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Neural correlates of prospection impairments in schizophrenia: Evidence from voxel-based morphometry analysis

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ABSTRACT

Prospection, which has a close relationship with motivation and goal-directed behavior, could be a potential target for alleviating negative symptoms. The present study aimed to examine the structural neural correlates of prospection impairments and the involvement of working memory in prospection in schizophrenia patients. Thirty-seven patients with schizophrenia and 28 healthy controls were recruited and all of them completed a prospection task. Working memory was assessed with the Letter Number Span test. In addition, all participants underwent a structural MRI scan. Voxel-based morphometry (VBM) analysis was used to measure grey matter (GM) volume. We found that in schizophrenia patients, GM loss in the right lateral prefrontal cortex (PFC) and the right ventral medial PFC was correlated with decreased internal details in the prospection task. Moreover, GM volume of the right lateral PFC was found to mediate the relationship between working memory and internal details in these patients. In conclusion, GM loss in the PFC is associated with prospection impairments in schizophrenia patients. Working memory deficits may partially account for prospection impairments in schizophrenia patients.

1. Introduction

Prospection refers to the ability to simulate personal future episodes in one's mind (Gilbert and Wilson, 2007). Substantial evidence suggests that prospection has a significant adaptive value and could facilitate emotion regulation (D'Argembeau and Van der Linden, 2007), decision making (Bechara and Damasio, 2005) and goal-directed behavior (Barsics et al., 2015). According to the constructive episodic simulation hypothesis (Schacter and Addis, 2007a, 2007b), prospection is based on flexible extraction and integration of details from past experience. Recently, researchers have started to investigate the relationship between working memory and prospection. Working memory can be likened to "the stage for prospection", as it serves as a platform where elements retrieved from long-term memory are flexibly recombined into future events (Suddendorf and Corballis, 2007). In fact, a previous study has found that working memory capacity correlates positively with future-oriented thinking (Baird et al., 2011).

Functional imaging studies in healthy samples suggest that there is a core brain network underlying prospection, which overlaps with the Default Mode Network (Andrews-Hanna et al., 2010). Important brain regions involved in this core network include the prefrontal cortex (PFC), the lateral and medial temporal regions (e.g., the hippocampus and the parahippocampal cortex [PHC]), the lateral parietal cortex and the posterior regions (e.g., the precuneus and the posterior cingulate cortex [PCC]) (Addis et al., 2007; Viard et al., 2011). Empirical findings suggest that the medial PFC may play an important role in integrating

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multimodal information into future episodes (Addiset al., 2009; Benoit et al., 2014), while the lateral PFC, which has been shown to be activated during working memory tasks (Markowitz et al., 2015), has also been found to be activated when simulating future events and correlated with executive demands of prospection (Ernst et al., 2015; Gerlach et al., 2014). As for the temporal region, the hippocampus and the PHC may be involved in episodic retrieval and scene construction when prospecting future events (Viard et al., 2012).

In recent years, researchers have started to investigate the mechanism and possible clinical applications of prospection, since it could be an effective target for boosting pleasure experience and facilitating goal achievement (Favrod et al., 2010; Favrod et al., 2015; Szpunar, 2010). Clinical studies have reported that disruption of any key node in the core network could lead to deficits in prospection. In patients with multiple sclerosis (MS), both GM volume and abnormal activation in the prefrontal area have been found to be correlated with the amount of details of future events generated by these patients (Ernst et al., 2015). Other studies that used VBM analysis have shown that prospection impairments are correlated with PCC, PHC and frontal pole volume loss in Alzheimer's disease patients (Irish et al., 2012; Irish et al., 2013), temporal gyrus volume loss in semantic dementia patients (Irish et al., 2012), and reduced GM volume of the frontopolar and medial temporal regions in frontotemporal dementia patients (Irish et al., 2013). Interestingly, although these patients exhibit similar impairments in prospection at the behavioral level, diverse neural deficit patterns could be found in different diseases.

Previous studies have found prospection impairments in schizophrenia patients, in terms of generating less specific and less detailed prospections compared with healthy controls (D'Argembeau et al., 2008a; Painter and Kring, 2016; Raffard et al., 2013; Yang et al., 2018). Prospection impairment has also been found to be closely related to negative symptoms (Painter and Kring, 2016; Raffard et al., 2013) in this clinical group. In addition, preliminary findings suggest that prospection training could enhance pleasure experience and daily activities of schizophrenia patients (Favrod et al., 2010; Favrod et al., 2015). Further investigating the mechanism of prospection impairments in schizophrenia could facilitate the development of more effective interventions.

Although working memory deficit is recognized as one of the key neurocognitive deficits in schizophrenia patients (Lett et al., 2014), it is unclear how working memory affects prospection in this clinical group. Moreover, little is known about the neural correlates of prospection impairment in schizophrenia patients. In a previous study, we found that altered resting-state functional connectivity of the ventral medial PFC is associated with prospection impairments in schizophrenia patients (Yang et al., 2019). On the other hand, the literature suggests distributed GM loss in schizophrenia patients (Fornito et al., 2009). A recent meta-analysis reported that schizophrenia patients exhibited reduced GM volume in several brain areas which are consistently linked to prospection in the healthy population, including the inferior and superior frontal gyrus, the middle temporal gyrus and the hippocampus (Fornara et al., 2017). However, GM correlates of prospection impairments in schizophrenia have seldom been investigated.

The present study aimed to investigate the structural correlates of prospection in schizophrenia patients. Moreover, we also examined how working memory affected prospection in these patients. We hypothesized that: (1) reduced GM volume of areas in the core network such as the PFC and the hippocampus would be correlated with prospection impairment in schizophrenia; and (2) working memory deficits would be closely correlated with prospection impairment in schizophrenia patients and GM volume in the lateral PFC would mediate the relationship between working memory and prospection deficit in schizophrenia patients.

2. Methods

2.1. Participants

Thirty-seven schizophrenia patients and 28 healthy controls (age-, gender- and years of education-matched) participated in this study. The schizophrenia group consisted of 27 outpatients from the Haidian District in Beijing and 10 inpatients from the Haidian District Mental Health Prevent-Treatment Hospital. The diagnosis of all participating patients was ascertained by an experienced psychiatrist using the Structured Clinical Interview (SCID-I) for DSM-IV (First et al., 1996). Healthy controls were recruited from the neighboring communities, who were screened using the non-patient edition of the SCID to confirm the absence of psychiatric disorders. Exclusion criteria for all participants were: (1) an IQ score lower than 70; (2) a history of brain injury or neurological disorders; (3) current substance abuse; (3) left-handedness; and (4) contraindications for MRI scanning such as claustrophobia, pregnancy and having metal implants in the body.

Apart from two patients who were receiving first generation antipsychotics, all participants in the schizophrenia group were prescribed second generation antipsychotic medications. The average antipsychotic dose was 299.76 mg per day in chlorpromazine equivalence (CPZeq).The study protocol was approved by the Ethics Committee of the Institute of Psychology, the Chinese Academy of Sciences (Protocol number: H15031). Written informed consent was provided by all participants.

2.2. Measures

2.2.1. Prospection task

The prospection task was the same as the one used in Yang et al. (2018). Participants were asked to generate future events which were likely to occur to themselves in response to cues in as much detail as possible. Nine pictures (three positive, three neutral and three negative ones) displaying common scenes in daily life were used as cues for this task and these pictures were selected from the International Affective Picture System (Lang et al., 1997) and the Chinese Affective Picture System (Bai et al., 2005). Participants were instructed to construct new events rather than recall past events. Furthermore, generated events should be spatiotemporally specific and should last no longer than a day.

All of their narratives were audio-recorded and scored by two trained raters according to a standardized manual adapted from the Autobiographical Interview (Levine et al., 2002). Details in the narratives were categorized as internal or external. Internal details referred to those which were episodic in nature and directly related to the main event, while semantic information and details unrelated to the main episode were classified as external. Raters were unaware of the diagnosis of the participants and agreement between the two raters was good (Intraclass Correlation Coefficient = 0.86) (Fleiss and Shrout, 1978). In order to control for the influence of positive and negative emotions on the prospection variables, only responses to positive and neutral cues were included in the analysis. Examples of internal and external details extracted from the coded responses of a participant are shown below:

"…We are going to Qinhuangdao (internal detail). Qinhuangdao is a beautiful coastal city (external detail)…My parents and I love travelling (external detail)… We are sitting on the beach (internal details). I can feel the breeze (internal detail)…"

2.2.2. Cognitive function

The Chinese version of the Letter Number Span (LNS) test was used to assess working memory (Chan et al., 2008). This test has been validated and widely used in diverse samples including healthy people (Lin et al., 2007) and schizophrenia patients (Cao et al., 2013). Rows of alternating digits and Chinese characters were read aloud to

participants and they were then asked to separately recall numbers and characters in the correct order. There were eight blocks with four trials in each. The length of each trial in the first block was two and increased by one in every successive block. The test would discontinue if a participant missed all trials within a block. The total number of correct span (LNS_C) and the longest span (LNS_L) were recorded. The short form of the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R, information, arithmetic, similarities and digit span) (Gong, 1992) was used to estimate IQ. Finally, the animal name semantic Verbal Fluency test (VF) (Spreen and Strauss, 1998) was used to assess verbal fluency.

2.2.3. Clinical symptoms

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Scale of Assessment for Negative Symptoms (SANS) (Andreasen, 1989) were used to assess clinical symptoms of schizophrenia patients by an experienced psychiatrist. Three subscales for negative, positive and general psychopathological symptoms are included in the PANSS. The SANS assesses five domains of negative symptoms in schizophrenia patients, including alogia, affective flattening, avolition, asociality and attentional impairment.

2.2.4. Image acquisition

Images were obtained using a 3T Siemens Trio Tim MRI scanner (Siemens, Germany) at the Beijing Chao-Yang Hospital. T1-weighted images were acquired with a sagittal oriented magnetization prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR) = 2530 ms, echo time (TE) = 2.34 ms, field of view (FOV) = 256 mm, flip angle = 7°, in-plane matrix resolution = 256 × 256, and slice thickness = 1 mm). All images were screened by a radiologist to exclude incidental structural abnormalities.

2.3. Statistical analysis

2.3.1. Behavioral data analysis

Statistical analyses were performed with the SPSS (version 22.0, Chicago, IL). Independent t tests were applied to examine group differences on the LNS, VF and prospection variables between schizophrenia patients and healthy controls. In addition, correlation analysis was used to investigate the relationship between scores on the LNS and prospection variables in each group. Correlations between PANSS scores, SANS scores and prospection variables were also examined in the schizophrenia group. Age, gender and years of education were taken as covariates in all correlation analysis. Significance level was set at $p < 0.05$. The Benjamini–Hochberg–Yekutieli FDR method was used to correct for multiple comparisons (Benjamini and Yekutieli, 2001).

2.3.2. Imaging data analysis

Voxel-based morphometry (VBM) was used to examine GM volume and the relationship between GM volume and prospection in schizophrenia. All analyses were performed using the Computational Anatomy Toolbox (CAT12; Jena University Hospital, Departments of Psychiatry and Neurology; http://www.neuro.uni-jena.de/cat) (Gaser and Dahnke, 2016) in Statistical Parametric Mapping software (SPM12; the Functional Imaging Laboratory of the Institute of Neurology at University College London, UK; http://www.fil.ion.ucl.ac.uk/spm) based on MATLAB R2014a (MathWorks Inc.; http://www.mathworks.com). All images were visualized with SPM12 and BrainNet Viewer (Xia et al., 2013).

In data preprocessing, images were carefully inspected. One control participant was excluded because of poor image quality. Noise was first removed by the spatial-adaptive Non-Local Means (SANLM) denoising filter. Then, T1 images were segmented into GM, white matter (WM) and cerebrospinal fluid (CSF), and spatially normalized to a MNI152 template space using the DARTEL algorithm. After a homogeneity check which excluded data with artefacts or of poor quality, all images were smoothed with an 8 mm full-width at half-maximum (FWHM) Gaussian kernel. Finally, the total intracranial volume (TIV) was estimated and taken as a covariate in the subsequent analysis to control for the influence of different brain sizes (Gaser and Dahnke, 2016).

Then group comparison and correlations between GM volume and prospection variables in each group were examined using GLM models. The number of internal details was included in the correlation analysis, similar to previous studies (Ernst et al., 2015; Irish et al., 2012; Irish et al., 2013). Age, gender, years of education and TIV were taken as nuisance covariates in all analyses. Absolute voxel signal intensity threshold masking was set at 0.2 and a whole brain mask which was constructed by Yan and Zang (2010) was also applied. Significance level was set at $p < 0.001$ with AFNI 3dClust 0.05 correction (10,000 iterations).

Clusters which showed significant correlations with internal detail in schizophrenia patients were taken as ROIs and GM volume of these ROIs was extracted by the Marsbar (http://marsbar.sourceforge.net/) (Brett et al., 2002). Correlations between these clusters and working memory were calculated, using age, gender, years of education and TIV as covariates. Correlations between duration of illness, medication dosage, severity of symptoms and these clusters were also examined. A significance level of 0.05 was used. Multiple comparisons were corrected by the Benjamini–Hochberg–Yekutieli FDR method (Benjamini and Yekutieli, 2001).

Finally, mediation analysis was applied to investigate whether working memory influenced prospection via GM volume of these ROIs in schizophrenia patients, using SPSS PROCESS macro (Hayes, 2017). In the hypothesized model, working memory was the independent variable (IV), internal detail was the dependent variable (DV), and GM volume of ROIs was the mediator. The direct effect of IV on DV after controlling for the mediator was *c'*, and the indirect effect of IV on DV via the mediator was *ab*. The bootstrapping method (5000 bootstrap samples) was used and 95% confidence intervals (CIs) were calculated.

3. Results

3.1. Behavioral results

Clinical ratings of schizophrenia patients and group comparisons on demographics, cognitive function and prospection task performance are shown in Table 1. The two groups were not significantly different in terms of gender ($p = 0.98$), age ($p = 0.55$), years of education ($p = 0.33$) and IQ ($p = 0.09$). Schizophrenia patients and healthy controls did not significantly differ in scores on the VF test ($p = 0.66$). However, schizophrenia patients scored significantly lower on the LNS test (LNS_C, $p = 0.006$; LNS_L, $p = 0.02$) than controls.

In the prospection task, schizophrenia patients generated less internal details ($p = 0.005$) than healthy controls. After controlling for age, gender and years of education, scores on the LNS_C were still significantly correlated with internal detail in the schizophrenia group ($r = 0.47$, $p = 0.006$). In addition, SANS_avolition scores were correlated with internal detail ($r = -0.43$, $p = 0.02$), which was no longer significant after controlling for multiple comparisons. Duration of illness, antipsychotic dosage and PANSS scores were not correlated with any prospection variables in schizophrenia patients ($ps > 0.05$). No significant correlations between LNS scores and prospection variables were found in the control group ($ps > 0.05$).

3.2. GM correlates of prospection

Compared with healthy controls, schizophrenia patients exhibited widespread GM loss across the whole brain. Brain areas which showed reduced GM volume in schizophrenia patients included the medial and lateral PFC, the medial temporal lobe and the hippocampus, the insula and several posterior regions (Figure S1, Table S1).

For schizophrenia patients, internal detail was correlated with GM

Table 1
Demographics, cognitive and prospection performance, and clinical ratings

	SZ (n = 37)	HC (n = 28)	t/X^2	p
Gender	21M/16F	16M/12F	0.001	0.98
Age	42.03(8.44)	40.54(10.87)	0.60	0.55
Education years	12.22(3.57)	13.04(3.02)	−0.98	0.33
IQ	108.29(17.00)	113.76(14.22)	−1.74	0.09
TIV	1536.47(126.19)	1518.58(130.71)	0.53	0.60
LNS_C	12.34(4.19)	15.37(4.05)	−2.86	0.006**
LNS_L	5.15(0.96)	5.82(1.18)	−2.44	0.02*
VF	20.85(5.57)	21.42(3.90)	−0.45	0.66
Internal detail	9.45(3.93)	12.40(4.27)	−2.88	0.005**
External detail	7.91(7.19)	11.30(7.45)	−1.85	0.07
Vividness	4.65(1.25)	5.33(0.94)	−2.42	0.02*
CPZeq (mg/day)	299.76(176.71)			
Duration of illness (years)	18.41(8.92)			
PANSS-N	15.32(5.35)			
PANSS-P	10.05(3.99)			
PANSS-G	25.78(7.04)			
SANS_Affect	6.71(3.92)			
SANS_Alogia	4.66(5.49)			
SANS_Avolition	4.69(3.47)			
SANS_Asociality	5.37(3.23)			
SANS_Attention	0.31(1.13)			

Note: *, p < 0.05; **, p < 0.01; SZ, schizophrenia patients; HC, healthy controls; TIV: total intracranial volume; LNS: the letter number span test; LNS_C: correct span of the LNS test; LNS_L: the longest span of the LNS test; VF: the verbal fluency test; CPZeq: chlorpromazine equivalence; PANSS, Positive and Negative Syndrome Scale; PANSS-P, subscale for positive symptoms in PANSS; PANSS-N, subscale for negative symptoms in PANSS; PANSS-G, subscale for general psychopathological symptoms in PANSS; SANS, Scale of Assessment for Negative Symptoms.

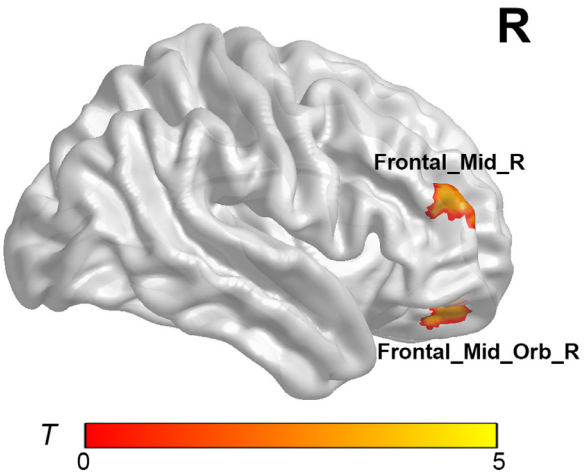

Fig. 1. VBM analysis showed brain regions in which GM loss was associated with decreased internal details in the schizophrenia group (p < 0.001, corrected).

volume of the right lateral PFC and the right ventral medial PFC (Fig. 1). These results are summarized in Table 2. No significant correlation between internal detail and GM volume was observed in controls.

3.3. Correlations and mediation analysis

In the schizophrenia group, after correcting for multiple comparisons, correlation between LNS_C score and GM volume of the right lateral PFC was significant (r = 0.56, p = 0.001), taking age, gender, years of education and TIV as covariates. Before multiple comparison correction, PANSS_N (r = −0.41, p = 0.02), SANS_Avolition (r = −0.35, p = 0.04) and SANS_Asociality (r = −0.36, p = 0.04) scores were found to be correlated with GM volume of the right lateral PFC. However, these correlations did not survive multiple comparisons correction.

Mediation analysis revealed that GM volume of the right lateral PFC mediated the correlation between LNS_C score and internal detail in schizophrenia patients (ab = 0.21, 95% CI [0.03, 0.42]). The direct effect of LNS_C score on internal detail was not significant (c' = 0.21, 95% CI [−0.09, 0.51]) (Fig. 2). Even after controlling for age, gender and negative symptoms, the mediation effect remained significant.

4. Discussion

To the best of our knowledge, the present study is the first to show a direct correlation between prospection impairments and GM loss in schizophrenia patients. Furthermore, we also found a significant correlation between working memory and prospection in these patients, which was mediated by GM volume of the right lateral prefrontal cortex.

We found a specific pattern of structural correlates underlying prospection impairments in schizophrenia patients. These results, along with one of our previous studies (Yang et al., 2019), highlight the correlation between abnormality in the PFC and prospection impairment in schizophrenia. Regions in the PFC could serve as critical hubs in the prospection core network (Andrews-Hanna et al., 2010). While the ventral medial PFC may play a significant role in emotion processing (D'Argembeau et al., 2008b) and information integration (Benoit et al., 2014), the lateral PFC could be responsible for executive control (Ernst et al., 2015; Gerlach et al., 2014) during prospection. Therefore, abnormality in the PFC may lead to disruption of top-down modulation during prospection. These findings suggest that detailed step-by-step instructions could be useful in guiding schizophrenia patients to construct future events in prospection training.

Interestingly, although similar prospection impairments have been found in schizophrenia and several other disorders (e.g. MS, semantic dementia and Alzheimer's disease) at the behavioral level (Ernst et al., 2015; Irish et al., 2012; Irish et al., 2013), these disorders could have different influence on regions in the core network underlying prospection. Our results highlight the involvement of both the ventral medial PFC and the lateral PFC in prospection impairments in schizophrenia, which may facilitate the development of more specific and effective interventions for schizophrenia patients in the future. However, as brain abnormalities other than GM loss may also have a significant impact on prospection in these patients, future studies applying other MRI modalities (e.g. task-related functional imaging) are needed to further explore the neural correlates of prospection impairments in

Table 2
Grey matter correlates of prospection in the schizophrenia group (p < 0.001, corrected)

	Peak MNI coordinates x	y	z	Peak intensity T value	Brain region (aal)	Cluster size
Internal						
	25.5	47.5	−11.5	4.22	Frontal_Mid_Orb_R	1268
	43.5	47.5	20.5	4.64	Frontal_Mid_R	969

Note: Frontal_Mid_Orb_R: right middle orbitofrontal cortex; Frontal_Mid_R: right middle frontal cortex.

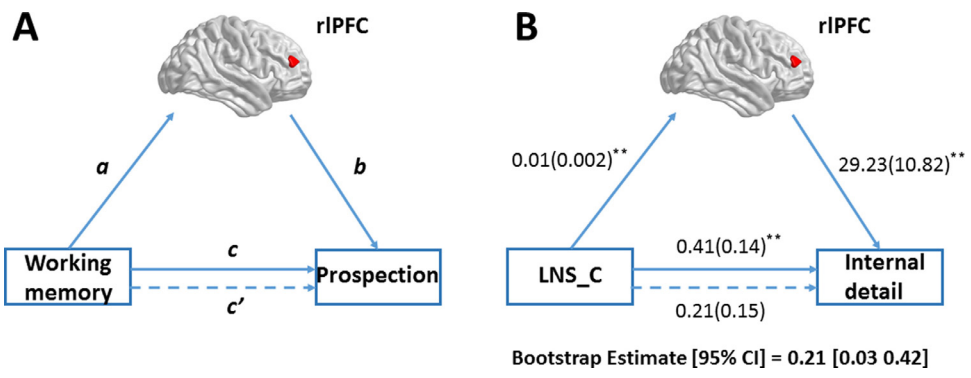

Fig. 2. Mediation analysis. A) Illustration of the mediation model. The total effect (*c*) is comprised of a direct effect (*c'*) and an indirect effect (*ab*). B) GM volume of the right lateral PFC mediates the association between the LNS_C and internal detail in the schizophrenia group. Unstandardized path coefficients are displayed with standard errors in parentheses. rlPFC, right lateral prefrontal cortex; LNS_C, correct span of the letter number span test. **, $p < 0.01$.

schizophrenia patients.

Another important finding is that prospection impairment was correlated with working memory deficit in schizophrenia patients. Moreover, GM volume of the right lateral PFC mediated this correlation. Deficit in working memory is well documented in schizophrenia patients (Lett et al., 2014). In addition, GM loss (Fornito et al., 2009) and abnormal activations (Tan et al., 2005; Stäblein et al., 2019) in the lateral PFC in schizophrenia patients have also been reported by previous researchers. Therefore, it is possible that impaired working memory capacity could be a critical factor which affects the ability to extract and manipulate details comprising future events in schizophrenia patients and the lateral PFC may play a significant role in this process.

There are several limitations in this study. First, we could not rule out the influence of antipsychotic medications, which may affect cognitive performance and GM volume. Future studies using un-medicated first-episode patients as participants could address this issue. Secondly, the hospitalization status of the participants could have an influence on our results. Nevertheless, the inpatients and outpatients in our study did not differ in their prospection performance (all *ps*' > 0.05). Moreover, further analysis of the behavioral data excluding inpatients yielded similar results. Thirdly, working memory was only measured by the LNS test in our study. Assessments capturing different components of working memory (e.g., the central executive, the visuospatial sketchpad, the phonological loop and the episodic buffer) (Baddeley, 2000) may provide more information on how this cognitive function influences prospection in schizophrenia patients. Fourthly, our sample size was relatively small and replication of our findings in larger samples is needed.

In conclusion, we found that reduced GM volume of the prefrontal regions is correlated with impaired prospection performance in schizophrenia patients. Furthermore, GM volume of the right lateral PFC appears to mediate the relationship between working memory and prospection in these patients.

Contributors

ZYY collected, analyzed and interpreted the data, and wrote up the first draft. SKW conducted clinical interview and helped administer the project. YL, HYZ and XLC collected the data and doing literature searching. YW and YMW helped analyzing the data and writing the first draft. EFCC, DHKS and DO commented the manuscript significantly. RCKC generated the idea, interpreted findings and commented the manuscript significantly.

Declaration of Competing Interest

The authors state that there is no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.110987.

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