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Prospective memory performance in patients with drug-naïve, first-episode psychosis

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ABSTRACT

Schizophrenia is associated with an impairment of prospective memory (PM) which refers to the ability to remember to carry out an intended action in the future. However, most of these studies were limited to chronic samples. The current study examined the event-based PM and time-based PM using a dual-task paradigm in 22 drug-naïve, first-episode psychosis (FEP) patients and 23 healthy controls. Results indicated that FEP patients performed significantly poorer than healthy controls in both event-based and time-based PM. However, the significant difference in time-based PM disappeared after controlling for working memory. Correlation analysis indicated that both types of PM did not correlate with positive symptoms or negative symptoms, duration of illness, or duration of untreated psychosis. However, time-based PM was correlated with the general psychopathology subscale of the PANSS. Taken together, these findings suggest that PM deficits are present in drug-naïve FEP patients; impairment of event-based PM appears to occur independently, whereas time-based PM impairment may be, in part, a secondary consequence of a working memory deficit.

1. Introduction

Neurocognitive deficits are key features of schizophrenia (Elvevag and Goldberg, 2000; Keshavan et al., 2008) and are a critical determinant of quality of life and functional outcome (Green et al., 2000; Kurtz et al., 2005; Matza et al., 2006; Kurtz et al., 2008). Substantial evidence also suggests that patients with schizophrenia have deficits in a diverse array of cognitive domains, including working memory, language function, executive function, episodic memory, processing speed, attention, inhibition and sensory processing (Chan et al., 2004; Fioravanti et al., 2005; Chan et al., 2006b; Reichenberg and Harvey, 2007; Mesholam-Gately et al., 2009). Within the context of generalized cognitive deficit, it has been suggested that the most severe impairments are episodic memory and executive control processes (Chan et al., 2004, 2006a, 2006b; Reichenberg and Harvey, 2007).

Prospective memory (PM) is a unique form of episodic memory and has been gaining increasing attention due to its theoretical and functional implications (Kliegel et al., 2008). PM by definition is the ability to remember to carry out an intended action in the future (Kliegel et al., 2008). According to the nature of the cue associated with the future intention, three subtypes of PM have been identified (Shum et al., 2004). The event-based PM refers to remembering to execute an intention when an event/cue appears (e.g., remembering to give a document to a colleague when attending the seminar chaired by that colleague). The time-based PM refers to remembering to execute an intention at a specific time or after a period of time (e.g., remembering to turn up for a medical appointment at 3:00 pm on Monday). The activity-based PM refers to remembering to execute an intention after completion of an activity (e.g., remembering to go shopping after finishing homework) (Wang et al., 2010). Moreover, PM can be divided into different phases of cognitive processing, comprising intention formation, intention retention, intention initiation and intention execution (Kliegel et al., 2011). Accordingly, some cognitive resources such as planning, storage, monitoring and switching of inhibition are required during the PM process (Kliegel et al., 2011). The study of PM is both clinically and theoretically important for patients with schizophrenia, for PM has been implicated in many everyday life activities; it is proposed that PM is mostly mediated by the frontal and medial temporal systems (Kliegel et al., 2011; McDaniel and Einstein, 2011), and dysfunction of the prefrontal cortex and the medial temporal cortex might be especially important for

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patients with schizophrenia (Antonova et al., 2004; Minzenberg et al., 2009).

Growing evidence has consistently identified PM deficits in schizophrenia patients (Elvevag et al., 2003; Shum et al., 2004; Henry et al., 2007; Altgassen et al., 2008; Chan et al., 2008; Ungvari et al., 2008; Wang et al., 2008a, 2008b). A recent meta-analysis found moderate to large effect sizes for PM deficits in patients with schizophrenia (Wang et al., 2009). Three types of PM were all significantly impaired in schizophrenia, with time-based PM being more impaired than event-based PM. Because it is commonly acknowledged that PM is a complex cognitive function involving multiple processes and cognitive variables, some researchers have tried to elucidate the components of PM impairment in patients with schizophrenia by controlling for other cognitive functions such as working memory, executive function and IQ. The results indicate that PM deficits in schizophrenia patients might be due to the impairment of the cue detection and intention retrieval stage (Woods et al., 2007; Wang et al., 2008a). Results of some studies also indicate that PM deficits are a primary impairment rather than a secondary consequence of other cognitive impairments (Henry et al., 2007; Woods et al., 2007; Wang et al., 2008a) whereas other studies found PM deficits to be associated with other cognitive deficits such as impaired retrospective memory (Xiang et al., 2010; Zhou et al., 2012).

However, most of these studies were limited to patients with a long duration of illness and the findings may have been confounded by medication effects and illness duration. There are only two studies identified from the literature that have specifically examined PM performance in patients with first-episode schizophrenia (Lui et al., 2011; Zhou et al., 2012). Lui et al. (2011) found that patients with first-episode schizophrenia performed poorly in both event-based PM and time-based PM as compared to healthy controls. However, when other cognitive functions were controlled, the significant group difference in time-based PM disappeared and the effect size of event-based PM was reduced from large to moderate. Zhou et al. (2012) replicated a similar finding of PM deficits in patients with first-episode schizophrenia using an ecologically-valid test of PM. Once again, when age, gender, education, and other neurocognitive tests were controlled, the event-based PM and time-based PM differences between groups disappeared. Despite the fact that these two studies recruited first-episode schizophrenia patients, most of their subjects were receiving atypical antipsychotic medication. It is still not clearly known whether PM deficits observed in patients with schizophrenia are the effect of the illness or a result of medication. A recent meta-analysis indicated that PM may have an inverse relationship with antipsychotic medication dosage (Wang et al., 2009). Therefore it is important to rule out the potential medication effect upon PM performance in patients with schizophrenia.

This study aimed to clarify these confounding factors by examining a first-episode drug-naïve sample with a relatively short illness duration. In the present study, only event-based PM and time-based PM based on a modified PM paradigm were evaluated. Activity-based PM was not included because a meta-analysis suggested that impairments of time-based PM and event-based PM in schizophrenia have larger mean effect sizes than activity-based PM (Wang et al., 2009). Moreover, the task for activity-based PM is different from the tasks for time-based PM and event-based PM (Wang et al., 2008b, 2009; Lui et al., 2011). We hypothesized that event-based PM and time-based PM in patients with first-episode psychosis (FEP) are both impaired. We also hypothesized that other cognitive domains, such as working memory, have differential effects on event-based and time-based PM in FEP patients.

2. Methods

2.1. Participants

This study was conducted at the Shanghai Mental Health Center. Those first episode psychosis patients with significant symptoms but in relatively stable clinical condition (e.g., be quiet and cooperative without obviously aggressive behavior or suicidal attempt) are admitted to the First Episode Psychosis Specialty Unit; psychotic patients in unstable clinical condition (e.g., risk to himself or herself, or others) are admitted to other units (ICU ward). Potential drug-naïve research subjects were recruited from the First Episode Psychosis Specialty Unit if their treating clinicians determined that they were capable of providing informed consent, met inclusionary and exclusionary criteria and were clinically stable enough to complete the testing procedure which took no more than 40 min. Twenty-two patients were enrolled; 15 were male and 7 female, the mean age was 26.6 years old, the mean education level was 12.6 years, and the mean duration of illness was 6.1 months. All patients were diagnosed with schizophrenia or schizophreniform disorder; 17 patients with schizophreniform disorder and 5 patients with schizophrenia. All subjects diagnosed with schizophreniform disorder at the time of study enrollment were subsequently diagnosed with schizophrenia after 6 months of illness duration.

A diagnosis of schizophrenia or schizophreniform disorder was confirmed by a research psychiatrist (D.L.) using MINI plus v 5.0 (Sheehan et al., 1998). Exclusion criteria for the study included: (1) inability to provide informed consent, (2) current substance abuse, (3) personality disorders, (4) mental retardation, (5) significant medical conditions including severe cardiovascular, hepatic, renal disease, and (6) pregnancy or breastfeeding.

Twenty-three healthy controls were recruited from the local community; 16 were male and 7 were female; the mean age was 26.8 years old; the mean education level was 13.6 years. All subjects completed the structured clinical interview performed by a research psychiatrist (D.L.) using MINI plus v 5.0. Those with other Axis I mental disorders, neurological diseases, or positive family history of mental illness were excluded.

Clinical symptoms were assessed using the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987, 1989); and the Clinical Global Impressions-severity scale (CGI) (Guy and Bonato, 1976). This study was approved by the Institutional Review Board of Shanghai Mental Health Center. Written informed consent was obtained from all participants.

2.2. Measures

2.2.1. Prospective memory tasks

Event-based PM and time-based PM computerized tasks were designed based on the dual-task paradigm of Einstein and McDaniel (1990). Compared to the traditional dual task paradigm, a different task design was adopted in our study. In the same session, participants were required to complete an event-based PM task and time-based PM task while simultaneously performing an on-going task.

The ongoing task was a simple category task: a noun was presented in green letters above the center of the screen, while 4 different words indicating the category were shown at the bottom of the screen (i.e. commodity, animal, plant and people). The participants were asked to respond by categorizing the noun by clicking on the appropriate category button, for example, commodity for fan and animal for elephant. Each session comprised 4 blocks and each block contained 50 trials. The task used 100 nouns which were selected from a text book and reading material used in Chinese primary schools (Shanghai Educational Publishing House). Each category contained 25 words; 50 words were randomly selected for block 1, and the remaining 50 words were included in the 2nd block. The selection of words for blocks 3 and 4 used the same procedure. There was a 1 minute time interval between each block during which short stories were presented.

The event-based PM task required participants to suspend the ongoing task and switch to the PM task by pressing the spacebar when the word was presented in blue (target cue). A method of

gradually increasing cued targets was adopted in the event-based PM task (Graf and Uttl, 2001; Zhao et al., 2003), i.e., 1 PM trial was presented in Block 1, 2 PM trials were presented in Block 2, 4 PM trials were presented in Block 3, and 6 PM trials were presented in Block 4. In total, 187 were ongoing task trials and 13 were PM task trials among the 200 trials.

Time-based PM required participants to monitor the clock which was presented on the upper left of the screen during the ongoing task. They were asked to press the ctrl key when the clock reached a multiple number of 2 min (i.e. 2:00, 4:00, 6:00, and 8:00). Responses within ±5 s (e.g. 1:55–2:05) were recorded as correct.

Detailed explanations were given to the participants by the researchers before the trial and their comprehension of the procedure was confirmed. Practice trials were given before each session. At the start of the session, following an introduction, instructions were given to the participants as follows: "there will be a noun in green presented above the center of the screen, and four different words indicating the category shown at the bottom of the screen; please judge the category of the noun by clicking on the appropriate category button, for example, commodity for fan, animal for elephant. Sometimes the word is shown in blue instead of green; please press the spacebar no matter which category the word belongs to — you need not click on the appropriate category button in this situation. At the same time, please monitor the time throughout the experiment, each time the clock reaches a number which is a multiple of 2 min, please press the ctrl key immediately. The latter two tasks are as important as the previous category judgment task. Do you understand?". Following the instruction a spatial span test lasting for about 5 min was presented as an interference task. After the interference task, a central fovea was presented on the screen for 1000 ms before the ongoing task began. The procedure in every trial was: stimulus presentation–reaction by the participant–trial end. The stimulus would disappear in 4 s if the participant didn't respond or took too long to respond (i.e. the longest duration of presentation was 4 s). Fig. 1 illustrates the ongoing task, event-based PM task and time-based PM task.

Following the ongoing task and PM task, participants were asked to tell whether words presented on the screen were shown in the previous session, which was a retrospective item-recognition memory (RM) task developed by our team. There were a total of 80 trials, including 40 words randomly selected from 100 words shown before and an additional 40 words which had not been used in the previous session (new words), all selected from the same text book and reading material. The rate of correct responses was recorded for each participant.

2.2.2. Working memory

The Spatial Span Task from the Wechsler Memory Scale, 3rd ed, was selected for measuring visuospatial (nonverbal) working memory (WM), which included forward and backward sections. The total score was the sum of the forward and backward total scores.

2.3. Procedure

Participants were given a general introduction to the study and all questions were answered before informed consent was obtained. The interference task (a spatial span test) was administered after instructions for the PM task and before actual performance of the ongoing task and PM task. Assessments following the PM task were given in the following order: retrospective memory task, clinical interview, PANSS and CGI evaluation.

2.4. Data analysis

Since event-based PM tasks were presented at an increasing frequency in successive blocks, a weighted scoring system was adopted. Scores for event-based PM task trials in Blocks 1 to 4 were weighted as 1, 1/2, 1/4, and 1/6 respectively (for 1 PM task trial in Block 1, 2 PM task trials in Block 2, 4 PM task trials in Block 3, and 6 PM task trials in Block 4). The total event-based PM score referred to the total score of weighted number of correct responses across blocks. Time-based PM scored 1 for each correct response. All PM scores were transformed to a Z score and added together to generate a single index (Z_PM).

Demographic variables and clinical characteristics were analyzed by a *t* test and chi-square test. PM, WM and RM scores were analyzed by *t* test. Since working memory was found to correlate with PM performance (West et al., 2006; Wang et al., 2008b; Kliegel et al., 2011), working memory was controlled as a covariate in subsequent analyses. Univariate analysis of covariance (ANCOVAs) was performed to assess the group difference on time-based PM and event-based PM controlling for working memory. Pearson correlation analysis was used to examine the relationship between PM and other cognitive functions, demographic variables and clinical characteristics, with α adjusted according to Bonferroni's correction (Cupples et al., 1984; Curtin and Schulz, 1998). Stepwise multiple linear regression analyses were used to identify factors that were independently associated with performance on two types of PM in patients. Cohen's *d* and partial η^2 were calculated as a measure of the extent of difference of PM and other memory performances between patients and healthy controls.

3. Results

3.1. Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristic of the two study groups (FEP patients and healthy controls). There were no significant differences between schizophrenia patients and healthy controls in age, gender and education.

3.2. Prospective memory and other memory performance

Table 2 and Fig. 2 show the prospective memory and other memory performance of the FEP patients and healthy controls.

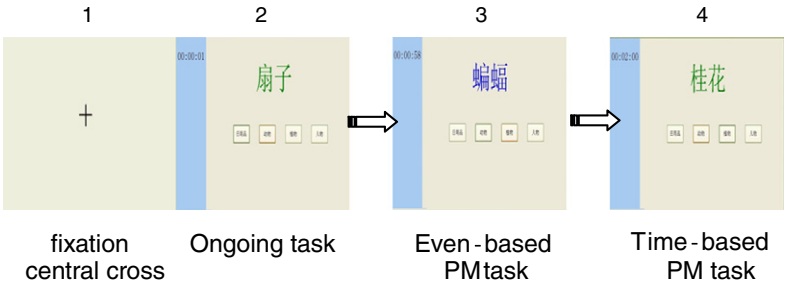

Fig. 1. Schema for event-based PM task and time-based PM task. (Frame 1: fixation on the central cross; Frame 2: ongoing task; Frame 3: event-based PM task; Frame 4: time-based PM task.)

For PM performance, patients scored significantly lower than healthy controls on both event-based PM ($t=-2.489$, $p=0.02$, Cohen's $d=0.76$) and time-based PM ($t=-2.459$, $p=0.019$, Cohen's $d=0.74$). All of the PM scores were transformed to a Z score and added together to generate a single index of PM function: Z_PM, which also significantly differed between FEP patients and healthy controls ($t=-3.445$, $p=0.002$, Cohen's $d=1.041$); first-episode patients performed significantly poorer than controls.

For working memory, FEP patients performed significantly poorer than healthy controls on the spatial span task ($t=-3.093$, $p=0.003$, Cohen's $d=0.922$). There was a trend difference between the two groups in retrospective memory ($t=-2.02$, $p=0.053$, Cohen's $d=0.612$).

After controlling for working memory, event-based PM significantly differed between FEP patients and healthy controls ($F(1, 42)=4.647$, $p=0.037$, partial $\eta^2=0.10$), while no significant difference was found between groups for time-based PM ($F(1, 42)=2.005$, $p=0.164$, partial $\eta^2=0.046$).

3.3. Correlational analysis

In the healthy control group, event-based PM and time-based PM were not correlated with age, education, working memory or retrospective memory (p's >0.05).

The results of correlational analyses in the patient group are shown in Table 3. Event-based PM performance was positively correlated with education level ($r=0.499$, $p=0.018$), and not correlated with age, other cognitive functions nor clinical symptoms. Time-based PM was positively correlated with the general psychopathology subscale scores ($r=0.62$, $p=0.002$), but not with other cognitive or psychopathology measures. After Bonferroni's correction of α level (Cupples et al., 1984; Curtin and Schulz, 1998), only the correlation between time-based PM and the general psychopathology subscale scores was still significant.

Stepwise multiple regression analysis was performed to identify potential predictors for event-based PM and time-based PM in FEP patients. Candidate predictors were those variables previously identified as potentially affecting PM performance in schizophrenia patients (Wang et al., 2009). Table 4 shows that lower education level contributed to poorer event-based PM performance, while higher general psychopathology symptoms contributed to better time-based PM performance.

Table 1
Demographic and clinical characteristics of the study sample.

Characteristics	FEP patients (n=22)	Healthy controls (n=23)	Group comparison	
	Mean (SD)	Mean (SD)	t	p
Age (years)	26.6 (7.2)	26.8 (6.5)	−0.111	0.912
Education (years)	12.6 (2.5)	13.6 (2.0)	−1.435	0.159
DUP (months)	14.1 (13.8)	–		
Course of illness (months)	6.1 (9.5)	–		
PANSS-total	78.7 (7.0)	–		
PANSS-positive	22.3 (5.1)	–		
PANSS-negative	16.5 (4.9)	–		
PANSS-general	39.9 (4.2)	–		
CGI-severity	5.7 (0.6)	–		
	N (%)	N (%)	x^2	p
Gender				
Male	15 (68.2)	16 (69.6)	0.010	0.920
Female	7 (31.8)	7 (30.4)		

Notes: 1) PANSS: Positive and Negative Syndrome Scale, which includes positive symptoms, negative symptoms and general psychopathology subscales. 2) CGI: Clinical Global Impression. 3) DUP: duration of untreated psychosis. 4) FEP: First-Episode Psychosis.

Table 2
Prospective memory and other memory performance between schizophrenia patients and healthy controls.

	FEP patients (n=22)	Healthy controls (n=23)	Group comparison		Cohen's d
	Mean (SD)	Mean (SD)	t	p	
Prospective memory					
Event-based PM	3.0 (1.38)	3.78 (0.49)	−2.489	**0.020**	**0.755**
Time-based PM	1.77 (1.69)	2.83 (1.11)	−2.459	**0.019**	**0.74**
Z_PM	−0.72 (1.73)	0.69 (0.86)	−3.445	**0.002**	**1.041**
Working memory					
Spatial span	13.36 (3.14)	16.09 (2.76)	−3.093	**0.003**	**0.922**
Retrospective memory					
Item recognition	0.8 (0.12)	0.86 (0.05)	−2.02	0.053	**0.612**

Notes: PM: prospective memory; Z_PM: sum of Z scores of PM performance; FEP: First-Episode Psychosis. In p column, those less than 0.05 were in bold; in Cohen's d column, those larger than 0.5 (absolute value) were in bold, indicating medium or greater effect size (Cohen, 1988).

4. Discussion

The current findings show that event-based PM and time-based PM in first-episode psychosis are impaired, which is consistent with previous studies on PM in chronic schizophrenia patients (Shum et al., 2004; Woods et al., 2007; Ungvari et al., 2008; Wang et al., 2008a) and two recent studies on PM in first-episode schizophrenia patients (Lui et al., 2011; Zhou et al., 2012). After controlling for working memory, the differences in event-based PM between groups remained significant, while no significant difference was found between groups for time-based PM. This finding suggests that working memory deficit may contribute to the time-based PM impairment in patients with first-episode psychosis.

In the study by Lui et al., the first-episode schizophrenia patients performed poorly in both event-based PM and time-based PM; however, when other cognitive functions were controlled, the significant group difference in time-based PM disappeared while the difference in event-based PM remained (Lui et al., 2011), suggesting that the event-based PM is more independent. The results from the present study support this conclusion. After controlling for working memory, the significant group difference in time-based PM disappeared, but the difference in event-based PM remained, indicating that working memory has a different effect on the event-based PM and time-based PM.

These results are understandable when the nature, experiment paradigm and theoretical distinction between event-based PM and time-based PM are considered. Event-based PM tasks must be performed when a specific target event occurs in the environment with PM tasks often embedded in the ongoing tasks. Attention is switched between the ongoing tasks and PM tasks when a PM task is prompted by an external event cue. However, time-based PM

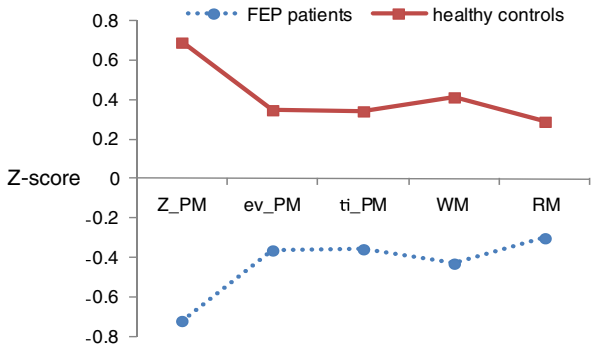

Fig. 2. Prospective memory and other memory profiles between FEP patients and healthy controls.

Table 3
Correlation between PM and demographic, clinical variables and other neurocognitive functions in first-episode psychosis patients.

	Event-based PM	Time-based PM
Age	−0.03	−0.33
Education	0.50	−0.03
DUP	0.19	0.33
Course of illness	0.03	<0.01
Retrospective memory	−0.06	0.13
Working memory	0.12	0.39
PANSS-total	0.02	0.39
PANSS-positive	0.20	−0.01
PANSS-negative	−0.15	0.05
PANSS-general	−0.04	0.62*
CGI-severity	−0.13	0.39

Notes: PM: prospective memory; PANSS: Positive and Negative Syndrome Scale, which includes positive symptoms, negative symptoms and general psychopathology subscales; CGI: Clinical Global Impression; DUP: Duration of Untreated Psychosis. According to the Bonferroni's rule, $\alpha' =$ overall-$\alpha/k = 0.0045$ (Cupples et al., 1984; Curtin and Schulz, 1998).
* $p < .0045$.

tasks involve an action that must be carried out at a certain clock time or after a set amount of time, which requires more self-initiation and perhaps more time monitoring. As a result, event-based PM and time-based PM might be correlated differently with other neurocognitive domains such as attention and working memory (Ellis, 1996; Kliegel et al., 2008; Rose et al., 2010). This is in line with a recent review which proposed that an impairment in proactive control reflecting deficits in dorsolateral prefrontal cortical function could underlie both time-based PM and WM impairments (Barch and Ceaser, 2012). Further research is warranted to explore the relationship between time-based PM impairment and working memory deficit in schizophrenia patients, for the working memory test used in the current study is relatively preliminary and crude, and the working memory loads were not manipulated.

It is of great interest for clinicians to link clinical characteristics to cognitive deficits. Previous studies found neurocognitive impairment to be significantly but modestly correlated with negative symptoms, but not with positive symptoms (Dibben et al., 2009; Dominguez Mde et al., 2009). Similarly, previous studies in chronic schizophrenia patients indicated that PM is not correlated significantly with positive symptoms, but correlated significantly with negative symptoms, duration of illness and medication dosage (Wang et al., 2009). We found no significant correlation between both types of PM and positive or negative symptoms, although time-based PM was found to be correlated with the general psychopathology subscale of the PANSS — a heterogeneous collection of 16 symptoms of schizophrenia exclusive of positive or negative symptoms. Additionally, no correlation between either type of PM and illness duration or duration of untreated psychosis (DUP) was found, which is consistent with another study in first-episode schizophrenia patients (Lui et al., 2011), but different from that of Zhou et al. (2012). These conflicting results may result from small sample sizes and might reflect the fact that patients at the very early stage of schizophrenia present with less severe negative symptoms. In addition, medications might affect PM performance in schizophrenia patients (Wang et al., 2009; Zhou et al., 2012). Longitudinal follow-up studies are required to further clarify the relationship between PM, negative symptoms and illness duration.

Table 4
Results of the stepwise multiple regression analyses in patients.

PM task	Predictor	Beta	*p*-Value	95% CI
Event-based PM $R^2 = 0.249$; $F(1,20) = 6.623$; $p = 0.018$	Education	0.275	0.018	0.052, 0.499
Time-based PM $R^2 = 0.384$; $F(1,20) = 12.477$; $p = 0.002$	PANSS-general	0.252	0.002	0.103, 0.401

Notes: PM = prospective memory; PANSS = Positive and Negative Syndrome Scale, PANSS-general indicates the general psychopathology subscales.

It is important to note several limitations of this study. First, the patient sample size is relatively small. Second, given the dual-task nature of PM tasks, it is understandable that PM involves or can be correlated with many other cognitive functions, such as working memory, other memory functions, cognitive flexibility and attention (Lui et al., 2011). In the present study, cognitive flexibility and attention were not measured and controlled and the working memory loads were not manipulated. Finally, some previous studies have indicated that PM impairment in schizophrenia might reflect impairment in the third phase of PM (intention initiation), that is, deficits in cue detection and intention retrieval underlie the PM impairment in schizophrenia (Woods et al., 2007; Wang et al., 2008a), however, the neuropsychological mechanisms accounting for PM deficits in schizophrenia were not addressed.

This study is one of the few studies to investigate PM deficits in FEP patients, and it is the first to eliminate the confounding factor of medication by recruiting drug-naïve patients. Our results indicate that event-based PM and time-based PM in first-episode psychosis are both impaired; the impairment of event-based PM appears to occur independently, whereas time-based PM impairment may be, in part, a secondary consequence of a working memory deficit and general psychopathology.

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Contributors
All authors were responsible for the analysis and interpretation of the data, and the writing of the paper.

Conflict of interest
All authors declare that they have no conflicts of interest.

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