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Prospective memory in schizophrenia: Relationship to medication management skills, neurocognition and symptoms in individuals with schizophrenia [pre-print]

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Prospective memory in schizophrenia: Relationship to medication management skills, neurocognition and symptoms in individuals with schizophrenia

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Abstract

Impaired adherence to medication regimens is a serious concern for individuals with schizophrenia linked to relapse and poorer outcomes. One possible reason for poor adherence to medication is poor ability to remember future intentions, labeled prospective memory skills. It has been demonstrated in several studies that individuals with schizophrenia have impairments in prospective memory that are linked to everyday life skills. However, there have been no studies, to our knowledge, examining the relationship of prospective memory to medication management skills, a key element of successful adherence. In this study 41 individuals with schizophrenia and 25 healthy adults were administered a standardized test battery that included measures of prospective memory, medication management skills, neurocognition and symptoms. Individuals with schizophrenia demonstrated impairments in prospective memory (both time and event-based) relative to healthy controls. Performance on the test of prospective memory was correlated with the standardized measure of medication management in individuals with schizophrenia. Moreover, the test of prospective memory predicted skills in medication adherence even after measures of neurocognition were accounted for. This suggests that prospective memory may play a key role in medication management skills and thus should be a target of cognitive remediation programs.

INTRODUCTION

Prospective memory (PM) is defined as the ability to remember a task and perform it at an assigned time in the future (e.g., Shum et al., 2004). For example, prospective memory is required to remember to attend a doctor's appointment in the future or to take medication at an assigned time. This process has been suggested to involve four stages (Shum et al. 2004). The first is forming the intention to perform the task, second is remembering this formed intention over a period of time; third is continually remembering the time and method of executing the intention. Finally, one must actually perform the intention and recall that it has been performed.

There has been increasing research interest in investigating PM impairments in people with schizophrenia (Altgassen et al., 2008; Elvevag et al., 2003; Henry, et al., 2007; Kondel, 2002; Kumar et al., 2005; Kumer et al., 2008; Ritch et al., 2003; Shum et al., 2004; Twamley et al., 2007; Ungvari et al., 2008; Wang et al., 2007; Woods et al., 2007). A number of studies have used computerized laboratory tasks modeled after that of McDaniel and Einstein (2000) (e.g., Ungvari et al., 2008). These laboratory based tasks all share important features including a delay between encoding and performance of the intended action, an ongoing task carried out during the delay, and no explicit reminder to perform the task when the cue appears. Tasks can be time-based (requiring the individual to keep track of the time) or event-based (where an external cue indicates that it is time to perform the intended action). Findings from these studies have demonstrated consistent impairments in PM in individuals with schizophrenia compared to a healthy adult sample in both time-based and event-based tasks. Although the

impairments appear to be greater for time-based tasks in some studies (Shum et al., 2004; Wang et al., 2009) others have not found a difference in performance on time-based tasks compared to event-based tasks (Henry et al., 2007; Woods et al., 2007).

Consistent findings in schizophrenia include a relationship between PM and retrospective memory and executive function, among others neurocognitive skills (Kumar et al., 2008; Shum et al., 2004; Ungvari et al., 2008; Wang et al., 2008; Woods et al., 2007), and severity of negative symptoms (Wang et al., 2009). Notably, performance on PM tasks in schizophrenia, however, cannot be reduced to performance on tests of traditional neurocognitive domains such as general cognitive skill, retrospective memory and executive function (Henry et al., 2007). There has also been recent interest in the relationship between PM performance and everyday tasks or activities of daily living (ADL) (Ritch et al., 2003; Twamley et al. 2007; Ungvari et al., 2008; Zogg et al., 2010). Ritch et al. (2003) reported that the sum score of time- and event-based PM tasks predicted more than 29% of the variance of ADL scores. Twamley et al. (2006) reported a positive relationship between a performance-based measure of ADLs (UPSA-Brief) and the Memory for Intentions Screening Test (MIST). Event-based prospective memory performance was the strongest predictor of everyday functioning. In contrast, Ungvari et al. (2008) did not find a relationship between PM performance and ADLs using the Functional Needs Assessment-Chinese Version. Discrepancies between studies may be linked to differences in aspects of daily functioning assessed, such as cognitive difficulty or automaticity: some everyday life tasks, such as appropriate grooming, would seem to be less dependent upon prospective memory skills than others, such as remembering a doctor's appointment in the community at a specific time of day.

One important daily activity that relies on PM is, of course, medication adherence. Individuals with schizophrenia have been shown to perform poorly on performance-based measures of medication management (Kurtz, et al., 2007). For example, Patterson and colleagues used the Medication Management Ability Assessment (MMAA) to test the medication management abilities of 104 older (over age 40) adults with schizophrenia (Patterson et al., 2002). This test consists of a doctor-patient role-play in which the subject is required to repeat a daily regime of medication. It was found that individuals with schizophrenia made significantly more errors in the task than normal controls. Construct validity for this task was supported by prescription refill records, relationship to performance-based measures of everyday functioning and self-reported quality of life. Those individuals that had more severe psychiatric symptoms performed worse than those with less severe symptoms, and those individuals that were older performed worse than those that were younger. Interestingly, performance on the MMAA correlated with performance on an overall measure of cognitive function.

Using a cognitive screening measure Jeste et al. (2003) evaluated the relationship between medication adherence and cognitive functioning in a sample of 104 outpatients with schizophrenia or schizoaffective disorder. These authors reported that level of cognitive functioning predicted ability to manage medications, with measures of retrospective memory and conceptualization most closely linked to medication management abilities.

Despite replicated findings that medication management skills are impaired in schizophrenia, reflect (at least in part) deficits in cognition, and that prospective memory would seem to be a fundamental skill necessary for medication management skills, to our

knowledge, medication management skills has not been studied specifically in relationship to PM performance, and other illness features in individuals with schizophrenia.

In this study we used the MIST as an assessment of PM. The MIST is one of only a few standardized clinical measures of PM (Raskin, Buckheit & Sherrod, 2011). The MIST has the advantage of having been shown to have good psychometric properties (Raskin, 2009; Woods et al., 2008), but to still allow for the analysis of various underlying causes for the PM failure. Thus, the MIST allows for the comparison of long and short delay times, event-based and time-based cues, and verbal and action responses across balanced trials. We compared performance on the various aspects of the MIST to a standardized measure of medication adherence, the MMAA, and performance on measures of attention, working memory, and executive-function. First, we predicted that prospective memory skills would be worse in individuals with schizophrenia compared to demographically matched healthy adults and that time- and event-based prospective memory would be equivalently impaired in individuals with schizophrenia relative to demographically matched healthy adults. Second, in those with schizophrenia, we predicted that prospective memory skills, measures of attention, learning and set-shifting would be linked to medication management skills. Third, in those with schizophrenia we predicted that prospective memory skills would explain variance in medication management skills beyond that explained by traditional neuropsychological measures.

METHODS

Participants

Forty-one individuals, (18 female), from the Schizophrenia Rehabilitation Program (SRP) at the Institute of Living at Hartford Hospital in Hartford, CT (n=37) and Intercommunity Mental Health Center in East Hartford, CT (n=4) participated. Twenty-five matched healthy adult individuals (12 female) were also tested.

Individuals with schizophrenia met criteria for schizophrenia or schizoaffective diagnosis as described in the DSM-IV (American Psychiatric Society, 2000) via the Structured Clinical Interview for the DSM-IV (SCID; First et al., 1995). Each patient also met inclusion criteria of sufficient hearing and visual abilities, completion of a minimum of eight years of schooling, and fluency in English. Exclusion criteria required that the patient be free from any current alcohol or substance abuse, mental retardation as evidenced by a history of services, or other neurologic or psychiatric illness, as well as current treatment with electroconvulsive therapy. The Positive and Negative Syndrome Scale (PANSS) scores were obtained to determine frequency and intensity of positive and negative symptoms associated with schizophrenia at the time of the study (Kay, Fiszbein, & Opler, 1987). Exclusion criteria for the healthy adults included auditory or visual impairments, evidence of mental retardation, traumatic brain injury with a sustained loss of consciousness, presence or history of any neurologic or psychiatric illness, lack of proficiency in English or history of substance abuse or dependence. Demographic data for individuals with schizophrenia and matched controls are presented in 1. There were no significant differences between the groups in terms of age, gender or education. The participants were compensated thirty dollars for their time.

Materials

The Medication Management Ability Assessment Manual (MMAA; Patterson et al. 2002):. This test involved a doctor-patient role play in which the patient was asked to remember a regime of medication similar to one required in a typical day. Detailed instructions were given to the participant explaining how to take the medication. The dosage required, time of day and whether it required food was explained. The participant was also shown the pill bottles that described the information that had just been explained.

After a delay of 45-60 minutes (during which other tests were administered) the participants were asked to explain what time they would wake up, when they would eat meals, and when they would go to sleep, explaining when they would take their medications relative to these events throughout the day. Four mock medications were included in this test; each represented with a different type of uncooked bean to simulate different pills. The test was then scored based on the number of pills taken each time, the number of times per day the pill was taken, and the total number of pills taken per day. A total correct score was selected for analysis this this study.

Memory for Intentions Screening Test (*MIST*; Raskin, Buckheit, & Sherrod, 2011). This was a prospective memory test that used both event-based and time-based cues to assess the participant's ability to remember tasks and carry them out. There were a total of eight tasks which the participant was required to remember to perform at an assigned time or when a specific cue was given. An example of an event-based cue was "when I hand you an envelope, self-address it." An example of a time cue was "in fifteen minutes, please tell me to take a break." The participant had access to a digital clock throughout the test. While remembering to complete the tasks, participants worked on an ongoing

task that was a word search puzzle. They were not permitted to write any information down.

Finally, a battery of standardized neuropsychological measures was administered chosen a priori to tap into underlying cognitive processes required for PM performance. The tests used included measures of attention Trail Making Test A [TMT, Tombaugh, 2004]), learning and memory(California Verbal Learning Test-II-CVLT, Delis, Kramer, Kaplan, & Ober, 2012]) and set-shifting (Trail Making Test B [TMT, Tombaugh, 2004]).

Procedure

Total testing lasted approximately one hour and fifteen minutes. All participants gave written, informed consent and all procedures met institutional ethical approval. When testing began, the first part of the MMAA was initially administered. During the interim period, the MIST and the neuropsychological measures were administered followed by the second, testing phase of the MMAA.

Data Analysis

None of the MIST measures were normally distributed as revealed by a series of Shapiro-Wilk W tests (all *p*s<.01). Thus a series of non-parametric tests and Cohen's d (Hedges and Olkin, 1985) values were used to compare healthy control and patient samples on variables from the MIST. In all cases reported ANOVA results on raw study data were confirmed with rank-transformed data; in no case was there a discrepancy in findings. Spearman rank-order correlations were calculated within the schizophrenia group to assess the relationship of the MIST scores and other neurocognitive variables, illness and demographic factors and medication management skills as measured by the MMAA. Logistic regression using a cut-off of 80% accuracy or greater for intact

medication management skills was selected in order to evaluate the relative contribution of neurocognitive and the MIST summary score to MMAA scores in a logistic regression analysis. Alpha was set at .05 and all analyses were two-tailed.

RESULTS

As can be seen in Table 2 individuals with schizophrenia performed significantly more poorly than healthy adults on the MIST summary score (*d*=-.88), on responses to time- (*d*=-.84) and event (*d*=-.67) based cues, and on 15-minute (*d*=-1.02) but not 2-minute delayed responses, and on action (*d*=-1.09) but not verbal responses. Recognition (*d*=-.54) performance and 24-hr (*d*=-.69) delay performance was impaired on the MIST in the schizophrenia sample relative to healthy controls. There was no significant difference in discrepancy between groups for the time and event-based cue responses (p=.22) or action and verbal responses (p>.05). There was greater impairment on the long as compared to short-delay items relative to healthy control performance (Group x Delay interaction, [F(1, 64)=5.02, p=.021]). For error type, only the no response error type was more common in individuals with schizophrenia (*d*=-.72). No response errors were selectively more common in individuals with schizophrenia as compared to controls relative to the other four error types as indicated by a group x error type interaction (F(4, 256)=5.09 p=.001).

Spearman rank-order correlations were conducted between clinical and demographic variables, neurocognitive variables, MIST variables and the MMAA in the schizophrenia sample (Table 3). CVLT-II T-scores (rho=.37), and Trails B time (rho=-.30) and Summary scores (rho=.45) from the MIST were all related to MMAA scores. With respect to subscales from the MIST, perfrormance on time (rho=.33*), and event

cued (rho=.55**) responses, and responses that required an action (rho=.61**) rather than a verbal statement were most closely linked to MMAA scores.

A forward stepwise logistic regression analysis was conducted to predict a person's ability to remember to take their medication using variables found to be signficant in the correlational analysis: the summary score of prospective memory ability from the MIST, the CVLT-II and Trails B. A binary variable was created for the MMAA with a cutoff of 20 (80% accuracy). Neuropsychological variables were entered in block one and summary score from the MIST was entered in block two. A test of the full model against a constant only model was statistically significant, indicating that the predictors as a set reliably distinguished between individuals having a total MMAA of less than 21 with those having a higher score (between 21 and 25) (chi square = 6.31, p =0.012 with df =1). Prediction success overall was 73%. The Wald criterion demonstrated that Total on the MIST made a significant contribution to prediction (p =.048). The remaining tested variables were not significant predictors.

DISCUSSION

A growing body of research has documented deficits in prospective memory in schizophrenia relative to demographically-matched, healthy adults. The current study was designed to build on this work by both replicating previous findings in samples of healthy adults and people with schizophrenia, and then investigating the relationship of impaired prospective memory skills, commonly measured cognitive skills and symptoms to performance-based medication adherence skills in individuals with schizophrenia. This study is among the very first studies in the literature to investigate this relationship. Consistent with our first hypothesis and a growing body of research (e.g., Woods et al.,

2007; Elvevag et al., 2003), our results showed that prospective memory in schizophrenia was impaired relative to demographically matched healthy adultperformance with effect-size impairment in the large range (d=.88 for the MIST summary score) which was remarkably consistent with previous reports. Consistent with previous reports using an identical index of prospective memory (Woods et al., 2007) there was no evidence that responses to time-based prospective memory cues were more impaired than responses to event-based cues. These findings provide more data that differences between performance on time and event-based prospective tasks in previous studies (e.g., Shum et al., 2004) may reflect the confounding of these conditions with the complexity of cue-intention pairings which are carefully matched for difficulty across time and event-based tasks on the MIST.

An analysis of error type revealed a selective deficit in no response (PM) errors as compared to healthy controls, relative to the frequency other error types. These errors reflect the participant giving no indication that there is an intention to be carried out. These findings suggest that when prospective memory performance skills break down in individuals with schizophrenia this most commonly reflects a failure to attend to or react to the prospective memory cues on the MIST. However, our findings also indicate that even when individuals with schizophrenia were able to detect a cue they more frequently made incorrect responses as compared to healthy controls, suggesting evidence of either poorly formed representations of cue-response pairings or problems with response retrieval even when the cue was accurately recognized.

Analysis of our recognition results did not support the contention reported in two previous studies with the MIST (Twamley et al., 2008; Woods et al., 2007) that

adequately formed cue-intention relationships can be detected in individuals with schizophrenia when strategic retrieval processes are minimized in the context of a recognition test format, although differences in recognition effect-size results between our study and previous studies were not large (*d*=.54 in the current study vs. *d*=.32 in the Woods et al. study), and may reflect slight differences in recognition scoring procedures. These findings coupled with our result that errors in response at a 15-minute delay (*d*=1.02) were twice as large as those at a 2-minute delay (*d*=.50) suggest that prospective memory skills may not conform to the common characteristics of retrospective memory impairment in schizophrenia in which encoding and retrieval processes are impaired but consolidation and maintenance processes remain largely intact (Aleman et al., 1999).

With respect to our second hypothesis, measures of set-shifting (Trails B), verbal learning (CVLT-II) (but not visual attention [Trails A]) and prospective memory skills were related to medication management skills (MMAA). These findings are consistent with previous work investigating the relationship of summary cognitive screening measures and medication management skills (e.g., Jeste et al. 2003) and extend these findings to two key and specific cognitive function domains in schizophrenia. These findings are also remarkably consistent with the reported relationship of prospective memory skills to measures of ADL functional capacity in schizophrenia (Twamley et al., 2008) and suggest similar magnitude relationships of prospective memory with the specific skills of remembering to take a sequence of medications in the correct amount at the correct times. The finding that errors for event cues were more closely related to medication management skills than time-based cues was unanticipated as both strategic

monitoring and self-initiated retrieval demands would seem greater for time-based cues and thus would be more likely to be linked to medication management skills.

With respect to hypothesis three, results of binary logistic regression predicting the adherence to a mock medication regimen, (defined as the likelihood of attaining 80% accuracy on the medication management skill tests), showed that prospective memory skills explained variance in adherence measures even after accounting for cognitive measures supporting the potential incremental clinical utility of including prospective memory measures for predicting medication management skills in schizophrenia.

Several limitations to the current study should be noted. First, study sample sizes were modest and significant relationships may have been overlooked secondary to limited power. Second, lack of adherence with prescribed medications involves a complex interplay of cognitive and attitudinal factors including illness insight. The medication management skill measure employed in the current study modeled cognitive skills necessary for taking a complex regimen of medications, a necessary but not sufficient skill for medication adherence. We note however that a paper published very recently extends these findings to medication refill records (Lam et al., 2013). Third, the neuropsychological test battery employed in the current study was limited in scope, capturing only a few of the separable neurocognitive domains defined in factor analyses using broad spectrum neurocognitive assessment batteries in schizophrenia.

In summary, the current results suggest that prospective memory is impaired in schizophrenia relative to demographically matched controls, deficits are of equivalent magnitude for time and event-based cues and this impairment is driven largely by failures to recognize cues as well as errors in accurate retrieval of intention-cue pairings. In

patients, both prospective memory measures and cognitive skills in set-shifting and verbal learning predicted performance on a performance-based measure of medication management skills. Importantly, prospective memory skills explained variance in medication management skills beyond that of standardized neurocognitive measures. These findings provide a rationale for the development of remediation strategies that facilitate the encoding of cue-response relationships (perhaps with extended encoding time or practice), and then provide environmental modifications that both increase the salience of cues and tie these cues more directly to the target response as a means of addressing the cognitive disabilities that interfere with medication adherence in schizophrenia (e.g., Raskin & Sohlberg, 2011).

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Table 1: Demographic and disease information for individuals with schizophrenia and healthy adults

	HA (*n* = 24)		SCZ (*n* = 41)		
	Mean	Std. Deviation	Mean	Std. Deviation	t
Age	43.44	23.13	44.17	10.74	0.174 (NS)
Gender (% male)	52	-	56	-	
Education(years)	13.92	2.23	12.37	2.54	-2.52 (NS)
Occupation*	7.2	0.58	7.10	0.81	-0.49 (NS)
Maximum Lifetime Duration of Employment (months)	*n/a*	*n/a*	30.19	45.13	-
Lifetime Hospitalizations	*n/a*	*n/a*	3.78	2.84	-
Duration of Illness (years)	*n/a*	*n/a*	12.50	9.9	-
PANSS					
Total Positive	*n/a*	*n/a*	15.05	5.57	-
Total Negative	*n/a*	*n/a*	17.35	6.99	-
Total General	*n/a*	*n/a*	34.59	9.89	-
Total PANSS	*n/a*	*n/a*	71.45	14.49	-

*Hollingshead (1977)

Note: HA = healthy adult; SCZ = schizophrenia; NS = not significant; n/a = not applicable; PANSS = Positive and Negative Syndrome Scale

Table 2: Prospective Memory and Medication Management Ability in the Study Samples

	HA (*n* = 25)		SCZ (*n* = 41)			
Variable	Mean	Std. Deviation	Mean	Std. Deviation	Mann-Whitney U	ES (95% CI)
MIST						
Summary score (of 48)	40.28	7.78	31.88	10.23	3.44**	-.88 (-1.40/-.36)
Time (of 8)	5.96	2.03	4.37	2.01	2.97**	-0.84 (-1.36/-0.33)
Event (of 8)	7.40	0.91	6.39	1.75	2.41*	-0.67 (-1.18/-0.16)
2-min (of 8)	7.48	0.96	6.63	1.97	1.74	-0.50 (-1.01/0)
15-min (of 8)	6.08	1.78	4.15	1.93	3.69**	-1.02 (-1.54/-.49)
Verbal (of 8)	6.52	1.83	5.76	2.13	1.69	-.37 (-.87/-.13)
Action (of 8)	6.76	1.36	5.07	1.62	3.87**	-1.09 (-1.62/-.56)
Recognition (of 8)	7.56	0.87	7.00	1.12	2.24*	-.54 (-1.09/-.03)
24-hr (of 2)	1.17	1.01	0.54	0.84	2.49**	-.69 (-1.20/-.17)
Errors						
NR	0.65	1.04	2.02	2.21	3.02**	-.72 (-1.24/-.22)
TS	0.32	0.48	0.71	0.95	1.73	-.48 (-.9/.02)
LC	0.44	0.58	0.54	0.71	.36	-.15 (-.65/.35)
LT	0.24	0.44	0.34	0.57	0.56	-.19 (-.69/.31)
PLO	0.00	0.00	0.02	0.16	0.78	-.16 (-.65/.34)
MMAA						
Total	22.72	2.56	17.00	6.56	3.58**	-1.04 (-1.57/-.52)

*Note: *p<.05; **p<.01; ***p<.001; HA = healthy adult; SCZ = schizophrenia; MIST = Memory for Intentions Screening Test; MMAA = Medication Management Ability Assessment; NR = no response error; TS = task substitution error; LC = loss of content error; LT = loss of time error; PLO = place losing error*

Table 3: Spearman correlations for individuals with schizophrenia between neurocognitive, MIST and MMMA variables (n=41)

	MMAA Total
Demographic and Clinical Variables	
Age	-0.26
Education	0.31
Duration of Illness	-0.08
Positive Symptoms	-0.23
Negative Symptoms	-0.18
MIST Variables	
MIST Summary	0.45**
Time Cue	.33*
Event Cue	.55**
Verbal Response	.13
Action Response	.61**
2-minute Delay	.29
15-minute Delay	.44
Neuropsychological Measures	
TMT-A	0.14
CVLT-II	0.37**
TMT-B	-0.30**

Note: *p<.05; **p<.01;; TMT= Trail Making Test; CVLT = California Verbal Learning Test

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