Perceived stress influences prefrontal cortex function in midlife women with HIV infection

Importance of identifying risk factors of cognition dysfunction in HIV

- **No cognitive impairment**: 50%
- **Milder forms of cognitive impairment**: 45%
- **HIV associated Dementia (HAD)**: 5%

HIV+ women show deficits in verbal learning and memory compared to at-risk HIV- women.

Beta (B) & 95% confidence intervals favor HIV-.

Maki, Rubin et al., Neurology (2014)

N=1521
Verbal Learning and Memory

- Broom
- Ham
- Pencil
- Chicken
- Notebook
- Sponge
- Turkey
- Detergent
- Scissors
- Hamburger
- Bleach
- Eraser
Verbal Learning and Memory

Broom
Ham
Pencil
Chicken
Notebook
Sponge
Turkey
Detergent
Scissors
Hamburger
Bleach
Eraser

Categories
Household items
Food
School supplies
Importance of identifying risk factors of cognition dysfunction in HIV

- No cognitive impairment: 50%
- Milder forms of cognitive impairment: 45%
- HIV associated Dementia (HAD): 5%

Why study stress as a contributor to verbal memory deficits in HIV+ women?

Negative life stressors:
- Prevalent in HIV+ individuals particularly women
- Risk factors for mood/anxiety disorders
- Impact physiologic systems (e.g., stress response system)
- Influence cognition and brain function
- Women are differentially vulnerable to cognitive effects of stress hormones compared to men

Perceived stress (higher vs. lower) is associated with the verbal memory domain and delayed recall only in the context of HIV

Note. *p<0.001. N=1499. Perceived Stress measured with Perceived Stress Scale-10—how unpredictable, uncontrollable, and overloaded respondents find their lives in past month. Higher stress ≥18 (top tertile).

Association between perceived stress and worse verbal memory in HIV+ women with high viral load

Note. *p<0.001. N=1003.

In HIV+ women, perceived stress is negatively associated with verbal memory and strategic encoding on the HVLT.

Cohen's $d$ Effect Size (ES)

-0.5 0.0 0.5 1.0 1.5

Learning domain
Trial 1
Trials 1-3
Memory domain
Delayed recall
Retention
Retrieval index
Recognition
Clustering domain
Trial 1 clustering
Trials 1-3 clustering
Delay clustering

Higher < Lower Stress

Note. N=38. *p<0.05

Rubin et al., Neurobiol Dis (in press)
Prefrontal volumes in the right hemisphere are associated with verbal memory

Note. *p<0.05. (A) Same pattern seen for middle and superior frontal gyri; (B) Partial plot from regression analysis controlling for age. Same pattern seen on percent retention, delayed free recall, and retrieval index (p’s<0.05). Right middle frontal gyrus associated with strategic encoding (p’s<0.05).

Rubin et al., Neurobiol Dis (in press)
Aim

To further understand the neural basis of this stress-related memory impairment, we examined the effects of stress on activation of the prefrontal cortex and strategic encoding during a verbal memory task in a sample of HIV+ midlife women.
Chicago WIHS Participants

<table>
<thead>
<tr>
<th>Perceived Stress</th>
<th>Lower (n=18), n (%)</th>
<th>Higher (n=18), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, $M (SD)$</td>
<td>42.56 (6.32)</td>
<td>44.89 (7.67)</td>
</tr>
<tr>
<td>Years of Education, $M (SD)$</td>
<td>12.94 (2.15)</td>
<td>12.14 (2.26)</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>18 (100)</td>
<td>17 (94)</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>8 (44)</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Recent heavy alcohol use</td>
<td>3 (17)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Recent marijuana use</td>
<td>3 (17)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Ever use cocaine</td>
<td>13 (72)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>CD4 &lt;200</td>
<td>2 (12)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Viral load $\geq$10,000</td>
<td>2 (11)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>HAART $\geq$95% compliance</td>
<td>12 (67)</td>
<td>12 (67)</td>
</tr>
</tbody>
</table>

Note. “Recent” refers to within 6 months of the most recent WIHS visit; Heavy alcohol use reflects $>7$ drinks/wk or $>4$ drinks in one sitting; HAART, highly active antiretroviral therapy.
In-scanner verbal memory task

Encoding
- 30 items
- 5 semantic categories

Free recall
- After 12-minute delay

Recognition
- 60 items
- Related and unrelated distractors

<table>
<thead>
<tr>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruits</td>
</tr>
<tr>
<td>Body parts</td>
</tr>
<tr>
<td>Furniture</td>
</tr>
<tr>
<td>Insects</td>
</tr>
<tr>
<td>Natural formations</td>
</tr>
</tbody>
</table>
In-scanner verbal memory task

Block design
- 3 second presentation

Experimental block
- Single presentation

Control block
- Repeated presentation

Note. Each experimental block contained 1 or 2 words from each semantic category so that clustering occurs within and across blocks.
Behavioral outcome measures

In-scanner verbal memory task
- Free recall total
- Semantic clustering
- Recognition (% correct)

Hopkins Verbal Learning Test (HVLT)
In HIV+ women, perceived stress is negatively associated with verbal memory and strategic encoding.

Higher stress is associated with lower Cohen's d Effect Size (ES) in the learning domain, including:
- Trial 1
- Trials 1-3
- Delayed recall
- Retention
- Retrieval index
- Recognition
- Clustering domain
- Trial 1 clustering
- Trials 1-3 clustering
- Delay clustering
- Recognition
- Delayed recall
- Delay clustering

Note. *p<0.05
Encoding Typical Pattern: lower stress + higher stress (n=36)

- Activation of bilateral parahippocampi
- Deactivation of the default mode network

Note. Encoding of novel words (experimental condition) minus repeated encoding of the same two words (control condition), $p<0.05$, $k>10$. 
Recognition Typical Pattern:
lower stress + higher stress (n=36)

- Activation of bilateral VLPFC, DLPFC, hippocampus, supplementary motor area, motor area, occipital vision regions
- Deactivation of the default mode network

Note. Recognition of novel words (experimental condition) minus repeated recognition of the same two words (control condition), $p<0.001$, $k>10$. 
Perceived stress is associated with lower activation in prefrontal cortex during recognition of words in HIV-infected women.
Greater deactivation in the right medial PFC correlates with decreased semantic clustering on a standardized verbal memory test.

Note. Same pattern seen for HVLT trial 1 cluster score and deactivation in the right medial PFC during recognition, $r=-0.32$, $p=0.06$. Pattern of associations remain the same after controlling for age and recent cd4 count.
Conclusions

• Stress-related verbal memory deficits, particularly with less efficient strategic encoding in midlife HIV-infected women, may be partially accounted for by alterations in prefrontal cortex functioning.

• Understanding the role of the prefrontal cortex in stress-related memory impairments will be particularly important for women aging in the context of HIV as the prefrontal cortex is also particularly vulnerable to aging.

• What are the clinical implications?
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