REVIEW

Prospective memory in non-psychotic first-degree relatives of patients with schizophrenia: a meta-analysis

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Abstract: Prospective memory (PM) could be impaired in the non-psychotic first-degree relatives of patients with schizophrenia. This meta-analysis systematically examined the PM of non-psychotic first-degree relatives of patients with schizophrenia. Both Chinese and English databases were systematically searched for articles from the inception of the databases through November 13, 2018. Case-control studies of PM in non-psychotic first-degree relatives of patients with schizophrenia were included in the analyses. Confidence intervals (CIs) and standardized mean differences (SMDs) were calculated utilizing the random effects model. Four studies (n=268) that compared PM performance between non-psychotic first-degree relatives of patients with schizophrenia (n=136) and healthy controls (n=132) were included. Three studies were rated as "high quality", while the quality of evidence of the three outcomes included in this meta-analysis was moderate. Compared with the healthy controls, the non-psychotic first-degree relatives of patients with schizophrenia showed impairments in overall PM (two studies, n=127; SMD: −0.46; 95% CI=−0.82, −0.11, P=0.01; I=0%), event-based PM (EBPM) (four studies, n=268; SMD: −0.56; 95% CI=−0.80, −0.31, P<0.00001; I=0%), and time-based PM (TBPM) (four studies, n=268; SMD: −0.66; 95% CI=−0.90, −0.41, P<0.00001; I=0%). This meta-analysis demonstrated that the overall PM, EBPM, and TBPM might be impaired in the non-psychotic first-degree relatives of patients with schizophrenia.

Keywords: schizophrenia, relatives, prospective memory, endophenotypes

Introduction

Schizophrenia is a recurrent, prolonged, and chronic mental illness with strong heritability,[1] and the genetic risk of schizophrenia is estimated to be as high as 80%.[2] Therefore, the risk of developing schizophrenia in non-psychotic first-degree relatives of patients with schizophrenia is higher than that of the general population.[3] Schizophrenia is often associated with various cognitive dysfunctions,[4–8] which may be related to the heritability of schizophrenia. Relevant studies have found that the non-psychotic first-degree relatives of patients with schizophrenia also exhibit cognitive defects that are similar but less severe than those of the patients.[9–14] In terms of memory impairment, one of the most extensively researched areas of cognitive impairment, verbal memory, has been found to be as deficient as working memory in non-onset biological relatives or healthy siblings of patients with schizophrenia.[15–19] Apparently, each of the studies have been restricted to retrospective memory, and there are few reports on prospective memory.

Prospective memory (PM) is defined as the capability of remembering to perform a planned action in the future.[20] To complete a typical PM task, an individual first needs to form an intent (when and what needs to be done) and then begins to engage in an ongoing task. When performing ongoing tasks, individuals need to maintain focus and monitor PM cues. When a prospective memory cue appears and is detected, the individual should retrieve the intent and respond, which is of vital importance for everyday life, as research has shown that up to "50–80%" of daily activities are largely affected by PM.[21] For example, remembering to attend a meeting tomorrow, remembering to sit for an exam next week, and remembering when to turn off the gas, etc., all require good PM function. We cannot imagine how severe and grave the consequences would be in our lives without PM. According to the nature of intention cues, PM falls into three categories: time-based prospective memory (TBPM), event-based prospective memory (EBPM), and activity-based prospective memory (ABPM).[22,23] TBPM requires a person to remember to execute one intention after one specific time period (such as attending an academic conference next Saturday); EBPM requires a person to perform an intent when the prompt appears (such as purchasing a toothbrush when passing a supermarket, which is an external cue); and ABPM requires a person to do a planned action at the end of an activity (such as sending an email after a wedding).

We have developed an understanding of cognitive profiles of non-psychotic first-degree relatives of patients suffering from schizophrenia both in working and verbal memory. In recent years, the PM function of the non-psychotic first-degree relatives of patients with schizophrenia has attracted increasing attention. To date, only a small number of case-control studies have been published, and these studies had small sample sizes and conflicting results.[24–27] By thoroughly searching the literature, no systematic review or meta-analysis can be located that specifically investigates the prospective memory of non-psychotic first-degree relatives of patients with schizophrenia, which provided an impetus for us to perform a comprehensive meta-analysis on the prospective memory of the non-psychotic first-degree relatives of patients with schizophrenia.

Methods

Search strategy and selection criteria

The inclusion criteria were identified by utilizing the PICOS acronym: Participants (P): non-psychotic first-degree relatives of patients with schizophrenia. Intervention (I): not applicable (NA). Comparison (C): healthy controls. Outcome (O): time-based PM, event-based PM, and overall PM. Study design (S): case-control studies exploring PM of non-psychotic first-degree relatives of patients with schizophrenia with the data required for the meta-analysis.

In accordance with the statement of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[28] two investigators (SZL, YKW) searched Chinese (China National Knowledge Infrastructure, WanFang and Chinese Biomedical databases) and English databases (Embase, PubMed, Cochrane Library, and PsycINFO databases) independently, from database inception through November 13, 2018. The following search keywords were adopted: (schizophrenia OR psychotic disorder) AND (relatives OR siblings OR parents OR children OR offspring OR family members) AND (prospective memory OR prospective memories OR prospective remembering OR delayed intention). In addition, hand searching of reference lists of the identified studies and related reviews was performed.

Data extraction

SZL and YKW checked, extracted, and analyzed data independently. The data is presented in forest plots. Any inconsistency during the collection and analysis of the data was attempted to be addressed by a consensus; if the inconsistency was not solved, a third reviewer (TMS) would get involved. The related variables were extracted from the articles using a pre-designed standard form. If the same data was reported in more than one study, only the study with complete data would be incorporated into the analysis. Moreover, the corresponding or first author was contacted to obtain more information if required.

Statistical approaches

In accordance with the recommendations from the Cochrane Handbook for Systematic Reviews,[29] the meta-analysis was performed utilizing Review Manager Version 5.3 software. Due to heterogeneity within the characteristics of this study (like sampling and sample size), a random effects model was adopted for each meta-analysis outcome.[30] In terms of continuous outcome data, the standard mean difference (SMD) and the 95% CI between the non-psychotic first-degree relatives of patients with schizophrenia and the controls were calculated using the inverse variance method. Notable heterogeneity of the meta-analysis results was defined when I^2 values were

>50% or $P<0.1$ within Q statistics.[31] In terms of primary outcome, a subgroup or sensitivity analysis was performed to investigate the cause of the heterogeneity.

Egger's intercept and funnel plots were used to assess the publication bias.[32] Each analysis was two-tailed, with 0.05 set as the significance level.

Study quality assessment

Two investigators (SZL, YKW) evaluated the quality of all studies utilizing the Newcastle-Ottawa Scale (NOS).[33]Following previous studies, an NOS score ≥7 points was rated as high-quality.[34,35] In addition, the grading of recommendation evaluation, development, and assessment (GRADE) system was utilized to assess the quality of evidence,[36,37]and the meta-analysis data results were rated as "high quality", "moderate quality", "low quality", and "very low quality".

Results
Search results

Figure 1 shows the PRISMA flow diagram demonstrating that 369 articles were discovered by searching the above-mentioned databases. Three studies were excluded because of overlapping data with other studies.[38–40]Four

published English studies were finally included in the meta-analysis.[24–27]

Studies, characteristics of the relatives, and PM measures

The four case-control studies (n=268) that compared the non-psychotic first-degree relatives of patients with schizophrenia (n=136) with healthy controls (n=132) were performed in Hong Kong, China, and India. The average age of the participants was between 11.33 and 50.02 years, and the average length of education of the participants was 11.71–14.94 years. In one study,[26] the Cambridge Prospective Memory Test-Chinese version (C-CAMPROMPT) was used for assessing PM.[41] In addition, one laboratory computerized dual-task paradigm was used for assessing PM in three studies (Table 1).[42–45]

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

Assessment of quality

NOS scores of the four studies were between 6 and 8 (Table 2), and three studies were rated as "high quality" (NOS ≥7).[24–26]The quality of evidence for the three meta-analysis outcomes was "moderate" according to the GRADE approach (Table 3).
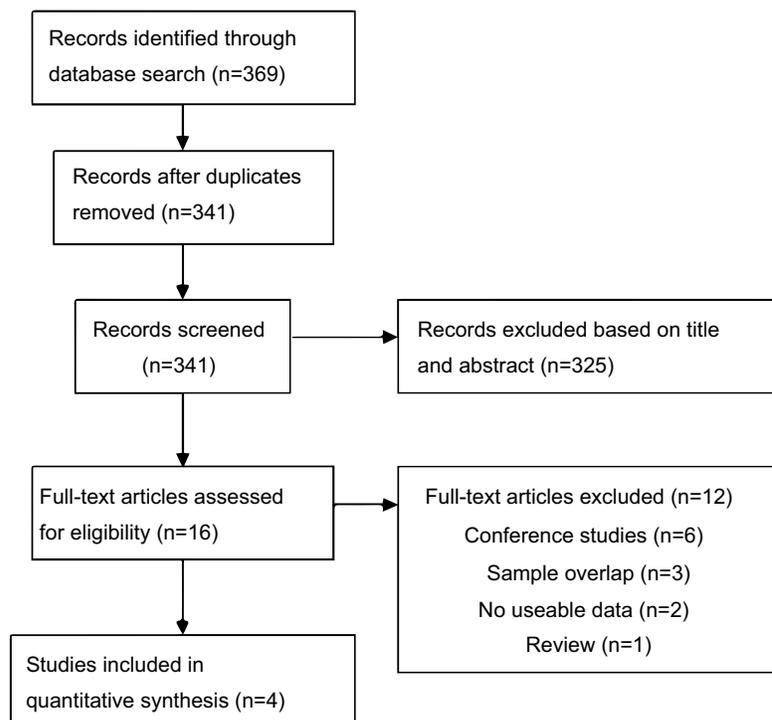

Figure 1 PRISMA flow.

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

Studies	Country/area	N	Design, n	Relative		Healthy control		PM measurement	PM type	NOS score
				Age (years)	Education (years)	Age (years)	Education (years)			
Wang et al (2010)[25]	China	52	Case control 26/26	50.02	11.71	43.38	11.15	Computerized dual task paradigm	Time, Event, Activity, Overall	8
Lui et al (2011)[24]	Hong Kong	75	Case control 40/35	23.33	13.13	23.17	13.6	Computerized dual task paradigm	Time, Event, Activity, Overall	7
Zhou et al (2014)[26]	China	101	Case control 50/51	28	14	24.3	16.1	C-CAMPROMPT	Time, Event	7
Saleem et al (2018)[27]	India	40	Case control 20/20	28.8	14.95	34.4	15.05	Computerized dual task paradigm	Time, Event	6

Abbreviations: C-CAMPROMPT, the Cambridge Prospective Memory Test-Chinese version; NOS, Newcastle–Ottawa Scale; PM, prospective memory.

Table 2 Methodological quality assessment by the Newcastle-Ottawa scale

Studies	Selection				Comparability		Exposure			Total quality score
	The case definition is adequate with independent validation	Representativeness of cases	Community controls	Controls with no history of disease	Cases and controls with comparable education	Cases and controls with comparable age	Ascertainment of outcome	Same method of ascertainment for cases and controls	Similar non response rate for both groups	
Wang et al (2010)[25]	–	–	–	–	–	–	0	–	–	8
Lui et al (2011)[24]	–	–	0	–	–	–	0	–	–	7
Zhou et al (2014)[26]	–	–	–	–	0	–	0	–	–	7
Saleem et al (2018)[27]	–	–	0	–	–	0	0	–	–	6

Table 2 Methodological quality assessment by the Newcastle-Ottawa scale

Table 3 GRADE analyses: prospective memory in non-psychotic first-degree relatives of patients with schizophrenia

Overall PM

In the two studies that had data available about overall performance of PM (n=127), the performance of non-psychotic first-degree relatives of patients with schizophrenia was poorer than that of healthy controls with a SMD of −0.46 (95% CI=−0.82, −0.11, P=0.01; I^2= 0%, Figure 2).

Time-based PM

In the four studies that had data available about time-based PM (n=268), the performance of non-psychotic first-degree relatives of patients with schizophrenia was poorer than that of healthy controls with a SMD of −0.66 (95% CI=−0.90, −0.41, P<0.00001; I^2=0%, Figure 2).

Event-based PM

In the four studies that had data available about event-based PM (n=268), the performance of non-psychotic first-degree relatives of patients with schizophrenia was poorer compared to that of healthy controls with a SMD of −0.56 (95% CI=−0.80, −0.31, P<0.00001; I^2=0%, Figure 2).

Activity-based PM

In the two studies that had data available about activity-based PM (n=127), the performance of non-psychotic first-degree relatives of patients with schizophrenia did not differ from healthy controls with a SMD of −0.11 (95% CI=−0.46, 0.24, P=0.55; I^2=0%, Figure 2).

Publication bias

Because only four studies were incorporated in the meta-analysis, the publication bias of the meta-analysis outcomes could not be carried out using Egger's test or a funnel plot.[46]

Discussion

To the best of our knowledge, this is the first meta-analysis on the PM performance of first-degree relatives of patients with schizophrenia. The analysis results demonstrated that the overall prospective memory and the two categories of PM were markedly impaired with a medium effect size (overall PM: SMD=−0.46; EBPM: SMD=−0.56; TBPM:

SMD=−0.66). These results are in line with the meta-analysis on working memory, verbal memory, and executive function in non-psychotic first-degree relatives of patients with schizophrenia.[13,17] The performance of the overall PM, TBPM, and EBPM in first-degree relatives was markedly lower than that of normal controls, which was similar to that in schizophrenic patients.[43,47,48] Although this impairment is less severe, this indicates that PM might be related to the heritability of schizophrenia. Additionally, the ABPM task was considered to be the simplest among the three memory tasks. Only two articles confirmed that the ABPM of first-degree relatives of patients with schizophrenia was not impaired in this task,[24,25] suggesting that the first-degree relatives of patients suffering from schizophrenia had certain neuro-cognitive impairments, but their impairments were not as serious as those of patients with schizophrenia.

We discovered that the effect size of TBPM (SMD=−0.66) was larger than that of EBPM (SMD=−0.56), which showed a similar trend as that observed in any other neuropsychiatric disorder. For instance, one meta-analysis on the prospective memory of patients with schizophrenia revealed that TBPM impairment (Cohen's d=−1.33) was more severe than EBPM impairment (Cohen's d=−0.827).[49] A larger effect size of TBPM than of EBPM was also reported in depression (SMD=−0.89 vs −0.44),[50] bipolar disorder (SMD=−0.82 vs −0.51),[51] Parkinson's disease (Hedges' g=−0.71 vs −0.55) and autism spectrum disorder (Hedges' g=−0.87 vs −0.41) .[52,53] This tendency can be explained by various TBPM and EBPM cognitive processes and their load on the prefrontal cortex.[54,55] TBPM has a more complicated cognitive process than EBPM, because there is not any specific external cue to trigger it. When performing tasks, much more effort is required to supervise time as well as self-initiate a prospective intention. In contrast, EBPM includes fewer demands for self-initiation, as it relies on one external cue as the trigger,[22] leading to less demanding EBPM in the prefrontal cortex.[55] Therefore, TBPM is more demanding and is more likely to be compromised in patients suffering from pathological or other neuropsychiatric disorders, which includes first-degree relatives of patients with schizophrenia.[22,55] This hypothesis was confirmed in the meta-analysis,[49] which suggested that the differences between TBPM and EBPM were heterogeneous.

Schizophrenia is an inherited disease,[1] but the results of conventional linkage and association studies on susceptibility loci are not consistent.[56] Therefore, in recent years, researchers have adopted endophenotype approaches to

Table 3 GRADE analyses: prospective memory in non-psychotic first-degree relatives of patients with schizophrenia

Meta-analytic outcomes	Studies (N)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Overall quality of evidence[a]
Overall PM	2 (127)	No	No	No	No	Serious[b]	No	+/+/±/; Moderate
Time-based PM	4 (268)	No	No	No	No	Serious[b]	No	+/+/±/; Moderate
Event-based PM	4 (268)	No	No	No	No	Serious[b]	No	+/+/±/; Moderate
Activity-based PM	2 (127)	No	No	No	No	Serious[b]	No	+/+/±/; Moderate

Notes: [a]GRADE Working Group 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]For continuous outcomes, N<400.
Abbreviations: GRADE, grading of recommendations assessment, development, and evaluation; PM, prospective memory.
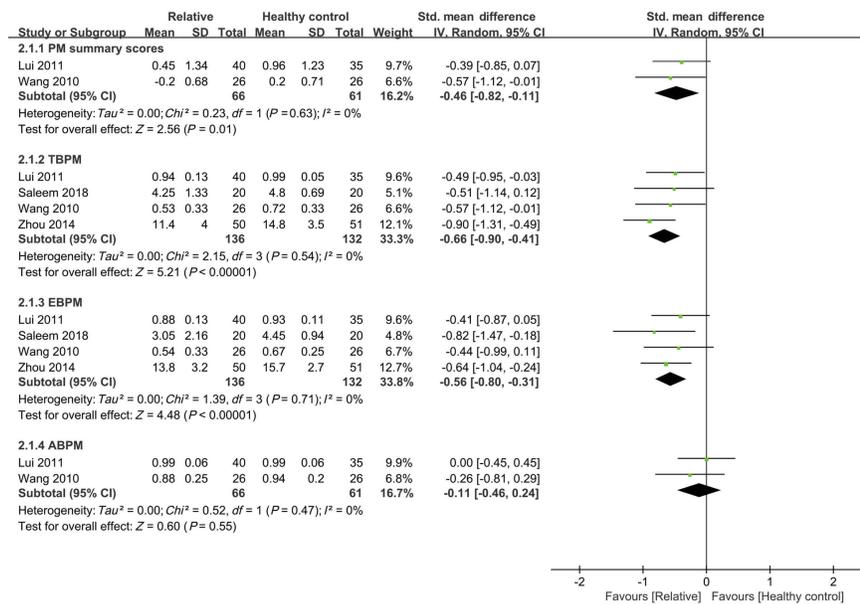

Figure 2 Prospective memory in non-psychotic first-degree relatives of patients with schizophrenia: forest plot of overall PM, time-based PM, event-based PM, and activity-based PM.
Abbreviation: PM, prospective memory.

investigate the genetic basis of schizophrenia.[57,58] An endophenotype is closer to the function of gene action than the diagnosis of schizophrenia itself; thus, it is easier to locate the locus of the endophenotype than the locus of schizophrenia.[57,59] There are a number of endophenotypes, and cognitive endophenotypes have been extensively studied. So far, some research has shown that the impairment of PM exists within schizophrenia patients, regardless of chronic,[47,60–63] first-episode, or even first-episode drug-naive status,[64–66] and meta-analyses and systematic reviews have been conducted.[49,67] In this study, it was found that the non-psychotic first-degree relatives of

patients with schizophrenia had defects in their prospective memory. Based on the above studies, we can determine that the characteristics of PM impairment of schizophrenia seem to conform to the disease association, state independence (regardless of first or chronic stages), family association, and the high-risk group of the endophenotype criterion proposed by Gottsman and Gould.[57] In summary, it is reasonable to speculate that PM might be an endophenotype of schizophrenia.

Due to some methodological limitations, the meta-analysis results should be interpreted cautiously. First, the sample sizes involved in this study were comparatively

small, and all meta-analysis results were rated only as "moderate quality" according to the GRADE score. Future studies may require larger samples and may be required to distinguish between parents, siblings, and offspring of the patients suffering from schizophrenia, since genetic studies have discovered that parents, siblings, and offspring of people with schizophrenia have different prevalence rates.[3] Second, only Chinese and English databases were searched, and only four studies were incorporated; therefore, the publication bias could not be tested. Third, different studies employed different PM measurement approaches, and the results were not the same. Therefore, we used a random effects model to provide conservative estimates.

Conclusion

The meta-analysis revealed that PM, especially TBPM, might be impaired in non-psychotic first-degree relatives of patients with schizophrenia. Further high-quality large sample studies are worthwhile and necessary. Furthermore, it is recommended that psychiatrists place more emphasis on early detection of PM deficits in first-degree relatives of patients with schizophrenia, and take into account the effective implementation of interventions to mitigate negative outcomes related to PM deficits.

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Disclosure

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