maximum). A feedback screen (2 s) 1) indicated the reward for a correct response, 2) asked participants to respond more quickly in the next trial if there was no response or 3) informed them that the response was wrong. In the modified version used here, the amount of money won following a correct response corresponded to a percentage of the trial-specific maximum amount. This percentage was calculated as the difference between the response time for the present trial and the mean response time for the 15 previous trials. This procedure ensured similar gains for both groups. The intertrial interval (ITI) was jittered (1 to 9 s, mean = 3.5 s). Every participant performed one training session outside the scanner (12 trials) to get familiar with the task and one training session inside the scanner (6 trials) to get familiar with the MRI answer boxes. They then performed two sessions (36 trials each, 12 trials per condition) inside the scanner. Each trial lasted about 10 s and each session lasted around 6 min. Participants were informed beforehand that they would receive the total amount of money won during the task. The task was implemented using the MATLAB toolboxes Cogent 2000 and Cogent Graphics.

2.4. Behavioral analyses

Behavioral analyses were conducted using R (R Core Team, 2019). The response time in the MID task was calculated as the time between the target presentation and the button press. We performed a repeated-measures ANOVA with diagnostic state (SZ or HC) as the between-subject factor and reward (high, low and no) as the within-subject factor. Post hoc tests were performed using Bonferroni-corrected pairwise comparisons. Correlations between reward-related response speeding or mean response time and total negative symptom scores, apathy or diminished expression scores were calculated using Pearson correlations and were corrected for multiple testing. Reward-related response speeding was calculated by subtracting the response time during the high reward condition from the response time during the no reward condition. Between-group comparisons on demographic variables were calculated with two-sample t-tests.

2.5. Functional image acquisition

Both studies used a Philips Achieva 3.0 T scanner at the MR Centre of the Psychiatric Hospital, University of Zurich with a 32-channel SENSE head coil. Each session consisted of 195 functional images using an echo-planar image (EPI) sequence with 38 slices covering the whole brain acquired in ascending order. The in-plane resolution was 3 × 3 mm, 3 mm slice thickness and 0.5 mm gap width over a field of view of 240 × 240 mm. Volumes had a repetition time of 2000 ms, an echo time of 25 ms and a flip angle of 82°. The first 5 scans were discarded to account for magnetic field equilibration. Both studies acquired anatomical data using an ultrafast gradient echo-T_1-weighted sequence in 160 sagittal plane slices of 240 × 240 mm resulting in 1 × 1 × 1 mm voxels.

2.6. Image preprocessing

Motion and susceptibility artifacts were detected using the Art toolbox (http://web.mit.edu/swg/software.htm). Outlier scans (head motion above 2 mm and/or changes in mean signal intensity above 9) identified by this procedure ($n_{SZ} = 14$, $n_{HC} = 10$) were then added as regressors of no interest for the next analyses. In total, 0.41% were outlier scans in the healthy control group and 0.71% in the patient group. The highest percentage of outlier scans per participant was 9.23% in one patient. Mean Framewise Displacement was higher in patients ($m = 0.23$, $sd = 0.10$) than in controls ($m = 0.19$, $sd = 0.06$; $f(1) = 5.66$, $p < .05$). No participant was excluded after performing this quality check. fMRI data were preprocessed and analyzed using SPM8 (Statistical Parametric Mapping, Welcome Trust Centre for Neuroimaging, London, UK) on MATLAB R2018b (Mathworks, Sherborn). Functional images were realigned and unwarped to correct for slice acquisition time and motion. Static and dynamic distortions were corrected with a fieldmap. The images were then segmented, corrected for bias, normalized using forward deformation and the MNI template from SPM 8 and smoothed using a 6 mm full-width at half-maximum Gaussian kernel.

2.7. Rois definition

Left (lVS, MNI coordinates [x y z] = −13, 8, −13; cluster size = 327), right ventral striatum (rVS, MNI coordinates [x y z] = 16, 7, −12; cluster size = 340; a visual comparison with probabilistic structural VS ROIs can be found in Supplementary Fig. 1), right anterior cingulate cortex (ACC, MNI coordinates [x y z] = 2, 17, 45; cluster size = 1578), left anterior insula (lAI, MNI coordinates [x y z] = −30, 30, −5; cluster size = 143), right anterior insula (rAI, MNI coordinates [x y z] = 33, 27, −11; cluster size = 579), seed regions were functionally defined with a whole-brain one-sample *t*-test contrasting "anticipation of high versus no reward" in

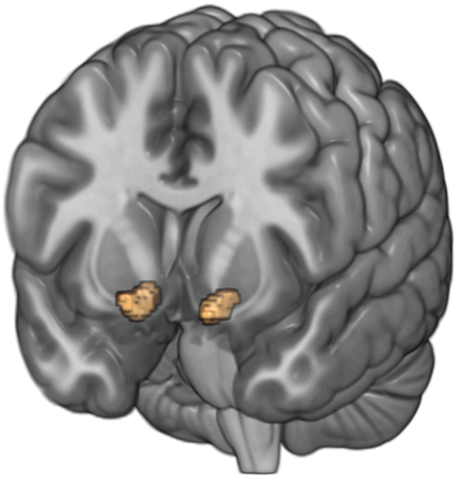

Fig. 1. The left ventral striatum (lVS, MNI coordinates [x y z] = -13, 8, -13; cluster size = 327) and right ventral striatum (rVS, MNI coordinates [x y z] = 16, 7, -12; cluster size = 340) seed regions were functionally defined based on a one-sample t-test on the whole brain analysis using the HC sample with a contract of high versus no reward using a defining threshold of p<.05 FWE whole-brain corrected.

HC. Because of the strong effect of this contrast in HC, we used a cluster defining threshold of p < .05 FWE whole-brain corrected (see Fig. 1).

2.8. First level definition

The general linear model (GLM) used to analyze the functional data comprised three regressors for the anticipation phase and three for the consumption phase (i.e. no reward, low reward and high reward; for both phases). The outcome regressors for the low and high reward conditions were also parametrically modulated with the actual amount received for each trial. An additional regressor modeled target presentation. Moreover, we included three regressors to account for the anticipation, target presentation and outcome phases of error trials. In total, there were 12 regressors in the GLM. The canonical hemodynamic response function was used to convolve the mentioned regressors. To assess the effect of reward anticipation, we calculated a contrast using regressors solely from the anticipation phase, namely [high reward > no reward].

2.8.1. PPI model

We conducted a PPI analysis to assess connectivity maps of lVS and rVS separately during reward anticipation (Friston et al., 1997). The psychological factor was defined as the contrast between the high versus no reward conditions. The interactions between the physiological and psychological factors were then calculated using the PPI toolbox in SPM8. PPI regressors (PPI Interaction, seed activity, psychological regressors) for each seed regions were modelled in an individual GLM for each participant, including two session constants.

2.9. Categorical and covariate Second level analyses

Whole-brain group comparison and correlation analyses were corrected for multiple comparisons using a cluster-defining threshold of p = .001 uncorrected and a cluster-level threshold of p < .05 FWE, whole-brain corrected.

2.9.1. Localized activity analyses

2.9.1.1. Ventral striatum localized analysis. Localized activations were calculated for the right and left VS functional ROIs as defined earlier. Categorical group differences in ventral striatal activity were assessed using a two-sample *t*-test between HC and SZ. In addition, covariate analyses were performed using a bivariate Pearson correlation (*r*) between mean beta weight from the lVS and rVS (extracted with Marsbar) and 1) the BNSS total negative symptoms scores, 2) the BNSS apathy factor and 3) the BNSS diminished expression factor.

2.9.1.2. Supplementary whole-brain analyses. We additionally performed whole-brain analyses on reward anticipation using a one-sample *t*-test to assess activity in HC and a two-sample *t*-test to assess the difference between HC and SZ.

2.9.2. Psychophysiological Interaction analysis

2.9.2.1. Categorical group comparison. To characterize categorical group differences in striatal connectivity during reward anticipation, we performed whole brain analyses by performing a two-sample *t*-test on individual connectivity maps with lVS and rVS seeds. We compared the reward anticipation contrast (high reward vs no reward) between HC and SZ ([SZ > HC] and [SZ < HC]), together with CPZ equivalence dose as a covariate of no interest to control for medication in SZ.

In addition, exploratory correlations (Pearson's *r* and Spearman's ρ) between functional connectivity betas extracted from a one-sample *t*-test in SZ and HC and reward-related speeding were performed to assess the link between functional connectivity and performance.

2.9.2.2. Regression with negative symptoms. To assess correlations between negative symptom severity and cortico-striatal connectivity during reward anticipation, we completed whole brain regression analyses using one-sample t-tests on individual connectivity maps with lVS and rVS seeds in SZ patients and 1) the BNSS total negative symptoms scores, 2) the BNSS apathy factor and 3) the BNSS diminished expression factor in three separate models. CPZ equivalence dose was added as a covariate of no interest to control for medication in SZ.

Additionally, exploratory correlations (Pearson's *r* and Spearman's ρ) between functional connectivity betas extracted from a one-sample *t*-test in SZ and psychopathology scores were performed to evaluate the specificity of the results found in the regression analyses. We also performed exploratory correlations between functional connectivity betas extracted from a one-sample *t*-test in SZ and VS activity betas extracted from a one-sample *t*-test in SZ.

Finally, we performed correlations between apathy and diminished expression scores and CPZ dose to evaluate the influence of medication on negative symptoms in SZ.

2.9.2.3. Exploratory analyses on supplementary seeds. To characterize categorical group differences in cortico-cingular and cortico-insular connectivity during reward anticipation, we performed whole brain analyses by performing a two-sample *t*-test on individual connectivity maps with lAI, rAI and ACC seeds. We compared the reward anticipation contrast (high reward vs no reward) between HC and SZ ([SZ > HC] and [SZ < HC]), together with CPZ equivalence dose as a covariate of no interest to control for medication in SZ.

3. Results

3.1. Sample characteristics

Sample characteristics of both groups are given in Table 1. Although age and gender did not differ between groups, we found a significant difference in education levels between SZ and HC ($t = 2.57$, $p < .05$). A repeated-measures ANOVA on reaction times across groups showed a main effect of reward ($F_{2,142} = 56.76$, $p < .001$) where all participants responded faster in high reward than no reward trials ($p < .01$). Patients with schizophrenia were globally slower than healthy controls (main effect of group, $F_{1,71} = 10.35$, $p < .001$). Moreover, reward interacted with group ($F_{2,142} = 3.32$, $p < .05$), such that patients with schizophrenia showed less reward-related response speeding. Finally, we found no correlation between reward-related response speeding or mean response time and total negative symptoms, apathy and diminished expression scores (all *ps* > 0.25).

3.2. Localized activity analyses

3.2.1. Ventral striatum

Localized analyses on lVS and rVS activity replicated previously published results (Kirschner et al., 2016; Stepien et al., 2018). Namely, we 1) did not find any categorical differences between HC and SZ in either lVS or rVS activity and 2) we found a specific association between VS activity and apathy ($r_{rVS} = -0.39$, $p < 0.05$, $r_{lVS} = -0.32$, $p < 0.05$), but not diminished expression ($r_{rVS} = -0.02$, $p > 0.05$, $r_{lVS} = -0.16$, $p > 0.05$) or total negative symptoms ($r_{rVS} = -0.13$, $p > 0.05$, $r_{lVS} = -0.03$, $p > 0.05$).

3.2.2. Supplementary whole-brain analyses

Supplementary whole brain analyses indicated that HC showed activation in the ventral striatum, ACC, AI, as well as in parietal, occipital and cerebellar regions, as well as deactivation in the angular gyrus (Supplementary Fig. 2). Categorical group difference analyses showed no significant cluster in any contrast (i.e. [HC > SZ] and [SZ > HC]) at a whole-brain corrected threshold of P < 05 FWE, but showed

differences at p < 0.001 uncorrected for [HC > SZ] in regions such as the striatum and medial orbitofrontal cortex (Supplementary Fig. 3).

3.3. Psychophysiological Interaction analysis

3.3.1. Categorical group differences

Whole brain PPI analysis of the lVS and rVS during reward anticipation revealed increased functional connectivity between the lVS and the right parahippocampal gyrus (rPHG) and the left precuneus (lPrec) in SZ when compared to HC ([SZ > HC]; Fig. 2, Table 2). The contrast [SZ < HC] revealed no significant difference in lVS connectivity. Whole brain analyses using the rVS seed showed no significant group effects for either contrast. Functional connectivity maps for each group addressed separately with one-sample t-tests can be found in the supplementary material (Supplementary Figures 4 and 5).

3.3.1.1. Exploratory correlations. Additionally, lVS to rPHG but not lVS to lPrec connectivity correlated with reward-related speeding in SZ ($\rho = 0.32$, $p < .05$; uncorrected), but not in HC (all $ps = 0.69$). Finally, the mean beta weight in functional connectivity between lVS and both lPrec and rPHG did not correlate with the localized activity of the lVS within and between both groups (all $ps > 0.28$).

3.3.2. Dimensional relationship with negative symptoms

Whole brain regression analyses revealed that the functional connectivity between lVS and the left ventral anterior insula / left putamen (lvAI/lPut) and the left inferior frontal gyrus / left dorsal anterior insula (lIFG/ldAI) correlated negatively with apathy scores from the BNSS (Fig. 3, Table 3, see Supplementary Figure 6 for a visual difference between the association with apathy and with diminished expression), with CPZ equivalence dose as a covariate of no interest. Note that although these regions did not show a significant difference in our categorical group analyses, they did appear when using a more liberal threshold (p < .05, uncorrected). We found neither whole-brain corrected correlation between lVS connectivity and diminished expression scores. The functional connectivity using the rVS as seed did not correlate with any BNSS measure.

3.3.2.1. Exploratory correlations. Exploratory correlational analyses between lVS to lvAI/lPut functional connectivity betas extracted from a one-sample *t*-test and psychopathology scores in SZ showed no correlation with the PANSS positive factor and Calgary depression scale ($\rho_{PANSSpositive} = -0.27$, $p > 0.05$; $\rho_{CalgaryDepression} = -0.16$, $p > 0.05$). Conversely, lVS to lIFG/ldAI functional connectivity betas showed significant negative correlations with the PANSS positive factor ($\rho = -0.39$, $p < 0.05$; uncorrected) and Calgary depression ($\rho = -0.31$, $p < 0.05$; uncorrected).

Additionally, exploratory correlations between lVS to lvAI/lPut and lVS to lIFG/ldAI functional connectivity betas and lVS activity betas during reward anticipation in SZ showed a positive correlation between lVS to lvAI/lPut connectivity and lVS activity ($r = 0.48$, $p < 0.05$), but not between lIFG/ldAI connectivity and lVS ($\rho = 0.25$, $p > 0.05$).

Finally, we found no correlation between apathy and diminished expression scores from the BNSS and CPZ dose (both ps > 0.33).

3.3.3. Exploratory analyses on supplementary seeds

Exploratory whole brain PPI analyses of the ACC revealed increased functional connectivity in SZ when compared to HC ([SZ > HC]) with the left inferior parietal gyrus (lIPG), the left supramarginal gyrus (lSMG), the left inferior temporal gyrus (lITG) and the right mid temporal gyrus (rMTG; Fig. 4, Supplementary Table 1). Analyses of the rAI revealed increased functional connectivity in SZ ([SZ > HC]) with the left fusiform gyrus (lFFG), the right mid occipital gyrus (rMOG), the right SMG, the right postcentral gyrus (rPCG), the left superior parietal gyrus (lSPG), the left MOG, the left mid cingulum (lMCing), the lPrec, the right SMG, the left lingual gyrus (lLing), the left posterior insula (lPIns). Whole brain PPI analyses of the lAI did not show any significant cluster on either contrast.

4. Discussion

The present fMRI study assessed categorical and dimensional effects in ventral striatal task-based functional connectivity during reward anticipation in patients with schizophrenia and healthy controls. Our data revealed increased functional connectivity between the ventral striatum and the parahippocampal gyrus and precuneus in patients with

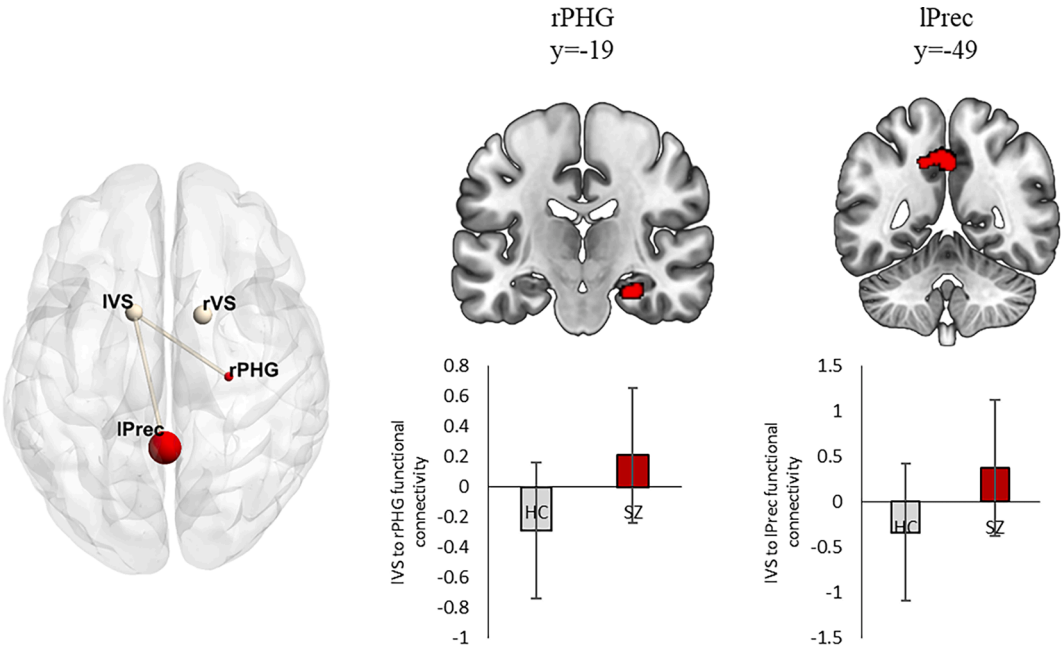

Fig. 2. Psychophysiological interaction results for the anticipation phase of the MID task. Whole-brain analyses showed higher connectivity between the left Ventral Striatum (lVS) and the right Parahippocampal gyrus (rPHG) and the left Precunneus (lPrec) for the Schizophrenia versus Healthy Controls contrast [SZ > HC]. Glass brain in this and all other figures were created using BrainNet (Xia et al., 2013).

Table 2
Whole-Brain Psychophysiological Interaction Results for the Contrast High Reward > No Reward.

Conditions	Seed	Side	Structures	MNI Coordinates			t	Voxel Size
				x	y	z		
SZ > HC	lVS	Right	Parahippocampal Gyrus	27	−19	−21	4.34	258*
		Left	Precuneus	0	−49	39	3.91	457*

Note. *p < .05 FWE corrected at the cluster level for the whole brain (underlying height threshold: p < .001, uncorrected), corrected for CPZ-equivalent dose. lVS: left ventral striatum; HC: healthy controls; SZ: patients with schizophrenia.

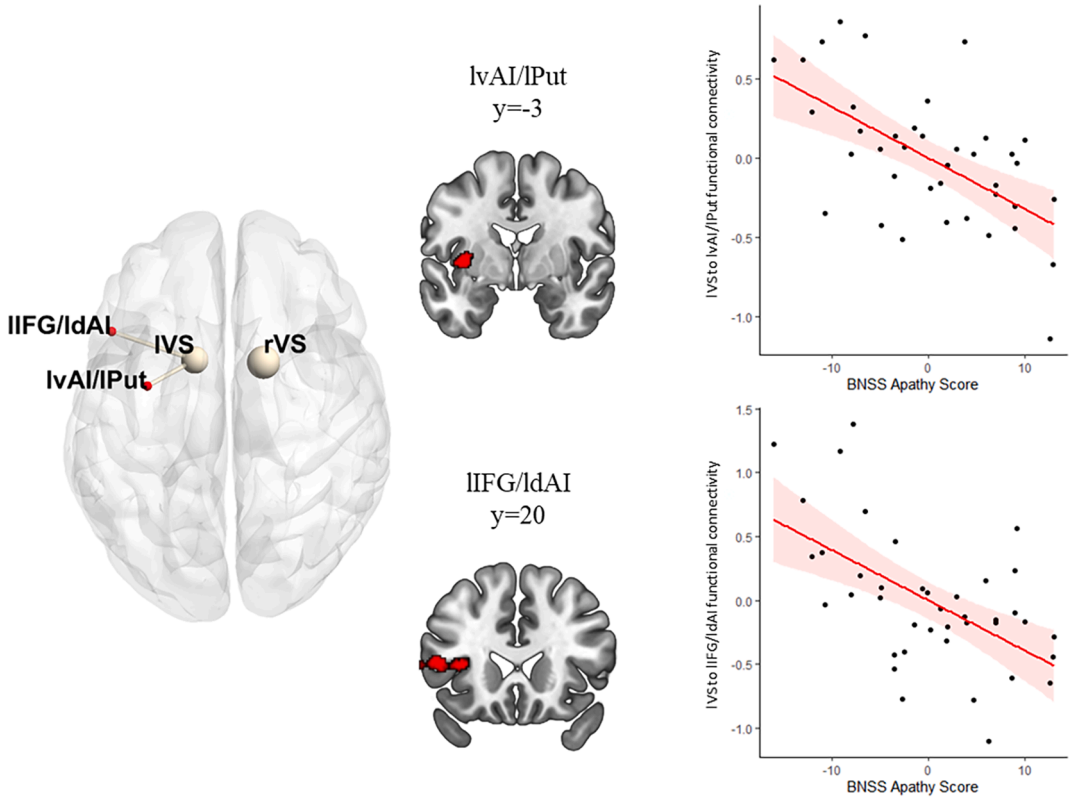

Fig. 3. Covariate analysis results for the anticipation phase of the MID task. Negative association between the left Ventral Striatum (lVS) to left ventral anterior insula/left putamen (lvAI/Put) and left dorsal anterior insula (lIFG/ldDAI) connectivity and the apathy score on the Brief Negative Symptom Scale (BNSS), using CPZ equivalance dose as a covariate of no interest. The plots on the right side of the figure are illustrations, plotting residuals of apathy scores and functional connectivity mean beta weights from correlation analyses where the influence of CPZ equivalence dose has been taken out.

Table 3
Whole-Brain Covariate Analysis on the SZ Group Using the Total Negative Symptoms Score Based on BNSS Scores.

Seed	BNSS Factor	Correlation	Structures	MNI Coordinates			t	Voxel Size
				x	y	z		
lVS	Apathy	Negative	lvAI/lPut	–33	−3	3	5,15	285*
			lIFG/ldAI	−48	20	10	5,06	285*

Note. *p < .05 FWE corrected at the cluster level for the whole brain (cluster-inducing voxel-level threshold: p < .001, uncorrected), corrected for CPZ-equivalent dose. lVS: left ventral striatum; lvAI/lPut: left ventral anterior insula / left putamen; lIFG/ldAI: left inferior frontal gyrus / left dorsal insula.

schizophrenia when compared to healthy controls. In contrast, there were no regions showing reduced connectivity with the ventral striatum. In addition, we found a negative correlation between insular-striatal and fronto-striatal functional connectivity and negative symptom expression in patients with SZ.

4.1. Increased cortico-striatal functional connectivity in patients with schizophrenia

Our analyses identified increased functional connectivity between the ventral striatum and the right parahippocampal gyrus (rPHG) and the left precuneus (lPrec) during reward anticipation in patients with schizophrenia. These results complement previous literature on categorical differences in localized striatum activity during reward anticipation, while it must be kept in mind that in the present dataset, no group differences were found for local activation. The increase in cortico-striatal connectivity was unexpected, as a previous study on ventral striatal activity and connectivity in patients with schizophrenia during reward anticipation using similar methods found a significant hypoconnectivity between the ventral striatum and the medial orbitofrontal cortex, the thalamus and the dorsal striatum (Simon et al., 2015). However, our analyses differed from the ones used by Simon et al.

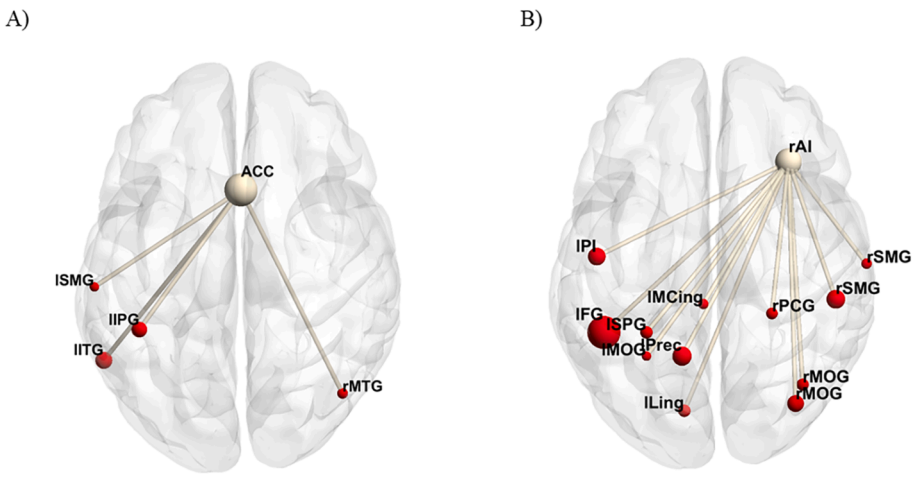

Fig. 4. Psychophysiological Interaction results for the anticipation phase of the MID task. For the Schizophrenia versus Healthy Controls contrast [SZ > HC], whole-brain analysis showed higher connectivity between A) the Anterior Cingulate Cortex (ACC) and the left Inferior Parietal gyrus (lITG) and the right mid Temporal gyrus; B) the right Anterior Insula (rAI) and the left Fusiform Gyrus (lFT), the right Mid Occipital Gyrus (rMOG), the right Suprammarginal Gyrus (rSMG), the right Postcentral gyrus (lMOG), the left Mid Cingulum (lMCing), the left Precunes (lPrec), the left Lingual gyrus (lLing) and the left Posterior Insula (lPI).

(2015), as we used functional VS seeds instead of anatomical seeds and Simon et al. (2015) used a control group stratified for psychotic-like symptom expression, which makes it difficult to compare with our control group. These discrepancies could in part explain the fact that we did not find the same pattern of results.

In our study, patients with schizophrenia showed increased task-related functional connectivity with the PHG and the Prec. These regions represent nodes of the default mode network as identified in studies using rs-fMRI (Aminoff et al., 2013; Ward et al., 2014; Yeo et al., 2011). Resting-state studies investigating cortico-striatal dysconnectivity in schizophrenia reported patterns of both hyper- and hypo-connectivity with anterior and posterior regions of the brain (Fornito et al., 2013; Tu et al., 2012). In addition, a recent study showed that at-rest activity within the default mode network predicts ventral striatal activity during reward anticipation (Mori et al., 2019). The increase in default mode network connectivity during reward anticipation observed here could then act as a direct or indirect compensatory mechanism to upregulate the activity in the ventral striatum. This could explain why the current patient sample did not show any categorical difference in localized ventral striatum activity, in contrast to the *meta*-analysis by Radua et al. (2015).

The parahippocampal gyrus is strongly involved in memory (e.g., Aminoff et al., 2013). Accordingly, the hyperconnectivity between the ventral striatum and the parahippocampal gyrus could reflect a compensatory mechanism related to retrieval difficulties regarding the rewards associated with each cue. This hypothesis is backed by our exploratory analyses, which showed that this specific hyperconnectivity is positively associated with reward-related speeding in patients with schizophrenia. In this case, a hyperconnectivity between the VS and PHG could be necessary for patients to motivationally regulate their performance.

Alternatively, the observed increase in default network connectivity during reward anticipation could reflect a process that is unrelated with ventral striatal activity and that is specific to patients with schizophrenia. Based on our data, we cannot favor one hypothesis over the other. Another explanation for the absence of categorical group differences in the ventral striatum could be the fact that all of our patients were treated with atypical antipsychotics, which have been shown to normalize ventral striatal activation in patients with schizophrenia (Nielsen et al., 2012a; Schlagenhauf et al., 2008). Further dynamic causal analyses could disentangle the role of the default mode network in these processes.

Overall, functional connectivity analyses should be investigated in more detail to help detecting categorical differences in this population and to specify the relationship with local activation patterns as it shows increased sensitivity compared to local activation analyses. Taken together, our results add to the previous literature on categorical dysfunctional connectivity in patients with schizophrenia by showing patterns of increased functional connectivity between the ventral striatum and posterior cortical regions. However, while there is now a consensus that schizophrenia is associated with global patterns of dysconnectivity, more research combining resting-state with task-based procedures is needed to better assess the functional impairments caused by cortico-striatal dysconnectivities.

4.2. *Negative association between cortico-striatal functional connectivity and apathy*

In addition to our categorical results showing hyperconnectivities in SZ, we identified two cortico-striatal dysconnectivity patterns including the left ventral anterior insula / left putamen (lvAI/lPut) and the left inferior frontal gyrus / left dorsal anterior insula (lIFG/ldAI) that are specifically associated with apathy but not diminished expression in patients with schizophrenia during reward anticipation. These results complement the previous literature on the specific association of blunted localized ventral striatal activity and apathy during reward anticipation in patients with schizophrenia (Kirschner et al., 2016; Stepien et al., 2018).

The two fronto-striatal pathways that were highlighted in this analysis are related to two different types of processing. First, the lVS to lvAI/lPut pathway is part of the salience network (Seeley et al., 2007), which is structurally and functionally impaired in schizophrenia (Palaniyappan & Liddle, 2012) and is involved in reward anticipation (Diekhof et al., 2012). Additionally, the AI has been shown to deactivate in patients with schizophrenia during reward anticipation in comparison to healthy controls (Smucny et al., 2021). Accordingly, our results showed a negative correlation between lVS to lvAI/lPut functional connectivity and apathy scores on the BNSS. We did not find such correlation with diminished expression. We also found a significant positive correlation between this functional connectivity pattern and the activity of the ventral striatum, indicating that patients with more severe apathy show lower functional connectivity and relative lower activity in the ventral striatum compared to patients with lower apathy. These results further strengthen the hypothesis that apathy and diminished expression do not share the same pathophysiological mechanism. Future research could investigate if insular neurostimulation could regulate functional connectivity and ventral striatal activity in patients with apathy.

Second, the lVS to lIFG/ldAI pathway is involved in cognitive processing and has been shown to be altered in schizophrenia, in terms of white matter tracts (Quan et al., 2013), grey matter volume (Iwashiro et al., 2016; Jirsaraie et al., 2018), activity (Iwashiro et al., 2016) and functional connectivity (Moran et al., 2013). In addition, a recent

hypothesis advances that cognitive symptoms and negative symptoms could share the same etiology in schizophrenia (Robison et al., 2020). Unfortunately, we could not explore the relationship between hyperconnectivity in this pathway and cognitive functioning scores, as patients from our two cohorts had performed different cognitive batteries. On the other hand, our exploratory correlational analyses indicated that the hyperconnectivity in this pathway was not specific to apathy and negative symptoms, but correlated also with positive and depressive symptoms in patients with schizophrenia. While there is now increasing evidence for processes underlying specific negative symptom factors, this does not exclude that there are also broader patterns of dysconnectivity contributing to a whole range of symptoms in schizophrenia.

Taken together, these results show that cortico-striatal functional connectivity patterns can reflect specific symptoms like apathy, but also more global deficits present in schizophrenia. Nevertheless, further analyses on the directionality of those results are necessary to better qualify the role of these associations in the pathophysiology of symptoms in schizophrenia.

4.3. Exploratory analyses on supplementary seeds

Finally, we performed exploratory functional connectivity analyses on two supplementary seeds belonging to the salience network, namely the bilateral AI and the ACC. We found that both regions showed increased functional connectivity in fronto-temporal, -parietal and -occipital pathways. These results complement previous rs-fMRI studies which showed disruptions in functional connectivity from the AI affecting the central executive network and the default mode network in schizophrenia (Manoliu et al., 2013b; Moran et al., 2013; Sheffield et al., 2020; Wotruba et al., 2013), with links to negative symptoms (Manoliu et al., 2013a), as well as from the ACC (Shukla et al., 2018b; Wang et al., 2015). Taken together, these results indicate that patterns of hyperconnectivity during reward anticipation in schizophrenia seem to generalize to the wider salience network.

4.4. Limitations

Several limitations of the present study have to be noted. First, even though we pooled participants from two studies, the sample size remains relatively modest. Second, although we did our best to match patients and controls, education differed between groups as is often the case in studies on schizophrenia. Additionally, since we excluded patients with florid psychotic symptoms, our results pertain only to a subgroup of patients and further research would be needed to test generalizability. It should also be noted that while we did our best to control for any influence of medication by including CPZ equivalents as a covariate in all analysis, we cannot entirely exclude medication effects on our results. Moreover, other measures such as cognitive functioning and parental education were not available. Finally, for the majority of patients rs-fMRI was not available, precluding a direct comparison of resting-state and task-based functional connectivity.

4.5. Conclusions

We observed categorical differences in ventral striatal functional connectivity during reward anticipation between patients with schizophrenia and healthy controls. In addition, we found a dimensional association between deficient cortico-striatal functional connectivity and negative symptoms. This pattern of categorical and dimensional effects can also be found in the literature on blunted ventral striatal activity during reward anticipation in patients with schizophrenia and its association with negative symptoms.

These findings provide initial evidence for a complex relationship between cortico-striatal hyperconnectivity and impaired striatal activity during reward anticipation, reflecting possible compensatory mechanisms to regulate performance and protective mechanisms against apathy symptoms. Future multimodal imaging studies should integrate localized task-related BOLD signal and different connectivity measures to further our understanding of how large-scale dysconnectivity impacts striatal activation and contributes to reward anticipation deficits in patients with schizophrenia.

CRediT authorship contribution statement

Fabien Carruzzo: Conceptualization, Formal analysis, Writing – original draft. **Stefan Kaiser:** Supervision, Writing – review & editing, Funding acquisition. **Philippe N. Tobler:** Writing – review & editing. **Matthias Kirschner:** Conceptualization, Validation, Writing – review & editing. **Joe Simon:** Conceptualization, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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