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Conflict of interest:

The authors declared no conflict of interest.

Contributors

Eric FC Cheung, Simon SY Lui, Raymond CK Chan designed the study; Eric FC Cheung, Simon SY Lui, Y Wang analyzed the data; Eric FC Cheung, Simon SY Lui, T Yang, Raymond CK Chan wrote up the paper; Simon SY Lui, Hera KH Yeung performed clinical interview and administered the neurocognitive tests to the participants. All authors contribute to and have approved the final text.

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Figure 1. Deficit in Time and Event-Based PM (Z-Scores) in Patients with First-Episode Schizophrenia at Baseline, 6 Month, and 12 Month

Note: x-axis = time points; y-axis = standardised Z PM score.

Figure 2. PANSS Subscale Scores of Patients with First-Episode Schizophrenia at Baseline, 6 Month, and 12 Month

Note: x-axis = time points; y-axis = the PANSS raw scores

Table 1. Demographical and Clinical Information, and PM performance in Patients with First-Episode Schizophrenia and Healthy Controls

	First episode schizophrenia		Healthy controls			
	(n=58)		(n=37)			
	mean	SD	mean	SD	F/ χ^2	p
Age	22.59	5.26	21.59	1.30	1.26	0.26
Gender (male : female)	32 : 26		16 : 21		1.29	0.26
Handedness (right : left : both)	52 : 5		35 : 1 : 1		2.86	0.24
Estimated IQ (baseline)	99.93	15.06	103.59	10.05	1.70	0.20
Time-based PM (baseline)	0.59	0.39	0.97	0.10	34.76	< 0.01
Event-based PM (baseline)	0.51	0.34	0.79	0.26	18.33	< 0.01
Time-based PM (6 th month)	0.80	0.30				
Event-based PM (6 th month)	0.55	0.33				
Time-based PM (12 th month)	0.84	0.28				
Event-based PM (12 th month)	0.69	0.29				
Dose of benzhexol (mg/d)	1.45	1.93				
Dose of antipsychotics (BNF max dose %)	34.07	34.99				
Duration of treatment (months)	2.88	4.40				
PANSS positive (baseline)	13.07	4.69				
PANSS negative (baseline)	13.65	6.14				
PANSS general (baseline)	24.93	7.25				
PANSS positive (6 th month)	8.79	2.95				
PANSS negative (6 th month)	12.82	7.02				
PANSS general (6 th month)	20.70	5.07				
PANSS positive (12 th month)	8.82	3.13				
PANSS negative (12 th month)	11.19	5.18				
PANSS general (12 th month)	19.86	4.41				

Note: PANSS = Positive and Negative Syndrome Scale; PM = prospective memory

Table 2. The Correlations (*P*-Values) between PM Performances and Clinical Symptoms in Patients with First-Episode Schizophrenia at Three Time Points

		Baseline		6 month		12 month	
		Time PM	Event PM	Time PM	Event PM	Time PM	Event PM
Baseline	Positive	.077 (.569)	.092 (.496)				
	Negative	.054 (.693)	-.127 (.345)				
	General	-.085 (.536)	-.055 (.692)				
6 month	Positive			.057 (.677)	.011 (.938)		
	Negative			-.207 (.123)	-.183 (.173)		
	General			-.028 (.834)	-.131 (.331)		
12 month	Positive					-.350 (.008)	-.030 (.824)
	Negative					-.193 (.150)	-.124 (.357)
	General					-.372 (.004)	-.148 (.273)

Note: Positive, Negative, General = PANSS subscale scores; PM = prospective memory, *p*-value (prior to Bonferroni correction) in parenthesis.

Time-based but not event-based prospective memory remains impaired one year after the onset of schizophrenia: A prospective study.

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Abstract

Background: Prospective memory (PM) deficits have been consistently found in people with schizophrenia. Although there is evidence to suggest that PM deficits may be putative markers for schizophrenia, no longitudinal study has investigated the persistence of PM deficits.

Aims: We examined whether PM deficits persist after the onset of schizophrenia, and compared the trajectories of time- and event-based PM performance 12 months after illness onset. We also examined whether the association between PM and clinical symptoms changes over time 12 months after illness onset.

Method: We recruited 58 individuals with first-episode schizophrenia for a 12-month follow-up study. Comparison participants were 37 healthy individuals who were matched in terms of demographics and intelligence with the patient group. PM functions and clinical symptoms were measured at baseline, the sixth month, and the twelfth month, using a computerised PM task and the Positive and Negative Syndrome Scale.

Results: People with schizophrenia showed a gradual improvement in both time- and event-based PM 12 months after illness onset. However, compared to event-based PM, deficit in time-based PM persisted and was relatively stable. At baseline, PM

functions were not associated with clinical symptoms. However, an association between time-based PM and PANSS positive and general symptoms emerged 12 months after the onset of schizophrenia.

Conclusion: People with first-episode schizophrenia exhibit persistent time-based PM deficit. Our findings support that PM deficit, in particular, time-based deficit, may be a putative neuropsychological marker of schizophrenia.

Key words: prospective memory; schizophrenia; first-episode; longitudinal stability

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Introduction

Prospective memory (PM) is defined as the ability to remember to carry out a delayed intention in the future (Einstein & McDaniel, 1990; Kvavilashvili & Ellis, 1996), and is typically classified into time-based (i.e., intended actions are appropriately carried out at a certain time) and event-based (i.e., intended actions are appropriately carried out at the occurrence of a certain event).

PM could be assessed using different experimental paradigms, which typically involve a dual-task design (Einstein & McDaniel, 1996), in which participants are asked to encode and maintain an intention to carry out a PM task, while they are continuously engaged in an ongoing task. In a dual-task paradigm, participants have to execute the PM task at a certain time or on the appearance of certain PM cues. The majority of previous PM studies in people with schizophrenia used this kind of well-controlled, dual-task PM paradigms (Elvevag et al., 2003; Shum et al., 2004; Wood et al., 2007; Altgassen et al., 2008; Twamley et al., 2008; Wang et al., 2008a; Wang et al., 2008b; Chan et al., 2008; Ungvari et al., 2008; Zhuo et al., 2013; Lui et al., 2014). Other studies (Henry et al., 2007; Zhou et al., 2012) used ecologically-valid paradigms, such as the Virtual Week Task and the Cambridge PM Task, which are not as well controlled as the dual-task paradigms but had the advantage of simulating real-life situations and allowing participants to adopt strategies, such as taking notes

as reminders, to facilitate PM performance.

PM ability has consistently been shown to be impaired in people with schizophrenia in both the chronic stage (Elvevag et al., 2003; Shum et al., 2004; Henry et al., 2007; Wood et al., 2007; Twamley et al., 2008; Wang et al., 2008a; Wang et al., 2008b; Chan et al., 2008; Altgassen et al., 2008; Ungvari et al., 2008) and at illness onset (Zhou et al., 2012; Zhuo et al., 2013; Lui et al., 2014). Individuals with self-reported schizotypal features (Wang et al., 2008a) and unaffected relatives of people with schizophrenia (Wang et al., 2010) have also been found to have PM deficits. Taken together, evidence suggests that PM deficits in people with schizophrenia are characterised by disease association, state-independence (present in both the first episode and chronic stage), familial association, and association with high risk populations. Therefore, PM deficits appear to have met several of the criteria of an endophenotype proposed by Gottesman & Gould (2003). However, most previous studies are cross-sectional in design and the longitudinal stability of PM impairment has rarely been studied in schizophrenia spectrum disorders. To date, only one longitudinal study had examined PM ability in people with psychiatric disorders; Wang et al. (2011) tested individuals with self-reported schizotypal features and found moderate test-retest correlations of 0.62 and 0.55 for event-based and time-based PM respectively. These results suggest a relatively stable PM deficit in these individuals.

Because longitudinal stability is an important criterion for a trait marker or an endophenotype, and given the paucity of evidence in this area, a longitudinal study is indicated to ascertain whether PM deficits persist in people with first-episode schizophrenia.

In this study, we aimed to address three issues: (1) whether PM deficits persist after the onset of schizophrenia; (2) the twelve-month trajectory of performance of different PM types (time- and event-based) 12 months after the onset of schizophrenia; and (3) whether the association between clinical symptoms and different PM deficits in schizophrenia change over time. We had the following hypotheses: (1) based on a previous study (Wang et al., 2011) in participants with self-reported schizotypal features, we hypothesised that PM deficits persist longitudinally after a 12-month period; (2) given that individuals with schizophrenia in different stages showed deficits in both types of PM, we hypothesised that there would be no difference in trajectory between different types of PM deficits; and (3) we hypothesised that PM is correlated with clinical symptoms at the three assessment time points.

Method

Participants

We recruited 58 individuals with DSM-IV diagnosis of first-episode schizophrenia

from the outpatient clinic of the joint research-based first-episode psychosis programme (Lui et al., 2011a) between Castle Peak Hospital of Hong Kong and the Key Laboratory of Mental Health, Institute of Psychology, the Chinese Academy of Sciences in Beijing led by the two senior authors (RCKC and EFCC). Psychiatric diagnoses of the participants were ascertained using the Structured Clinical Interview for DSM-IV Axis I diagnoses (First et al., 1996) by experienced psychiatrists, supplemented by information from medical records obtained in frequent follow-ups (average interval 4-8 weeks). All participants with schizophrenia recruited in this study were clinically stable to undertake neuropsychological assessment. We recruited 37 demographically matched healthy individuals from the neighbouring community as controls. These individuals were screened by a qualified psychiatrist using structured interviews to ascertain that none of them had any lifetime or family history of psychosis. Inclusion criteria for participants with schizophrenia included: (1) clinically-stable mental condition as assessed by their treating psychiatrists; and (2) absence of adjustments of antipsychotic medications in the past one month prior to the assessments. Exclusion criteria for both the schizophrenia participants and controls included: (1) life-time history of substance abuse, (2) history of electroconvulsive therapy in the past six months, (3) history of neurological disorders, (4) history of head injury with loss of consciousness for more than 30 minutes, and (5) mental

retardation. All participants were Chinese in ethnicity. This study was approved by the Institutional Review Board of the Institute of Psychology, the Chinese Academy of Sciences and Castle Peak Hospital. All participants provided written informed consent before the assessment.

Measures

Prospective memory

We used a validated dual-task laboratory paradigm to measure PM (Einstein & McDaniel, 1996). This paradigm has been described in detail elsewhere (Wang et al.; 2008a; Lui et al., 2011b). Although the original paradigm comprised four conditions, only two (viz., semantic time- and event-based) were used in this study, because an earlier study from our group (Chan et al., 2013) showed that these conditions were more sensitive than the remaining ones (viz., perceptual time- and event-based) in detecting PM deficits in people with schizophrenia.

In the event-based condition, a series of four-character phrases in Chinese was presented at the centre of the computer screen at a rate of one phrase every 4s.

Participants were asked to judge whether the phrases were idioms or not by pressing two pre-specified response buttons. At the same time, participants were also instructed before the start of this task to press another pre-specified button when they

saw the appearance of an animal character (e.g., monkey) in the phrases (i.e., the PM task). The time-limit for execution of a correct response in this condition was approximately 4s. There were five PM targets embedded in the ongoing lexical-decision task in the event-based condition, and each PM cue was presented approximately (and irregularly) 60s after another.

In the time-based PM condition, the same lexical-decision task was used as the ongoing task. However, participants were required to monitor the passage of time and to press a pre-specified button when the digital clock situated near the keyboard reached a full minute (e.g., 12:00). The time-limit for execution of a correct response in this condition was 10s. As in the event-based condition, there were a total of five opportunities for participants to respond to the PM task, once for each one-minute interval.

Each condition lasted for approximately six minutes. After the participants completed both conditions, we also asked them to recall the instructions provided in the beginning of the session. The time- and event-based PM scores were calculated by dividing the total number of correctly executed PM tasks (event-based PM: pressing a pre-specified button when animal characters appeared on the screen; time-based PM: pressing a pre-specified button as the clock reached a full minute) by the total number of expected PM responses (i.e., five).

IQ and clinical symptoms assessment

Participants' intelligence was estimated using a prorating method based on the Arithmetic, Similarities and Digit Span subscales of the Chinese version of the Wechsler Adult Intelligence Scale-Revised (Gong et al., 1989). Clinical symptoms of the participants with schizophrenia were rated by trained psychiatrists using the Positive and Negative Syndrome Scale (PANSS; Kay SR, Fiszbein & Opler, 1987).

Time-points for sequential assessment

Participants with schizophrenia completed three time points of assessment using the PM task and PANSS rating (at baseline, 6-month, and 12-month), while healthy controls were only assessed once using the same assessment instrument at baseline.

Statistical analysis

Demographics of the two groups were compared using ANOVAs for parametric data (i.e., age) and Chi-square tests for non-parametric data (i.e., gender and handedness).

We used three MANOVAs and six follow-up ANOVAs to compare the time- and event-based PM scores (baseline, 6-month, 12-month) in participants with schizophrenia with PM scores (baseline) of the comparison group. The 12-month

longitudinal stability of PM in participants with schizophrenia (n=58) was examined by repeated measures ANOVAs: Time Point (baseline, 6-month, 12-month) $\times$ PM type (event-, and time-based). The change in clinical symptoms over 12 months was also examined using repeated measures ANOVAs: Time Point (baseline, 6-month, 12-month) $\times$ type of symptoms (positive, negative, general psychopathology of the PANSS). The relationships between PM and the PANSS scores at baseline, 6 months and 12 months were examined using Pearson's correlational coefficients.

Results

Table 1 shows that the schizophrenia and comparison groups did not differ in age, $F(1,93) = 1.26, p = 0.26$, gender ($\chi^2 = 1.29, p = 0.26$), handedness ($\chi^2 = 2.86, p = 0.24$) and estimated IQ ($F[1,93] = 1.70, p = 0.20$). Participants with first-episode schizophrenia were clinically stable and had a short duration of illness since entry into the programme ($M = 2.88$ months, $SD = 4.40$ months).

At baseline, 46 schizophrenia participants were receiving antipsychotics, 10 schizophrenia participants were medication-free, 23 schizophrenia participants were receiving anticholinergics (benzhexol 2-6mg daily), and one participant was receiving lorazepam 1mg/daily. At six months, 57 participants with schizophrenia were receiving antipsychotics, 25 participants were receiving anticholinergics (benzhexol

2-6mg daily), and none was receiving benzodiazepines. At 12 months, 57 schizophrenia participants were receiving antipsychotics, none was receiving benzodiazepines, and 19 were receiving anticholinergics (benzhexol 2-6mg daily).

PM impairments: cross-sectional findings

At baseline, participants with first-episode schizophrenia performed significantly poorer than healthy participants in PM ($F[2,92] = 22.34, p < 0.001, \eta_p^2 = 0.33$); manifesting in both time- ($F[1,93] = 34.76, p < 0.01, \eta_p^2 = 0.27$) and event-based PM ($F[1,93] = 18.33, p < 0.01, \eta_p^2 = 0.17$). Both participants with schizophrenia ($M = 0.86, SD = 0.23$) and healthy participants ($M = 0.94, SD = 0.15$) were able to recall the PM instructions at the end of the task, and there was no significant difference between the two groups ($F[1,93] = 3.78, p = 0.06, \eta_p^2 = 0.04$).

At six months, participants with first-episode schizophrenia still had significantly poorer PM performances compared to healthy individuals ($F[2,92] = 10.32, p < 0.01, \eta_p^2 = 0.18$), which manifested in both time-based PM ($F[1,93] = 11.32, p < 0.01, \eta_p^2 = 0.11$) and event-based PM ($F[1,93] = 14.45, p < 0.01, \eta_p^2 = 0.13$).

At 12 months, participants with first-episode schizophrenia were still impaired in PM ($F[2,92] = 4.32, p = 0.02, \eta_p^2 = 0.09$), manifesting mainly in time-based PM ($F[1,93] = 7.34, p = 0.01, \eta_p^2 = 0.07$). The group difference in event-based PM did not

reach statistical significance ($F[1,93] = 3.16, p = 0.08, \eta_p^2 = 0.03$).

Trajectories of PM impairments and clinical symptoms

The trajectories of time- and event-based PM deficit (standardised Z scores among all participants) in participants with first-episode schizophrenia is presented in Figure 1.

For the Time Point (baseline, 6-month, 12-month) $\times$ PM type (event-, and time-based)

ANOVA, there was a statistically significant main effect of Time Point ($F[2,114] =$

$17.62, p < 0.01, \eta_p^2 = 0.24$), a significant main effect of PM type ($F[1,57] = 22.98, p <$

$0.01, \eta_p^2 = 0.29$), and a significant 2-way interaction ($F[2,114] = 3.42, p < 0.05, \eta_p^2 =$

0.06). Two further ANOVAs were conducted to examine this interaction. The first

Time Point (baseline, 6 month) $\times$ PM type (event-, and time-based) ANOVA showed

a significant interaction ($F[1,57] = 4.80, p = 0.03, \eta_p^2 = 0.08$), and further simple

effect analysis revealed that time-based PM improved from baseline to six months (p

< 0.01), while event-based PM did not ($p > 0.05$). The second Time Point (6-month,

12-month) $\times$ PM type (event-, and time-based) ANOVA found that the interaction

was not significant ($F[1,57] = 3.33, p = 0.07, \eta_p^2 = 0.06$). Given the trend of

significance and the moderate effect size (η_p^2), we performed further simple effect

analysis, and found that event-based PM improved from six months to 12 months ($p <$

0.01), while time-based PM did not ($p > 0.05$).

The trajectories of the PANSS scores are shown in Figure 2. There was a significant main effect of Time Point ($F[2,50] = 14.67, p < 0.01, \eta_p^2 = 0.37$), a significant main effect of type of symptoms ($F[2,50] = 868.45, p < 0.01, \eta_p^2 = 0.97$), and a significant interaction ($F[4,204] = 8.39, p < 0.01, \eta_p^2 = 0.14$). Two further ANOVAs were conducted to identify the source of the 2-way interaction. The first Time Point (baseline, 6-month) $\times$ type of symptoms (positive, negative, general) ANOVA showed a significant interaction ($F[2,104] = 11.89, p < 0.01, \eta_p^2 = 0.19$). Further analysis showed that positive symptoms ($p < 0.01$) and general psychopathology ($p < 0.01$) decreased with time while negative symptoms did not ($p > 0.05$). The second Time Point (6-month, 12-month) $\times$ type of symptoms (positive, negative, general) ANOVA showed a significant interaction ($F[2,108] = 4.65, p = 0.01, \eta_p^2 = 0.08$), with negative symptoms decreasing with time ($p = 0.03$), while other symptoms remained static ($ps > 0.05$).

Relationship between PM and clinical symptoms

The relationship between PM and PANSS scores at each time point are shown in Table 2. None of the correlations at baseline and at six months reached statistical significance ($ps > 0.05$). At 12 months, time-based PM performance was negatively and significantly correlated with the PANSS positive subscale score ($r = -0.35, p =$

0.01) and the PANSS general psychopathology score ($r = -0.37, p < 0.01$).

Discussion

To our knowledge, this is the first longitudinal study that examines the stability of PM deficits in first-episode schizophrenia. We found that participants with first-episode schizophrenia were impaired in both time- and event-based PM at baseline and six months. However, 12 months after illness onset, the deficit of time-based PM remained while impairment in event-based PM gradually dissipated. Moreover, there was a gradual unfolding of an association between time-based PM deficit and clinical symptoms as the illness progressed over one year. At initial presentation, PM deficit did not correlate with clinical symptoms. However, at the end of the first year, the significant association between PM and clinical symptoms emerged, and time-based PM became modestly and negatively correlated with the PANSS positive subscale and general subscale scores.

It is clinically important to note that time-based PM deficit is identified cross-sectionally in participants with first-episode schizophrenia and also persists after one year. PM has long been found to be related to activity of daily living and functionality (Ritch et al., 2003; Twamley et al., 2008). Moreover, PM has particular relevance to management and treatment for schizophrenia. A recent study (Lam et al.,

2013) has demonstrated that PM significantly predicted schizophrenia participants' ability to manage medications, and significantly modulated medication adherence in the community. The persistence of time-based PM deficit over one year may be responsible for many clinical problems in people with schizophrenia. For example, people with schizophrenia who have problems in prospective remembering may forget to attend medical appointments and take medications, even if their insights towards treatment are reasonably intact. Notably, clinicians should not rely on an individual's self-report to identify possible PM deficits, because several previous studies (Chan et al., 2008) have found a dissociation between objective and subjective PM performance in people with schizophrenia in different stages of the illness. As the persistence of time-based PM deficit one year after illness onset coincides with the time of clinical stabilisation, cognitive remediation strategies may benefit individuals with schizophrenia having such problems to reduce unintentional non-adherence to treatment.

Longitudinal stability is an important trait-like property for a neuropsychological marker. This study is the first systematic examination of this property in PM and provides empirical evidence to support that time-based PM deficit may be a relatively stable marker of schizophrenia. In contrast, event-based PM deficit did not persist one year after the onset of schizophrenia. One possible reason to explain the dissipation of

event-based PM deficit and the reduction of time-based PM deficit may be related to their close association with other neuropsychological deficits (Zhou et al., 2012; Zhuo et al., 2013), which have been consistently found to improve over the course of schizophrenia (Szoke et al., 2008; Bozikas & Andreou, 2011). Medications and reduction of psychotic symptoms might also have contributed to the improvement in PM functions in our first-episode schizophrenia sample. However, it remains unclear as to why event- and time-base PM deficits showed different trajectories. From a theoretical perspective, event- and time-based PM are similarly associated with retrospective memory, attention and executive functions, yet time-perception and self-initiation are two features which distinguish time-based PM from event-based PM functions. If time-perception and self-initiation abilities remain relatively impaired one year after the onset of schizophrenia, it might explain the finding of a relatively stable time-PM deficit in this study.

This longitudinal study also reveals the gradual unfolding of an association between PM deficit and clinical symptoms of schizophrenia. Contrary to previous PM studies (Zhou et al., 2012; Zhuo et al., 2013) in people with first-episode schizophrenia, our findings suggest that, at initial presentation, there is a lack of association between prospective remembering and clinical symptomatology. However, as the illness progresses over time, such an association gradually strengthens and

becomes detectable.

Limitations and implications

Our findings must be interpreted in the context of several limitations. The follow-up duration was relatively short. Additional sequential assessments and a longer follow-up duration could improve our results. Secondly, the sample size of this study was small. Thirdly, the majority of our participants with schizophrenia were medicated at 12-month follow-up. The possible effects of antipsychotic medications on PM function could not be excluded. Fourthly, the control group did not have follow-up PM assessments, and therefore, practice effect in schizophrenia participants had not been controlled for. This might have confounded the trajectory of PM deficits. Lastly, this was a behavioural study of PM deficits in schizophrenia. To ascertain the property of a putative endophenotype, genetic analyses and neuroimaging investigations should be conducted to understand the neural and genetic underpinnings of PM deficits in schizophrenia.

Notwithstanding the above limitations, this longitudinal PM study in people with first-episode schizophrenia contributes significantly to the growing literature, by examining an important endophenotypic property of PM deficits in schizophrenia. Further longitudinal PM studies should be conducted to examine this important area

in schizophrenia using improved methods such as a parallel design to follow-up both individuals with schizophrenia and healthy controls.

In conclusion, individuals with schizophrenia who are cared for in a standard early psychosis intervention service are found to be making gradual improvements in PM functions over a 12-month follow-up period. However, time-based PM deficit persists in these individuals with schizophrenia. Our findings provide additional evidence of the longitudinal stability of PM deficit to the growing body of literature which supports that PM deficit may be a putative neuropsychological marker for schizophrenia.

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