NEUROPSYCHOLOGICAL FUNCTIONING IN POSTTRAUMATIC STRESS DISORDER

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Outline

- Neuropsychological functioning in PTSD and alcohol abuse: Teasing out the effects of comorbid conditions
- Longitudinal changes in brain anatomy and neuropsychological functioning in PTSD: Is PTSD a risk factor for cognitive aging?
- Neuropsychological functioning and inflammation in current, remitted, and past PTSD
- Future research goals
Neuropsychological Functioning in PTSD and Alcohol Abuse

Prior research: deficits in verbal memory, working memory, attention in patients with PTSD (Gilbertson et al., 2002; Vasterling et al., 1998; Vasterling et al., 2002)

Unclear if deficits were in fact due to PTSD or common comorbid conditions -- alcohol abuse

Neuropsychological Functioning in PTSD and Alcohol Abuse

- Prior studies had statistically controlled for effects, or excluded patients with alcohol abuse from PTSD studies.

- Ideal model – removes effect of alcohol AND examines interactive effects of PTSD and alcohol.
Neuropsychological Functioning in PTSD and Alcohol Abuse

2x2 Design

<table>
<thead>
<tr>
<th>PTSD</th>
<th>ETOH</th>
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PTSD assessed via Clinician-Administered PTSD Scale (CAPS)

Alcohol abuse and dependence assessed via Structured Clinical Interview for DSM Disorders (SCID) – past 5 year history

128 veterans, ages 20-60 (M = 47), 90% male, 73% White, majority Vietnam era
## Sample

<table>
<thead>
<tr>
<th></th>
<th>PTSD+ ETOH+ (N=30) Mean (SD)</th>
<th>PTSD+ ETOH- (N=37) Mean (SD)</th>
<th>PTSD- ETOH+ (N=30) Mean (SD)</th>
<th>PTSD- ETOH- (N=31) Mean (SD)</th>
<th>F</th>
<th>p</th>
<th>Significant Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48.57 (7.7)</td>
<td>47.89 (9.4)</td>
<td>43.6 (12.0)</td>
<td>46.42 (9.6)</td>
<td>F (3, 121) = 7.863 F (3,121) = .089 F (3,121) = .349</td>
<td>.065 .537 .315</td>
<td>None</td>
</tr>
<tr>
<td>Education</td>
<td>13.50 (1.6)</td>
<td>14.89 (2.4)</td>
<td>14.17 (1.7)</td>
<td>15.39 (2.0)</td>
<td>F (3, 124) = 2.69 F (3, 124) = 13.58 F (3, 124) = .059</td>
<td>.104 .000 .809</td>
<td>ETOH+ &lt; ETOH-</td>
</tr>
<tr>
<td>SCL-90 Depression</td>
<td>1.77 (.72)</td>
<td>1.85 (.96)</td>
<td>.70 (.47)</td>
<td>.46 (.72)</td>
<td>F (3, 124) = 85.14 F (3, 124) = .346 F (3, 124) = 1.40</td>
<td>.000 .557 .240</td>
<td>PTSD+ &gt; PTSD-</td>
</tr>
<tr>
<td>WAIS-III Vocabulary</td>
<td>46.40 (10.63)</td>
<td>50.08 (9.58)</td>
<td>51.47 (7.54)</td>
<td>53.87 (8.17)</td>
<td>F (3, 124) = 7.55 F (3, 124) = 3.56 F (3, 124) = .157</td>
<td>.007 .061 .693</td>
<td>PTSD+ &lt; PTSD-</td>
</tr>
<tr>
<td>LDH Total Drinks</td>
<td>88,614 (85039)</td>
<td>23,183 (38704)</td>
<td>48,453 (41218)</td>
<td>17,761 (45412)</td>
<td>F (3, 122) = 5.34 F (3, 122) = 23.78 F (3, 122) = 3.106</td>
<td>.022 .000 .081</td>
<td>PTSD+ &gt; PTSD- ETOH+ &gt; ETOH-</td>
</tr>
</tbody>
</table>
Neuropsychological Functioning in PTSD and Alcohol Abuse

Individual ANCOVAs (covarying for education, premorbid IQ estimate, depression, current alcohol use) on measures of:

- Verbal Learning
- Verbal Delayed Memory
- Visual Immediate Memory
- Visual Delayed Memory
- Working Memory
- Attention
- Processing Speed

Applied Bonferroni correction
Assessed main and interactive effects
Neuropsychological Functioning in PTSD and Alcohol Abuse

- Main effect of PTSD on:
  - Verbal learning
    - CVLT Total: $F(3, 121) = 7.863, p = .006$
  - Working memory
    - Digit Span: $F(3, 121) = 12.90, p < .001$
    - Letter Number Sequencing: $F(3, 112) = 12.48, p = .001$
  - Processing Speed
    - Digit Symbol: $F(3, 109) = 11.73, p = .001$
Neuropsychological Functioning in PTSD and Alcohol Abuse

- **Main effect of Alcohol Abuse on:**
  - Visual Immediate Memory
    - WMS-III Visual Immediate Memory Index: $F(3,121) = 6.41, p = .013$

- **No interaction effects or main effect of PTSD**

- **Significant differences, but functioning still in average range**

- **Neuropsychological differences are attributable to PTSD, and not confounding alcohol abuse diagnoses.**
PTSD and the Aging Brain

Is PTSD a risk factor for dementia or accelerated aging?

- Examined longitudinal trajectory of neurocognitive performance and neuroanatomical changes in a sample of 47 primarily Vietnam-era veterans:


Longitudinal Changes in Brain Anatomy and Neuropsychological Functioning in PTSD

Longitudinal images and neuropsychological data were analyzed to:

- Determine the extent to which PTSD accelerates brain atrophy and neurocognitive deficits
- Determine anatomy underlying any cognitive decline
## Sample

<table>
<thead>
<tr>
<th></th>
<th>PTSD-</th>
<th>PTSD+</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Baseline Age (yrs)</strong></td>
<td>52 ± 6 (39-60)</td>
<td>51 ± 7 (33-60)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Follow-up Age (yrs)</strong></td>
<td>55 ± 6 (41-63)</td>
<td>53 ± 7 (37-63)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Education (yrs)</strong></td>
<td>16 ± 2 (12-20)</td>
<td>15 ± 2 (12-20)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Interval (yrs)</strong></td>
<td>2.6 ± 0.4 (2.0-3.4)</td>
<td>3.0 ± 0.6 (2.0-4.0)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Baseline CAPS</strong></td>
<td>2 ± 3 (0-11)</td>
<td>61 ± 15 (31-92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Follow-up CAPS</strong></td>
<td>2 ± 3 (0-11)</td>
<td>52 ± 18 (19-84)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- N = 47, assessed over 2-5 years
- Primarily Vietnam veterans
- ALL PTSD+ participants continued to meet PTSD diagnostic criteria at T2
Longitudinal Changes in Brain Anatomy and Neuropsychological Functioning in PTSD

- No evidence of a group x time x age interaction on neuropsychological performance

- Inconsistent with Yehuda et al. (2006) findings of worse decline in verbal memory performance in Holocaust survivors with PTSD

- Middle aged sample, high mean education (almost 16 years)
Longitudinal Changes in Brain Anatomy and Neuropsychological Functioning in PTSD

- No differences between PTSD+ and PTSD- groups: Longitudinal course of PTSD heterogeneous

- No evidence for accelerated aging in PTSD+ patients with improving symptomatology

- Stable or declining PTSD+ patients show accelerated aging in frontal and temporal lobes, subcortical white matter, brainstem, and cerebellum

- Longitudinal atrophy in the precuneus predicted longitudinal decline in verbal memory
  - Decreased precuneus activation during encoding in PTSD (Geuze et al., 2008); associated with dementia (Buckner, 2004)
PTSD and the Aging Brain

- Archival Dementia Study at SFVA – N = 181,903. Vets with PTSD had almost twice risk of dementia (10.6% to 6.6%) (Yaffe et al., 2010, Archives of General Psychiatry)

- Current SFVA Study: Effects of TBI and PTSD on Alzheimer’s disease in Veterans (Weiner, PI)
  - Longitudinal study of Vietnam veterans (age 60-80) with TBI or PTSD
    - Will TBI and PTSD groups show accelerated rates of atrophy and cognitive decline (amyloid PET scans, MRI, neuropsych testing)?
Neuropsychological Functioning and Inflammation in Current versus Remitted PTSD

- Do neuropsychological deficits persist following remission of PTSD symptoms?

- Are the neuropsychological deficits associated with PTSD a risk factor or a consequence of the disorder?

- What are the potential mechanisms underlying the process of remission in PTSD?

Neuropsychological and Neurological Abnormalities in PTSD: Cause or Effect?
VULNERABILITY?

Neurocognitive Performance/Smaller Hippocampi

TRAUMATIC EVENT

PTSD

Neurocognitive Performance/Smaller Hippocampi

TOXICITY?
Apfel et al. 2011, *Biological Psychiatry*:

- Examined hippocampal volume in current, remitted, and no PTSD
- Current PTSD had significantly smaller hippocampal volume compared to other 2 groups
- Suggest hippocampal volume loss is reversible and a consequence of PTSD
  - Or, smaller hippocampi is associated with resistance to recovery
Neuropsychological Functioning and Inflammation in Current versus Remitted PTSD

- Chronically elevated levels of systemic inflammatory markers (Interleukin-6 (IL-6) and Tumor necrosis factor-alpha (TNF-α)) are found in PTSD (meta-analysis: Passos et al., 2015)

- Associated with memory deficits (Reichenberg et al., 2001; Yirmiya & Goshen, 2011)
Neuropsychological Functioning and Inflammation in Current versus Remitted PTSD

Neural Plasticity

- High levels of IL-6 and TNF-α inhibit neurogenesis and suppress neuronal proliferation which impairs neural plasticity (Ben-Hurr et al., 2003; Monje et al, 2003; Vallieres et al., 2002)

- Fluctuations in inflammation may also be the mechanisms which drives the chronicity, and remission of PTSD
Purpose of the Study:

- Determine if improved verbal memory functioning is seen in PTSD remission
- Examine if inflammation mediates the relationship between PTSD status and neuropsychological functioning
Methods

Gulf War Study:
Effects of Gulf War service on the brain

- \( N = 241 \)
  - Current PTSD (\( n = 45 \))
  - Past PTSD (\( n = 40 \))
  - No PTSD (\( n = 156 \))

- Interlukin-6 (IL-6) –
- Tumor Necrosis Factor – alpha (TNF-\( \alpha \)) - Soluble receptor II of TNF-\( \alpha \) (sTNF-RII)
- CVLT
- Logical Memory of WMS
## Demographic Differences: PTSD Status

<table>
<thead>
<tr>
<th></th>
<th>No PTSD</th>
<th>Past PTSD</th>
<th>Current PTSD</th>
<th>F or Chi-Square</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>45.32</td>
<td>43.21</td>
<td>41.49</td>
<td>3.01</td>
<td>.051</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>138 M/18 F</td>
<td>31 M/8 F</td>
<td>35 M/8 F</td>
<td>2.58</td>
<td>.257</td>
</tr>
<tr>
<td><strong>Years of Education</strong></td>
<td>14.82</td>
<td>14.39</td>
<td>14.19</td>
<td>2.14</td>
<td>.120</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td>27.52</td>
<td>29.51</td>
<td>28.13</td>
<td>3.68</td>
<td>.027</td>
</tr>
<tr>
<td><strong>GWI status</strong></td>
<td>69(84%)</td>
<td>10(12%)</td>
<td>3(4%)</td>
<td>24.97</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Vocabulary Score</strong></td>
<td>46.36</td>
<td>46.28</td>
<td>44.80</td>
<td>.454</td>
<td>.635</td>
</tr>
<tr>
<td><strong>Lifetime CAPS Score</strong></td>
<td>8.10</td>
<td>63.03</td>
<td>81.69</td>
<td>424.99</td>
<td>&lt; .001</td>
</tr>
<tr>
<td><strong>Current CAPS Score</strong></td>
<td>3.25</td>
<td>18.95</td>
<td>62.89</td>
<td>562.53</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

**Note.** GWI = Gulf War Illness; CAPS = Clinician Administered PTSD Scale
# PTSD Group Differences in Verbal Memory

<table>
<thead>
<tr>
<th></th>
<th>No PTSD</th>
<th>Past PTSD</th>
<th>Current PTSD</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT Immediate Recall</td>
<td>.043 (51.38)</td>
<td>-.183 (48.84)</td>
<td>-.210 (48.74)</td>
<td>1.58</td>
<td>.208</td>
</tr>
<tr>
<td>CVLT Percent Retention&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.443 (87.3%)</td>
<td>.456 (84.0%)</td>
<td>.504 (78.1%)</td>
<td>3.36</td>
<td>.036</td>
</tr>
<tr>
<td>LM Immediate Recall</td>
<td>-.032 (41.28)</td>
<td>.162 (43.03)</td>
<td>-.112 (40.33)</td>
<td>1.19</td>
<td>.306</td>
</tr>
<tr>
<td>LM Percent Retention</td>
<td>.005 (59.4%)</td>
<td>.246 (61.8%)</td>
<td>-.333 (55.8%)</td>
<td>3.76</td>
<td>.025</td>
</tr>
</tbody>
</table>

**Note.** CVLT = California Verbal Learning Test; LM = Logical Memory; Raw values are presented in parentheses; <sup>a</sup>CVLT Percent Retention was transformed with a reflection and log 10 transformation; Covariates appearing in the model are Vocabulary score and Gulf War Illness.
PTSD Group Differences on Delayed Verbal Memory Tasks

**Figure 1**

![Graph showing CVLT Percent Retention for No PTSD, Past PTSD, and Current PTSD groups.](image)

**Note.** Raw scores presented.

**Figure 2**

![Graph showing LM Percent Retention for No PTSD, Past PTSD, and Current PTSD groups.](image)

**Note.** Raw scores presented.
Cytokines Results

- No significant differences were seen between PTSD groups on cytokines.

- Cytokines were not related to memory measures in overall sample.
  - In veterans with current and past PTSD only, higher sTNF-RII was related to poorer CVLT immediate ($p = .004$) and Logical Memory delayed ($p = .020$) performance.

- Inflammatory markers did not mediate relationship between PTSD status and neuropsychological performance.
Discussion

- Differences between current PTSD and past PTSD groups suggest that verbal memory deficits remit when symptoms improve.

- Verbal memory deficits may be a feature of current PTSD rather than a risk factor.

- Provide preliminary support for the exploration of anti-inflammatory interventions in the treatment of PTSD.
  - SSRI use – improvements in neuropsychological performance?
Discussion

- No group differences in PTSD status on cytokines
  - Heterogeneity in PTSD/subset of individuals with elevated inflammatory levels – further exploration needed
  - Issue with Gulf War Illness control group?

- Current and Past PTSD
  - sTNF-RII uniquely accounted for:
    - 10.8% of variance in verbal learning (CVLT)
    - 3.17% in immediate memory (LM)
    - 8.20% in delayed memory (LM)
Current Research

- Neuropsychological functioning in mTBI and PTSD in OEF/OIF/OND veterans

- Interventions for neuropsychological impairments related to PTSD and mTBI
Future Research Plans

Extinction Learning, Neuropsychological Functioning, and Cognitive Training

- Impaired extinction learning in PTSD (Milad et al., 2008; 2009)
- Decreased hippocampal and vmPFC (rostral ACC) activation during extinction retention in PTSD
- Extinction retrieval is associated with vmPFC activity and thickness (Milad et al., 2005, 2007)
- Strengthening vmPFC activation is a target for clinical interventions that could improve extinction learning
Rostral ACC – inhibitory control and emotion regulation

Tasks of inhibitory control associated with decreased rostral ACC activation in PTSD (Carrion et al., 2008; Falconer et al., 2008)
Extinction Learning, Neuropsychological Functioning, and Cognitive Training

- PFC is a neuroplastic brain region (changes following SSRI, therapy)

- Neuroplasticity-based computer trainings — improve response inhibition and emotion reactivity \(\rightarrow\) bolster extinction learning

- Prior fMRI support with MDD and GAD (Gvurak et al. 2013)
Questions and Comments

Thank you!