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Deficits in Cue Detection and Intention Retrieval Underlie Prospective Memory Impairment in Schizophrenia

Steven Paul Woods^{1,*}, Elizabeth W. Twamley¹, Matthew S. Dawson¹, Jenille M. Narvaez¹, and Dilip V. Jeste^{1,2}

¹ Department of Psychiatry, University of California, San Diego, La Jolla, CA, 92093, USA

² Division of Geriatric Psychiatry, VA San Diego Healthcare System, San Diego, CA, 92161, USA

Abstract

Emerging evidence indicates that individuals with schizophrenia (SCZ) may exhibit deficits in prospective memory (ProM), a dissociable and ecologically important aspect of episodic memory entailing the formation, maintenance, and execution of future intentions. The present study aimed to elucidate the component processes of ProM impairment in 41 individuals with SCZ relative to 41 demographically similar healthy comparison (HC) participants. Results revealed that the SCZ group performed worse than HCs on overall ProM, with comparable deficits on time- and event-based ProM trials. In the SCZ cohort, better ProM performance was associated with younger age and less severe negative symptoms. Although a significantly greater number of task substitution and loss of time errors were evident in the SCZ group as compared to HCs, the most prevalent error type in SCZ was characterized by a complete failure to respond to the ProM cue. Importantly, the SCZ and HC groups did not differ on a post-test multiple-choice recognition trial, suggesting adequate formation and maintenance (i.e., retention) of the ProM cue-intention pairing when self-directed monitoring and retrieval demands were minimized. Findings indicate that SCZ is associated with impairment in the cue detection and self-initiated retrieval components of executing future intentions, which is consistent with a possible prefrontostriatal loop neuropathogenesis. Further studies are needed to explore the neurobiological mechanisms of SCZ-associated ProM impairment and the impact of such deficits on daily functioning (e.g., medication compliance).

Keywords

Schizophrenia; neuropsychological assessment; cognitive processes; episodic memory

1. Introduction

Schizophrenia (SCZ) is associated with mild-to-moderate impairment in several cognitive domains, including attention, language, executive functions, and memory (e.g., Bowie & Harvey, 2005; Elvevåg & Goldberg, 2000; Heaton et al., 2001). Episodic memory impairment is particularly prevalent in SCZ (Aleman et al., 1999) and is associated with more severe negative symptoms (Aleman et al., 1999) and poorer functional outcomes (Green et al., 2004). The profile of SCZ-associated episodic memory deficits typically involves deficient

* Corresponding author. HIV Neurobehavioral Research Center (0847), University of California, San Diego, 150 West Washington Street, 2nd floor, San Diego, California, 92103, USA. Telephone: (619) 543-5004. Fax: (619) 543-1235. Electronic mail may be sent to spwoods@ucsd.edu..

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strategic encoding and retrieval, with broadly intact consolidation (i.e., the capacity to retain information over time; Aleman et al., 1999). Dysfunction within prefrontal systems and, to a lesser extent, medial temporal networks, is thought to underlie SCZ-associated episodic memory deficits (Achim & LePage, 2005).

To date, research on episodic memory in SCZ has focused on retrospective memory (i.e., explicitly prompted recall of past events), whereas studies of prospective memory (ProM) (i.e., “remembering to remember”) have been relatively scarce (Shum et al., 2001). ProM refers to the formation, maintenance, and execution of future intentions (Kvavilashvili & Ellis, 1996), which can be classified as either event-based (e.g., remembering to take a medication after every meal) or time-based (e.g., remembering to take a medication at a particular time of day). ProM is of considerable theoretical relevance because it is singly dissociable from retrospective memory (i.e., retrospective memory is necessary, but not sufficient for ProM). Moreover, pervasive ProM failures may hinder the performance instrumental activities of daily living (IADLs; e.g., medication adherence). Thus, the clinical and theoretical importance of understanding the prevalence, cognitive and neurobiological mechanisms, and functional impact of ProM impairment in SCZ is clear.

To our knowledge, only four studies have been published on ProM in SCZ. Kondel (2002) reported that individuals with SCZ-associated executive dysfunction were slowed in recognizing the content of intended actions. More recent SCZ studies revealed evidence of impairment on simple measures of event-based ProM in which an external stimulus (e.g., a target word imbedded in a general knowledge test) served as the cue for performing the intention (Elvevåg et al., 2003; Kumar et al., 2005; Shum et al., 2004). Shum et al. (2004) went on to demonstrate a disproportionate deficit in time-based ProM in SCZ, perhaps indicating a particular impairment in the executive aspects of ProM (Shum et al., 2004).

Importantly, however, no prior studies have explicated the component processes of SCZ-associated ProM deficits, which may clarify cognitive substrates, inform remediation planning, and improve functional outcomes (Kurtz et al., 2001). The current study was therefore guided by a 4-stage conceptual model of ProM component processes (see Carey et al., 2006): (1) The *intention formation* stage of ProM is the formation of the intention and its corresponding action, which involves the generation and encoding of an action plan. (2) The *delay maintenance interval* stage describes the delay between initial encoding and the point at which the intention is realized, during which time another activity is ongoing so as to prevent overt rehearsal. (3) The *self-initiated cue recognition and intention retrieval* stage involves recognizing a cue and searching retrospective memory for the correct intention. This stage, which is considered the defining feature of ProM, differs from conventional tasks in which an experimenter explicitly prompts the search for recall. (4) The *intention execution* stage involves performing the ProM task and evaluating its accuracy and completeness.

In light of the profile and neural substrates of SCZ-associated episodic memory deficits, we hypothesized that individuals with SCZ would evidence impairment in the first (i.e., intention formation) and third (i.e., self-initiated cue recognition and intention retrieval) stages of the conceptual model of ProM as compared to demographically similar healthy comparison subjects (HCs). Considering the findings of Shum et al. (2004), we also hypothesized that individuals with SCZ would demonstrate a greater deficit in time-based than event-based ProM. Finally, the severity of the global ProM impairment was expected to correlate with SCZ disease burden variables (e.g., negative symptoms).

2. Method

2.1 Participants

The present study used a cross-sectional, static-group comparison design that included 41 outpatients with SCZ and 41 demographically comparable HCs (see Table 1). Diagnoses of SCZ were made by treating psychiatrists according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., American Psychiatric Association, 1994) and were confirmed by retrospective chart reviews. SCZ volunteers were self-referred via waiting room flyers or by their health care providers to participate in a cognitive training study. The community-based HC volunteers were recruited via public flyers and newspaper advertisements. Individuals with mental retardation, current substance-related disorders, neurological conditions known to affect cognition (e.g., seizure disorders), or head injuries with loss of consciousness greater than 30 minutes were excluded.

2.2 Materials and Methods

The local Institutional Review Board approved the study protocol. All participants were administered the Memory for Intentions Screening Test (MIST; Raskin, 2004). As shown in Table 2, the MIST is a standardized test comprised of eight ProM tasks that are counterbalanced on delay interval (i.e., 2- vs. 15-minutes), cue type (i.e., event- vs. time-based), and response (action vs. verbal). Word search puzzles are provided as a distracter task to prevent overt rehearsal of the intention. MIST items are scored on a three-point scale, ranging from 0 (i.e., no response or an incorrect response to an event-based trial or at an incorrect time) to 2 (i.e., completely correct) points. Each item contributes to three of the six subscales (range = 0–8) displayed in Table 2 as determined by that item's specific delay, cue, and response characteristics. The subscales are subsequently summed to create a summary score ranging from 0 to 48. The MIST also includes a 3-choice recognition trial that is administered following the completion of all eight ProM tasks (range = 0–8). A Retrieval Index (Carey et al., 2006) was constructed by subtracting the total free recall accuracy (range = 0–8) from the number of recognition hits (range = 0–8). Finally, a 24-hour probe was administered in which participants were instructed to leave a telephone message for the examiner the following day to report the number of hours they slept the prior night. Prior research supports the reliability (Raskin, 2004) and construct validity of the MIST (Carey et al., 2006; Raskin, 2004; Woods et al., in press).

The MIST also provides standardized qualitative error coding methods. A No Response error is recorded when the participant does not respond to a ProM cue. A Task Substitution error is coded when a participant: (1) substitutes an action for a verbal task (or *vice versa*); (2) performs a prior task from any part of the complete test; or (3) performs a novel response. Loss of Content errors are those in which participants recognize the ProM cue and indicate that they are supposed to do something, but cannot remember what to do. Place Losing Omissions occur when a participant performs part of a task, but gets distracted prior to its completion. A Loss of Time error is coded when the participant performs the correct task at the incorrect time (i.e., more than 2 minutes from the appropriate execution time). Finally, a Random Error denotes incorrect responses that cannot be classified into one of the above-described categories. Each error variable was calculated as the proportion of total MIST errors committed (range = 0–100).

Statistical Analysis

A series of Shapiro-Wilk W Tests revealed that the MIST variables were non-normally distributed (all $ps < 0.01$). Wilcoxon Rank Sums tests and unbiased Cohen's d effect sizes (Hedges & Olkin, 1985) were therefore used to perform between- and within-group analyses of the MIST. Nonparametric Spearman's rho correlation coefficients were computed to

examine the associations between the MIST summary score and SCZ clinical characteristics. The study sample sizes provided adequate statistical power to detect medium-to-large effect sizes ($1-\beta > .80$, critical $\alpha = .05$) for all between- and within-group analyses.

3. Results

MIST scores and demographic factors were not significantly associated with different SCZ diagnoses (i.e., schizophrenia vs. schizoaffective disorder), antipsychotic regimens, or medication dosages (all $ps > .10$), so the SCZ sample was collapsed for all analyses ($n = 41$). As displayed in Table 2, the SCZ group performed worse than HCs on the MIST Summary Score (Cohen's $d = -1.29$) and Retrieval Index ($d = 1.22$). No significant between-group differences were observed on the multiple-choice recognition trial ($d = 0.32$). When both study groups were collapsed ($N = 82$), a significant main effect was observed for time-based ($M = 5.4$, $SD = 1.7$) versus event-based ($M = 6.4$, $SD = 1.8$) ProM ($p < .001$, $d = -0.57$). The SCZ sample performed worse than the HC group on both time-based ($d = -1.21$) and event-based ($d = -0.83$) trials, with no significant group differences in the discrepancy between time- and event-based subscale scores ($\chi^2 = 0.11$, $p = .737$, $d = -0.16$).

Larger proportions of No Response ($d = 0.99$), Loss of Time ($d = 0.94$), and Task Substitution ($d = 0.62$) errors were evident in the SCZ group relative to HCs (all $ps < .01$). The SCZ and HC samples did not differ in the proportion of any other error type (all $ps > .05$). Within the SCZ group, No Response errors were more prevalent than Loss of Time ($\chi^2 = -158.5$, $p < .001$, $d = 0.90$) and Task Substitution ($\chi^2 = -107.5$, $p = .011$, $d = 0.72$) errors. In the HC group, however, No Response ($\chi^2 = -73.5$, $p = .007$, $d = 0.56$) and Task Substitution ($\chi^2 = -38$, $p = .001$, $d = 0.52$) errors were more common than Loss of Time errors, but did not differ from each other ($\chi^2 = -9.5$, $p = .792$, $d = 0.10$).

A negative association was observed between the MIST and the PANSS Negative Syndrome subscale scores ($\rho = -0.33$, $p = .036$; Figure 1). In contrast, there were no significant correlations between the MIST and the PANSS Positive Syndrome ($\rho = 0.00$, $p = .987$) or General Psychopathology ($\rho = -0.11$, $p = .491$) subscales. A negative relationship was also evident between the MIST and age at SCZ onset ($\rho = -0.54$, $p = .0003$), but not SCZ disease duration ($\rho = 0.02$, $p = .882$). However, age was also significantly correlated with the MIST in the SCZ group ($\rho = -0.47$, $p = .002$). When both variables were entered into a linear regression as predictors of MIST performance, age ($t = -2.39$, $p = .022$), but not age at onset ($t = -1.39$, $p = 0.172$), emerged as a significant independent contributor to the model ($R = 0.25$, $p = .005$).

4. Discussion

Deficits in retrospective memory are common in SCZ; however, the nature and extent of SCZ-associated ProM impairment are poorly understood (Shum et al., 2001). This is an important area of investigation because ProM is of both theoretical and clinical relevance. In the current study, SCZ volunteers demonstrated greater than one standard deviation worse ProM performance than demographically comparable HCs, which is commensurate with effect size estimates from prior research (e.g., Elvevåg et al., 2003). Importantly, the SCZ and HC groups did not differ on a post-test recognition trial. Thus, the SCZ sample adequately formed (stage 1 of the model) and maintained the ProM cue-intention pairing over the delay interval (stage 2), which allowed for the recognition of the intention when self-directed retrieval demands were minimized. Although the lack of gross encoding deficits suggests that adequate memory traces of the intentions were formed, we cannot rule out impairment in higher-level strategic ProM encoding that may have interfered with optimally effective intention retrieval. Indeed, SCZ is associated with impairment in the executive aspects of retrospective memory encoding, such as limited use of semantic clustering strategies (e.g., Aleman et al., 1999). More rigorous

experimental procedures are needed to further evaluate this hypothesis, as well as the effectiveness of training in active ProM encoding strategies (e.g., organizational mnemonics).

Although the intention formation and delay maintenance components of ProM appear broadly intact, SCZ is nevertheless associated with impairment in self-initiated intention retrieval (stage 3 of the model). Specifically, individuals in the SCZ sample were more likely to fail ProM trials during distraction conditions (i.e., the word search), despite being able to correctly identify the ProM intention-cue pairings on the recognition test. Results extend prior data indicating that individuals with SCZ experience difficulty recalling the content of a prescribed intention without the aid of external prompts (Kumar et al., 2005). This finding also converges with the profile of retrospective memory deficits in SCZ, which is characterized by retrieval deficits in the setting of unimpaired consolidation (Aleman et al., 1999).

No Response errors were the most prominent error type in SCZ, suggesting that SCZ participants did not properly monitor, notice, or react to the ProM cues. Thus, in addition to deficient ProM retrieval, SCZ is associated with impairment in ProM cue detection (also stage 3 of the conceptual model). In contrast, the absence of group differences in Loss of Content and Place Losing Omission errors suggest that the ability to execute an intention that has been adequately formed, maintained, cued, and retrieved (i.e., stage 4) is broadly intact in SCZ. Although controversy exists regarding whether such a pattern of cue detection and retrieval deficits may reflect automatic versus strategic cue monitoring and detection processes (see McDaniel & Einstein, 2000), it is possible that the time-based ProM deficit in SCZ relates to impairment in strategic time estimation and monitoring. The deficit may relate to difficulties allocating cognitive resources to properly manage the simultaneous burden of the ongoing task and ProM cue monitoring. The increased rate of No Response and Loss of Time errors in this study, the latter of which were exclusive to time-based trials, further supports this contention. Moreover, Shum et al. (2004) found a positive correlation between overt time monitoring and time-based ProM performance in SCZ. Time estimation abilities are reduced in SCZ, and may be associated with fronto-striato-thalamo-cortical dysfunction (Volz et al., 2001).

Indeed, the profile of ProM impairment in SCZ is most consistent with a disruption of prefronto-striato-thalamo-cortical loops. The effective allocation of attentional resources to monitor the environment and detect cues and the ability to interrupt an ongoing activity to initiate strategic retrieval of an intention are neuropsychological functions commonly linked to frontal systems (Shallice, 1988). To this end, modest correlations are evident between global ProM and putative measures of frontal system functions (e.g., planning and design fluency) in SCZ (e.g., Shum et al., 2004). In addition, both clinical (e.g., Katai et al., 2003) and *in vivo* neuroimaging studies (e.g., Simons et al., 2006) implicate frontal systems (e.g., Brodmann area 10) in the retrieval of future intentions. Finally, the deficits in strategic encoding and retrieval from retrospective memory in SCZ are known to be associated with prefrontal system dysfunction (Achim & LePage, 2005).

Contrary to our *a priori* hypotheses and prior research (Shum et al., 2004), the SCZ samples displayed generally comparable deficits on time- and event-based ProM. Although the effect size for time-based tasks was slightly larger than that observed for event-based tasks, ProM failures occurred with comparable frequency across these two different retrieval cues. In contrast to prior ProM research in SCZ, the time- and event-based tasks used in this study were designed to be comparable on important administration factors, such as delay interval and response modality. It may be that ProM functions depend on the complexity of the cue-intention pairing and their associated retrieval processing demands, more so than whether the task is specifically time- or event-based (e.g., Henry et al., 2004).

Within the SCZ group, greater levels of global ProM impairment were associated with later age at disease onset and increased severity of negative symptoms (see Figure 1). The latter finding echoes prior studies demonstrating a similar association between retrospective memory and negative symptoms (Aleman et al., 1999). However, the relationship between younger age at schizophrenia onset and *better* ProM performance is puzzling and directly contrasts with the existing neuropsychological literature (e.g., Jeste et al., 1998). Possible explanations for this unexpected finding include Type I error and, perhaps more likely, the moderating effects of age. A series of hypothesis-driven *post hoc* analyses revealed that younger age was significantly associated with better MIST performance in the SCZ group. Importantly, the relationship between the MIST and age at onset was nonsignificant when age was entered into the statistical model, which is consistent with a moderation effect, as well as the aging literature on ProM (Henry et al., 2004).

It is important to note several potential limitations to the interpretation of these data. The cognitive task used in this study provides only indirect evidence of the neural substrates of ProM; as such, we cannot exclude the possible contribution of temporolimbic systems, which are commonly disrupted in SCZ and play an essential role in episodic memory (e.g., Moscovitch, 1994). The current findings may nevertheless guide future, hypothesis-driven studies of the neuropathogenesis of SCZ-associated ProM deficits. A second notable limitation is the relatively small SCZ study sample ($n = 41$), which was largely comprised of middle-aged, Caucasian outpatients with at least a high school education. As such, the generalizability of these findings to more diverse patient cohorts (e.g., inpatients and ethnic minorities) will be an essential topic for future research. Finally, distributions of the MIST errors were positively skewed (and no participant committed a Random Error), which may limit the robustness of the statistical analyses.

From a clinical perspective, impaired cue detection and intention retrieval may increase the risk of problems in independently performing IADLs; for example, failure to notice prompts to take prescribed medications may lead to poor treatment adherence and worse long-term clinical outcomes. Clinical evaluation of ProM may therefore enhance the prediction of IADL dysfunction in SCZ by measuring an important aspect of memory that is ubiquitous in daily life. Cognitive rehabilitation efforts for SCZ will ostensibly benefit from consideration of ProM (e.g., increasing the saliency of external cues), which may ultimately enhance the independent performance of IADLs (e.g., Kurtz et al., 2001; Twamley et al., 2002). Further investigations into the role of SCZ-associated ProM deficits in IADLs and their responsiveness to pharmacologic, cognitive, and/or behavioral therapies are clearly indicated.

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Figure 1. Scatterplot displaying the negative correlation between the MIST Summary Score and the PANSS Negative Symptoms subscale

MIST = Memory for Intentions Screening Test; PANSS= Positive And Negative Syndrome Scale.

Table 1
Demographic and Clinical Characteristics of the SCZ and HC Participants

Variable	HC (<i>n</i> = 41)	SCZ (<i>n</i> = 41)	<i>t</i>	χ^2	<i>p</i>
Age (years)	45.4 (11.0)	48.3 (9.5)	1.25	----	0.214
Education (years)	13.7 (1.9)	13.1 (1.6)	-1.52	----	0.133
Estimated Verbal IQ ^a	----	108.0 (9.9)	----	----	----
Gender (% Women)	51.2%	65.9%	----	1.81	0.179
Ethnicity (% Caucasians)	51.2%	65.9%	----	1.81	0.179
Age at SCZ Onset (years)	----	22.1 (9.5)	----	----	----
Duration of SCZ (years)	----	26.1 (11.8)	----	----	----
PANSS Total	----	60.7 (15.5)	----	----	----
Primary Diagnosis (%)					
Schizophrenia	----	39.0%	----	----	----
Schizoaffective Disorder	----	61.0%	----	----	----
Medications:					
% on atypical antipsychotics	----	75.6%	----	----	----
CPZE ^b	----	368.7 (336.4)	----	----	----

Note. Data represent means (with *SD*) unless otherwise indicated.

^a American National Adult Reading Test (*n* = 37) Grober & Sliwinski, 1991).

^b Antipsychotic dosages (*n* = 38) were converted into chlorpromazine equivalents (CPZE) according to standard formulae (Jeste & Wyatt, 1982; Woods, 2003), except for participants taking clozapine or long-acting injectable medications, for which conversion formulae do not exist; HC = healthy comparison participants; PANSS = Positive And Negative Syndrome Scale (Kay et al., 1987); SCZ = Schizophrenia.

The Memory for Intentions Screening Test (MIST; Raskin, 2004)

Table 2

Presentation Order	Instruction	Time Delay	Execution Order	Cue Type	Response Type
1	"In 15 minutes, tell me it is time to take a break."	15 minutes	4	Time	Verbal
2	"When I hand you a red pen, sign your name on your paper."	15 minutes	5	Event	Action
3	"In 2 minutes, ask me what time this session ends today."	2 minutes	1	Time	Verbal
4	"When I hand you a postcard, self-address it."	15 minutes	6	Event	Action
5	"When I hand you a Request for Records form, write your doctors' names on it."	2 minutes	2	Event	Action
6	"In 15 minutes, use that paper (i.e., the word search) to write the number of medications you are currently taking."	15 minutes	8	Time	Action
7	"When I show you the tape recorder, tell me to rewind the tape."	2 minutes	3	Event	Verbal
8	"In 2 minutes, please tell me two things you forgot to do this past week."	2 minutes	7	Time	Verbal

Table 3
Prospective Memory Performance in the HC and SCZ Study Samples

MIST Variable	HC (<i>n</i> = 41)	SCZ (<i>n</i> = 41)	X^2	<i>p</i>	Cohen's <i>d</i> (95% CI)
Summary Score	42.0 (36.0, 45.0)	33.0 (21.0, 36.0)	24.48	<0.0001	-1.29 (-1.76, -0.81)
Time-Based Cues	6.0 (5.5, 7.0)	5.0 (3.0, 6.0)	21.09	<0.0001	-1.21 (-1.68, -0.74)
Event-Based Cues	8.0 (6.0, 8.0)	6.0 (4.0, 8.0)	11.78	0.0006	-0.83 (-1.28, -0.38)
Errors					
No Response (%)	0.0 (0.0, 1.0)	40.5 (22.5, 50.0)	19.27	<0.0001	0.99 (0.53, 1.45)
Loss of Time (%)	0.0 (0.0, 0.0)	17.0 (0.0, 29.0)	16.89	<0.0001	0.94 (0.48, 1.40)
Task Substitution (%)	0.0 (0.0, 22.5)	25.0 (0.0, 36.5)	7.08	0.0078	0.62 (0.18, 1.07)
Loss of Content (%)	0.5 (0.0, 33.0)	0.0 (0.0, 33.0)	0.11	0.746	0.03 (-0.40, 0.46)
PLO (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	3.08	0.080	0.35 (-0.13, 0.83)
Random Error (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.00	1.000	----
Recognition Trial	8.0 (7.0, 8.0)	8.0 (7.0, 8.0) ^a	1.18	0.277	0.32 (-0.12, 0.77)
Retrieval Index	2.0 (0.0, 2.5)	3.0 (2.0, 4.0) ^a	21.32	<0.0001	1.22 (0.74, 1.69)
24hr Delay	0.5 (0.0, 2.0)	0.0 (0.0, 1.8) ^a	1.91	0.167	-0.31 (-0.75, 0.13)

Note. Data are presented as medians with the interquartile range in parentheses. X^2 values were derived from Wilcoxon Rank Sums tests.

^a SCZ group *N* = 39. CI = confidence interval; HC = healthy comparison participants; MIST = Memory for Intentions Screening Test; PLO = Place Losing Omissions; SCZ = Schizophrenia.