HIV, METH AND THE BRAIN: IMPLICATIONS FOR HIV RISK

Igor Grant, M.D.

HIV Neurobehavioral Research Center
University of California, San Diego
http://www.hnrc.ucsd.edu/
HIV NEUROBEHAVIORAL DISTURBANCES

NEUROCOGNITIVE

Primary
Asymptomatic Neurocognitive Impairment
Mild Neurocognitive Disorder
Dementia

Secondary
Infection
Neoplasia
Cerebrovascular
Nutritional
Treatment Related

EMOTIONAL & OTHER BEHAVIORAL

New Onset
Depression
Anxiety
Adjustment Disorders
HIV Mania
HIV Psychosis

Recurrent/Comorbid
Mood Disorders
Substance Use Disorders
Other Mental Disorders
Prevalence of Neurocognitive Disorders by Stage of HIV Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>NP Impaired</th>
<th>MCMD</th>
<th>Demented</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV- (n=212)</td>
<td>15.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC A (n=437)</td>
<td>26.5%</td>
<td>4.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>CDC B (n=213)</td>
<td>25.4%</td>
<td>18.3%</td>
<td>1.9%</td>
</tr>
<tr>
<td>CDC C (n=113)</td>
<td>17.7%</td>
<td>28.3%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>
Meaning of NP Impairment: Employment

- Normal (N=152): 7.9%
- Impaired (N=80): 17.5%

\[ p < 0.05 \]
Mean Number of Accidents on City Driving Simulation

Number of Accidents

- NP Normal: 1.5
- NP Impaired: 2.1
- MCMD: 3.2
Adherence to Antiretrovirals Related to Neurocognitive Impairment

% That Followed Schedule “Most of the Time”

% That Followed Specific Instructions Re Meds “Most of the Time”

NP Unimpaired (N=19)  NP Impaired (N= 8)

NP Unimpaired (N=15)  NP Impaired (N= 8)
Proportions of Persons Judged to have Global NP Impairment that have Specific Ability Deficit

<table>
<thead>
<tr>
<th>Ability</th>
<th>% Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>61%</td>
</tr>
<tr>
<td>Learning</td>
<td>57%</td>
</tr>
<tr>
<td>Verbal</td>
<td>44%</td>
</tr>
<tr>
<td>Motor</td>
<td>41%</td>
</tr>
<tr>
<td>Memory</td>
<td>38%</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>32%</td>
</tr>
<tr>
<td>Sensory</td>
<td>28%</td>
</tr>
<tr>
<td>Abstraction</td>
<td>24%</td>
</tr>
</tbody>
</table>
## Percent of Various Cells at Autopsy Having HIV

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microglia</td>
<td>80</td>
</tr>
<tr>
<td>Astroglia</td>
<td>?</td>
</tr>
<tr>
<td>Endothelial</td>
<td>10</td>
</tr>
<tr>
<td>Neurons</td>
<td>0</td>
</tr>
</tbody>
</table>
HIV-Associated Brain Damage Involves Neuronal Pathology

Post-synaptic Injury is Prominent
Synaptophysin & MAP-2 Immunostaining

HIV- HIV+

HIV NEUROBEHAVIORAL RESEARCH CENTER
Dendritic Complexity in Subjects with Varying Levels of Cognitive Impairment

HIV NEUROBEHAVIORAL RESEARCH CENTER
Possible Mechanisms of Neurotoxicity in HIV-1 Infection

- Macrophage
  - GP120
  - Cytokines (e.g., TNFα, IL-6)

- Astrocyte
  - QA
  - NMDA Receptor
  - Cytokines

- Neurone
  - VIP Receptor
  - Chemokine Receptor
  - GAL C
  - Ca++

- Protective Factors
Cofactors in HIV Associated Neurocognitive Complications

- Drug Abuse - example of methamphetamine
- Coinfection with Hepatitis C [HCV]
- Neurotoxic Treatments
MA and HIV

- ~60% of persons seeking MA tx are HIV infected (Peck et al., 2005)
- MA use associated with
  - Loss of interneurons (Chana et al., 2007)
  - Additive NP effects (Rippeth et al., 2004)
    - Immunocompromise (Carey et al., 2006)
  - HIV drug resistance (Colfax et al., 2007)
  - Problems in everyday functioning (Sadek et al., in press)
    - Poor ARV adherence (Reback et al., 2003)
% Having Global NP Impairment by Methamphetamine Abuse and HIV Status Accounting for Acute Intoxication on Day of NP Examination

- HIV- Non-Meth Abusing Group
- HIV+ Meth Abusing Group
- HIV- Meth Abusing Group
- HIV+
### Pattern of neuropsychological impairment according to risk factor

<table>
<thead>
<tr>
<th>Deficit</th>
<th>Meth</th>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Retention</td>
<td>-</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Attention/Working Memory</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Speed of Information Processing</td>
<td>?</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Visuospatial Functioning</td>
<td>?</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>++</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Slowing</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>
## Pattern of neuropsychological impairment according to risk factor

<table>
<thead>
<tr>
<th>Deficit</th>
<th>Meth</th>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Executive Functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problem-Solving/Planning</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cognitive Disinhibition</td>
<td>++</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Decision-making</td>
<td>+++</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td><strong>Frontal Systems Behavioral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>++</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Apathy</td>
<td>-</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Executive</td>
<td>+</td>
<td>++</td>
<td>?</td>
</tr>
</tbody>
</table>
Significant regional volume alterations related to METH and/or HIV

- Red: METH (increases)
- Yellow: HIV (decreases)
- Orange: METH & HIV (opposing effects)
Association of Cortical Volumes with Impairment

HIV+

METH+

$r = -.41, p < .05$

$r = .46, p < .05$
Association of Cortical Volumes with Attention Deficits

- HIV+:
  \[ \beta = -0.43, p = 0.003 \]

- METH+:
  \[ \beta = 0.26, p = 0.025 \]
Meth have larger Accumbens volume for age relative to controls.
A) Preserved neuronal and dendritic structure in HIV patient HIVE (-) METH (-).
B) Moderate neuronal and dendritic damage in a HIVE (-) METH (+) patient.
C) Moderate to severe neuronal damage in an HIVE (+) METH (-) patient.
D) Severe neuronal and dendritic damage in an HIVE (+) METH (+) patient.
Bar = 25 microns
Degeneration of Interneurons in HIVE+METH Users

<table>
<thead>
<tr>
<th></th>
<th>HIV- Meth-</th>
<th>HIV+ Meth-</th>
<th>HIV+ Meth+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calbindin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parvalbumin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No Alterations, Neuronal Damage, Severe Neuron Loss
Loss of calbindin interneurons is associated with cognitive impairment and memory loss.

- HIV+ (control)
- HIVE+ METH-
- HIVE+ METH+

Calbindin immunoreactive interneurons

- HIV+ control
- HIVE+ METH-
- HIVE+ METH+

Heaton Global Score

- r = -0.5, n=20, p<0.05

Memory Score

- r = -0.695, n=20, p<0.01.
Mechanisms of neurodegeneration mediated by HIV and METH

1. Oxidative stress
2. Excitotoxicity
3. Mitochondrial dysfunction
4. Alterations in calcium metabolism
5. Interference with signaling pathways of trophic factors
6. Caspase mediated apoptosis
7. Cytokines, chemokines and other neuro-inflammatory factors
Possible Mechanisms of Neurotoxicity in HIV-1 Infection

Macrophage

- GP120

HIV

- QA

Neurone

- NMDA Receptor
- VIP Receptor
- Chemokine Receptor
- GAL C

Astrocyte

- Cytokines (e.g., TNFα, IL-6)

Protective Factors

Cytokines
METH and Inflammation

More Inflammation in METH Users

- METH users had higher levels of 5 markers of macrophage activation* in plasma
  - 3 were also higher in CSF
- Similar to HIV RNA, levels varied with recency of METH use
  - HIV-METH- lowest
  - METH+Utox- intermediate
  - METH+Utox+ highest

\[ P < .001 \]

*MCP-1, sCD14, sTNFR-II, TNF-alpha, and MIP-1 beta
Predictors of Meth Relapse after 2 yrs

• 53% of a sample of HIV+ MA abusers relapsed over a 2-year follow-up period

• Predictors of relapse in HIV included:
  – Younger age
  – Fewer years of education
  – Earlier age at MA use onset
  – Greater amounts of MA use
  – Higher baseline HIV RNA in plasma
  – No AIDS diagnosis
  – ASPD, absence of depression
  – Cognitive impairment
Cognitive & Psychiatric Status Correlates of Meth Relapse

Relapse
Nonrelapse
Medication Adherence

- Prospective memory impairment predicts ARV nonadherence at 5 weeks in HIV+ substance abusers ($d = -1.1$)
Relapse to METH Abuse or Dependence diagnosis during 12 month follow-up is associated with higher plasma HIV RNA ($n=63$)
Antiretroviral Drug Resistance

Methamphetamine is Associated with DR

- Resistance mutations were determined in 63 subjects enrolled in NIDA-funded projects
- 45% had resistance mutations for at least one antiretroviral
- Among METH dependent individuals, DR was associated with shorter durations of METH abstinence

Hightower et al, XIV International HIV Drug Resistance Workshop, Submitted

HIV NEUROBEHAVIORAL RESEARCH CENTER
Acknowledgments

Coordinating Core: JH Atkinson MD, JA McCutchan MD, RJ Ellis MD PhD, T Marcotte PhD

Neuromedical Core: RJ Ellis MD PhD, JA McCutchan MD, S Letendre MD, E Capparelli PharmD, R Schrier PhD

Neurobehavioral Core: RK Heaton PhD, JH Atkinson MD, SP Woods PsyD, M Cherner PhD

Neurobiology Core: E Maslia MD, I Everall MD PhD

Neuroimaging Core: T Jernigan PhD, JR Hesselink MD, S Archibald MA, J Annese PhD, MJ Taylor PhD, B Schweinsburg PhD, O Alhassoon PhD

Neurovirology Core: D Richman MD, D Smith MD

Developmental Core: I Everall MD PhD, SA Lipton MD PhD

International Core: JA McCutchan MD

Statistics: I Abramson PhD, D Lazzaretto MS, R Deutsch PhD, T Wolfson MA
Funding support provided by:

NeuroAIDS: Effects of Methamphetamine and HCV, NIDA P01 DA12065

HIV Neurobehavioral Research Center (HNRC), NIMH P30 MH62512

CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER), NIMH N01 MH22005

California NeuroAIDS Tissue Network (CNTN), NIMH R24 MH59745
HIV, METH AND THE BRAIN: IMPLICATIONS FOR HIV RISK

Igor Grant, M.D.

HIV Neurobehavioral Research Center
University of California, San Diego
http://www.hnrc.ucsd.edu/
## Rates of Global NP Impairment as determined by GDS cut-off scores

<table>
<thead>
<tr>
<th>Group</th>
<th>% Impaired</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+/METH+ (n=43)</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>HIV-/METH+ (n=47)</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>HIV+/METH- (n=50)</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>HIV-/METH+ (n=60)</td>
<td>18%</td>
<td></td>
</tr>
</tbody>
</table>
Relation of Dendritic Damage to Neurocognitive Impairment

rho = -.67; p < .001
HIV NEUROBEHAVIORAL RESEARCH CENTER

HIVE-

HIVE+

Abnormal White Matter
### Example sections from morphometric analysis

<table>
<thead>
<tr>
<th>Cerebral Lobes</th>
<th>Subcortical Regions</th>
<th>Other Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal Cortex/White</td>
<td>White Matter</td>
<td>Insular Cortex</td>
</tr>
<tr>
<td>Temporal Cortex/White</td>
<td>Basomesial Diencephalon</td>
<td>Cingulate Cortex</td>
</tr>
<tr>
<td>Parietal Cortex/White</td>
<td>Caudate Nucleus</td>
<td>Hippocampus</td>
</tr>
<tr>
<td>Occipital Cortex/White</td>
<td>Lenticular Nucleus</td>
<td>Amygdala</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Nucleus Accumbens</td>
<td>Parahippocampal Gyrus</td>
</tr>
<tr>
<td></td>
<td>Thalamus</td>
<td>White Matter w/ Elevated Signal</td>
</tr>
<tr>
<td></td>
<td>Substantia Nigra</td>
<td></td>
</tr>
</tbody>
</table>
Abnormal white matter volume predicts HIV encephalitis and dendritic loss at autopsy