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Detrimental Impact of Remote Methamphetamine Dependence on Neurocognitive and Everyday Functioning in Older but not Younger HIV+ Adults: Evidence for a Legacy Effect?

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Abstract

Prior studies examining the combined adverse effects of HIV and methamphetamine (MA) on the central nervous system (CNS) have focused on younger to middle-aged adults with recent MA use diagnoses. Aging, HIV, and MA all converge on prefrontal and temporolimbic neural systems and confer independent risk for neurocognitive and functional decline. Thus, this study sought to determine the residual impact of a remote history of MA dependence on neurocognitive and real-world outcomes in older people living with HIV (PLWH). Participants included 116 older (≥ 50 years) and 94 younger (<40 years) adults classified into one of six study groups based on HIV serostatus (HIV+/HIV-) and lifetime histories of MA dependence (MA+/MA-): Older HIV-MA- (n=36), Older HIV+MA- (n=49), Older HIV+MA+ (n=31), Younger HIV-MA- (n=27), Younger HIV+MA- (n=33), and Younger HIV+MA+ (n=34). No participant met criteria for current MA use disorders and histories of MA dependence were remote in both the Older (average of nearly 9 years prior to evaluation) and Younger (average of over 2 years prior to evaluation) HIV+MA+ groups. Findings revealed that a remote history of MA dependence exerts a significant detrimental impact on specific aspects of neurocognitive performance (e.g., memory) and a broad range of real-world functioning outcomes (e.g., employment) among Older, but not Younger PLWH. These results suggest that MA-associated neurotoxicity may have significant “legacy” effects on both neurocognitive and functional outcomes to which older PLWH are particularly vulnerable.

Keywords

Aging; HIV-associated neurocognitive disorders; Substance use; Neuropsychology; Disability; Comorbidities

Introduction

The past decade has witnessed notable increases in the incidence and prevalence of older persons living with HIV (PLWH; e.g., May & Ingle, 2011). A growing body of evidence suggests that older PLWH are at greater risk for adverse central nervous system (CNS)

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CONFLICTS OF INTEREST

The authors, Drs. Jennifer E. Iudicello, Erin E. Morgan, Assawin Gongvatana, Scott Letendre, Igor Grant, and Steven Paul Woods, declare that they have no conflict of interest.

injury relative to both younger- and middle-aged PLWH and their older seronegative counterparts. HIV and aging have independent adverse structural and functional effects on the CNS, and in combination, are associated with additive neural injury, primarily within the frontostriatal and temporolimbic systems (Chang et al., 2005; Langford et al., 2011). High rates of neurocognitive impairment (NCI) have also been observed in older PLWH, particularly those with more advanced disease (e.g., Valcour et al., 2004; cf. Valcour et al., 2011). The most prominent neurocognitive deficits in older PLWH are typically observed in episodic memory and executive functions (Woods et al., 2010). However, the underlying biopsychosocial mechanisms of NCI in older PLWH are not fully understood. Given the clinically relevant associations between NCI and adverse real-world outcomes (e.g., dependence in activities of daily living; Morgan et al., 2012) and poorer health-related quality of life (HRQoL; Rodriguez-Penney et al., 2013) in older PLWH, there is a clear need for research aimed at identifying and remediating risk factors for NCI in this highly affected and growing subpopulation of the epidemic.

Toward that end, recent efforts have been focused on role of various HIV-associated non-AIDS (HANA) comorbid conditions in the increased prevalence of NCI in older PLWH. For example, older PLWH have significantly higher rates of medical comorbidities that have been linked with HIV-associated NCI (e.g., vascular disease, Becker et al., 2009). While active substance use is less frequent amongst older PLWH relative to their younger and middle-aged counterparts, lifetime histories of substance use disorders (SUD) are nevertheless very common among older PLWH (Morgan et al., 2011) and therefore represent a particularly prevalent HANA condition in PLWH that may worsen the clinical course of HIV, including augmentation of HIV-associated neural injury and NCI (Gannon et al., 2011). Importantly, lifetime SUD history may exert long-term effects on brain structure and function (e.g., Fama et al., 2010; cf. Byrd et al., 2011) that could increase vulnerability to future CNS complications.

Methamphetamine (MA) is one of the most commonly abused substances by PLWH, and chronic MA use may directly (e.g., increased viral replication; Ellis et al., 2003) and indirectly (e.g., nonadherence; Hinkin et al., 2007) confer additional risk for poorer HIV health outcomes (e.g., Carrico, 2011). Studies on the combined effects of HIV and MA on the CNS have found increased inflammation and viral replication (e.g., Gavrilin et al., 2002; Letendre et al., 2005), reduced blood brain barrier integrity and function (Mahajan et al., 2008), as well as neurodegeneration and altered brain metabolism, particularly in frontostriatal regions (Chana et al., 2006; Chang et al., 2005). Consequently, high rates of NCI are also found in HIV+ MA-dependent individuals, particularly in the areas of learning and memory, attention, and motor skills (e.g., Rippeth et al., 2004), which can be observed in the setting of recent infection (Weber et al., 2013). Moreover, the NCI associated with comorbid HIV and MA plays a major role in disability among persons with early (Doyle et al., 2013) and chronic (Blackstone et al., 2013) HIV infection. Chronic MA use among PLWH also has a negative public health impact given that MA use is a significant risk factor for HIV transmission (Buchacz et al., 2005).

While this body of research provides strong evidence of the combined adverse effects of HIV and MA on the CNS, existing studies have focused on younger and middle-aged adults who are recent MA users. To our knowledge, no studies have evaluated the effects of chronic MA use among older PLWH, who may be particularly vulnerable to its detrimental effects on brain structure and function. Indeed, aging, MA, and HIV infection converge on prefrontal and temporolimbic neural systems and affect associated executive and memory abilities (Hedden & Gabrieli, 2010; Scott et al., 2007; Woods et al., 2009). One plausible hypothesis is that a history of chronic MA use exerts more damaging effects on neurocognitive and real-world functions in older PLWH than it does in younger PLWH.

Alternatively, it is possible that the adverse effects of MA and aging on NCI are temporally independent and therefore quite modest in older PLWH. It is widely known that the lifetime prevalence of MA use is lower among older adults and that, like with other illicit substances, active MA use decreases with older age (Substance Abuse and Mental Health Services Administration, 2012). Thus, older PLWH are likely to have used MA in their 30s and 40s. This means that at least partial neural (Volkow et al., 2001) and neurocognitive (Iudicello et al., 2010) recovery with sustained abstinence may have occurred, in which case the observable residual effects of MA on NCI in older PLWH would be minimal. With these two competing hypotheses in mind, this study aimed to determine whether a history of chronic MA use exerts a particularly detrimental effect on neurocognitive and real-world functioning outcomes in older versus younger PLWH.

Methods

Participants

This study retrospectively identified 116 older (> 50 years of age) and 94 younger (< 40 years of age) individuals enrolled in an NIMH-funded R01 examining the neurocognitive effects of HIV and aging at the HIV Neurobehavioral Research Program (HNRP) at the University of California, San Diego (UCSD). All subjects were recruited from the local community and clinics. HIV status was determined by either by enzyme linked immunosorbent assays (ELISA) and a Western Blot confirmatory test, or MedMira Multiplo rapid test (MedMira Inc., Nova Scotia, Canada). Exclusion criteria included histories of neurological conditions (e.g., seizure disorders, head injury with loss of consciousness greater than 30 minutes) or psychiatric disorders (e.g., schizophrenia) that could impact neurocognitive performance, a premorbid verbal IQ estimate below 70 as determined based on the Wechsler Test of Adult Reading (WTAR; The Psychological Corporation, 2001), a substance abuse or dependence disorder diagnosis within 30 days of evaluation, or a positive urine drug screen (UDS) for drugs of abuse or Breathalyzer test for alcohol on the day of evaluation.

Participants were classified into one of three groups based on HIV serostatus (HIV+ or HIV-) and lifetime history of MA dependence (i.e., MA+ or MA-) as determined by the Composite International Diagnostic Interview (CIDI, World Health Organization, 1998), using criteria as determined by the DSM-IV (American Psychiatric Association, 1994). This approach yielded a total of 6 study groups, which included 46 Older HIV-MA-(OH-MA-), 49 Older HIV+MA- (OH+MA-), 31 Older HIV+MA+ (OH+MA+), 27 Younger HIV-MA- (YH-MA-), 33 Younger HIV+MA- (YH+MA-), and 34 Younger HIV+MA+ (YH+MA+). Note that, for the MA- groups, we excluded individuals who met criteria for lifetime alcohol and substance dependence as determined by the CIDI. Below we describe the clinical characteristics of the Older and Younger study cohorts separately. Descriptive data regarding the prevalence of abuse diagnoses across the older and younger groups are displayed in Tables 1 and 2, respectively.

Clinical Characteristics for the Older Study Samples (See Table 1)—The OH+MA+ group was significantly younger, less educated, and had lower premorbid verbal IQs as compared to the OH-MA- and OH+MA- study groups ($p < 0.05$). Relative to the OH-MA-, the two older HIV+ groups had higher proportions of lifetime affective disorders, substance abuse, and comorbid conditions ($p < 0.05$). The OH+MA-group had a slightly higher proportion of individuals who tested positive for prescription drugs that might influence cognition (e.g., benzodiazapines) relative to the other samples ($p < 0.10$). Regarding HIV disease characteristics, the OH+MA+ sample had shorter estimated durations of

infection and lower current CD4 counts ($p < 0.05$) relative to the OH+MA- group; other disease or treatment variables did not differ ($p > 0.10$).

Clinical Characteristics for the Younger Study Samples (See Table 2)—The YH+MA+ group was significantly older, and had higher rates of lifetime non-MA substance abuse as compared to the remaining study samples, and had higher proportions of contributing comorbidity ratings relative to the YH-MA- group ($p < 0.05$). Relative to the YH-MA- group, both younger HIV+ groups were less educated, and had higher proportions of males and lifetime affective disorders ($p < 0.05$). The YH+MA+ group had fewer individuals with positive prescription UDSs on the day of testing relative to the YH+MA- group, and higher rates of non-MA substance abuse disorders relative to both the remaining groups ($p < 0.001$). The YH+MA+ group had a higher proportion of AIDS diagnoses as compared to the YH+MA- group ($p < 0.05$), but did not differ on other HIV disease and treatment characteristics ($p > 0.10$; See Table 2).

HIV Disease Characteristics for the Older versus Younger HIV+ Groups—As compared to the younger HIV+ groups, the older HIV+ groups had longer durations of infection, lower nadir CD4 counts, higher proportions of AIDS, and were older at the time of HIV diagnosis ($p < 0.05$), though were comparable for all other HIV disease and treatment characteristics ($p > 0.10$).

Substance Use Characteristics for the Older and Younger H+MA+ Groups—MA dependence and other non-MA substance use characteristics for the MA+ study groups are displayed in Table 3. Relative to the YH+MA+ group, the OH+MA+ group was older when they first met criteria for MA dependence ($p < 0.001$), and were significantly older at the time of their most recent MA dependence diagnosis (i.e., $p < 0.001$). The older and younger H+MA+ groups did not differ in the duration of MA dependence diagnoses ($p > 0.10$). On average, the YH+MA+ group's last MA dependence diagnosis was more recent relative to the OH+MA+ group (2.6 versus 8.8 years; $p < 0.01$). The YH+MA+ group had higher rates of lifetime alcohol and sedative dependence ($p < 0.05$) and a slightly smaller proportion of individuals with lifetime cocaine dependence ($p < 0.10$) relative to the OH+MA+ group.

Materials and Procedures

This study was approved by UCSD's Human Research Protections Program. Each participant provided written, informed consent and underwent a comprehensive medical, psychiatric, neurocognitive, and functional assessment.

Medical and Psychiatric Evaluation

The medical evaluation included an assessment of comorbid conditions common in HIV, MA, and aging that might impact cognitive functioning (e.g., cardiovascular disease, learning disorders, hepatitis C virus) and was used to derive a Comorbidity Rating in accordance with current research criteria for HAND (Antinori et al., 2007). The Comorbidity Rating was assigned to each participant by a clinical neuropsychologist (SPW) blind to neurocognitive status to indicate whether the comorbidity burden was "incidental" or "contributing" (see Heaton et al., 2011). Lifetime Affective Disorder diagnoses were determined using the CIDI (World Health Organization, 1998), and included Major Depressive Disorder, Generalized Anxiety Disorder, and/or Panic Disorder diagnoses.

Neurocognitive Assessment

Each participant was administered a comprehensive neurocognitive evaluation which included an estimate of premorbid intellectual functioning (Wechsler Test of Adult Reading, WTAR; The Psychological Corporation, 2001) alongside a neuropsychological test battery that assessed cognitive ability domains commonly affected by HIV, MA and aging. The domains and neuropsychological tests included in each domain are as follows: (1) *Learning*: Total Learning Trials 1–5 from the California Verbal Learning Test – Second edition (CVLT-II; Delis et al., 2000) and Logical Memory I from the Wechsler Memory Scale – Third Edition (WMS-III; Psychological Corporation, 1997); (2) *Memory*: CVLT-II Delayed Free Recall and WMS-III Logical Memory II; (3) *Attention*: Digit Span subtest from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Psychological Corporation, 1997) and Trial 1 from the CVLT-II; (4) *Executive Functions*: Total Move Score from the Tower of London (ToL) – Drexel (Culbertson & Zilmer, 2001), Action Fluency (Woods et al., 2005b), and Trail Making Test (TMT) Part B (Reitan & Wolfson, 1985); (5) *Speed of Information Processing (SIP)*: ToL – Drexel Total Execution Time and TMT Part A; and (6) *Motor Skills*: dominant and nondominant hand total scores from the Grooved Pegboard test (Kløve, 1963).

Raw scores on the neurocognitive tests were converted to demographically corrected T-scores to minimize the effect of demographic factors using the best available published normative standards, which correct for age, education, sex, and ethnicity, as appropriate (Heaton et al., 2004; Norman et al., 2011; Woods et al., 2005b), and used to create neurocognitive domain T-scores and a global T-score. Individual T-scores were also converted to deficit scores ranging from 0 (no impairment) to 5 (severe impairment) and averaged to create a global deficit score (GDS; Carey et al., 2004). The global and domain T-scores and the GDS were used for analyses (see below).

Everyday Functioning Assessment

The everyday functioning outcome assessment included self-report measures assessing performance in basic and instrumental activities of daily living, cognitive symptoms, and employment. Basic and instrumental activities of daily living were assessed using a modified version of the Lawton & Brody Activities of Daily Living Scale (Lawton & Brody 1969), which asks participants to rate their current level of functioning on five basic ADLs (BADLs; i.e., laundry, dressing, bathing, housekeeping, home repairs) and 11 instrumental ADLs (IADLs; medication management, shopping, grocery shopping, managing finances, transportation, understanding reading and television material, planning social activities, cooking, child care, and work functioning). Participants were classified as BADL or IADL dependent (i.e., impaired) if they reported current difficulties in two or more BADLs or IADLs, respectively. This cutoff is recommended by Heaton et al. (2004), who, upon examination of the distributions of 168 neuropsychologically normal individuals on this scale determined that increased dependence on two or more of the aforementioned areas of functioning was relatively rare, and occurred in fewer than 10% of those cases. In addition, these are the criteria for determination of functional impairment in neurological and psychiatric disorders according to the DSM-IV. Self-reported everyday cognitive symptoms were assessed using the Confusion/Bewilderment subscale of the Profile of Mood States (POMS; McNair et al., 1981), which is a 65-item self-report measure of current affective distress. Raw scores on the Confusion/Bewilderment Scale were converted to age and gender-corrected scores (Nyenhuis et al., 1999) and converted to z-scores for standardization purposes. Individuals with a z-score greater than or equal to 1 were classified as impaired. Employment status (i.e., employed, unemployed, retired, disability) was determined via clinical interview. Individuals who were unemployed or on disability were classified as impaired for this domain.

For the primary functional outcome analyses, an Overall Functioning Composite score was calculated for each participant by summing the total number of domains in which he/she was classified as impaired (range 0–4; see Blackstone et al., 2013).

Statistical analyses were conducted using JMP 10.0.2 statistical software (SAS; Cary, NC) and the critical alpha for analyses was set at 0.05.

Results

Effects of MA on Neurocognitive Performance in the Older Groups (See Table 4)

A series of separate multiple linear regressions were conducted in the Older sample to examine the association between HIV/MA risk group (OH-MA-, OH+MA-, and OH+MA+) and neurocognitive performance (i.e., global and individual neurocognitive domain T-scores) while controlling for potentially confounding factors (i.e., Comorbidity Rating, diagnoses of affective disorder or lifetime non-MA substance abuse, and prescription UDS status). Although age and education also differed between the older groups, these variables were not included as covariates since the neurocognitive outcome variables were normatively corrected for these two characteristics. Note that, inclusion of age and education in the models nevertheless did not alter the primary findings.

Results of the multiple linear regression analyses in the Older groups revealed significant overall models for global neurocognitive performance and for the individual neurocognitive domains of learning, memory, attention, executive functions, and motor ($p < 0.05$; See Figure 1 and Table 4), but not for information processing speed ($p > 0.10$). HIV/MA risk group emerged as a significant predictor in each of the significant models ($p < 0.01$). Planned follow-up pairwise comparisons revealed that the OH+MA+ had lower global T-scores relative to both the OH+MA- and OH-MA- groups ($p < 0.05$; Cohen's $d = 0.48$ and 1.01 , respectively). The OH+MA- also had lower global T-scores relative to the OH-MA- group ($p < 0.05$; Cohen's $d = 0.51$). Regarding individual neurocognitive domains, the OH+MA+ group demonstrated significantly poorer performance within the domains of learning and memory relative to the other groups ($p < 0.01$), and had significantly worse T-scores for the attention and motor domains relative to the OH-MA- group ($p < 0.05$). A trend level finding was observed for worse performance within the executive functions domain in the OH+MA+ group relative to the OH-MA- group ($p = 0.072$, Cohen's $d = 0.43$). The OH+MA- sample had significantly worse attention T-scores ($p < 0.05$) relative to the OH-MA- group, and trend-level differences were observed for worse T-scores within the learning, memory, and motor domains ($p < 0.10$; See Figure 1).

Effects of MA on Neurocognitive Performance in the Younger Groups

A similar series of regression analyses were conducted in the younger groups to determine whether MA history was a significant predictor of demographically adjusted global and individual neurocognitive domain T-scores while accounting for confounding factors, including Comorbidity Rating, lifetime affective disorder or non-MA substance abuse disorders, and prescription UDS status. In contrast to the results observed within the older groups, the overall regression model predicting global T-score in the younger group was not significant ($F[6, 86] = 1.53$; $p = 0.177$). A significant regression model was observed for learning T-scores ($F[6, 86] = 2.31$; $p = 0.040$), though not for any of the other individual neurocognitive domains ($p > 0.05$). Risk group emerged as a significant predictor of the learning T-score among the younger groups ($p = 0.020$), whereby the YH+MA- sample performed worse than the younger YH-MA- group ($p = 0.007$, Cohen's $d = 0.84$).

Effects of MA on Functional Impairment in the Older Groups

Next, a multiple linear regression was conducted within the Older group to explore the effects of HIV/MA risk group (OH-MA, OH+MA-, and OH+MA+) on overall functional impairment (as indexed by the Overall Functioning Composite), while accounting for NCI (i.e., global deficit score), Comorbidity Rating, lifetime affective and non-MA substance abuse disorders, and prescription UDS status. Demographic variables that differed amongst the Older groups (i.e., age, education) were also included in this model to account for the fact that, unlike for the neurocognitive analyses described above, the functional variables are not demographically-corrected. This overall model was significant ($p<0.001$; See Table 5). HIV/MA risk group was a significant predictor of functional impairment ($p=0.025$), such that the OH+MA+ group had greater impairment relative to both the OH+MA- and OH-MA- groups (Cohen's d s=0.40 and 1.21, respectively; $ps<0.01$). Approximately 90% of the OH+MA+ group was functionally dependent in at least one area, relative to 74% of the OH+MA- and 47% of the OH-MA- group (see Figure 2).

Frequency of impairment within each specific functional domain, including BADLs, IADLs, perceived everyday cognitive symptoms, and employment for the three older groups are displayed in Figure 2. Within the older group, HIV/MA risk group emerged as a significant predictor of IADL impairment ($p=0.038$; model $F[9, 104]=5.10$, Adjusted $R^2=0.25$, $p<0.001$) and unemployment ($p=0.028$; model $\chi^2=38.18$; $p=0.004$), and approached significance in the model predicting BADLs ($p=0.077$; model $F[9, 104]=2.91$, Adjusted $R^2=0.13$, $p=0.004$). Both older HIV+ groups had higher proportions of IADL impairment and unemployment relative to the older unaffected group (OH-MA-; $ps<0.05$). For BADLs, the OH+MA+ group had higher rates of impairment relative to the other groups ($ps<0.05$).

Effects of MA on Functional Impairment in the Younger Groups (See Table 5)

The multiple linear regression analyses conducted in the Younger groups examining HIV/MA risk group as a predictor of global functional impairment (i.e., the Overall Functioning Composite) while accounting for confounding factors (as described above for the Older cohort) was significant ($F[10, 82]=3.02$; Adjusted $R^2=0.18$; $p=0.003$). Predictors of global functional impairment within the Younger cohort were older age, lower education, and having a lifetime affective disorder diagnosis ($ps<0.05$; See Table 5). MA risk group was not a significant contributor to this model ($p>0.10$). Similarly, each of the overall regression models predicting dependence in the individual functioning domains were significant ($ps<0.05$), though HIV/MA risk group was once again not a significant predictor of any of domain.

Relationships between clinical characteristics, NCI, and functional decline

Correlational analyses conducted separately in the OH+MA+ and YH+MA+ groups examining associations between MA dependence characteristics and neurocognitive and functional outcomes revealed a significant association between an earlier age at onset of MA dependence and poorer Global T-scores (Spearman's $\rho=0.41$; $p=0.023$) in the Older (but not Younger) groups. No other MA dependence characteristics were significantly associated with neurocognitive or functional impairment in either study groups ($ps>0.10$). Correlational and chi-square analyses conducted within the older group revealed no significant associations between HIV disease characteristics and global neurocognitive and functional outcomes (all $ps>0.10$).

Discussion

Although aging, MA and HIV disease all converge on prefrontal and temporolimbic neural systems, the impact of MA on NCI in older PLWH had not previously been characterized. In

this study, we found significant detrimental effects of remote MA dependence on overall neurocognitive performance in older PLWH. These medium-to-large MA effects were independent of potentially influential cofactors, including lifetime affective and non-MA substance abuse disorders, prescription drug use, and other common comorbidities (e.g., HCV, vascular disease). Of note, remote history MA dependence did *not* exert similar effects in the younger cohort.

Learning and memory appear to be particularly vulnerable among older HIV+MA+ individuals, who also showed deficits within the domains of auditory attention, fine motor skills, and to a lesser extent, executive functions (e.g., visual planning, verbal fluency, divided attention). Collectively, the domain-specific impairments observed in the older HIV+MA+ individuals are consistent with the neurocognitive domains and underlying neural circuits (i.e., frontostriatal and temporolimbic systems) that are affected in aging, MA, and HIV (e.g., Ances et al., 2011; Volkow et al., 2001). Of clinical relevance, impairment in these domains, and in memory in particular, are consistently linked to everyday functioning problems in HIV, MA, and aging (e.g., Hinkin et al., 2002; Weber et al., 2012; Cahn & Weiner, 2002), thus are an even greater concern in older prior MA-using PLWH. The larger effects on learning versus delayed recall in this study suggest that the memory profile may be one of poor encoding rather than rapid forgetting. This interpretation is consistent with research showing that aging, HIV, and MA are characterized by deficient strategic (i.e., executive) but not automatic processes involved in encoding and retrieval (Gongvatana et al., 2007; Morgan et al., 2012; Woods et al., 2005a), which is consistent with underlying frontostriatal neuropathogenesis. Older prior MA using PLWH may therefore benefit from learning and applying specific targeted neurocognitive mnemonic strategies (e.g., visualization) in their daily lives.

Interestingly, the speed of information processing (SIP) domain was not significantly affected by remote MA use among our older PLWH, which is somewhat surprising since SIP deficits are hallmarks of all three risk conditions (e.g., Reger et al., 2002; Scott et al., 2007; Verhaeghen & Salthouse, 1997). However, these studies also note that age- and HIV-associated SIP deficits accelerate after age 50 (Verhaeghen & Salthouse, 1997) and worsen with HIV disease progression (Reger et al., 2002), respectively. Since the older prior MA-using HIV+ sample was on average about 54 years old and relatively healthy, they may not yet have experienced the decline that might occur at older ages and more advanced disease stages. Moreover, evidence suggests that SIP abilities may be more amenable to recovery following extended periods of MA abstinence (Iudicello et al., 2010; Volkow et al., 2001) relative to other domains, in which deficits appear to be more longstanding (e.g., memory and executive functions; McCann et al., 2008). Thus, this may suggest some degree of recovery of simple processing speed from MA-associated neurotoxicity following cessation of MA use. Future studies may evaluate this question with more detailed measures of both cognitive and motor processing speed, including experimental reaction time paradigms.

The striking effects of remote MA use on neurocognitive functioning in older PLWH are particularly concerning given the consistent links between neurocognitive impairment and everyday functioning outcomes independently in MA and HIV, as well as in older PLWH (Hinkin et al., 2004; Iudicello et al., 2012b; Weber et al., 2012). Indeed, findings from this study demonstrate significant overall functional impairment in older HIV+ with remote MA histories across a broad range of daily activities (i.e., basic and instrumental activities of daily living, perceived everyday cognitive problems, and employment). In fact, over twice as many individuals in the older prior MA using HIV+ group reported impairment on at least one of the four functional domains relative to the older HIV seronegative non-MA using comparisons. Akin to the neurocognitive findings, the effect of remote MA use among the older PLWH was independent of important cofactors, including psychiatric and other

substance use disorders. In contrast, within the younger groups, we observed the expected HIV effects on functional outcomes, but no apparent moderating of remote MA dependence. This suggests that a remote history of active MA use may be particularly detrimental to everyday functioning in older versus younger HIV+ individuals. This extends our previous research showing that both age (Morgan et al., 2012) and MA (Blackstone et al., 2013) can independently exacerbate HIV-associated disability across a variety of everyday life activities.

There are several possible explanations for the observed effect of remote MA dependence on neurocognitive and functional outcomes in older, but not younger HIV+ adults. One explanation is that the findings reflect a “legacy” effect of MA-associated neurotoxicity, akin what has been found for low nadir CD4+ T-cell counts as a risk factor for NCI in HIV (e.g., Ellis et al., 2011). Consistent with this notion, we observed that an earlier age at first MA dependence diagnosis was associated with poorer overall neurocognitive performance in the older group. It is possible that early CNS damage due to MA-associated neurotoxicity may cause damage that may be particularly resistant to recovery and possibly further compounded with aging. Relatedly, it is possible that older HIV+ individuals may not recover as effectively as younger adults from MA-associated neurotoxicity. In support of this possibility, very recent data from our group found significant correlations between NCI and abstinence in individuals who stopped using early in life, but not in those who stopped using later (Cattie et al., 2013). These preliminary data highlight a significant impact of MA on the CNS that may persist into old age and may be particularly resistant to recovery in older HIV+ adults.

While we did not find significant associations between HIV disease characteristics and our neurocognitive and functional outcomes, other HIV disease indicators may have greater utility in detecting injury and disease progression (e.g., CD8+ T-cell counts, CD4/CD8 ratios). Increased CD8 T-cell migration – particularly effector memory cells – into the brain has been linked to neurocognitive impairment in HIV (Johnson & Nath, 2011; Lescure et al., 2013) and has been found in both MA and aging populations, indicating a possible role in neurocognitive impairment during cART. Lastly, MA- and HIV-associated CNS disturbances may be exacerbated by common comorbid conditions (e.g., non-MA substance use disorders), or by age-related vulnerabilities (e.g., vascular and metabolic disease), which are common (e.g., Guaraldi et al., 2011; Kilbourne et al., 2001; Magalhães et al., 2007), may occur at earlier ages in older PLWH (Onen et al., 2010) and have been linked to neurocognitive impairment, functional declines, and poorer health related quality of life (e.g., Becker et al., 2009; Foley et al., 2010; Morgan et al., 2012; Rodriguez-Penney et al., 2013; Valcour et al., 2004). Even more problematic is that many of these medical comorbidities (e.g., vascular disease) are also common among MA users (e.g., Buttner, 2011; Polesskaya et al., 2011), thus their expression in older HIV+ MA dependent individuals may have an even more substantial impact on the brain, which would be consistent with our findings demonstrating associations between both contributing comorbidity ratings and non-MA substance use disorders and poorer overall neurocognitive performance.

A number of limitations of this study are worth noting. First, we did not assess a sample of older HIV seronegative individuals with remote histories of MA dependence, which are necessary to draw firm conclusions regarding the specificity of the HIV effect in the context of remote MA use in older adults. Second, our sample sizes are relatively small, and our older HIV+ samples are relatively young compared to traditional aging studies. However, despite the size and age range of the sample, robust effects of prior MA use were observed older HIV+ participants. Third, as mentioned above, detailed MA use characteristics (e.g., route and total quantity of use, last use of MA) were also not available in this sample and

would have been informative with regard to questions of abstinence or pattern of remote MA use. Lastly, this analysis was cross sectional in design, which limits interpretation regarding the directionality of causal effects and prevents a detailed examination of factors that may have contributed to decline over time (e.g., HIV disease progression, MA relapse, development of age-related illness). Longitudinal studies would provide valuable insight into the legacy effects of MA in this population and potentially remediable mechanisms underlying neurocognitive and functional decline.

In conclusion, these results provide preliminary evidence to suggest a significant impact of remote MA use on neurocognitive and functional outcomes in older HIV+ adults. These findings are of clinical concern, particularly given the increasing prevalence of older PLWH with lifetime substance use disorders, and suggest that efforts to prevent, detect, and remediate such difficulties are warranted. Prior studies indicate that among older PLWH, those with a history of stimulant dependence are less likely to spontaneously use effective strategies (e.g., chunking) during cognitively demanding tasks (Woods et al., 2010). Thus, they may benefit from the provision of structured empirically supported compensatory approaches (e.g., simple mnemonics) to improve performance in the laboratory (e.g., Iudicello et al., 2012a). There is also preliminary evidence to suggest that PLWH with these risk factors may benefit from neurocognitive rehabilitation (see Weber et al., 2013a). Thus, a thorough understanding of the profile of neurocognitive impairment in this high-risk population represents the first step in developing targeted, more effective rehabilitation strategies that may improve neurocognitive abilities, everyday functioning, and health-related outcomes.

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Figure 1.

Global neurocognitive performance (i.e., mean Global T-scores) among the older groups (OH-MA-, OH+MA-, and OH+MA+) relative to the younger study samples (YH-MA-, YH+MA-, and YH+MA+), and mean neurocognitive domain T-scores for the older study groups.

Figure 2. Global functional impairment among the older groups (OH+MA+, OH+MA-, OH-MA-) relative to the younger study samples (YH+MA+, YH+MA-, and YH-MA-), and proportions of impairment within the older samples on individual functional domains.

Table 1
Demographic, medical, psychiatric, and substance use characteristics of the older study groups.

	Older Groups (n=116)			p	Group Differences*
	H-MA- (n=36)	H+MA- (n=49)	H+MA+ (n=31)		
Demographic Variables					
Age (years)	57.1 (5.0)	57.3 (5.9)	53.9 (3.2)	0.009	H+MA+ < H+MA-, H+MA-
Education (years)	15.0 (2.6)	15.2 (2.3)	13.7 (2.4)	0.018	H+MA+ < H+MA-, H+MA-
Gender (% male)	69.4%	85.7%	80.7%	0.256	-----
Ethnicity (% Caucasian)	66.7%	81.6%	71.0%	0.191	-----
Estimated Premorbid Verbal IQ	106.3 (9.6)	105.8 (10.5)	100.2 (10.6)	0.028	H+MA+ < H+MA-, H+MA-
HIV Disease Variables					
Age at Diagnosis (years) ^a	-----	38.3 (32.3, 45.4)	26.1 (2.6, 29.1)	0.673	-----
Duration of HIV Disease (years) ^a	-----	20.5 (15.2, 23.8)	15.9 (4.6, 21.4)	0.035	H+MA+ < H+MA-
AIDS Status (% AIDS)	-----	63.3%	67.7%	0.682	-----
cART Status (% on)	-----	89.8%	93.6%	0.555	-----
Nadir CD4+ T-cell count (cells/ε) ^a	-----	170.0 (50.0, 260.0)	120.0 (54.0, 236.0)	0.686	-----
Current CD4+ T-cell count (cells/ε) ^a	-----	584.0 (426.0, 818.5)	458.5 (325.0, 595.5)	0.013	H+MA+ < H+MA-
Plasma HIV RNA VL (% < 50c/mL on ART)	-----	79.5%	89.7%	0.242	-----
Medical Variables					
Comorbidity Rating (% contributing)	19.4%	63.3%	58.1%	<0.001	H+MA+, H+MA- > H+MA-
Prescription UDS Status (% positive)	13.9%	31.3%	12.9%	0.070	NS
Psychiatric/Substance Use Variables					
LT Affective Disorder (%)	36.1%	63.3%	74.2%	0.004	H+MA+, H+MA- > H+MA-
LT Non-MA Substance Abuse (%)	13.9%	26.5%	64.5%	<0.001	H+MA+ > H+MA-, H+MA-
LT Cannabis Abuse (%)	11.1%	24.5%	38.7%	0.028	H+MA+ > H+MA-
LT Alcohol Abuse (%)	25.0%	34.7%	22.6%	0.434	-----
LT Cocaine Abuse (%)	0.0%	2.0%	9.7%	0.070	H+MA+ > H+MA-
LT Opioid Abuse (%)	0.0%	0.0%	12.9%	0.004	H+MA+ > H+MA-, H+MA-
LT Sedative Abuse (%)	0.0%	0.0%	22.6%	<0.001	H+MA+ > H+MA-, H+MA-

	Older Groups (n=116)			<i>p</i>	Group Differences [*]
	H-MA- (n=36)	H+MA- (n=49)	H+MA+ (n=31)		
LT Other Substance Abuse (%)	5.6%	10.2%	32.3%	0.007	H+MA+ > H+MA-, H-MA-

Note. Values are mean (standard deviation) unless otherwise noted.

^a Median (interquartile range).

^{*} $p < 0.05$. NS > 0.10.

UDS = Urine drug screen.

Table 2

Demographic, medical, psychiatric, and substance use characteristics of the younger study groups.

	Younger Groups (n=94)			p	Group Differences*
	H+MA- (n=27)	H+MA- (n=33)	H+MA+ (n=34)		
Demographic Variables					
Age (years)	29.7 (4.4)	31.7 (4.1)	33.9 (4.9)	0.002	H+MA+ > H+MA-, H+MA-
Education (years)	15.1 (2.4)	12.9 (2.0)	12.4 (1.7)	<0.001	H+MA+, H+MA- < H+MA-
Gender (% male)	55.6%	84.9%	91.2%	0.003	H+MA+, H+MA- > H+MA-
Ethnicity (% Caucasian)	37.0%	33.3%	50.0%	0.349	-----
Estimated Premorbid Verbal IQ	102.9 (10.8)	98.5 (12.8)	103.4 (9.2)	0.160	-----
HIV Disease Variables					
Age at Diagnosis (years) ^a	-----	26.1 (22.6, 29.1)	38.3 (32.3, 45.4)	0.491	-----
Duration of HIV Disease (years) ^a	-----	4.0 (2.2, 8.6)	4.3 (2.9, 11.5)	0.387	-----
AIDS Status (% AIDS)	-----	27.3%	50.0%	0.055	-----
cART Status (% on)	-----	78.8%	88.2%	0.294	-----
Nadir CD4+ T-cell count (cells/εl) ^a	-----	250.0 (144.5, 383.0)	233.0 (134.5, 441.8)	0.841	-----
Current CD4+ T-cell count (cells/εl) ^a	-----	544.0 (409.0, 760.8)	584.0 (363.0, 855.3)	0.700	-----
Plasma HIV RNA (% < 50c/mL on ART)	-----	92.0%	78.6%	0.163	-----
Medical Variables					
Comorbidity Rating (% contributing)	11.1%	27.3%	44.1%	0.014	H+MA+ > H+MA-
Prescription UDS Status (%)	11.1%	39.4%	12.1%	0.009	H+MA- > H+MA+, H+MA-
Psychiatric/Substance Use Variables					
LT Affective Disorder (%)	18.5%	72.7%	73.5%	<0.001	H+MA+, H+MA- > H+MA-
LT Non-MA Substance Abuse (%)	14.8%	9.1%	55.9%	<0.001	H+MA+ > H+MA-, H+MA-
LT Cannabis Abuse (%)	14.8%	6.1%	17.7%	0.306	-----
LT Alcohol Abuse (%)	22.2%	21.2%	23.5%	0.974	-----
LT Cocaine Abuse (%)	0.0%	3.0%	26.5%	<0.001	H+MA+ > H+MA-, H+MA-
LT Opioid Abuse (%)	0.0%	0.0%	17.7%	<0.001	H+MA+ > H+MA-, H+MA-
LT Sedative Abuse (%)	0.0%	0.0%	23.5%	<0.001	H+MA+ > H+MA-, H+MA-

	Younger Groups (n=94)			<i>p</i>	Group Differences [*]
	H-MA- (n=27)	H+MA- (n=33)	H+MA+ (n=34)		
LT Other Substance Abuse (%)	0.0%	0.0%	29.4%	<0.001	H+MA+ > H+MA-, H-MA-

Note. Values are mean (standard deviation) unless otherwise noted.

^aMedian (interquartile range).

^{*}*p*<0.05. NS > 0.10.

UDS = Urine drug screen.

Table 3

Lifetime MA dependence and non-MA abuse and dependence diagnoses for the older and younger HIV+ and MA+ groups

	Younger H+MA+ (n=34)	Older H+MA+ (n=31)	<i>p</i>
Lifetime MA Dependence Characteristics			
Age at first MA dx (years) ^a	23.0 (21.0, 28.3)	32.0 (25.0, 45.0)	<0.001
Age at most recent MA dx (years) ^a	31.0 (27.0, 37.0)	47.0 (40.0, 53.0)	<0.001
Span between diagnoses (years) ^a	5.5 (1.0, 11.0)	7.0 (1.0, 19.0)	0.392
Time since recent dx (years) ^a	1.0 (1.0, 3.3)	5.0 (1.0, 15.0)	0.008
Lifetime Non-MA Substance Use Disorders			
Cannabis Dependence (%)	38.2%	22.6%	0.169
Alcohol Dependence (%)	67.7%	41.9%	0.036
Cocaine Dependence (%)	23.5%	45.2%	0.065
Opioid Dependence (%)	20.6%	12.9%	0.406
Sedative Dependence (%)	23.5%	6.5%	0.049
Other Substance Dependence * (%)	11.8%	9.6%	0.786

Note. Values are mean (standard deviation) unless otherwise noted.

^aMedian (interquartile range).

* Other = PCP, Inhalants, Hallucinogens, Other

Table 4

Multiple linear regression analyses examining predictors of neurocognitive performance and functional impairment in the older study groups (OH-MA-, OH+MA-, OH+MA+).

	Adj R ²	F	Estimate	95% CI	p-value
Global T-Score	0.15	4.27	-----	-----	<0.001
HIV/MA Risk Group ^d			-----	-----	-----
H+MA-			-2.14	-4.87, 0.58	0.122
H+MA+			-6.22	-9.40, -3.04	<0.001
Comorbidity Rating [contributing]			-2.28	-4.62, 0.06	0.056
Affective Diagnoses [yes]			0.22	-2.15, 2.58	0.857
LT Non-MA Substance Abuse [yes]			2.70	0.18, 5.22	0.036
UDS Status [positive]			-1.25	-3.96, 1.46	0.362
Learning T Score	0.14	4.12	-----	-----	<0.001
HIV/MA Risk Group ^d			-----	-----	-----
H+MA-			-1.83	-6.23, 2.57	0.411
H+MA+			-9.17	-14.31, -4.04	<0.001
Comorbidity Rating [contributing]			-4.25	-8.03, -0.47	0.028
Affective Diagnoses [yes]			0.58	-3.24, 4.39	0.765
LT Non-MA Substance Abuse [yes]			2.08	-1.99, 6.15	0.314
UDS Status [positive]			-1.16	-5.34, 3.21	0.599
Memory T Score	0.12	3.52	-----	-----	0.003
HIV/MA Risk Group ^d			-----	-----	-----
H+MA-			-2.08	-6.24, 2.09	0.325
H+MA+			-7.86	-12.73, -3.00	0.002
Comorbidity Rating [contributing]			-3.79	-7.37, -0.20	0.038
Affective Diagnoses [yes]			1.15	-2.47, 4.76	0.531
LT Non-MA Substance Abuse [yes]			1.03	-2.82, 4.89	0.596
UDS Status [positive]			-2.03	-6.17, 2.11	0.333
Attention T Score	0.15	4.26	-----	-----	<0.001

	Adj R ²	F	Estimate	95% CI	p-value
HIV/MA Risk Group ^a			-----	-----	-----
H+MA-			-4.36	-8.38, -0.34	0.034
H+MA+			-9.05	-13.75, -4.36	<0.001
Comorbidity Rating [contributing]			-3.37	-6.83, 0.09	0.056
Affective Diagnoses [yes]			1.28	-2.21, 4.77	0.469
LT Non-MA Substance Abuse [yes]			5.09	1.37, 8.81	0.008
UDS Status [positive]			-0.24	-4.24, 3.76	0.905
Executive Functions T Score	0.06	2.19	-----	-----	0.049
HIV/MA Risk Group ^a					
H+MA-			-1.97	-5.60, 1.67	0.286
H+MA+			-5.75	-9.99, -1.51	0.008
Comorbidity Rating [contributing]			0.03	-3.10, 3.15	0.986
Affective Diagnoses [yes]			-0.03	-3.19, 3.12	0.983
LT Non-MA Substance Abuse [yes]			4.75	1.39, 8.11	0.006
UDS Status [positive]			-2.92	-6.53, 0.69	0.112
SIP T Score	0.01	0.81	-----	-----	0.563
HIV/MA Risk Group ^a			-----	-----	-----
H+MA-			-0.85	-4.63, 2.94	0.658
H+MA+			-0.90	-5.32, 3.52	0.687
Comorbidity Rating [contributing]			-0.11	-3.36, 3.15	0.948
Affective Diagnoses [yes]			-0.08	-3.36, 3.21	0.964
LT Substance Abuse [yes]			2.21	-1.29, 5.71	0.214
UDS Status [positive]			-3.14	-6.90, 0.63	0.101
Motor T Score	0.06	2.28	-----	-----	0.041
HIV/MA Risk Group ^a			-----	-----	-----
H+MA-			-0.77	-5.30, 3.75	0.735
H+MA+			-3.40	-8.68, 1.88	0.205
Comorbidity Rating [contributing]			-3.77	-7.64, 0.11	0.057
Affective Diagnoses [yes]			-1.05	-4.97, 2.87	0.598

	Adj R ²	F	Estimate	95% CI	p-value
LT Substance Abuse [yes]			-1.56	-5.74, 2.61	0.460
UDS Status [positive]			-2.01	-6.50, 2.48	0.376

^aNote. Reference group is H-MA-.

LT = Lifetime. UDS = Urine drug screen. SIP = Speed of information processing.

Table 5

Predictors of daily functioning impairment in older and younger groups.

	Adj R ²	F	Estimate	95% CI	p-value
OLDER GROUPS					
Overall Functioning Composite	0.32	6.99	-----	-----	<0.001
HIV/MA Risk Group ^d			-----	-----	-----
H-MA- [H+MA-]			0.32	-0.20, 0.85	0.229
H-MA- [H+MA+]			0.87	0.24, 1.50	0.007
Age			0.00	-0.04, 0.05	0.852
Education			0.03	-0.05, 0.12	0.441
Global Deficit Score			0.43	-0.15, 1.01	0.152
Comorbidity Rating [contributing]			0.47	0.01, 0.94	0.048
Affective Diagnoses [yes]			1.05	0.60, 1.50	<0.001
LT Non-MA Substance Abuse [yes]			-0.18	-0.66, 0.30	0.464
UDS Status [positive]			-0.05	-0.57, 0.48	0.864
YOUNGER GROUPS					
Overall Functioning Composite	0.18	3.01	-----	-----	0.002
HIV/MA Risk Group ^d			-----	-----	-----
H-MA- [H+MA-]			-0.24	-0.94, 0.46	0.490
H-MA- [H+MA+]			-0.05	-0.80, 0.70	0.886
Age			0.05	0.00, 0.10	0.034
Education			-0.12	-0.23, 0.00	0.045
Gender [female]			-0.24	-0.81, 0.33	0.410
Global Deficit Score			0.04	-0.55, 0.62	0.903
Comorbidity Rating [contributing]			-0.12	-0.63, 0.40	0.653
Affective Diagnoses [yes]			0.75	0.23, 1.26	0.005
LT Non-MA Substance Abuse [yes]			-0.26	-0.80, 0.29	0.355
UDS Status [positive]			0.24	-0.46, 0.94	0.490

^dNote. Reference group is H-MA-.