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Prospective memory in schizophrenia: A meta-analysis of comparative studies

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ABSTRACT

Background: Impairment of prospective memory (PM) in schizophrenia has gained increasing attention. This meta-analysis systematically examined PM impairment in schizophrenia.
Methods: Both English (PubMed, PsycINFO, EMBASE, and Cochrane Library) and Chinese (WanFang, Chinese Biomedical and China Journal Net databases) databases were systematically searched from their inception until August 14, 2017. Case-control studies of PM in schizophrenia were included. Standardized mean differences (SMDs) and their 95% confidence interval (CI) were calculated using the random-effects model.
Results: Twenty-nine case-control studies ($n = 2492$) were included in the analyses. The overall and three subtypes of PM were compared between patients with schizophrenia ($n = 1284$) and healthy controls ($n = 1208$). Compared to healthy controls, patients performed significantly poorer in overall (SMD = −1.125), time-based (SMD = −1.155), event-based (SMD = −1.068), and activity-based PM (SMD = -0.563). Subgroup analyses revealed significant differences between older and younger patients (SMD = -1.398 vs. -0.763), higher male predominance and no sex predominance (SMD = -1.679 vs. -0.800), lower and higher education level (SMD = -1.373 vs.-0.637), chronic and first-episode patients (SMD = -1.237 vs. -0.641) and between eco-valid and dual-task laboratory measurements (SMD = -1.542 vs. -0.725) regarding overall PM. Meta-regression analysis showed that higher negative symptom score was significantly associated with more severe overall PM impairment in patients ($P = 0.022$).
Conclusions: In this meta-analysis the overall PM and all its subtypes, particularly the time-based PM, were significantly impaired in schizophrenia.

1. Introduction

A core feature of schizophrenia (SCZ) is related to a wide range of cognitive impairment including attention, memory, processing speed, and executive functions (Green et al., 2004). Although antipsychotic treatment has robust efficacy regarding positive symptoms (Stroup et al., 2000), they lack significant efficacy on cognitive symptoms (Savilla et al., 2008; Tsapakis et al., 2015). Of the various cognitive dimensions, memory and executive functions are significantly impaired in different stages of the illness (Bora and Murray, 2013; Dickinson et al., 2007; Massuda et al., 2013; Mesholam-Gately et al., 2009; Orellana and Slachevsky, 2013).

Memory deficits have been extensively studied in schizophrenia, but most studies focused only on the retention of past information, i.e., retrospective memory (RM) (Burgess and Shallice, 1997). However, up to 85% of memory impairment could be attributed to the failure to remember to perform something in the future, which is defined as prospective memory (PM) (Kliegel and Martin, 2010). PM involves a time delay between the formation and execution of the prospective intention thus the person has to keep in mind the

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previously formed intention while participating in ongoing other activities during the period of delay. These features make PM important to daily living and perhaps more complex than RM. Prospective memory consists of three subtypes according to the cues that prompt a PM task: time-based (TBPM), event-based (EBPM) and activity-based PM (ABPM) (Einstein and McDaniel, 1990).

A number of measurements have been developed to assess PM, including laboratory, eco-valid, and self-report measurements. Laboratory measures are based on the widely used dual-task paradigm, where PM tasks are embedded in ongoing tasks (Einstein and McDaniel, 1990). However, the dual-task laboratory paradigm and the related measures have relatively low ecological validity, as they concentrate on only one type of PM task performed repeatedly (Delprado et al., 2012). To overcome this shortcoming, four clinic-based measures have been developed: the Memory for Intentions Screening Test (MIST) (Raskin and Buckheit, 2004), the Cambridge Prospective Memory Test (CAMPROMPT) (Raskin and Buckheit, 2004), the Virtual Week (Rendell and Henry, 2009) and the Royal Prince Alfred Memory Test (Radford et al., 2011). These tests are considered as ecologically valid measurements with good psychometric properties (Raskin et al., 2018).

The neurocognitive processes underlying PM involve four stages (Carey et al., 2006; Raskin et al., 2018): (1) the formation or encoding of an action plan. (2) The delay maintenance interval stage when a distracting activity is ongoing. (3) The cue recognition and intention retrieval stage, which is self-initiated and considered the defining feature of PM. (4) The execution and evaluation of the previously formed intention. Schizophrenia patients exhibit significant impairment in cue detection and intention retrieval during the execution of PM tasks (Woods et al., 2007). The hippocampus plays a key role in information retrieval by reactivating neurons that are responsible for learning (Tanaka et al., 2014) while the execution of delayed intention relies on the prefrontal cortex (PFC) that allocates attentional resources, monitors the environment and detects PM cues (Shallice, 1988). PM is dependent on a network circuitry involving the PFC, temporal lobe and their interconnections.

The PFC and hippocampus are also key brain regions implicated in the neural circuit of schizophrenia (Barch and Ceaser, 2012; Heckers and Konradi, 2010; Small et al., 2011) as structural and functional impairment and dysconnectivity involving the two brain regions have been found in schizophrenia (Liang et al., 2006; Pettersson-Yeo et al., 2011). Impairment in PM has been observed in all stages of schizophrenia, in first-episode, and chronic patients, and even in non-psychotic first-degree relatives (Lui et al., 2011; Wang et al., 2010b; Zhou et al., 2012; Zhuo et al., 2013). PM deficits are posited as an endophenotype reflecting both the core neural circuit and the risk for developing schizophrenia (Henry et al., 2012; Saleem et al., 2017).

It is debatable whether PM deficits are specifically related to schizophrenia, as PM impairment also occurs in other neuropsychiatric disorders, such as depression (McFarland and Vasterling, 2017; Zhou et al., 2017), bipolar disorder (Zhou et al., 2018), obsessive-compulsive disorder (Bhat et al., 2018; Racsmany et al., 2011; Yang et al., 2015), and Parkinson's disease (Costa et al., 2018; Ramanan and Kumar, 2013). There is a continuum in genetic variation, clinical manifestation and cognitive deficits across these neuropsychiatric disorders (Owen and O'Donovan, 2017), but in schizophrenia patients there are more severe impairment in PFC and temporal lobe compared to bipolar disorder or major depression (Barch et al., 2003; Birur et al., 2017). Schizophrenia patients also have poorer performance in neuropsychological tests in terms of processing speed, working and verbal memory, and verbal fluency (Lynham et al., 2018).

Findings on PM impairment in schizophrenia have been inconsistent. Significant difference on overall PM between patients and controls was found with very large (−11.43) (Lian et al., 2015), but also with small effect size (−0.14) (Chen et al., 2016). In addition, given that TBPM relies more on PFC function, which is impaired in schizophrenia, TBPM should theoretically be more impaired than EBPM in schizophrenia. However, the effect size of TBPM impairment (SMD = -0.27) was unexpectedly smaller than that of EBPM (SMD = -0.54) (Chan et al., 2013). Furthermore, there were also discrepancies in the association between PM deficits and symptoms of schizophrenia particularly negative symptoms (Kumar et al., 2005; Twamley et al., 2008; Wang et al., 2008b; Woods et al., 2007).

A meta-analysis of 11 studies of PM in schizophrenia (Wang et al., 2009) found impairment in all three subtypes of PM, with TBPM being the most impaired (Wang et al., 2009). A systematic review (Ordemann et al., 2014) also examined PM impairment in schizophrenia. However, due to the relatively small number of included studies, these two reviews could not explore the impact of measurement (eco-valid vs. dual-task laboratory) and the stages of illness (first-episode vs. chronic) on PM impairment in schizophrenia. Recent findings on PM in schizophrenia (Au et al., 2014; Cao and Song, 2016; Chan et al., 2013; Chen et al., 2015; Chen et al., 2016; Cheung et al., 2015; Lian et al., 2015; Lu et al., 2016; Lui et al., 2011; Lui et al., 2015; Man et al., 2016; Raskin et al., 2014; Wang et al., 2008a; Wang et al., 2010a; Wang et al., 2012; Xie et al., 2014; Yang, 2016; Zhou et al., 2012; Zhuo et al., 2011; Zou, 2012), have been inconsistent. In addition, many studies had been published in Chinese-language journals (Cao and Song, 2016; Chen et al., 2015; Lian et al., 2015; Wang et al., 2012, 2013; Xie et al., 2014; Yang, 2016; Zou, 2012), which were not included in the previous meta-analysis. This was the rationale to conduct an updated meta-analysis of case-control studies of PM impairment in schizophrenia and its moderating factors by including the recently published papers as well as those in Chinese journals.

The hypotheses were as follows: first, schizophrenia patients will show significant impairment in the overall and all subtypes of PM; second, PM subtypes will be disproportionally impaired, with TBPM being the most impaired one; third, PM deficits will be associated with negative symptoms of schizophrenia, given that both PM impairment and negative symptoms are related to PFC dysfunction (Burgess et al., 2001, 2003; Okuda et al., 2007; Wolkin et al., 1992); fourth, eco-valid measurements will be more sensitive to detect PM impairment, as this approach is considered to represent real-world situation (Burgess et al., 2006); fifth, chronic patients will have more severe PM impairment compared to first-episode patients, as chronic patients have more gray matter loss in the prefrontal cortex (Shenton et al., 2001).

2. Materials and methods

2.1. Selection criteria and search strategy

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Moher et al., 2009), the inclusion criteria used following the *PICOS* acronym were: ***P***articipants: patients with schizophrenia diagnosed according to study-defined criteria. ***I***ntervention: not applicable (NA). ***C***omparison: healthy controls. ***O***utcomes: primary outcome was overall PM; the key secondary outcomes were PM subtypes, i.e., TBPM, EBPM and ABPM. Study design (*S*): case-control or cohort studies comparing PM between patients and healthy controls reporting accessible and meta-analyzable data (only the baseline data of cohort studies were analyzed). Exclusion criteria were as follows: (1) studies without a healthy control group; (2) healthy controls were not matched to patients in age or education; (3) studies that did not report meta-analyzable data.

English (PubMed, PsycINFO, EMBASE, Cochrane Library) and Chinese (WanFang, Chinese Biomedical and China Journal Net) databases, from their inception until August 14, 2017, were independently searched by two authors (YYW and LL) using the following search terms: (prospective memor* OR memor*, prospective) AND

(schizophrenic disorder OR disorder, schizophrenic OR schizophrenic disorders OR schizophrenia OR dementia praecox). Additionally, reference lists of the included case-control studies and relevant reviews or meta-analyses were hand-searched for further studies.

2.2. Data extraction

Data were independently extracted by two authors (YYW and LL), who had an inter-rater concordance of ≥0.9. Any inconsistencies in the process of data extraction were resolved by consensus and, if necessary, by involving a third researcher (FCZ). If more than one paper had the same dataset or had data overlapping with another publication, only the study with complete dataset was included. If meta-analyzable data (mean ± sd) of PM performance were not reported in the included studies, the first or corresponding authors were contacted for information. If participants were recruited from the same institution within a study period overlapping with another publication, or more than one paper was published by the same group, the authors were contacted to avoid duplication of datasets.

2.3. Assessment of study quality

In order to increase the fidelity of the findings, two authors (YYW and LL) independently assessed the study quality with the Newcastle-Ottawa Scale (NOS) (O'Connell, 2002). Following previous studies (Hernandez et al., 2015; Zhu et al., 2014), NOS total score of ≥7 was considered 'high quality'. Furthermore, the above two authors independently assessed the overall evidence level of meta-analytic results using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Atkins et al., 2004; Balshem et al., 2011). The inter-rater concordance between the two raters was 0.9. Any inconsistencies were resolved by a discussion involving a third author (FCZ).

2.4. Statistical methods

Data were analyzed with the Comprehensive Meta-Analysis software, Version 2 (https://www.meta-analysis.com/). For continuous outcomes, standard mean differences (SMDs) with their 95% confidence interval (CI) were calculated using the random-effects model due to the likely heterogeneity across studies (DerSimonian and Laird, 1986) in terms of sample size and demographic characteristics. If the PM performance was examined with multiple measure instruments in a single study, the data were separately extracted and analyzed. For example, if one study used two measures (A and B) to assess PM, in order not to inflate the number of participants, half of the patients and controls formed a group evaluated with the same instrument. Heterogeneity of significance was examined using I^2 values or the Q statistics; I^2 values ≥50% or $P < 0.1$ indicated high heterogeneity (Higgins and Thompson, 2002).

In order to detect the source of heterogeneity across studies, the following subgroup analyses were conducted: 1) patients' age (years): ≥32.3 vs. <32.3 (using the mean split of patients' age); 2) patients' school education (years): ≥12.9 vs. <12.9 (using the mean split of patents' school education); 3) gender predominance in the patient group: male predominance (≥60%) vs. no sex predominance; 4) first-episode vs. chronic schizophrenia (studies including chronic patients and those without data on illness stage); 5) PM paradigms (ecological-valid vs. dual-task); 6) year of publication (before 2009 vs. after 2009). Moreover, meta-regression analyses for the four continuous variables were performed for overall PM to investigate their potential mediating effects: 1) study quality; 2) PANSS total score; 3) PANSS positive symptom score; and 4) PANSS negative symptom score.

Publication bias for overall PM and its subtypes was examined with funnel plots, Egger's intercept (Egger et al., 1997), the Duval and Tweedie's trim and fill method (Duval and Tweedie, 2000), and the Rosenthal's fail-safe *N* (Rosenthal, 1979) using the Comprehensive Meta-Analysis software, Version 2 (https://www.meta-analysis.com/). All analyses were 2 tailed, with significance level set at 0.05.

3. Results

3.1. Literature search

The literature search yielded 1207 electronic records (Fig. 1). Having eliminated irrelevant publications, eventually altogether 29 studies entered the meta-analysis: 19 were published in English (Altgassen et al., 2008; Au et al., 2014; Chan et al., 2013; Chan et al., 2008; Chen et al., 2016; Cheung et al., 2015; Henry et al., 2007; Henry et al., 2012; Kumar et al., 2008; Lu et al., 2016; Lui et al., 2011; Lui et al., 2015; Man et al., 2016; Raskin et al., 2014; Ungvari et al., 2008; Wang et al., 2010a; Wang et al., 2008b; Zhou et al., 2012; Zhuo et al., 2011) and 10 were published in Chinese language (Cao and Song, 2016; Guo and Yang, 2006; Lian et al., 2015; Lu et al., 2016;Charac Wang et al., 2008a, 2012, 2013; Xie et al., 2014; Yang, 2016; Zou, 2012).

3.2. Characteristics of the studies and patients

All the 29 case-controlled studies ($n = 2492$), compared schizophrenia patients ($n = 1284$) and healthy controls ($n = 1208$). The mean age ranged from 21.8 to 67.5 years in 28 studies with available data; the mean percentage of males ranged from 36.8% to 100% in 26 studies with available data. The patients received 10.2 to 13.7 mean years of school education in 23 studies with available data and had a mean illness duration between 0.2 and 31.0 years.

3.3. Quality assessment

The NOS total score of the 29 studies ranged from 5 to 8 (Table 1); 23 studies were rated "high quality" (NOS ≥7). The overall evidence quality in the 4 meta-analyzable outcomes ranged from "moderate" (50%) to "high" (50%) based on the GRADE approach (Table 2).

3.4. Overall PM

Patients had significantly poorer performance than healthy controls in overall PM, with a large effect size ($n = 1044$, SMD = -1.125, 95%CI: −1.461, −0.789, $P < 0.001$; $I^2 = 83\%$, Fig. 2). Subgroup analyses found that age, gender, education level, illness stage, and PM measurements were significantly associated with overall PM performance (Table 3).

Meta-regression analyses showed that higher negative symptom score was significantly associated with more severe PM impairment ($P = 0.022$). A symmetrical funnel plot was found (Supplementary Fig. 6). Egger's regression did not reveal significant publication bias ($P = 0.352$). In the trim-and-fill test, no study was trimmed and filled on the opposite side of zero. The fail-safe method indicated that 1313 additional studies would be needed to obtain a non-significant result.

3.5. Time-based PM

Meta-analysis of TBPM found that patients showed impairment with a large effect size compared to healthy controls ($n = 1632$, SMD = -1.155, 95%CI: −1.329, −0.980, $P < 0.001$; $I^2 = 60\%$, Supplementary Fig. 1). Subgroup analyses revealed that illness stage was significantly associated with time-based PM performance (Supplementary Table 1). Meta-regression analyses showed that lower study quality (NOS score) was significantly associated with poorer time-based PM performance in patients ($P = 0.005$).

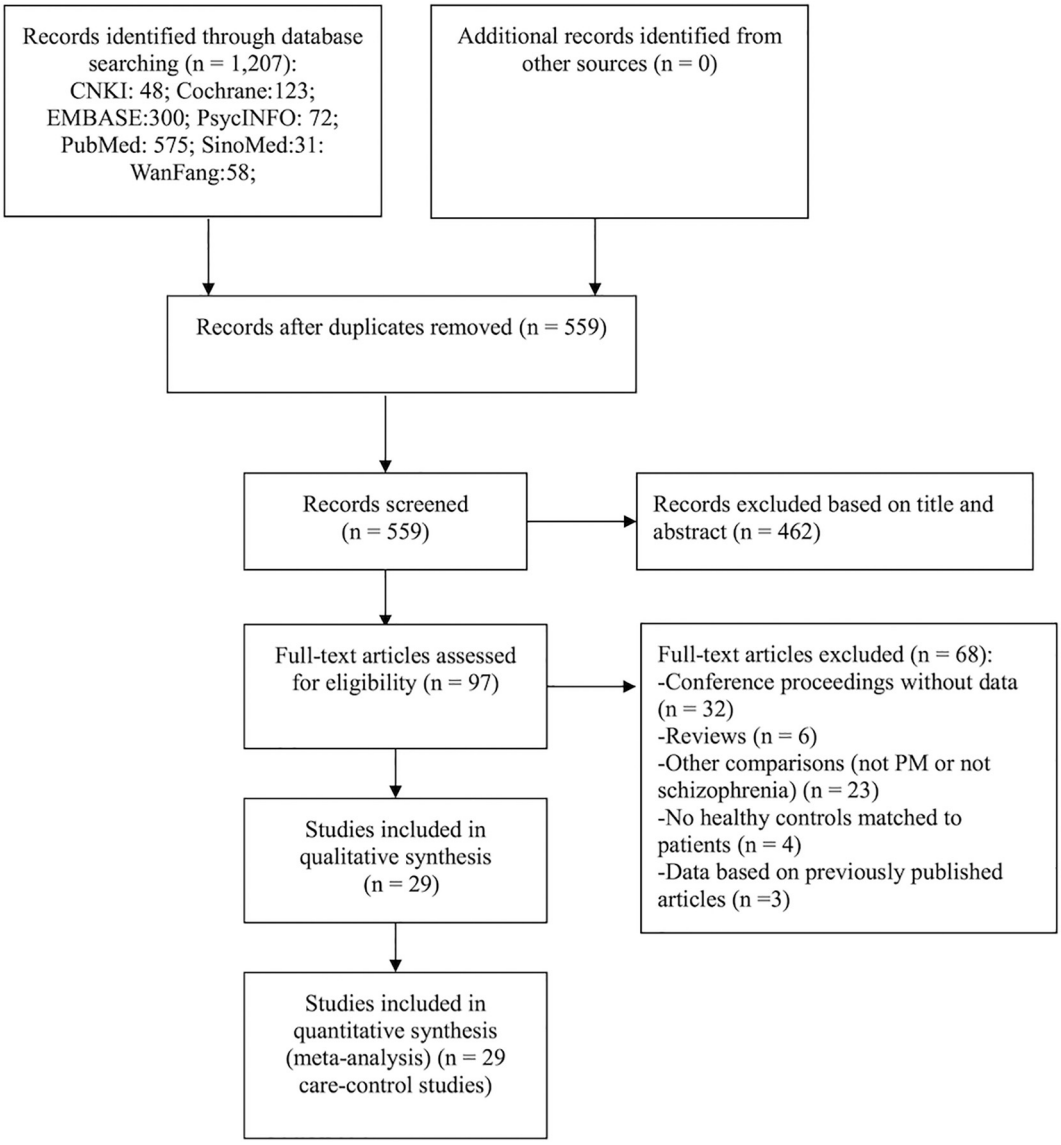

Fig. 1. PRISMA flow diagram.

The funnel plot was symmetrical (Supplementary Fig. 2). Egger's regression intercept ($P = 0.259$) did not find any publication bias. In the trim-and-fill procedure, no study was trimmed and filled on the opposite side of zero. The fail-safe method indicated that 2193 additional studies would be needed to obtain a non-significant result.

3.6. Event-based PM

In the meta-analysis of EBPM patients had significantly more severe impairment compared to healthy controls ($n = 2042$, SMD = -1.068, 95%CI: −1.346, −0.790, $P < 0.001$; $I^2 = 88\%$, Supplementary Fig. 3). In subgroup analyses age, gender, education level, gender, illness stage, and PM measurements were significantly associated with event-based PM performance (Supplementary Table 2). In meta-regression analyses lower study quality ($P < 0.001$) and PANSS total score were significantly associated with event-based PM performance.

The funnel plot was again symmetrical (Supplementary Fig. 4). Egger's regression intercept ($P = 0.056$) did not reveal any publication bias. In the trim-and-fill procedure, no study was trimmed and filled on the opposite side of zero. The fail-safe method indicated that 2915 additional studies would be needed to obtain a non-significant result. Sensitivity analysis were conducted by removing an outlying study (Lian et al., 2015), but the primary results did not significantly change ($n = 2002$, SMD = -0.968, 95% CI: −1.202, −0.733, $P < 0.001$; $I^2 = 83\%$).

3.7. Activity-based PM

Meta-analysis of ABPM showed significant impairment in the patient group compared to healthy controls ($n = 401$, SMD = -0.563, 95%CI: −0.849, −0.278, $P = 0.0001$; $I^2 = 50\%$, Supplementary Fig. 5). In subgroup analyses gender, illness stage, and publication years were significantly associated with activity-based PM performance (Supplementary Table 3).

Publication bias for activity-based PM could not be examined using the funnel plot or Egger's test due to the small number of studies on activity-based PM.

4. Discussion

All the hypotheses were confirmed by the results of the meta-analysis: the overall PM and all the subtypes were significantly impaired in schizophrenia patients compared to heathy controls,

Table 1
Characteristics of the studies in the meta-analysis.

First author, publication year	Country/Region	N	Design, n	Schizophrenia patients								PM type	NOS score
				Age (yrs)[a]	Education (yrs)	Male (%)	Criteria	Illness duration (yrs)	PANSS/ BPRS total score[a]	Illness phase	PM tools		
Altgassen 2008	Switzerland	46	Case-control, 23	40.48	13.72	NR	ICD-10	10.17	NR	NR	Dual-task laboratory test	overall PM	7
Au 2014	Hong Kong	88	Case-control, 44	37.68	10.34	50.00	DSM-IV	10.25	25.7	Chronic phase	Ecological-valid test	Time-, event- PM and overall PM	7
Cao 2016	China	60	Case-control, 30	28.2	NR	100.00	CCMD-3	NR	NR	Rehabilitation phase	Dual-task laboratory test	overall PM	8
Chan 2008	China	64	Case-control, 36	31.28	12.39	83.33	DSM-IV	8.32	60.58	NR	Dual-task laboratory test	Time-, event-, activity-based PM and overall PM	8
Chan 2013	China	75	Case-control, 38	21.76	12.58	36.80	ICD-10	19.84 months	49.89	Early psychosis	Dual-task laboratory test	Time-, event-, activity-based PM	6
Chen 2015	China	40	Case-control, 20	23.65	10.35	100.00	DSM-IV-TR	27.15 months	48.45	Remitted phase	Dual-task laboratory test	Event-based PM	7
Chen 2016	China	50	Case-control, 25 "implementation intention group"	31.24	12.84	44.00	DSM-IV	5.72	52.84	NR	Dual-task laboratory test	overall PM	8
			Case-control, 25 "control PM instruction group"	28.52	13.44	52.00	DSM-IV	4.68	60.92	NR	Dual-task laboratory test		
Cheung 2015	China (Hong Kong & Beijing)	95	Case-control, 58	22.59	NR	61.54	DSM-IV	NR	NR	First-episode	Dual-task laboratory test	Time- and event-based PM	7
Guo 2006	China	58	Case-control, 28	29	NR	42.86	NR	NR	NR	NR	Dual-task laboratory test	overall PM	5
Henry 2007	Australia	59	Case-control, 30	35.70	NR	53.33	DSM-IV	12.70	NR	Stable phase	Ecological-valid test	overall PM	7
Henry 2012	Australia	59	Case-control, 30	39.1	13.1	50.00	DSM-IV	15.4	NR	NR	Dual-task laboratory test	overall PM	7
Kumar 2008	India	84	Case-control, 42	31.62	12.3	100.00	ICD-10	4.71	23.00	NR	Dual-task laboratory test	activity-based PM	8
Lian 2015	China	40	Case-control, 20	39.4	11.1	NR	CCMD-3	NR	NR	NR	Dual-task laboratory test	Event-based PM	7
Lu 2016	China	100	Case-control, 55	27	12	47.27	DSM-IV	NR	NR	NR	Ecological-valid test	Time- and event-based PM	8
Lui 2011	Hong Kong	70	Case-control, 35	22.66	12.8	42.86	DSM-IV	11.31 month	57	First-episode	Dual-task laboratory test	Time-, event-, activity-based PM and overall PM	7
Lui 2015	Hong Kong	174	Case-control, 91	21.85	NR	49.45	DSM-IV	2.3	NR	First-episode	Dual-task laboratory test	Time-, event-based PM and overall PM	7
Man 2016	Hong Kong	70	Case-control, 28	40.29	10.57	82.14	DSM-IV	NR	NR	First-episode	Dual-task laboratory test	Time-, event-, activity-based PM and overall PM	6
Raski 2014	US	65	Case-control, 41	44.17	12.37	56.10	DSM-IV	12.5	71.45	NR	Ecological-valid test	Time-, event-based PM and overall PM	7
Ungvari 2008	Hong Kong	220	Case-control, 110	31.7	10.2	65.45	DSM-IV	8.4	NR	NR	Dual-task laboratory test	Time-and event-based PM	7
Wang 2008b	China	108	Case-control, 54	30.02	12.37	90.74	DSM-IV	7.23	59.52	NR	Dual-task laboratory test	Time-, event-, and activity-based PM	7
Wang 2008a	China	39	Case-control, 19	28.11	11.67	100.00	CCMD-3	NR	NR	NR	Dual-task laboratory test	Event-based PM	7
Wang 2010	China	60	Case-control, 30	28.9	13.2	90.00	DSM-IV	6.06	65.63	NR	Dual-task laboratory test	Time-, and event-PM	6
Wang 2012	China	99	Case-control, 52	NR	NR	51.92	ICD-10	NR	NR	NR	Dual-task laboratory test	Time-, and event-based PM	8
Wang 2013	China	70	Case-control, 40	25	13	52.50	DSM-IV	NR	24.8	NR	Dual-task laboratory test	Time-, and event-PM	7
Xie 2014	China	100	Case-control, 50	59	11	50.00	DSM-IV	31	NR	Chronic phase	Ecological-valid test	Time-, event-based PM and overall PM	8
Yang 2016	China	80	Case-control, 40	67.52	NR	NR	CCMD-3	NR	NR	NR	Ecological-valid test	Time-, event-based PM and overall PM	7

Zhou 2012	China	93	Case-control, 51	25.4	13.7	64.70	DSM-IV	NR	NR	First-episode	Ecological-valid test	Time-, and event-PM	8
Zhou 2011	China	100	Case-control, 23	26.9	12. 2	60.87	ICD-10	7.0 months	84	First-episode	Dual-task laboratory test	Event-based PM	5
			Case-control, 28	33	13.30	78.57	ICD-10	111 months	85	Chronic phase	Dual-task laboratory test	Event-based PM	
Zou 2012	China	116	Case-control, 58	30.57	10.4	46.55	CCMD-3	7.61	NR	NR	Dual-task laboratory test	Event-based PM	5

CCMD-3 = China's Mental Disorder Classification and Diagnosis, standard 3th edition; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revision; ICD-10 = the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems; PANSS = Positive and Negative Syndrome Scale; BPRS = Brief Psychiatric Rating Scale; yrs. = years; NR = not reported; NOS = Newcastle-Ottawa Scale.

[a] Mean at baseline.

with large effect sizes according to Cohen's criterion (Cohen, 1988). As hypothesized, the TBPM impairment had the largest effect size, confirming TBPM as the most impaired PM subtype. Negative symptoms, eco-valid PM measurement and chronic illness stage were significantly and positively associated with more severe overall PM impairment as hypothesized.

Similar findings regarding PM impairment have been reported in a previous meta-analysis (Wang et al., 2009). The effect size of TBPM and ABPM was slightly smaller than earlier reported (Wang et al., 2009) (TBPM: −1.155 vs. -1.33; ABPM: −0.563 vs. -0.729), while EBPM impairment was slightly larger in this study (−1.068 vs. -0.827). The discrepancy in effect sizes between the two meta-analyses could be due to the inclusion of recently published studies and those in Chinese databases in the current meta-analysis.

The effect size in TBPM was larger (−1.155) than in EBPM (−1.068) and ABPM (−0.563) indicating that TBPM is more likely to be impaired in schizophrenia. This disproportionate impairment between TBPM and EBPM was also observed bipolar disorder (Zhou et al., 2018), depression (Zhou et al., 2017), Parkinson's disease (Hedges'g: −0.71 vs. -0.55) (Ramanan and Kumar, 2013) and autism spectrum disorder (Hedges'g: −0.87 vs. -0.41) (Landsiedel et al., 2017). It may well be that more self-initiation is involved in TBPM placing more cognitive demands on the PFC, which is more susceptible to dysfunction in schizophrenia and patients' first-degree relatives (Boos et al., 2007; McIntosh et al., 2011). However, TBPM performance is not always more impaired than EBPM (Au et al., 2014; Lui et al., 2011; Lui et al., 2015; Raskin et al., 2014) and its effect size (SMD = -0.27) could be smaller than that of EBPM's (SMD = -0.54) (Chan et al., 2013). Other possible reasons may point to confounding factors in PM assessment, such as the frequency of performing PM tasks, duration of the time-delay (Raskin et al., 2014), and the focality (focal or non-focal) of PM cue in EBPM tests (Kliegel et al., 2008).

Since PM deficits are also found in a host of other neuropsychiatric disorders, PM is regarded as a transdiagnostic marker related to the expression of common genetic variations and neurocognitive abnormalities (Ellisonwright and Bullmore, 2010; Ivleva et al., 2010; Potash and Bienvenu, 2009; Yu et al., 2010). The effect sizes of TBPM and EBPM in schizophrenia are larger than in bipolar disorder (−0.82, and −0.51, respectively) (Zhou et al., 2018), depression (−0.89, and −0.44, respectively) (Zhou et al., 2017), autism spectrum disorder (Hedges'g = −0.87 and −0.41) (Landsiedel et al., 2017), and Parkinson's disease (Hedges'g = −0.71 and −0.55) (Ramanan and Kumar, 2013). Schizophrenia, bipolar disorder and depression all exhibit prefrontal and temporal lobe dysfunction, which could result in PM impairment.

Meta-regression analyses found significant positive associations between psychopathology, particularly negative symptoms, and PM impairment, which confirms earlier findings (Wang et al., 2009). Likewise, other meta-analyses found significant relationship between negative symptoms and neurocognitive functions such as working memory and executive functions (Dibben et al., 2009; Nieuwenstein et al., 2001). This may be attributable to frontal lobe dysfunction, which is assumed to be responsible for both negative symptoms and neurocognitive deficits (Liddle et al., 2001).

Subgroup analyses revealed significant associations between poor overall PM performance and older age, lower education and male sex. The brain of schizophrenia patients may be affected by abnormally accelerated aging processes, decline in frontotemporal gray matter (Mathalon et al., 2001) and white matter integrity (Wright et al., 2014). In addition, the execution of PM needs the capacity of self-initiation, which is also compromised with aging (Craik, 1986). Healthy men perform better than women in PM (Bahrainian et al., 2013; Huppert et al., 2000), but the sexual dimorphism in healthy individuals on certain cognitive function could also be disturbed in schizophrenia (Guillem et al., 2009;

Table 2
GRADE analyses: prospective memory in schizophrenia.

Meta-analytic outcomes	Arms (N)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Overall quality of evidence[a]
Overall PM	22 (1044)	No	Serious[b]	No	No	Serious[c]	Large[d]	+/+/+/−/; Moderate
Time-based PM	20 (1632)	No	Serious[b]	No	No	No	Large[d]	+/+/+/+/; High
Event-based PM	27 (2042)	No	Serious[b]	No	No	No	Large[d]	+/+/+/+/; High
Activity-based PM	5 (401)	No	Serious[b]	No	No	No	No	+/+/+/−/; Moderate

GRADE = Grading of Recommendations Assessment, Development, and Evaluation.
[a] GRADE Working Group's grades of evidence: High quality = further research is very unlikely to change our confidence in the estimate of effect. Moderate quality = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality = we are very uncertain about the estimate.
[b] All studies reported having a serious inconsistency had $I^2 > 50\%$.
[c] The funnel plot or Egger's regression intercept suggests a high risk of publication bias.
[d] Studies with large effects provide robust quality of evidence. Large effects = standard mean differences<−0.8.

Jiménez et al., 2010). For example, male schizophrenia patients are more likely to have cognitive deficits than their female counterparts in cognitive domains (Goldstein et al., 1998; Seidman et al., 1997).

In the subgroup analysis, first-episode patients had less severe overall PM impairment (SMD = -0.641) compared with chronic patients (SMD = -1.237), indicating the association between impaired PM and chronic illness course. Chronic patients have longer antipsychotic treatment, multiple episodes and hospitalizations, all of which could result in greater cognitive impairment (Braw et al., 2008; Terry Jr. et al., 2005, 2006a, 2006b). Publications before 2009 reported more severe PM impairment. All the three studies published before 2009 focused on chronic schizophrenia patients, which could explain the more severe PM impairment in this subgroup.

Eco-valid PM measurements were associated with more severe PM impairment compared to dual-task laboratory tests probably because they are more sensitive to PM impairment in schizophrenia. Ecological validity refers to generalizability and representativeness of cognitive assessments (Burgess et al., 2006) and is particularly important in assessing PM for psychosocial interventions and rehabilitation (Dawson and Marcotte, 2017). However, PM is often examined in laboratories but even carefully designed tests based on the dual-task paradigm do not have sufficient ecological validity due to the discrepancy between laboratory and real-world situations (Kliegel and Jager, 2006).

The strengths of this meta-analysis are the large number of studies and sample size (29 studies with 2492 participants), and the examination of various types of PM measurements (eco-valid vs. dual-task laboratory) and illness stages (first-episode vs. chronic) on PM performance, as well as the inclusion of both English and Chinese databases. However, the results need to be interpreted with caution due to the following methodological limitations. First, the sample characteristics were heterogeneous. In addition, different settings (inpatients or outpatients) and illness phases (first episode, acute phase, or chronic phase) were included, which increased the heterogeneity of the results and bias the findings to an uncertain extent. Despite adding subgroup and sensitivity analyses to the methods heterogeneity still remained in some subgroup. Second, PM measures were also different across the included studies. Finally, other factors related to PM performance, such as antipsychotic treatment and severity of side effects, could not be examined due to lack of information.

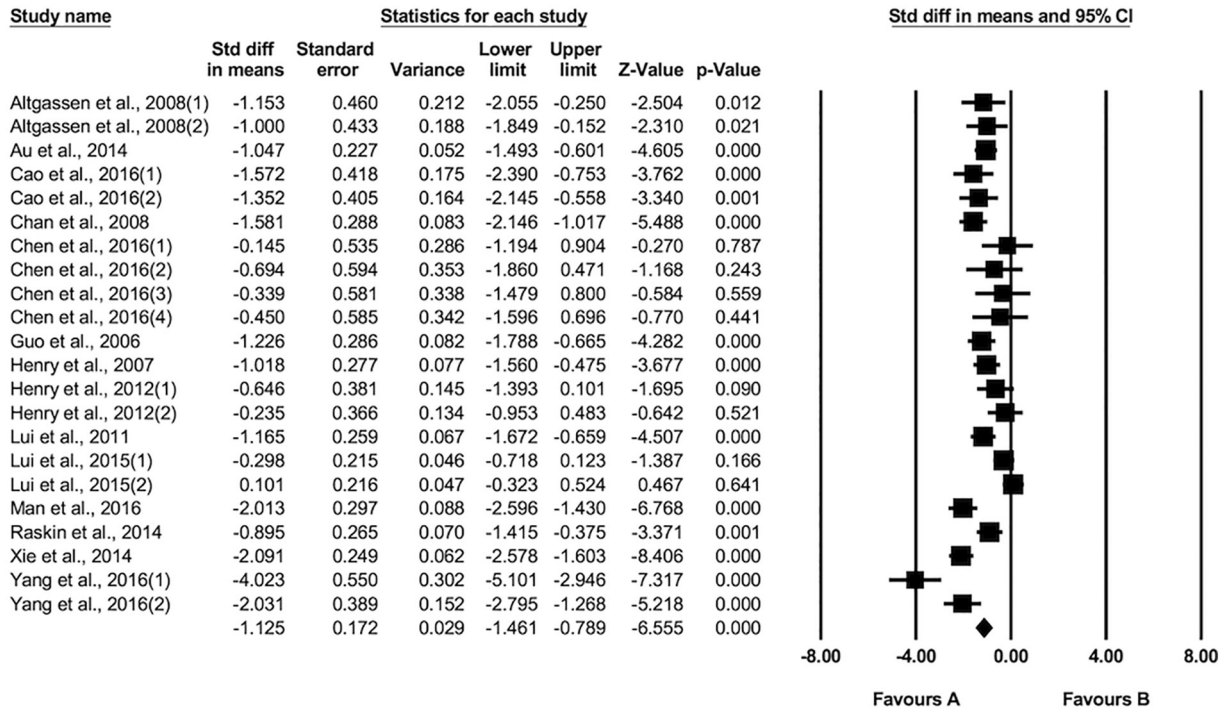

Fig. 2. Prospective memory (PM) in schizophrenia: forest plot of overall PM. Lines indicate 95% confidence intervals (CI); the square at midpoint of each line indicates the standardized mean difference (SMD) for each study; the diamond indicates the overall SMD and 95% CI.

Table 3
Subgroup analyses of overall prospective memory.

Variables	Arms (subjects)	SMDs (95%CI)	I^2 (%)	*P*-value for each subgroup	Between group Q-value	*P*-value for between group Q value
1. Age (years)[a] of patients: ≥32.3	10 (509)	−1.398 (−1.598, −1.197)	84.627	<0.001	21.384	<0.0001
<32.3	12 (535)	−0.763 (−0.942, −0.583)	74.223	<0.001		
2. School education (years)[b] of patients*: ≥12.9	6 (129)	−0.637 (−0.994, −0.281)	0	<0.001	12.725	<0.0001
<12.9	10 (544)	−1.373 (−1.563, −1.182)	65.690	<0.001		
3. Gender predominance in patients*: Male predominance (≥60%)	4 (194)	−1.679 (−2.009, −1.348)	0	<0.001	22.242	<0.0001
No sex predominance	14 (724)	−0.800 (−0.955, −0.645)	78.688	<0.001		
4. First-episode schizophrenia*,*	4 (314)	−0.641 (−0.876, −0.406)	92.452	<0.001	16.686	<0.0001
Chronic schizophrenia	18 (730)	−1.237 (−1.400, −1.074)	74.309	<0.001		
5. Eco-valid measurements	7 (463)	−1.542 (−1.756, −1.328)	86.238	<0.001	34.186	<0.0001
Dual-task laboratory measurements	15 (581)	−0.725 (−0.896, −0.553)	68.764	<0.001		
6. Chinese	16 (814)	−1.112 (−1.265, −0.958)	87.014	<0.001	2.565	0.109
Non-Chinese	6 (276)	−0.872 (−1.122, −0.623)	0	<0.001		
7. Publication year after 2009	17 (817)	−0.993 (−1.144, −0.841)	86.465	<0.001	2.011	0.156
Publication year before 2009	5 (227)	−1.226 (−1.511, −0.942)	0	<0.001		

NA = not applicable; SMDs = Standard mean differences.
* Subgroup analyses with available data.
[a] Including one study conducted in China and UK.
[b] Analyzed using a mean split.

In conclusion, in this meta-analysis overall PM and all its subtypes, particularly the TBPM, were significantly impaired in schizophrenia. Chronic illness stage, more severe negative symptoms and eco-valid PM measurements were significantly associated with more severe PM impairment. More high-quality studies with large sample sizes are needed to confirm these findings.

Contributors

Study design: Fu-Chun Zhou, Yu-Tao Xiang. Data collection, analysis and interpretation: Fu-Chun Zhou, Wei Zheng, Li Lu, Yuan-Yuan Wang, Jun Li. Drafting of the manuscript: Fu-Chun Zhou, Wei Zheng, Yu-Tao Xiang. Critical revision of the manuscript: Gabor S. Ungvari, Chee H. Ng. Approval of the final version for publication: all co-authors.

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Declaration of competing interest

The authors have no conflicts of interest.

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N/A.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.08.010.

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