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Habitual Prospective Memory in HIV Disease

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Abstract

HIV-associated neurocognitive disorders (HAND) are associated with deficits in prospective memory (PM). However, most PM research in HIV has used single-event tasks as opposed to habitual PM paradigms, which may be more relevant to clinical populations for whom many healthcare behaviors must be performed both frequently and routinely. The current study examined habitual PM and its associations with real-world functioning outcomes in 36 HIV+ individuals with HAND (HAND+), 70 HIV+ individuals without HAND (HAND-), and 115 HIV- individuals. The ongoing task consisted of 24 one-minute Stroop trial blocks in which the emotive and cognitive load was manipulated. The habitual PM task required participants to press the spacebar once per block, but only after twenty seconds had elapsed. A series of MANOVAs covarying for relevant clinicodemographic factors revealed a main effect of study group on habitual PM, such that the HAND+ cohort made significantly more repetition errors compared to the HIV- and HAND- groups, particularly during early trial blocks. There was no main effect of ongoing task demands. There was no interaction between HAND group and task demands. Within the entire HIV+ sample, poorer habitual PM was associated with deficits in learning and dysfunction in real-world outcomes, including medication nonadherence and failures on a naturalistic healthcare task. Findings indicate that HAND may be associated with deficient internal source monitoring or temporal discrimination for habitual PM output that may play a critical role in real-world functioning, including HIV disease management.

There is a growing body of evidence indicating that HIV disease is associated with deficits in prospective memory (PM), which is a complex cognitive ability that allows an individual to remember to perform a deferred intended action in response to a specific cue that may be based on an environmental event (e.g., remembering to drop off a letter at the post office) or time (e.g., remembering to take a prescribed medication at noon). According to Kliegel's neuropsychological process model (Kliegel, Jäger, Altgassen, & Shum, 2008), successful

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execution of a PM task requires: (1) formation of the intention to defer an action; (2) retention of the deferred action over a delay interval; (3) initiation of the deferred action upon detecting the appropriate cue; and (4) execution of the deferred action. PM is a form of episodic memory that is related to, but uniquely dissociable from retrospective memory (Einstein & McDaniel, 1990) and executive functions (e.g., planning, cognitive flexibility, inhibition; Gupta, Woods, Weber, Dawson, & Grant, 2010), including the specific executive function of working memory (Basso, Ferrrari, & Palladino, 2010). At the level of neural systems, PM is heavily reliant upon both prefrontal systems (notably Brodmann's area 10; Burgess, Quayle, & Frith, 2001) and the medial temporal lobe (Gordon, Shelton, Bugg, McDaniel, & Head, 2011).

Given that the neuropathologies of HIV disease preferentially affect prefrontal and temporolimbic networks (e.g., Everall et al., 2009), it is not surprising that HIV-infected individuals evidence mild-to-moderate deficits in both time- and event-based PM (Carey et al., 2006). The profile of PM deficits in HIV disease is predominantly characterized by poor strategic monitoring for PM cues (Doyle et al., 2013a), which is largely dependent on executive functions supported by prefrontal circuitry (Einstein, McDaniel, Richardson, Guynn, & Cunfer, 1995). HIV-associated PM dysfunction is a unique predictor of problems in several real-world functioning domains, including antiretroviral non-adherence (e.g., Woods et al., 2009). Individuals with HIV-associated neurocognitive disorders (HAND), who represent 30–50% of HIV-infected individuals (Heaton et al., 2010), appear to be at particular risk for PM deficits (e.g., Morgan et al., 2012) and poorer functional outcomes (Heaton et al., 2004).

To date, PM research in HIV (and most other populations) has largely utilized what Einstein, McDaniel, Smith and Shaw (1998) termed "single-event PM tasks," in which participants must perform a PM action either once, or on several different occasions, in response to a discrete single event or at a specified time(s). For example, on the Memory for Intentions Screening Test (MIST; Raskin, Buckheit, & Sherrod, 2010), which is the measure that has been most frequently utilized to examine PM deficits in the HIV literature, subjects are prescribed 8 unique cue-intention pairings to execute; sample MIST items include, "when I show you a postcard, self-address it" and "in fifteen minutes, tell me it is time to take a break." Individuals with HIV also show difficulties on computerized single-event PM tasks, which require participants to press a pre-determined response key whenever a certain type of stimulus (e.g., certain words, a certain syllable) is presented during a concurrent ongoing task (Loft et al., 2014; Woods et al., 2014).

However, many PM tasks that occur in everyday life are more habitual in nature, in that they occur frequently and in a routine manner (Meacham & Leiman, 1982). Habitual PM tasks may be particularly relevant to clinical populations like HIV disease, as many healthcare behaviors (e.g., daily doses of medications, home-based vital sign readings) need to be performed frequently at a consistent time or place. Habitual PM tasks are thought to differ from single-event PM tasks in that they are more heavily reliant on intact internal source (or output) monitoring during the intention execution phase of the PM process model. Internal source monitoring theory (Johnson & Raye, 1981) describes one's ability to distinguish thoughts from actions. For example, consider the need to take a medication every four hours.

As the action of taking the medication is performed so frequently, it necessarily becomes an action that is thought about often, and thus it becomes difficult to differentiate between actual performance and thoughts. Deficient internal source monitoring poses a problem for habitual PM tasks, as different types of PM errors can occur. An error of omission (i.e., not taking the required medication does at the appropriate time) can occur if a person confuses a thought about taking the medication with a memory for having taken the medication. An error of repetition (i.e., erroneously repeating a medication dose) can occur if a person confuses a memory for taking the medication for a thought about having taking the medication. Problems in temporal discrimination, aspects of which are impaired in HIV disease (Woods et al., 2013), could also lead to habitual PM error (Friedman, 1993). Memory of taking medication might be estimated as being more distant than it actually was (resulting in taking an extra dose), or memory of taking medication might be estimated as being more recent that it actually was (resulting in missed dose).

Despite the apparent clinical relevance of habitual PM, to our knowledge, there have been just four studies examining habitual PM populations using rigorous experimental approaches. These studies have been conducted in schizophrenia (Elvevåg, Maylor, & Gilbert, 2003), type 2 Diabetes (Vedhara et al., 2004), and aging (Einstein et al., 1998; McDaniel, Bugg, Ramuschkat, Kliegel, & Einstein, 2009). In the original habitual PM study, Einstein and colleagues (1998) asked participants to press a designated key once per three-minute trial of an ongoing task (e.g., vocabulary, perceptual speed), but only after the first 30 seconds had elapsed. Older adults made significantly more errors of repetition and omission compared to younger adults, particularly when the attentional demands of the ongoing task were high (i.e., when a demanding auditory working memory task was administered concurrently with the standard ongoing task). Notably, the older adults evidenced elevated omission errors in early but not late trials, and the opposite pattern for repetition errors, suggesting that the various error types may manifest differently as habit learning progresses. Surprisingly, the provision of an explicit cue to execute the PM task was not effective in reducing PM errors in the older adults, which supported the notion that habitual PM errors may be due to deficient internal source monitoring or temporal discrimination. In clinical populations, the same types of experimental habitual PM paradigms have been utilized, in which participants are asked to press a specific key after approximately 30 seconds have elapsed in each ongoing task trial. Elvevåg et al. (2003) found that schizophrenia was associated with increased omission errors and outcome evaluation errors as compared to a healthy group, suggesting an internal source monitoring or temporal discrimination deficit. Finally, Vedhara et al. (2004) reported that errors of omission and repetition on a laboratory habitual PM task were associated with lapses in medication adherence in a cohort of older adults with type 2 diabetes. Such findings suggest that deficits in habitual PM may play an important role in healthcare behaviors.

The current study sought to determine the nature and extent of habitual PM deficits in HIV disease by way of an experimental habitual PM paradigm inspired by Einstein and colleagues (1998). Additionally, we aimed to extend the literature on the role of the ongoing task within habitual PM, and how the demands of which might affect performance within HIV disease. Whereby previous studies have utilized the addition of a taxing working memory task to the standard ongoing task (Einstein et al., 1998; McDaniel et al., 2009), the

current study examines the impact of systematically varying the emotional and cognitive load of the ongoing task itself. Our hypothesis was that individuals with HAND would evidence significantly elevated habitual PM errors as compared to HIV+ individuals without HAND and a seronegative group, and that this effect would increase under cognitively or emotionally demanding ongoing task conditions. With regard to cognitive load, we used a traditional Stroop paradigm to tax executive (i.e., prepotent response inhibition) demands that has been shown the increase RT and thereby should take resources away from the PM task. While the literature on emotional cognition in HIV disease is to date not extensive, a few studies have provided evidence that HIV-infected individuals exhibit deficits within this domain, including slower processing of emotional stimuli (e.g., Emotional Stroop response time; Novara et al., 2000) and poor emotion recognition (Clark, Cohen, Westbrook, Devlin, & Tashima, 2010), particularly among individuals with HAND (Lane, Moore, Batchelor, Brew, & Cysique, 2012). Such difficulty with emotional processing purportedly taxes top-down attentional control systems among individuals with HIV disease (Schulte, Müller-Oehring, Sullivan, & Pfefferbaum, 2011), and as such it is likely that fewer cognitive resources can be devoted to the ongoing monitoring and temporal discrimination demands required for successful habitual PM. Additionally, we sought to gain an understanding of the cognitive architecture of habitual PM by examining associations with neurocognitive domains, and expected that performance would be driven by ability in executive functions and attention/working memory. Finally, we hypothesized that habitual PM performance within HIV would be independently associated with real-world functioning status across several different functional domains.

Methods

Participants

This study was approved by the institution's human research protections program. The study sample included 36 HIV+ individuals with HAND (HAND+), 70 HIV+ individuals without HAND (HAND-), and 115 HIV- comparison subjects. All participants were recruited from local HIV clinics and the San Diego community. HAND was diagnosed based on results from a comprehensive neuropsychological evaluation (detailed below), consistent with current Frascati criteria (Antinori et al., 2007). Exclusion criteria across groups included the following: a history of severe psychiatric (e.g., schizophrenia) or neurologic (e.g., seizure disorder) illness; a verbal IQ estimate <70 (based on the Wechsler Test of Adult Reading, WTAR; Psychological Corporation, 2001); a diagnosis of substance dependence (according to DSM-IV criteria; American Psychological Association, 1994) within one month of evaluation as determined by the Composite International Diagnostic Interview (CIDI version 2.1; World Health Organization, 1998); a Breathalyzer test positive for alcohol; or a urine toxicology screen positive for illicit drugs (excluding marijuana). While the HAND+ group was found to have a significantly higher proportion of individuals whose urine toxicology was positive for marijuana, recent marijuana use was not related to any of the habitual PM outcomes in any of the three groups (ps>.05). Of note, all participants were enrolled in a NIH-funded R01 study examining the combined effects of HIV and aging on PM, which used a discrepant age classification approach such that no individuals between the ages of 40 and 50 were enrolled in the study.

Table 1 shows the demographic, psychiatric, and disease characteristics of the study groups. In addition to determining histories of substance dependence, the CIDI was also used to establish histories of psychiatric disorders. For the current study, "affective disorder" was defined as lifetime history of meeting criteria for Major Depressive Disorder or Generalized Anxiety Disorder. Regarding the demographic characteristics of the study groups, the HIV- cohort was younger and included a larger proportion of women than both HIV+ groups (*p*s<.05). Participants in the HIV- group were also less likely to meet criteria for lifetime affective disorder and methamphetamine dependence than the HIV+ groups (*p*s<.05). Finally, the HIV+ groups were similar on all HIV disease and treatment variables (*p*s>.05), but had higher rates of hepatitis C (HCV) infection than the HIV- group (*p*s<.05).

Materials and Procedure

After providing informed consent, participants completed comprehensive prospective memory, general neuropsychological, real-world functioning, psychiatric, and medical evaluations.

Habitual PM Experiment—Participants were administered a computerized habitual PM task inspired by the original Einstein and colleagues (1998) habitual PM paradigm. The ongoing task consisted of 24 one-minute Stroop blocks. Within each one-minute block of trials, 24 words were randomly presented (one at a time) for three seconds each in duration, and participants were required to press a key indicating the font color of the presented word (i.e., red, blue, green or yellow). Response time and accuracy were recorded. There were four types of Stroop blocks: 1) Low Emotional Load (i.e., "boat," "truck," "car," "train"); 2) High Emotional Load (i.e., "failure," "fungus," "venom," "weapon"); 3) Low Cognitive Load: all items were presented as "XXXX"); and 4) High Cognitive Load (i.e., "Red," "Blue," "Green," "Yellow"). The words used for the high and low emotional Stroop were selected from a published normative database. There were six different blocks for each of the four Stroop types, and the order of presentation of Stroop blocks was randomized such that each type of trial block occurred within a set of four blocks. The order of presentation of stimuli within each Stroop block was also randomized.

The habitual PM instructions were similar to tasks that have been employed in prior habitual PM literature (e.g., Einstein et al., 1998). Participants were instructed to press the spacebar one time per one-minute block of trials (but not within the first 20 seconds of the block). A running clock in the bottom corner of the computer screen displayed how many seconds had elapsed (in ascending fashion) in the current trial. The main dependent variables obtained from the habitual PM task included: 1) total number of PM omissions (i.e., the number of blocks in which the spacebar was not pressed); and 2) total number of PM repetitions (i.e., the number of times the spacebar was pressed more than once per block).

General Neuropsychological Assessment—All participants received a comprehensive neuropsychological test battery that assessed domains of attention/working memory, executive functions, information processing speed, learning, retrospective memory, motor skills, and verbal fluency (see Morgan et al., 2012 for details). Raw scores obtained from the measures were converted into demographically-adjusted T-scores based on

published normative standards, which were subsequently converted into domain and global clinical ratings and are displayed in Table 2 (see Woods et al., 2004 for details). Global clinical ratings greater than 4 indicated impairment consistent with a diagnosis of HAND. Of those with HAND diagnoses (*n*=36), 15 (41.7%) met criteria for asymptomatic neurocognitive impairment (ANI), and 21 (58.3%) met criteria for mild neurocognitive disorder (MND).

Real-World Functioning (RWF) Assessment—Three RWF domains were used to classify participants as "impaired" or "unimpaired" (see Table 2).

(1) General Functional Impairment: To represent general functioning status, a composite variable was created from the outcomes of five different functional subdomains (see Blackstone et al., 2013). Participants were classified as "impaired" in this domain if they met criteria for impairment in at least two of the subdomains (range = 0–5). The subdomains are as follows:

- **a.** *Employment Status.* Participants self-reported current employment status during a semi-structured interview, and were subsequently categorically classified as "employed" (i.e., full- or part-time) or "unemployed."
- **b.** *Basic Activities of Daily Living (BADLs).* Participants completed a modified version (Heaton et al., 2004) of the Activities of Daily Living Scale (ADL; Lawton and Brody, 1969), which included five items that assessed BADLs (i.e., housekeeping, home repairs, bathing, dressing, and laundry). Participants indicated perceived "current" and "best" functioning levels within the five BADL domains, and were classified as "impaired" in BADLs if two or more domain declines were reported (i.e., "current" was reported as worse than "best" for the given domain).
- **c.** *Instrumental Activities of Daily Living (IADLs).* IADL impairment status was also derived from the modified version of the ADL scale, which included 11 items that assessed IADLs (i.e., finance management, grocery shopping, shopping, understanding reading material/television, social involvement, communication, medication management, transportation, cooking, child care, and work). Participants were classified as "impaired" in IADLs if two or more domain declines were reported.
- **d.** *Functional Performance Status.* During the medical evaluation, a certified nurse assigned participants an overall functional impairment rating via the Karnofsky Scale of Performance Status (Karnofsky and Burchenal, 1949). Scores range from 100 (i.e., normal/no complaints/no evidence of disease) to 0 (i.e., death), and for the current study a cutpoint score of <90 was used to categorize participants as "impaired" (Schag, Heinrich, & Ganz, 1984).
- **e.** *Cognitive Symptoms.* The Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981) is a 65-item self-report evaluation of current mood states, in which participants rate various adjectives (e.g., "forgetful") on a five-point Likert-type scale ranging from 0 ("not at all") to 4 ("extremely") based on their mood during the week prior to evaluation. For this study, the Confusion/Bewilderment

subscale was used. Raw subscale scores were converted to sample-based Z scores, with a Z score cutoff of >1 indicating impairment (Nyenhuis et al., 1999).

(2) Antiretroviral Adherence: HIV+ participants were classified as "adherent" (i.e., "unimpaired") or "nonadherent" (i.e., "impaired") based on results of a four-week observation period (beginning the day after the neuropsychological assessment) using the Medication Event Monitoring System (MEMS; Aprex Corporation, Union City, CA). Participants were instructed to fill the MEMS bottle with the target ARV (identified by the examiner) and to remove only one dose at a time. The MEMS bottle uses a cap microchip device (Trackcap©) that recorded the dates and times at which the bottle was opened. Adherence impairment was defined as <90% adherence to the target ARV on at least one of the following criteria: 1) percent of days that the correct number of doses were taken; 2) percent of prescribed number of doses taken; and 3) percent of prescribed doses taken on schedule (Woods et al., 2009).

(3) Semi-naturalistic Healthcare Compliance Task: Participants were instructed to leave a voicemail message for the examiner 24 hours after the exam, indicating the number of hours slept the night following the evaluation (see Zogg et al., 2010). Scores on the naturalistic task ranged from 0–2, and for the current study participants were categorized as "compliant" with a score of 1 or 2 (i.e., partial or full credit), or "non-compliant" with a score of 0.

Results

Ongoing Task

The ongoing task data are presented in Table 3 as a function of HAND group. Two mixed effects ANOVAs were conducted in order to determine the effects of HAND on the Stroop task. In the first model, Stroop accuracy across the four conditions served as the within-subject factor, with HAND as the between-subjects factor. Age, sex, lifetime affective disorder, lifetime substance dependence, and hepatitis C infection were entered as covariates in these models. Results revealed a main effect of HAND (p=.02), such that the HAND+ group was less accurate as compared to the two other groups (ps>.05). There was no effect of Stroop condition (p=.16), and no interaction between HAND and condition (p=.53). In the second model, average response time across the four Stroop conditions served as the within-subjects factor, with the same between-subjects factor and covariates as the previous model. Results revealed a main effect of HAND (p=.04), such that the HAND- and HAND+ groups were slower (and not significantly different from each other) as compared to the HIV- group across the conditions (ps<.01). There was also a main effect of Stroop condition (p<.01), such that participants evidenced slower response times on the high cognitive and emotional conditions as compared to the low cognitive and emotional conditions (ps<.01). There was no interaction between HAND and condition (p=.23).

Habitual PM Task Errors

Two mixed effects ANOVAs were used in order to determine the effects of HAND group on habitual PM errors (see Table 4). In the first model, omission errors across the four Stroop

conditions served as the within-subjects factor, with HAND and the covariates listed above as the between-subjects factors. Results revealed no main effect of HAND, Stroop condition, or covariates, and no interaction between HAND and Stroop condition (*p*s>.05). In the second model, repetition errors across the four Stroop conditions served as the within-subjects factor, with the same between-subjects factors as the first model. Results revealed a significant effect of HAND group ($F(2, 211)=4.1$, $p=.02$), such that the HAND+ group made more repetition errors than the HAND- (Cohen's $d=.36$; $p=.03$) and HIV- (Cohen's $d=.65$; $p<.01$) comparison groups. There was no main effect of Stroop condition or interaction between HAND and condition (*p*s>.05).

In concordance with other studies examining the pattern of omission and repetition errors over the course of the habitual PM task (e.g., Einstein et al., 1998), we conducted planned comparisons examining number of repetition errors made in early blocks (i.e., blocks 1–12) compared to late blocks (i.e., blocks 13–24). As shown in Figure 1, results indicated that the HAND+ group made significantly more repetition errors in early blocks as compared to the HAND- (Cohen's $d=.49$; $p<.01$) and HIV- groups (Cohen's $d=.66$; $p<.01$), but no group differences were observed for later blocks (*p*s>.10).

Neurocognitive Correlates of Habitual PM

For our secondary group of analyses, we utilized a summary habitual PM variable in order to decrease Type I error. The summary variable consisted of the total number of correct habitual PM blocks (i.e., no repetition or omission errors; range=0–24). A three-way ANOVA using total correct trials as the within-subjects factor confirmed an omnibus effect of group ($\chi^2=9.30$, $p<.01$), with the HAND+ group producing significantly fewer correct trials than the HAND- ($t(104)=-2.12$, $p=.02$, Cohen's $d=.43$) and HIV- ($t(149)=-3.23$, $p<.01$, Cohen's $d=.62$) groups. Table 5 shows Spearman's rho correlations between the habitual PM summary variable and the neuropsychological domain-based ratings, across HIV-, HAND+, and the overall HIV+ groups, in which HAND status was collapsed. In the HIV+ group, habitual PM was significantly correlated with domains of learning ($\rho=-.28$, $p< .01$), retrospective memory ($\rho=-.25$, $p<.01$), executive function ($\rho=-.30$, $p<.01$), and attention/working memory ($\rho=-.20$, $p=.04$). Within the HIV- group, habitual PM was significantly correlated with learning ($\rho=-.26$, $p<.01$) and retrospective memory ($\rho=-.21$, $p=.02$). Similarly, in the HAND+ group, habitual PM was associated with learning ($\rho=-.43$, $p<.01$) and retrospective memory ($\rho=-.42$, $p=.01$). In the HIV+ group, we then conducted a follow-up regression predicting habitual PM from domains of learning, executive functions, and attention/working memory (retrospective memory was excluded due to its collinearity with learning, and evidenced a weaker correlation than learning). The overall model was significant ($F(3, 102)=5.1$, adjusted $R^2=.10$, $p<.01$), with learning emerging as the only significant predictor of habitual PM ($t(103) = -3.1$, $p<.01$). Such follow-up regressions were not conducted in the HIV- or HAND+ groups given the collinearity of learning and retrospective memory in those samples.

Real-world Correlates of Habitual PM

A series of logistic regressions were conducted in order to investigate the relationship between real-world functioning and habitual PM in the overall HIV+ group, as subjects

without HAND also experience declines in real-world functioning that may be related to cognitive difficulties (Morgan et al., 2012). In these models, habitual PM (i.e., total correct trials) and clinicodemographic factors on which real-world functioning groups (i.e., functionally impaired or normal) differed were entered as predictors of each of the three real-world functioning impairment classifications. As shown in Table 6, results indicated that habitual PM predicted incremental variance in real-world functioning status amongst all three functional domains, independent of the variance in real-world functioning status predicted by the covariates upon which the groups differed.

Given the learning domain's unique association with habitual PM across the study groups, a series of post hoc analyses were conducted in order to determine habitual PM's relationship to real-world functioning in the presence of learning. Raw learning domain scores were added as a predictor to each of the three real-world functioning models noted above. The overall global functional impairment model was significant (χ^2=28.66, p<.01), with learning emerging as the sole significant predictor (χ^2=7.15, p<.01) such that habitual PM was no longer associated with the outcome (p=.28). A Sobel test confirmed that learning was serving as a mediator in the relationship between habitual PM and global real-world functioning relationship (Sobel statistic=-2.23, p=.03). In the logistic regression predicting medication adherence, the overall model was significant (χ^2=7.30, p=.03), with the effect of habitual PM reducing slightly to the level of a trend (p=.07) and no effect of learning (p=.37). In the logistic regression predicting the semi-naturalistic healthcare compliance task, the overall model was significant (χ^2=28.89, p<.01), with habitual PM remaining a unique predictor (χ^2=5.00, p=.03) and no effect of learning (p=.53).

Discussion

Habitual PM describes intentions that are performed both frequently and routinely are highly relevant to healthcare behaviors, including medication adherence. Extending the limited prior research on this ecologically relevant aspect of cognition, the current study sought to evaluate the nature of habitual PM and its effects on real-world functioning outcomes among persons with HIV disease. Analyses showed that individuals with HAND evidenced moderate deficits on an experimental measure of habitual PM as compared to seronegatives and HIV-infected persons without HAND. This deficit was independent of clincodemographic factors, as well as the emotional and cognitive load of the ongoing task in which the habitual PM task was embedded. These findings converge with prior studies on single-event PM in HAND (e.g., Carey et al., 2006), as well as the few previous studies examining habitual PM within other neuropsychological populations, including aging (Einstein et al., 1998) and schizophrenia (Elvevåg et al., 2003).

In contrast to these prior studies of habitual PM, however, there was no evidence of elevated rates of omission (i.e., no response) errors in HAND; instead, the habitual PM effect in the HAND cohort was driven by errors of repetition. Individuals with HAND may have made more errors of repetition because they confused memories for pressing the spacebar for thoughts about having pressed the spacebar (Johnson & Raye, 1981). Alternatively, memories of pressing the spacebar might have been estimated by individuals with HAND as being more distant than they actually were (Friedman, 1993). Interestingly, planned

comparisons revealed that the HAND+ group made more repetition errors than the HAND- and HIV- groups in early, but not late trials. This pattern is in contrast to what Einstein and colleagues (1998) observed in older adults, who evidenced higher rates of repetition errors in later but not early trials. As learning was significantly related to habitual PM in the HAND+ group, it may be that individuals with HAND evidenced higher rates of repetition errors in earlier trials before having mastered the task in the later trials. Future studies may wish to explore mechanisms that may be responsible for varying error time-course presentation among different populations.

One novel aspect of this study was an examination of the cognitive correlates of habitual PM. Our findings suggest that episodic learning plays an important role in overall habitual PM performance across the HIV-, HIV+, and HAND+ groups (see Table 5). Within the overall HIV+ group, memory, attention/working memory, and executive functions were also associated overall habitual PM. To delineate the predictive utility of these neurocognitive domains in the HIV+ group, we conducted a follow-up regression in which learning emerged as the sole predictor of habitual PM. Thus, it is possible that habitual PM errors may be driven by difficulty in aspects of habit learning. Furthermore, given that the HAND+ sample demonstrated elevated levels of repetition errors relative to omission errors, it may be that this group had difficulty with learning mastery as opposed to learning acquisition.

The original habitual PM study by Einstein and colleagues (1998) revealed that older adults' PM deficits were exacerbated under demanding attentional conditions; however, no effects of manipulating the emotional or cognitive demands of the ongoing task on habitual PM were observed in the current study. However, our results did reveal evidence of elevated response times to the ongoing task as a function of both HAND status and high load condition (cognitive and emotional), which leads to the possible explanation that habitual PM tasks are reasonably resilient to subtle manipulations in cognitive and emotional load by virtue of their repetitive nature. Another possible interpretation is that the original Einstein et al. (1998) study employed a manipulation that was much more demanding upon attentional resources than that which was employed in our study; while Einstein et al. added a taxing working memory task to be completed concurrently with the ongoing task that essentially created a situation in which attention was divided between three tasks, we simply altered a single ongoing task (i.e., a Stroop paradigm) to systematically vary the emotional and cognitive load. That is, despite observing the desired effect of the manipulation on the ongoing task itself, even the high load conditions may not have produced a difficulty level substantial enough to elicit an effect on habitual PM. A similar pattern has been observed in other studies of single-event PM tasks, including a recent study in multiple sclerosis that revealed significant effects of disease status (i.e., MS versus healthy adults) and emotional valence manipulation, but no disproportionate effect of the emotional valence on PM in the MS group (Rendell et al., 2012).

Perhaps the most compelling finding from this study was habitual PM's unique and independent associations with real-world functioning outcomes. Specifically, within the HIV + sample, total correct habitual PM trials predicted an index of global functioning (see Blackstone et al., 2013; Doyle et al., 2013b), electronically monitored antiretroviral adherence, and a performance-based semi-naturalistic measure of healthcare compliance.

Notably, the effects of habitual PM in this regard were above and beyond demographic, psychiatric, and medical factors. Collectively, these data support the literature regarding PM impact on real-world functioning outcomes in HIV (e.g., Contardo et al., 2009; Martin et al., 2007; Woods et al. 2008, 2009, 2011). Findings are also consistent with Vedhara et al. (2004), who found that errors of omission and repetition on a laboratory habitual PM task were associated with lapses in medication adherence in a cohort of older adults with type 2 diabetes. Given that repetition errors were driving habitual PM dysfunction in HAND, such deficits may manifest as mistakenly repetitive healthcare behaviors, such as taking an additional dose of medication, particularly in the early stages of learning a new regimen. Future studies wishing to examine repetition errors within real-world habitual PM tasks may wish to utilize everyday functioning tasks in which repetition errors may be directly measured.

Furthermore, when the domain of learning was added to these models given its associations with both habitual PM and real-world functioning, results indicated that (1) the effects of habitual PM on medication adherence and the semi-naturalistic healthcare compliance task appear to operate largely independent of learning, and (2) learning may help to better explain the relationship between habitual PM and global real-world functioning, as the results of a Sobel test revealed that learning may mediate the relationship between these two constructs. That is, for more general real-world functioning tasks like those included in our global domain, habitual PM's effect on these tasks appears to be channeled through deficits in learning. Interpretively, this mediation effect is consistent with our hypothesis that individuals with HAND committed more errors in early versus late trials due to problems with proper learning of the task. In terms of clinical relevance, targeting mastery of the habitual PM task may be an important point of intervention in order to improve real-world outcomes.

Strengths of this study include a large, well-characterized group of subjects and a multimodal assessment of real-world outcomes. Nevertheless, the current study also has several limitations that warrant consideration. First, our hypothesis that deficient habitual PM in HAND was driven by poor internal source monitoring or temporal discrimination would have been strongly bolstered by including a simple measure of these constructs during the task; in future studies, having the examiner query participants after each habitual PM trial whether or not they executed the task and their confidence in that response would help in identifying such deficits. As for the real-world functioning assessment, the majority of indices used in the global functional status variable were mostly taken from self-report measures, which have a tendency to be biased by mood and social desirability factors (e.g., Blackstone et al., 2012). Especially since the adherence and semi-naturalistic real-world functioning domains (which are performance-based versus self-report) appeared to be particularly sensitive to habitual PM deficits, future use of objective functional capacity measures (e.g., financial management, health literacy) would strengthen credibility of the habitual PM/real-world functioning finding. Finally, the sample size of the HAND+ group was relatively small in comparison to the two other groups. However, the ratio of HAND+ participants to the overall HIV+ group is consistent with epidemiological estimates, and the number of covariates included in our models was appropriate for the overall sample size.

Collectively, the findings described herein indicate moderate levels of habitual PM impairment in HAND that was characterized by elevated repetition errors associated with learning, and were predictive of declines in real-world functioning. Previous research of PM within HIV has focused on the use of single-event PM tasks, which, as evidenced by this study, may be less relevant to healthcare behaviors that need to be performed frequently and routinely. Given our post hoc analyses which revealed that poor habitual PM may be related to deficient learning processes, rehabilitation efforts may find that intervening early on in the disease process (e.g. habit learning interventions), when medication adherence and other healthcare behaviors are being implemented, could improve healthcare maintenance in this group. Although this is only the first study to examine the role of habitual PM and its role in real-world functioning outcomes within HIV, the findings describe herein elucidate a unique form of PM that might better tap in to the PM difficulties that this group struggles with in their day-to-day lives.

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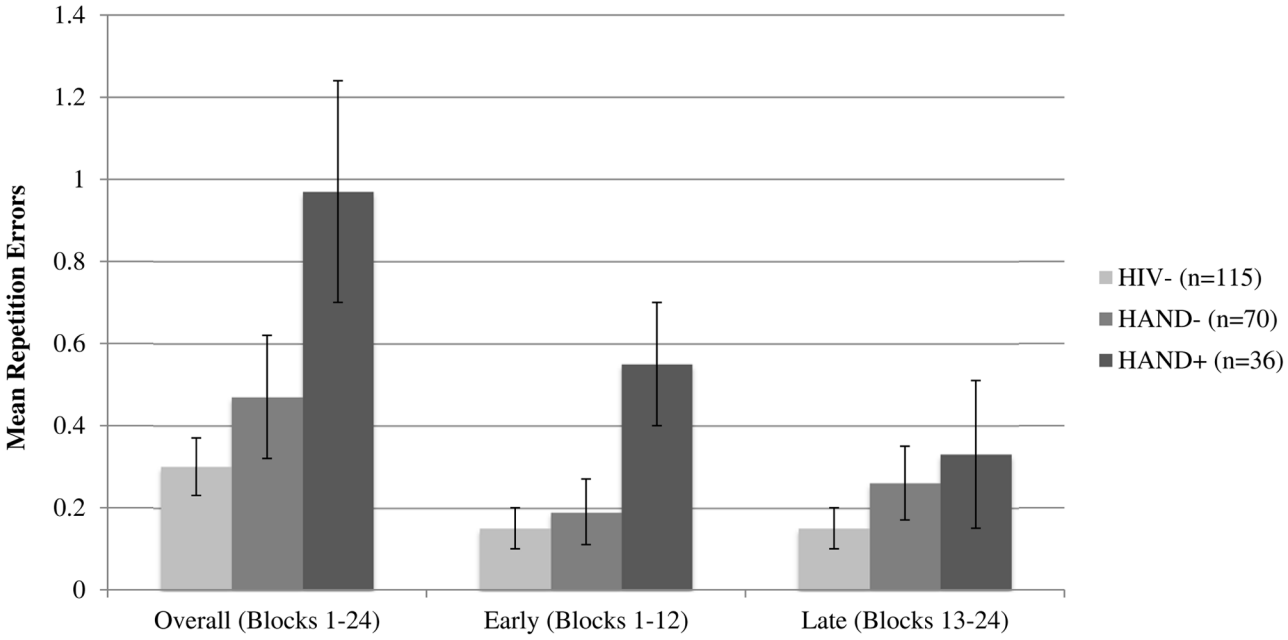

Figure 1.
Temporal Distribution of Repetition Errors Across the Study Groups

Table 1

Demographic, Psychiatric, and HIV Disease Characteristics of the Study Samples.

Characteristics	HIV- (n=115) (a)	HAND- (n=70) (b)	HAND+ (n=36) (c)	p
Demographics				
Age (years)	41.7 (14.9)	49.2 (12.1)	49.7 (11.5)	.002; a<b,c
Education (years)	14.0 (2.7)	13.8 (2.4)	13.4 (3.0)	.458
Estimated VIQ (WTAR)	103.3 (10.4)	104.6 (9.3)	99.8 (11.7)	.126
Sex (% female)	33.9	15.7	16.7	.009; a>b,c
Ethnicity (% Caucasian)	57.3	67.1	63.9	.397
Psychiatric (Lifetime)				
LT Affective disorder[a] (%)	39.1	67.1	75.0	<.001; a<b,c
LT Substance use dependence (%)	44.3	58.6	50.0	.172
Alcohol (%)	30.4	30.0	33.3	.934
Cannabis (%)	13.9	18.6	11.1	.539
Cocaine (%)	12.2	22.9	13.9	.146
Methamphetamine (%)	22.6	41.4	30.6	.025; a<b,c
Opiates (%)	12.2	8.6	5.6	.459
HIV Disease				
Estimated duration of infection (mos.)[b]	-	189 (56, 251)	188 (99, 258)	.535
Nadir CD4 T-cell count[a] (cells/μl)[b]	-	195 (85, 300)	151 (46, 239)	.167
Current CD4 T-cell count[a] (cells/μl)[b]	-	526 (372, 775)	519 (316, 725)	.601
Plasma HIV RNA (log10 copies/mL)[b]	-	1.6 (1.6, 1.6)	1.6 (1.6, 1.7)	.523
Current ART Rx (%)	-	97.1	100.0	.306
HCV (%)	11.4	24.6	30.6	.012; a<b,c

Note. VIQ = Verbal IQ. WTAR = Wechsler Test of Adult Reading – Fourth Edition. LT = lifetime. ART = antiretroviral therapy. HCV = hepatitis C virus.

[a] Affective disorder = diagnosis of Major Depressive Disorder and/or Generalized Anxiety Disorder.

[b] Data represent medians and interquartile ranges.

Table 2

Neuropsychological and Real-World Functioning Outcomes Across the Study Groups.

	HIV- (n=115) (a)	HAND- (n=70) (b)	HAND+ (n=36) (c)	p
Neuropsychological Rating[a]				
Global	3.44 (1.12)	3.19 (0.92)	5.67 (0.79)	<.001; a,b<c
Attention/Working Memory	2.33 (1.18)	2.29 (0.87)	3.94 (2.00)	<.001; a,b<c
Executive Functions	2.99 (1.56)	2.63 (1.38)	4.61 (2.02)	<.001; a,b<c
Learning	2.03 (1.30)	1.90 (0.68)	2.97 (1.52)	<.001; a,b<c
Retrospective Memory	1.88 (1.17)	1.73 (0.99)	2.53 (1.13)	.002; a,b<c
Motor	2.51 (1.32)	2.69 (1.49)	4.11 (1.98)	<.001; a,b<c
SIP	2.23 (1.11)	1.97 (1.02)	3.83 (1.76)	<.001; a,b<c
Verbal Fluency	2.63 (1.45)	2.51 (1.36)	4.31 (1.49)	<.001; a,b<c
Real-World Functioning[b]				
Global Functioning	20.00	47.14	63.89	<.001; a<b<c
Medication Adherence	--	44.29	50.00	.576
Semi-naturalistic Task	55.65	67.14	66.67	.225

Note.

[a] Clinical ratings range from 1 (above average) to 9 (severely impaired), with scores of 5 or greater indicating definite neurocognitive impairment.

[b] Percent impaired. SIP = speeded information processing.

Table 3

Ongoing Task Performance as a Function of HAND Group

	HIV- (n=115) (a)	HAND- (n=70) (b)	HAND+ (n=36) (c)	p
Accuracy[a]				
Low Cognition	97.94 (.03)	97.61 (.03)	96.25 (.05)	.055
High Cognition	95.08 (.12)	94.68 (.12)	88.40 (.20)	.067
Low Emotion	97.98 (.03)	97.75 (.04)	96.34 (.05)	.384
High Emotion	97.96 (.03)	97.76 (.04)	96.83 (.04)	.120
Response Time[b]				
Low Cognition	1223 (189)	1316 (177)	1354 (185)	<.001; a<b,c
High Cognition	1311 (187)	1390 (191)	1424 (195)	.003; a<b,c
Low Emotion	1249 (182)	1333 (184)	1357 (184)	<.001; a<b,c
High Emotion	1259 (183)	1332 (166)	1387 (198)	<.001; a<b,c

Note.

[a] Percent correct.

[b] Data are presented in milliseconds, as means and standard deviations.

Table 4

Nominal Logistic Regressions Predicting Habitual PM Errors

	F	p
Omission Errors		
HAND	1.75	.18
Stroop Condition	0.59	.62
HAND x Stroop Condition	1.07	.38
Covariates		
Age	1.11	.29
Sex	0.64	.43
Affective Disorder[a]	0.01	.93
Substance Use Dependence	2.02	.16
Hepatitis C Infection	0.69	.41
Repetition Errors		
HAND	3.47	.03
Stroop Condition	1.29	.28
HAND x Stroop Condition	1.56	.16
Covariates		
Age	0.57	.45
Sex	0.64	.42
Affective Disorder[a]	0.32	.57
Substance Use Dependence	1.02	.31
Hepatitis C Infection	0.07	.80

Note. HAND = HIV-associated neurocognitive disorder.

[a]Affective disorder = diagnosis of Major Depressive Disorder and/or Generalized Anxiety Disorder.

Table 5

Correlations between Habitual PM and Neuropsychological Domains.

	HIV- (n=115)	HIV+ (n=106)	HAND+ (n=36)
Domain Ratings			
Attention/Working Memory	−.15	−.20*	−.06
Executive Functions	−.07	−.30**	−.09
Learning	−.26**	−.28**	−.43**
Retrospective Memory	−.21*	−.25**	−.42*
Motor	−.06	.07	−.10
SIP	−.17	−.15	−.27
Verbal Fluency	−.20	−.12	−.32

Note. Data represent Spearman's rho correlation coefficients. SIP = speed of information processing.

* p<.05

** p<.01

*** p<.001

† p<.10

Table 6

Logistic Regressions Predicting Functional Outcomes in the HIV+ Sample.

	χ^2	Odds Ratio	*p*
Everyday Functioning			
Global Functional Impairment	21.52		<0.01
Habitual PM	4.07	1.25	0.04
Affective Disorder[a]	4.97	2.88	0.03
Age	4.44	1.05	0.04
Estimated Duration of Infection	0.02	1.00	0.89
Hepatitis C Infection	4.66	3.08	0.03
MEMS Adherence	4.61		0.03
Habitual PM	4.61	1.24	0.03
Naturalistic Healthcare Task	26.77		<0.01
Habitual PM	4.97	1.33	0.03
AIDS	9.71	5.13	<0.01
CD4	11.93	1.00	<0.01
Cognitive Reserve[b]	2.30	2.07	0.13

Note.

[a] Affective disorder = diagnosis of Major Depressive Disorder and/or Generalized Anxiety Disorder.

[b] Cognitive reserve = average Z-score of population-based education and WTAR-estimated verbal IQ.