The relationship between synaptodendritic neuropathology and HIV-associated neurocognitive disorders is moderated by age

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Aging & HAND in HIV

- Evidence that older people living with HIV (PLWH) show higher rates of HAND
- Older PLWH may experience accelerated brain/cognition aging
- Additive effects of HIV and aging on mechanisms of neural injury? (e.g. chronic inflammation, oxidative stress)
- Need to determine whether older PLWH are more vulnerable to effects of HIV disease processes on cognitive function
**AIM:** Examine whether age moderates the relationship between synaptodendritic neuropathology and cognitive performance and rates of HAND.

**HYPOTHESIS:**

- **Minimal/Moderate Neuropathology**
  - YOUNGER HIV+
  - OLDER HIV+
  - ALL AGES

- **Severe Neuropathology**
  - ALL AGES
  - Cognitive Dysfunction/HAND
PARTICIPANTS

- 100 HIV+ post-mortem cases enrolled in the National NeuroAIDS Tissue Consortium (NNTC)
  - Age at death ranged from 27 to 69
- Completed a neuropsychological test battery within one year of death
- Characterized for HIV-related neuropathology
Measure of Neuropathology

- Defined by density of synaptodendritic marker immunoreactivity (neuronal simplification) in frontal cortex (Bryant et al., 2015, AIDS; Bryant et al., 2017, AIDS; Levine et al., 2016, J Neurovirol)
  - synaptophysin = marker of presynaptic terminals
  - microtubule-associated protein-2 (MAP2) = marker of neuronal cell bodies & dendrites

- A composite score of synaptophysin & MAP2 was divided into tertiles representing: (1) minimal, (2) moderate & (3) severe neuronal simplification
Cognitive Function

- Neurocognitive tests assessed verbal fluency, working memory, processing speed, verbal and visual learning and delayed recall, executive function, and complex motor function.

- Raw test scores transformed into age-, education-, sex-, and race/ethnicity-adjusted T-scores

- Global T-score = T-scores averaged across tests

- HAND diagnosed according to Frascati criteria
### Age By Neuropathology Groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Minimal Neuronal Simplification (n=34)</th>
<th>Moderate Neuronal Simplification (n=30)</th>
<th>Severe Neuronal Simplification (n=36)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger (&lt; 50 yrs)</td>
<td>21 (34%)</td>
<td>15 (25%)</td>
<td>25 (41%)</td>
<td>61</td>
</tr>
<tr>
<td>Older (≥ 50 yrs)</td>
<td>13 (33%)</td>
<td>15 (38%)</td>
<td>11 (28%)</td>
<td>39</td>
</tr>
</tbody>
</table>

Fisher’s Exact Test: 2.6, p=.29
# Sample Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Younger Cases (n=61)</th>
<th>Older Cases (n=39)</th>
<th>p-value</th>
<th>Minimal Neuronal Simplification Cases (n=34)</th>
<th>Moderate Neuronal Simplification Cases (n=30)</th>
<th>Severe Neuronal Simplification Cases (n=36)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death, M (SD)</td>
<td>40.3 (5.4)</td>
<td>56.7 (4.3)</td>
<td>&lt;.001</td>
<td>46.7 (9.7)</td>
<td>48.3 (8.9)</td>
<td>45.3 (9.7)</td>
<td>.45</td>
</tr>
<tr>
<td>Education, M (SD)</td>
<td>13.0 (2.2)</td>
<td>12.7 (3.7)</td>
<td>.60</td>
<td>13.9 (2.1)</td>
<td>12.3 (3.1)</td>
<td>12.3 (3.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% White</td>
<td>68.8%</td>
<td>61.5%</td>
<td>.45</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Black</td>
<td>22.9%</td>
<td>28.2%</td>
<td>.55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Other</td>
<td>8.3%</td>
<td>10.3%</td>
<td>.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity (% Hispanic)</td>
<td>32.8%</td>
<td>17.9%</td>
<td>.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>80.3%</td>
<td>87.2%</td>
<td>.37</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRAT score, M (SD)</td>
<td>97.6 (14.6)</td>
<td>100.2 (13.4)</td>
<td>.46</td>
<td>100.8 (11.9)</td>
<td>93.7 (16.0)</td>
<td>100.7 (14.1)</td>
<td>.17</td>
</tr>
<tr>
<td>Lifetime substance (cocaine, opiate, meth) disorder diagnosis (%)</td>
<td>36.6%</td>
<td>24.1%</td>
<td>.10</td>
<td>26.1%</td>
<td>25.0%</td>
<td>40.7%</td>
<td>.41</td>
</tr>
</tbody>
</table>
## HIV Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Younger Cases (n=61)</th>
<th>Older Cases (n=39)</th>
<th>p-value</th>
<th>Minimal Neuronal Simplification Cases (n=34)</th>
<th>Moderate Neuronal Simplification Cases (n=30)</th>
<th>Severe Neuronal Simplification Cases (n=36)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadir CD4, median (IQR)</td>
<td>17.0 (47.0)</td>
<td>59.0 (82.3)</td>
<td>.03</td>
<td>41.0 (76.5)</td>
<td>28.0 (78.5)</td>
<td>18.0 (66.0)</td>
<td>.62</td>
</tr>
<tr>
<td>Premortem CD4, median (IQR)</td>
<td>40.0 (96.0)</td>
<td>135.5 (328.0)</td>
<td>.01</td>
<td>110.0 (210.0)</td>
<td>34.0 (111.0)</td>
<td>30.0 (176.5)</td>
<td>.09</td>
</tr>
<tr>
<td>Premortem log 10 viral load, median (IQR)</td>
<td>4.6 (2.5)</td>
<td>2.6 (3.1)</td>
<td>.33</td>
<td>2.7 (2.4)</td>
<td>4.8 (2.7)</td>
<td>4.4 (4.4)</td>
<td>.03</td>
</tr>
<tr>
<td>Duration of infection, M (SD)</td>
<td>10.2 (5.8)</td>
<td>13.9 (7.1)</td>
<td>.007</td>
<td>12.1 (6.5)</td>
<td>10.1 (6.4)</td>
<td>12.5 (6.7)</td>
<td>.31</td>
</tr>
<tr>
<td>Non AIDS-Related Comorbidity Score, M (SD)</td>
<td>12.1 (0.3)</td>
<td>12.8 (0.9)</td>
<td>.001</td>
<td>12.5 (0.9)</td>
<td>12.3 (0.6)</td>
<td>12.3 (0.7)</td>
<td>.42</td>
</tr>
</tbody>
</table>
RESULTS

Percent with HAND

- Young, Minimal Neuronal Simplification (n=21)
- Young, Moderate Neuronal Simplification (n=15)
- Young, Severe Neuronal Simplification (n=25)
- Old, Minimal Neuronal Simplification (n=13)
- Old, Moderate Neuronal Simplification (n=15)
- Old, Severe Neuronal Simplification (n=11)

p = .001
ns
p = .08
RESULTS

Age X Neuronal Simplification Interaction, $p=.04$

<table>
<thead>
<tr>
<th>Group</th>
<th>Neuronal Simplification</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young, Minimal</td>
<td>Minimal</td>
<td>19</td>
</tr>
<tr>
<td>Young, Moderate</td>
<td>Moderate</td>
<td>13</td>
</tr>
<tr>
<td>Young, Severe</td>
<td>Severe</td>
<td>16</td>
</tr>
<tr>
<td>Old, Minimal</td>
<td>Minimal</td>
<td>9</td>
</tr>
<tr>
<td>Old, Moderate</td>
<td>Moderate</td>
<td>12</td>
</tr>
<tr>
<td>Old, Severe</td>
<td>Severe</td>
<td>8</td>
</tr>
</tbody>
</table>

Mean Global T-scores

- Young, Minimal: $p=.03$
- Old, Severe: $p=.001$
Summary

- Age moderates relationship between neuronal simplification & cognitive function
  - When minimal neuronal simplification:
    - Younger: ↓ HAND  Older: ↑ HAND
  - When severe neuronal simplification:
    - Younger: ↑ HAND  Older: ↑ HAND
  - However, global T-scores suggest that HAND is more severe in older vs. younger PLWH
Conclusions

▪ Aging and age-related comorbidities in the context of HIV may have deleterious effects on brain health and deplete resources and “reserves” used in compensating for neuropathology during cognitive performance

▪ Other markers of HIV-associated neuropathology should be examined in relation to age and cognition
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  - NNTC.org

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