Self-Generation of Prospective Memory in HIV-Infected Methamphetamine Users

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Clinical Psychology by

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ABSTRACT OF THE DISSERTATION

Self-Generation of Prospective Memory in HIV-Infected Methamphetamine Users

by

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Rationale

Methamphetamine (MA) dependence frequently co-occurs with HIV infection and increases the likelihood of poorer outcomes, including neurocognitive impairment. One aspect of cognition affected in both HIV and MA and may be a target for intervention is prospective memory (PM), or remembering to perform an intended action at a specific time. Self-generation is a potentially powerful approach to improve PM, hypothetically by supporting strategic aspects of encoding and cue monitoring that underlie PM impairment in HIV/MA individuals. This dissertation project sought to: 1) evaluate the
efficacy of self-generation on PM in HIV/MA adults on basic, clinical, and naturalistic PM paradigms; 2) determine neurocognitive mechanisms of self-generation on PM in HIV/MA; and 3) explore potential correlates of self-generation on PM in HIV/MA.

Design

Using a 3-group design (N=83), this study examined the effectiveness of self-generation in HIV+MA- and HIV+MA+ individuals compared to healthy comparison individuals (HIV-MA-) across three PM tasks of varying ecological validity. Participants were also administered a structured psychiatric interview, neuropsychological battery, and neuromedical examination.

Results

Across tasks utilizing within-subjects designs (basic, clinical PM tasks), participants were more likely to respond to the PM cue at recall and recognition for self-generated cues relative to didactically-learned cues (ps<0.05; Hedge’s gs=0.28-0.53); group and interaction factors were non-significant (ps>0.05). On the basic PM task, participants responded more quickly to the ongoing lexical decision-making task during the self-generated PM trials relative to the didactic trials (p=0.033; Hedge’s g=0.18). Neurocognitively-impaired HIV+ participants experienced greater benefit from self-generation on the basic PM task relative to their neurocognitively-normal counterparts (p=0.008; Hedge’s g difference=0.42). No main or interaction effects were observed on the naturalistic PM task, but longitudinal analyses revealed a trend-level effect of self-generation in the combined clinical sample. Across all tasks, no neurocognitive, psychiatric, HIV disease, or MA use characteristics were associated with self-generation benefit.

Relevance
This study establishes potential effectiveness of self-generation to improve PM in healthy and HIV-infected adults, yielding effects in the small-to-medium range. Future research should seek to expand test mechanisms to health-related behaviors as well as the utility of a combined approach with manipulations designed to enhance PM cue monitoring.
Introduction

Methamphetamine (MA) dependence is a major risk factor for HIV infection, and these two conditions commonly co-occur. High rates of recalcitrant medication nonadherence in HIV-infected MA users has led healthcare providers to be reluctant to initiate combination antiretroviral therapy (cART) for these patients, which subsequently adversely affects HIV disease outcomes. In spite of therapeutic advancements in managing the virologic aspects of HIV infection, HIV-associated neurocognitive disorders (HAND) persist and result in significant problems in everyday functioning, particularly medication nonadherence. Yet there are no empirically supported medical or psychological treatments to improve HAND. This dissertation project evaluates the usefulness of a new neurorehabilitation technique for enhancing one particularly impactful aspect of HAND (i.e., prospective memory) in a high-risk population of HIV-infected MA users.

Below, I will first review the independent effects of HIV infection and MA use on the central nervous system (CNS), followed by a discussion of the existing literature of the concomitant effects of HIV infection and MA use on cognition and resulting everyday functioning impairments. I will then provide a general discussion of multidisciplinary efforts to improve cognition in these populations, including the introduction of a candidate paradigm to improve memory, self-generation, and its efficacy in various neurological populations. Next, I will detail the existing research on theoretical models of prospective memory (PM), a dissociable and ecologically relevant aspect of episodic memory, as well as PM deficits evident in the clinical populations of interest, and discuss the potential application of self-generation to PM. After presenting the background research, I will state the aims and hypothesis of this dissertation and present the methods and analyses used to test the stated hypotheses, followed by the results of the
present study. Finally, I will interpret these findings in the context of the broader HIV, MA, PM, and self-generation literatures, and then discuss implications for future research.

**NeuroAIDS**

HIV is a lentivirus, which belongs to the class of enveloped viruses known as *Retroviridae* that replicate by integrating themselves into the DNA of the host cell. HIV preferentially infects T-helper cells (e.g., CD4+ lymphocytes), along with monocytes and macrophages. Accordingly, HIV infection can severely compromise the host’s immune system, making them vulnerable to contracting various opportunistic infections (e.g., toxoplasmosis) and cancers (e.g., Kaposi’s sarcoma). Although its primary adverse effects are immunological, HIV is also highly neurotropic, meaning that it is able to infiltrate the central nervous system (CNS). In fact, the brain is the second most commonly organ infected by HIV (Masliah, DeTeresa, Mallory, & Hansen, 2000), and causes widespread neurological damage (Gonzalez-Scarano & Martin-Garcia, 2005). Since it is blocked from crossing the blood brain barrier (BBB) on its own, HIV enters the CNS through a “Trojan Horse” mechanism via infected monocytes and cluster of differentiation 4 (CD4+) lymphocytes (Hult, Chana, Masliah, & Everall, 2008). Although the virus does not directly infect neurons, it often causes damage to brain parenchyma through both direct (e.g., viral proteins) and indirect (e.g., inflammatory) processes. After crossing the BBB, HIV-infected monocytes may differentiate into perivascular macrophages or infect microglia, which causes brain injury through the release of neurotoxic substances, such as chemokines and cytokines (Kaul, Garden, & Lipton, 2001). Following in this cascade of events, astrocytes become activated from the neurotoxic molecules released by the infected monocytes and microglia, resulting in increased inflammatory processes (e.g., increased glutamate concentrations) that cause
further neuronal damage (e.g., Genis et al., 1992). Beyond this process, infected macrophages and monocytes may also fuse together to form multi-nucleated giant cells. Overall, brain pathology has been observed in over 50% of HIV-infected adults with dementia (Ellis, Langford, & Masliah, 2007). The neuropathology of HIV has changed since the early days of the epidemic, which included higher rates of HIV encephalitis (Ellis, Calero & Stockin, 2009). In the post-cART era, noninfectious findings and minimal nondiagnostic abnormalities such as white matter hyperintensities (e.g., Filippi, Ulu, Ryan, Ferrando, & van Gorp, 2001), in the absence of overt parenchymal pathology due to HIV or opportunistic infections, are more commonly found and are associated with cognitive disorders (Everall et al., 2009).

Despite the generalized nature of viral dispersion across the BBB, HIV preferentially affects fronto-striatal-thalamo-cortical (FSTC) circuitry, resulting in both structural (e.g., white matter hyperintensities) and functional (e.g., abnormal brain perfusion) damage evident throughout the frontal cortex, cerebral white matter, and striatum. For example, the frontal cortex and striatum of HIV infected individuals appear to be especially susceptible to structural abnormalities (e.g., Castelo, Courtney, Melrose, & Stern, 2007), neuroinflammation (e.g., elevated myoinositol and choline; Chang, Ernst, Speck, & Grob, 2005), neuronal injury (i.e., decreased N-acetyl aspartate; Chang et al., 2005), and altered blood-oxygen-level dependent (BOLD) response during the performance of cognitive tasks (e.g., Melrose, Tinaz, Castelo, Courtney, & Stern, 2008). Beyond these frontostriatal pathways, imaging evidence also implicates abnormalities in medial temporal structures (e.g., hippocampus), which may in combination with FSTC injury increase the risk of episodic memory impairment (e.g., Maki et al., 2009). Such neural abnormalities are typically most prevalent in individuals with more severe disease (e.g., reduced brain volumes; Stout et al., 1998). For instance, Jernigan and colleagues
(2011) reported that lower nadir CD4 was a significant factor in most measures of structural damage (e.g., less cerebral white matter) as determined via morphometric analyses. However, neuropathology may still be evident in medically asymptomatic individuals with optimal viral control (e.g., Wilkinson et al., 1997) as well as newly infected individuals (Ragin et al., 2012), suggesting that neural abnormalities are prevalent beyond the long-term immunocompromised.

These HIV-associated neuropathologies can produce mild-to-moderate impairment in numerous lower- (e.g., motor skills) and higher-order (e.g., executive functions and episodic memory) cognitive abilities upon which successful everyday functioning relies. Depending on stage of HIV disease, HIV-associated neurocognitive disorders (HAND) are evident in an estimated 30-50% of individuals with HIV (e.g., Heaton et al., 2010), with yearly incidence rates of approximately 10-25% (e.g., Robertson et al., 2007). Although these overall rates of impairment are roughly equivalent to the prevalence of HAND prior to the introduction of cART in the mid-1990s, it is important to note that the severity and profile of HAND has evolved, likely due to the improved immunological and neuropathological outcomes as a result of effective systemic pharmacotherapy. For instance, data from the Multicenter AIDS Cohort Study (MACS) suggested that shortly after the introduction of cART, the incident rates of HIV-associated dementia (HAD), the most severe of HAND diagnoses, decreased by nearly 50% relative to rates prior to the cART era (e.g., Sacktor et al., 2001). Alongside this decrease in HAD, however, there has been an increase in the prevalence of milder forms of HAND, suggesting a persistent level of mild, yet clinically relevant, neurocognitive involvement, that has been immune to immunovirologically-focused treatment efforts (Heaton et al., 2011).
In an effort to encourage research efforts on HIV-associated neurocognitive impairment in the earlier days of the epidemic, the AIDS Task Force of the American Academy of Neurology (1991) proposed specific guidelines for the diagnosis of HAND, which included HAD and minor cognitive-motor disorder (MCMD). In 1995, Grant and Atkinson extended the HAND nosology to include "subsyndromic neuropsychological impairment" to capture patients who exhibit mild neurocognitive deficits that do not noticeably interfere with everyday functioning. More recently, an NIH working group in Frascati (Antinori et al., 2007) updated the research diagnostic criteria for HAND, taking into consideration the many clinical and scientific advancements in treatment (i.e., the introduction of cART) and neuropsychological assessment (e.g., new tests and improved normative standards) of HIV infection, as well as emerging appreciation of important comorbidities (e.g., hepatitis C co-infection). These updated HAND criteria allow for three possible diagnoses: 1) HIV-associated Asymptomatic Neurocognitive Impairment (ANI); 2) HIV-associated Mild Neurocognitive Disorder (MND); and HAD. For each of these diagnoses, an individual must demonstrate at least mild neuropsychological impairment (i.e., > 1 SD below the appropriate normative mean) in at least two cognitive domains that is attributable, at least in part, to HIV infection. Since HIV infection is sometimes associated with comorbidities that may affect CNS functioning, the updated HAND criteria provide guidelines for secondary (e.g., an individual with remote alcohol abuse that is unlikely to have residual cognitive effects from their alcohol use), contributing (e.g., an individual with alcohol dependence within 6 months that may be affecting cognition, but who nevertheless shows clear evidence of HIV-related cognitive and functional difficulties), and confounding (e.g., an individual experiencing acute withdrawal from alcohol dependence in whom it is not possible to attribute cognitive problems to HIV infection) conditions (Antinori et al., 2007).
Asymptomatic Neurocognitive Impairment. The most notable (and controversial) addition to the updated HAND nosology is the diagnosis of ANI, which requires demonstrable evidence of impairment (i.e., > 1 SD below the mean of demographically-adjusted normative scores) in at least two areas of cognitive functioning in the absence of noticeable functional impairment. It has been argued that this diagnosis encompasses a sizeable and previously ignored portion of the HIV-infected population (Grant & Atkinson, 1995). It is estimated that ANI diagnoses make up over 50% of HAND diagnoses and approximately 15-30% of the HIV population overall (Grant, Sacktor, & McArthur, et al., 2005). Nevertheless, critical questions remain regarding the diagnostic methods for distinguishing between ANI and the “syndromic” HAND conditions, which have historically relied upon self-report (e.g., questionnaires), rather than performance-based laboratory measures of daily functioning that may be more sensitive to functional declines (e.g., Mitchell & Miller, 2008). Despite much research in favor of including ANI in the collection of HAND diagnoses, dissenting opinions have posited that this new addition will cause unnecessary stress for individuals now deemed “neurocognitively impaired” despite no reported symptoms (Gisslen, Price, & Nilsson, 2011; Becker et al., 2013). However, Blackstone and colleagues (2012) recently demonstrated that many of these “asymptomatic” individuals may actually evidence functional impairment via alternate methods of assessment (e.g., performance-based everyday functioning tests) and oftentimes may not report such functional difficulties for a variety of reasons (e.g., poor insight). Therefore, identifying ANI may be useful to clinicians in that it may spotlight individuals with unreported functional impairment as well as those most at risk for functional decline. Indeed, individuals with ANI appear to be at greater risk for developing syndromic forms of HAND, therefore warranting greater monitoring over time (Grant et al., 2014), which is consistent with recent
recommendations through the Mind Exchange Program that suggest screening for HAND early in the course of the infection, as individuals may be less aware of their own deficits as they emerge (Antinori et al., 2013). Furthermore,

**Mild Neurocognitive Disorder.** Although ANI is the most prevalent form of HAND in the cART era (Heaton et al., 2010), approximately 30-50% of individuals with HIV-associated neuropsychological impairment experience problems with their basic and/or instrumental activities of daily living (ADLs) as a consequence of their neurocognitive deficits (Antinori et al., 2007; Grant et al., 2005). The epidemiology of MND is not well understood, but it is estimated that approximately 20-40% of those with HAND and 5-20% of the HIV population overall may meet criteria for MND (Grant et al., 2005). Formerly referred to as minor cognitive-motor disorder (MCMD), a diagnosis of MND requires acquired mild-to-moderate impairment (i.e. > 1 SD below the normative mean) in at least two areas of cognitive functioning, which also interferes with daily functioning and cannot be entirely explained by comorbidities or delirium. The mild functional decline requirement for a diagnosis of MND may be met by evidence of two or more of the following that are not exclusively attributable to a comorbid condition: 1) self- or proxy-report of declines in ≥ 2 IADLs (e.g., financial management); 2) unemployment or a significant reduction in job responsibilities secondary to reduced cognitive abilities; 3) decline in vocational functioning (e.g., increased errors, decreased productivity, or greater effort is required to achieve prior levels of productivity); 4) self- or proxy-report of increased problems in ≥ 2 cognitive ability areas in day-to-day life (NB. this criterion cannot be used if based only on the self-report of an individual with current depression, since depression may bias self-report); or 5) scores > 1 SD below mean on a performance-based laboratory measure of everyday functioning (e.g., medication management).
**HIV-associated Dementia.** A diagnosis of HAD is defined by an acquired moderate-to-severe impairment (i.e., at least 2 SDs below demographically-adjusted normative means) in at least two cognitive domains along with marked ADL declines that are not fully attributable to comorbidities or delirium. Thus, HAD represents the most severe form of HAND, both in the magnitude and breadth of the observed neurocognitive impairment and its impact on daily functioning, which requires two or more of the following: 1) unemployment due to cognitive impairment; 2) self- or proxy-report of dependence in > 2 IADLs related to cognitive problems; 3) self- or proxy-report of declines in ≥ 4 cognitive ability areas in day-to-day life (NB. As with a diagnosis of MND, this criterion is not applicable if based exclusively on the self-report of an individual with current depression, which can be defined as having a BDI score > 17); 4) performance that is > 2 SD below the mean on a performance-based laboratory measure of everyday functioning (e.g., or > 1 SD below the mean on two functional tests).

The incidence of HAD has decreased dramatically since the introduction of cART in the mid-1990s (e.g., Sacktor et al., 2001), but prevalence rates remain fairly constant and, relative to the pre-cART era, may be slightly higher among individuals who are not immunosuppressed (e.g., Grant et al., 2005). Unlike the classic neurodegenerative dementias (e.g., Alzheimer’s disease), HAD is not invariably progressive; in fact, there is considerable variability in the long-term course of all of the HAND classifications, which may improve, deteriorate, or fluctuate over time (Antinori et al., 2007). This is influenced by a variety of factors, such as incident and remitting comorbidities (e.g., psychiatric disorders) and treatment effects (e.g., commencement of cART). A diagnosis of “HAD in remission” may be given to individuals with a prior diagnosis of HAD who no longer meet the neurocognitive and/or functional criteria. Given this lack of immutability in the diagnostic criteria of HAND relative to other neurological conditions, opportunities for
improving cognitions in this population should be strongly considered.

**Profile of HAND.** The neurocognitive profile of HIV infection has been historically described as “spotty” (e.g., Butters et al., 1990), which has recently been supported by objective, psychometric evidence of neurocognitive variability (e.g., Morgan et al., 2011) suggestive of the damage to the FSTC loops that has been observed by neuropathologists. Although approximately half of HIV-infected adults experience impairments significant enough to be considered a neurocognitive disorder, many glimpses into neuropsychological constructs have demonstrated group differences (compared to demographically similar seronegative adults) on a range of cognitive abilities beyond the impact of HAND. In other words, it appears that while some individuals may be spared from a diagnosable neurocognitive disorder, neurocognitive vulnerabilities may exist within the broadly normally HIV-infected population and can adversely affect daily functioning (Morgan, Woods, Grant & The HIV Neurobehavioral Research Program (HNRP) Group, 2012). Impairment is most commonly observed in the areas of executive functions, working memory, information processing speed, episodic memory, and motor skills, with relative sparing of simple attentional, language, visuoperceptual, and somatosensory functions (e.g., Heaton et al., 1995; Heaton et al., 2011). In fact, numerous studies demonstrate direct associations between biomarkers of frontostriatal neural injury and HIV-associated neuropsychological impairment; for example, Paul et al. (2008) found robust correlations between basal ganglia volumes and measures of executive dysfunction, bradykinesia, and bradyphrenia in HIV. Nevertheless, the specificity of these associations is tempered by studies that demonstrate the contributions of pathologies in the medial temporal (e.g., Moore et al., 2006) and posterior parietal (Thompson et al., 2005) cortices to the cognitive expression of HAND.
Beyond the evolution of the severity of HAND, patterns of neurocognitive impairment have also shifted since the introduction of cART. Heaton and colleagues (2011) compared impairment profiles from the pre-cART era to the current treatment guidelines and observed a shift from primary deficits in the domains of verbal fluency, information processing speed, and psychomotor skills to greater impairments of episodic memory and executive functions. More specifically, the pattern of episodic memory impairment in HAND is most consistent with the prototypical mixed encoding and retrieval profile that is often observed in populations with compromised frontostriatal systems (e.g., Parkinson’s disease), with impairment most evident on more executive demanding free recall tasks but normalized performance on more structured recognition trials. HAND is also marked by limited use of higher-order strategic organizational encoding strategies (e.g., Delis et al., 1995; Cattie et al., 2012), including semantic clustering during list learning (e.g., Gongvatana et al., 2007). Regarding executive functions, many individuals with HIV evidence deficits on a wide variety of higher-order processes, the most studied of which are abstraction and novel problem solving (e.g., Heaton et al., 1995), cognitive flexibility (e.g., Reger, Welsh, Razani, Martin & Boone, 2002), pre-potent response inhibition (e.g., Martin et al., 2004), and planning (e.g., Bartok et al., 1997). Emergent data also indicate that individuals infected with HIV may be prone to risky decision-making (Hardy, Hinkin, Levine, Castellon, & Lam, 2006; Iudicello et al., 2013), perhaps as a function of cognitive impulsivity (Martin et al., 2004). Beyond these primary domains, executive aspects of other cognitive areas are frequently affected. For instance, within the broad area of language functioning, verbal fluency deficits are a common feature of HAND, which is associated with comparably mild impairment on measures of letter and category fluency (Iudicello et al., 2007), thereby suggesting a common mechanism of deficient strategic search and retrieval
from lexico-semantic memory stores (Woods et al., 2004a). The process of switching between lexico-semantic categories during verbal fluency appears to be particularly affected in HAND, especially during alternating fluency trials (Iudicello et al., 2008). Similarly, although simple attention (e.g., forward digit span) is generally spared in non-demented persons with HIV infection, deficits on measures of complex attention, working memory, and executive functions are considerably more prevalent (e.g., Heaton et al., 1995; Reger et al., 2002). Overall, etiological commonalities throughout neurocognitive findings in HIV seem to point to a primarily dysexecutive syndrome, which may impact various domains of functioning through deficient higher-order strategic abilities (e.g., semantic clustering in verbal learning; Woods et al., 2004a) as well as weakened mechanisms for cognitive control (e.g., intraindividual variability; Morgan et al., 2011).

**Functional impact of HAND.** The myriad medical, psychiatric, and neurocognitive complications that may accompany HIV infection can decrease one’s efficiency in completing instrumental and even basic ADLs. Neurocognitive impairment is an important and independent contributor to ADL declines, which are the defining characteristic of symptomatic HAND (i.e., MND and HAD). Since the majority of HIV-related cognitive deficits are in the mild-to-moderate range of severity, gross impairment of basic ADLs exclusively due to a cognitive etiology is relatively rare. However, even subtle HIV-associated neurocognitive deficits can contribute to problems in numerous aspects of everyday functioning (Morgan et al., 2012), including dependence in instrumental ADLs (IADLs; Heaton et al., 2004a), poorer health-related quality of life (e.g., Trepanier et al., 2005), increased engagement in risk behaviors (e.g., Gonzalez et al., 2005), and even higher mortality rates (e.g., Ellis et al., 1997). For instance, Heaton et al. (2004a) found that individuals with HAND performed significantly worse than unimpaired HIV-infected persons on a series of performance-based tasks that were
designed to mimic real-world IADLs (e.g., medication management, cooking, and financial management). Research shows that individuals with deficits in psychomotor speed (van Gorp, Baerwald, Ferrando, McElhiney, & Rabkin, 1999), attention and executive functions (Marcotte et al., 2006), and episodic memory (e.g., prospective memory; Woods et al., 2008) may be at greatest risk for declines in everyday functioning.

Of particular importance, medication nonadherence (most commonly classified as less than 90% compliance) is a domain of everyday functioning that is especially relevant to individuals with HIV, given that it is associated with poorer HIV disease outcomes, including higher rates of virologic failure (Perno et al., 2002), the development of drug-resistant viral mutations (Harrigan et al., 2005), and an increased risk of mortality (Lima et al., 2007). Prior studies have identified a variety of factors that influence nonadherence, including demographics (e.g., age), psychiatric comorbidity (e.g., depression, substance abuse), psychosocial variables (e.g., attitudes and beliefs related to medications, familial support), and systemic factors (e.g., limited access to healthcare). Beyond these predictors, neurocognitive impairment is frequently cited as an independent predictor of cART nonadherence (e.g., Andrade et al., 2013). In fact, Chesney et al. (2000) found that nearly 70% of individuals who were non-adherent to cART reported that they “simply forgot” to take their medication. Subsequent research demonstrated that HIV-associated neuropsychological impairment is associated with poorer performance on laboratory medication management tasks (e.g., Albert et al., 1999; 2003; Heaton et al., 2004a), higher rates of self-reported problems with medication management (e.g., Avants et al., 2001; Benedict, Mexhir, Walsh, & Hewitt, 2000; Waldrop-Valverde et al., 2006; Woods et al., 2008b), and non-adherence as measured by electronic medication monitors (e.g., Barclay et al., 2007; Hinkin et al., 2002; 2004). Hinkin et al. (2002) reported that individuals with neuropsychological
impairment experienced a twofold risk of non-adherence, even when the potentially confounding effects of demographic factors and psychiatric comorbidities were considered. Across this literature, the domains of episodic learning and memory (including prospective memory), executive functions, and psychomotor speed have emerged as the most robust and reliable cognitive predictors of cART non-adherence (e.g., Hinkin et al., 2002). The complex relationship between neurocognition and adherence is also cyclical, in that significant evidence demonstrates that poor adherence worsens disease outcomes, which in turn, increases risk for cognitive decline (Ettenhofer, Foley, Castellon, & Hinkin, 2010). The lack of awareness of one’s own deficits may also play a role in an individual’s decision to implement compensatory strategies to support medication adherence, and as such is likely to reduce adherence rates further in individuals already at risk (e.g., Blackstone et al., 2013). Therefore, it is prudent to identify and remediate neurocognitive deficits that may strongly impact cART adherence.

Methamphetamine

Methamphetamine (MA) is a highly addictive, potent, and neurotoxic psychostimulant that is frequently abused within the HIV-infected population. It is estimated that approximately 12 million people in the US have tried MA in their lives, with 1.3 million individuals reported MA use within the past year of assessment (Substance Abuse and Mental Health Services Administration, 2012). MA dependence is associated with a host of adverse psychosocial (e.g., limited social support; Cretzmeyer et al., 2003), economic (e.g., unemployment; Iritani, Hallfors, & Bauer, 2007), and health (e.g., pulmonary hypertension; Chin et al., 2006) consequences. Given its high lipid solubility, MA is able to cross the BBB more easily than other similarly structured drugs (e.g., amphetamine; Barr et al., 2006). Once within the CNS, MA
incites the release of dopamine and other monoamine neurotransmitters through several molecular mechanisms, including enhanced dopamine transport-mediated reverse transport across the plasma membrane, resulting in increased levels of dopamine in the synapse (Kokoshka et al., 1998). Chronic MA use results in the altered function of nigrostriatal pathways, thereby impacting the integrity of dopamine rich fronto-striato-thalamo-cortical loops (Cass, 1997). These neuronal-level findings corroborate the abnormalities that have been observed in both structural and functioning imaging studies. For instance, structural imaging has revealed reduced volumes in the hippocampus and gray matter of the cingulate as well as hypertrophy of cerebral white matter (e.g., Thompson et al., 2004). These mixed effects on brain volume are both hypothesized to be the effects of neurotoxicity, either resulting in cell death (hypotrophy) or compensatory processes like astrogliosis (hypertrophy). Regardless of brain volume, functional imaging studies have largely revealed hypoactivity in affected areas (e.g., frontal systems; Nestor, Ghahremani, Monterosso, & London, 2011). Giving weight to the broader impact of these imaging findings, Jernigan et al. (2005) observed greater frontostriatal (e.g., nucleus accumbens) volume increases in younger MA-dependent individuals, which were associated with more severe neurocognitive impairment and hypothesized to reflect neural sprouting and/or microglial activation.

Chronic MA use is associated with mild-to-moderate deficits across a wide range of neurocognitive functions, most notably in the domains of learning and memory, executive functions, information processing speed, attention/working memory, and motor skills (Scott et al., 2007). By examining superordinate trends across these affected domains, it appears that many of the neurocognitive deficits evident in MA use are driven by strategic, frontally mediated abilities. To this end, Woods and colleagues (2005a) observed deficits in verbal list learning and delayed recall, which were primarily
related to the lack of semantic clustering strategy usage and repetition errors, while demonstrating intact recognition abilities. Considerable amounts of research has been done on ecologically relevant aspects of executive functions, such as risky decision-making and delay discounting (e.g., Hoffman et al., 2006; Monterosso, Ainslie, Xu, Cordova, Domier, & London, 2007) which may be directly related to functioning outcomes (e.g., risk behaviors). While this profile of neurocognitive deficits is consistent with the neurotoxic effects of MA on the structure and function of frontostriatal systems (e.g., Chang et al., 2002; 2007), the nature and extent of MA-associated impairment does not reliably correlate with historical MA use parameters (e.g., age of first MA use; Scott et al., 2007). In fact, the magnitude of MA-associated neurocognitive deficits is thought to be larger than that which is observed in association with other substances of abuse, including cannabis (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003) and cocaine (Jovanovski, Erb, & Zakzanis, 2005), which may increase MA users’ relative risk of experiencing declines in everyday functioning (Henry, Minassian, & Perry, 2010). Indeed, cognitive factors in MA users have been implicated in general poorer everyday functioning (e.g., Morgan et al., 2014) as well as more specific outcomes like unemployment (Weber et al., 2012a).

**Comorbid HIV Infection & Methamphetamine Use**

MA dependence is a major risk factor for becoming infected with HIV (e.g., risky sexual behaviors during periods of MA intoxication), and as such, these two conditions commonly co-occur (Buchacz et al., 2005), particularly in Southern California (Cohen, 2012). Within such high-risk situations, HIV-infected MA users are more likely to transmit the virus to non-infected sexual or needle-sharing partners, due to increased viral load as a result of medication nonadherence frequently observed in MA users (e.g., Moore et
al., 2012). The combination of these conditions appears to be more neurotoxic than either condition by itself. First, MA increases the expression of HIV cofactors (e.g., CXCR-2) and can increase replication of the virus in astrocytes (e.g., Gavrilin, Mathes, & Podell, 2002). At the neuronal level, MA decreases the function of the BBB, allowing greater numbers of HIV-infected leukocytes to transport into the brain (e.g., Liang et al., 2008). Additionally, HIV-induced damage of the BBB may also allow for increased concentration of MA within the neural pathways (Kousik, Napier, & Carvey, 2012). These neurobiological changes result in significant ill effects for neuronal integrity; for example, magnetic resonance spectroscopy has shown relationships between increased cerebral metabolites (e.g., myo-inositol) and HIV plasma viral load in this population, suggesting that MA use may moderate CNS effects of HIV (Chang et al., 2005).

At the imaging level, the comorbid presentation of HIV and MA presents a less clear picture. Although associated with similar neural pathway dysfunction, the resulting independent neuropathology of MA use on frontostriatal systems (e.g., increases in cortical and basal ganglia volume; Jernigan et al., 2005) appears to be distinct from that of HIV infection (e.g. frontal cortex and caudate atrophy), which may be a result of differential mechanisms of injury (e.g., inflammation, neuronal loss). Indeed, MA use in the presence of HIV may produce an additive neuronal injury (e.g., interneuron loss; Chana et al., 2006) and abnormal brain metabolism in frontostriatal pathways (Chang et al., 2005). Given the opposing neurotoxic effects of these conditions on brain structure, it is not surprising that interaction effects are absent when examining overall impact on volume (e.g., Jernigan et al., 2005). However, the expected additive deficit on brain function from these two neurotoxic conditions has been notably absent in a number of studies. For instance, Ances and colleagues (2011) observed independent trend-level and significant effects of HIV and MA, respectively, on cerebral blood flow surrounding
the lenticular nuclei, but no interaction of the two conditions on this outcome on a functional task. Similar findings in magnetic resonance spectroscopy failed to find an interaction of these conditions on cerebral metabolites, but some evidence suggests that MA decrease neuronal integrity in the context of poorly controlled HIV disease (Taylor et al., 2007). Even more unexpectedly, Archibald and colleagues (2012) found that the combination of HIV and MA appeared to *ameliorate* the negative effect of either condition alone of decreased blood flow during a complex motor task. In sum, these mixed findings suggest that further research, perhaps using different technology (e.g., diffusion tensor imaging) or methodology (e.g., fMRI with executive tasks) is necessary to elucidate the interaction of HIV and MA on macro neural systems.

Despite the complexity of the imaging literature, the combination of HIV/MA has been solidly associated with higher rates of neuropsychological impairment than either of the independent conditions, in addition to specific deficits in learning, memory, motor skills, and attention/working memory (Rippeth et al., 2004), with evidence of amplified cognitive deficits also observed in mouse models (Kesby et al., 2015). Carey and colleagues (2006a) observed additive deleterious effects of HIV and MA, such that individuals in the immunosuppressed comorbid sample were impaired on more neurocognitive domains than all other HIV/MA comparison groups. In fact, MA use has been linked to worse neurocognitive functioning in acute and early HIV infection, a critical period of immune activation and alterations of brain metabolism that is hypothesized to set the stage for future neurocognitive outcomes (Weber, Morgan et al., 2013). Speaking to the pattern of neural injury observed in this group, Gonzalez, Bechara, & Martin (2007) found increased working memory deficits and risky decision-making in a sample of HIV-infected MA users relative to substance free individuals with HIV. Importantly, these neurocognitive deficits may amplify the risk of poorer functional
impairments (e.g., Ludicello et al., 2013) and outcomes (e.g., Blackstone et al., 2013). In fact, neurocognitive deficits in this population may greatly increase the likelihood of poorer disease outcomes (Ellis et al., 2003), in part due to this population’s high rate of antiretroviral (ARV) nonadherence (Moore et al., 2012). Yet we presently have no effective cognitive or behavioral interventions to improve ARV adherence in this high-risk cohort. Consequently, physicians are often reluctant to prescribe ARVs to MA users given the risk of nonadherence and viral mutation (Parienti et al., 2004), which decreases the likelihood of viral suppression and positive health outcomes (Taniguchi et al., 2012), and also contributes to risk of HIV transmission (Kalichman, 2008). Accordingly, discovering new and effective ways to improve neurocognitive deficits in HIV/MA may be of tremendous value toward determining remediable targets for novel neurorehabilitation interventions to improve adherence. Given the paucity of effective interventions to maintain ARV adherence in HIV/MA, using theory-guided studies to validate neurocognitive targets represents a potentially significant initial step toward effective, low cost interventions to improve health outcomes.

Cognitive Rehabilitation in HIV Infection & Methamphetamine Use

In contrast to the remarkable advances in clinical management of immunological aspects of HIV, the armamentarium for effective management of HAND remains relatively barren (Weber, Blackstone & Woods, 2013). Pharmacological research on interventions for HAND has identified two potential candidates: cART and non-ART medications. In general, the initiation of cART has been associated with improvements in neurocognition (Joska et al., 2010), especially in ART-naïve individuals (e.g., Letendre et al., 2004). Beyond this first line of standard-of-care cART, it may be possible to prescribe ART regimens that better penetrate the central nervous system (CNS), thereby
more effectively controlling the direct and indirect effects of HIV replication on neural structure and function. While cross-sectional evidence exists to suggest that higher CNS penetrating regimens are associated with better neuropsychological outcomes (e.g., Letendre et al., 2008, Smurzynski et al., 2011), randomized controlled trials of the efficacy of CNS penetrating ART regimens on HAND are presently underway and are needed to support an evidence-based practice recommendation. Clinical research on non-ART medications for HAND has produced mixed results on neurocognitive outcomes. For instance, a single-arm study with lithium showed some neurocognitive improvement among participants (Letendre et al., 2006); this same group also found an association between use of serotonin reuptake inhibitors and neuropsychological outcomes (Letendre et al., 2007). Other non-ARV medications that have shown promise in this regard in pilot trials (e.g., selegiline, memantine, minocycline) have not held up in larger, more rigorous trials (Sacktor et al., 2000; Schifitto et al., 2007, and Nakasujja et al., 2013, respectively).

Considering the limited success of pharmacological interventions, recent efforts have focused on adapting cognitive neurorehabilitation approaches to remediate HAND, but have thus far been limited in quantity and scope. The first study on this topic was performed in a population of HIV-infected children in Uganda (Boivin et al., 2010) and examined the effectiveness of a memory- and attention-based cognitive rehabilitation training program (i.e., Captain's Log CCRT), which produced moderate improvements on measures of simple attention and information processing speed. More recently, Becker and colleagues (2012) revealed that a multi-domain computerized cognitive stimulation program (i.e., SmartBrain) was effective in improving global cognitive abilities in HIV-infected adults who utilized the program most in their intervention sample. Similarly, a speed of information processing training program yielded improvements on the Timed
Activities of Daily Living Test and the Useful Field of View Test (Vance, Fazeli, Ross, Wadley, & Ball, 2012), suggesting that such computerized programs may warrant further study in the remediation of cognitive and functional deficits in HAND. However, these few studies reveal limitations that necessitate clarification on the notion of broad-based cognitive rehabilitation in HIV. For instance, it remains unclear whether study designs and results reported could suggest that the interventions used were effective beyond what would typically be seen from practice effects on their criterion cognitive battery. Additionally, the use of generalized cognitive training protocols and analysis of global cognitive indices leaves questions as to the distal and proximal mechanisms behind neurocognitive improvement (i.e., effective aspects of the treatment as well as domains of cognition that are amenable to remediation). Finally, it will be important to determine whether laboratory-based improvements in daily functioning abilities translate to improved everyday functioning outcomes that are particularly relevant to this population (e.g., medication adherence).

To further explore this latter question, some promise lies within the applied cognitive psychology literature, in which a few studies have identified theory-driven, targeted techniques adapted from the cognitive psychology and rehabilitation literatures that may have potential for remediating HAND. An early study (Neundorfer et al., 2004) used spaced retrieval, a common technique in the rehabilitation literature that uses successive approximation to extend an individual’s recall abilities for specific information over time (e.g., Schacter, Rich, & Stampp, 1985). Spaced-retrieval demonstrated some efficacy in improving self-reported memory performance in HIV when used in conjunction with external compensatory strategies, such as a pillbox (Neundorfer et al., 2004). Spontaneous deployment of higher-order meta-cognitive compensatory strategies in the laboratory has also been implicated in better working memory performance in older HIV-
infected adults (Woods et al., 2010), potentially speaking to the additional importance of meta-cognition and insight in rehabilitation of neurocognition. The cognitive neurorehabilitation literature suggests that strategy use is effective in normalizing working memory dysfunction in healthy older adults (e.g., Wegesin, Jacobs, Zubin, Ventura, & Stern, 2000) and in various clinical populations (e.g., mild traumatic brain injury [TBI]; Cicerone, 2002). In fact, even healthy adults who spontaneously deploy meta-cognitive strategies, such as chunking, during the performance of a complex working memory task reliably demonstrate fewer errors as compared to persons who do not use a strategy (e.g., Bryan & Luszcz, 2001). This phenomenon is also consistently reported in persons with central nervous system insults such as TBI (e.g., Schmitter-Edgecombe & Chaytor, 2003). It is theorized that the use of meta-cognitive strategies minimizes the complexity of the working memory task (e.g., concurrent processing) and allows for deeper levels of encoding, which in turn liberates cognitive resources that may be used to facilitate higher levels of overall performance. Furthermore, older HIV+ adults who reported using compensatory memory strategies in their daily lives were more likely to remember to perform a task outside of the laboratory (Weber et al., 2011), suggesting that these individuals may be adept at utilizing techniques to aid them on a day-to-day basis. Technologically based compensatory strategies (e.g., cell phone texting) have also been effective in improving medication adherence in individuals with memory impairment (Andrade et al., 2005).

While several studies have identified the importance of intact neurocognitive functioning in the successful treatment of substance use disorders (e.g., Bechara, 2005), very few studies have attempted to determine the efficacy of cognitive remediation protocols to improve cognition and everyday functioning in these populations. Within MA use specifically, growing evidence suggests that extended periods of abstinence may
allow for improved neurocognitive functioning. At the neurobiological level, there is some evidence to suggest neural recovery from MA damage following prolonged (i.e., greater than 6 months) periods of abstinence (e.g., Nordahl et al., 2005; Chang et al., 2002). Additionally, there may be partial cognitive improvement in areas including attention, information processing speed, and psychomotor skills (e.g., Salo et al., 2009; Iudicello et al., 2010; Volkow et al., 2001). However, other MA-associated cognitive deficits may persist or even worsen despite discontinued use of MA (e.g., Johanson et al., 2006; Simon, Dacey, Glynn, Rawson, & Ling 2004) and continue to adversely impact important everyday functioning abilities, thereby highlighting the need for more explicit methods of improving cognition in this population.

More recently, pharmacological interventions have been posited as a potential target for improving cognition in substance users, with non-addictive drugs (e.g., cholinesterase inhibitors; Sofuoglu, 2010) with cognitive enhancing properties being suggested for future study; however, early evidence appears to be mixed, with some studies reporting improvement in limited aspects of cognition (e.g., new learning; modafinil in MA; Ghahremani et al., 2011; cf. Mereu et al., 2013) but others reporting no benefit (e.g., rivastigmine in MA; Kalechstein et al., 2011). Despite the promise of a medicinal remedy for neurocognitive deficits in this population, the success of this option for treatment is inherently limited due to the high risk of nonadherence in MA use. In terms of cognitive interventions, Goldstein and colleagues (2005) reported neurocognitive improvement on tests of attention and cognitive flexibility due to computer-assisted cognitive rehabilitation protocols during alcohol detoxification beyond natural recovery (compared to an active control group). Other studies have reported positive treatment-based outcomes (e.g., level of engagement in treatment, longer periods of abstinence post-treatment) due to cognitive rehabilitation within residential
substance use treatment programs (e.g., Fals-Stewart & Lam, 2010). Beyond this limited collection of studies, few efforts appear to have been made to use cognitive interventions to address neuropsychological deficits within substance use disorders, specifically in MA.

**Prospective Memory**

Considering its unique role in medication nonadherence and vulnerability in HIV/MA, prospective memory (PM) is a prime target for cognitive enhancement. Colloquially known as “remembering to remember,” PM is a multi-faceted cognitive ability referring to the initiation, retrieval, and execution of previously encoded intentions at an appropriate moment in the future (McDaniel & Einstein, 2007). Particularly relevant to the HIV/MA population, remembering to take one’s medications as prescribed is a classic example of PM in everyday life, since one is required to form an intention to take one’s medications, sustain that intention over a delay period (e.g., time until bedtime) despite numerous ongoing activities, recall the correct intention (e.g., which medication to take) at the correct time (e.g., bedtime), and successfully execute the intention (e.g., take the medication; Park & Kidder, 1996). Other examples of PM in everyday life include remembering to mail the household bills and attend a job interview on time. In fact, PM deficits are independently associated with a host of poorer everyday functioning outcomes, including medication nonadherence (Woods et al., 2009), unemployment (Woods et al., 2011), and functional dependence (Woods et al., 2008a).

One of the most influential theories that might guide efforts to improve PM is McDaniel and Einstein’s (2000) Multiprocess Theory (MPT) of PM, which posits that PM is heavily reliant on frontally-mediated strategic (i.e., executive) processes, including planning (i.e., forming and executing an intention), monitoring for the appropriate
moment to initiate the intended action, inhibition of ongoing activities, and flexible switching from ongoing activities to the planned action, as well as more automatic (i.e., spontaneous) processes mediated by medial temporal systems. Furthermore, this framework suggests that the strategic encoding, monitoring, and retrieval demands of a given PM task may vary by the particular characteristics of the target cue upon which intention retrieval is based. For instance, an important distinction is often made between time- and event-based PM (Einstein & McDaniel, 1990). While time-based PM tasks require the execution of an intention at a specified time (e.g., taking a medication at 8:00am), event-based PM tasks involve executing an intention upon detection of an external stimulus (e.g., mailing a letter when you see a mailbox). Due to the absence of an overt environmental cue, time-based tasks are thought to place greater demands on cognitive control processes, most notably self-initiated monitoring of time that, under normal circumstances, strategically increases as the cue approaches (e.g., Costa, Peppe, Caltagirone, & Carlesimo, 2008). Thus, it is argued that time-based PM is more reliant on executive functions and the integrity of frontal systems than is event-based PM. For example, Raskin et al. (2011) showed that patients with Parkinson’s disease, a classic basal ganglia disease, demonstrate disproportionate impairment in time-based PM, which was associated with executive dysfunction. The Test-Wait-Test-Exit Model, initially described by Miller, Galanter, & Pribram (1960), speaks to the MPT-based executive resources required for attentional monitoring, particularly for time-based PM tasks, whereby the attentional costs of monitoring are sufficiently high enough to discourage continuous monitoring. The primary tenet of this model specifies that it is likely for an individual to test (e.g., check a clock) earlier than necessary as to prevent PM task failure (e.g., performing a task too late), and will repeat this process of testing and waiting (e.g., returning to ongoing activities) until it is determined that it is the
appropriate time to perform the given PM action. Throughout this process, executive abilities are required to monitor and appropriately judge the passage of time, disengage from the ongoing task, assess the environment to determine whether to perform a given action, and correctly judge the relative costs and benefits to performing the Test-Wait-Test-Exit cycle again. Although thought to rely less on strategic resources than general time-based PM tasks, there are also characteristics by which an event-based PM task can be relatively more strategically demanding. For example, such a manipulation would be the semantic relatedness of the PM cue-intention pairings. Semantically linked pairings (e.g., remembering to buy stamps when mailing a parcel at the post office) are thought to rely on automatic-associative memory. In contrast, semantically unrelated cue-intention pairings (e.g., remembering to buy stamps when at the grocery store) are posited to draw more heavily on strategic encoding and retrieval processes (e.g., McDaniel, Robinson-Riegler, & Einstein, 1998. Overall, McDaniel & Einstein’s MPT highlights the importance of both strategic and automatic processes in intact PM performance, and provides a useful framework upon which to assess mechanisms of PM failure when translated to use in clinical populations.

As a complex cognitive construct, numerous brain regions have been implicated in intact PM performance. Overall, most studies point to the bilateral frontal poles (Brodmann’s Area 10; Burgess et al., 2001; 2003), with additional input from the right lateral prefrontal cortex, right parietal lobe, and precuneus bilaterally (Burgess et al., 2001). The requirements of these brain regions are likely to temporally shift as the task evolves (e.g., maintaining the intention over the delay versus spontaneous retrieval of intention). Indeed, the realization of the appropriate cue/intention pairing has been related to increased activation in the thalamus and decreases in the right dorsolateral prefrontal cortex (Burgess et al., 2001). Further assessment of BA 10 in light of PM
demands has similarly revealed enhanced activation of the lateral BA 10 for maintaining internally generated thought (e.g., rehearsing the intention) and the medial BA 10 for its suppression (Burgess et al., 2003), particularly when demands on intention retrieval are high (Simons, Scholvinck, Gilbert, Frith, & Burgess, 2006). Speaking to the retrospective memory demands inherent in any PM task, independent studies have found significant associations with the medial temporal lobe, particularly on focal PM tasks (e.g., PM cue is embedded within the ongoing task), which is thought to rely more on spontaneous retrieval processes than strategic, effortful processing (Gordon, Shelton, Bugg, McDaniel, & Head, 2011). Altogether, these studies highlight the primary role of frontostriatal pathways in the intact PM performance.

**PM in HIV infection.** In accordance with its preferential pattern of frontostriatal neural injury (Ellis et al., 2009), HIV infection is broadly associated with moderate deficits in both time- and event-based PM (Carey et al., 2006b; Martin et al., 2007; Zogg et al., 2011) that are characterized by difficulties in self-initiated encoding, monitoring, and retrieval, highlighting difficulty with the frontally-mediated and strategic aspects of PM as per the MPT. For instance, studies analyzing qualitative errors common in the HIV population revealed difficulties with strategic processes such as self-monitoring previous behavior (e.g., performing the same task twice) and initiating PM responses (e.g., acknowledging that a response was required; Carey et al., 2006b). Although findings are mixed, several studies have found disproportionately greater deficits in time-based PM, thought to require more strategic resources (McDaniel & Einstein, 2000) than event-based PM (e.g., Carey et al., 2006b; Martin et al., 2007). Furthermore, these deficits are exacerbated over longer delay intervals (e.g., Morgan et al., 2012), suggesting that the self-initiated cognitive resources involved in time-based PM may become less accurate as task demands increase. Doyle and colleagues (2013) reported that time-based PM
deficits were primarily driven by deficits in monitoring time over delay intervals, such that individuals with HIV checked a clock significantly less than their seronegative counterparts. Follow-up analyses showed that time monitoring was related to executive functions and not internal time estimation abilities, thereby further implicating frontally-driven mechanisms. Although considered to be less reliant on strategic processes, a similar pattern has been seen in parallel aspects of event-based PM in HIV infection. For example, Woods and colleagues (2010) demonstrated that older HIV-infected adults performed significantly worse on semantically-unrelated cue-intention paired PM tasks, which would require more explicit and higher-level encoding processes, compared to more automatic semantically-related cue-intention pairings.

Consistent with the neuropathology of HIV infection and proposed mechanisms of PM, the pattern of PM deficits observed in this population has been associated with executive functions, aspects of retrospective memory (i.e., delayed free recall), and verbal working memory (Carey et al., 2006b). Diverging from other cognitive functions, this pattern is starkly different than what may be seen in more cortical neuropathologies (e.g., Alzheimer’s Disease), which frequently observes difficulty in the retrospective memory and automatic aspects of PM (i.e., PM task content; van den Berg, Kant, & Postma, 2012), whereas individuals with HIV frequently perform comparably to seronegative counterparts on recognition aspects of PM tasks (e.g., Carey et al., 2006b). Speaking to this divergence, Gupta and colleagues (2010) demonstrated the cognitive dissociability of PM in HIV infection, such that a confirmatory factor analysis maintained PM as a distinguishable cognitive factor, when compared with other related cognitive abilities (e.g., retrospective memory, executive functions).

Speaking to the ecological relevance of these findings, HIV-associated PM deficits in the laboratory are associated with a range of poorer everyday functioning
outcomes and self-report of PM difficulties (e.g., Woods et al., 2007), including dependence in instrumental activities of daily living (Woods et al., 2008a), medication non-adherence (Contardo, Black, Beauvais, Dieckhaus, & Rosen, 2009; Woods et al., 2009), and unemployment (Woods et al., 2011). For example, Woods and colleagues (2008a) found that HIV+ individuals who demonstrated impairment on a laboratory-based PM task possessed a fourfold risk of reporting declines in the independent management of their instrumental activities of daily living, an effect that was independent of other cognitive impairments, psychiatric comorbidity, and HIV disease severity. Importantly, these relationships with everyday functioning declines are most often related to the executive aspects of PM; Woods and colleagues (2009) found that HIV-infected adults who exhibited difficulty in monitoring time during a PM task were 5.8 times more likely to be considered nonadherent to their cART regimen based on a 30-day Medication Electronic Monitoring System assessment. Similarly, impairment on tasks utilizing longer PM delays was predictive of nonadherence (Poquette et al., 2013).

Further complicating the impact on everyday functioning, evidence suggests that individuals with HIV are poor at predicting their own PM abilities, which may impair their abilities to gauge the need for compensatory strategies that may support daily tasks requiring intact PM (Casaletto et al., 2014).

**PM in MA use.** In comparison to the more extensive PM literature in HIV infection, only two studies to date have examined PM abilities within the MA-using population. First, in a cohort of 20 recently abstinent MA-dependent and 20 MA-naïve individuals, Rendell, Mazur, & Henry (2009) assessed PM using the Virtual Week task, which requires the participant to remember to perform a series of actions as part of a board game (see Rendell & Henry, 2009, for a review). The MA-dependent group made fewer correct PM responses than the MA-naïve group (Cohen’s $d = 1.25$), which
included a series of primarily event-based intentions, as well as time-check tasks. The MA effects remained significant after covarying for other cognitive abilities, including a standard clinical test of retrospective memory (i.e., Auditory-Verbal Learning Test). However, this study contained a number of flaws and limitations (e.g., lack of time-based trials, lack of free recall [only recognition-based] cues, limited generalizability to US-based MA-using populations), thereby warranting further study of the PM construct in MA. In response, Ludicello and colleagues (2011) examined time- and event-based PM with well-characterized MA sample using a well-validated measure of PM (i.e., MIST), revealing worse PM performance of nearly a standard deviation (d=0.87) between MA-dependent adults and demographically similar healthy comparison participants, after accounting for factors upon which the groups differed (e.g., lifetime alcohol dependence). Furthermore, through examination of process errors and correlational analyses, this study was able to characterize the cognitive architecture driving PM failure within this population. Specifically, PM deficits were significantly associated with executive dysfunction as measured by standard clinical tests (e.g., Wisconsin Card Sorting Test; perseverative responses; Kongs et al., 2000), thereby corroborating the aforementioned hypothesized cognitive and neural substrates of PM, which is thought to rely heavily on executive functions (e.g., McDaniel & Einstein, 2000) and frontostriatal systems (e.g., Burgess et al., 2003). This result also converges with the findings of Rendell and colleagues (2009), who reported a significant association between PM impairment on the Virtual Week task and cognitive impulsivity among MA users. Also consistent with the Rendell study, the association between MA-associated PM impairment and executive dysfunction was specific; that is, PM was not correlated with tests of retrospective memory or information processing speed. Such weak associations were somewhat surprising when considered in the context of prior research in other clinical
populations (e.g., HIV; Carey et al., 2006b) showing that the MIST relates to these cognitive abilities. When paired with the findings of Rendell and colleagues and interpreted within the scope of MPT, these data give credence to the hypothesis that PM deficits in MA users are driven by difficulties performing the strategic aspects of PM (e.g., monitoring), a pattern similar to what has been observed in HIV infection.

Despite limited research in this area, there are significant indications that PM deficits in MA use are likely to be related to difficulties with everyday functioning. For instance, Iudicello, Weber, and colleagues (2011) found that failure to perform a PM-based naturalistic task (i.e., calling the examiner 24 hours later with a specific message) was significantly related to laboratory-based PM impairment. Similar findings regarding the ecological validity of PM exist in the broader substance use literature. In a mixed substance use sample that included MA users, Weinborn and colleagues (2011) reported that laboratory-based PM deficits correlated with self-reported PM errors in daily life, above and beyond other known predictors of self-reported cognitive complaints (e.g., depression).

**PM in HIV infection and MA use.** Consistent with the overlapping pattern of neurocognitive deficits in MA and HIV populations, this comorbid group may be at increased risk for PM dysfunction, which could exacerbate functional outcomes and worsen HIV disease outcomes (see Figure 1). More specifically, the pattern of PM dysfunction exhibited in each risk group may be compounded, thereby showing increased impairment of frontally mediated strategic aspects of encoding and retrieval (e.g., monitoring), while automatic processes remain primarily intact (Iudicello et al., 2011; Zogg et al., 2011), as presently observed in HIV and MA alone. Considering what is known and hypothesized regarding the cognitive architecture of PM deficits in HIV/MA, development of neurorehabilitation techniques that are designed to support
dysfunctional strategic processes may enhance PM abilities in this high-risk population by circumventing the mechanisms of their overall deficit, and subsequently improve everyday functioning.

**Self-Generation**

One promising technique for remediating PM deficits is the use of self-generation to support strategic PM processes in this high-risk population. *Self-generation* (or “the generation effect”) is theorized to facilitate memory recall by deepening encoding of the information to be remembered, as initially described in Craik and Lockhart’s (1972) theories on levels of processing in memory, thereby reducing strategic demands on
memory and resulting in enhanced retrieval (Slamecka & Graf, 1978). This technique has been classically examined in retrospective memory paradigms (see Bertsch, Pesta, Wiscott, & McDaniel, 2007). A common self-generation experiment is a paired word associate task, whereby participants are presented with word pairs in either a didactic format (i.e., explicitly presented) or a self-generated condition. In the self-generation condition, individuals are presented with a complete first word of the pair, but only the first letter of the second word is presented (Basso, Lowery, Ghormley, Combs, & Johnson, 2006). To generate the second word, the participant is provided a semantic cue that delineates a relationship between the paired word associates. For example, a didactic presentation of a word pair might be “drive – car”, whereas the parallel self-generation condition would be “drive – c__”. In the latter case, an individual would be asked to generate a word beginning with ‘c’ that is semantically related to the word “drive”. Later in the experiment, the item of interest to be remembered, by either retrieval or recognition processes, would be “car”. Self-generated encoding has also been used in numerical formats (e.g., addition; 2+2 = __), which has demonstrated robust effects on improving memory (average effect size = 0.92; Bertsch et al., 2007).

Borne out of the cognitive psychology literature, Slamecka and Graf first described the robust effects of self-generation among cognitively normal adults (1978). This seminal paper examined the nature of the effect among a variety of conditions and described its persistence across cued and uncued recognition, cued and uncued recall, across encoding rules (i.e., semantic or phonemic categories), timed or self-paced generation, and between- or within-subjects designs. With increased study of the generation effect revealing slight discrepancies among study designs and results, considerable debate grew over the cognitive mechanisms that moderate the phenomenon, to which one paper remarked that “it is only a mild exaggeration to note
that the number of accounts for the generation effect is slightly less than the number of reports of the effect itself” (McDaniel, Waddill, & Einstein, 1988). For instance, as several research groups reported the lack of a generation effect among between-subjects designs, multiple theories arose suggesting that the act of item generation did not confer cognitive benefits due to an enhanced level of processing, but instead, that this process was more similar to the control condition of simply reading the item to be remembered. To this end, the selective rehearsal displacement theory (Slamecka & Katsaiti, 1987) states that when read and generated items are presented in a mixed (cf. blocked) fashion, individuals forego rehearsal of the read items and spend more mental energy on the generated items. Regardless of the specific submechanism of action, self-generation appears to be robust in deepening encoding and ultimately improving recall of items to be learned.

After considerable study in healthy adults (and primarily college students), a translational effort was made to study the effects of this paradigm in the context of brain injury. Of clinical relevance, self-generation has been effective in ameliorating verbal recall deficits in a variety of neurological conditions including multiple sclerosis (e.g., Chiaravalloti & DeLuca, 2002; Basso et al., 2006), traumatic brain injury (e.g., O'Brien, Chiaravalloti, Arango-Lasprilla, Lengenfelder, & DeLuca, 2007), and mild dementia (e.g., Lipinska, Bäckman, Mäntylä, & Viltanen, 1994). More recently, the generation effect has been validated in international clinical samples in non-English languages (e.g., Spanish; Arango-Lasparilla et al., 2012). The generation effect has been extended beyond the immediate laboratory to everyday functioning. Goverover and colleagues (2008) demonstrated the effectiveness of self-generation to improve meal preparation and managing finances in adults with multiple sclerosis, with later research demonstrating a more robust effect on the functionally relevant task stimuli (e.g., meal preparation words).
rather than basic laboratory task stimuli (Goverover et al., 2014). However, it is important to note that the generation effect is not necessarily effective in all clinical populations, including frontotemporal dementia (e.g., Souliez, Pasquier, Lebert, Leconte, & Petit, 1996) and advanced Alzheimer's disease (e.g., Dick, Kean, & Sands, 1989), potentially due to overall dementia severity and remaining intact cognitive mechanisms that might be required for ideal utilization of self-generation strategies (e.g., category fluency).

Importantly, self-generation is highly effective in increasing retrospective memory free recall and recognition in persons living with HIV infection (Weber et al., 2012b); analyses demonstrated large effects (Cohen's $d_s > 0.8$) of self-generation across all conditions in the HIV-infected cohort. Furthermore, this paradigm was effective for improving retrospective memory in HIV-infected adults with demonstrated verbal memory impairment (Cohen's $d_s$ range $[0.6, 0.84]$; $p_s < 0.001$), suggesting that the generation effect is present in the individuals for whom such an intervention is arguably most indicated. This study also furthered the clinical self-generation literature by examining the cognitive processes implicated in the success of the self-generation paradigm. Although memory was modestly correlated (but not statistically significant) with self-generation gains at delayed recall, semantic verbal fluency (noun switching) emerged as the sole significant predictor. Speaking to the specificity of this verbal fluency finding, generation gains at delayed recall were not associated with broader executive dysfunction (e.g., planning, set shifting). Thus, while prior studies have largely focused on the contribution of episodic memory impairment to the better recall performance on self-generated trials (e.g., O'Brien et al., 2007), the executive aspects of semantic verbal fluency may also be important, particularly in terms of within-subject gains. Although one might argue this association could be driven by degradation of semantic memory stores themselves, a subsequent post-hoc analysis showed that the
generation difference score was not correlated with a test of semantic memory (i.e., Pyramids and Palm Trees; Spearman’s $\rho = 0.13; p>0.10$). Indeed, more recent research in MS highlighted the role of intact executive functioning in “responders” to self-generation (Goverover et al., 2013). In sum, these data suggest that the self-initiated search and retrieval aspects of generative fluency are more relevant to realizing benefits from self-generation episodic memory paradigms than the integrity of the semantic memory stores themselves in HIV infection, which highlights the higher-order processing supported by self-generation in this population.

Given the efficacy of self-generation for retrospective memory in HIV infection and the ecological relevance of PM, it is reasonable to adapt this approach to this dissociable aspect of episodic memory. Not only will this study expand the cognitive neuropsychology literature on self-generation to exploring its utility in PM, but it also will do so in a clinical population that is in dire need of novel cognitive interventions to improve daily functioning outcomes. Mechanistically, the theoretical basis for self-generation maps onto the theorized cognitive architecture of PM as guided by MPT. As particularly relevant to HIV/MA, the enhanced encoding provided by self-generation may capitalize on the HIV/MA population’s relatively intact automatic PM processes (e.g., spontaneous recall) and support impaired strategic PM processes of encoding, monitoring and cue detection (see Figure 2). In other words, by providing a higher-level

![Figure 2. Theoretical mechanisms of self-generation on PM enhancement.](image-url)
encoding strategy (i.e., self-generation) for the PM cue, it is likely that supported encoding will minimize the cognitive resources needed to maintain the cue-intention pairing over the delay interval, which allows for additional resources available for cue monitoring and detection. With this simple manipulation providing structure for improved encoding and reducing burdens on impaired executive systems, it can be hypothesized that self-generation could improve PM performance in HIV-infected MA users.

As such, this dissertation project sought to test this experimental intervention in a PM paradigm given a) the ecological relevance of PM, b) the prevalence of PM impairment in this high-risk population, and c) the relevance of the generation effect’s mechanisms of action to the specific profile of memory impairment in HIV/MA (i.e., impaired encoding and retrieval). As such, this study aimed to examine the efficacy of self-generation on PM performance in HIV/MA by using a theoretically-driven approach to remediate a cognitive deficit that directly impacts ARV non-adherence (e.g., brief self-generation interventions could be incorporated into manualized cognitive rehabilitation programs for HIV-associated neurocognitive disorders).

Drs. Woods, Grant, Gilbert, Twamley, and Mattson are co-authors on this section of the manuscript, which will be prepared for publication.
Specific Aims & Hypotheses

Specific Aim 1: Evaluate the efficacy of self-generation on PM performance in HIV and MA on basic, clinical, and naturalistic PM paradigms.

Hypothesis 1a: Self-generated encoding will enhance PM performance relative to didactic (i.e., explicitly presented) encoding across HIV/MA groups.

Hypothesis 1b: Self-generated encoding in the clinical samples will normalize PM performance, such that self-generated scores will be comparable to didactic scores in the comparison sample.

Hypothesis 1c: As compared to didactic encoding, self-generation will allow for enhanced automatic PM processes (i.e., better ongoing task performance) in HIV/MA groups in the basic and clinical tasks.

Specific Aim 2: Determine the neurocognitive correlates of self-generation on PM in HIV and MA.

Hypothesis 2a: The benefit of self-generation on PM performance in HIV and MA adults will be most pronounced in persons with neurocognitive impairment.

Hypothesis 2b: The benefit of self-generation on PM performance in HIV and MA individuals will be most associated with strategic (e.g., executive functions, working memory, semantic clustering) more so than automatic (e.g., consolidation, semantic memory) neurocognitive functions.

Exploratory Aim 3: Explore demographic (e.g., age), psychiatric (e.g., depression), addiction (e.g., recency of MA use), and HIV disease (e.g., nadir CD4) correlates of self-generation on PM in HIV/MA.
Preliminary Studies

Preliminary Study #1: PM Deficits in HIV+MA+ Adults

First, a sample of 20 HIV+MA+ adults and 26 demographically comparable HIV-MA- subjects were administered a clinical test of PM (i.e., Memory for Intentions Screening Test; MIST; Raskin, Buckheit, & Sherrod, 2010) as part of Dr. Woods' R01 and a pilot grant linked to the HNRP, drawn from Iudicello, Weber and colleagues (2011). The HIV+MA+ sample was predominantly male (95%), in their mid-forties, and had a median CD4 count of 354 (IQR: 249.5, 580.25). The entire sample met criteria for MA dependence within the last 12 months and had used approximately 880.9 (IQR=150.7, 1608.4) grams of MA in their lifetimes, last used 90 (IQR=21,180) days prior to assessment, and were subject to exclusion criteria similar to those outlined for the present study (see below for details). In a multiple linear regression, HIV+MA+ participants exhibited poorer PM performance \( (p = 0.005) \), even when taking into account variables on which the groups differed (e.g., alcohol dependence). This effect was primarily driven by a statistically significant difference between groups on the more strategically demanding TB PM subscale \( (p < 0.01; d = 0.81) \), but no effect on the more associative recognition posttest \( (p > 0.10; d = 0.23) \) or error types \( (p > 0.10; d = 0.18) \). These data suggest a PM deficit in HIV+/MA+ individuals, which appears to be driven by more strategic (i.e., TB PM) than automatic processes.

Preliminary Study #2: Self-Generation Improves RM in HIV+ Substance Abusers

Second, the potential efficacy of a self-generation intervention on a retrospective memory task was tested in a HIV+ substance-abusing sample drawn from Weber and colleagues (2012b). This study sample included 35 HIV-infected participants with a history of substance abuse diagnosed on the CIDI at least one month prior to
assessment; participants’ demographic and disease characteristics were roughly equivalent to those in Pilot Study #1. Participants were presented with 100 word pair associates (Slamecka & Graf, 1978) through either self-generated or didactic encoding (Weber et al., 2012b). In brief, the didactic condition was administered such that

participants were shown 50 word pairs that they were instructed to read aloud (e.g., autumn-fall). In the self-generation condition, participants received 50 word pairs in which they were presented the first word, but were asked to produce the second word based on its first letter (e.g., autumn-f___) and its lexico-semantic relationship with the stem word (e.g., synonym). As hypothesized, participants benefited substantially from the memory intervention, remembering significantly more words learned under the self-generation condition than the didactic condition at immediate (d = 1.19; p < 0.001), and delayed recall (d = 1.10; p < 0.001), and in the recognition test (d = 0.86; p < 0.001) (the

Figure 3. Self-generation improves retrospective memory (RM) in HIV+ substance abusers.
reader is referred to Figure 3). Thus, self-generation greatly facilitates retrospective memory performance in HIV-infected substance users.

Drs. Woods, Grant, Gilbert, Twamley, and Mattson are co-authors on this section of the manuscript, which will be prepared for publication.
Methods

The proposed study design and methods have been adapted from F31-DA034510.

Participants

To test the above hypotheses, this study included 83 participants, comprising three sub-samples: 1) HIV-seronegative individuals with no history of MA use (HIV-MA-; n=22), 2) HIV-seropositive individuals with no history of MA use (HIV+MA-; n=33), and 3) HIV-seropositive seronegative adults with a history of MA dependence (HIV+MA+; n=28). All participants were at least 18 years of age and drawn from larger NIH-funded grants and centers housed at the HNRP (e.g., Translational Methamphetamine AIDS Research Center). Inclusion of a healthy comparison group was included because the impact of self-generation has not yet been explored in PM, which will not only aim to contribute to the general PM literature, but to provide a basis of comparison for generation effects across varying levels of medical, psychosocial, and neurocognitive burden. HIV serostatus was determined by enzyme-linked immunosorbent assay (ELISA) and a confirmatory Western Blot or rapid HIV test. In regards to individuals in the HIV+MA+ cell, participants must have met criteria for MA dependence in the past according to the Diagnostic and Statistical Manual (4th ed.; DSM-IV; American Psychiatric Association, 1994) as determined by the Composite International Diagnostic Interview (CIDI; World Health Organization, 1998) or Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1991). We will exclude potential subjects who meet DSM-IV criteria for current abuse or dependence on alcohol or any other substance (e.g., cocaine, opioids). Participants who test positive for alcohol on a Breathalyzer or for illicit drugs (except marijuana) on a urine toxicology screen conducted on the day of testing were
rescheduled. Individuals who were unable to remain abstinent and produce a second positive urine test on the return evaluation were excluded. We also excluded participants with histories of severe learning disabilities (e.g., word reading standard scores < 70, as assessed by the Wechsler Test of Adult Reading; Psychological Corporation, 2001 or Wide Range Achievement Test; Wilkinson, 1993), psychosis unrelated to MA (e.g., schizophrenia, etc.) or major neurological conditions (e.g., head injury with loss of consciousness >30 min, stroke, seizures, etc.).

**Procedures**

Potential participants were approached regarding their interest in participating in this study for additional compensation on the day of their HNRP visit (NB. all potential subjects will have signed IRB-approved study consents that include language confirming their willingness to be recruited in this fashion). Additionally, participants were drawn retrospectively from previous HNRP studies if they meet the aforementioned criteria and have previously completed comprehensive visits.

**Self-generation PM tasks.** Three variations of PM tasks were chosen in which to test the proposed self-generation paradigm in order to assess the potential generation effect at varying levels of ecological relevance: a basic computerized laboratory task, clinical paper-and-pencil experimental test, and a naturalistic paradigm. Across the basic and clinical PM tasks, ease of self-generation of word pairs was assessed prior to task construction. Sixty-two incomplete word pairs were administered to 47 undergraduate students and scored for correctness. The word pairs with the lowest rate of generation errors were selected as task stimuli across both tasks (n=18). The remaining word pairs with the lowest errors rates were selected for lure stimuli (n=8).

**Basic PM task.** To examine the impact of self-generation on PM in the laboratory, participants completed a 15-minute computer task based on the classic
McDaniel & Einstein PM paradigm (Einstein, McDaniel, Richardson, Guynn, & Cunter, 1995), in which PM cues are embedded within an ongoing lexical decision making task. This task has been designed using E*Prime and were conducted on a PC. The ongoing task is comprised of 3 blocks of 100 randomized trials, in which participants are instructed to quickly decide whether a string of letters presented is a word and press a computer key (Y/N) to indicate their choice. The first block of trials is strictly devoted to the ongoing task in order to assist in task familiarity. The second and third blocks of trials each include a set of 4 PM trials, which were given at the beginning of each block. In the beginning of these blocks, participants were told that they must follow the instructions of the lexical decision making task, unless the word shown is one of four pre-determined words in that block, in which case they should press the ‘q’ key. The blocks were randomized per participant by encoding condition: didactic or self-generation. In the didactic condition, the presentation of the PM target words were shown as part of conceptually related word pairs, where the second word of the pair is the PM cue (e.g., "knife" for fork – knife). Participants were asked to read the second word. In the self-generation condition, PM target words were presented as part of conceptually related word pairs, but only the first letter of the second word was present (e.g., fork – k__). To determine the PM target word, the participant generated the second word of the pair, which they were asked to say aloud. Note that the timing in which the PM cues appear within each block remained stable across blocks and conditions, such that they are interspersed throughout. Prior to beginning each PM block, participants completed a 2-minute distractor task (i.e., visual puzzles). Outcome variables within each block are the number of correct PM trials, PM trial response time, correct ongoing task responses and ongoing task response time, which were calculated separately for each encoding condition.
**Clinical PM task.** Participants also completed a 12-minute paper-and-pencil clinical PM experiment designed in the spirit of the clinical PM test for which the most evidence of construct validity has been published (i.e., Memory for Intentions Screening Test; Raskin, Buckheit, & Sherrod, 2010). The primary outcome measures were overall performance on 8 PM tasks split evenly across both blocks, with trials in each block counterbalanced across encoding presentation (i.e., didactic or self-generation) and word list. At the beginning of each block, the participant will be informed that they were instructed to perform a specific task (i.e., filling out medications into an organizer) at given points in the future (i.e., when they are presented with cards with the PM cue words), while they were engaged in an ongoing task (i.e., complex visual mazes). They were then taught the 4 PM cues for that trial using either didactic or self-generated encoding. During each block, cards were turned over to reveal the PM cue words at prespecified intervals, intermixed with cards with non-cues (i.e., lures). After each block, a recognition trial was administered, with PM cues, lures, and 4 additional novel words. Prior to beginning each PM block, participants completed a 1-minute distractor task (i.e., serial 7s).

**Naturalistic PM task.** The third experiment used a between-subjects naturalistic PM task, modeled after the classic telephone tasks in the PM literature (e.g., Raskin, Buckheit, & Sherrod, 2010). Participants were asked to call the examiner on a given day of the week (beginning two days after their initial appointment) for a series of four weeks to tell her how many hours of sleep they got the night before. Participants were randomized into one of two conditions: didactic or self-generated presentation. For the didactic presentation, individuals were shown a card with a word pair, such that the first word is “day” and the second word is the day that they are told to call (e.g., “day – Wednesday” vs. “day – W_____”). (NB. For Tuesday, Thursday, Saturday, and Sunday,
the first two letters of these words will be written.) Moreover, we used the highly effective numeric self-generation approach for the actual time of the call (e.g., “4 + 5 = 9 am” vs. “4 + 5 = _____am”). All participants were asked not to use any additional compensatory strategies to remember to complete the task; while they were allowed to write down the examiner’s phone number, they were explicitly asked not to add it to their calendar or associate it with an alarm. Performance in each encoding condition group was scored as a sum of all four trials in a fashion similar to the above-described clinical experimental task.

**Neuromedical, psychiatric, and neurocognitive evaluations.** To answer questions related to the exploratory aim of this study, information regarding the neuropsychological, neuromedical, and psychiatric characteristics of the participants were drawn from their linked HNRP study visit.

**Neuromedical.** Laboratory and neuromedical data collected included: 1) current and nadir CD4 counts; 2) CDC staging; 3) HIV RNA measured in plasma; 4) estimated duration of HIV infection; 5) current ARV regimen; 6) ACTG adherence questionnaire; 7) HIV Dementia Scale; and 8) hepatitis C infection.

**Psychiatric.** A comprehensive psychiatric research evaluation yielded: 1) DSM-IV diagnoses of current and lifetime substance use (e.g., alcohol, MA, opiates, etc.), mood (e.g., major depression and bipolar), and developmental (e.g., attention-deficit/hyperactivity disorder) disorders based on the CIDI; 2) substance use quantification (e.g., onset, recency, duration, quantity, and frequency) of MA based on a semi-structured time-line follow-back interview; 3) current affective distress as measured by the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981); and 4) Lawton & Brody ADL (Lawton & Brody, 1969), a self-report measure of functional decline as assessed in multiple domains (e.g., shopping, medication management). The
Mnemonics subscale from the Memory Functioning Questionnaire (MFQ; Gilewski, Zelinski, & Schaie, 1990) was administered to obtain information on the use of compensatory strategies reported. The Martin and Park Environmental Demands (MPED) Questionnaire examined participants' self-reported busyness and level of daily routine (Martin & Park, 2003).

**Neurocognitive.** For individuals with shared HNRP visits containing neurocognitive data (n=74), we obtained their results from a 2-3 hour standardized battery (conducted by trained HNRP psychometrists) of well-validated tests designed to assess the cognitive domains most affected in neuroAIDS (Antinori et al., 2007; for a complete description, please see Heaton et al., 2010). Domains tests included 1) episodic learning and memory (i.e., the immediate and delayed recall totals of the Hopkins Verbal Learning Test-Revised [HVLT-R; Benedict, Schretlen, Groninger, & Brandt, 1998] and the Brief Visuospatial Memory Test-Revised [BVMT-R; Benedict, 1997]); 2) executive functions (i.e., perseverative responses from Wisconsin Card Sorting Test-64 [Kongs et al., 2000] and total time to complete Part B of the Trail Making Test [Reitan & Wolfson, 1985]); 3) attention/working memory (i.e., Letter Number Sequencing from the Wechsler Adult Intelligence Scale – 3 [WAIS-III; Psychological Corporation, 1997] and the Paced Auditory Serial Addition Test [PASAT; Diehr, Heaton, Miller, & Grant, 1998]); 4) information processing speed (i.e., the Digit Symbol and Symbol Search tests from the WAIS-III [Psychological Corporation, 1997] and the total time to complete Part A of the Trail Making Test [Reitan & Wolfson, 1985]); 5) verbal fluency (i.e., total words from the letter [FAS; Benton, Hamsher, & Sivan, 1983], animal [Benton et al., 1983] and action fluency [Woods et al., 2005b] tasks); and 6) motor (i.e., time to complete the dominant and non-dominant hands of the Grooved Pegboard Test [Kløve, 1963]). For all neurocognitive measures, raw scores were converted to
demographically adjusted T-scores (Heaton, Miller, Taylor, & Grant, 2004b; Norman et al., 2011) and used to construct 6 domain-based average T-scores as well as a Global Deficit Score (Carey et al., 2004); for ideal sensitivity and specificity, a cut-off of 0.5 was used to signify neurocognitive impairment.

**Data and Power Analyses**

Overall, critical alpha was set at 0.05 for planned analyses *a priori*. For exploratory analyses, critical alpha was corrected to 0.01 to reduce the likelihood of committing Type I error while protecting statistical power. Clinically relevant demographic, psychiatric, HIV disease, and MA dependence characteristics were examined across groups for which those variables exist (e.g., HIV disease characteristics only within HIV+ samples). Groups significantly differed on age, ethnicity, and lifetime diagnoses of Major Depressive Disorder and non-MA substance dependence (please see Table 1 for participant characteristics). None of these variables were statistically related to any primary outcome measure (i.e., recall or recognition scores on either didactic or self-generated trials) for the basic and clinical PM tasks, although age and ethnicity were significantly correlated with several ongoing task variables. Specifically, both age and ethnicity were associated with ongoing task (visual puzzles) performance in the clinical PM task (age: Spearman’s rho = -0.32, p=0.003; ethnicity: Hedge’s g=0.62, p=0.006). Lastly, age was significantly correlated with performance on the naturalistic PM task (Spearman’s rho = 0.362; p<0.001). As such, age and/or ethnicity was included as covariates in models for these outcome variables.

**Basic & Clinical PM tasks. Hypothesis 1a** was examined using a mixed model ANOVA, with performance on didactic PM trials and self-generated PM trials (recall and recognition) as repeated measures dependent variables and group status as the primary independent variable. The analysis of the within-subjects factor is well-powered (1-β
=0.80) to detect small to medium effect sizes (f = 0.19), and the between-subjects factor is well-powered (1- β=0.80) to detect medium to large effect sizes (f = 0.29). Additionally, the analysis of the interaction between these factors is well-powered (1- β=0.80) to detect medium to large effect sizes (f = 0.35). For the experimental PM task, this same analysis was repeated using ongoing task reaction time and accuracy variables across encoding condition as the within-subjects variable. Hypothesis 1c was analyzed using a mixed model ANOVA, with ongoing task (i.e., lexical decision-making task speed and accuracy in basic task, visual puzzles in clinical task) performance on the didactic and self-generation condition blocks as the within-subjects variables and group status as the between-subjects variable. Power analyses follow the same pattern as listed for Hypothesis 1a. As outcome variables were non-normally distributed, Hypothesis 2a was analyzed using pair-wise Wilcoxon Rank-Sum tests within the combined HIV+ sample (i.e., HIV+MA-, HIV+MA+), with a self-generation benefit scores (i.e., difference score between self-generated and didactic trials) on recall and recognition tasks as the dependent variables and impairment status as the primary independent variable; this analysis is powered (1- β=0.80) to detect large effect sizes (d=0.74). For Hypothesis 2b, Spearman’s rho correlational analyses were performed on the self-generation difference scores between encoding type trials and collapsed outcome scores from the NP battery to examine cognitive mechanisms that may be associated with self-generated PM success. These analyses are well-powered (1- β=0.80) to detect small to medium effect sizes (ρ=0.35). Hypothesis 3 exploratory analyses were conducted using Wilcoxon Rank-Sum tests or Spearman’s rho correlations were appropriate, and within relevant subgroups (i.e., MA dependence analyses only performed within HIV+MA+ sample). HIV disease characteristics of interest included current and nadir CD4 counts, AIDS status, duration of HIV infection, and viral detectability in blood serum. MA use characteristics
of interest included age at first MA use, recency of MA use, duration of MA dependence, and estimated quantity of lifetime MA used.

**Naturalistic PM task.** Considering that, in this portion of the study, participants were randomized into either encoding condition, the analysis for **Hypothesis 1a** was performed between subjects, as opposed to the repeated measures techniques used in the previous experiments. PM performance was examined using a multiple linear regression, with encoding condition and HIV/MA group status as the primary independent variables along with their interaction, with total naturalistic PM score as the sole dependent variable. As described above, age was included as a covariate in this model given its significant relationship to the outcome. This analysis is well-powered (1-\(\beta\)=0.80) to detect large effect sizes (\(f^2=0.41\)). Given the longitudinal nature of this task, a MANOVA was also conducted across PM task datapoints, with independent variables as described above. **Hypothesis 2a** will be examined within the combined HIV+ sample using multiple linear regression, with encoding condition and impairment group status as the primary independent variables along with their interaction. This analysis is powered (1-\(\beta\)=0.80) to detect large effect sizes (\(f^2=0.47\)), with age included in the model. **Hypothesis 2b** will also be examined in the clinical sample using individually-analyzed multiple linear regressions, with encoding condition, neurocognitive domain scores, and all interactions as independent variables. These analyses are well-powered (1-\(\beta\)=0.80) to detect large effect sizes (\(f^2=0.46\)). **Hypothesis 3** will also be explored using individually-analyzed multiple linear regressions, with each variable of interest, encoding condition, and its interaction as independent variables, and naturalistic PM score as the dependent variable. Follow-up Wilcoxon Rank-Sum tests or Spearman’s rho correlational analyses were performed on variables for which the exploratory critical
alpha level ($p=0.01$) was observed. Correlates of interest parallel those analyzed for the basic and clinical PM tasks.

Drs. Woods, Grant, Gilbert, Twamley, and Mattson are co-authors on this section of the manuscript, which will be prepared for publication.
Results

Basic PM Task

Aim 1. PM accuracy. A mixed-model ANOVA was conducted, with participant group as the between-subjects independent variable and PM task accuracy for each encoding condition per participant as repeated-measures dependent variables. A main effect of encoding condition was observed \([F(1,78)=8.82; p=0.004]\), such that participants were more accurate at the PM task under self-generated conditions relative to didactic (Hedge’s \(g = 0.36\); see Figure 1), but there was no main effect for group \((p=0.687)\) or interaction \((p=0.584;\) Hedge’s \(gs: HIV-MA- = 0.47; HIV+MA- = 0.20; HIV+MA+ = 0.46)\).

PM recognition. A similar pattern was observed for the recognition component of this task, such that there was a main effect of PM encoding condition \([F(1,78)=15.55; p<0.001;\) Hedge’s \(g=0.44]\) and higher recognition scores on self-generated trials. There was no significant main effect for group \((p=0.652)\) or interaction \((p=0.484;\) Hedge’s \(gs: HIV-MA- = 0.17; HIV+MA- = 0.69; HIV+MA+ = 0.53)\).
**Ongoing task. Reaction time.** Effects of encoding condition on ongoing task (i.e., reaction time speed on lexical decision making task, accurate trials only) were observed across all groups \([F(2,77)=167.34; p<0.001]\) (see Figure 5). Follow-up analyses revealed that individuals responded significantly faster on baseline trials relative to both self-generated \([t(80)=15.22; p<0.001; \text{Hedge’s } g=1.64]\) and didactic \([t(80)=17.63; p<0.001; \text{Hedge’s } g=1.86]\) trials. In addition, participants responded more quickly on self-generated trials relative to didactic trials \([t(80)=-2.17; p=0.033; \text{Hedge’s } g=0.18]\). No group \((p=0.552)\) or interaction \((p=0.512)\) effects were observed on reaction time.

**Accuracy.** A second mixed model ANOVA was performed with accuracy rates on lexical decision-making task across the two encoding condition blocks in addition to the baseline (i.e., lexical decision-making without PM task) block. A within-subjects effect for block was significant \([F(2,77)=40.67; p<0.001]\). Post-hoc analyses revealed significant differences between baseline and didactic blocks (Hedge’s \(g=1.09; p<0.001\)) and baseline and self-generated blocks (Hedge’s \(g=0.98; p<0.001\)), such that participants were more accurate in their responses on baseline trials (see Figure 6). There was no
significant difference between blocks requiring PM tasks (Hedge’s $g=0.04$; $p=0.685$). No significant between-subjects ($p=0.291$) or interaction ($p=0.507$) terms were statistically significant.

**Aims 2 & 3. Neurocognitive impairment and relationships.** Within the combined clinical (HIV+) sample, individuals with neurocognitive impairment were better able to benefit from the self-generation manipulation on recall ($t=-2.89$; $p=0.008$; Hedge’s $g=0.68$) relative to neurocognitively normal participants (Hedge’s $g=0.26$); this effect was not differentially found by MA status ($p>0.10$). No differential self-generation benefit by impairment was found on the recognition trial ($p>0.10$). Benefit from self-generation on either recall or recognition was not significantly correlated with strategic (e.g., executive functions, working memory, verbal fluency) or automatic (e.g., memory savings scores) neurocognitive performances (all $p$s $>0.10$); MA dependence did not affect these relationships (all $p$s $>0.10$).

**HIV disease, psychiatric, MA use relationships.** In the overall HIV+ sample, no HIV disease characteristics or psychiatric diagnoses were related to self-generation

Figure 6. Basic PM task ongoing task accuracy by encoding condition and HIV/MA group
benefit on recall or recognition. Within the HIV+MA+ sample, no MA use characteristics were significantly correlated with benefit from self-generation.

Clinical PM Task

Aim 1. PM accuracy. A mixed-model ANOVA was conducted, with participant group as the predictor and PM task accuracy for each encoding condition per participant as repeated-measures dependent variables. A main effect of PM encoding condition was observed \( [F(1,79)=7.43; p=0.008] \), such that participants were more accurate at the PM task under self-generated conditions relative to didactic (Hedge’s \( g = 0.28 \); see Figure 7). There was no main effect of group \( (p=0.289) \) or interaction \( (p=0.515) \) between group and encoding condition (Hedge’s \( gs: HIV-MA- = 0.46; HIV+MA- = 0.18; HIV+MA+ = 0.22 \)).

There was no interaction between encoding condition and group membership on lure response \( (p=0.386) \).

PM recognition. In the recognition trial, a main effect of self-generation was observed \( [F(1,80)=13.27; p<0.001; \text{Hedge’s } g=0.53] \), with no main effect of group \( (p=0.215) \). A trend-level interaction emerged \( (p=0.069) \), such that self-generation appeared to be significantly beneficial for recognition in the HIV-MA- group \( (p=0.005; \text{Figure 7}) \).
Hedge’s $g=0.43$) and HIV+MA+ group ($p=0.015$; Hedge’s $g=0.68$), but not the HIV+MA-sample ($p=0.152$; Hedge’s $g=0.32$).

**Ongoing task.** With regard to the ongoing task performance, a trend-level group effect emerged ($p=0.068$; Hedge’s $g$s: HIV-MA-=0.20; HIV+MA-=0.14; HIV+MA+=0.11). However, this effect was no longer significant when age ($p=0.003$; mean performance Spearman’s rho=-0.318) and ethnicity ($p=0.006$; mean performance Hedge’s $g=0.62$) were included in the model. There was no self-generation benefit observed on the ongoing task ($p=0.294$), nor was there an interaction with group membership ($p=0.189$).

**Aims 2 & 3. Neurocognitive impairment and relationships.** Within the combined clinical (HIV+) sample, participants did not appear to differentially benefit from self-generation (recall or recognition) based on neurocognitive impairment ($ps>0.10$); this finding was not affected by inclusion of MA dependence into the model. Benefit from self-generation on either recall or recognition was not significantly related to strategic (e.g., executive functions, working memory, verbal fluency) or automatic (e.g., memory savings scores) neurocognitive performances (all $ps > 0.10$); MA dependence did not affect these relationships (all $ps >0.10$).

**HIV disease, psychiatric, MA use relationships.** There were no significant relationships between HIV disease characteristics or psychiatric factors and benefit from self-generation (recall and recognition) in the overall HIV+ sample (all $ps > 0.10$). With regard to MA use characteristics, no other relationships with self-generation were significant (all $ps>0.10$).

**Naturalistic PM Task**
Aim 1. PM accuracy. A 2x2 ANOVA was conducted, with total naturalistic PM score as the outcome variable, and the independent variables as HIV/MA group, encoding condition, and their interaction. No main effects or interaction effect was observed (all \( p > 0.10 \); see Figure 8), although age was an overall predictor of task performance \( [F(1, 82) = 8.61; \quad p = 0.004; \quad \text{Spearman’s rho} = 0.36] \). Exploratory analyses within the HIV+ sample revealed that greater daily routine did indeed predict naturalistic task performance (Spearman’s rho = 0.27; \( p = 0.034 \)), with age as an independent predictor in the statistical model (\( p = 0.022 \)). However, when viewed longitudinally across PM data points (i.e., weekly calls), a trend-level interaction between condition and weekly response emerged such that a modest effect was seen in the persistence of the PM intention in the overall HIV+ sample \( [F(3, 57) = 2.27; \quad p = 0.095] \). Post-hoc pair-wise comparisons demonstrated that individuals in the self-generated condition were more likely than those in the didactic condition to perform the task in Weeks 3 (\( p = 0.028 \); Hedge’s \( g = 0.55 \)) and 4 (\( p = 0.023 \); Hedge’s \( g = 0.58 \)), with no differential relationship by MA status. No interactions by time were observed in the HIV- sample (\( p > 0.10 \)).
Aims 2 & 3. **Neurocognitive impairment and relationships.** Within the combined clinical (HIV+) sample, no interaction between neurocognitive impairment and encoding condition was observed ($p>0.10$); this finding was not affected by inclusion of MA dependence into the model. There were no significant interactions between encoding condition and any strategic or automatic neurocognitive performances (all $p$s $>0.10$); MA dependence did not affect these relationships (all $p$s $>0.10$).

**HIV disease, psychiatric, MA use relationships.** Among the HIV+ samples, no interactions with HIV disease or psychiatric variables were predictive of naturalistic PM score ($p$s $>0.10$). Within the HIV+MA+ sample, there were no significant interactions between MA use characteristics and encoding condition on outcome ($p$s $>0.10$).

Drs. Woods, Grant, Gilbert, Twamley, and Mattson are co-authors on this section of the manuscript, which will be prepared for publication.
Discussion

PM is a cognitively distinct subtype of episodic memory that is quite common in everyday life and a frequent complaint in both healthy adults and neurocognitive populations, such as HIV-infected adults and MA users. Within these populations, poor PM performance has been associated with worse functional outcomes, such as suboptimal medication adherence, unemployment, dependence in activities of daily living, and poorer health-related quality of life. However, there have been few scientifically rigorous efforts to improve PM in HIV and addictions. The present study examined the utility of self-generation, a cognitive technique that reliably improves RM, to enhance PM performance in HIV infection and MA dependence. Overall, results suggest that self-generation may produce moderate gains in PM accuracy across the translational assessment spectrum (i.e., basic laboratory, clinical, and naturalistic PM tasks). In other words, these data suggest that individuals are more likely to remember to complete a designated PM task for cue words that they learned under self-generated conditions (i.e., completed word pair based on semantic-relatedness and cued initial letter of target word) versus words learned under control didactic conditions (i.e., target word simply spoken aloud). Indeed, the magnitude of overall effects of self-generation on PM was comparable to what has been established within the RM literature (i.e., approximately one-half standard deviation improvement relative to didactically learned conditions). There were no interactions between group and self-generation condition on any PM outcomes, suggesting that this approach to enhancing PM is comparably effective among persons with and without HIV disease and comorbid MA use disorders. To our knowledge, this study represents the first hypothesis-driven attempt to improve PM performance using self-generation in healthy adults as well as clinical populations.
In the RM literature, self-generation is thought to deepen the encoding of the information to be remembered thereby rendering it more easily recalled and recognized after a delay. Extending this established RM notion to PM cue-intention pairings, we hypothesized that self-generating the PM cue would enhance encoding at the intention formation stage of McDaniel & Einstein’s Multiprocess Theory of PM, which would in turn ease the burden on strategic processes utilized for cue monitoring and enhance the likelihood that cue detection and intention execution will be successful. Overall results from this study provided mixed support for this overarching hypothesis and will be reviewed in detail below. Indeed, many findings from this study suggest that when a self-generated PM cue appears, it was more easily identified as a target cue that triggered an intended action. The increased cue detection post-monitoring phase and subsequent PM task performance on self-generated cues relative to didactic cues is certainly consistent with a picture of enhanced encoding, as is improved performed on strictly RM-based recognition memory tasks for self-generated cues.

The magnitude of the generation effect in the basic and clinical tasks were small-to-medium for the recall component (basic Hedge’s $g=0.36$, clinical Hedge’s $g=0.28$) and medium for the recognition component (basic Hedge’s $g=0.44$, clinical Hedge’s $g=0.53$). As previously stated, these effects are comparable to what is commonly found across the literature, as per a recent meta-analysis (Bertsch et al., 2007), in which the average effect size for free recall tasks across studies was Cohen’s $d=0.32$, and $d=0.46$ for recognition tasks. Furthermore, effects were broadly consistent given the within-subjects nature of these two tasks ($d = 0.50$), as well as types of self-generated mechanisms used (i.e., generating words based on the same category [$d=0.41$], synonyms [$d=0.41$], word fragments [$d=0.37$]) and other aspects of task design (i.e., retention of learned cue 1 minute to 1 day [$d=0.41$]). The consistency of these effects with the broader literature
is heartening in that it extends the generation effect into an area of episodic memory which holds great bearing on everyday functioning and could benefit from the validation of novel, cost-effective, and easily-implemented interventions. Additionally, this comparability to existing literature demonstrates the robustness of the generation effect, in that it appears to be portable to novel task designs. Beyond the mechanics and paradigm of task, it should be noted that the Bertsch meta-analysis analyzed studies that were performed solely on healthy adults, with the lone discussion of population differences restricted to older (k=18) versus younger (k=427) adults. In light of self-generation effects being largely restricted to college-aged samples, establishing utility in clinical populations, for whom cognitive interventions may be necessary to support independent daily living, is an important endeavor. The present study further expands upon work in RM performed in HIV infection, TBI, MS, and aging to comorbid HIV and MA dependence.

Interestingly, however, the magnitude of the generation effect observed in the PM tasks in this study were approximately half of that observed in prior work on generation of RM in HIV (Weber et al., 2011). In this study, self-generation was associated with retrospective memory delayed recall and recognition benefits that were on average one full standard deviation greater than for didactically learned items using a word pair completion paradigm. While this previously observed effect was notably higher relative to effects typically found in the literature and may represent sampling or methodological differences that yield its findings relatively atypical, it still raises the question of what may have produced a relatively diminished (albeit normative) effect in the present study. In particular, the application of self-generation to a PM paradigm highlights the relative complexity of the intact PM process. By their nature, PM tasks include a combination of cognitive processes, with intact RM required (i.e., remembering
content of what must be observed [cue] in order to perform a given task [intention]) as well as separable strategic components needed to monitor for the PM cue and initiate the PM intention (i.e., “PM proper” components; Graf & Uttl, 2001). McDaniel and Einstein also take care to note that the steps involved in PM task performance all involve a combination of strategic and automatic processes. So while self-generation appears to assist with encoding the PM cue (i.e., acting on the RM component of the task) and supporting cognitive resources to be used for PM proper subcomponents (e.g., cue monitoring) such that other tasks may be performed more efficiently (i.e., ongoing task), it may not be sufficient to fully support the relatively increased cognitive load required to fulfill the strategic PM components of these tasks, relative to the simpler RM task. One possible example of this paradigm discrepancy is that the effect of self-generation was somewhat more robust on the recognition component of these tasks relative to the recall component, in which PM processes were required. Nevertheless, self-generation appears to enhance overall performance of the PM task across multiple strata of McDaniel and Einstein’s Multiprocess Theory, without requiring direct interventions on PM proper processes (e.g., direct monitoring interventions). This is consistent with data from other studies demonstrating that interventions designed to improve RM components (e.g., imagery) may still yield an improvements in PM accuracy (Kardiasmenos et al., 2008).

Furthermore, it is important to recognize that PM tasks essentially require two separate RM components (i.e., memory for PM cue and memory for content of intention). The present study chose to manipulate the PM cue rather than the PM intention (or both), primarily for reasons of generalizability and ecological validity. Although the self-generation literature demonstrates robust effects in RM on the content of the material to be remembered (i.e., PM intention), this would be largely unhelpful in rehabilitating PM
deficits since it is typically the intention that is the most permanent aspect of the cue-intention pairing compared to the often more flexible cue. For example, if an individual is required to take a given medication in the evening, they would not be able to generate that part of the intention, since it is essential that the medication be taken as prescribed. However, they would be able to generate the cue (e.g., after dinner, beginning of a TV show) more easily without harming the integrity of the medication taking behavior. The current study provides some evidence that the PM intention may require less cognitive support and is more robust than the PM cue in this regard. Even without self-generation intervention on the PM intention, there were few occurrences of individuals who made task substitution errors (i.e., performing incorrect PM intention; basic task: 0%; clinical task: 16% of participants made at least 1 task substitution error, evenly divided across HIV/MA groups), relative to those forgetting to perform the intention when presented with the PM cue (basic task: 99%, clinical task: 86% of participants made at least 1 omission error, evenly divided across HIV/MA groups). This highlights the importance of supporting processes that are relatively more strategic (i.e., cue monitoring) in these populations, rather than those that may be more automatic (i.e., intention recall) in this population.

With self-generation thus providing additional support to the encoding process that enable PM cue detection, we hypothesized that fewer strategic resources would be necessary for individuals to monitor for and correctly identify the PM cue. In other words, self-generation may free up cognitive resources used in monitoring for the PM cue under normal conditions to instead be allocated to the ongoing task. In the basic task overall, reaction times on test blocks with a PM component were significantly slower relative to baseline (i.e., lexical decision-making task only) test blocks, suggesting that the cognitive energy that would have been funneled toward ongoing task speed are
subsumed by other processes (e.g., cue monitoring) when a PM intention is online. Between the two PM test blocks, individuals had quicker reaction times to the lexical decision-making trials during self-generated encoding test blocks compared to their reaction times during didactically-encoded test blocks. Taken together, this suggests that, while performing the PM task within the self-generated condition, participants were able to redistribute cognitive resources away from the PM task (given the enhanced support from self-generation) toward the ongoing task, resulting in quicker response times. This finding is consistent with other literature utilizing similar PM paradigms, in which ongoing task reaction time is a commonly cited and well-validated metric that quantifies effects of strategic process support from task manipulations. One such example is Woods and colleagues’ recent work (2014), in which PM task importance was manipulated to encourage participants to shift attention resources toward and away the PM task relative to the ongoing task. As in the present study, a quicker response to ongoing task trials in intervention conditions (i.e., high PM task importance) suggest that overall cognitive processes during the monitoring phase of McDaniel & Einstein’s model of PM are aided and can present as speeded processing on the non-PM task (in addition to enhanced PM task performance). It should be noted, however, that the magnitude of this impact was considerably larger (effect size difference = 0.44 between PM blocks) relative to our study (effect size difference = 0.18 between PM blocks), which may be due to the relatively more direct attempt to manipulate strategic processes (e.g., cue monitoring).

However, cost analysis of the ongoing task in the clinical PM experiment did not show the same benefits of self-generation as were observed on the basic PM experiment. While calculating differences in PM task reaction time has been often used in basic PM paradigms to gauge effectiveness of task manipulations on strategic resources, this study was the first to our knowledge to attempt to extend this approach to
a more demanding, multi-determined clinical task. There are several possible reasons why costs analyses observed on basic tasks may not extend to a more complex clinically-oriented task. First, the clinical PM task utilized a significantly more macro approach to calculating performance (i.e., total mazes completed), especially relative to the fine-grained nature of reaction time as used in the basic PM task. Second, the completion of mazes requires speed dependent on accuracy (i.e., participants were not allowed to progress to the next maze until they had successfully completed the current maze), whereas the structure of the basic PM task allowed speed and accuracy variables to be assessed independently. In the basic PM task, only the reaction time variable yielded a self-generation effect across encoding conditions, whereas lexical decision-making accuracy did not. Therefore, the absorption of newly available cognitive resources secondary to self-generation may be only applicable to more automatic and basic components of the ongoing task. Third, the ongoing task in the clinical PM paradigm was not designed to be equivalent to that in the basic PM paradigm and therefore had other dissimilar characteristics (i.e., problem-solving, visual, non-computerized, longer, fewer) that may have prevented the task from yielding self-generation effects on the ongoing task, as has been established in the basic task. As such, while it is possible that an effect yielded from self-generating PM cues may have been able to occur in a more clinically oriented PM task, task design may have precluded its measurement. Future research may seek to determine whether a more fine-grained approach to the ongoing task in this test may reveal evidence of attentional resource reallocation, or whether that cognitive energy is absorbed into other aspects of the task (e.g., enhanced PM intention retention) and its environment (e.g., greater awareness of test-taking environment, ongoing analysis of performance).
Despite the above-described multiple lines of support for the hypothesis that the process by which self-generation enhances PM performance occurs through cue encoding and support of strategic mechanisms, analysis of the neurocognitive correlates of self-generation benefits were largely null. Although we hypothesized that the degree to which one can benefit from self-generation would be related to more strategically-driven cognitive domains (e.g., executive functions, working memory, verbal fluency), the self-generation difference scores in the within-subject tasks were not correlated with these cognitive abilities in the clinical sample. In fact, throughout all PM tasks, there were no statistically significant relationships between benefit from self-generation and other neurocognitive functions. Within the context of applying self-generation to RM, verbal fluency ability has been cited as a significant factor that is associated with increased benefit from self-generation in HIV infection (Weber et al., 2011). Most other studies have simply examined correlates of self-generated recall performance, which unsurprisingly are associated with episodic memory ability (e.g., O'Brien et al., 2007), but recent work by Goverover and colleagues (2014) found support for our hypothesis in an MS sample, in which self-generation “responders” had better executive functioning performances. The multifactorial nature of PM (i.e., dependent on both strategic and automatic neurocognitive abilities) may be dissipating the strength of any one particular factor (i.e., multiple small components from several cognitive abilities) that cannot be detected given the statistical power of the present study. Beyond the discussion of what may be expected for the true neurocognitive nature of self-generation benefit, the broader recruitment and assessment structure of the current study may have negatively impacted the prospect of significant findings. Specifically, the comprehensive neurocognitive battery was not performed at the same assessment as the self-generation PM battery, given the necessity of recruiting eligible individuals once they
had completed their parent HNRP visit. As such, most participants’ associated neurocognitive data is at least a month removed from their self-generation visit. Given that test-retest reliability of many neurocognitive tests assessing fluid neurocognitive abilities is typically in the moderate range depending on domain (e.g., Dikmen et al., 1999), it is certainly possible that assessments over time may not yield congruent relationships that may have existed if assessments were concurrent. The lone exception to this pattern of non-significance was the enhanced self-generation effect in neurocognitively impaired individuals in the basic PM task, as described below.

Thus, in total, findings provided mixed evidence for the overarching hypothesis that self-generation may improve PM by deepening encoding of the PM cue and therefore alleviating burden on strategic resources required for monitoring and cue detection. Of course, there are other potential theoretical implications of these findings, although we unfortunately were unable to directly test them. For example, an alternate interpretation would be offered by selective displacement rehearsal theory (Slamecka & Katsaiti, 1987), which posits that individuals opt to use greater encoding resources and subsequent mental rehearsals of the items on self-generated items compared to didactic items. This finding is typically strongest in mixed encoding conditions (compared to blocked encoding conditions), whereby self-generated items to be learned occur alongside didactic items, and so the “displacement” of rehearsal resources is more salient. Although, this theory could be tested within the paradigms used in the present study, the use of mixed encoding conditions often yields worse overall performance (despite greater generation effect), and so such an endeavor may sacrifice clinical utility.

With regard to the clinical implications of these data, an important focus of approaches to improving cognition such as self-generation must be its efficacy within populations who need it most. Specifically, neurocognitive impairment is often
associated with poorer functional outcomes, and such individuals could arguably experience greater generalized benefit from compensatory strategies across multiple spheres of everyday life. Unfortunately, many internal cognitively driven compensatory strategies, self-generation included (e.g., moderate-severe Alzheimer’s disease; Dick et al., 1989), are unsuitable for neurocognitively-impaired populations due to the requirements for intact functioning on which those interventions rely (e.g., self-generation requiring intact verbal fluency ability). As such, the second aim of this study was to assess the applicability of the intervention to individuals with neurocognitive impairment in the clinical samples, as a substantial number of individuals with HIV and MA dependence present with global neurocognitive impairment. Within the present samples, approximately 30% of our HIV+MA- sample and 46% of our HIV+MA+ were globally impaired on a comprehensive battery of neuropsychological tests administered at a previous visit. A significant interaction between impairment and encoding condition was observed in the basic PM task, such that impaired individuals showed a stronger generation effect relative to their unimpaired peers. In fact, the impaired HIV+ individuals performed significantly worse than their unimpaired counterparts on the didactic portion of the task (Hedge’s $g=0.62; \ p=0.018$) but were then virtually indistinguishable in their performances when their PM cues were self-generated (Hedge’s $g=0.07; \ p=0.741$). This finding highlights not only the efficacy of self-generation for PM in HIV-infected individuals with neurocognitive impairment, but extends to suggest that it may improve performance in these individuals even beyond the performance level of unimpaired HIV+ individuals without intervention (Hedge’s $g=0.27$). (Of note, our hypothesis regarding normalization of scores to the level of HIV-seronegative participants was unable to be tested in each PM task, given the non-significant differences between groups.) This enhanced generation effect was not found across other aspects of the basic PM task
(i.e., recognition) or any primary outcome measures in the clinical PM task. Although not as powerful as what was observed on the basic PM recall component, the lack of an interaction between impairment and encoding condition is encouraging in that neurocognitively impaired individuals are able to benefit as much as their unimpaired counterparts from the effects of self-generation. The ability of these HIV-infected participants to benefit from self-generation in PM is broadly consistent with the literature regarding the use of self-generation in RM in other clinical populations, such that it is most impactful in healthy individuals ranging to mild and moderate cognitive deficits (e.g., HIV infection, Weber et al., 2011; multiple sclerosis, e.g., Chiaravalloti & DeLuca, 2002; traumatic brain injury, e.g., O’Brien, Chiaravalloti, Arango-Lasprilla, Lengenfelder, & DeLuca, 2007; mild dementia, e.g., Lipinska, Bäckman, Mäntylä, & Viltanen, 1994).

Beyond neurocognitive variables, no exploratory analyses with regard to HIV disease, MA use, psychiatric, or demographic factors yielded significant relationships with benefit from self-generation in the basic and clinical PM tasks. While this may be due in part to the assessment structure as described in the Methods, it is common for weak, inconsistent associations to be observed between disease severity and neurocognitive outcomes in both HIV infection and addictions. Within HIV disease, many disease indicators are often only marginally related to neurocognitive abilities, with the exception of historically poor immune functioning (i.e., nadir CD4, AIDS diagnosis; e.g., Heaton et al., 2011). Similarly, within MA dependence, substance use characteristics are most often self-report and remote in nature, relying upon the individuals’ accurate memory to report specific aspects of their use. This is particularly problematic given the neurocognitive effects of many of these substances on memory encoding during the periods that the individual is asked to later recall (i.e., being asked to remember amount of substance used while they were under the influence). One factor that tends to be
more reliable in its prediction of neurocognitive abilities is recency of use or period of abstinence (e.g., Iudicello et al., 2010). However, in the present MA+ sample, individuals were only required to have met criteria for MA dependence in their lifetime, and so we may have been unable to find significant MA-related findings due to the temporal distance from participants’ last MA use (approximately 4.5 years prior to testing). Indeed, there were no significant group or interaction findings throughout any of the PM tasks. While it is possible that this remote use and other factors (e.g., lower rates of AIDS) may have contributed to our MA+ sample being less representative of the HIV-infected MA-using population, they appear consistent with MA samples in the literature in other ways (e.g., higher rates of neurocognitive impairment and depression).

Most importantly, the lack of group by encoding condition interactions suggests that there is no differential generation effect within our samples, thereby speaking to this intervention’s broad applicability across individuals in the HIV and MA population. This is consistent with what has been generally found with self-generation in clinical samples with mild to moderate neurocognitive impairment (e.g., TBI, MS) as well as our prior study of RM in HIV infection. Moreover, that study did not find substance use to be a relevant factor in self-generation benefit (Weber et al., 2011), and our preliminary study in HIV+ substance users showed comparable generation effects to our comparison and HIV+ non-substance-using sample. This study represents the first attempt to explore the use of self-generation in a substance use population and thereby lends evidence to its potential effectiveness in adults with history of MA use. The utility of self-generation for a population such as HIV-infected MA users is important for a multitude of reasons. MA dependence has been implicated in exacerbating HIV-related cognitive impairment (e.g., Rippeth et al., 2004) and functional dependence (Blackstone et al., 2013). Specifically, frontal systems are preferentially affected (albeit in non-overlapping ways compared to
HIV; Marquine et al., 2014), and so cognitive interventions designed to support executive deficits and their effects on other cognitive domains would be particularly applicable to this group. Such literature on neurocognitive deficits in HIV-infected substance users has begun to pave the way for applicable interventions to treat functional deficits. For example, translational intervention studies have demonstrated improved PM performance in this population when PM task importance is emphasized, thereby allowing participants to appropriately reallocate cognitive resources (Woods et al., 2014).

In order to increase the ecological validity of such work, such efforts may be applied to behavioral outcomes in the future (e.g., highlighting relative importance of medication taking compared to daily tasks occurring at the time of ideal adherence).

Although relatively more statistically subtle than its basic and clinical PM task counterparts, the naturalistic PM task also demonstrated a potential effect of self-generation. Participants randomized to the self-generated condition performed 32% better on the task relative to their didactic condition counterparts (didactic condition mean=1.1; self-generated condition mean 1.45), but given the relatively high variability in scores (didactic SD=1.91; self-generated SD=2.70) and halved sample size relative to within-subjects designs, statistical tests failed to yield significant findings for the task as a whole. However, a pattern emerged when the task was analyzed longitudinally within the HIV+ group as a whole, such that HIV-infected adults in the self-generated encoding condition had higher task scores (relative to individuals in the didactic condition) as temporal distance from the task assignment increased. In other words, it appears that self-generation may have allowed the PM task to persist in these individuals' memory, such that they were better able to remember to perform the task in the latter weeks of the assignment (three and four weeks from task instruction), yielding at least a medium effect. This demonstrates that self-generation can be efficacious outside of the
laboratory, in situations less well-controlled and subject to numerous other competing factors. With this example of an observable generation effect in a naturalistic setting, stronger implications may be made for the potential utility of self-generation to improve real-world outcomes, given this closer step to ecological validity. For instance, a close parallel to this task would be to assist patients in remembering the day or time when they must call a pharmacy for a refill, or to check regular lab results.

It should be noted that the response rate for the naturalistic task was quite low, albeit consistent with published literature using similar tasks (e.g., Zogg et al., 2010). One primary difference between this task and the laboratory tasks is the use of self-generation in time-based prospective memory relative to event-based prospective memory. Although the event-based tasks used in this study required a significant amount of strategic processing (i.e., non-focal cues, unrelated cue-intention pairings) relative to other event-based PM tasks, time-based PM tasks are more consistently reliant on strategic processes, particularly monitoring of time. Given the lack of a standardized ongoing task in the naturalistic experiment, we are unable to determine whether self-generation may have freed up cognitive resources that could be reallocated to strategic processes, rather than simply enhancing the RM component of the PM cue. The vast majority of errors in this task were errors of omission, not commission, suggesting that those who were able to remember to perform the task likely did so correctly. Indeed, the naturalistic PM task also utilized a particularly robust form of self-generation for part of the PM cue: calculation. In the broader literature, using calculation to generate the item to be remembered is associated with a large effect size (Cohen’s $d=0.92$; Bertsch et al., 2007).

Beyond the direct impact of self-generation on these tasks, many hypotheses have arisen in the PM literature regarding the characteristics of individuals who
remember to complete such tasks in and out of the laboratory setting, which should be considered when interpreting this data. Most notably, older age is one of the more commonly cited factors as a protective characteristic for naturalistic PM performance. The “age / prospective memory paradox” describes the phenomenon in which older adults are more likely to be impaired on laboratory tests of PM, but tend to perform naturalistic PM tasks at comparable or higher rates than their younger counterparts (Rendell & Thomson, 1999). This paradox has been explored in normal aging (e.g., Rendell & Thomson, 1999) as well as a handful of clinical populations (e.g., Raskin et al., 2011), including HIV infection (Weber et al., 2011). Indeed, age was the most robust predictor of naturalistic PM performance across all samples (HIV-: Spearman’s rho = 0.43, \( p=0.47 \); HIV+: Spearman’s rho = 0.34, \( p=0.008 \)), above and beyond any impact of self-generation; no interaction with self-generation was observed. Several hypotheses have been raised as to why this discrepancy exists, including personality characteristics common in older adults (e.g., increased conscientiousness; Patton & Meit, 1993), increased use of compensatory strategies (e.g., Maylor, 1990), and decreased busyness and/or increased lifestyle structure (e.g., Schnitzspahn et al., 2011). Testing these hypotheses within the present clinical sample, greater daily routine did indeed predict naturalistic task performance (Spearman’s rho = 0.27; \( p=0.034 \)), even with age as an independent predictor in the statistical model. These simultaneous significant and trend-level findings suggest that it is not solely routine that may account for the age benefit on naturalistic PM tasks, and that other factors, included those mentioned above, may also play independent roles beyond manipulations like self-generation.

Outside of these factors, we also assessed individuals’ confidence that they would remember to perform the PM task. Unlike other experiments in which meta-cognition ratings are designed to assess the individual’s confidence in the ability to
perform such a task, this instance is unique in that it also may have tapped into the individual’s *intention* to perform the task, given its occurrence outside the bounds of the laboratory session. As such, it is not surprising that a significant correlate of naturalistic task performance in the clinical sample was their confidence rating (Spearman’s rho=0.34; \( p=0.009 \)), regardless of encoding condition (\( p=0.329 \)). It should also be noted that this rating might have also served a bidirectional purpose. While it is likely that participants may have rated themselves as highly likely to perform the task based on confidence in their abilities to perform such tasks and their intention to follow these instructions, there may also have been individuals who were overconfident in their innate abilities and therefore increased the strength of their intention, thereby causing a self-fulfilling prophecy. This is consistent with other PM research suggesting that individuals can moderate their PM performance based on task importance (i.e., examiner suggesting that the PM task has more relative importance compared to the ongoing task, or that it is personally meaningful to the examiner; e.g., Woods et al., 2014, Kvavilashvili & Ellis, 1996).

This study is not without its limitations. First, while the tasks used to assess the viability of self-generation in a PM paradigm are based on commonly-used, valid, and reliable PM tasks and principles, they were all altered from originally validated formats for the purposes of this dissertation study. As such, they have largely untested reliability and validity in their altered states. Unfortunately, no other validated tests of PM were administered during this assessment, therefore preventing analyses of construct validity. At face value, however, these tasks follow the basic structure of their parent tasks, and primary results are generally consistent with performance in those tasks’ published research in HIV-infected samples (basic: e.g., Loft et al., 2014; clinical: e.g., Carey et al., 2006; naturalistic: e.g., Zogg et al., 2010).
With these altered tasks (and as is an issue with their parent tasks), their use has been largely restricted to the experimental realm and therefore do not have published normative data, to which individuals’ results can be compared. The use of a HIV-seronegative comparison group was utilized to provide a basis for comparison of scores; however, no group differences were found across tasks. The lack of a group effect may have occurred for several reasons. First, these tasks were primarily designed to assess cognitive mechanisms of a complex neurocognitive construct rather than provide discriminative validity, as is the case with many commonly used neuropsychological tests validated for clinical practice as well as research. Second, our analyses may have been underpowered to detect the level of group difference that we would have expected in these populations, in which affected individuals tend to have mild neurocognitive deficits. Indeed, these analyses were powered to medium to large effect sizes between groups, and at least large effect sizes for interaction effects. An increased sample size within each group may have assisted in sharpening this signal. Beyond the statistical implications, it is also possible that these three samples were more alike than not. For instance, we sought to recruit an HIV-seronegative comparison sample, rather than a “healthy adult” sample, for maximal generalizability and specification of an HIV effect. As such, this sample had greater neurocognitive impairment (26.7%) and diagnosis of MDD (36.4%) than would be expected in the general healthy population of HIV-seronegative adults. Despite this potentially leading to the lack of a group finding, it provides further encouraging evidence that self-generation may be efficacious in adults with psychiatric illness and neurocognitive impairment, even without the context of HIV infection. On the other end of the recruitment continuum, our HIV+MA+ contained many individuals with long-standing sobriety and may therefore have experienced some degree of neural recovery from the damaging effects of MA use by the time they were assessed.
Additionally, many of these individuals had histories of dependence on other substances in addition to MA, and so the neurocognitive pattern observed may have been altered to due effects of those other substances. The decision to extend beyond current and recent MA users was made to protect statistical power with regard to increased sample size; however, this may have reduced the expected effect, therefore dampening power. Indeed, while all three groups appear to be different in terms of relevant discriminative characteristics, specifically neurocognitive impairment (HIV-MA-: 26.7%, HIV+MA-: 30.3%, HIV+MA+: 46.2%), this finding was not statistically significant. Conceptually, this scenario may have borne out in some of the primary PM tasks as well.

While the present study yields promising results that self-generation of a PM cue may indeed increase the likelihood that the PM intention will be carried out in the future, it also suggests that other methods used to enhance encoding of a PM cue or intention may also produce similar effects. Self-generation was chosen as the intervention of choice in this dissertation study primarily due to its prior validation in HIV infection in RM contexts, but other approaches not yet validated in HIV or MA dependence may ultimately be equally or more effective. A look to the social psychology literature reveals the potential utility of implementation intentions to enhance encoding of both the PM cue and intention via verbalization. It has been noted that stronger intentions (e.g., “I must do x”) are related to greater probability of a performed action. Additionally, identifying more specific intentions that specify how/when/where to achieve a given goal has been more successful in producing behavior change. Research on implementation intentions in healthy populations has demonstrated that by placing the emphasis of the PM task off of the self and onto the relationship between a situation and an action (e.g., “when situation x arises, I will perform response y”), a more concrete mental connection can be formed that is more easily accessible and automatized (Gollwitzer, 1999). The use of
implementation intentions has been explored in multiple sclerosis as a method by which to improve PM performance in a neurocognitively impaired population (Kardiasmenos et al., 2008). Another analog of this method is the use of directed visualization, although it has been hypothesized that this may be automatically occurring within implementation intentions paradigms as well (Kardiasmenos et al., 2008). By asking an individual to visualize themselves performing the PM task when presented with the PM cue, it is possible that encoding of that cue-intention pairing is enhanced, thereby supporting strategic processes needed for monitoring, allowing for better overall performance of the task. These two variations on similar theme of enhancing intentions and strengthening cue-intention pairings also allow for versatility across individuals and populations with varying levels of verbal vs. visual deficits.

Beyond the strict encoding benefit of self-generation on the PM cue, it would be worth exploring whether a more freeform and participant-driven version self-generation would be even more effective. At face value, it seems quite obvious that if an individual were to generate his/her own cue to perform a task, they would naturally remember that cue better because it was something they chose; in other words, it would have been relatively more meaningful to them. Indeed, this concept has utilized in one study to our knowledge, although self-generation of the PM cue or task was not the central mechanism of interest in the study (i.e., authors examined participants’ abilities to remember to perform self-generated PM tasks based on spontaneous mental rehearsals of that information; Szarras et al., 2011). The authors highlight the literature on task importance and personal relevance, suggesting that individuals may have more motivation to perform tasks if they are more connected to it or feel that is it worthwhile (e.g., Kliegel et al., 2001). As the present study has established the non-personalized effect of self-generation on prospective remembering, future research may seek to
explore any additional benefits in performance from full self-generation of the PM cue, thereby benefitting from a range of other variables (e.g., significance, personalization, ease). Furthermore, other mechanisms of self-generation that have shown greater overall efficacy than word-pair completion alone (e.g., calculation; Bertsch et al., 2007) should be examined in greater detail.

Another approach to improving PM in HIV and MA would be to directly support the processes requiring the most strategic (and impaired) processing, specifically, cue monitoring. The need for improvement was particularly salient during the clinical PM task. Although a generation effect was still observed, the most frequent error across encoding conditions was an error of commission, which qualitatively appeared to be driven by poor monitoring and inability to disengage from the ongoing task. In fact, 69% of participants had at least one trial during which the examiner coded that they appeared to have missed the occurrence of the PM cue (i.e., flipping over the cue cards on the table in front of them for two seconds); this finding was consistent across HIV/MA groups (HIV-MA-: 72.7%, HIV+MA-: 66.7%, HIV+MA+: 67.9%). The clinical PM task sought to bridge the translational gap from a single paradigm platform (i.e., PM task embedded within a computerized ongoing task) and the messiness of everyday life (i.e., PM task likely highly separate and temporally removed from life’s ongoing activities), by separating the content and context of the ongoing task from the PM task, albeit still on one tabletop in an examination room. It was at this step where the increased need for monitoring enhancement was already palpable.

Within both the PM and clinical literature, several avenues for monitoring interventions have been explored. For instance, Fish et al. (2007) extended goal management principles often utilized with executive dysfunction to content-free cueing to promote PM task adherence. Participants with non-progressive brain injury received text
messages with a cue word to remind them of their PM task. They used the mnemonic “STOP” (Stop-Think-Organize-Plan), which they had taught participants at baseline in order to allow them to prepare to execute the given task. By texting this cue word without content of the PM task, participants with brain were better able to remembering to perform a PM task on cued days relative to days in which they did not receive this cue. Such research mimics clinical recommendations often prescribed in neuropsychological evaluations, telling participants to set alarms to remind them of tasks they need to perform. While Fish’s paradigm enhanced the strength of this content-free cue by encouraging preparation for PM task execution, considerable benefit may be seen just from external or environmental monitoring strategies alone. Within the context of HIV infection and MA use, applying these strategies to medically relevant outcomes (e.g., medication adherence) could be a simple yet powerful intervention to improve health.

Finally, use of a combination of numerous strategies to enhance PM functioning at various levels of McDaniel & Einstein’s model of PM may be the most efficacious for populations such as HIV and MA dependence, in which failures in strategic may occur across multiple aspects of PM task performance. For example, a PM cue may be more deeply encoded using self-generation, the cue-intention pairing enhanced through visualization and implementation intentions, and external cueing provided to encourage monitoring for PM cue recognition and task execution. This comprehensive approach may provide more support for individuals with a greater range of deficits and thereby increase the likelihood of improving PM functionality across a range of populations.

The present dissertation study marks the first extension of self-generation to prospective memory in both healthy individuals and clinical populations. Across a translational range and populations, self-generation enhanced PM task performance in recall and recognition components of the task, theoretically by supporting necessary
strategic processes. Within the HIV-infected and MA dependent populations, such interventions are necessary to improve PM, an integral aspect of episodic memory that is strongly associated with everyday functioning outcomes. Expansion on the current research should seek to extend these findings beyond laboratory mechanisms to test the effectiveness of self-generation in improving real-world outcomes (e.g., enhancing medication adherence by asking individual to generate the cue by which they remember to take their prescriptions).

Drs. Woods, Grant, Gilbert, Twamley, and Mattson are co-authors on this section of the manuscript, which will be prepared for publication.
Table 1. Participant demographic, psychiatric, MA use, and HIV disease characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIV-MA- (n=22)</th>
<th>HIV+MA- (n=33)</th>
<th>HIV+MA+ (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.7 (15.0)</td>
<td>52.7 (12.5)</td>
<td>45.8 (8.0)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.5 (2.2)</td>
<td>14.1 (3.1)</td>
<td>87.9%</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>77.3%</td>
<td>87.9%</td>
<td>92.9%</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)*</td>
<td>36.4%</td>
<td>66.7%</td>
<td>71.4%</td>
</tr>
<tr>
<td>Estimated premorbid IQ</td>
<td>102.9 (11.8)</td>
<td>103.5 (14.3)</td>
<td>101.9 (11.2)</td>
</tr>
<tr>
<td>Neurocognitive impairment (%)</td>
<td>26.7%</td>
<td>30.3%</td>
<td>46.2%</td>
</tr>
<tr>
<td><strong>Psychiatric characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Depressive Disorder * ^1</td>
<td>36.4%</td>
<td>54.6%</td>
<td>85.7%</td>
</tr>
<tr>
<td>MA Dependence * ^1</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Non-MA Substance Dependence * ^1</td>
<td>9.1%</td>
<td>21.2%</td>
<td>67.9%</td>
</tr>
<tr>
<td><strong>MA use characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first MA use (years)</td>
<td>--</td>
<td>--</td>
<td>21.7 (7.8)</td>
</tr>
<tr>
<td>Total days used MA</td>
<td>--</td>
<td>--</td>
<td>2225.3 (2433.8)</td>
</tr>
<tr>
<td>Days since last MA use</td>
<td>--</td>
<td>--</td>
<td>1656.4 (2880.4)</td>
</tr>
<tr>
<td><strong>HIV disease characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIDS (%)</td>
<td>--</td>
<td>75.0%</td>
<td>48.2%</td>
</tr>
<tr>
<td>Duration of infection (years) ^2</td>
<td>--</td>
<td>15.6 (4.0, 25.6)</td>
<td>11.0 (5.2, 20.9)</td>
</tr>
<tr>
<td>Current CD4 ^2</td>
<td>--</td>
<td>584 (330, 798)</td>
<td>661 (442, 868.5)</td>
</tr>
<tr>
<td>Nadir CD4 ^2</td>
<td>--</td>
<td>105.5 (61, 273)</td>
<td>200.5 (29.8, 408.5)</td>
</tr>
<tr>
<td>Detectable viral load * (%) ^3</td>
<td>--</td>
<td>7.4%</td>
<td>36.0%</td>
</tr>
<tr>
<td>cART (% prescribed)</td>
<td>--</td>
<td>100.0%</td>
<td>92.6%</td>
</tr>
</tbody>
</table>

Note: * p<0.05. ^1Met criteria for DSM-IV diagnosis over lifetime. ^2Median (interquartile range). ^3Subset of individuals prescribed cART
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