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Prospective Memory in HIV-associated Neurocognitive Disorders (HAND): The Neuropsychological Dynamics of Time Monitoring

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Abstract

Strategic monitoring during a delay interval is theorized to be an essential feature of time-based prospective memory (TB PM), the cognitive architecture of which is thought to rely heavily on frontostriatal systems and executive functions. This hypothesis was examined in 55 individuals with HIV-associated neurocognitive disorders (HAND) and 108 seronegative comparison participants who were administered the Memory for Intentions Screening Test (MIST), during which time monitoring (clock checking) behavior was measured. Results revealed a significant interaction between HAND group and the frequency of clock checking, in which individuals with HAND monitored checked the clock significantly less often than the comparison group across the TB PM retention intervals of the MIST. Subsequent analyses in the HAND sample revealed that the frequency of clock checking was positively related to overall TB performance, as well as to standard clinical measures of retrospective memory and verbal fluency. These findings add support to a growing body of research elucidating TB PM's reliance on strategic monitoring processes dependent upon intact frontostriatal systems. HIV-associated TB strategic time monitoring deficits may manifest in poorer functioning outcomes, including medication non-adherence and dependence in activities of daily living. Future research is needed to further delineate the cognitive mechanisms underlying strategic time monitoring in order to advise rehabilitation strategies for reducing HAND related TB PM deficits.

Keywords

HIV/AIDS; Prospective memory; Executive functions; Time perception; AIDS dementia complex

Time-based prospective memory (TB PM) is the neurocognitive capacity to remember to execute an intention at a specified future moment (e.g., remembering to take a medication at 2:00 pm). A number of component processes underlying successful TB PM have been identified (e.g., Kliegel, Jäger, Altgassen, & Shum, 2008), including: (a) formation of an intention; (b) encoding the intended action with the appropriate cue (i.e., the cue-intention pairing) for execution; (c) maintenance of the cue-intention pairing over a delay interval; (d)

retrieval of the intention from retrospective memory upon detection of the appropriate cue; and (e) successful execution of the intention. In both laboratory-based and naturalistic tasks of TB PM, individuals are engaged in other ongoing activities during the delay interval (i.e., step c), and must interrupt these activities in order to detect the cue. One essential feature of TB PM is that there are no external agents that direct individuals to engage in the memory task; in order for the intended action to be performed at the appropriate time, the passage of time must be checked, or monitored periodically during the delay interval. In this way, TB PM differs from its counterpart, event-based prospective memory (EB PM), for which the appropriate instance for execution is marked by an explicit external cue (i.e., remembering to take a medication when a lunch box is opened). Assuming that no external prompts are used to support prospective remembering (e.g., an alarm), TB PM tasks are proposed to be heavily reliant on voluntary self-initiated strategic time monitoring processes (McDaniel & Einstein, 2000). In contrast, EB PM cue detection is thought to rely more on involuntary automatic retrieval processes, but can also rely on attentional control processes under some task conditions (see Multiprocess theory; Einstein & McDaniel, 2005).

Although we have learned much about the cognitive mechanisms underlying monitoring in EB PM (for the Multiprocess theory see McDaniel & Einstein, 2005; for Preparatory Attentional and Memory [PAM] theory see Smith, Hunt, McVay, & McConnell, 2007), less empirical attention has been directed to examining the cognitive mechanisms underlying TB PM time monitoring. The *test-wait-test-exit* model of TB PM (TWTE; Harris & Wilkins, 1982) posits that individuals cycle through stages of testing (clock checking) to see if the time is appropriate to perform the intended action. That is, individuals test time (e.g., by checking a clock), which is followed by a “wait period” that lasts until another time check is deemed necessary. Individuals tend to check the clock at the beginning of retention intervals and particularly during the short period before the time at which they are required to act (Harris & Wilkins, 1982; Logie, Maylor, Della Sala, & Smith, 2004). In other words, participants typically display a J-shaped pattern of time monitoring. Although the TWTE model has intuitive appeal, it does not specify the underlying cognitive processes responsible for the initiation of clock checks (see Kvavilashvili & Fisher, 2007), though the model does suggest there may be a role for internal, biological time estimation, a theory some have suggested may be responsible for time monitoring frequency (Coren & Ward, 1989). However, the only study to examine this hypothesis found no association between clock checking behavior and tests of time estimation (Mäntylä & Carelli, 1995). Nevertheless, theoreticians broadly recognize that time monitoring during the delay interval in a TB PM tasks requires significant cognitive resources (Hicks, Marsh, & Cook, 2005), and thus is likely dependent on executive functions supported by prefrontal circuitry (Einstein, McDaniel, Richardson, Gynn, & Cunfer, 1995).

In fact, there is a growing body of evidence showing that TB PM deficits are mediated by disproportionately low levels of strategic monitoring in populations with prefrontal dysregulation, including schizophrenia (Shum, Ungvari, Tang, & Leung, 2004), Parkinson’s disease (Costa, Peppe, Calatagirone, & Carlesimo, 2008), traumatic brain injury (Carlesimo, Casadio, & Calatagirone, 2004), and aging (Mäntylä & Carelli, 2005). That is, individuals in these populations monitor external clocks less often as compared to healthy adults, including during the period in which the target time approaches (i.e., a lack of J-shaped clock checking behavior). However, it is of note that these studies examined time monitoring exclusively in the laboratory with typically short intervals of one to ten minutes; it is unclear whether these findings would translate to more naturalistic day-to-day PM tasks. Nevertheless, these studies have found significant correlations between clock checking frequency and TB PM task performance, highlighting the importance of time monitoring for successful TB PM retrieval. Furthermore, TB PM performance has been found to be related to measures of

executive functions in both Parkinson's disease (Costa et al., 2008) and schizophrenia (Shum et al., 2004).

One pertinent clinical population in which TB PM time monitoring has not been directly examined is HIV-associated neurocognitive disorders (HAND), which is the neurobehavioral hallmark of the neurological complications of HIV/AIDS (neuroAIDS). It is estimated that 30–50% of HIV infected individuals suffer from HAND in the present era of combination antiretroviral therapy (cART; Heaton, Franklin, Ellis, McCutchan, Letendre, et al., 2010); as such, it is important that we focus our efforts on exploring the cognitive architecture of PM in those individuals who evidence neurobehavioral deficits (Morgan, Woods, Delano-Wood, Bondi, Grant et al., 2011; Delis, Jacobson, Bondi, Hamilton, Salmon, et al., 2003) and are thus at greatest risk of HIV-associated disability (e.g., Heaton, Marcotte, MIndt, Sadek, Moore, et al., 2004). Despite the immunovirological effectiveness of combination antiretroviral therapies, HIV-associated neuropathologies are found throughout the central nervous system (CNS; Di Stefano, Sabri, & Chiodi, 2005). Specifically, the prefrontostriatal circuits are especially susceptible (Everall, Vaida, Khanlou, Lazzaretto, Achim, et al., 2009) as evidenced by neurobehavioral (e.g., Wilkie, Goodkin, van Zuilen, Tyll, Lecusay, et al., 2000), structural (Küper, Rabe, Esser, Gizewski, Husstedt, et al., 2011), functional (Chang, Ernst, Leonido-Yee, & Speck, 2000) and metabolic (e.g., Chang, Ernst, Speck, & Grob, 2005) studies. Neurobehavioral markers of HAND in the cART era include deficits in executive functions and episodic memory (e.g., Reger, Welsh, Razani, Martin, & Boone, 2002), two neurocognitive domains essential for PM (Gupta, Woods, Weber, Dawson, Grant, et al., 2010). Given HIV's propensity for dysregulation of prefrontal circuitry and executive dysfunction, it is not surprising that HIV-infected individuals self-report more PM failures in their daily lives (Woods, Carey, Moran, Dawson, Letendre, et al., 2007) and consistently exhibit worse performance on laboratory-based measures of TB PM compared to healthy seronegative individuals (e.g., Carey, Woods, Rippeth, Heaton, Grant, et al., 2006; Martin, Nixon, Pitrak, Weddington, Rains, et al., 2007). Importantly, from a standpoint of clinical relevance, HIV-associated TB PM deficits confer an increased risk of negative everyday functioning outcomes, including poorer health-related quality of life (Doyle, Weber, Atkinson, Grant, Woods, et al., 2012), medication non-adherence (Woods, Dawson, Weber, Gibson, Grant, et al., 2009), and dependence in instrumental activities of daily living (Woods, Iudicello, Moran, Carey, Dawson, et al., 2008).

There is a growing body of evidence suggesting that HIV-associated deficits in TB PM may be driven by dysfunction of strategic time monitoring. Two studies have found larger effect sizes for TB PM deficits compared to EB PM deficits in HIV-positive populations (Martin et al., 2007; Zogg, Woods, Weber, Doyle, Grant, et al., 2011). Also, individuals with HIV are particularly more likely than their seronegative counterparts to exhibit time loss errors (i.e., responding too early or too late) and omission errors (i.e., failure to respond at all) (Carey et al., 2006; Woods et al., 2009), both of which suggest dysfunction in monitoring time. Recently, Morgan and colleagues found that poor TB performance within HIV was exacerbated as the delay interval lengthened, suggesting that longer delays may heighten demands upon the strategic aspects of time monitoring (Morgan, Weber, Rooney, Grant, Woods, et al., 2012) and adversely impact cART adherence (Poquette, Moore, Gouaux, Morgan, Grant, et al., in press). Studies have also shown significant correlations between TB PM and cognitive ability measures tapping prefrontal systems, including executive functions, attention/working memory, and verbal fluency (Zogg et al., 2011; Gupta et al., 2010). Finally, TB PM impairment seems not to be caused by problems with other fundamental components of PM, including encoding or ongoing task absorption; no differences have been found between HIV-infected cohorts and controls on post-test recognition or on performance on the ongoing distractor tasks (Carey et al., 2006; Zogg et

al., 2011). Taken together, these data suggest that HIV-infected individuals may strategically monitor time disproportionately less during TB PM tasks as compared to seronegative control samples. To our knowledge however, no prior studies have measured clock checking behavior to directly test this hypothesis and to examine its cognitive architecture, including possible associations with time estimation and production.

Although we have learned much about TB PM impairment and its associated functional impact in HIV, the present study aimed to extend this literature in several novel and important ways. First, no prior studies have examined the cognitive mechanisms underlying HIV-associated TB impairment, which is prevalent and strongly associated with IADL dependence, including ART non-adherence (Woods et al., 2009). Thus, by drilling down to the specific cognitive mechanisms underlying HIV-associated TB PM dysfunction, we can better inform interventions to improve ART adherence (e.g., by sharpening the “dosing” of text messaging reminder systems) in this at-risk population. Second, only a handful of prior studies have examined time monitoring behavior during TB PM tasks in clinical populations; as such, the current study intends to extend the clinical PM literature. Even fewer prior studies have examined the neuropsychological correlates of TB monitoring and none have gone beyond executive functions to include other relevant cognitive domains (e.g., retrospective memory); as such, the current study intends to explore these potential correlational relationships in both a clinical and healthy comparison sample. Finally, the current study is the first to employ a proprietary clinical measure of PM (MIST) in order to investigate time monitoring behavior in TB PM. Although the MIST does not afford the same mechanistic precision as some experimental paradigms (e.g., Einstein, McDaniel, Thomas, Mayfield, Shank, et al., 2005; Hicks et al., 2005), it better informs clinical practice and also allows for the study of time monitoring while multiple different PM intentions are “online,” which may better reflect time monitoring requirements during real-world health care situations.

The current study therefore aimed to examine the effects of HAND on strategic TB PM monitoring within a well-characterized sample of persons with and without HIV infection. Given the neuropathological and neurobehavioral pattern of dysregulation of frontal systems in HAND, it was hypothesized that individuals with HAND would monitor time (check the clock) during a laboratory-based clinical PM task significantly less than seronegative comparison participants, and that this clock checking behavior would be significantly positively correlated with overall TB PM performance. Additionally, we expected to see that clock checking would be strongly associated with poorer performance on clinical tests of executive functions, but not with measures of time estimation or production.

METHOD

Participants

This study was approved by the institution’s human research protections program. The study sample included 108 seronegative comparison subjects and 55 individuals with HAND, who were recruited from the San Diego community and local HIV clinics. Of note, all participants were enrolled in an NIH-funded R01 to study the combined effects of HIV and aging on PM that used a discrepant age classification approach (i.e., no subject between the ages of 40 and 50 were enrolled in the parent study); as such, this dichotomous age grouping variable was used in our primary model so as to rule out any possible effects of this criteria. HAND was diagnosed by way of multidisciplinary case conference according to current Frascati criteria (Antinori, Arendt, Becker, Brew, Byrd, et al., 2007). Diagnoses were based on results from a comprehensive neuropsychological, medical, and psychiatric evaluation, in which measures of PM were excluded (see Woods, Moran, Carey, Dawson, Iudicello, et al., 2008). Sixty percent of the HAND group was classified as having “asymptomatic

neurocognitive impairment” (ANI; i.e., global neurocognitive impairment without endorsement of major functional disability), and 40% met criteria for mild neurocognitive disorder (MND; i.e., global neurocognitive impairment with endorsement of mild-to-moderate functional disability). No participants met criteria for HIV-associated dementia (HAD; i.e., moderate-to-severe global neurocognitive impairment with endorsement of at least moderate functional disability). Exclusion criteria included a diagnosis of a severe psychiatric (e.g., schizophrenia) or neurologic illness (e.g. seizure disorders, closed head injury with loss of consciousness greater than 15 minutes, or active CNS opportunistic infections), or a verbal IQ estimate of <70 (based on the Wechsler Test of Adult Reading, WTAR; Psychological Corporation, 2001). Additionally, participants were excluded if they met criteria for substance dependence within one month of evaluation (as determined by the Composite International Diagnostic Interview, CIDI version 2.1; World Health Organization, 1998), had a urine toxicology screen positive for illicit drugs on the day of evaluation (excluding marijuana), or a Breathalyzer test positive for alcohol.

Table 1 shows the demographic, psychiatric, neurocognitive, and HIV disease characteristics of the study samples. The HAND sample had lower verbal IQ scores, higher rates of lifetime Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and greater current affective distress as measured by the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981) ($p < .05$).

Materials and Procedure

After providing written, informed consent, participants completed a comprehensive neuropsychological, psychiatric, and medical evaluation.

PM assessment—Participants were administered the research version (Woods, Moran, Dawson, Carey, Grant, I., et al., 2008) of the Memory for Intentions Screening Test (MIST; Raskin, Buckheit, & Sherrod, 2010), which is a standardized, performance-based measure of PM with excellent reliability (e.g., subscale Cronbach’s $\alpha = .886$; Woods et al., 2008) and validity (e.g., Carey et al., 2006; Raskin, 2009). The MIST consists of 8 PM trials, during which the participant is engaged in an ongoing word search distractor task. The eight PM trials are counterbalanced on the following six subscales: (1) a 2-minute or 15-min delay; (2) a time-based (e.g., “In 15 minutes, tell me that it is time to take a break”) or event-based (e.g., “When I show you a postcard, self-address it”) cue; and (3) a verbal (e.g., “In 2 minutes, ask me what time this session ends”) or physical (e.g., “e.g., “In 15 minutes, use that paper to write down the number of medications are you currently taking”) response. Each trial on the MIST is worth a total of two points: one point is awarded for a correct response, and one point for responding (in some manner) at the correct time (i.e., within ± 1 minute of the target time for 2-minute TB trials, and within ± 2 minutes of the target time for 15-minute TB trials) or to the appropriate cue (for event-based trials). Each PM trial contributes to three of the six MIST subscales, which is determined by the trial’s delay, cue, and response characteristics; each subscale therefore consists of four PM trials with a range of 0 to 8. Finally, the six subscales are then summed to create a summary score, which ranges from 0 to 48. Consistent with previous studies, errors were coded as follows: (1) no-response (i.e., no reaction to a PM cue); (2) loss of time (i.e., executing a response 15% of the target time); (3) task substitution (i.e., responding incorrectly to the cue); or (4) loss of content (i.e., awareness that a response is required but failure to recall the correct intention). After the MIST was completed, participants were administered an eight-item, three-choice recognition task (range = 0 to 8). Finally, a 24-hr delay trial was administered for which participants were instructed to leave a voicemail message for the examiner 24 hours after the exam (rounded to the nearest hour) indicating the number of hours the participant slept the night after the evaluation. The 24-hr trial was scored using the same criteria as the other

eight MIST trials, with the exception that participants had a two-hour window to respond (i.e., within ± 1 hour of the target time). Unlike the other MIST items, participants were allowed to use compensatory mechanisms for the 24-hr task (e.g., setting an alarm in their phone), but were not explicitly instructed to do so.

We added a measure of time monitoring (clock checking) behavior during the MIST using a web-based application that was designed using PHP and Javascript. A server-side clock generated time and the time at which participants checked the clock was written to a SQL server database. The program required participants to press any key to display a digital clock on the monitor, which would appear for 6 seconds per press. Participants were instructed that they could check the clock at any point during the test in order to keep track of time, but that they were not required to do so (i.e., monitoring was voluntary). No other time-keeping devices were allowed, nor were participants permitted to take notes. For the purposes of this study, the variables derived from the raw data files included how many clock checks occurred over each of six 4-minute intervals of the MIST. Each 4-minute interval varied in terms of the number of time-based instructions given and responses due (see Figure 1).

General neuropsychological assessment—Participants received a comprehensive neurocognitive assessment in accordance with Frascati research guidelines for assessing HAND (Antinori et al., 2007). The following neurocognitive domains that were assessed and their associated tests are as follows: (1) retrospective memory: long-delay discriminability index of the California Verbal Learning Test – Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) and the Logical Memory II (LM-II) subtest of the Wechsler Memory Scales-III (WMS-III; Psychological Corporation, 1997); (2) attention/working memory: Digit Span subtest of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Psychological Corporation, 1997) and trial 1 from the CVLT-II; (3) executive functions: total move score from the Tower of London – Drexel (ToL-DX; Culbertson & Zillmer, 2001) and Trail Making Test (TMT) Part B (Reitan & Wolfson, 1985); (4) speed of information procession: Digit Symbol subtest of the WAIS-III and TMT Part A; (5) learning: CVLT-II trials 1–5 total and Logical Memory I (LM-I); (6) verbal fluency: Action Fluency test (Woods, Scott, Sires, Grant, Heaton, et al., 2005); and (7) motor skills: Grooved Pegboard Test (Kløve, 1963). A global clinical rating score was generated from participants' neurocognitive test scores across these seven domains, which range from 1 (above average) to 9 (severely impaired). Global clinical rating scores greater than or equal to 5 were used to determine HAND diagnoses (see Woods, Rippeth, Frol, Levy, Ryan, et al., 2004). Additionally, participants completed an experimental measure of time estimation and production (see Mimura, Kinsbourne, & O'Connor, 2000), in which a series of time lengths (i.e., 30, 90, 45, and 15 seconds) were first estimated, and then produced. From this, a total absolute value time discrepancy score was generated for both time estimation and production.

Data Analysis—To investigate the dynamic course of time monitoring in HAND, we used a repeated-measures mixed-model ANOVA with group (i.e., HAND vs. seronegative controls) as the between-subjects variable and the number of clock checks across each of six four-minute intervals as the within-subjects factor. The model was covaried for age, premorbid verbal IQ (based on the WTAR), and affective distress (using a dichotomous variable indicating any lifetime mood or anxiety disorder diagnoses based on the CIDI). Wilcoxon's Rank-Sum tests (due to non-normal distributions) with Cohen's *d* effect size estimates were employed for planned follow-up pair-wise comparisons. Within each group, raw scores from tests across the seven neurocognitive domains were converted to population-based *z* scores, which were then averaged across each domain to create composite *z* scores for each cognitive ability area. Spearman's rank correlation coefficients were then gathered to assess associations between clock checking and the various domain-

based *z* scores, as well as with other components of the MIST. We then used multiple regression techniques to identify which cognitive domains and MIST variables (i.e., that were significantly correlated with clock checking in bivariate analyses) uniquely predicted clock checking.

RESULTS

Table 1 shows that the HAND group had significantly lower scores on both the MIST TB and EB subscales as compared to seronegatives ($p < .05$). The mixed model ANOVA examining clock checking over the course of the MIST and covarying for age, mood/anxiety diagnoses, and WTAR revealed a significant effect of HAND ($F(1, 158) = 7.0, p = .009, \eta_p^2 = .042$), age ($F(1, 158) = 4.18, p = .04, \eta_p^2 = .026$), and WTAR ($F(1, 158) = 7.1, p = .009, \eta_p^2 = .043$). Additionally, there was a significant interaction between HAND and time interval ($F(5, 154) = 2.45, p = .036, \eta_p^2 = .086$). As shown in Figure 1, planned group comparisons showed a significant effect of HAND on clock checking in four of the six time intervals of the MIST; there was no difference between groups in the number of clock checks over minutes 4 to 8 ($p = .09$, Cohen's $d = .29$) and 16 to 20 ($p = .35$, Cohen's $d = .10$), but the HAND group checked the clock significantly fewer times during minutes 1 to 4 ($p < .01$, Cohen's $d = .44$), 8 to 12 ($p = .01$, Cohen's $d = .42$), 12 to 16 ($p < .01$, Cohen's $d = .55$), and 20 to 24 ($p < .01$, Cohen's $d = .61$). Post-hoc analyses of HAND diagnostic subtypes versus healthy adults on clock checking revealed a small-to-medium trend-level effect size for ANI ($d = .36, p = .10$), but a very large and significant effect for MND ($d = .96, p < .001$). In line with this, there was a trend for the MND group to check the clock less than the ANI group ($d = .56, p = .053$). Further, consistent with the notion that clock checking facilitates TB PM, the MND group performed significantly worse ($M = 3.64, SD = 1.73$) than the ANI group ($M = 4.76, SD = 1.46$) on the overall TB MIST subscale ($d = .71, p = .006$).

Table 2 shows Spearman's rho correlations between clock checking (i.e., total clock checks over the course of the MIST) and the various MIST components and domain-based *z* scores in both HAND and the seronegative group. Within the HAND cohort, clock checking frequency was positively correlated with the MIST summary score ($\rho = .46, p < .01$), as well as the TB ($\rho = .45, p < .01$) and EB ($\rho = .36, p < .01$) subscales. Clock checking frequency was also correlated with the 15-minute delay subscale ($\rho = .52, p < .01$) and errors of omission ($\rho = .47, p < .01$). All other MIST variables (i.e., distractor task total, 2-minute delay subscale, post-test recognition score, and other error types) were not significantly associated with clock checking ($p > .10$). Given that both the TB and EB subscales were correlated with clock checking in HAND, we conducted a follow-up regression predicting clock checking frequency from these two subscales; the overall model was significant ($F(2, 52) = 7.05$, adjusted $R^2 = .18, p = .002$), with the TB subscale emerging as the only predictor ($\beta = .39, p = .009$). A similar pattern emerged in the seronegative group, in which clock checking was correlated with the MIST summary score ($\rho = .31, p < .01$), the TB ($\rho = .34, p < .01$) and 15-minute delay subscales ($\rho = .31, p < .01$), as well as PM errors ($\rho = .38, p < .01$). All other MIST variables were not associated with clock checking frequency ($p > .05$).

To investigate relationships between clock checking behavior and neurocognitive functioning within each group, we used the total number of time checks and the domain-based *z* scores (i.e., speed of information processing, verbal fluency, motor skills, learning, retrospective memory, attention, and executive functions). Clock checking frequency was significantly positively correlated with retrospective memory ($\rho = .40, p < .01$), verbal fluency ($\rho = .49, p < .01$), and executive functions ($\rho = .28, p = .04$). We then conducted a follow-up multivariate regression analysis predicting clock checking frequency from these three cognitive *z* scores; the overall model was significant ($F(3, 50) = 7.97$, adjusted $R^2 = .$

28, $p < .001$), with retrospective memory ($\beta = .32$, $p = .015$) and verbal fluency ($\beta = .36$, $p < .01$) emerging as the significant predictors; executive functions was nonsignificant ($p > .10$). In the HAND group, neither time estimation ($\rho = -.10$, $p = .45$) nor production ($\rho = -.12$, $p = .42$) were associated with the frequency of clock checking, nor were they related to overall TB PM performance (time estimation $\rho = -.15$, $p = .28$; time production $\rho = -.20$, $p = .16$). Finally, we conducted separate bivariate analyses within the seronegative group examining relationships between total clock checks and domain-based z scores; both the SIP ($\rho = .21$, $p = .03$) and verbal fluency ($\rho = .21$, $p = .03$) domains were significantly correlated with clock checking frequency. In a follow-up model predicting clock checks from these two domains in the seronegative group, the overall model was significant ($F(2, 105) = 3.92$, adjusted $R^2 = .05$, $p = .02$), with verbal fluency emerging as the sole predictor of clock checking frequency ($\beta = .22$, $p = .02$). All other cognitive domains as well as the measures of time estimation and time production were nonsignificant ($ps > .10$).

DISCUSSION

Theoreticians have argued that TB PM tasks place great resource demands upon strategic, self-initiated monitoring processes which are largely driven by executive functions (Einstein et al., 1995; Hicks et al., 2005). Given the pattern of frontostriatal neuropathology and executive dysfunction evident in HIV-associated neurocognitive disorders (HAND), it is reasonable to expect that individuals with HAND may exhibit poor voluntary strategic time monitoring strategies during TB PM tasks. The findings from the present study are largely consistent with both these predictions and with findings from studies examining other populations with known frontal lobe dysregulation (e.g., Costa et al., 2008); that is, individuals with HAND monitored the external clock disproportionately less than their seronegative counterparts during a laboratory-based PM task. Specifically, there was a significant interaction between group (i.e., HAND vs. healthy adults) and time monitoring frequency across six four-minute time intervals of the MIST, which was not better explained by psychiatric factors, age, or premorbid verbal IQ. Furthermore, consistent with Mäntylä and Carelli's findings (2005), follow-up analyses revealed that clock checking frequency was not related to measures of internal biological time estimation or production; an alternate theory which some have suggested may be responsible for time monitoring performance (Coren & Ward, 1989). However, one limitation to the generalizability of this study is the exclusion of HIV-infected persons without HAND, who represent 50–70% of the current epidemic in the United States (Heaton et al., 2009). As such, our findings do not speak directly to the immunovirological mechanisms of TB monitoring in HIV, but rather are specific to individuals with the neurobehavioral syndrome that commonly accompanies HIV. Given our interests in the cognitive architecture of TB monitoring, we focused our efforts on HAND in order to ensure an adequate neurocognitive signal, methodologically minimize the Type I error risk associated with a third study group, and examine the study cohort at greatest risk of HIV-related disability for whom PM interventions will likely be targeted.

Follow-up pairwise comparisons revealed a significant effect of HAND at four out of a possible six time intervals in the MIST; that is, there was no significant difference between the number of time checks between minutes 4 to 8 (i.e., interval 2) and minutes 16 to 20 (i.e., interval 5). In fact, both groups monitored significantly less during these two intervals as compared to the other intervals (see Figure 1). Interestingly, these are the intervals of the MIST in which no TB instruction was given, nor was any TB intention due. By way of contrast, the intervals for which significant HAND effects were observed (i.e., intervals 1, 3, 4 and 6) all contained some combination of TB encoding and/or execution point time. However, there were also TB PM task retention intervals during non-significant intervals 2 and 5. It is thus reasonable to hypothesize that the HAND sample did not employ an increase

in clock checking frequency as the execution point for the TB PM tasks neared (i.e., in intervals 1, 3, 4, and 6). This pattern of data is both consistent with the *test-wait-test-exit* (TWTE; Harris & Wilkins, 1982) model, which posits that individuals cycle through stages of testing (clock checking) that become more frequent as the target time nears, and findings in the experimental PM literature for J-shaped patterns of time monitoring (e.g., Hicks et al., 2005; Logie et al., 2004). The current data are also consistent with the pattern of time monitoring deficits found in the other aforementioned clinical populations with frontostriatal dysfunction. However, it is crucial to acknowledge that a substantial limitation of this study is that we were unable to delineate time monitoring behavior on a trial-by-trial basis due to the nature of the MIST, which consists of overlapping TB trials; thus, we were not able to directly assess for clock checking patterns for each TB trial in isolation. It is also possible that the added cognitive “load” of the overlapping event-based trials may have absorbed strategic resources that impeded time-based monitoring behavior, making our hypothesis regarding a lack of J-shaped clock-checking behavior in the HAND group somewhat speculative. Accordingly, it would be advantageous for future HAND research to employ laboratory TB PM tasks with separable TB trials (see Hicks et al., 2005), in order to more specifically investigate patterns of time monitoring in the HAND population. Nevertheless, we also note that our approach to studying TB monitoring in this study may have added ecological relevance for real-world health care situations in which individuals must carry multiple EB and TB PM intentions “online”.

Consistent with prior research on syndromic HAND (e.g., Heaton et al., 2010) and the role of HIV-associated PM impairment in everyday functioning (e.g., Woods et al., 2009), we observed a larger effect of MND (i.e., syndromic HAND) versus ANI (i.e., subsyndromic HAND) on overall TB performance and specifically strategic time monitoring. ANI was associated with small-to-medium effect sizes versus the seronegative group, whereas very large effects were observed for MND. Thus, although we cannot conclude that the HAND effects on TB monitoring were solely attributable to those individuals with more severe forms of the disorder, it is clear that persons with MND were at somewhat greater risk of reduced time monitoring during the MIST. This step-wise increase in effect sizes is commensurate with previous data showing that individuals with syndromic HAND (i.e., declines in IADLs) are more likely to evidence PM deficits than their subsyndromic counterparts (e.g., Woods et al., 2008).

Within the HAND group, time monitoring was associated with several other MIST components. First, clock checking frequency was found to be related to the overall MIST summary score, and, interestingly, to both TB and EB subscales. While a follow-up regression revealed that the TB subscale predicted clock checking frequency beyond the EB subscale, one could posit that the moderate correlation between TB monitoring and EB performance could reflect the Multiprocess Theory in that EB monitoring does rely, in part, on effortful and strategic monitoring (McDaniel & Einstein, 2000). Also, longer (i.e., 15-min), not shorter (i.e., 2-min), delay intervals were correlated with clock checking behavior, perhaps reflecting the difficulty of maintaining higher level strategic and voluntary time monitoring strategies as delay intervals lengthen. Indeed, longer ongoing delay intervals (i.e., 15-min) can exacerbate poor PM performance within HAND (Morgan et al., 2012), and tends to be driven by TB PM trials. Moreover, longer delay intervals are most strongly associated with markers of executive dysfunction (i.e., appearing to be related to markers of strategic dyscontrol), and correspond to an increased risk of cART non-adherence (Poquette et al., in press). Finally, the only TB PM error type that was associated with clock checking was that of omission (i.e., failure to respond to a cue), which is consistent with prior HIV research in that poor TB PM performance is typically driven by omission errors (Woods et al., 2009). This finding is conceptually consistent with our hypotheses in that effective time monitoring is associated with TB PM retrieval; all other MIST error types (i.e., loss of time,

loss of content, and task substitution) require that a cue is first detected, which is not the case for omission errors.

In contrast to the laboratory-based monitoring impairment in HAND, post-hoc analyses showed only a trend-level effect of HAND on the MIST's 24-hr delay trial ($d = .26$, $p = .078$). Given the fact that the 24-hr delay trial has only a single data point and thus suffered from low power (compared to number of data points and associated power of the TB scale), this trend level effect suggests that lab-based data can potentially translate to the more naturalistic time-based tasks of everyday life (Blackstone et al., in press). However, one other possible interpretation is that the HAND group may have employed compensatory strategies (e.g., a note to oneself) for the 24-hr task; as such, the use of such a strategy would lessen the need for strategic time monitoring, and would increase reliance on automatic processing. This interpretation is consistent with the tenets of the age-prospective memory paradox; for example, a recent study found that while an older HIV+ group performed significantly worse than a younger HIV+ group on the lab-based portion of the MIST, the older group performed comparably to the younger group on the 24-hr trial, and was also significantly more likely to report use of PM-based strategies and external aids than was the younger group (Weber, Woods, Delano-Wood, Bondi, Gilbert, et al., 2011). Whether the prospective use (or prescription) of external reminding aids that minimize strategic time monitoring demands (e.g., context-free cueing) actually improve HIV-associated PM deficits in daily life remains to be determined.

To our knowledge, this was the first study to examine relationships between clock checking and several domains of cognitive functioning (i.e., beyond traditional measures of executive functioning). Within the HAND group, time monitoring (clock checking) was related to domains of retrospective memory, verbal fluency, and executive functions, but not with psychomotor skills. Interestingly, retrospective memory and verbal fluency were the only domains that held to be predictive of time monitoring in a follow-up regression model. Similarly, within the seronegative group, verbal fluency was the only domain that was significantly associated with clock checking behavior. Verbal fluency is reliant on frontal systems and executive processes (Moscovitch, 1994), most notably "switching," which describes the effortful, self-initiated, and rule-guided search and retrieval of words from semantic memory stores, in which the individual moves from one semantic cluster (e.g., "fruits) to another (e.g., "furniture") (Troyer, Moscovitch, & Winocur, 1997). Indeed, HIV-associated verbal fluency declines appear to be driven by deficits in switching (i.e., executive dyscontrol), rather than by an inability to generate adequate cluster sizes (i.e., medial temporal dyscontrol). Specifically, HIV-infected cohorts have shown switching impairment in both letter and category fluency (Iudicello, Woods, Parsons, Moran, Carey, et al., 2007), which are exacerbated in explicit switching conditions (Iudicello, Woods, Weber, Dawson, Scott, et al., 2008) that may be ameliorated by providing structured semantic cues (Iudicello, Kellogg, Weber, Smith, Grant, et al., 2012). Furthermore, these HIV-associated switching deficits were found to be uniquely associated with executive dysfunction (Iudicello, Woods, Deutsch, Grant, & The HNRP Group, 2012). Relatedly, Kliegel and colleagues (Kliegel, Altgassen, Hering, & Rose, 2011) proposed a model of PM which demonstrates that the latter stages of a PM task, in addition to being reliant on time monitoring behavior and the ability to inhibit absorption in the ongoing task (Bisiacchi, Schiff, Ciccola, & Kliegel, 2009), is dependent upon the cognitive flexibility (driven by frontal systems) required to switch engagement to the PM task at hand (Kliegel, Mackinlay, & Jäger, 2008). Thus, the observed relationship between monitoring and verbal fluency may reflect monitoring's sensitivity to the executive aspects of task switching abilities within verbal fluency tasks.

Regarding the unexpected predictive value of retrospective memory on TB monitoring in HAND, in hindsight, several explanations come to light. First, it could be simply that individuals with poor time monitoring in the HAND group simply forgot some critical aspect of the TB PM task, including the details of the TB task itself, or the time at which the intention was due, in which case participants would not have monitored the clock. However, this explanation is unlikely, given that clock checking did not correlate with the MIST recognition task, and given the extensive body of literature which reveals memory impairment in HAND to be a mixed encoding/retrieval profile rather than one of rapid forgetting (e.g., Woods, Morgan, Marquie-Beck, Carey, Grant, I., et al., 2006). Another approach to interpreting this finding is by way of Moscovitch's (1994) ideas regarding "working with memory". The theory posits that there is an "associative" component (driven by temporolimbic networks), that is responsible for the effective retention of raw memories, as well as a "strategic" component (driven by frontal systems), which is hypothesized to "work with memory" in order to initiate, monitor, and enhance the organizational and strategic features of encoding and retrieving memories. Indeed, HIV cohorts as well as other clinical populations with prominent frontal lobe damage evidence dysfunction of the strategic component of retrospective memory functioning (i.e., by showing a lack of use of organizational strategies and high rates of interference and repetition errors) as opposed to the associative component (e.g., rapid forgetting) (Gongvatana, Woods, Taylor, Vigil, Grant, et al., 2007). In fact, a post hoc analysis revealed that frequency of clock checking in the HAND sample was significantly associated with semantic clustering on the long delay trial of the CVLT-II ($p = .29$, $p = .03$). To this end, the association between retrospective memory and time monitoring could theoretically be viewed as a result of the dysregulation of the strategic component of memory functioning within the HAND group.

Although significant at the bivariate level, the relationship between clock checking and executive functions became non-significant when included in a model with other significant neurocognitive predictors in HAND (i.e., verbal fluency and retrospective memory) and was not associated with clock checking in the seronegatives. Considered in the context of the previously mentioned evidence supporting strategic underpinnings of time monitoring, a possible culprit for this apparent discrepancy is the multi-factorial nature of executive functions. Verbal fluency is oftentimes considered within the umbrella term of executive functions (e.g., Lezak, Howieson, & Loring, 2004); however, consistent with neuroAIDS research recommendations (Antinori et al., 2007), it comprised its own domain, whereas the "executive functions" domain consisted of tests heavily reliant on visual planning (i.e., Tower of London-DX) and speeded divided attention (i.e., Trail-Making Test – Part B). It may be possible that these specific abilities within the executive functions are relatively less implicated in intact time monitoring as compared to other strategic abilities (e.g., strategic switching).

Overall, the aforementioned pattern of relationships between TB PM, clock checking, and the various tests of neurocognitive functioning in HAND are consistent with the idea that there is a dissociation between internally and externally driven (clock) time checking processes in TB PM. That is, if a participant can effectively remember to periodically check the clock, there is little need to track time internally. Kvavilashvili and Fisher (2007) demonstrated rehearsal of TB PM task requirements (and possible subsequent clock checking) pre-dominantly occurs in response to incidental external (and/or internal) cues that remind participants of their TB PM task goals periodically during the delay period, rather than by self-initiated internal time keeping. Thus, it is the capacity to switch attention between the ongoing task and PM task goals (verbal fluency, "working with memory") that is crucial for participants to remember to periodically check the external clock, rather than internal time estimation/production mechanisms. Of course, internal time keeping may become more crucial as the correct time to perform the action nears.

The findings described herein support previous research elucidating TB PM's reliance on voluntary strategic time monitoring processes which appear to be driven by frontostriatal networks and executive functions. The possible clinical implications of these findings are worth consideration; as TB PM may be a valuable predictor of everyday functioning declines in HIV infection (Martin et al., 2007; Woods et al., 2009; Poquette et al., in press), evaluation of specific component TB PM processes which may drive impairment could prove valuable in terms of rehabilitation techniques. For example, individuals with monitoring deficits may profit from techniques such as Goal Management Training (Levine, Robertson, Clare, Carter, Hong, et al., 2000), which involves teaching individuals to engage in an "executive review" of their plans and intentions (e.g., "What do I have to do today and when?"), and has proven to be effective in patients with traumatic brain injury (Fish, Evans, Nimmo, Martin, Kersel, et al., 2007). Other remediation techniques may focus on reducing the cognitive load of TB PM tasks by minimizing distractions during delay periods, or by using self-regulatory strategies such as redirecting attention to PM tasks at appropriate time intervals. Of course, one strategy that is likely very valuable in successful TB PM is the use of compensatory mechanisms (e.g., external reminders such as an alarm). In support of this, a recent study found that older HIV+ individuals who reported utilizing external mnemonic strategies in their daily lives were significantly more likely to successfully complete a semi-naturalistic task of TB PM as opposed to older HIV+ individuals who did not report employment of such strategies (Weber et al., 2011). Further investigation into what techniques and strategies may benefit TB PM in HIV-positive populations is clearly warranted, given the recent emergence of literature illuminating the prominent dysregulation of this important component of cognitive functioning.

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Figure 1.

Time monitoring performance on the MIST between the two study groups (i.e., total number of time checks across six 4-minute time intervals).

Note: TB = time-based; IG = instruction given; RD = response due. * $p < .05$.

Table 1

Demographic, Psychiatric, Cognitive and HIV Characteristics of the Study Participants

Characteristics	HIV- (n=108)	HAND (n=55)	p
Demographics			
Age (years)	44.5 (14.7)	48.2 (12.9)	.149
Education (years)	13.9 (2.6)	13.5 (2.7)	.243
WTAR verbal IQ	102.5 (10.7)	97.7 (11.2)	.009
Sex (% female)	22.2	14.6	.243
Ethnicity (% Caucasian)	59.3	54.6	.565
Psychiatric			
Lifetime major depression (%)	38.0	56.4	.025
Lifetime generalized anxiety (%)	4.6	18.2	.005
Lifetime alcohol use disorder (%)	33.3	29.1	.583
Lifetime non-alcohol use disorder (%)	35.0	32.7	.668
POMS total ^a	38 (24, 57)	58 (38, 77)	<.001
HIV Disease			
Estimated duration of infection (years)	-	13.2 (8.4)	-
AIDS (%)	-	63.6	-
cART (%)	-	90.9	-
Nadir CD4 ^a (cells/ μ l)	-	148 (50, 300)	-
Current CD4 ^a (cells/ μ l)	-	528 (377, 737)	-
Plasma HIV RNA log ₁₀ (% detectable)	-	11.9	-
Cognitive			
Global NP Clinical Rating ^a	4 (2, 4)	6 (5, 6)	<.001
HAND Classification: ANI (%)	-	60.0	-
HAND Classification: MND (%)	-	40.0	-
MIST			
Summary score	36.3 (7.9)	29.1 (9.3)	<.001
Time-based subscale	5.8 (1.5)	4.3 (1.7)	<.001
Event-based subscale	6.3 (1.6)	5.4 (1.9)	.002

Note. ANI = Asymptomatic neurocognitive impairment. cART = combination antiretroviral therapy. MIST = Memory for Intentions Screening Test. MND = Mild neurocognitive disorder. POMS = Profile of Mood States. WTAR = Wechsler Test of Adult Reading.

^aMedian (interquartile range)

Table 2

Correlations between clock checking and neurocognitive tasks in the study samples.

Variable	HIV- (n=108)	HAND (n=55)
MIST		
Summary score	.31 *	.46 *
TB subscale	.34 *	.45 *
EB subscale	.17	.36 *
2-min delay subscale	.15	.23
15-min delay subscale	.31 *	.52 *
24-hr delay trial	.08	.15
Distractor task total	.17	.04
Error Types		
PM	.38 *	.47 *
LT	.14	.17
LC	.04	.02
TS	.07	.01
Clinical Domains		
Attention	.18	.21
Executive functions	.05	.28 *
Learning	.09	.41 *
Memory	.07	.40 *
Motor	.12	.20
SIP	.21 *	.03
Verbal Fluency	.21 *	.49 *

Note. Data are presented as Spearman's rho correlation coefficients.

* $p < .05$.

TB = Time-based. EB = Event-based. PM = Prospective memory. LT = Loss of time. LC = Loss of Content. TS = Task Substitution. SIP = Speed of Information Processing.