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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