Measurement and Classification of Neurocognitive Disability in HIV/AIDS

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University of California San Diego

Ancient History
### Group Means for NP and MMPI Variables

<table>
<thead>
<tr>
<th>Employment:</th>
<th>Full-time</th>
<th>Part-time</th>
<th>Unemployed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 171</td>
<td>n = 40</td>
<td>n = 170</td>
</tr>
<tr>
<td>PIQ</td>
<td>107.3</td>
<td>103.2</td>
<td>96.5</td>
</tr>
<tr>
<td>AIR</td>
<td>1.11</td>
<td>1.26</td>
<td>1.84</td>
</tr>
<tr>
<td>Trails B</td>
<td>80.9</td>
<td>93.0</td>
<td>152.0</td>
</tr>
<tr>
<td>MMPI-Hs</td>
<td>54.8</td>
<td>64.5</td>
<td>68.2</td>
</tr>
<tr>
<td>MMPI-D</td>
<td>59.8</td>
<td>67.3</td>
<td>74.7</td>
</tr>
<tr>
<td>MMPI-Sc</td>
<td>57.8</td>
<td>70.3</td>
<td>75.0</td>
</tr>
</tbody>
</table>

**Classification Accuracy**

- Base Sample: 85%
- Crossvalidation: 82%

### Background of HAND Definitions

- In 1991, the AIDS Task Force of the American Academy of Neurology (AAN) published
  - Nomenclature and research case definitions to guide the diagnosis of neurological manifestations of HIV-1 infection

- 16 years later, NIMH & NINDS charged an international working group to critically review the adequacy and utility of these definitional criteria and to identify aspects that require updating. This led to
### Frascati Definition of Neuropsychological Impairment

- At least mild impairment in at least 2 ability domains

- **Mild:** > 1 SD below mean on *demographically corrected* scores in > 2 ability domains

- **Moderate-Severe:** > 2 SD below mean on > 2 ability domains, or > 2.5 sd below mean on one domain and at least > 1 SD on another domain
**Example NP Test Battery**

<table>
<thead>
<tr>
<th>Verbal Fluency</th>
<th>Cognitive Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category Fluency (Animals)</td>
<td>Trail Making Test Part A</td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>WAIS-III Digit Symbol</td>
</tr>
<tr>
<td><strong>Executive Functions</strong></td>
<td>WAIS-III Symbol Search</td>
</tr>
<tr>
<td>Category Test – computer version</td>
<td>Stroop Color Naming</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test (64 item version)</td>
<td><strong>Learning and Memory (2 domains)</strong></td>
</tr>
<tr>
<td>Trail Making Test Part B</td>
<td>Hopkins Verbal Learning Test - Rev</td>
</tr>
<tr>
<td>Stroop Interference Ratio</td>
<td>Brief Visuospatial Memory Test - Rev</td>
</tr>
<tr>
<td><strong>Attention/Working Memory</strong></td>
<td>Story Learning and Memory</td>
</tr>
<tr>
<td>Paced Auditory Serial Addition Test</td>
<td>Figure Learning and Memory</td>
</tr>
</tbody>
</table>

**Verbal Fluency**

- Category Fluency (Animals)
- Letter Fluency

**Executive Functions**

- Category Test – computer version
- Wisconsin Card Sorting Test (64 item version)
- Trail Making Test Part B
- Stroop Interference Ratio

**Attention/Working Memory**

- Paced Auditory Serial Addition Test
- WAIS-III Letter Number

**Why Demographic Corrections?**

Examples from WAIS-III/ WMS-III
### WAIS-III/WMS-III Factor Score Composition Primary Scores

<table>
<thead>
<tr>
<th>Verbal Comprehension</th>
<th>Working Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
<td>Spatial Span</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>Letter-Number</td>
</tr>
<tr>
<td>Similarities</td>
<td>Sequencing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perceptual Organization</th>
<th>Processing Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block Design</td>
<td>Digit Symbol</td>
</tr>
<tr>
<td>Picture Completion</td>
<td>Symbol Search</td>
</tr>
<tr>
<td>Matrix Reasoning</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Auditory Memory</th>
<th>Visual Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logical Memory I and II</td>
<td>Family Pictures I and II</td>
</tr>
<tr>
<td>Verbal Paired Associates I</td>
<td></td>
</tr>
<tr>
<td>and II</td>
<td>Visual Reproductions</td>
</tr>
<tr>
<td>I and II</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>and II</td>
</tr>
</tbody>
</table>

### Subject Samples

<table>
<thead>
<tr>
<th></th>
<th>WAIS-III</th>
<th>WMS-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2312</td>
<td>1073</td>
</tr>
<tr>
<td>Age</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Education</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>46.5</td>
<td>46.9</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% White)</td>
<td>75.8</td>
<td>73.6</td>
</tr>
<tr>
<td>(% African American)</td>
<td>13.0</td>
<td>13.8</td>
</tr>
<tr>
<td>(% Hispanic)</td>
<td>7.7</td>
<td>8.9</td>
</tr>
<tr>
<td>(% Other)</td>
<td>3.5</td>
<td>4.5</td>
</tr>
<tr>
<td>FSIQ</td>
<td>99</td>
<td>91.1</td>
</tr>
</tbody>
</table>
Verbal Comprehension Factor

Verbal Comprehension Education Corrected Z-Score

$R^2 = <0.01$

Perceptual Organization Factor

Perceptual Organization Education Corrected Z-Score

$R^2 = 0.27$
Processing Speed Factor

Processing Speed Factor
Education Corrected Z-Score

$R^2 = 0.45$

Age

Working Memory Factor

Working Memory Factor
Education Corrected Z-Score

$R^2 = 0.24$

Age
Auditory Memory Factor

R² = 0.20

Visual Memory Factor

R² = 0.45
Percent Misclassified at 1SD for Factor Scores by Education

*Based on Age-Corrected Z-Scores

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Percent Misclassified at 1SD for Factor Scores by Education

*Based on Age-Corrected Z-Scores

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Percent Misclassified at 1SD for Factor Scores by Sex

Based on Age and Education-Corrected Z-Scores

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Percent Misclassified at 1SD for Factor Scores by Ethnicity

*Based on Age, Education, and Sex-Corrected Z-Scores

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Frascati Comorbid Conditions

- **MINIMAL:** could have minor effects on NP test results, but unlikely to cause even mild global impairment (does not preclude diagnoses of HAND).

- **MODERATE:** likely to have at least mild effects on NP test results but unlikely to cause clinically significant global NP impairment by itself (does not preclude diagnoses of HAND).

- **SEVERE:** likely to have major effects on NP test results, with significant neurocognitive impairment and functional disability, or NP results invalid due to poor effort (precludes diagnoses of HAND at baseline assessment).

Frascati guidelines for classifying confounds to HAND

- Depression
- History of remote traumatic brain injury (TBI)
- History of developmental disability (cognitive / academic)
- History of alcohol or other substance use disorder
- HIV-related opportunistic CNS disease
- Non-HIV-related Neurologic Condition
- Systemic disease
- Co-infection with Hepatitis-C Virus (HCV)
### CHARTER Comorbidity Group Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Minimal</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Impaired</td>
<td>41%</td>
<td>59%</td>
<td>84%</td>
</tr>
<tr>
<td>% Employed</td>
<td>33.0%</td>
<td>19.7%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Depression (BDI)</td>
<td>12.3 (10.0)</td>
<td>15.7 (11.1)</td>
<td>16.5 (11.9)</td>
</tr>
<tr>
<td>Cognitive Symptoms (PAOFI)</td>
<td>4.9 (6.3)</td>
<td>7.4 (8.0)</td>
<td>9.3 (9.0)</td>
</tr>
<tr>
<td>IADL Declines</td>
<td>1.3 (1.8)</td>
<td>1.9 (2.1)</td>
<td>2.1 (2.3)</td>
</tr>
</tbody>
</table>

### Mild Functional Decline

Requires at least two of the following that are not readily attributable to comorbid conditions in the judgment of the examiner:

- **(a)** Self report or other report of some increased assistance needed with at least two IADLs such as medication management, financial management, shopping, meal preparation, light housekeeping, laundry, driving, use of public transportation, maintaining personal schedules, understanding media events, and child care. (More IADLs could be considered as appropriate to the individual.)

- **(b)** Patient is unable to perform some aspects of a previous job. This is not due to medical symptoms.

- **(c)** Although patient may maintain employment and/or full IADL independence, he/she reports less efficiency, reduced productivity, more

- **(d)** In the absence of significant depression (e.g., Beck Depression Inventory, >17, which may bias reporting of symptoms, patient reports that he/she is experiencing increased difficulty with >2 aspects of cognition in daily life. These may include difficulties with memory for recent events (people, conversations, names, commitments, where things are placed, etc.), understanding conversations or reading materials, word finding, planning activities, problem solving, concentrating, thinking clearly or logically, finding his/her way about, calculating, following directions or instructions, etc. Reports of these difficulties also may be obtained from a knowledgeable informant.
Requires two or more of the following, that are not readily attributable to medical or other comorbid conditions in the judgment of the examiner:

(a) Patient is unable to maintain former employment and this is not due to systemic illness or other factors not related to cognitive impairment (e.g., healthcare coverage being dependent upon disability status).

(b) Patient requires substantially greater assistance (or is dependent) with more than two IADLs, as listed above.

(c) Patient or a knowledgeable informant reports that he/she experiences/shows significantly greater difficulty with >4 aspects of cognition, as listed above. However, self report is not sufficient (would need confirmation by another informant) if patient is significantly depressed (e.g., BDI > 17).

(d) If performance-based, standardized functional tasks are administered, patient scores >2 SD below

Approaches to Measuring Everyday Functioning

- Self-report
- Proxy (e.g., confidant, caregiver)
- Direct observation
- Performance-based measures
Effects of HIV-Related Brain Dysfunction on Everyday Functioning

HIV+ Brain

Cognitive Impairment

Impaired Performance of Daily Tasks

Poor Life Functioning

NP Testing

Work Samples
- Financial Mgt. Tasks
- Cooking Task
- Restaurant Task
- Shopping Task
- Medication Mgt. Tasks
- Driving Simulator

Symptoms (complaints)
- Unemployment
- ADL dependence
- Poor Medication Adherence
- Poor driving record

NP Impairment and Employment

UNEMPLOYED

DECREASED WORK PERFORMANCE

All Subjects

Subjects without Medical Disability
Functional Impact Study
(N=282 HIV+)

- Refine laboratory measures of everyday functioning
- Determine the relationships among NP status, laboratory ADL measures, and measures of life functioning
- Identify everyday functioning measures that have utility for treatment outcome assessment

Total Cognitive Complaints by NP Status

- Total Complaints
- NP Normal vs. NP Impaired
- p < 0.0001
Laboratory Measures of Activities of Daily Living

- Finances (budget, pay bills, manage checkbook)
- Shopping (from memory and with list)
- Meal Planning and Preparation
- Restaurant Scenario
- Medication Management
- Standardized Work Samples

Percent Failed Activities of Daily Living by NP Status

- All p’s < 0.01
Cognitive Complaints by Measures of Everyday Functioning

- Shopping: Passed, Failed
- Meal Planning: Passed, Failed
- Restaurant: Passed, Failed
- Medication Management: Passed, Failed
- Finances: Passed, Failed
- Work Assessment: Passed, Failed

* p<0.05
** p<0.0001

% Employed by FDS Status in Non-AIDS Participants

- FDS Pass (n=199): 40%
- FDS Fail (n=67): 10%

p < .001
**Viral Load by FDS Status**

![Bar chart showing viral load by FDS status](chart.png)

* p < 0.05  ** p < 0.01

(n= 264)  (n= 268)

**IADL Dependence Questionnaire: 13 Domains**

"Dependent" = Participant gets assistance in ≥ 2 domains

<table>
<thead>
<tr>
<th>Dependency Status</th>
<th>Mean IADL Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent (n = 219)</td>
<td>0.6 (0.9)</td>
</tr>
<tr>
<td>Dependent (n = 43)</td>
<td>6.1 (3.7)</td>
</tr>
</tbody>
</table>
% Receiving Assistance

p < .0001

% Getting Assistance in Specific ADL Tasks by Dependency Groups

Independent (n=219)
Dependent (n=43)

% Getting Assistance in Specific ADL Tasks by Dependency Cont.

Independent (n=219)
Dependent (n=43)

% Employed

0 10 20 30 40
Independent Dependent Pass Fail

IADL Vocational Performance p < .001

NY Study of Return to Work

vanGorp et al., JINS, 2007, 80-89

118 job seeking HIV+ participants (79% with AIDS)

52% obtained some work during the 2 years followup

Best Predictors:
  » Learning efficiency* (p=.005)
  » Young age (p=.03)
  » Shorter unemployment (p=.03)
  » AIDS status (p=.04)

*Only unique predictor
Likelihood of Driving Last Year by FDS Status

<table>
<thead>
<tr>
<th>Percent</th>
<th>FDS Pass (n=141)</th>
<th>FDS Fail (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
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<tr>
<td>30</td>
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<tr>
<td>40</td>
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<td>50</td>
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<tr>
<td>60</td>
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<tr>
<td>70</td>
<td></td>
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<tr>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
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</tr>
</tbody>
</table>

\( p < .001 \)

Self-Reported Decline in Driving

Have your driving abilities decreased since becoming infected with HIV?

- No Change: 75%
- A Little Worse: 17%
- A Lot Worse: 8%

n = 247
Driving Study Procedures

A. Neuropsychological Testing

B. Driving Simulations (2)

C. On-Road Evaluation

PC-based Driving Simulator

Systems Technology, Inc.
Simulation #1:

Advanced Routine and Emergency Driving

- 12 minute drive
- City and country driving
- Straight, curved, and inclined roads
- Speed limit ranged from 35 mph to 65 mph
- Subjects must pass cars, stop at traffic lights, drive around stalled vehicles, adjust to fog
- Accident avoidance: n=5
- Primary outcome: Number of accidents

Mean Number of Accidents on City Driving

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HIV-</th>
<th>HIV+ Normal</th>
<th>HIV+ Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Accidents</td>
<td>1.4</td>
<td>1.2</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Virtual City

Number of Blocks Beyond Optimal Performance

- HIV-: 3.8
- HIV+ Normal: 3.0
- HIV+ Impaired: 9.6
On-Road Driving Evaluation

- 30 minute evaluation modeled after the California DMV Driving Performance Evaluation (DPE)
- Assesses:
  - traffic checks
  - speed control
  - lane position
  - merging
  - dangerous maneuvers
- Residential, business sections; freeway driving; destination task
- Evaluation completed by driving rehabilitation instructor and trained research assistant

On-Road Driving Examination

<table>
<thead>
<tr>
<th></th>
<th>HIV+ (n=11)</th>
<th>HIV+ NL (n=29)</th>
<th>HIV- (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Unsafe on the Road</td>
<td>36.4%</td>
<td>6.9%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>
### Laboratory Predictors of On-Road Driving Performance

<table>
<thead>
<tr>
<th>Variable</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP Global Deficit Score</td>
<td>0.017</td>
</tr>
<tr>
<td>Simulator Accidents</td>
<td>0.029</td>
</tr>
<tr>
<td>Virtual City Return Blocks</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Overall model p < 0.001
47.6% of on-road variance explained

(Education and miles driven in past year differed between groups, but were not significant in the model (p > .30) and were dropped from the model)

Impairments in Executive Functioning, Attention/Working Memory were the best predictors of on-road failure

Marcotte et al., 2004
Percent of Subjects with Neurobehavioral Disorders (n = 975)

Domain-Specific Impairment Rates for HIV+ Subjects Classified as Impaired
### Definition of Impairment Categories

<table>
<thead>
<tr>
<th>Conceptual Category</th>
<th>T-Score</th>
<th>Percentage of Normals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 40</td>
<td>85.4</td>
</tr>
<tr>
<td>Mild Imp</td>
<td>35-39</td>
<td>8.6</td>
</tr>
<tr>
<td>Mild-Mod Imp</td>
<td>30-34</td>
<td>4.0</td>
</tr>
<tr>
<td>Moderate Imp</td>
<td>25-29</td>
<td>1.5</td>
</tr>
<tr>
<td>Mod-Sev Imp</td>
<td>20-24</td>
<td>0.4</td>
</tr>
<tr>
<td>Severe Imp</td>
<td>&lt; 20</td>
<td>0.1</td>
</tr>
</tbody>
</table>