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Review

Meta-analysis of prospective memory in schizophrenia: Nature, extent, and correlates

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ABSTRACT

Prospective memory (PM) is the ability to remember to carry out an intended action in the future and it is an important function for everyday living. Studies have found that the neural basis of PM is located mainly in the prefrontal lobes (particularly in Brodmann Area 10) and patients with schizophrenia have functional deficits in this area. The present study provided a meta-analytic review of PM performances in patients with schizophrenia in 11 studies. A total of 485 patients with schizophrenia and 409 controls were included. Results showed that patients with schizophrenia exhibited impairments in all time- ($d=-1.33$), event- ($d=-0.827$), and activity-based ($d=-0.729$) PM, with time-based PM more impaired than event-based PM. In addition, PM was found to be significantly correlated with negative symptoms ($r=-0.18$), general psychopathology ($r=-0.168$), medication dosage ($r=-0.119$), duration of illness ($r=-0.131$), age ($r=-0.23$), education ($r=0.249$), IQ ($r=0.439$) and premorbid IQ ($r=0.356$). It has theoretical and clinical implications. Theoretically, the results indicate time-based PM involves more initiation than event-based PM. Clinically, the results indicate patients on high dose of antipsychotic medication and with long duration of illness need special attention from care givers for PM problems.

1. Introduction

Schizophrenia is associated with a wide range of cognitive dysfunctions (Heinrichs and Zakzanis, 1998) and memory impairment is one of its core deficits (Aleman et al., 1999; Lee and Park, 2005; Piskulic et al., 2007). Although in the past schizophrenia researchers have focused on the study of retrospective memory (RM), they have started to examine the nature and process of another type of memory called prospective memory (PM), which is the ability to remember to carry out an intended action in the *future* (Brandimonte et al., 1996). In contrast, RM refers to the ability to remember to recall or recognize *past* information. The main characteristics of PM include: (a) a delay between the encoding and carrying out of the intended action; (b) during the delay one has to engage in an ongoing task; and (c) there is no external reminder when the PM cue for the intended action appears, thus compared to RM there is more demand on self-initiation (Craik, 1986; Ellis,

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1996). In a typical PM experiment, participants are required to engage in an ongoing task (e.g., answer general knowledge questions) and when a cue appeared (e.g., the word "police" in a sentence), participants have to remember to perform an intended action (e.g., to press a key on a computer keyboard). In addition, PM can be divided into three types: time-based, event-based, and activity-based according to the nature of the cue associated with the future intention. Time-based PM involves remembering to perform an intention at a specific time or after a period of time (e.g., remember to meet someone at 10:00 am). Event-based PM involves remembering to perform an intention when a cue appears (e.g., remember to mail a letter when one comes across a post office). Activity-based PM involves remembering to perform an intention upon the completion of an activity (e.g., remember to answer an email after lunch).

The study of PM has its origin in the ageing literature (Einstein and McDaniel, 1990; Einstein et al., 1992) and has attracted more and more attention because of its applied implications. In recent years, quite a number of studies have been conducted to examine if various clinical populations (especially those with structural or functional impairment in the prefrontal lobes) in different types of PM (Bravin et al., 2000; Brunfaut et al., 2000; Duchek et al., 2006; Fish et al., 2007; Kliegel et al., 2005; Shum et al., 2003; Woods et al., 2008). While most studies have used either psychometric tests or experimental tasks to assess PM, a few studies have started to use ERP and imaging techniques to monitor the activity of the brain while someone is performing a PM task (Burgess et al., 2003, 2008; West et al., 2007; West, 2008). Despite these developments, one of the challenges is to identify/isolate the component(s)/stage(s) these clinical participants are having problem with (Kliegel et al., 2008).

PM is considered very important for everyday functioning because most of our daily actions and behaviours rely on our ability to carry out intended actions at the right moment. According to Smith et al. (2000), more PM than RM failures have been reported in daily living in normal older individuals and dementia patients. Moreover, PM failures could lead to hazardous consequences, for example, failure to turn off the oven after cooking could cause a fire (Shum et al., 2001). Finally, in clinical setting, Alzheimer disease patients' PM failures have been reported to be of more concerns to relatives than RM failures (Smith et al., 2000).

1.1. Neural basis of PM and its impairment in schizophrenia

Human lesion studies (Burgess et al., 2000; Daum and Mayes, 2000) and imaging studies (Burgess et al., 2001, 2003; Okuda et al., 1998, 2007) have consistently found that PM involves the function of prefrontal lobes, particularly Brodmann Area (BA) 10. Prefrontal lobes were activated when participants perform PM tasks under both event-based and time-based conditions (Okuda et al., 2007), and in both the cue detection and intention retrieval stages (Simons et al., 2006). Reynolds et al. (2009) found that both sustained and transient processes were needed in PM, and sustained processes involve a network that includes the anterior prefrontal cortex (lateral BA 10).

Patients with schizophrenia have been reported to have functional connectivity impairment (Andreasen et al., 1999; Fletcher et al., 1999; Friston and Frith, 1995; Stephan et al., 2006), for example, cortical–thalamic–cerebellar–cortical circuit impairment, prefronto–temporal integration disruptions, suggesting patients with schizophrenia are impaired in the frontal lobes, temporal lobes and other areas. Imaging studies in healthy population found that imagined future events recruited a network including frontopolar prefrontal cortex and right hippocampus, bilateral middle and inferior frontal gyri, bilateral fusiform gyrus, etc. (Addis et al., 2007, 2009; Schacter et al., 2008; Schacter and Addis, 2009). These areas are known to be affected in schizophrenia patients structurally and functionally. Based on these findings, it is logical to assume that individuals with schizophrenia would be impaired on PM (Burgess et al., 2000; Shum et al., 2001). Understanding the nature and extent of PM deficits in these patients would offer important information about their behaviours and give suggestions to effective management and rehabilitation (Shum et al., 2001).

To date, several empirical studies on PM in schizophrenia have been published. In general, these studies have found that schizophrenic patients are impaired on one or more types of PM (Altgassen et al., 2008; Chan et al., 2008; Elvevag et al., 2003; Henry et al., 2007; Kumar et al., 2005, 2008; Shum et al., 2004; Wang et al., 2008a,b). It is suggested that PM might constitute schizophrenia endophenotype because persons with schizotypal features and nonpsychotic first-degree relatives of patients with schizophrenia show a selective impairment of PM, but not verbal and visual memory (Wang et al., 2008b, in press). Also, PM deficits in schizophrenia are primary rather than secondary consequences of impairments in working memory, verbal or visual memory, or executive function (Henry et al., 2007; Wang et al., 2008a). All these findings that make clarification of the nature of PM impairment in schizophrenia are not only important for its management, but also for disease prevention in terms of identification of vulnerable individuals and gene candidates.

However, there are still a number of issues that need to be clarified; for example, whether time- or event-based PM are differentially impaired in schizophrenic patients. In previous studies, some (Henry et al., 2007; Woods et al., 2007) have found that these two types of PM were impaired to the same degree, while others (Shum et al., 2004; Ungvari et al., 2008) have found that time-based PM is significantly more impaired than event-based PM. Clarifying this issue would have theoretical implication on whether the time-based PM needs more self-initiation than the event-based PM. These inconsistent findings might have been complicated by a number of potentially confounding variables including duration of illness, medication doses, and clinical symptoms. Unfortunately, the relationships between PM and clinical manifestations, medication, duration of illness and demographic variables are not well understood, The results of previous studies were inconsistent, for example, some studies found significant relationships between PM and negative symptoms (Twamley et al., 2008; Woods et al., 2007) but some did not (Kumar et al., 2005; Wang et al., 2008a). Thus, clarifying these relationships is important for understanding the nature and extent of PM impairment in these patients. A systematic review addressing these important issues is, therefore, needed to progress this field of research. The main purpose of the present study was to provide a quantitative evaluation of the magnitude and consistency of different types of PM impairment in patients with schizophrenia and to gauge if these patients are significantly more impaired on a particular

Table 1
Studies included in meta-analysis.

Studies	Sample	Diagnostic criteria	PM type
Altgassen et al. (2008)	23 patients with chronic schizophrenia and 23 controls	ICD-10	Event-based
Chan et al. (2008)	36 patients with chronic schizophrenia, 34 individuals with schizotypal features, and 28 controls	DSM-IV	Time-, event-, and activity-based
Elvevag et al. (2003)	20 patients with chronic schizophrenia (most were incomplete response to conventional treatments) and 20 controls	DSM-IV	Habitual (time-based)
Henry et al. (2007)	30 patients with schizophrenia or schizoaffective disorder and 29 controls	DSM-IV	Regular, irregular, time check
Kumar et al. (2005)	42 patients with schizophrenia (30 drug free for at least 3 months and 12 drug naïve) and 42 controls	ICD-10	Event-based
Kumar et al. (2008)	42 patients with schizophrenia (30 drug free for at least 3 months and 12 drug naive) and 42 controls	ICD-10	Activity-based
Twamley et al. (2008)	72 outpatients with schizophrenia or schizoaffective disorder, no control group	DSM-IV	Time-, event-based
Ungvari et al. (2008)	110 patients with schizophrenia and 110 controls	DSM-IV	Time-, event-based
Wang et al. (2008a)	54 patients with schizophrenia and 54 controls	DSM-IV	Time-, event-, and activity-based
Wang et al. (2008b)	15 schizophrenic patients, 41 individuals with schizotypal features, and 20 controls	DSM-IV	Time-, event-, and activity-based
Woods et al. (2007)	41 outpatients with schizophrenia and 41 controls	DSM-IV	Time-, event-based

type of PM. It also attempted to identify the degree of correlations between PM and demographic and clinical variables. In so doing, aim to tease out whether PM deficits are mediated by these variables.

2. Method

2.1. Literature search

We used two approaches to identify potentially relevant articles. First, we searched Elsevier and PsycINFO using the key words: schizophrenia + prospective memory; schizophrenia + prospective remembering; schizophrenia + delayed intention. Second, we searched the reference list of these articles for additional papers. The time period of literature search was from 1990 (the year that the commonly used experimental paradigm of PM was developed) to May 1, 2009.

We found 14 empirical study articles (see Table 1) using the above two approaches. Among them, Kondel (2002) and Ritch et al. (2003) did not include a control group and did not report enough data to calculate the effect size. Therefore, they were not included in the current meta-analysis. Twamley et al. (2008) did not include a control group but the effect size of their correlation data could be calculated, so this study was retained. The time- and event-based PM data in Shum et al. (2004) were included as part of a larger data set in Ungvari et al. (2008). Therefore, the Shum et al. data were not used in the meta-analysis. In total 11 studies were included in the current meta-analysis and all of them met the following criteria: a) patients were diagnosed formally using DSM-IV or ICD-10; b) enough data were reported for computing effect sizes.

2.2. Meta-analytical procedure

For differences between schizophrenic patients and controls on PM tasks, we computed effect sizes (Cohen's d) using means and SDs. When these data were not available, we used the effect sizes reported in the articles or calculated them based on t- and F-values and sample sizes using the Comprehensive Meta Analysis program (Version 2.0). Negative effect sizes reflected better performance in controls. Time-, event-, activity-based PM performance and overall/summary PM performance were analyzed separately.

For the correlations between PM and other variables, we used the Pearson's correlation coefficient (r) and sample sizes to calculate the effect sizes using the Comprehensive Meta Analysis program (Version 2.0). For the clinical symptom measures, the positive symptom measures include: positive and negative syndrome scale (PANSS) positive scale score, brief psychiatric rating scale (BPRS) positive scale score, and Scale for the Assessment of Positive Symptoms (SAPS) total score; the negative symptom measures include: PANSS negative scale score, BPRS negative scale score and Scale for the Assessment of Negative Symptoms (SANS) total score; the general psychopathology measure refers to PANSS general psychopathology score. Some of the correlation coefficients were requested from authors.

3. Results

3.1. Group differences in PM performance

The Q statistics in all conditions were not significant, which implies that the results of these studies are homogenous.

Table 2
Results of meta-analysis of PM in patients with schizophrenia.

								Heterogeneity	
	K	N patient group	N control group	d	Z	p	95% CI	Q	p
Time-based PM	6	276	273	−1.33	−14.07	<0.001	(−1.515, −1.145)	2.083	0.838
Event-based PM	7	321	318	−0.827	−9.99	<0.001	(−0.989, −0.665)	6.66	0.353
Activity-based PM	4	147	144	−0.729	−5.997	<0.001	(−0.968, −0.491)	2.092	0.554
Summary PM score	7	259	255	−1.353	−13.799	<0.001	(−1.545, −1.161)	2.708	0.844

K = number of studies; N = number of participants; d = pooled effect size; CI = confidence interval.

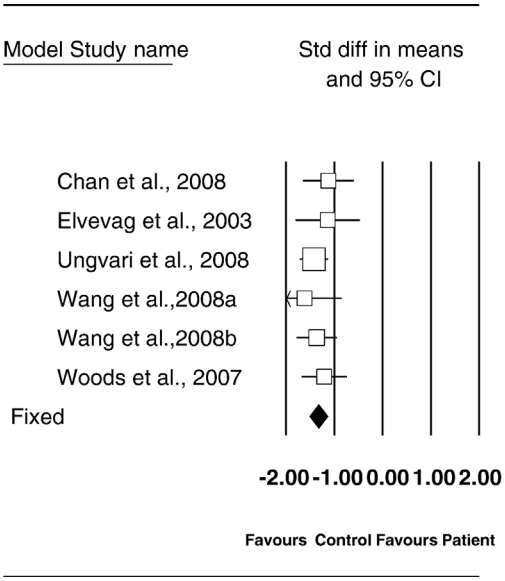

Fig. 1. Comparison of time-based PM between patients and controls.

Among time-, event-, and activity-based PM, time-based PM had the largest mean weighted d (−1.33, 95% confidence interval −1.515 to −1.145) and activity-based PM had the smallest mean weighted d (−0.729, 95% confidence interval −0.968 to −0.491), the mean weighted of event-based PM (−0.827, 95% confidence interval −0.989 to −0.665) was between time- and activity-based PM. The summary PM score was also found to have large effect size (d = −1.353, 95% confidence interval −1.545 to −1.161) (see Table 2 and Figs. 1–4). All the effect sizes (absolute value) were significantly larger than 0. Based on Cohen's (Cohen, 1988) criteria ($d \geq .80$ for large effect size), both time-based and event-based PM tasks were found to have large mean effect sizes. To test if patients with schizophrenia are significantly more impaired on one type of PM than the others, the PM type (time-, event-based) was used as a moderator. Results suggested that these two types of PM were heterogeneous (Q = 16.052, p<0.001), suggesting that the effect size of time-based was significantly larger than that of event-based PM (absolute value). Since the task of activity-based PM was different from time- and event-based PM, the activity-based PM was not compared to the other two types of PM.

Publication bias analysis found that 268, 173, and 31 studies with negative results are needed to reject the present significant findings for time-, event-, and activity-based PM respectively. For PM summary score, 325 studies with negative result are needed to reject the present finding. Results of Egger's

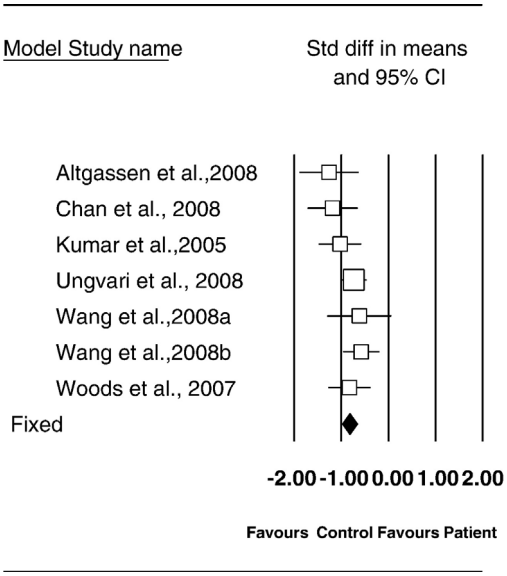

Fig. 2. Comparison of event-based PM between patients and controls.

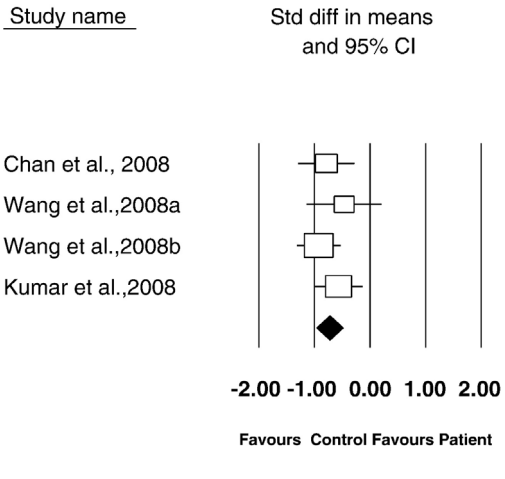

Fig. 3. Comparison of activity-based PM between patients and controls.

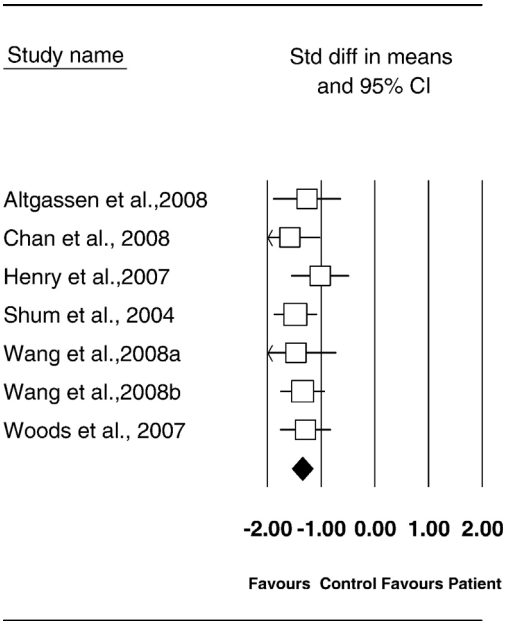

Fig. 4. Comparison of PM summary score between patients and controls.

test are: $t(4)=0.672$, $p=0.538$ for time-based PM; $t(5)=1.328$, $p=0.242$ for event-based PM; $t(2)=1.105$, $p=0.384$ for activity-based PM; $t(5)=0.228$; $p=0.828$ for summary PM score. Based on these results, it can be safely concluded that publication bias does not exist for PM impairments in patients with schizophrenia.

3.2. Correlations between PM, clinical and demographic data

In this correlation analysis, we only used the PM summary score, since it includes all the different types of PM and is most reliable. The correlational data between summary PM score and other variables indicate that for clinical symptoms, PM did not correlate significantly with positive symptoms ($r=-0.094$, $p=0.067$), but significantly with negative symptoms ($r=-0.18$, $p<0.001$) and general psychopathology ($r=-0.168$, $p=0.05$). However, it should be noted that only 4 studies were included in the general psychopathology correlation analysis (see Table 3). PM summary score was also found to correlate significantly with medication dosage ($r=-0.119$, $p=0.028$), and duration of illness ($r=-0.131$, $p=0.009$) but it did not correlate significantly with age of onset ($r=0.035$, $p=0.564$). For demographic variables, PM summary score was found to correlate significantly with age ($r=-0.23$, $p<0.001$), education ($r=0.249$, $p<0.001$), IQ ($r=0.439$, $p<0.001$), and premorbid IQ ($r=0.356$, $p<0.001$) (see Table 3). Among the significant correlations, demographic variables had the strongest relationships with PM. Egger's test showed that publication bias did not exist in any of these test, p-value ranged from 0.073 to 0.901.

4. Discussion

The present study provided a systematic and quantitative review of the magnitude of PM impairments in patients with schizophrenia, and strength of association between PM and a number of variables. Through the quantitative meta-analysis, it was found that schizophrenic patients were significantly impaired in all three types of PM (viz., time-, event-, and activity-based) and the summary/overall PM. The variance for all four types of impairment was homogeneous, indicating the results of different studies are consistent. All the effect sizes are large or near large according to Cohen's criterion (Cohen, 1988). In a previous meta-analysis, Mesholam-Gately et al. (Mesholam-Gately et al., 2009) found that schizophrenic patients showed impairment in RM and the globe domain effect sizes were −0.85 to −1.20 (including verbal, nonverbal, immediate and delayed memory). In the present study similar pooled effect sizes were found for PM. Through moderator analysis, it was found that the variances were heterogeneous between PM types (time- vs event-based), suggesting that time-based PM was more impaired in schizophrenia than event-based PM. This is consistent with the commonly held view that time-based PM is more difficult since it needs more self-initiation (Einstein et al., 1995). Thus, the current meta-analysis have resolved the inconsistent results among the studies published and found the extent of PM deficits in patients with schizophrenia; and it also affirms the theoretical distinction between time- and event-based PM.

Regarding the meta-analytic correlation analyses, PM was not found to correlate significantly with positive symptoms, but significantly with negative symptoms and general psychopathology. This is consistent with results of previous meta-analyses that showed significant relationships between clinical symptoms and neurocognitive functions such as working memory and executive functions (Dibben et al., 2009; Dominguez et al., 2009; Nieuwenstein et al., 2001). These studies have found that neurocognitive functions were significantly correlated with negative symptoms and disorganization/general psychopathology to a medium degree, but did not correlate with positive symptoms. These results suggest that negative symptoms and disorganization may reflect different psychopathologies compared to positive symptoms (Dominguez et al., 2009). The results that negative symptoms correlated significantly with PM also supported the frontal lobe hypothesis of negative symptoms which suggested that the negative symptoms were associated with malfunction of prefrontal cortex (Liddle, 2001).

PM was found to have an inverse relationship with medication dosage. This means that the higher the dosage of medication the patients take, the worse their PM performances. This is an important finding that previous studies had not reported and it has implications for care of these patients. For example caregivers or health workers should pay special attention to those patients who are on high dose of antipsychotic medication because they might have particularly more PM problems. Because of the way results were reported in the studies that we reviewed, there are no enough data to clarify whether typical and atypical medication had differential effect on PM.

Table 3
Results of meta-analysis of correlation between PM summary score and other variables in patients with schizophrenia.

							Heterogeneity	
	K	*N*	*r*	*Z*	*p*	95% CI	Q	*p*
Positive symptoms	8	400	−0.094	−1.833	0.067	(−0.193, 0.007)	7.512	0.378
Negative symptoms	8	400	−0.18	−3.527	<0.001	(−0.276, −0.081)	21.32	0.003
General psychopathology	4	146	−0.168	−1.961	0.05	(−0.326, 0)	2.268	0.519
Medication dosage	7	358	−0.119	−2.194	0.028	(−0.222, −0.013)	6.204	0.401
Duration of illness	9	423	−0.131	−2.623	0.009	(−0.226, −0.033)	12.439	0.133
Age onset	7	290	0.035	−0.577	0.564	(−0.153, 0.084)	30.548	<0.001
Age	9	423	−0.23	−4.653	<0.001	(−0.321, −0.135)	11.036	0.2
Education	7	358	0.249	4.672	<0.001	(0.147, 0.346)	5.712	0.456
IQ	5	176	0.439	5.97	<0.001	(0.306, 0.555)	12.179	0.016
Premorbid IQ	3	125	0.356	4.008	<0.001	(0.188, 0.504)	0.94	0.625

K = number of studies; *N* = number of participants; *r* = pooled effect size; *CI* = confidence interval.

PM was also found to correlate significantly with the duration of illness, with longer duration of illness associated with poorer PM performance. This is an interesting finding that has not been reported before. It suggests that PM performance may deteriorate along the course of schizophrenic illness and this may be caused by neurotoxicity, hospitalization, illness severity, etc. This finding is consistent with the findings of Pelletier et al. (2005) that recognition RM was moderated by illness chronicity.

Among the demographic variables examined, PM was not found to correlate with age of onset but was found to correlate with age of patients. This suggests that with increasing age, PM performance tends to decrease. This finding is consistent with the results of the meta-analysis conducted by Henry et al. (2004) which conclude that ageing has a negative effect on PM. Education was found to have a significant relationship with PM, with more educated patients showing better PM performance. This may be because patients with higher education or higher IQ had more opportunities to undertake and practice PM tasks (e.g., bringing homework to school on a certain date, asking a particular teacher for information when he/she appears) during their schooling than patients with less education or persons with better PM are more likely to cope with the demands of education. Finally, PM was found to have a positive relationship with IQ and premorbid IQ, this suggests that PM relies on basic cognitive functions (e.g., attention, retrospective memory) to a large degree, so individuals with higher IQ would do better on PM.

There are several limitations in the present study: First, the number of studies included in the present meta-analysis is relatively small. Second, the PM tasks are rather different in these studies. Third, for the relationship between PM and positive symptoms, it might be mediated by medication and its dosage, since medication in schizophrenia mainly targets positive symptomatology. It could be that positive symptoms and PM are related, but medication removes this effect by controlling positive symptoms. Further studies on medication naive patients are needed to address this issue.

The current findings implicate several lines of research for studying PM in schizophrenia. First, while there are studies that investigated the neural basis of PM and neural impairment in schizophrenia, to our knowledge none has examined the neural impairment of PM in schizophrenia directly. This is a worthy topic because it would provide a direct and stronger link between schizophrenia and PM deficits and clarify the underlying process of these deficits. Second, the present meta-analysis found that medication dosage was significantly correlated with PM performance. However, the studies included did not report typical or atypical medications separately. To clarify this issue, future studies could explore the differential effect of typical and atypical medications on PM performance, and also medication naive cases. Third, studies conducted so far have not identified the stage (e.g., encoding, maintenance, retrieval) of PM impairment in schizophrenic patients, further studies (behavioral, ERP, and fMRI) with well-designed experiments might help to identify the specific stage of impairment and the specific brain region responsible for the impairment.

In conclusion, the current meta-analysis found the extent of impairments in three types of PM in patients with schizophrenia, and the relationships between PM performance and clinical and demographic variables, these findings have important clinical implications.

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Contributors

Ya Wang and Raymond Chan generated the idea, analyzed the data and wrote up the first draft of the paper; Jifang Cui helped in searching the literature and in data analysis; Jifang Cui, Yongyu Deng, Haisong Shi, Xiaohong Hong, Zhanjiang Li, Xin Yu were involved in the writing; Qi-yong Gong read the manuscript and made some comments; David Shum was involved in the discussion and in improving the draft of the paper. All authors contribute to and have approved the final text.

Conflict of interest

None.

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