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Problems in remembering to carry out future actions in first-episode schizophrenia: Primary or secondary impairment?

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ABSTRACT

Prospective memory (PM) is the ability to remember to carry out intended actions in the future. Empirical evidence suggests that PM deficits exist in individuals with chronic schizophrenia. However, it is unclear whether PM deficits in first-episode schizophrenia exist independently from other neuropsychological deficits. Moreover, prior research using patients with first-episode has been limited to small inpatient samples. We aimed to clarify the nature and extent of PM deficits in individuals with first-episode schizophrenia, using a large outpatient sample. Participants were 91 clinically stable outpatients with first-episode schizophrenia and 83 healthy controls. PM was assessed using both a subjective self-reported checklist and a laboratory-based task capturing time- and event-based PM. A battery assessing verbal and visuo-spatial working memory, as well as executive functions was also administered. ANOVA analyses showed that patients with first-episode schizophrenia performed significantly poorer than healthy controls in time- and event-based PM. Stepwise linear regression analyses suggested that cognitive flexibility predicted time- and event-based PM; and working memory predicted event-based PM. Subgroup analyses showed that “cognitive-preserved” patients with first-episode schizophrenia tended to perform poorer in time-based PM deficit than healthy controls who were matched in IQ and other neuropsychological functions. Overall, our results provide substantial evidence to support that time-based PM deficits in first-episode schizophrenia are apparent and not entirely attributable to other neuropsychological deficits. PM may constitute a neuropsychological marker for schizophrenia.

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1. Introduction

Prospective memory (PM) refers to the ability to remember to carry out intended actions in the future (Einstein and McDaniel, 1990; Kvavilashvili and Ellis, 1996), and is typically classified into time-based (e.g., remembering to attend a meeting at a certain time) and event-based (e.g., remembering to pass on a message when a classmate shows up). This type of memory has attracted a

growing research interest in the healthy ageing populations (Einstein and McDaniel, 1990) and psychiatric patients, including people with schizophrenia (Wang et al., 2009). Impairments in prospective remembering could lead to difficulties in everyday life, and contribute to non-adherence to medications and treatment in people with schizophrenia (Lam et al., 2013; Raskin et al., 2014). In contrast to retrospective memory (RM), PM is a complex cognitive function that is thought to be dependent on other cognitive functions such as RM, attention, and cognitive flexibility (Lui et al., 2011; Shum et al., 2004).

Ellis (1996) proposed that prospective remembering involves five stages, namely, (1) intention formation and encoding, (2) maintenance of the intention, (3) detection of cue and retrieval of

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the intention, (4) execution of the intention, and (5) evaluation of outcome. Among the 17 previous laboratory-based PM studies conducted in patients with schizophrenia (see Table 1), the majority (Kondel, 2002; Ritch et al., 2003; Elvevag et al., 2003; Shum et al., 2004; Kumar et al., 2005; Woods et al., 2007; Twamley et al., 2008; Wang et al., 2008a,b; Altgassen et al., 2008; Ungvari et al., 2008; Kumar et al., 2008; Chan et al., 2008; Lui et al., 2011; Zhuo et al., 2013) administered well-controlled “dual-task” paradigms to assess prospective remembering. “Dual-task” paradigms typically comprised an ongoing task and a PM task, and therefore required maintenance of intention to carry out the PM task while being cognitively engaged in the ongoing task. However, other studies (Henry et al., 2007; Zhou et al., 2012) administered ecologically-valid PM paradigms, which did not involve ongoing tasks and allowed individuals to use strategies such as reminders to assist prospective remembering. The successful completion of PM paradigms, in particular for those of “dual-task” design, depends on other neuropsychological functions, for example, the timely switching between the ongoing and the PM tasks depends on cognitive flexibility, the successful maintenance of intention to carry out the PM task under the distraction of the ongoing task depends on working memory, the detection of PM cues depends on attention. Although previous studies (see Table 1) consistently demonstrated that patients with schizophrenia performed poorly in PM, it remains unclear whether such PM deficits could be attributable to the executive function and memory impairments commonly found in this clinical population (Heinrichs and Zakzanis, 1998). Among the several studies (Henry et al., 2007; Twamley et al., 2008; Ungvari et al., 2008; Wang et al., 2008a; Lui et al., 2011) which measured other neuropsychological functions, evidence consistently support that PM is significantly correlated with working memory and executive functions. In addition, three studies (Henry et al., 2007; Wang et al., 2008a; Lui et al., 2011) attempted to control for the effect of working memory and executive functions. The results of two studies (Henry et al., 2007; Wang et al., 2008a) studies suggested that PM deficits remained significant in patients with chronic schizophrenia even after controlling for other neuropsychological functions, whereas the results of another study (Lui et al., 2011) suggested the time-

based PM deficit ceased to exist when other neuropsychological functions were controlled for.

A recent meta-analysis (Wang et al., 2009) concluded that patients with schizophrenia were impaired in time- and event-based PM, with effect sizes (Cohen's *d*) of 1.33 and 0.83 respectively. However, all studies included in the meta-analysis had recruited patients with chronic schizophrenia. Disease chronicity is confounded by long-term effects of psychotropic drugs and institutionalisation, which are likely to affect PM functions (Wang et al., 2009). Given that findings in patients with chronic schizophrenia might not be generalisable to patients at the early stage of the illness, two studies (Zhou et al., 2012; Zhuo et al., 2013) specifically examined PM in first-episode schizophrenia. Although their findings suggested that patients with first-episode schizophrenia were impaired in both time- and event-based PM, it is unclear as to whether PM deficits were secondary to other neuropsychological deficits. One study (Zhou et al., 2012) reported that the group difference in both time- and event-based PM disappeared after controlling for verbal memory and executive functions; whereas the other study (Zhuo et al., 2013) reported that the group difference between schizophrenia and healthy participants in time-based PM disappeared after controlling for working memory, but the group difference in event-based PM remained statistically significant. The inconsistency in findings of these two previous studies may be attributable to limitations of medication confounds (Zhou et al., 2012), or inadequate inclusion of other neuropsychological functions (Zhuo et al., 2013), and the small sample size (Zhou et al. (2012): *n* = 51 medicated patients; Zhuo et al. (2013): *n* = 22 medication-naïve patients).

Because of these limitations, the nature and extent of PM deficit, and the relationship between PM, other neuropsychological functions and medications remains unclear in first-episode schizophrenia. To ascertain whether PM deficit constitutes a biological marker of schizophrenia (Lui et al., 2011; Chan et al., 2013), it is necessary to clarify whether PM deficit could be demonstrated independently from confounds such as other neuropsychological deficits and medications. Moreover, there is a paucity of evidence regarding the relationship between laboratory-based PM and self-report PM performance in first-episode schizophrenia. While a previous study (Chan et al., 2008) has reported that laboratory-based PM correlated poorly with self-report PM performance, this finding is limited to samples with a mean duration of illness of 8.32 years.

To rectify the abovementioned methodological limitations of previous PM studies and to ascertain whether PM deficits in first-episode schizophrenia constitute a primary deficit, we conducted a comprehensive examination of time- and event-based PM in a large sample of clinically stable out-patients with first-episode schizophrenia. We examined the relationships between PM and other variables such as neuropsychological functions and medications in first-episode schizophrenia. With the benefit of a large sample, we were able to conduct subgroup analyses in order to clarify whether PM deficits exhibit in “cognitively-preserved” patients with first-episode schizophrenia. Finally, we examined the relationships between objective ratings and subjective PM performance in this group of patients. This large sample study aimed to (1) replicate and extend that the previous finding that PM deficits exist in first-episode schizophrenia, and (2) to ascertain whether PM deficits constitute a primary deficit. We hypothesised that (1) PM deficits exist in first-episode schizophrenia, (2) PM is closely related to other neuropsychological functions; and (3) patients with first-episode schizophrenia perform poorer in PM than healthy controls who were carefully matched in other neuropsychological functions.

Table 1
Summary of previous PM studies in patients with schizophrenia.

Study (reference)	Patients with schizophrenia		Healthy controls
	Sample size	Mean duration of illness/stage of illness	Sample size
Kondel (2002)	20	Chronic sample	Nil
Ritch et al. (2003)	50	Not reported	Nil
Elvevag et al. (2003)	20	Chronic stage	20
Shum et al. (2004)	60	7 years	60
Kumar et al. (2005)	42	Not reported	42
Henry et al. (2007)	30	12.7 years	30
Woods et al. (2007)	41	26.1 years	41
Twamley et al. (2008)	72 ^a	22 years	Nil
Wang et al. (2008a)	54	7.2 years	54
Wang et al. (2008b)	15	6.8 years	20
Chan et al. (2008)	36	8.3 years	28
Altgassen et al. (2008)	23	10.1 years	23
Ungvari et al. (2008)	110	8.4 years	110
Kumar et al. (2005, 2008)	42	4.7 years	42
Lui et al. (2011)	35	0.94 years	35
Zhou et al. (2012)	51	First-episode	42
Zhuo et al. (2013)	22	First-episode	23

^a Including schizoaffective disorder.

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