At the Intersection of Methamphetamine Use, Aging, and HIV Disease

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Does Drug Abuse Play a Role in Neurocognitive Outcomes in Older Persons with HIV Disease?

- HIV, aging, and the brain
- Drug abuse as a comorbidity in older HIV+
  - Methamphetamine (MA) use
- Preliminary data
  - Effects of MA use on neurocognitive and functional outcomes in younger and older HIV+
- Questions to guide future research
HIV and Aging Affect Overlapping Neural Circuits

Becker et al., 2012
HIV and Age Confer Additive Risk of Neurocognitive Impairment

% NP Impaired

Younger HIV-  Older HIV-  Younger HIV+  Older HIV+

PM Aging Cohort  HNRC Cohort

R01 MH073419 (Woods), P30 MH062512 (HNRC, Grant)
Comorbidities are Prevalent in Older HIV+ and May Influence the Age Effects on HAND

Rodriguez-Penney et al., 2013
Substance Disorders Are Prevalent in the Older HIV+ Population

Any Substance  Alcohol  Illicit Drug

Percent (%)

Any Disorder  Abuse  Dependence

N01 MH022005 (CHARTER; n=349)
Methamphetamine (MA) is a Common Illicit Drug of Choice in HIV

N01 MH022005 (CHARTER; n = 1,583)
Methamphetamine (MA)

- Highly potent and addictive psychostimulant
- MA use is highly prevalent
  - In the U.S., approximately 12 million individuals age 12 or older (~4.6%) have tried MA at least once in their lives (SAMHSA; 2012)
    - 439,000 (~0.2%) reported MA use in the past month
- MA is associated with numerous adverse public health outcomes (Gonzales et al., 2010)
  - Infectious disease transmission risk
  - Social, economic, and legal problems
  - Increased risk of morbidity and mortality
Chronic MA Use Adversely Affects CNS Structure and Function

Striatum

Neurocognitive Functions

Volkow et al., 2001; Scott et al., 2007
MA Enhances HIV-Associated Neural Injury (interneurons)

Calbindin

Parvalbumin

Chana et al., 2006
MA Use Increases Risk of Neurocognitive Impairment and Poorer Everyday Functioning

\[ \text{H-M}^-(n=60) \quad \text{H-M}^+(n=47) \quad \text{H+M}^- (n=50) \quad \text{H+M}^+ (n=43) \]

\[ \text{H-M}^-(n=217) \quad \text{H-M}^+(n=237) \quad \text{H+M}^- (n=155) \quad \text{H+M}^+ (n=189) \]

\[ *p < 0.01 \]

Rippeth et al., 2004; Blackstone et al., 2013
The Prevalence of Older Adults with MA Use Disorder Histories is Growing

Prevalence of Older HIV+MA+

HNRP NIDA Program Project and TMARC Cohorts

P01 DA012065 (NIDA Program Project); P50 DA026306 (TMARC)
MA Use Decreases With Older Age in HIV

![Graph showing MA use (%)]

- **MA Use (%)**
- **Age (years)**
  - <30
  - 30-39
  - 40-49
  - 50-59
  - 60+

- **Legend**
  - Yellow: Lifetime
  - Purple: Past 90 Days

*NO1 MH022005 (CHARTER; n=1,583)*
Recovery From MA Neurotoxicity is Possible With Extended Abstinence

Striatal Metabolism

Neurocognitive Impairment

Volkow et al., 2001; Iudicello et al., 2010
A Developmental Model of Aging With HIV and MA
A Preliminary Study: Participants

- 3 groups of ≥ 50 yo participants drawn from a UCSD HNRP R01 on aging and memory
  - Older HIV-/MA- (n=36)
  - Older HIV+/MA- (n=49)
  - Older HIV+/MA+ (n=31)
    • MA+ group met DSM-IV criteria for lifetime MA dependence

- 3 groups of ≤40 yo subjects drawn for comparison purposes
  - Younger HIV-/MA- (n=28)
  - Younger HIV+/MA- (n=34)
  - Younger HIV+/MA+ (n=34)
    • MA+ group met DSM-IV criteria for lifetime MA dependence
Study Exclusions

- Any current alcohol or other illicit substance use diagnoses
  » Positive breathalyzer or urine toxicology screen for illicit drugs on the day of evaluation
- Any lifetime alcohol or illicit substance dependence diagnoses in the non-MA+ groups
- History of confounding major medical (e.g., severe liver disease), neurologic (e.g., TBI, CVA), or psychiatric (e.g., schizophrenia) conditions
- Verbal IQ estimate of < 70
Demographic and Psychiatric Characteristics in Older Groups

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>H-M- (n=36)</th>
<th>H+M- (n=49)</th>
<th>H+M+ (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>57.1 (5.0)</td>
<td>57.3 (5.9)</td>
<td>53.9 (3.2)</td>
</tr>
<tr>
<td>Education (years)*</td>
<td>15.0 (2.6)</td>
<td>15.2 (2.3)</td>
<td>13.7 (2.4)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>69.4%</td>
<td>85.7%</td>
<td>80.7%</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>66.7%</td>
<td>81.6%</td>
<td>71.0%</td>
</tr>
<tr>
<td>Estimated Premorbid VIQ*</td>
<td>106.3 (9.6)</td>
<td>105.8 (10.5)</td>
<td>100.2 (10.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric Characteristics</th>
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</thead>
<tbody>
<tr>
<td>LT Major Depressive Disorder (%)*</td>
<td>33.3%</td>
<td>51.0%</td>
<td>71.0%</td>
</tr>
<tr>
<td>LT Generalized Anxiety Disorder (%)*</td>
<td>5.6%</td>
<td>16.3%</td>
<td>38.7%</td>
</tr>
<tr>
<td>LT Alcohol Abuse (%)</td>
<td>25.0%</td>
<td>34.6%</td>
<td>22.5%</td>
</tr>
<tr>
<td>LT Non-MA Substance Abuse (%)*</td>
<td>13.9%</td>
<td>26.5%</td>
<td>64.5%</td>
</tr>
</tbody>
</table>

*p < 0.05
## Substance Dependence Characteristics in Younger and Older HIV+ Groups

<table>
<thead>
<tr>
<th>MA Dependence Parameters</th>
<th>Younger H+M+ (n=34)</th>
<th>Older H+M+ (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis onset (years)*</td>
<td>24.1 (6.5)</td>
<td>34.7 (10.9)</td>
</tr>
<tr>
<td>Age at most recent diagnosis (years)*</td>
<td>31.3 (5.3)</td>
<td>45.1 (10.6)</td>
</tr>
<tr>
<td>Duration of diagnosis (years)</td>
<td>7.17 (7.0)</td>
<td>10.3 (9.9)</td>
</tr>
<tr>
<td>Recency of diagnosis (years)*</td>
<td>2.6 (3.1)</td>
<td>8.8 (10.2)</td>
</tr>
</tbody>
</table>

### Lifetime Other Substance Disorders

<table>
<thead>
<tr>
<th>Substance Dependence (%)</th>
<th>Younger H+M+</th>
<th>Older H+M+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Dependence (%)*</td>
<td>67.7%</td>
<td>41.9%</td>
</tr>
<tr>
<td>Marijuana Dependence (%)</td>
<td>38.2%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Cocaine Dependence (%)+</td>
<td>23.5%</td>
<td>45.2%</td>
</tr>
<tr>
<td>Opioid Dependence (%)</td>
<td>20.6%</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

*p < 0.05; +p < 0.10
### Medical and HIV Disease Characteristics in Older Groups

<table>
<thead>
<tr>
<th>Medical Characteristics</th>
<th>H-M- (n=36)</th>
<th>H+M- (n=49)</th>
<th>H+M+ (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidity Rating (% cont)*</td>
<td>16.7%</td>
<td>46.9%</td>
<td>32.3%</td>
</tr>
<tr>
<td>Hepatitis C (% seropositive)*</td>
<td>2.8%</td>
<td>26.5%</td>
<td>41.9%</td>
</tr>
<tr>
<td>Rx Drug U-tox Positive (%)</td>
<td>13.9%</td>
<td>31.3%</td>
<td>12.9%</td>
</tr>
<tr>
<td>HIV Disease Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Infection (years)*</td>
<td>-----</td>
<td>20.5 (15.2, 23.8)</td>
<td>15.9 (4.6, 21.4)</td>
</tr>
<tr>
<td>Age at HIV Diagnosis (years)</td>
<td>-----</td>
<td>38.6 (32.5, 44.4)</td>
<td>37.8 (31.2, 46.6)</td>
</tr>
<tr>
<td>AIDS Status (% AIDS)</td>
<td>-----</td>
<td>63.3%</td>
<td>67.7%</td>
</tr>
<tr>
<td>Nadir CD4 (cells/μL)</td>
<td>-----</td>
<td>170.0 (50.0, 260.0)</td>
<td>120.0 (54.0, 236.0)</td>
</tr>
<tr>
<td>Current CD4 (cells/μL)*</td>
<td>-----</td>
<td>584.0 (426.0, 818.5)</td>
<td>458.5 (325.0, 595.5)</td>
</tr>
<tr>
<td>cART Status (% on)</td>
<td>-----</td>
<td>89.8% (n=44)</td>
<td>93.6% (n=29)</td>
</tr>
<tr>
<td>Plasma VL (% det on cART)</td>
<td>-----</td>
<td>20.5%</td>
<td>10.3%</td>
</tr>
<tr>
<td>CSF VL (% det on cART)</td>
<td>-----</td>
<td>9.4%</td>
<td>20.8%</td>
</tr>
</tbody>
</table>

*p < 0.05
# Neurocognitive and Functional Assessment

<table>
<thead>
<tr>
<th>Neurocognitive Domain</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning &amp; Memory</td>
<td>WMS-III Logical Memory (Immediate &amp; Delayed Recall); CVLT-II (Learning Trials 1-5, Long Delay Free Recall)</td>
</tr>
<tr>
<td>Attention</td>
<td>WAIS-III Digit Span; CVLT-II (Trial 1)</td>
</tr>
<tr>
<td>Executive Functions</td>
<td>Drexel Tower of London (Total Moves); Action Fluency; Trail Making Test Part B</td>
</tr>
<tr>
<td>Information Processing Speed</td>
<td>Drexel Tower of London (Total Execution Time); Trail Making Test Part A</td>
</tr>
<tr>
<td>Motor</td>
<td>Grooved Pegboard (Dominant and Non-dominant hands)</td>
</tr>
</tbody>
</table>

## Daily Functioning

<table>
<thead>
<tr>
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<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities of Daily Living</td>
<td>Lawton &amp; Brody (1969) Basic and Instrumental Activities of Daily Living (BADLs &amp; IADLs)</td>
</tr>
<tr>
<td>Everyday Cognitive Symptoms</td>
<td>Profile of Mood States (Confusion/Bewilderment Scale)</td>
</tr>
<tr>
<td>Employment</td>
<td>Clinical Interview (employed/unemployed/disabled)</td>
</tr>
</tbody>
</table>
Neurocognitive Findings

- HIV
- MA
- Aging
MA is Associated with Poorer Global Neurocognitive Functioning in Older but not Younger HIV+ Persons

Older (≥ 50 years old) vs. Younger (≤ 40 years old)
Earlier Onset of MA Dependence is Associated with Worse Neurocognitive Functioning in Older HIV+MA+

$\rho < 0.05$

$r = 0.40$
(NS in Y+M+)
Specific Neurocognitive Domains Are Affected by MA in Older HIV+

![Graph showing T-Score for different domains such as Learning, Memory, Attention, Executive Functions, Speed, and Motor Skills.](image)

**Domain T-Score**

*H-M- (n=36)*

*H+M- (n=49)*

*H+M+ (n=31)*

*\( *p < 0.05; **p < 0.01 \)*
Shallower Verbal Learning Slope Among Older HIV+ MA Users

![Graph showing CVLT-II Z-scores for different conditions and delays.](image)
Everyday Functioning Findings

- HIV
- MA
- Aging
MA Adversely Impacts Daily Functioning in Older but not Younger HIV+

**p < 0.05; *p < 0.10**
MA Affects a Broad Range of Daily Functioning Outcomes in Older HIV+

**p < 0.05; *p < 0.10**
Higher Prevalence of Syndromic Neurocognitive Impairment (NCI)\textsuperscript{a} Among Older HIV+ MA Users

\textsuperscript{a}Syndromic NCI = NCI + Functional Dependence

\*p < 0.05
Summary

- Prior MA use affects neurocognitive and everyday functioning in older, but not younger HIV+ adults
  - MA effects in O+ were independent of cofactors
    - Between groups (e.g., demographics, depression)
    - Within O+ (e.g., HCV, other substance use disorders)

- Specific neurocognitive domains were vulnerable
  - Memory (acquisition), auditory attention, and fine-motor skills

- Broad range of everyday functioning outcomes were affected in O+ former MA users
  - Basic and instrumental ADLs, cognitive symptoms, employment
Possible Mechanisms

- "Legacy" effect of MA-associated neurotoxicity
  » Incomplete neural recovery in O+?
  » Immunovirologic factors?
    • Lower CD4, shorter EDI
    • Poorer virologic control
    • Hepatitis C co-infection
  » Vulnerability to age-related co-factors?
    • Vascular, metabolic, inflammation
  » Neurodegeneration?

NCI and Abstinence from MA

Cattie et al., 2013
A Developmental Model of Aging With HIV and MA
The Sixth Decade May Bring Even More Neurocognitive Complications for Older HIV+ Substance Users

Gongvatana et al., in prep
Future Directions

- Longitudinal studies with older MA seronegative comparisons are needed
  - Animal models?
- Role of MA (and other SUD) use parameters
  - Active users, density, route, etc.
- Other relevant neurocognitive and real-world functions
  - Decision-making, social cognition, prospective memory
  - Health literacy, cART adherence, HIV transmission risk, quality of life
- Neural substrates
  - Prefrontal and medial temporal systems
- Biomarkers of neural injury common to HIV, MA, and aging
  - Inflammation, vasculopathy
Older HIV+ MA Users May Benefit from Cognitive Neurorehabilitation

- MA affects cognitive strategy use and effectiveness in older HIV+
- Possible strategies
  - Prophylactic
  - Stimulation
  - Compensatory
    - Encourage and assist mnemonics
    - Break information down into manageable chunks

Woods et al., 2010  *p<.05
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