Available online at www.sciencedirect.com
ScienceDirect
Schizophrenia Research 105 (2008) 114 – 124
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

Prospective memory in schizophrenia: Further clarification of nature of impairment

Ya Wang [a,b], Raymond C.K. Chan [a,c,d,*,1], Xiaohong Hong [e], Zheng Ma [f], Tianxiao Yang [a], Lan Guo [b], Xin Yu [g], Zhanjiang Li [f], Yanbo Yuan [g], Qi-yong Gong [h], David Shum [i]

[a] Neuropsychology and Applied Cognitive Neuroscience Laboratory, Department of Psychology, Sun Yat-Sen University, Guangzhou, China
[b] School of Life Sciences, Sun Yat-Sen University, Guangzhou, China
[c] Neuropsychology and Applied Cognitive Neuroscience Laboratory, Institute of Psychology, Chinese Academy of Sciences, Beijing, China
[d] Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China
[e] Mental Health Center, Shantou University, Shantou, China
[f] Beijing Anding Hospital, Beijing, China
[g] Institute of Mental Health, Peking University, Beijing, China
[h] Huaxi MR Research Centre, Department of Radiology, West China Hospital/West China School of Medicine, Sichuan University, Chengdu, China
[i] Griffith Institute of Health and Medical Research, Griffith University, Brisbane, Australia

Received 21 April 2008; received in revised form 16 June 2008; accepted 1 July 2008
Available online 15 August 2008

Abstract

Prospective memory (PM) refers to the ability to execute a delayed intention and is different from retrospective memory (RM) in its nature and underlying mechanism (e.g., intention formation, maintenance, detection of PM cue and intention execution). Although preliminary studies have found PM impairment in patients with schizophrenia, the nature and magnitude of this problem in this clinical group is not yet fully known. The current study aimed to further clarify the nature of this impairment in schizophrenia. Fifty-four patients with schizophrenia and fifty-four healthy volunteers matched on demographic variables, IQ and executive functions took part in the study. Time-, event-, and activity-based PM tasks and a set of neurocognitive tests were administered to the participants. Results showed that patients with schizophrenia performed significantly worse on all sub-types of PM tasks, even after controlling for neurocognitive functions such as working memory, verbal memory, visual memory, and executive function. These findings suggest PM deficit is a primary deficit rather than a secondary consequence of neurocognitive impairments in schizophrenia. Analysis found that PM deficits may be mainly due to the impairment of the cue detection and intention retrieval stage.

Keywords: Schizophrenia; Prospective memory; Neurocognitive function, Cue detection

1. Introduction

Meta-analytic studies have indicated that patients with schizophrenia show severe memory impairment in various domains (Aleman et al., 1999; Heinrichs and

* Corresponding author. Institute of Psychology, Chinese Academy of Sciences, 4A Datun Road, Beijing 100101, China. Tel.: +8610 64836274.
E-mail addresses: rckchan@psych.ac.cn, rckchan2003@yahoo.com.hk (R.C.K. Chan).
[1] Raymond Chan and the Neuropsychology and Applied Cognitive Neuroscience Laboratory have moved to the Institute of Psychology.

0920-9964/$ - see front matter
doi:10.1016/j.schres.2008.07.002

Zakzanis, 1998; Lee and Park, 2005; Pelletier et al., 2005; Piskulic et al., 2007). However, most previous studies were limited to the study of retrospective memory (RM), that is, the memory for past information.

In recent years, researchers have shifted their attention to study memory deficits in schizophrenia involving prospective memory (PM), the ability to remember do something at a particular moment in the future, or the timely execution of an intended goal. PM is considered important for both healthy people and clinical groups because impairments in PM (e.g., forgetting to turn up for appointments or take medication) have implications for everyday functioning and independent living in the community. Preliminary findings also suggest that there may be dissociation between subjective complaints of PM impairments in everyday life and corresponding objective performances (Chan et al., 2008b). PM impairments have also been reported by caregivers of Alzheimer's patients as more frustrating than RM impairments (Smith et al., 2000). These findings have significant implications for the management and rehabilitation of patients with schizophrenia and other neurological disorders (Kurtz et al., 2001; Shum et al., 2003; Smith et al., 2000).

Theoretically, PM can be divided into three types according to the nature of cues. They are time-based PM, meaning to execute an intention at an exact time or after a specific period of time (e.g., to remember to have a meeting at 6:00 pm); event-based PM, meaning to execute an intention when an event or cue appears (e.g., to remember to give a message when a classmate turn up); and activity-based PM, meaning to execute an intention after finishing another task (e.g., to remember to reply to an email after lunch) (Einstein and McDaniel, 1990; Kvavilashvili and Ellis, 1996). Moreover, there are several stages underlying PM performance, namely (1) forming an intention; (2) maintaining the intention; (3) detection of cue for retrieval of the intention; and (4) execution of the intention (Ellis, 1996).

To date, nine studies have examined the PM deficits in schizophrenia (Chan et al., 2008b; Elvevag et al., 2003; Henry et al., 2007; Kondel, 2002; Kumar et al., 2005; Shum et al., 2004; Twamley et al., in press; Wang et al., in press; Woods et al., 2007). Among these studies, two (viz., Kondel, 2002; Twamley et al., in press) did not include a control group, and two (viz., Elvevag et al., 2003; Kumar et al., 2005) focused on only one type of PM. Only five of the studies adopted a more systematic approach to examine PM in schizophrenia.

Shum et al. (2004) found that patients with schizophrenia performed significantly worse than controls on all three types of PM (time-, event-, and activity-based). However, Shum et al. did not study the relationship between PM performance and clinical variables such as medication and duration of illness.

Woods et al. (2007) used the Memory for Intentions Screening Test (MIST) and found that these patients had comparable deficits on time- and event-based PM tasks; and the participants did not show significant difference on recognition trials after completion of all PM tasks. The authors, therefore, concluded that the PM deficits of schizophrenic patients occurred mainly in the cue detection and intention retrieval stage, and that the first two stages (viz., intention formation and intention maintenance) were relatively intact. Henry et al. (2007) used the virtual week test and found that schizophrenia patients were impaired on PM, irrespective of specific PM task demands. The authors demonstrated that the PM deficits in patients still remained significant after controlling for IQ, executive function and RM, and suggested that the PM deficits observed in these patients were primary not secondary impairments of schizophrenia. However, the Henry et al. (2007) and Woods et al. (2007) studies had relatively small ($N=30$ for Henry et al., 2007; $N=41$ for Woods et al., 2007) sample sizes and were limited by the heterogeneous sample with a wider range of participants such as schizoaffective disorder patients. We need to validate their results in another sample with reasonable sample size.

Wang et al. (in press) found that patients with schizophrenia and individuals with psychometrically defined schizotypal personality were impaired in time- and event-based PM. However, the generalizability of their findings was limited by the small sample size. Although a subsequent independent study (Chan et al., 2008b) with a larger sample corroborated the original findings, these two studies have not specifically addressed the issue of whether PM deficit is a primary or secondary cause in schizophrenia (refer to Henry et al., 2007).

It has been found that executive function plays an important role in PM (Kondel, 2002; Shum et al., 2004; Woods et al., 2007), and that IQ may also be related to PM. However, previous studies that examined PM in patients with schizophrenia did not measure executive function (Elvevag et al., 2003; Wang et al., in press; Woods et al., 2007) or did not match this function in of patients and controls (Chan et al., 2008b; Henry et al., 2007; Shum et al., 2004). Similarly, many of the previous studies did not measure or match the IQ of patients and controls (Chan et al., 2008b; Kumar et al., 2005; Shum et al., 2004; Wang et al., in press; Woods et al., 2007). Careful matching of these two variables between patients and control is important to determine and clarify the nature of PM in schizophrenia.

The purpose of this study was twofold. The main purpose was to recruit an independent sample of patients with schizophrenia (matched in demographics, executive function and IQ with controls) to further examine whether PM deficit shown in schizophrenia is a primary deficit or secondary to other aspects of neurocognitive functions associated with schizophrenia. Given the prior preliminary findings of Henry et al. (2007), we hypothesized that patients with schizophrenia would have impairments in time- and event-based PM; and these deficits would be the primary deficits not secondary to other neurocognitive functions. The second and subsidiary purpose was to examine the specific effect of cue detection on PM performances in schizophrenia. Given that Woods et al. (2007) showed that patients with schizophrenia could recognize the PM tasks requirements following the completion of the PM test, we hypothesized that the observed PM deficits would mainly occur in the cue detection and intention retrieval phases.

2. Method

2.1. Participants

Fifty-four patients fulfilling the diagnostic criteria of DSM-IV (American Psychiatric Association, 1994) for schizophrenia based on diagnostic interviewing (using the Structural Clinical Interview for DSM-IV and medical record reviews) were recruited from three regional psychiatric hospitals in China (Mental Health Center of Shantou University; Beijing Anding Hospital; and Institute of Mental Health of Peking University). Patients with a history of neurological illness or alcohol/drug dependence (according to clinical records, information from clinician and interview with the patients) were excluded. Subtypes of schizophrenic patients in the sample included: paranoid, catatonic, and undifferentiated. All the patients were taking typical or atypical antipsychotic medications (Chlorpromazine equivalence see Table 1). Clinical symptoms were rated using the Positive and Negative Symptom Scale (PANSS, Kay et al., 1987). Medication side effects were assessed using the Abnormal Involuntary Movement Scale (AIMS, Smith et al., 1979) and Barnes Akathisia Rating Scale (BARS, Barnes, 1989).

Fifty-four healthy controls were recruited from a number of colleges and communities in China. A semi-structured interview was conducted by a trained research assistant to ascertain that none of the healthy controls had any family history of psychiatric illness, or suffered from a neurological illness or alcohol/drug dependence.

Table 1
Demographic and clinical information of participants

	Schizophrenia (N= 54)		Control (N= 54)		p
	Mean	SD	Mean	SD	
Male:female	49:5		31:23		0.0005
Right handed percentage	92.59		98.15		0.214
Age	30.02	9.79	29.54	9.92	0.800
Education	12.37	2.92	12.70	3.20	0.573
IQ	101.37	20.32	105.43	18.34	0.279
WCST perseverative error	4.73	6.46	3.70	6.84	0.481
WCST category	4.25	2.00	4.78	1.89	0.221
Verbal fluency correct	19.59	5.36	20.08	5.53	0.657
Duration of illness (year)	7.23	8.51			
Medication*	345.86	250.43			
Medication side effect					
Abnormal Involuntary Movement Scale	2.18	1.96			
Barnes Akathisia Rating Scale	1.24	1.59			
Positive and Negative Symptom Scale					
Positive symptoms	14.22	4.32			
Negative symptoms	16.02	4.88			
General psychopathology	29.28	5.69			
Total score	59.52	10.67			

*Chlorpromazine equivalence mg/day. WCST = Wisconsin Card Sorting Test.
Forty-four patients and 40 controls finished WCST; 46 patients and 53 controls finished verbal fluency test.

Intellectual functioning was estimated by the short form (information, arithmetic, similarity, and digit span subtests) of the Chinese version of the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (Gong, 1992). This method of prorating has been used previously to estimate IQ in schizophrenia (Allen et al., 1997; Blyler et al., 2000; Chan et al., 2005). Handedness was assessed by the Annett Handedness Scale (Spreen and Strauss, 1991). The demographic information of the participants is shown in Table 1. Although there was a significant difference between the two groups in gender proportion (p=0.0005), gender did not significantly correlate with PM performances (p ranges from 0.062 to 0.777) or other neuropsychological tests (p ranges from 0.150 to 0.841) in the current sample. Therefore, we did not perform any detailed gender effects in the subsequent analyses. The two groups did not differ significantly in age, education, IQ, or executive function (as measured by Wisconsin Card Sorting Test and verbal fluency), refer to Table 1 for details. The present study was approved by the ethics committees of all the corresponding institutes. Written informed consent was obtained from each participant.

2.2. Measures

2.2.1. PM tasks

Detailed description of the PM tasks used in this study can be found in Wang et al. (in press). Briefly, there were two versions of the task (i.e., semantic and perceptual) in order to control for semantic memory. In the semantic event-based PM (se_ev) task, a four-character phrase was presented in the center of the screen and the participants were asked to judge whether the phrases were idioms or not. They were asked to press the "J" key to answer affirmatively and the "F" key to answer negatively (this was defined as the ongoing task). If there was an animal character (e.g., horse) in the phrase, they were asked to press the spacebar (this was defined as the PM task). A total of 5 animal characters appeared during the session and the time interval between the appearances of each animal character was approximately 1 min. The participants were told that the two tasks (the ongoing and the PM task) were of equal importance. There were 88 ongoing task trials and 5 PM task trials in this session.

The semantic time-based PM (se_ti) task was basically the same as the semantic event-based PM task except that a clock was placed to the upper right of the keyboard (to ensure time monitoring is not confounded by movement agility, the clock was placed in a position such that participants could see the time clearly without much physical movement of the head). In undertaking this task, participants were asked to monitor the time throughout the experimental session. Each time the clock reached the minute (e.g., 12:23:00, the last two digits are 00), they were asked to press the spacebar (PM task). This session lasted about five and a half minutes. Also, there were no animal characters included in any of the phrases of this task. There were 90 ongoing task trials and 5 PM task trials in this session.

The perceptual event-based PM (pe_ev) task was basically the same as se_ev except that the ongoing task was to judge whether a perceptually degraded digit in the center of the screen was an '0'. Participants were asked to press the "J" key if it was and the "F" key if it was not. On occasions that there was a down arrow under the degraded digit, participants were asked to press the spacebar irrespective of whether the digit was 0 or not, and this was defined as the PM task. There were 122 ongoing task trials and 5 PM task trials in this session.

The perceptual time-based PM (pe_ti) task was basically the same as the pe_ev except that a clock was placed to the upper right of the keyboard and participants were asked to monitor the clock and press the spacebar each time the clock reach the minute. No down arrows appeared under any of the digits in this session. There were 135 ongoing task trials and 5 PM task trials in this session.

At the end of each of the above sessions, participants saw the words "Thank you for your participation! Bye" on the screen and were instructed to press the "Enter" key upon seeing this sentence. This was defined as the activity-based PM task. The activity-based PM performance was the proportion of "Enter" key pressed for these four occasions. For graphic illustration of the experiment flow, see Fig. 1.

To clarify the stage (s) of PM that are likely to be impaired, after finishing each session the participants were asked to recall the PM requirements of the task in that session to check if they could remember the task requirements. If they could not recall, they were given a prompt by asking in which condition they were supposed to press the "spacebar".

2.2.2. Other neurocognitive tests

A set of comprehensive tests capturing neurocognitive functions was also administered to all participants. Details of these tests have been described elsewhere (Chan et al., 2006a,b, 2004, 2008b). In brief, working memory was assessed by the Chinese version of Letter–Number Span Test (Chan et al., 2008a) and n-back[2] (2-back data were used in the present study) (Callicott et al., 1998); verbal memory and visual memory were assessed by the logical memory and visual reproduction subscales of the Wechsler Memory Scale—Revised (Wechsler, 1987; Chinese version, Gong et al., 1989); executive function was evaluated by the modified Wisconsin Card Sorting Test (WCST, Nelson, 1976) and the animal name semantic verbal fluency test (Spreen and Strauss, 1998).

2.3. Procedure

Participants were given a general introduction to the study as well as the opportunity to ask questions. Participants and their guardians gave informed consent before testing began. IQ subscales were administered to the participants first. The four PM tasks were given in the following order: semantic time-based, perceptual event-based, semantic event-based and perceptual time-based.

[2] In the n-back test, subjects viewed randomly presented numbers on the computer screen; during the 0-back task, subjects are required to identify the number currently seen; during the 1-back task, subjects are required to identify the number seen in the previous screen; during the 2-back task, subjects are required to identify the number seen two screens before.

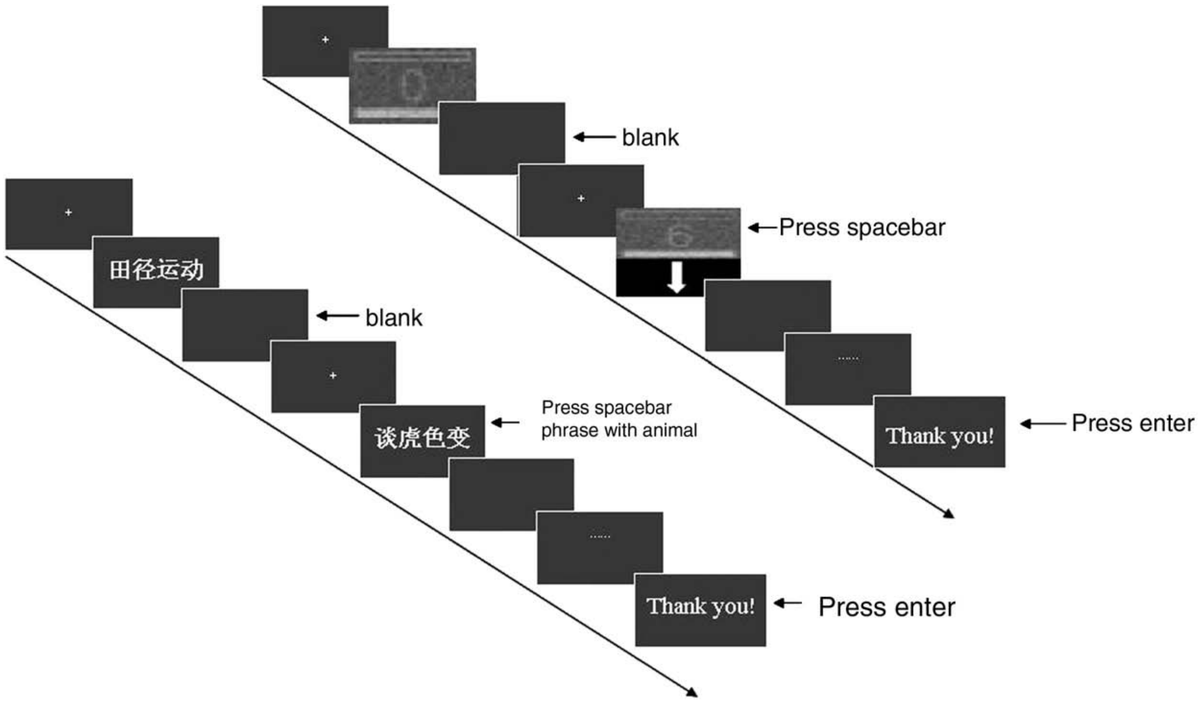

Fig. 1. Illustration of the prospective memory experiment.

Finally, participants were interviewed and patients were rated using the PANSS, AIMS, and BARS.

2.4. Data analysis

Semantic event-based and perceptual event-based PM task performance were averaged to generate an event-based PM score; semantic time-based and perceptual time-based PM were averaged to generate a time-based PM score; semantic event-based, perceptual event-based, semantic time-based, perceptual time-based PM, and activity-based PM were standardized (save as standardized values variables in SPSS) and averaged to generate a summary PM score Z_PM.

First, a one-way ANOVA was performed to examine the group difference in PM measures and other neurocognitive function measures, and a mixed repeated measure analysis was conducted to examine the main effects and interaction of PM type and subject group. Second, to test whether PM was a primary or secondary deficit of the patients, we conducted correlation analysis between PM measures and other neurocognitive measures, and then a series of ANCOVAs were conducted to examine the group effect sizes in PM performances when controlling for measures such as IQ, logical memory respectively. Third, further analyses were conducted to examine the likely PM stage of impairment, we selected the participants (including patients and controls) who could free recall the task requirements and then compared their PM performance using ANOVA.

3. Results

3.1. Neurocognitive function comparisons

3.1.1. PM performances

For PM performance (measured in terms of accuracy), event-based PM performance in controls was significantly better than patients [$F(1,106)=9.33$, $p=0.003$]; time-based PM performance in controls was significantly better than patients [$F(1,106)=49.65$, $p=0.0005$]; activity-based PM performance in controls was significantly better than patients [$F(1,106)=21.60$, $p=0.0005$]; and the summary PM score in controls was significantly better than patients [$F(1,106)=47.54$, $p=0.0005$] (see Table 2).

A 2×2 mixed ANOVA was conducted to explore the individual and combined effects of two independent variables (viz., PM type and group) on PM performance. PM type (event-based vs., time-based) was a within-subject variable group (schizophrenic patients, controls) was a between-subject variable, and PM performance was the dependent variable. Activity-based PM was not included as a PM type in the ANOVA because it was different from time- and event-based PM in terms of nature of task and scale of measurement. Results show that

Table 2
Comparison of neurocognitive performance in participants

	Schizophrenia			Control			F	p	Cohen's d
	N	Mean	SD	N	Mean	SD			
Prospective memory									
Event-based PM	54	0.62	0.27	54	0.76	0.21	9.33	**0.003**	**−0.59**
Time-based PM	54	0.44	0.38	54	0.85	0.19	49.65	**0.0005**	**−1.36**
Activity-based PM	54	0.71	0.34	54	0.95	0.14	21.60	**0.0005**	**−0.89**
Z_PM	54	−0.37	0.70	54	0.37	0.34	47.54	**0.0005**	**−1.33**
Working memory									
CLN_corr	43	12.88	4.30	51	14.63	3.95	4.19	**0.044**	−0.42
CLN_lg	43	5.21	1.28	51	5.92	1.20	7.73	**0.007**	**−0.57**
n-back_acc	42	0.30	0.20	51	0.41	0.21	6.52	**0.012**	**−0.53**
n-back_rt	38	720.34	247.90	49	639.16	221.40	2.59	0.111	0.35
Verbal and visual memory									
LM_imme	53	9.74	4.67	53	12.55	4.26	10.48	**0.002**	**−0.63**
LM_delay	50	7.98	4.53	53	11.06	4.54	11.84	**0.001**	**−0.68**
VR_imme	53	21.66	3.25	53	22.34	2.17	1.60	0.209	−0.25
VR_delay	50	20.32	4.00	53	21.94	2.54	6.12	**0.015**	−0.48

Z_PM = average of Z scores of PM performance; CLN_corr = Chinese Letter–Number span total correct; CLN_lg= Chinese Letter–Number span longest passed; n-back_acc = n-back accuracy; n-back_rt = n-back reaction time of correct responses; LM_imme = logical memory immediate recall; LM_delay = logical memory delayed recall; VR_imme = visual reproduction immediate recall; VR_delay = visual reproduction delayed recall. In p column, those less than 0.05 were presented as bold; in cohen's Cohen's d column, those larger than 0.5 (absolute value) were presented as bold, according to Cohen (1988), it's medium effect size.

the main effect of group was significant, $F(1,106)=38.93$, $p<0.001$, the main effect of PM type was not significant, $F(1,106)=2.46$, $p=0.120$; and the interaction between group and PM type was significant, $F(1,106)=22.11$, $p<0.001$. The interaction indicated that compared to event-based PM, the patients performed disproportionately worse in time-based PM than controls.

3.1.2. Other neurocognitive functions

There were significant group differences in other memory functions. For working memory, Chinese Letter–Number span total correct [$F(1,92)=4.18$, $p=0.044$] was significantly less in patients than controls; Chinese Letter–Number span longest passed [$F(1,92)=7.73$, $p=0.007$] was significantly shorter in patients than controls; n-back accuracy [$F(1,91)=6.52$, $p=0.012$] was significantly lower in patients than controls, n-back reaction time [$F(1,85)=2.59$, $p=0.11$] was not significantly different between patients and controls. For logical memory, patients performed significantly poorer than controls in immediate recall [$F(1,104)=10.48$, $p=0.002$] and delayed recall [$F(1,101)=11.84$, $p=0.001$]. For visual reproduction, immediate recall [$F(1,104)=1.60$, $p=0.209$] was not significantly different between the two groups of participants but delayed recall [$F(1,101)=6.12$, $p=0.015$] was significantly different between groups, with patients performing significantly poorer.

3.2. Relationship between PM and other neurocognitive measures

To control for the number of correlation coefficients calculated, only one measure from each of the tests was included in examining the relationship between PM and other neurocognitive measures (see Table 3). For schizophrenic patients, significant correlations were found between PM and other neurocognitive functions. Significant correlation coefficients were obtained between the summary score of PM (Z_PM) and other variables: IQ ($r=0.569$, $p<0.01$), logical memory delay ($r=0.212$, $p<0.05$), visual reproduction ($r=0.316$, $p<0.05$), Chinese Letter–Number span total correct ($r=0.586$, $p<0.01$), n-back accuracy ($r=0.441$, $p<0.01$), WCST category ($r=0.642$, $p<0.01$), verbal fluency correct ($r=0.420$, $p<0.01$), details see Table 3. Similar correlation pattern but attenuated coefficients were found in healthy controls.

To partial out the influence of these neurocognitive functions on PM deficits in the patients, we performed a series of ANCOVAs with subject group as the independent variable, Z_PM as the dependent variable, and IQ, logical memory delay, visual reproduction delay, Chinese Letter–Number span total correct, n-back accuracy, WCST category, and verbal fluency as covariates respectively. When none of the covariates were controlled, the group effect size partial η^2 was 0.310. The partial η^2

Table 3
Correlation between prospective memory and other neurocognitive functions in schizophrenia patients

		event PM	time PM	activity PM	Z_PM	IQ	LM	VR	CLN	n-back	WCST
event PM	*r*	–									
	N	–									
time PM	*r*	0.555**									
	N	54									
activity PM	*r*	0.033	0.168								
	N	54	54								
Z_PM	*r*	0.798**	0.858**	0.447**							
	N	54	54	54							
IQ	*r*	0.456**	0.619**	0.063	0.569**						
	N	54	54	54	54						
Logical memory delay	*r*	0.325*	0.26	−0.022	0.292*	0.364**					
	N	50	50	50	50	50					
Visual reproduction delay	*r*	0.214	0.213	0.288*	0.316*	0.343*	0.085				
	N	50	50	50	50	50	50				
Chinese LN span total correct	*r*	0.539**	0.600**	−0.06	0.586**	0.628**	0.147	0.323*			
	N	43	43	43	43	43	43	43			
n-back accuracy	*r*	0.396**	0.340*	0.164	0.441**	0.408**	0.559**	0.282	0.465**		
	N	42	42	42	42	42	42	42	41		
WCST category	*r*	0.573**	0.577**	0.105	0.642**	0.514**	0.385*	0.238	0.494**	0.477**	
	N	44	44	44	44	44	43	43	42	41	
Verbal fluency correct	*r*	0.404**	0.466**	−0.095	0.420**	0.610**	0.215	0.108	0.668**	0.338*	0.330*
	N	46	46	46	46	46	45	45	41	40	43

*$p<0.05$, **$p<0.01$. Z_PM = single index of prospective memory; LM = logical memory delay; VR = visual reproduction delay; CLN = Chinese Letter–Number span total correct; n-back = n-back accuracy; WCST = Wisconsin Card Sorting Test category.

was changed to 0.326, 0.245, 0.266, 0.246, 0.261, 0.326, and 0.315 following the entry of covariate of IQ, logical memory delay, visual reproduction delay, Chinese Letter–Number span total correct, n-back accuracy, WCST category, verbal fluency respectively. When all the variables were controlled, the partial η^2 decreased from 0.310 to 0.285. Thus, for the individual test, logical memory delay (RM) and Chinese Letter–Number span (working memory) contributed most to the PM deficit in patients. According to Cohen (1988), 0.14 of partial η^2 means large effect size, which means the group difference in PM performance is large despite controlling all other cognitive variables. For all these ANCOVAs, the group effects of PM remained significant (all ps<0.001).

3.3. Relationship between clinical variables and PM

To examine the relationship between clinical variables and PM performance in schizophrenia patients, correlation analyses were conducted between event-based PM, time-based PM, activity-based PM, Z_PM and clinical variables such as duration of illness, medication, AIMS, BARS, PANSS positive symptoms, PANSS negative symptoms, and PANSS general psychopathology. No significant correlations were found except between duration of illness and event-based PM ($r=-0.375$, $p=0.005$), Z_PM ($r=-0.307$, $p=0.024$). These two correlations may also become nonsignificant after multiple comparison adjustment.

3.4. Stage of PM impairment

To explore the stage of PM impairment in schizophrenia patients, we compared the recall performance which was done after the PM task. For the free recall of PM task requirement, the free recall of semantic event-based PM [$F(1,106)=4.64$, $p=0.033$] was worse in patients than in controls; the free recall of perceptual time-based task [$F(1,106)=11.97$, $p=0.001$] was worse in patients than in controls; the free recall of semantic time-based task [$F(1,106)=16.92$, $p=0.0005$] was worse in patients than in controls; but the free recall of perceptual event-based task [$F(1,106)=0.71$, $p=0.400$] was not significantly different between groups. For those participants who could not recall the task requirements, all of them could recall when prompted, that is, when they were asked under which condition they should press the "spacebar".

To examine whether the PM deficit was affected by patients' inability to remember the task requirements, we compared the PM performance between patients and controls who could free recall the task requirements correctly. Results showed that for the perceptual event-based task, 48 schizophrenia patients and 51 controls (these two subgroups did not have any significant differences in demographic variables) could remember all the task requirements and performance on this task [$F(1,97)=1.06$, $p=0.306$] was not significantly different between these two subgroups. For semantic event-based task, 48 schizophrenia patients and 53 controls (these two subgroups did not have any significant differences in demographic variables) could remember all the task requirements and performance on this task [$F(1,99)=16.58$, $p=0.0005$] was significantly different between these two subgroups, with patients performing significantly poorer. For perceptual time-based task, 39 schizophrenia patients and 52 controls (these two subgroups did not have any significant differences in demographic variables) could remember all the task requirements and performance on this task [$F(1,89)=37.30$, $p=0.0005$] was significantly different between these two subgroups, with patients performing significantly poorer than controls. For semantic time-based task, 37 schizophrenia patients and 52 controls (these two subgroups did not have any significant differences in demographic variables) could remember all the task requirements and performance on this task [$F(1,87)=6.94$, $p=0.01$] was significantly different between these two subgroups, with patients performing significantly poorer than controls.

4. Discussion

The present study found that schizophrenia patients were impaired in PM. The effect size (Cohen's *d*) of the summary PM score was 1.33 and it was in accordance with previous studies (viz., Chan et al., 2008b; Shum et al., 2004; Wang et al., in press; Woods et al., 2007) that ranged from 1.21 to 1.62.

As to difference between event-based and time-based PM tasks, result of the present study was consistent with Shum et al. (2004), with patients performed disproportionately poorer in time-based PM than in event-based PM. Nevertheless, result of the present study was inconsistent with Henry et al. (2007) and Woods et al. (2007) who found that the two types of PM were comparatively impaired in patients with schizophrenia. The difference in findings between these studies could be due to the nature and demand of the ongoing tasks used. In the Henry et al. (2007) and Woods et al. (2007) studies, games were used as the ongoing task and participants might be absorbed in doing the ongoing task in both the event-based and time-based condition, thus resulting in similar level of performance. In contrast, for the event-based PM task of the present study and Shum et al.'s (2004) study, the ongoing task is less absorbing as a game and PM cues were embedded in and focal to the ongoing task. As a result, the event-based PM tasks in these latter two studies might be easier to perform than their respective time-based task, resulting in a disproportionately lowered level of time-based than event-based PM in patients.

For correlations between PM and other neurocognitive functions, West et al. (2006) and Wang et al. (in press) found that PM performance was associated with working memory. This finding was again confirmed in the present study. Henry et al. (2007) found significant correlations between PM and IQ, executive function, and RM. When they controlled these neurocognitive function measures in comparing PM performance between groups, the patients still performed worse on PM with large effect sizes. They, therefore, suggested that PM deficits were primary not secondary impairment of schizophrenia patients. Significant correlations between PM and IQ, RM, working memory, and executive functions were also found in the present study. Similar to Henry et al. (2007), we included these neurocognitive measures as covariates in comparing the PM performance between groups and still found significant differences, with similar effect sizes (from 0.245 to 0.326) compared to Henry et al. (2007) (from 0.14 to 0.32). Our results, therefore, confirmed that the PM impairments in schizophrenia to be the primary rather than secondary deficits.

As a primary deficit, PM impairment in schizophrenia has implications for clinical practice. This impairment may mean that patients are likely to forget to take medication or to turn up for an appointment with doctors. In turn, this impairment may reduce patients' ability to function independently in the community. Finally, as mentioned in the Introduction, PM impairment has been reported by caregivers of Alzheimer's patients to be more frustrating than RM (Smith et al., 2000). In turn, this will affect the relationship between patients and their caregivers and the quality of support the caregivers provide. Clarifying the nature of PM impairment in schizophrenia is therefore, important for the management and treatment of this group of patients.

By checking whether participants could remember the task requirements, we were able to clarify the specific stage of PM impairment in schizophrenia. Woods et al. (2007) showed that their patients could recognize PM task requirements after completion of the test. This means that the intention formation and maintenance stages were relatively intact in these patients, and that impairment of PM was most likely due to problems arising from the cue detection and intention retrieval stage. Our current findings were consistent with those of Woods et al. (2007). Furthermore, Woods et al. found a significant difference in retrieval index (subtracting the free recall accuracy from the number of recognition hits) between patients and controls, but it is not known whether the PM difference between groups was caused by those who could not correctly free recall the PM tasks. To address this issue, we selected all those patients and controls who could correctly free recall the PM task requirements and compared their PM performance. We still found a significant difference between these two subgroups in semantic event-based, perceptual time-based, and semantic time-based PM. In terms of PM impairment not arising from problems in the encoding and maintenance stages, this could be because adequate time was provided to the participants to encode relatively short task requirements before the test began. As a result, most of them could remember and recall the task requirements after the PM test. In terms of PM impairment arising from problems in the cue detection and intention retrieval stages, this could be because of the limited working memory capacity commonly found in patients with schizophrenia. This would make it more difficult for the patients detect PM cues while undertaking an ongoing task. More studies are needed to confirm these assertions. These findings suggest that cue detection and intention retrieval, which are core characteristics of PM, and required self-initiation, are impaired in schizophrenia patients. This self-initiation process involves prefrontal lobe function as revealed by neuroimaging studies (Burgess et al., 2001, 2003; den Ouden et al., 2005; Okuda et al., 2007, 1998; Simons et al., 2006), and patients with schizophrenia have been shown to be associated with abnormalities in prefrontal areas (Callicott et al., 2000; Fu et al., 2005; Goldman-Rakic, 1999; Ritter et al., 2004). Further studies using brain imaging approach should be conducted to detect the brain activation abnormality in schizophrenia.

The current study has several limitations. First, our results suggest that cue detection and intention retrieval stages of PM were likely to be impaired in schizophrenia. However, design of the present study did not allow us to determine whether one or both of these two stages are impaired in schizophrenia. Further study is needed to answer this question. Second, the results of the current study were limited to those patients who have been treated with medication and may not be generalized to patients with first-onset schizophrenia. Third, although the PM tasks used in the present study were found to be sensitive in discriminating between patients and controls, the relationships between these tasks and everyday functioning are generally assumed rather than demonstrated. Further study is needed, therefore, to establish the ecological validity of these PM tasks. Fourth, the gender ratio of patients and controls in the present study was different. Although gender difference was not found for PM performance, it would be better to match the two groups in terms of gender ratio. Fifth, some participants of the present did not complete. Therefore, the data for some of the variables were not based on the total number of participants tested.

In conclusion, the major findings of the current study show that (1) patients with schizophrenia were impaired in PM and other neurocognitive functions; (2) PM impairment seems to be a primary deficit rather than a secondary consequence of other neurocognitive impairments in schizophrenia; (3) problem arising from the cue detection and intention retrieval stages might be the major cause of PM impairment observed in schizophrenia.

Role of funding source

This study was supported partially by the 100-Scholar Plan of Sun Yat-Sen University, and the Research Initiation Fund (O7CX031003) and the Research Fund (KSCX2-YW-R-131) from the Institute of Psychology, Chinese Academy of Sciences to Raymond Chan, and the National Basic Research Programme (973 Programme No. 2007CB512305) to Qi-yong Gong. These funding agents had no further role in the study design; in the collection, analysis and interpretation of the data; in the writing of the manuscript; and in the decision to submit the paper for publication.

Contributors

Ya Wang and Raymond Chan designed the study, analyzed the data, and wrote up the first draft of the paper; Ya Wang, Tianxiao Yang and Lan Guo administered the neuropsychological tests and questionnaires to the participants; Zheng Ma, Xiao-hong Hong, Yanbo Yuan, Zhanjiang Li and Xin Yu performed clinical interview and rating on patients; David Shum contributed to the design of the research paradigms and was involved in improving the draft of the paper; Q Gong was the last reader of the paper and gave suggestions for the improvement of the text. All authors contribute to and have approved the final text.

Conflict of interest

The authors disclaim there is no conflicts of interest for this study.

Acknowledgements

The authors would like to acknowledge the funding sources of the Sun Yat-Sen University, the Institute of Psychology, Chinese Academy of Sciences (O7CX031003; KSCX2-YW-R-131) and the National Basic Research Programme (973 Programme No. 2007CB512305).

References

Aleman, A., Hijman, R., de Haan, E.H.F., Kahn, R.S., 1999. Memory impairment in schizophrenia: a meta-analysis. Am. J. Psychiatry 156, 1358–1366.

Allen, D.N., Huegel, S.G., Gurklis, J.A., Kelley, M.E., Barry, E.J., van Kammen, D.P., 1997. Utility of WAIS-R short forms in schizophrenia. Schizophr. Res. 26, 163–172.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, DC.

Barnes, T.R., 1989. A rating scale for drug-induced akathisia. Br. J. Psychiatry 154, 672–676.

Blyler, C.R., Gold, J.M., Iannone, V.N., Buchanan, R.W., 2000. Short form of the WAIS-III for use with patients with schizophrenia. Schizophr. Res. 46, 209–215.

Burgess, P.W., Quayle, A., Frith, C.D., 2001. Brain regions involved in prospective memory as determined by positron emission tomography. Neuropsychologia 39, 545–555.

Burgess, P.W., Scott, S.K., Frith, C.D., 2003. The role of the rostral frontal cortex (area 10) in prospective memory: a lateral versus medial dissociation. Neuropsychologia 41, 439–453.

Callicott, J.H., Ramsey, N.F., Tallent, K., Bertolino, A., Knable, M.B., Coppola, R., Weinberger, D.R., 1998. Functional magnetic resonance imaging brain mapping in psychiatry: methodological issues illustrated in a study of working memory in schizophrenia. Neuropsychopharmacology 18, 186–196.

Callicott, J.H., Bertolino, A., Mattay, V.S., Langheim, F.J.P., Duyn, J., Coppola, R., Goldberg, T.E., Weinberger, D.R., 2000. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cereb. Cortex 10, 1078–1092.

Chan, R.C.K., Chen, E.Y.H., Cheung, E.F.C., Cheung, H.K., 2004. Executive dysfunctions in schizophrenia: relationships to clinical manifestations. Eur. Arch. Psychiatry Clin. Neurosci. 254, 256–262.

Chan, E.L.S., Chen, E.Y.H., Chan, R.C.K., 2005. Three subtest short form of the Wechsler Adult Intelligence Scale-III for uses in patients with schizophrenia: a preliminary report. Hong Kong J. Psychiatry 15, 39–42.

Chan, R.C.K., Chen, E.Y.H., Law, C.W., 2006a. Specific executive dysfunction in patients with first-episode medication-naïve schizophrenia. Schizophr. Res. 82, 51–64.

Chan, R.C.K., Chen, E.Y.H., Cheung, E.F.C., Chen, R.Y.L., Cheung, H.K., 2006b. The components of executive functioning in a cohort of patients with chronic schizophrenia: a multiple single-case study design. Schizophr. Res. 81, 173–189.

Chan, R.C.K., Wang, Y., Deng, Y., Zhang, Y., Yiao, X., Zhang, C., 2008a. The development of a Chinese equivalence version of Letter–Number Span Test. Clin. Neuropsychol. 22, 112–121.

Chan, R.C.K., Wang, Y., Ma, Z., Hong, X., Yuan, Y., Yu, X., Li, Z., Shum, D., Gong, Q., 2008b. Objective measures of prospective memory do not correlate with subjective complaints in schizophrenia. Schizophr. Res. 103, 229–239.

Cohen, J., 1988. Statistical power analysis for the behavioral sciences, 2nd ed. ed. Lawrence Earlbaum Associates, Hillsdale, NJ.

den Ouden, H.E.M., Frith, U., Frith, C.D., Blakemore, S.J., 2005. Thinking about intentions. NeuroImage 28, 787–796.

Einstein, G.O., McDaniel, M.A., 1990. Normal aging and prospective memory. J. Exp. Psychol. Learn. Mem. Cogn. 16, 717–726.

Ellis, J.A., 1996. Prospective memory or the realization of delayed intentions: a conceptual framework for research. In: Brandimonte, M., Einstein, G.O., McDaniel, M.A. (Eds.), Prospective Memory: Theory and Applications. Erlbaum, Mahwah, NJ, pp. 1–22.

Elvevag, B., Maylor, E.A., Gilbert, A.L., 2003. Habitual prospective memory in schizophrenia. BMC Psychiatry 3.

Fu, C.H.Y., Suckling, J., Williams, S.C.R., Andrew, C.M., Vythelingum, G.N., McGuire, P.K., 2005. Effects of psychotic state and task demand on prefrontal function in schizophrenia: an fMRI study of overt verbal fluency. Am. J. Psychiatry 162, 485–494.

Goldman-Rakic, P.S., 1999. The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. Biol. Psychiatry 46, 650–661.

Gong, Y.X., 1992. Manual of Wechsler Adult Intelligence Scale—Chinese Version. Chinese Map Press, Changsha.

Gong, Y.X., Gong, Y.X., Jiang, D.W., Deng, J.L., Dai, Z.S., Zhou, Q.Z., Xie, G.R., Li, Y., Hua, X.X., 1989. Manual of Wechsler Memory Scale—Chinese Version. Hunan Medical College Press, Changsha.

Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 12, 426–445.

Henry, J.D., Rendell, P.G., Kliegel, M., Altgassen, M., 2007. Prospective memory in schizophrenia: primary or secondary impairment? Schizophr. Res. 85, 179–185.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kondel, T.K., 2002. Prospective memory and executive function in schizophrenia. Brain Cogn. 48, 405–410.

Kumar, D., Nizamie, S.H., Jahan, M., 2005. Event-based prospective memory in schizophrenia. J. Clin. Exp. Neuropsychol. 27, 867–872.

Kurtz, M.M., Moberg, P.J., Mozley, L.H., 2001. Effectiveness of an attention- and memory-training program on neuropsychological deficits in schizophrenia. Neurorehabil. Neural Repair 15, 75–80.

Kvavilashvili, L., Ellis, J.A., 1996. Variety of intentions: some distinctions and classifications. In: Brandimonte, M., Einstein, G.O., McDaniel, M.A. (Eds.), Prospective memory: theory and applications. LEA, Mahwah, NJ, pp. 23–52.

Lee, J., Park, S., 2005. Working memory impairments in schizophrenia: a meta-analysis. J. Abnorm. Psychology 114, 599–611.

Nelson, H.E., 1976. A modified card sorting task sensitive to frontal lobe defects. Cortex 12, 313–324.

Okuda, J., Fujii, T., Yamadori, A., Kawashima, R., Tsukiura, T., Fukatsu, R., Suzuki, K., Ito, M., Fukuda, H., 1998. Participation of the prefrontal cortices in prospective memory: evidence from a PET study in humans. Neurosci. Lett. 253, 127–130.

Okuda, J., Fujii, T., Ohtake, H., Tsukiura, T., Yamadori, A., Frith, C.D., Burgess, P.W., 2007. Differential involvement of regions of rostral prefrontal cortex (Brodmann area 10) in time- and event-based prospective memory. Int. J. Psychophysiol. 64, 233–246.

Pelletier, M., Achim, A.M., Montoya, A., Lal, S., Lepage, M., 2005. Cognitive and clinical moderators of recognition memory in schizophrenia: a meta-analysis. Schizophr. Res. 74, 233–252.

Piskulic, D., Olver, J.S., Norman, T.R., Maruff, P., 2007. Behavioural studies of spatial working memory dysfunction in schizophrenia: a quantitative literature review. Psychiatry Res. 150, 111–121.

Ritter, L.M., Meador-Woodruff, J.H., Dalack, G.W., 2004. Neurocognitive measures of prefrontal cortical dysfunction in schizophrenia. Schizophr. Res. 68, 65–73.

Shum, D., Fleming, J., Neulinger, K., 2003. Prospective memory and traumatic brain injury: a review. Brain Impair. 3, 1–16.

Shum, D., Ungvari, G.S., Tang, W.K., Leung, J.P., 2004. Performance of schizophrenia patients on time-,event-, and activity-based prospective memory tasks. Schizophr. Bull. 30, 693–701.

Simons, J.S., Scholvinck, M.L., Gilbert, S.J., Frith, C.D., Burgess, P.W., 2006. Differential components of prospective memory? Evidence from fMRI. Neuropsychologia 44, 1388–1397.

Smith, G., della Sala, S., Logie, R.H., Maylor, E.A., 2000. Prospective memory and retrospective memory in normal ageing and dementia: a questionnaire study. Memory 8, 311–321.

Smith, J.M., Kucharski, L.T., Oswald, W.T., Waterman, L.J., 1979. A systematic investigation of tardive dyskinesia in inpatients. Am. J. Psychiatry 136, 918–922.

Spreen, O., Strauss, E., 1991. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary. Oxford University Press, NY.

Spreen, O., Strauss, E., 1998. A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary, 2nd ed. Oxford University Press, New York.

Twamley, E.W., Woods, S.P., Zurhellen, C.H., Vertinski, M., Narvaez, J.M., Mausbach, B.T., Patterson, T.L., Jeste, D.V., in press. Neuropsychological substrates and everyday functioning implications of prospective memory impairment in schizophrenia. Schizophr. Res. doi:10.1016/j.schres.2007.10.030.

Wang, Y., Chan, R.C.K., Yu, X., Shi, C., Cui, J., Deng, Y., in press. Prospective memory deficits in subjects with schizophrenia spectrum disorders: a comparison study with schizophrenic subjects, psychometrically defined schizotypal subjects, and healthy controls. Schizophr. Res. doi:10.1016/j.sch.res.2007.07.020.

Wechsler, D., 1987. Wechsler Memory Scale Manual. Psychological Corp, New York.

West, R., Bowry, R., Krompinger, J., 2006. The effects of working memory demands on the neural correlates of prospective memory. Neuropsychologia 90, 197–207.

Woods, S.P., Twamley, E.W., Dawson, M.S., Narvaez, J.M., Jeste, D.V., 2007. Deficits in cue detection and intention retrieval underlie prospective memory impairment in schizophrenia. Schizophr. Res. 90, 344–350.