Cortisol, learning, memory, and attention in relation to smaller hippocampal volume in police officers with posttraumatic stress disorder

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PTSD

Chronic psychiatric disorder that can occur in patients who have been exposed or witnessed traumatic experience of extreme nature

Develops after stressor

Have alterations in biological stress response

Hypothalamic-pituitary-adrenal (HPA) axis regulates stress response

Studies explored response of HPA axis in PTSD

Background

- Mechanism of altered HPA axis function in PTSD
  - Enhanced feedback sensitivity
  - Decreased pituitary sensitivity
  - Reduced adrenal sensitivity
  - Enhanced bioavailability of dexamethasone
  - Alterations in vasopressin release
Background

- Studies exposed PTSD subjects to non-pharm stressors
  - More elevated cortisol in response to stressor compared to controls

- CRH challenges
  - To assess responsivity of pituitary to CRH
  - Elicits higher cortisol response in PTSD in one study
  - Others found no difference

- ACTH stimulation test
  - Measures reactivity at level of adrenals
  - One study found larger increase in cortisol to stim test in PTSD cf to controls
Background

- **Dexamethasone suppression test**
  - Measures feedback inhibition of dex on HPA
  - Overall, studies show enhanced suppression of cortisol compared to controls
  - Supports hypothesis that PTSD patients have inhibition at level of pituitary

- **Metyrapone challenge**
  - Enhanced stimulation of adrenals in PTSD
  - Higher ACTH levels and 11-DOC in PTSD
  - Supports enhanced feedback inhibition at level of pituitary
  - Other studies have not confirmed this
PTSD and Hippocampus

- Patients with PTSD found to have smaller hippocampus volumes
- Have deficits in immediate and delayed verbal memory and short-term memory
- Few studies linking hippocampus volume and memory task performance
  - Limited evidence that those with smaller volumes perform worse on tasks
Hippocampus and HPA Axis

- One hypothesis
  - Prolonged exposure to excessive cortisol levels leads to atrophy of hippocampus
  - Leads to memory deficits
- Need for final link of structure to function
Police officers with PTSD and smaller hippocampal volumes will show significantly higher cortisol levels than controls and will perform more poorly on measures of verbal and visuospatial memory.
Study Design

- Case-matched control study
- Recruited Dutch police officers
- Mean experience of PTSD of 1.7 years
Endpoints

- **Primary**
  - Examine hippocampal volumes in subjects with PTSD

- **Secondary**
  - Examine salivary cortisol levels
  - Assess neuropsychological function
  - Correlate hippocampal volumes, cortisol levels, learning, memory, and attention performance in PTSD
Subjects

- 24 police officers
  - 12 with PTSD (by DSM-IV)
    - 3 had concurrent major depression
  - 12 controls—had traumatic experience but no PTSD

- Exclusion criteria:
  - Current major medical or psychiatric illness
  - Drug abuse
Measurements

- **Cortisol**
  - 3 salivary samples
  - Early AM, 1600 hr, bedtime

- **Hippocampus**
  - MRI
  - Measured manually

- **Learning, memory, attention**
  - Used California Verbal Learning Test (CVLT)
    - Assesses range of verbal learning and recall
  - Used Wechsler Memory Scale
    - Measures immediate and delayed visual recall
  - Used Stroop Color-Word Test
    - Measures attention and interference
Stats

- For demographic and clinical variables
  - Used two tailed $t$ test for continuous
  - Used $\chi^2$ test for categorical

- Volumes
  - Used multivariate analysis of covariance

- Cortisol
  - Multivariate ANOVA
  - Measured area under curve as well

- Neuropsych variables
  - Multivariate ANOVA

- Correlation analyses
  - For volume, cortisol, neuropsych, clinical variables
### Results - Baseline Variables

Table 1. Demographic and Clinical Variables in a Sample of Traumatized Police Officers With and Without PTSD

<table>
<thead>
<tr>
<th>Variables</th>
<th>PTSD Subjects (n = 12)</th>
<th>Control Subjects (n = 12)</th>
<th>F/χ²</th>
<th>p²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>35.1 (11.4)</td>
<td>36.7 (10.1)</td>
<td>-.36</td>
<td>.72</td>
</tr>
<tr>
<td>Education (y)</td>
<td>11 (2.3)</td>
<td>10.7 (1.8)</td>
<td>.39</td>
<td>.70</td>
</tr>
<tr>
<td>Duration of PTSD Symptoms (y)</td>
<td>1.7 (1.7)</td>
<td>0 (0)</td>
<td>3.35</td>
<td>.006</td>
</tr>
<tr>
<td>No. of traumas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In police work</td>
<td>16.8 (10)</td>
<td>16.5 (6.3)</td>
<td>.10</td>
<td>.92</td>
</tr>
<tr>
<td>Outside police work</td>
<td>2.6 (2.4)</td>
<td>1.7 (1.4)</td>
<td>1.15</td>
<td>.26</td>
</tr>
<tr>
<td>PTSD Total Score</td>
<td>9.8 (1.9)</td>
<td>.5 (1.2)</td>
<td>14.25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Re-experiencing Score</td>
<td>3.0 (1.3)</td>
<td>.2 (0.6)</td>
<td>6.99</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Avoidance Score</td>
<td>3.6 (5.2)</td>
<td>0 (0)</td>
<td>24.11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperarousal Score</td>
<td>3.3 (1.9)</td>
<td>.3 (.8)</td>
<td>8.15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HADS Total Score</td>
<td>17.6 (7.6)</td>
<td>5.6 (5.1)</td>
<td>4.55</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depression score</td>
<td>8.3 (4.3)</td>
<td>1.7 (2.1)</td>
<td>4.87</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anxiety score</td>
<td>9.3 (3.8)</td>
<td>3.9 (3.2)</td>
<td>3.72</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (58.3)</td>
<td>7 (58.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (41.7)</td>
<td>5 (41.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood Traumas, n (%)</td>
<td>2 (16.7)</td>
<td>0 (0)</td>
<td>2.18</td>
<td>.14</td>
</tr>
<tr>
<td>Mild Major Depression, n (%)</td>
<td>3 (25)</td>
<td>0 (0)</td>
<td>3.43</td>
<td>.064</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>6 (50)</td>
<td>7 (58.3)</td>
<td>.19</td>
<td>.67</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD), unless otherwise noted. PTSD, post-traumatic stress disorder; HADS, Hospital Anxiety and Depression Scale.

²Two-tailed, independent t test for continuous variables and χ² test for categorical variables.

*Age and gender were matching factors.*
## Results-Hippocampus Volumes

<table>
<thead>
<tr>
<th>Hippocampus</th>
<th>PTSD N=12</th>
<th>Controls N=12</th>
<th>F</th>
<th>P</th>
<th>Effect Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>2.0 (0.3)</td>
<td>2.4 (0.2)</td>
<td>10.29</td>
<td>0.004</td>
<td>0.62</td>
</tr>
<tr>
<td>Right</td>
<td>2.2 (0.2)</td>
<td>2.4 (0.3)</td>
<td>5.00</td>
<td>0.036</td>
<td>0.37</td>
</tr>
<tr>
<td>Total Brain Volume (cm³)</td>
<td>1214420 (100061)</td>
<td>1258748 (126822)</td>
<td>0.90</td>
<td>0.35</td>
<td>0.19</td>
</tr>
</tbody>
</table>
## Results - Salivary Cortisol

**Table 2. Cortisol, Neuropsychological, and Hippocampal Volume Variables in Police Officers with PTSD and a Traumatized, Non-PTSD Control Group**

<table>
<thead>
<tr>
<th>Variables</th>
<th>PTSD Subjects (n = 12)</th>
<th>Control Subjects (n = 12)</th>
<th>F</th>
<th>p*</th>
<th>Effect Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (nmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early morning</td>
<td>28.6 (25.7)</td>
<td>9.9 (7.0)</td>
<td>5.92</td>
<td>.024</td>
<td>.44</td>
</tr>
<tr>
<td>4:00 PM</td>
<td>8.8 (5.5)</td>
<td>7.2 (3.4)</td>
<td>.69</td>
<td>.42</td>
<td>.17</td>
</tr>
<tr>
<td>Bedtime</td>
<td>5.0 (4.5)</td>
<td>3.2 (2.4)</td>
<td>1.47</td>
<td>.24</td>
<td>.24</td>
</tr>
<tr>
<td>AUC*</td>
<td>25.6 (17.5)</td>
<td>13.8 (5.4)</td>
<td>4.97</td>
<td>.036</td>
<td>.41</td>
</tr>
</tbody>
</table>
Results - Neuropsychological Variables

For group, there was significant main effect (p=0.036) on variables
Results-Correlations

- **Negative Correlations**
  - Between severity of PTSD clinical symptoms and immediate recall scores \((r=-0.58)\)
  - Between re-experiencing scores and left hippocampal volume \((r=-0.58)\)

- **Positive Correlation**
  - Between salivary cortisol in early AM and right hippocampal volume \((r=0.58)\)

- **No Correlations**
  - Between volume and memory variables
  - Between cortisol and memory
  - Between cortisol and volume
Strengths and Weaknesses

- Homogeneous population
- Matched controls
- Minimal comorbidities
- Combines structure and function

- Cannot draw causal conclusions from this study
- Small sample size
- Focuses on early changes in PTSD, not chronic
Conclusions of Study

- PTSD subjects have smaller hippocampal volumes
- There is a link between the size of the hippocampus and the severity of PTSD
- PTSD subjects have higher AM cortisol levels that correlate positively with hippocampal volume
- PTSD subjects have poorer delayed recall and more perseveration
- Cannot conclude that there is stress-induced hippocampal damage due to high cortisol levels
Future Directions

- Confirmation of findings
- Look at changes in hippocampal volume over time
- Consider other structures in PTSD
  - Pituitary and HPA axis correlation
Thank you