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Neuropsychological Substrates and Everyday Functioning Implications of Prospective Memory Impairment in Schizophrenia

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Abstract

Individuals with schizophrenia demonstrate impairment in prospective memory (ProM), which describes the multifaceted ability to execute a future intention. Despite its clear implications for everyday functioning, the neuropsychological substrates and functional correlates of ProM impairment in schizophrenia remain poorly understood. In this study, the Memory for Intentions Screening Test (MIST), a standardized measure of ProM, was administered to 72 outpatients with schizophrenia or schizoaffective disorder as part of a comprehensive neuropsychological and psychiatric research evaluation. Results showed that ProM was positively correlated with standard clinical tests of attention, working memory, processing speed, learning, and executive functioning, but not delayed recall. In the context of multiple neuropsychological predictors, learning ability was the only domain that independently contributed to ProM. Importantly, better ProM was predictive of higher functional capacity (as measured by the UCSD Performance-Based Skills Assessment—Brief Version), above and beyond the variability explained by demographic and disease factors. Analysis of component processes revealed that event-based ProM, as well as no response (i.e., omission) and task substitution errors were the strongest predictors of everyday functioning. Overall, these findings suggest that ProM impairment in schizophrenia is associated with multiple cognitive substrates, particularly episodic learning deficits, and plays an important role in everyday living skills. Studies regarding the potential effectiveness of ProM-based remediation strategies to improve functional outcomes in schizophrenia are indicated.

Keywords

learning; cognition; psychotic disorders

1. Introduction

The cognitive impairments of schizophrenia are numerous and disabling (Elvevag and Goldberg, 2000; Green et al., 2004; Heaton et al., 2001; Twamley et al., 2002). Episodic learning and memory deficits are particularly common and involve higher-level encoding and retrieval difficulties in the context of intact retention of learned information (Aleman et al.,

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1999); functional neuroimaging studies implicate prefrontal systems dysfunction rather than temporal lobe dysfunction in the learning and memory deficits of schizophrenia (Seidman et al., 1994; Achim and LePage, 2005).

Prospective memory (ProM), known colloquially as “remembering to remember,” is an aspect of episodic memory that involves the formation, maintenance, and execution of future intentions and has significant implications for daily functioning (Kvavilashvili and Ellis, 1996). However, ProM has been relatively understudied in schizophrenia, particularly in comparison to retrospective memory. ProM is a multi-step cognitive process conceptualized to function in four stages (Carey et al., 2006; Einstein and McDaniel, 1990; Knight, 1998): (1) *Intention formation* involves encoding the intention and its corresponding action, requiring both organizational and planning skills. (2) The *delay maintenance interval* requires retaining the intention during unrelated activities, and may require time monitoring to respond to time cues. (3) *Self-initiated cue recognition and intention retrieval* involves recognizing a cue (a specified time or event) and retrieving the appropriate response; this is a defining feature of ProM because the recall must be self-initiated. (4) *Intention execution* involves performing the intended task. Given the inherent complexity of this model, ProM is purported to depend upon the integrity of multiple cognitive abilities associated with frontostriatal and temporolimbic systems (Simons et al., 2006), including executive functions, working memory, episodic retrospective memory, and information processing speed (e.g., Carey et al., 2006).

The literature on ProM in schizophrenia suggests that affected individuals are slow in recognizing the content of intended actions (Kondel, 2002) and are impaired on event-based ProM tasks (Elvevag et al., 2003; Kumar et al., 2005; Shum et al., 2004). Although Shum and colleagues (2004) found disproportionate impairment on time-based versus event-based ProM tasks, our group (Woods et al., 2007b) observed no such discrepancy using a pair of psychometrically balanced tasks. We found that outpatients with schizophrenia were comparably impaired on time- and event-based ProM, performing over one standard deviation worse than healthy comparison participants, but demonstrating intact multiple-choice recognition of intentions (Woods et al., 2007b). ProM impairment was not related to diagnosis (schizophrenia vs. schizoaffective disorder), medication type or dosage, or disease duration, but was associated with older age and more severe negative symptoms. The most common types of ProM failures were omission errors (i.e., not responding to the cue at all), responding to the cue at the wrong time, or performing the wrong intention in response to a cue. We concluded that ProM deficits in our sample were due to impaired cue detection and self-initiated intention retrieval, rather than consolidation problems; further, we suggested that the executive components of ProM, such as time monitoring and self-directed retrieval, play an important role in everyday ProM failures.

Extending our prior work, this study aimed to examine the neuropsychological substrates and day-to-day impact of ProM impairment in schizophrenia. First, we hypothesized that ProM performance would be positively correlated with performance on tasks of attention, working memory, learning, and executive functioning, and lower negative symptom severity. Our second hypothesis was that ProM performance would be significantly associated with functional skills performance. Despite the clear implications of ProM integrity for the performance of instrumental activities of daily living, no prior studies have evaluated this issue in schizophrenia. For example, ProM abilities are needed to remember event-based or time-based activities (e.g., remembering to take a medication with breakfast or at a certain time of day, respectively). Indeed, data from other clinical samples (e.g., HIV infection and traumatic brain injury) show that ProM is a robust predictor of everyday functioning (e.g., Woods et al., in press-a; Fortin et al., 2003). Greater understanding of the neuropsychological substrates and functional correlates of ProM impairment will advance our understanding of ProM impairment in schizophrenia and may inform rehabilitation planning to improve everyday behaviors reliant

on ProM, such as taking medications, working, engaging in social activities, and managing a household.

2. Materials and Method

2.1. Participants

Participants included 72 outpatients with DSM-IV (American Psychiatric Association, 1994) diagnoses of schizophrenia (n=33), schizoaffective disorder (n=37), or psychosis not otherwise specified (n=2). All diagnoses were made by the treating psychiatrist and confirmed via diagnostic chart reviews by trained research staff using DSM-IV criteria. Demographic and clinical variables are presented in Table 1. The mean age of the sample was 46 years and the mean education level was 13 years. The majority of participants were male (67%) and Caucasian (58%), however, minority participants were also well represented in the sample, which was 18% Hispanic/Latino, 15% African American, 4% Asian, 1% American Indian, and 4% mixed/other ethnicity. Participants were chronically ill, with a mean duration of illness of 23 years, and the mean daily antipsychotic dose was 368 mg chlorpromazine equivalent (CPZE). Most were taking atypical antipsychotic medications only (83%), while 7% took typical antipsychotics only, 4% took both atypical and typical antipsychotics, and 6% took no antipsychotic medication. Participants were community-dwelling outpatients enrolled in parent studies of psychosocial rehabilitation programs (supported employment or cognitive training). Most participants (50%) lived with someone else (14% were living with a partner), whereas 31% lived alone, 14% lived in a board and care facility, and 3% were homeless. Those reporting substance abuse or dependence within the past month and those with a history of mental retardation, dementia, loss of consciousness >30 minutes, or other neurological disorders were excluded from the parent studies. Data from 41 of the 72 participants were included in a prior report (Woods et al., 2007b). All participants provided written informed consent to participate in research. The study was approved by the IRB and carried out in accordance with Declaration of Helsinki.

2.2. Procedure

At study entry, participants were administered a comprehensive battery of assessments, including measures of neuropsychological performance, psychiatric symptom severity, and performance-based functional capacity. Examiners were trained to a high level of interrater reliability (ICCs>.90). Antipsychotic medication dosages were converted into CPZE according to standard formulae (Jeste and Wyatt, 1982; Woods, 2003), except for participants taking clozapine or long-acting injectable medications (n=3), for which conversion formulae do not exist.

2.3. Measures

Premorbid verbal intellectual functioning was assessed with the American National Adult Reading Test (ANART; Grober and Sliwinski, 1991). Cognitive measures assessed the domains of *information processing speed* (Trail Making Test, Part A [Reitan and Wolfson, 1993], Symbol Search and Digit Symbol subtests of the WAIS-III [Wechsler, 1997a]); *attention* (Continuous Performance Test-Identical Pairs d-prime [Cornblatt et al., 1989], Digit Span Forward subtest of the WAIS-III [Wechsler, 1997a], Digit Span Distractibility distracted and non-distracted total scores [Oltmanns and Neale, 1975]); *working memory* (Letter Number Sequencing and Digit Span Backward subtests of the WAIS-III [Wechsler, 1997a]); *learning* (total immediate recall scores from the Hopkins Verbal Learning Test-Revised [Benedict et al., 1998], Logical Memory from the Wechsler Memory Scale-Third Edition [Wechsler, 1997b], and Brief Visuospatial Memory Test-Revised [Benedict, 1997]); *memory* (percent retention at delay for each of the learning tests); and *executive functioning* (Trail Making Test, Part B minus Part A [Reitan and Wolfson, 1993], Wisconsin Card Sorting

Test-64 card version total correct [Kongs et al., 2000], Stroop Color-Word Interference Test interference measure [Golden, 1978], Controlled Oral Word Association Test FAS total correct [Benton and Hamsher, 1989]). Mean Z-scores on each test were calculated and averaged within each cognitive domain.

ProM was measured by the Memory for Intentions Screening Test (MIST; Raskin, 2004), which is a standardized, 30-minute task whose psychometric properties (Woods et al., in press-b) and construct validity are well supported (e.g., Carey et al., 2006; Woods et al., 2007a,b, Woods et al., in press-b). The MIST includes eight ProM tasks counterbalanced for 1) length of delay (2 or 15 minutes); 2) response type (verbal or action); and 3) cue type (time-based, e.g., “In 2 minutes, ask me what time this session ends,” or event-based, e.g., “When I hand you a postcard, self-address it”). Participants solve word-search puzzles as a distracter task to prevent rehearsal of the intentions. Following the ProM tasks, a 3-choice recognition trial is provided for any incorrect items. A 24-hour delay task (leaving a telephone message for the examiner the following day) was also administered. The following variables were calculated from the MIST: 1) summary score (6 points are possible for each of the 8 items, for a maximum score of 48); 2) time-based scale (8 points possible); 3) event-based scale (8 points possible); 4) recognition total (8 points possible); 5) a retrieval index (i.e., recognition hits - free recall; see Carey et al., 2006); 6) 24-hr delay (2 points possible); and 7) four error types, including No Response, Task Substitutions (i.e., performance of the wrong task), Loss of Content (i.e., remembering that an intention should be performed, but forgetting the content of the intention), and Loss of Time errors (i.e., executing a correct intention that is $\pm 15\%$ of the target time).

The UCSD Performance-Based Skills Assessment-Brief Version (UPSA-Brief; Mausbach et al., 2007), a 10-minute measure that uses two of the original five UPSA subscales, captures the same variance as the original UPSA, and predicts living independence, was used to assess functional capacity in 58 of the 72 participants. The role-plays in the UPSA-Brief involve Finance and Communication activities such as making change, paying a bill by check, and communicating with a physician’s office by telephone. The percentage of items correct on each subscale is multiplied by a weight of 50, and the two subscale scores are summed to create a total score (range = 0-100). Previous studies have shown relationships between the UPSA-Brief subscales and neuropsychological performance (Twamley et al., 2002; Bowie et al., 2006). The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1967) were used to assess severity of positive, negative, and depressive symptoms.

2.4. Data Analyses

MIST scores were not associated with gender, ethnic minority status (Caucasian vs. non-Caucasian), diagnosis (schizophrenia vs. schizoaffective disorder), or parent study (all t s < 1.07 , all p s $> .293$), so the entire sample was used for all analyses. All variables were normally distributed. Associations between the variables of interest were tested with two-tailed Pearson correlations, followed by linear regression models. Alpha for significance was set at .05.

3. Results

The mean MIST scores in our sample were consistent with those in our prior study comparing outpatients with schizophrenia to healthy comparison participants (Woods et al., 2007b). Participants exhibited, on average, impaired performance on the MIST summary score, subscales, and error types, with broadly normal scores on the 24-hour delay and recognition posttest (see Table 1).

Our first hypothesis was that better MIST performance would be associated with better performance on tasks of attention, working memory, learning, and executive functioning, better

functional skills, and lower negative symptom severity. This hypothesis was supported (see Table 2); the MIST summary score was moderately and significantly correlated with all of the neuropsychological domain Z scores except memory, showing the strongest correlation with learning performance. As predicted, better MIST performance was also significantly associated with lower severity of negative symptoms, although it was also associated with lower severity of positive symptoms. Better MIST performance was also associated with younger age, higher levels of education, and higher premorbid intellectual functioning levels (see Table 2). MIST performance was not associated with age of onset ($r = -.157$, $p = .198$), as we had found in our earlier study with a smaller sample size (Woods et al., 2007b).

To further examine the associations between neuropsychological performance and MIST performance, we conducted a linear regression, entering the five mean Z-scores that were significantly correlated with MIST performance simultaneously in one block. The model explained 37% of the variance in MIST summary scores ($F = 7.65$, $df = 5, 66$, $p < .001$). In the context of multiple predictor variables, only learning performance was uniquely predictive of variance in MIST performance ($\beta = .336$, $p = .029$).

As predicted in our second hypothesis, better overall MIST performance was significantly associated with better functional skills performance on the UPSA-Brief ($r = .46$, $p < .001$). Among the MIST components, UPSA-Brief performance correlated with time-based ($r = .32$, $p = .014$) and event-based ($r = .43$, $p < .001$) subscales, the retrieval index ($r = -.42$, $p = .001$) and no response errors ($r = -.37$, $p = .004$). A follow-up linear regression predicting the UPSA-Brief from the MIST's time- and event-based scales was significant ($R^2 = .19$, $p < .001$), but only the event-based scale was a significant, unique contributor to the model ($p = .005$). Similarly, a follow-up linear regression predicting the UPSA-Brief from the error types of the MIST was significant ($R^2 = .22$, $p = .002$), with no response ($p = .008$) and task substitution ($p = .02$) errors emerging as the only significant, unique predictors.

To further examine the predictors of functional capacity, we conducted a hierarchical linear regression predicting variance in UPSA-Brief performance. In the first block of variables, we entered age, education, and the PANSS positive and negative symptom scores, which together explained 24% of the variance. In the second block, we entered the MIST summary score, which explained an additional 8% of the variance, bringing the total explained variance to 32%. Although negative symptom severity predicted significant variance in UPSA-Brief performance in the first block, it became non-significant in the second block, where only the MIST summary score was a significant predictor of variance in functional skills performance (see Table 3).

4. Discussion

Prior research shows that schizophrenia is associated with impairments in several aspects of ProM, which correlate with negative symptom severity (Woods et al., 2007b). Extending these results, the present study was undertaken to examine the neuropsychological substrates and functional implications of ProM impairment in schizophrenia. Consistent with the findings of Shum et al. (2004), our results showed a modest correlation between ProM and executive functions; however, ProM performance was also associated with performance in several neuropsychological domains, including attention, working memory, processing speed, and learning. Such associations are commensurate with conceptual models suggesting that optimal ProM functioning relies on multiple cognitive substrates (e.g., Carey et al., 2006). Interestingly, learning, but not delayed recall, uniquely predicted variance in ProM performance. Furthermore, given that recognition of cue-intention pairings was normal, we suspect that the executive component of learning ability is especially involved in ProM. These results support the notion that everyday ProM failures in schizophrenia may be due to inefficient higher-level

encoding of the cues, intentions, or cue-intention pairings of ProM tasks. Considering data regarding the role of frontal systems in the episodic encoding deficits of schizophrenia (e.g., Achim and LePage, 2005), such findings also provide further support to the view that ProM impairment in schizophrenia is most consistent with prefrontostriatal loop dysfunction. Future functional neuroimaging research could further illuminate the brain regions involved in learning and executing future intentions. We are aware of only one cognitive remediation intervention targeting ProM in schizophrenia (Kurtz et al., 2001; see Twamley et al., 2003). These data indicate that cognitive remediation to improve ProM in schizophrenia might focus on effective, planful encoding of cue-intention pairings, which should be simple, conceptually consistent, and meaningful to the individual (McDaniel and Einstein, 2007).

In our sample, better ProM performance was positively correlated with functional capacity as measured by the UPSA-Brief. In fact, ProM predicted variance in functional skills above and beyond demographics and negative symptom severity. These results are consistent with findings from other clinical populations in which ProM failures can result in poor treatment adherence (Vedhara et al., 2004) and declines in functional independence (Woods et al., in press-a). Such results help establish ProM as a cognitive domain worth measuring both clinically and in studies assessing cognition and functional skills in schizophrenia. Clinical trials researchers may also wish to use assessments of ProM to help understand medication adherence rates in their studies (Park and Kidder, 1996).

It is widely held that, relative to event-based tasks, time-based ProM may be a better predictor of daily functioning due to its increased demands on strategic monitoring and self-initiated retrieval (e.g., Einstein et al., 1995). However, in the current study, event-based ProM demonstrated the strongest relationship with functional capacity, which may be a function of the relatively strong strategic processing demands of the MIST event-based scale (Woods et al., in press-b, Martin et al., 2007). Analysis of error types suggest that the event-based effect was driven by impaired cue detection (i.e., elevated no response errors) and intention-cue pairings (i.e., elevated task substitution errors), which are particularly prevalent in schizophrenia (e.g., Woods et al., 2007b). The no response (i.e., omission) errors indicate that compensatory time-monitoring strategies, such as using a calendar or a watch with an alarm function, could assist with cue detection. Yet even when subjects were able to accurately recognize a ProM cue, they nevertheless had an elevated number of task substitution errors, in which an incorrect intention was performed. Consistent with our interpretation of the association between ProM and learning, the task substitution errors indicate that the subjects experienced difficulty encoding (and perhaps also retrieving) the original intention-cue association. In addition to the encoding remediation strategies described above, interventions might also use highly specific task reminders; for example, an electronic medication reminding intervention should notify the patient when to take the medication, but also provide the name, dosage, and exact instructions (e.g., take with food) (Carey et al., 2006).

In summary, findings from this investigation suggest that ProM impairment in schizophrenia is associated with multiple cognitive substrates, particularly episodic learning deficits, and plays an important role in everyday living skills. Limitations to the current study include the nature of the sample, which was comprised largely of middle-aged, chronically ill outpatients with schizophrenia-spectrum disorders who were receiving psychiatric care and interested in psychosocial interventions. The results of the study may not generalize to first-episode, non-treatment-seeking, or inpatient samples. Although our results lead us to conclude that ProM may play a role in everyday functioning due to its relationship with functional skills performance, we did not include a measure of community functioning. Nevertheless, the current findings may guide future, hypothesis-driven studies of ProM's effects on real-world community functioning. Medication management, social functioning, independent living abilities, and vocational functioning are all areas deserving future study.

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Table 1**Sample Characteristics (n = 72)**

Demographic Variables	Mean (SD)	Range
Age	45.8 (10.5)	25-69
Years of education	12.7 (1.8)	8-16
Disease Burden Variables		
Duration of illness, years	22.9 (12.2)	3-53
Total antipsychotic dose, CPZE	368.2 (324.0)	0-1467
HAM-D	12.1 (7.0)	1-34
PANSS positive symptoms	16.8 (6.0)	7-32
PANSS negative symptoms	14.5 (5.3)	7-30
ANART estimated IQ (SD)	106.3 (10.3)	84-124
UPSA-Brief	75.4 (14.8)	24-95
MIST Variables		
Summary score	30.1 (9.1)	12-45
Time-based	4.4 (1.7)	0-8
Event-based	5.7 (2.0)	2-8
Error types		
No response	1.9 (1.2)	0-5
Task substitutions	1.4 (1.1)	0-5
Loss of content	0.6 (0.7)	0-2
Loss of time	0.6 (0.6)	0-2
Recognition post-test	7.7 (0.6)	5-8
Retrieval index	3.1 (1.5)	1-7
24 hr delay	0.7 (0.9)	0-2

Note. CPZE = Chlorpromazine Equivalent; HAM-D = Hamilton Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; ANART = American National Adult Reading Test; UPSA-Brief = UCSD Performance-Based Skills Assessment-Brief Version; MIST = Memory for Intentions Screening Test; SD = standard deviation.

Table 2
Correlations between MIST Summary Score and Other Variables

	<i>r</i>	<i>p</i>
Demographic Variables		
Age	-.28	.019
Education	.33	.004
Duration	-.16	.198
Antipsychotic dosage (CPZE)	-.15	.227
ANART IQ	.38	.001
Neuropsychological Measures (mean Z-scores)		
Attention	.42	<.001
Working memory	.49	<.001
Processing speed	.48	<.001
Learning	.57	<.001
Memory	.10	.383
Executive functioning	.46	<.001
Clinical Variables		
HAM-D	-.20	.117
PANSS positive symptoms	-.29	.021
PANSS negative symptoms	-.49	<.001

Note. MIST = Memory for Intentions Screening Test; CPZE = Chlorpromazine Equivalent; ANART = American National Adult Reading Test; HAM-D = Hamilton Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale

Table 3

Hierarchical Linear Regression Predicting Variance in Functional Skills (UPSA-Brief) Performance

	β	p
Block 1 ^a		
Age	.149	.255
Education	.149	.239
PANSS positive symptom severity	-.185	.146
PANSS negative symptom severity	-.365	.010
Block 2 ^b		
Age	.219	.091
Education	.047	.716
PANSS positive symptom severity	-.118	.343
PANSS negative symptom severity	-.256	.070
MIST summary score	.346	.020

^aR² = .24, F = 4.19, df = 4,53, p = .005.

^bR² = .32, F = 4.81, df = 5,52, p = .001.