



Relationship of Prospective Memory to Neuropsychological Function and Antiretroviral Adherence

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Abstract

Prospective memory is defined as the ability to “remember to remember” something at a future time despite intervening distractions and may be particularly important in remembering to take prescribed medication among people infected with HIV. Ninety-seven HIV-positive participants in a clinical trial had their adherence measured by electronic pillcaps and were administered neuropsychological screening tests and the memory for intentions screening test (MIST). Factor analysis of the MIST and other neuropsychological measures identified four factors. Two were derived from MIST subscales and accounted for approximately 50% of the variance in cognitive functioning. Only one factor was significantly correlated with adherence, and this was a MIST factor. In this preliminary study, the MIST assessed a memory function that (a) could be distinguished from traditional retrospective recall and executive functioning and (b) was correlated with antiretroviral adherence.

Keywords: HIV; Neuropsychological function; Adherence; Medication compliance; Substance use

Introduction

When patients with HIV are appropriately prescribed highly active antiretroviral therapy (HAART) and adhere to it, the medication reliably suppresses HIV replication so that detectability of the virus in RNA falls below the standard limits (Palella et al., 1998). For many HAART regimens, near-perfect adherence is needed to prevent the emergence of HIV that is resistant to the regimen (Paterson et al., 2002) because if medication doses are missed, HIV may emerge that is resistant to the prescribed medication (Perno et al., 2002). Unfortunately, perfect adherence to HAART is extremely difficult and largely because of medication non-adherence, continued significant replication of HIV occurs in almost one-half of HAART recipients in community settings (Andrade et al., 2005). The most common reason patients give for having missed a dose of medication is that they “forgot” (Chesney, 2002) but the role of actual memory impairment or other objectively demonstrated neuropsychological deficits in non-adherence is not well understood. Impaired retrospective memory has been correlated with adherence to HAART in some (Hinkin et al., 2002) but not all (Ammassari et al., 2003) studies, but retrospective memory may not assess the neuropsychological function required for medication adherence.

Prospective memory involves “remembering to remember” and has an intuitive similarity to remembering when to take medication. The steps by which intentions are carried out at a future time have been outlined succinctly (Carey, Woods, Rippeth, Heaton, & Grant, 2006; Knight, 1998) and involve the forming of an intention, retaining the intention in the presence of distracters, a self-initiated recall of the intention, then recalling and executing the action. The steps in prospective memory can be applied to medication adherence—intending to take the medication, retaining the intention, recall of the intention, and taking the medication.

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The steps in prospective memory are heavily dependent on frontal, executive functions (i.e., initiation, inhibition), and intact hippocampal functioning (memory). Evidence for the role of frontal systems comes from studies by Burgess, Quayle, and Frith (2001) and Okuda and colleagues (1998), using positron emission tomography, which describe increases in rCBF in frontal regions (e.g., right lateral prefrontal cortex, superior frontal gyrus) during prospective memory tasks. Deficits in prospective memory in patients with Parkinson's disease also suggest the need for intact frontal and temporal functioning in prospective memory (Katai, Maruyama, Hashimoto, & Ikeda, 2003; Whittington, Podd, & Stewart-Williams, 2006).

HIV infection is associated with both pathology in the anatomical domains that influence prospective memory and with deficits in neuropsychological functions involved in remembering to remember. The HIV may reside in the central nervous system (Dunfee et al., 2006) and up to 40%–50% of symptomatic HIV-positive individuals demonstrate some form of cognitive impairment (Heaton et al., 1995). HIV infection is thought to primarily damage frontostriatal circuits (Ernst, Itti, Itti, & Chang, 2000; Stankoff et al., 2001) including major white matter tracts (Pomara, Crandall, Choi, Johnson, & Lim, 2001; Thurner et al., 2005). The most commonly reported deficits among HIV-positive people are in the areas of memory, processing speed, attention, and concentration (Kelly, Grant, Heaton, & Marcotte, 1996; Reger, Welsh, Razani, Martin, & Boone, 2002). In people with advanced disease, cognitive impairment from HIV infection can resemble subcortical dementias such as Parkinson's disease and Huntington's disease (Marcotte, Grant, Atkinson, & Heaton, 2001; Waldrop-Valverde et al., 2005), with specific deficits in working memory and executive skills. Although most studies have focused on frontal areas in HIV-positive populations, the memory deficits in HIV-positive people and fMRI studies (Castelo, Sherman, Courtney, Melrose, & Stern, 2006) suggest that there is impairment in functions mediated by the temporal lobe (i.e., hippocampal formation) as well. In summary, people infected with HIV have anatomical and functional evidence of impairment in areas involved in prospective memory.

Not surprisingly, given the overlap between prospective memory functions and functions impacted by HIV, people infected with HIV perform worse on measures of prospective memory than control populations. In a study comparing neuropsychological test results from 42 HIV-positive participants to data from 29 control participants, HIV-positive participants had significantly worse prospective memory (Carey et al., 2006) as measured by the memory for intentions screening test (MIST; Raskin, 2005). As expected, prospective memory was correlated with working and verbal memory, verbal learning, and measures of executive function such as the Trails B test. This study was notable for the strict exclusion of participants with comorbid psychiatric conditions or substance-related disorders within 2 years of admission, allowing differences between the groups to be attributed to HIV, but the relationship between different neuropsychological domains may not generalize to clinical populations, in whom high rates of substance abuse and psychiatric comorbidity are common (Galvan, Burnam, & Bing, 2003). A second study comparing prospective memory in a sample of substance-dependent HIV-positive people to that in HIV-negative people also described impaired prospective memory among the HIV-positive people, using a prospective memory task that required a response every 7 min (Martin et al., 2007). In this population, prospective memory was correlated with a measure of retrospective memory.

To our knowledge, this is one of the first studies to examine the relationship between prospective memory and objectively measured medication adherence. In a recent paper, Woods, Iudicello, and colleagues (2008) demonstrated an association between prospective memory and perceived medication management efficacy in a highly educated population with HIV disease, above and beyond what other neuropsychological measures accounted for. However, the authors pointed out that medication management may not have been a valid measure of adherence because of the limitations of self-report and the self-report measures' lacking the correlation with biological markers seen with valid adherence measures (e.g., Liu et al., 2001). Additionally, Woods and colleagues (2009) have demonstrated not only that non-adherent patients had significantly worse prospective memory scores on the MIST than did adherent counterparts, but also that failures to initiate responses based on a time cue was predictive of poor adherence as measured by MEMS caps. We hope to extend the recent work by Woods and colleagues by utilizing the MIST and MEMS caps in a more impaired population (i.e., higher CD4 count, less education, and more recent substance abusers). The aims of the current study were (a) to describe the factor structure of a neuropsychological test battery that included the MIST to determine whether MIST subscales loaded on distinct factors and (b) to determine whether factors representing the MIST or other tests were correlated with antiretroviral adherence.

Materials and Methods

Participants

Ninety-nine HIV-positive participants were recruited during their regularly scheduled clinic visits for participation in a randomized controlled trial of an adherence-focused intervention (Rosen et al., 2007). Two participants were excluded from the

data analysis because they did not complete the neuropsychological testing, leaving 97 for this study. Inclusion criteria consisted of being HIV-positive, between the ages of 18 and 65, currently treated with anti-retroviral medication, having a history of substance abuse, having the ability to give voluntary consent, and a mini-mental status exam score >23 . Exclusion criteria included an inability to use MEMS pillcaps and receiving medication in a controlled, supervised setting. Patients were screened for study participation during a 4-week baseline period in which they used MEMS caps but did not receive any counseling. Only patients with suboptimal adherence at the end of the baseline period went on to be randomized to one of two interventions. The adherence data in this paper are from the 4-week, pre-randomization baseline period, and include data from people whose adherence was 100% and who did not go on to be randomized. The local institutional review boards approved the study and informed consent was obtained from all participants.

Participants had a mean age of 44.5 years ($SD = 7.5$, range 24–65) and had completed an average of 11.5 years of education (range 6–18). The sample was 58.8% men. The majority were African American (52%), followed by Hispanic (28%), Caucasian (17%), and Native/Alaskan Indian (2%). Thirty-nine percent of the sample reported having used cocaine in the preceding 30 days, and 17% had used alcohol to intoxication. With regard to HIV infection status, mean CD4+ count was 347 ($Mdn = 275$, $IQR: 102–549.5$) indicating relatively advanced disease and 38 (40.8%) had an undetectable viral load. The mean duration since patients had been diagnosed with HIV was 10.4 years ($SD = 5.1$ years). Information regarding whether or not participants had been diagnosed with AIDS or their nadir CD4 counts was not available. Mean adherence was 71% ($SD = 27.7\%$). According to BDI scores, 34% did not report signs consistent with depression, 24% of the sample reported symptoms consistent with mild depression, 23% reported symptoms consistent with moderate levels of depression, and 19% had a self-report of symptoms consistent with severe depression.

Measures

Adherence to prescribed medication. Participants had electronic monitoring caps (MEMS, MicroElectronic Monitoring Systems, Aardex) placed on their pill bottles. These electronic caps record each time the cap is removed and in our studies, such cap removals have consistently been validated as measures of actual medication ingestion (Rigsby et al., 2002; Rosen et al., 2007). Adherence data for this study were collected for ~ 4 weeks during a baseline observation phase, prior to randomization into the clinical trial. Adherence was calculated as the percentage of prescribed bottle openings that occurred, with bottle openings that exceeded a days' recommended number of doses disregarded so that adherence did not exceed 100% on any day.

Neuropsychological Testing

The MIST was administered as part of a broader neuropsychological battery. Executive functioning was assessed by Trails B (Reitan & Wolfson, 1985) and the controlled oral word association test (COWAT) (Benton, Hamsher, & Sivan, 1994). Verbal memory was assessed by the Hopkins verbal learning test (HVLT)-R (Brandt & Benedict, 2001), and processing speed and psychomotor abilities were assessed by Trails A (Reitan & Wolfson, 1985). These non-MIST outcomes were all part of the battery administered in the prior study of MIST effects on HIV-positive people and the relationship between MIST results and other neuropsychological outcomes (Carey et al., 2006).

Memory for intentions screening test

The MIST takes ~ 30 min to administer. Examinees are given a series of cued tasks to complete either in response to a certain amount of time or when another event occurs. Between tasks, examinees are given a series of word search puzzles as a distracter task. The MIST requires participants to respond to a cue that is either an event “When I hand you a piece of paper . . .” or a time “In 2 minutes . . .” The response can either be a verbalization (e.g., “In 15 minutes, tell me that it is time to stop”) or an action (e.g., “In 15 minutes, use that pen and paper to write your telephone number”). Thus, the MIST subscales have a $2 \times 2 \times 2$ factorial structure with the following factors: Type of cue (event or time), type of response (verbal or action), and duration between the cue and the requested response (2 or 15 min).

Participants are seated with a large digital clock in front of them so that the duration since the instructions is readily viewable. Following completion of all tasks, a recognition trial is administered in which participants are asked multiple-choice questions on omitted responses from each of the eight prospective memory tasks that had been assigned (e.g., “When I gave you a pen, were you supposed to . . .”).

The MIST yields summary scores based on the number of tasks performed with partial scores for tasks performed incorrectly (e.g., the wrong task is performed at the right time). Summary scores are also computed for each factor (e.g., number

of tasks completed that were due in 2 min, number completed due in 15 min, etc.). It also yields a score for the number of retrospective recall questions answered correctly.

Statistical Analyses

Data analysis proceeded in several steps. First, *z*-scores of Trails A and B, as well as the COWAT, were computed based on age (and education for COWAT scores) corrected norms (Spreeen & Strauss, 1998). HVLT *t*-scores were computed from the HVLT manual (Brandt & Benedict, 2001). Then, the relationship between MIST raw scores and other neuropsychological measures was described by conducting bivariate correlation analyses between the raw scores (standardized scores for the neuropsychological data are presented in Table 1, however; all analyses were conducted with raw scores due to the possibility of overestimating the degree of impairment on the MIST). Spearman's ρ coefficient of correlation was used because of the non-normal distribution of MIST raw scores.

To reduce the number of items to correlate with adherence and to determine the underlying structure of variables, the non-MIST measures and MIST subscale outcomes (2 min, 15 min, time cue, event cue, action response, verbal response, and retrospective recall) were entered into an exploratory factor analysis (EFA). EFA with varimax rotation was used because of the preliminary nature of the study and the interdependent scores of the MIST. However, promax rotation with extracted factors set to 4 revealed a similar factor structure with similar variance explained, suggesting that the orthogonal constraint did not significantly change the results. Mean summary score indices for each factor were also calculated for each participant and entered into correlational analyses. Post-hoc analyses considered whether factors showing bivariate correlation with adherence were correlated with adherence in multivariate analyses and were associated with optimal adherence, defined as 95% or more of prescribed doses taken.

Following the results of the EFA, hierarchical multiple regression analysis was used to determine the incremental contribution of one of the MIST factors (factor 2, composed of 15 min recall, action response, and event cue subscales) to the prediction of adherence after controlling for alcohol and cocaine use in the last 30 days, scores on the BDI, HVLT total score, Trails A and B time variables, and CD4 count.

Finally, to determine whether factor 2 differentiated “adherers” from “non-adherers” (defined as medication adherence $\geq 95\%$, and $< 95\%$, respectively), an independent-sample *t*-test was conducted, comparing factor 2 scores across groups.

Results

Sample Means

The study sample performed below population norms in every test administered (Table 1) with higher-than-average standardized scores on tests in which higher scores indicated dysfunction (e.g., time to complete trails) and negative scores on tests in which negative values indicate more impairment (FAS summary score, and Hopkins verbal learning test). On the MIST

Table 1. Means and standard deviations (raw and standardized scores)

	<i>n</i>	Raw mean	Raw <i>SD</i>	Standardized mean	Standardized <i>SD</i>
Trails A seconds ^a	90	45.21	36	1.42	3.65
Trails B seconds ^a	88	145.97	87.33	3.90	4.43
HVLT total	95	20.93	4.69	33.38	10.09
HVLT delayed	92	6.92	2.5	35.19	11.33
HVLT % retention	92	76.18	20.72	39.73	12.07
FAS total	95	30.94	11.36	−.94	1.01
MIST retro score ^b	91	6.35	1.40		
MIST 2 min recall ^b	92	6.5	1.82		
MIST 15 min recall ^b	92	4.22	1.86		
MIST event cue ^b	92	6.38	1.66		
MIST time cue ^b	92	4.34	1.84		
MIST action ^b	92	5.06	1.75		
MIST verbal ^b	92	5.66	1.92		
MIST summary score ^b	92	32.18	8.49		

Notes: *SD* = standard deviation.

^aPositive scores indicate impairment.

^bAppropriate norms were not available at the time of writing.

subscales, scores were substantially lower, on average, when a time was used to cue a response than when the response was to occur after an event ($M = 4.34$ and $M = 6.38$, respectively), suggesting that the passage of time was a less salient cue than an event. Time to complete Trails B, a measure of executive function, was considerably impaired (mean standardized score = 3.9) but verbal fluency was on average within 1 *SD* of the mean.

Correlation Between MIST Scores and Other Neuropsychological Measures

Prospective memory, as summarized by the MIST total score, was significantly correlated with time to complete Trails A ($r_s = -.318, p = .003$) and with several of the subscales of the HVLТ: Total recall ($r_s = .315, p = .002$), delayed recall ($r_s = .320, p = .002$), and retention ($r_s = .259, p = .015$). MIST total scores were not correlated with the two measures of executive function collected, the Trails B and COWAT.

Relationship Between Adherence and Neuropsychological Measures

The factor loadings demonstrated that the MIST, Trails, and HVLТ scores measured different domains (Table 2). Factors 1 and 2, each consisting entirely of MIST subscales, accounted for 26.76% and 23.70% of the variance explained, respectively. Factor 3 consisted of HVLТ scores and factor 4 consisted of Trails A and B.

The mean summary score (defined as the participant's average score on each of the responses which made up the individual factors), for each participant, on each of the four factors was calculated. Then, the Spearman correlation of this score with the percentage of medication doses taken was determined (Table 3). Only factor 2, a factor composed of three MIST subscales, was correlated with medication adherence at $p < .05$ ($r_s = .229, p = .028$). It should be noted, however, that whereas the bivariate correlations between factors 1 and 4 with medication adherence were not significantly different from 0 ($r_s = .078$ and $r = -.110$, respectively), the correlation between factor 3 and medication adherence was relatively stronger, but was not statistically significant ($r_s = .156; p = .131$).

Hierarchical Multiple Regression

A post-hoc regression analysis was used to determine the incremental contribution of factor 2 to the prediction of adherence after controlling for potentially confounding variables: Alcohol and cocaine use in the last 30 days, scores on the BDI, HVLТ total score, Trails A and B time variables, and CD4 count. Because raw adherence scores were negatively skewed (skewness/SE

Table 2. Rotated component matrix and communalities

	Component			
	1	2	3	4
Verbal response	.961	.086	.030	-.023
Time cue recall	.895	.238	.044	.029
2 min recall	.848	.124	.042	-.341
Retrospective recall	.684	.464	.139	.099
Action response	.129	.925	.167	-.151
15 min recall	.289	.846	.149	.156
Event cue recall	.230	.836	.167	-.226
HVLТ delayed recall	.030	.199	.937	-.070
HVLТ-R raw total recall	.281	-.002	.797	.041
HVLТ percentage of retention	-.175	.370	.701	-.188
Trails B	.033	.092	-.240	.750
Trails A	-.189	-.309	.134	.687

Notes: Extraction method: Principal component analysis and rotation method: Varimax with Kaiser normalization. Bold = Factor loading $> |0.6|$.

Table 3. Correlation between each factor and adherence

	F1 (MIST)	F2 (MIST)	F3 (HVLТ)	F4 (Trails)
Adherence	.078	.229*	.156	-.110

* $p < .05$.

skewness = -4.03), scores were cubed to better approximate a normal distribution (skewness/SE skewness = $.183$). Of the predictors included in the first block of the hierarchical regression model, only “Cocaine Use” was statistically significant ($t = -2.22$; $p = .029$). After controlling for “Cocaine Use,” factor 2 was a significant predictor of “Adherence” ($t = 2.13$, $p = .041$). The model containing these two predictors explained $\sim 10\%$ of the variance in adherence ($R^2 = .098$, R^2 change = $.045$).

T-Test

Using a criterion of 95% adherence, 21 participants were identified as adherers and 71 non-adherers. Results of the *t*-test revealed statistically significant group differences on factor 2 scores ($t(90) = 3.12$; $p = .002$; $d = 0.79$; Cohen’s *d* was calculated as $[M_{adh} - M_{non}]/SD_{non}$). Mean scores on the factor favored the adherent group ($M_{adh} = 6.16$, $SD = 1.61$; $M_{non} = 4.95$, $SD = 1.54$), signifying better average performance by that group on tasks that involved a 15 min delay, event-cued response, and action responding.

Discussion

The findings support the hypothesis that there is a prospective memory function assessed by the MIST that is distinct from abilities measured by traditional neuropsychological tests of verbal memory and executive function, as evidenced by the presence of distinct factors derived from MIST subscales. Further support is garnered from the factor analysis, as well as the pattern of correlations between the MIST summary score and the other neuropsychological tests. These findings largely replicate recent work exploring prospective memory impairment in people with HIV and extend the construct validity of prospective memory with the finding that a MIST factor was correlated with adherence to prescribed medication.

Another study employing the MIST measure of prospective memory in people with HIV (Carey et al., 2006) had similar findings to this one, in that the HIV-positive samples’ scores were considerably below population norms in both studies. As in the prior study, prospective memory scores were correlated with verbal retention. The correlation with verbal retention has been attributed (Martin et al., 2007) to overlapping pathways that are involved in both prospective memory and retrospective recall but not working memory (West & Krompinger, 2005). Neither study found a correlation between prospective memory and executive function as assessed by the verbal fluency task. Prospective memory was not correlated with the time needed to complete Trails B in the current study but was in the prior study. Given the wide range of dysfunction (visual scanning, attention, cognitive flexibility) that the Trails B is sensitive to, it is difficult to give a definitive explanation for this finding. One possible explanation for the difference between the two studies is that the prior study excluded people with substance use, psychiatric illness, and neurological disorders and not excluding participants with similar confounds may have increased the range of scores on Trails B.

As summarized by Waldrop-Valverde and colleagues (2005), there have been reports that patients who do worse on tests of executive functioning have lower adherence (Hinkin et al., 2002) and less consistent relationships between other aspects of neuropsychological functioning and adherence. Although the correlation between the prospective memory function and adherence in this study was modest, the finding of a significant correlation between a MIST factor and adherence is particularly important because many of the participants in this study had recent substance use and active HIV disease—yet the prospective memory signal emerged despite these potentially confounding influences. When examining the literature in relationship to this finding, two previous studies were found that related prospective memory to a real-world behavior. Martin and colleagues’ (2007) finding related prospective memory impairment to having engaged in high-risk sexual and injection behaviors and Woods, Moran, and colleagues (2008) demonstrated that impairment on the MIST was related to a significantly greater likelihood of impairment on activities of daily living.

This study extends the recent work by Woods and colleagues (2009) examining the relationship between an objective measure of medication adherence (MEMS caps) and prospective memory. Although Woods and colleagues demonstrated that loss of time errors (time-based recall) was significantly related to medication adherence, the current work raises the possibility that, in a more impaired sample (disease progression, substance abusers, less education), associative-based cues may be more salient to the process of prospective memory. Factor 2, a MIST-derived factor, was significantly correlated with medication adherence; slightly more so than other factors in the factor analysis. The MIST components of factor 2 were intuitively consistent with the cognitive requirements to adhere to prescribed medications (i.e., responses to be given in 15 min, and responses based on an event [or associative] cue). The longer delay (while not ideal) may be a more appropriate approximation of the process by which information is encoded and stored. The MIST tasks that have to be completed only 2 min after the instruction may be more consistent with working memory and auditory attention span than tests of more long-term prospective memory. In order to “remember to remember” to take prescribed medication, this information must be remembered long after it is encoded. The association with

adherence of responses based on an event-based cue may be more consistent with how patients take prescribed medication (using cues in the environment, e.g., getting ready for bed or work, before or after meals, etc.) rather than time-based cues. However, as noted above, Woods and colleagues (2009) have shown that errors of time-based cues are most strongly associated with poor medication adherence and further analysis of the MIST with behavioral measures of medication adherence is needed.

Limitations to the current study include the unavailability of more detailed indications of the extent of HIV progression such as nadir CD4 counts, and the lack of more detailed data on substance abuse (polysubstance abuse, duration, severity, DSM-IV classification), which may have elucidated the impact of substance abuse on the results.

In summary, the MIST demonstrated many qualities of a useful neuropsychological test of prospective memory. It showed convergent validity with the related measures of retrospective recall and discriminant validity from other neuropsychological measures such as the verbal fluency test. The MIST showed construct validity in that it correlated with electronically measured adherence. Research examining the utility of the MIST as a measure of adherence in an HIV-positive sample, as well as other populations should be pursued. In the current study, the MIST assessed the cognitive functions most strongly linked to medication adherence, and a MIST-related factor was independently associated with adherence in multivariate analysis.

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Conflict of Interest

None declared.

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