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Reduced resting state functional connectivity in the hippocampus-midbrain-striatum network of schizophrenia patients

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ABSTRACT

Contemporary preclinical models suggest that abnormal functioning of a brain network consisting of the hippocampus, midbrain and striatum plays a critical role in the pathophysiology of schizophrenia. Previous neuroimaging studies examined individual aspects of this model in schizophrenia patients and individuals at clinical high risk for psychosis. However, this exact preclinical brain network has not been translated to human neuroimaging studies with schizophrenia patients and therefore it is currently unknown how functioning of this network is altered in patients. Here we investigated resting state functional connectivity in the hippocampus-midbrain-striatum network of schizophrenia patients, using functional Magnetic Resonance Imaging. Based on preclinical models, a network of functionally validated brain regions comprising the anterior subiculum (SUB), limbic striatum (LS), ventral tegmental area (VTA) and associative striatum (AS) was examined in 47 schizophrenia patients and 51 healthy controls. Schizophrenia patients demonstrated significantly lower functional connectivity in this hippocampus-midbrain-striatum network compared with healthy controls ($p = 0.036$). Particular reductions in connectivity were found between the SUB and LS (0.002 ± 0.315 and 0.116 ± 0.224, $p = 0.040$) and between the VTA and AS (0.230 ± 0.268 and 0.356 ± 0.285, $p = 0.026$). In patients, functional connectivity was not significantly associated with positive, negative or general symptom scores. Reduced connectivity is consistent with the concept of functional brain dysconnectivity as a key feature of the disorder. Our results support the notion that functioning of the hippocampus-midbrain-striatum network is significantly altered in the pathophysiology of schizophrenia.

1. Introduction

A contemporary animal model proposes that abnormal functioning of a brain network consisting of the hippocampus, midbrain and striatum plays a critical role in the pathophysiology of psychotic disorders, such as schizophrenia (Grace, 2016; Lodge and Grace, 2011). In particular, preclinical data suggest that in schizophrenia, neural hyperactivity in a hippocampal sub-region (i.e. ventral subiculum) excites the nucleus accumbens (i.e. limbic striatum) via glutamatergic projections, which in turn drives increased dopamine neuron activity in the ventral tegmental area (VTA). This increased VTA activity ultimately results in higher dopamine concentrations in the associative striatum (Grace, 2016; Lodge and Grace, 2011), which has particularly been related to the positive symptoms of schizophrenia (Howes et al., 2009; Kegeles et al., 2010; Winton-Brown et al., 2014).

Individual aspects of this preclinical model have been investigated in previous neuroimaging studies with both individuals at clinical high risk (CHR) for the development of psychosis and schizophrenia patients (reviewed by Modinos et al., 2015) (Modinos et al., 2015). For example, elevated striatal dopamine function is considered one of the most robust pathophysiological features of schizophrenia, as it has consistently been demonstrated in both CHR individuals and patients (Howes et al., 2009; Howes and Kapur, 2014; Kegeles et al., 2010; Winton-Brown et al., 2014). In CHR individuals, higher hippocampal glutamate

Abbreviations: AS, associative striatum; CHR, clinical high risk; LS, limbic striatum; PANSS, Positive and Negative Syndrome Scale; SUB, anterior subiculum; VTA, ventral tegmental area.

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Table 1
Demographics and clinical characteristics of patients and healthy controls.

Characteristic	Patients (n = 47)	Controls (n = 51)
Age, median (IQR), y[a]	27.8 (9.0)	27.3 (14.0)
Sex, M/F[b]	36/11	35/16
Parental education,<!–Soft-enter Run-on– > **level (No.)**[c,d]	1(1), 2(1), 3(2), 4 (9), 5(16), 6(10), 7 (7)	1(0), 2(1), 3(0), 4(4), 5(16), 6(18), 7(12)
Diagnosis, No. (%)		
Schizophrenia	32 (68)	
Schizoaffective disorder	14 (30)	
Schizophreniform disorder	1 (2)	
Duration of illness, median (IQR), y	5.1 (9.6)	–
PANSS total score, mean (SD)	64.1 (11.8)	–
Positive symptom score	14.8 (4.0)	
Negative symptom score	17.4 (5.0)	
General symptom score	31.9 (5.8)	
Antipsychotic mediation		
Type, No. (%)		
Typical	6 (13)	
Atypical	34 (72)	
Typical and atypical	3 (6)	
None or N/A	4 (9)	
Dose, median (IQR), mg/day [e]	7.5 (5.0)	

IQR = interquartile range, PANSS= Positive and Negative Syndrome Scale, SD = standard deviation, y = years.

[a] No statistically significant difference between groups, Mann-Whitney U = 1295, p = 0.493.

[b] No statistically significant difference between groups, Pearson χ^b (1, n = 98) = 0.778, p = 0.498.

[c] No statistically significant difference between groups, Pearson χ^b (6, n = 98) = 8.289, p = 0.218.

[d] Paternal education level defined as highest education level of one of the parents, ranging from 1 (i.e. <6 years of primary education) to 7 (i.e. university degree).

[e] Antipsychotic medication in haloperidol dose equivalents per day.

concentrations were associated with adverse clinical outcomes (Bossong et al., 2018) and increased resting state perfusion was demonstrated in hippocampal, midbrain and striatal areas, which attenuated with symptomatic remission (Allen et al, 2016, 2017). During reward anticipation, which is dependent on striatal dopamine function, CHR individuals showed increased connectivity between the limbic striatum and midbrain that was significantly correlated with the severity of their abnormal beliefs (Winton-Brown et al., 2017). In schizophrenia patients, elevated hippocampal glutamate levels were found as well (Kraguljac et al., 2013; Merritt et al., 2016). However, using resting state functional connectivity with the striatum and VTA as seed regions, patients showed significant reductions in connectivity with the hippocampus (amongst several other brain regions), which increased with symptomatic improvement after antipsychotic treatment (Hadley et al., 2014; Sarpal et al., 2015). In general, functional connectivity is lower in schizophrenia compared with controls. This dysconnectivity has been demonstrated to be present, and progressing, across the stages of the disorder (i.e. from healthy controls, to CHR to first episode psychosis) (Pettersson-Yeo et al., 2011).

As the proposed preclinical hippocampus-midbrain-striatum model has not directly been translated to clinical research, it is unknown how functioning within this particular network is altered in patients with schizophrenia. In the present study, we investigated resting state functional connectivity in the hippocampus-midbrain-striatum network of schizophrenia patients, and how connectivity in this network is related to symptomatology. Based on the abovementioned preclinical model, resting state connectivity was assessed using functional Magnetic Resonance Imaging (fMRI) within a network of functionally validated brain regions comprising the anterior subiculum (the human equivalent of the rodent ventral subiculum), limbic striatum (predominantly comprising the nucleus accumbens), VTA and associative striatum in 47 schizophrenia patients and 51 healthy controls. Altered network connectivity was expected in schizophrenia patients, with significant correlations between connectivity strength and symptomatology.

2. Materials and methods

2.1. Study population

Data from 47 patients with a schizophrenia spectrum disorder and 51 healthy controls (HC) was used for this study. Groups were matched for age, gender, and parental socio-economic status (regarded as highest educational level of one of the parents). Data were collected as part of The Outcome of Psychosis and Fitness Therapy (TOPFIT) study, which was described previously (Scheewe et al., 2012). In short, patients were recruited from four centres for mental health care in the Netherlands, including the University Medical Center (UMC) Utrecht. Diagnosis was confirmed by psychiatrists using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen, 1992). Patients were stable on antipsychotic medication (i.e. unaltered doses or types from four weeks before study inclusion), showed no evidence for somatic disorders and had no primary diagnosis of alcohol or substance abuse. HC subjects had no DSM-IV diagnosis as assessed with the CASH and no first-degree relative with a psychotic or depressive disorder. Symptomatology was assessed in patients using the Positive and Negative Syndrome Scale (PANSS) (Kay SR, Fiszbein A, 1987). Doses of antipsychotic medication were converted to haloperidol equivalents in milligrams (mg) per day. Table 1 depicts the demographic and clinical characteristics of patients and HCs.

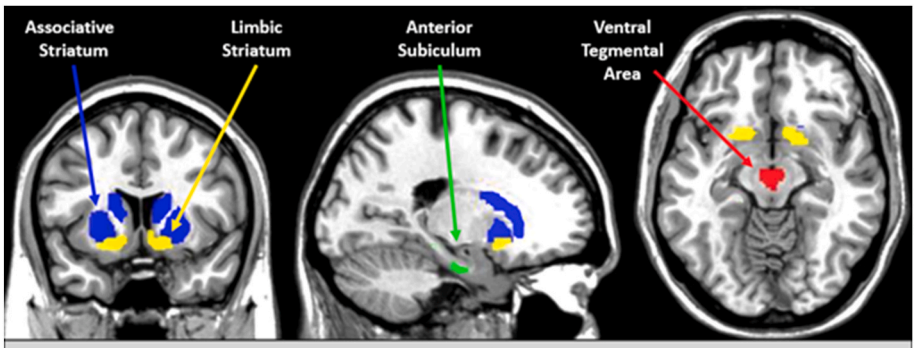
This study was conducted in accordance with all relevant laws and regulations. All volunteers provided written informed consent before study participation and the study was approved by the Research Ethics Committee of the UMC Utrecht and research committees of participating centres.

2.2. Image acquisition

Anatomical T1-weighted and resting state fMRI scans were obtained on a 3.0 Tesla Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands) located at the Department of Radiology of the UMC Utrecht. The three dimensional (3D) anatomical T1-weighted images of the head were acquired with a fast field echo sequence using parallel imaging (sequence parameters: repetition time (TR) = 10 ms, echo time (TE) = 4.6 ms, flip angle = 90°, 200 contiguous slices, slice thickness = 0.8 mm, voxel size = 0.8 × 0.75 × 0.75 mm^3, Field of View (FOV) = 160 × 240 × 240 mm^3). Resting state functional images were obtained using a 3D PRESTO-SENSE pulse sequence (Neggers et al., 2008). The functional scan covered the brain and was acquired over a single run of 1000 volumes with an acquisition time per volume of 0.609s (sequence parameters: TR = 22.5 ms, TE = 33.2 ms, flip angle = 10°, 40 slices, voxel size = 4x4x4mm^3, FOV = 160 × 256 × 256mm^3).

2.3. Preprocessing

Functional images were realigned, coregistered with the anatomical T1-weighed scan and spatially normalised into standard Montreal Neurological Institute (MNI) space using SPM8 (The Wellcome Center for Human Neuroimaging, London, United Kingdom). Subsequently, individual time series were de-trended (i.e. removal of linear trends and first-order drifts), band-pass filtered (filter: 0.01–0.08 Hz) and corrected for global effects by regressing out the mean time courses of motion (six motion parameters), cerebrospinal fluid (CSF, eroded mask thresholded at 0.4), and white matter (WM, eroded mask thresholded at 0.8) with the Resting-State fMRI Data Analysis Toolkit plus V1.2 (RESTplus V1.2; http://www.restfmri.net/forum/RESTplusV1.2; Song et al., 2011). Thirteen participants of the original TOPFIT dataset were excluded from these analyses. In twelve participants data acquisition (MRI) was not



Brain Region	Volume (mm^3)	x	y	z
Anterior Subiculum L	584	-24	-14	-27
Anterior Subiculum R	464	26	-13	-27
Limbic Striatum L	1544	-14	12	-8
Limbic Striatum R	1224	12	11	-9
Ventral Tegmental Area	1472	0	-16	-14
Associative Striatum L	6960	-20	12	5
Associative Striatum R	7136	18	12	4

Fig. 1. Brain regions in the hippocampus-midbrain-striatum network. Regions of interest (green = anterior subiculum, yellow = limbic striatum, red = ventral tegmental area, blue = associative striatum) overlaid on a T1-weighted MNI template (MNI coordinates of displayed slices: x = 71, y = 136, z = 61). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

performed or unsuccessful and in one participant analysis was not possible due to structural abnormalities. None of the remaining participants were excluded due to excessive motion, which was defined as a mean relative displacement (Root-Mean Squared-Framewise Displacement) < 0.55 mm (Satterthwaite et al., 2013). This resulted in 47 patients and 51 HC subjects.

2.4. ROI definition

Functional connectivity was examined in a network of brain regions comprising the bilateral anterior subiculum, limbic striatum, associative striatum and the VTA. These regions of interest (ROIs) correspond to those comprising the preclinical schizophrenia model as proposed by Grace and colleagues (Grace, 2016; Lodge and Grace, 2011), and were all individually validated in previous neuroimaging studies. The anterior subiculum was identified by Chase et al. (2015) using a combination of modelling the co-occurrence of significant activations across thousands of neuroimaging experiments and subsequent data-driven clustering of these data. Importantly, they also showed that the identified anterior subiculum was functionally connected to the limbic striatum and midbrain (Chase et al., 2015). The VTA was defined by Murty and colleagues (2017), who applied a 75% threshold to a probabilistic atlas in MNI space, which was based on manual VTA delineations in 50 individuals (Murty et al., 2014). Seed-based functional connectivity analyses with this definition of the VTA confirmed compatibility with the meso-striatal pathway (Gonen et al., 2016). Finally, the limbic and associative striatum were obtained from an atlas composed of the three functional subdivisions of the striatum (limbic, associative and sensorimotor striatum), which is commonly applied in Positron Emission Tomography (PET) research (Bossong et al., 2015). Functional striatal subdivisions are anatomically analogous to the ventral striatum (limbic striatum), precommissural dorsal putamen, precommissural dorsal caudate and postcommissural dorsal caudate (associative striatum) and postcommissural putamen (sensorimotor striatum) (Martinez et al., 2003). Fig. 1 shows the ROIs of the hippocampus-midbrain-striatum network used to examine functional connectivity in this study.

2.5. Data analysis

Individual time series were extracted from all ROIs. Based on preclinical models, correlation coefficients were calculated for the following three functional connections: anterior subiculum - limbic striatum (SUB-LS), limbic striatum - VTA (LS-VTA), VTA - associative striatum (VTA-AS) (Grace, 2016). These correlation coefficients were normalised using Fisher Z-transformation, which were then regarded as measures of functional connectivity strength. To compare functional connectivity between patients and HCs, a multivariate analysis of variance (MANOVA) was used with group as dependent variable (two levels: patients and HCs) and functional connectivity as independent variables (three levels: SUB-LS, LS-VTA and VTA-AS). Post hoc univariate tests were performed to further investigate differences in functional connectivity between groups. In patients, functional connectivity strength (independent variables: SUB-LS, LS-VTA and VTA-AS) was related to positive, negative and general symptom scores in three separate hierarchical multiple regression analyses. Haloperidol dose equivalents were added as a first block to the hierarchical regression models to correct for treatment effects. Statistical analyses were conducted in SPSS statistics V22.0 (IBM Corp, Armonk, NY, USA). A p-value below 0.05 was considered statistically significant for the MANOVA. P-values below 0.017 were considered statistically significant for the three regression analyses (Bonferroni corrected).

3. Results

3.1. Functional connectivity in the hippocampus-midbrain-striatum network

Functional connectivity in the hippocampus-midbrain-striatum network was statistically different between patients and HCs, as indicated by a significant overall effect of group in the MANOVA ($F(3, 94) = 2.958$, $p = 0.036$). Post hoc univariate analyses showed that schizophrenia patients had lower connectivity than HCs between the anterior subiculum and limbic striatum (SUB-LS; 0.002 ± 0.315 and 0.116 ±

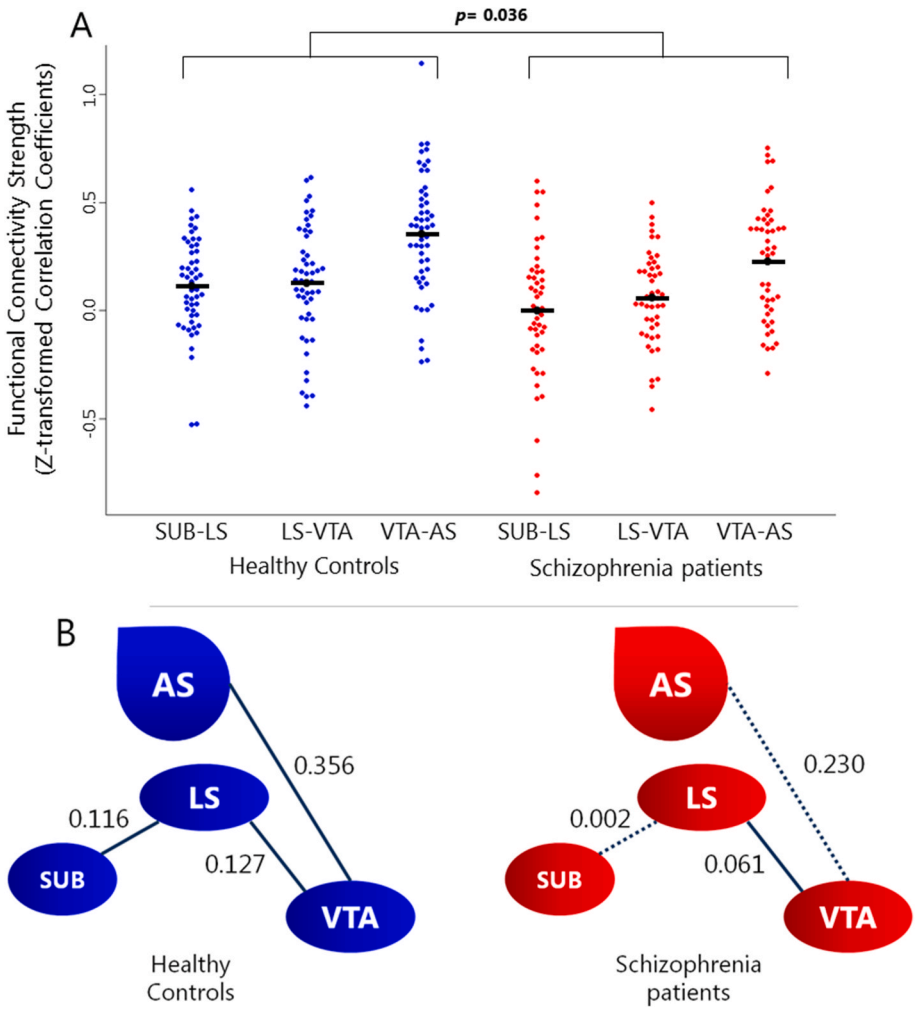


Fig. 2. Functional connectivity measures in the hippocampus-midbrain-striatum network of schizophrenia patients and healthy controls. A. Schizophrenia patients (red) showed a significant overall decrease in functional connectivity compared with healthy controls (blue), as measured with Z-transformed correlation coefficients (p = 0.036). Black lines indicate the mean. B. Dotted lines represent lower functional connectivity in schizophrenia patients compared with healthy controls between the anterior subiculum and limbic striatum (p = 0.040), and between the ventral tegmental area and associative striatum (p = 0.026). The numbers next to the lines connecting the brain regions indicate the mean values of the Z-transformed correlation coefficients of those connections. SB = anterior subiculum, LS = limbic striatum, VT = ventral tegmental area, AS = associative striatum. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

0.224, respectively; F (1, 96) = 4.331, p = 0.040) and between the VTA and associative striatum (VTA-AS; 0.230 ± 0.268 and 0.356 ± 0.285, respectively; F (1, 96) = 5.094, p = 0.026). Functional connectivity between the limbic striatum and VTA was not different between patients and HCs (LS-VTA; 0.061 ± 0.212 and 0.127 ± 0.267, respectively; F (1, 96) = 1.813, p = 0.181) (Fig. 2).

3.2. Associations between functional connectivity and symptomatology

In patients, functional connectivity was not significantly associated (considering Bonferroni corrected p < 0.017) with positive symptom scores (R^2 = 0.128, F (3, 38) = 0.528, p = 0.253), negative symptom scores (R^2 = 0.226, F (3, 38) = 0.054, p = 0.041) or general symptom scores (R^2 = 0.194, F (3, 38) = 1.229, p = 0.078), after correcting for antipsychotic treatment.

4. Discussion

To our best knowledge, this is the first study that investigated resting state functional connectivity of schizophrenia patients in an a priori defined hippocampus-midbrain-striatum network based on the contemporary preclinical schizophrenia model of Grace (Grace, 2016). Schizophrenia patients demonstrated significantly lower functional connectivity in the hippocampus-midbrain-striatum network compared with healthy controls, with particular reductions in connectivity between the anterior subiculum and limbic striatum and between the VTA and associative striatum. In patients, lower network connectivity was not related to the degree of positive, negative or general symptoms.

Our findings of reduced functional connectivity in the hippocampus-midbrain-striatum network of schizophrenia patients are consistent with the concept that functional brain dysconnectivity represents an important feature of the disorder (Pettersson-Yeo et al., 2011). An increasing amount of MRI studies with schizophrenia patients have been showing diminished interactions within functional brain systems, such as the default mode network (O'Neill et al., 2019; Whitfield-Gabrieli et al., 2009) and specific frontostriatal circuits (Dandash et al., 2014; Fornito et al., 2013) (see for a review van den Heuvel and Fornito, 2014). Interestingly, our findings are also in line with studies that showed reduced striatal-cortical functional connectivity in healthy individuals after a pharmacologically induced increase in dopamine availability with L-3,4-di-hydroxy-phenylalanine (L-DOPA) administration (Kelly et al., 2009; Rössler et al., 2018). In addition, previous functional connectivity studies, with medication-naïve patients using the striatum and VTA as seed regions, demonstrated significant reductions in connectivity with the hippocampus (amongst several other brain regions), which increased with symptomatic improvement after antipsychotic treatment (Hadley et al., 2014; Sarpal et al., 2015).

Our results are consistent with preclinical models that suggest that alterations in the hippocampus-midbrain-striatum network are involved in the pathophysiology of schizophrenia (Grace, 2016; Lodge and Grace, 2011). Paradoxically, increases in dopaminergic and glutamatergic transmissions as suggested in the preclinical model, may have resulted in decreased functional connectivity in patients. Because functional dysconnectivity between brain regions most likely reflects abnormal

N-methyl-D-aspartate (NMDA)-dependent synaptic plasticity (a core pathology of schizophrenia) (Stephan et al, 2006, 2009), one possible explanation is that reduced functional connectivity in the hippocampus-midbrain-striatum network, as demonstrated in the current study, is an indication of aberrant synaptic plasticity in this network. This is further supported by data underlying the preclinical schizophrenia model. Dopamine neuron activity in the VTA, striatal dopamine release and the behavioural response to amphetamine are all dependent on activation of glutamatergic N-methyl-D-aspartate (NMDA) receptors in the ventral subiculum (Floresco et al., 2003; Grace, 2016; Lodge and Grace, 2007, 2011).

We showed that reduced functional connectivity within the hippocampus-midbrain-striatum network was not significantly associated with the degree of positive, negative or general symptoms experienced by patients. Possible explanations for this absence of a correlation between connectivity and symptomatology include the relatively long duration of illness (on average 5 years, with a maximum of 10 years) and the use of antipsychotic medication (90% of the patient population). Although we corrected in our analyses for the current daily dose of antipsychotics, the best part of patients had been treated with antipsychotics for several years, which may have influenced our results.

Some limitations have to be taken into account when interpreting the results of this study.

First, as mentioned above, the vast majority of patients that participated in the current study used antipsychotic medication. Several neuroimaging studies with schizophrenia showed that functional connectivity measures could be affected by treatment with antipsychotics (Hadley et al., 2014; Sarpal et al., 2015). However, because functional connectivity appears to be re-established rather than reduced by antipsychotics, it is unlikely that our findings are a confound of antipsychotic medication. Even though we are the first to implement the preclinical model in schizophrenia patients, future studies could further evaluate the clinical relevance of this hippocampus-midbrain-striatum network. Especially longitudinal studies into individuals at CHR, medication-naïve first episode and chronic schizophrenia patients would provide valuable information on the functioning and relevance of this brain network. Second, although the anterior subiculum closely corresponds to the preclinical model, fMRI analyses are sub-optimal with small ROIs. Signals from neighbouring brain regions may have been included while calculating FC. More advanced fMRI acquisition could account for this limitation in the future.

In conclusion, schizophrenia patients showed significantly reduced resting state functional connectivity in the hippocampus-midbrain-striatum network,. Reduced connectivity is consistent with the concept of functional brain dysconnectivity as a key feature of the disorder. Our results support the notion that functioning of the hippocampus-midbrain-striatum network is significantly altered in the pathophysiology of schizophrenia.

Contributors

SSG – contributed to study conceptualization and conducted data analysis and interpretation, drafting of the article, revision of the article, and final approval.

WC – contributed to data interpretation and revision of the article.

TWS – conducted data collection

HEH – contributed to data interpretation and revision of the article.

MGB – conceptualized the study and contributed to data analysis and interpretation, drafting of the article, revision of the article, and final approval.

Role of the funding source

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Declaration of competing interest

The authors declare no conflicts of interest.

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