MRI In TBI And PTSD

Norbert Schuff, PhD
Wang Zhen, PhD

Center for Imaging Of Neurodegenerative Diseases / VA Medical Center
University of California San Francisco

TBI - Problem Statement

• Most knowledge comes from hospitalized civilians
• TBI in returning veterans can be different
  ‣ In many cases less severe
  ‣ Much less documentation
  ‣ Diagnosis relies on symptoms
  ‣ Symptoms overlap with PTSD
  ‣ TBI and PTSD may co-exist
• Huge need for biomarkers of TBI and PTSD
• Our MRI studies in TBI are in progress!
Veteran TBI – Complications

- Objective detection of TBI and PTSD
- Improve differential diagnosis
- Predict progression
- Assess efficacy of therapeutic interventions
- Monitor treatments
- Elucidate mechanisms
MRI In PTSD: The Hippocampus

- Plays an important role in
  - Memory (declarative, spatial, and contextual)
  - Perception of chronic pain
- Susceptible to stress hormones (animal studies)
  - Suppressed neurogenesis in the dentate gyrus
  - Remodeling of dendrites in the CA3 region
  - Elevated excitability of hippocampal neurons

Problems

- Findings of hippocampal atrophy in PTSD have been inconsistent
- Alterations are subtle
- Normal aging and many brain disorders affect the hippocampus too

MRI Of Hippocampus in PTSD

- Hippocampal atrophy in PTSD is subtle
- Reduction of N-acetylaspartate can be substantial but highly variable

MRI Of Hippocampal Subfields

- Refine imaging of the hippocampus by resolving its subfields
- Determine if PTSD impacts specific hippocampal subfields

HYPOTHESES

- The dentate gyrus is selectively reduced in PTSD
- The pattern of reduced subfields in PTSD is different from that in aging and other brain disorders, e.g. Alzheimer’s disease

High-Field MRI of Subfields

Histology

Resolution 0.4 x 0.5 x 2mm³

4 Tesla MRI
Subfield Volumes In PTSD

17 PTSD +
CAPS: 61 ± 14

19 Control
CAPS: 8 ± 7

Differential Effects Of PTSD And Age
**Total Hippocampal Volume**


**Subfields In Other Conditions**


Table 1. Subfield and Total Hippocampal Volumes in mm3

<table>
<thead>
<tr>
<th>Subfield</th>
<th>Control (N=47)</th>
<th>MCI (N=14)</th>
<th>AD (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERC</td>
<td>202.4 ± 54.0</td>
<td>188.4 ± 48.0</td>
<td>145.0 ± 63.4*</td>
</tr>
<tr>
<td>Subiculum</td>
<td>200.2 ± 36.1</td>
<td>184.7 ± 38.1</td>
<td>154.2 ± 44.9*</td>
</tr>
<tr>
<td>CA1</td>
<td>331.4 ± 47.0</td>
<td>295.1 ± 42.5*</td>
<td>254.4 ± 63.1*</td>
</tr>
<tr>
<td>CA1-2 transition</td>
<td>20.5 ± 5.5</td>
<td>15.1 ± 3.4*</td>
<td>14.1 ± 3.8*</td>
</tr>
<tr>
<td>CA3B/CA5</td>
<td>224.4 ± 37.7</td>
<td>227.2 ± 34.3</td>
<td>230.3 ± 54.7</td>
</tr>
<tr>
<td>Total Hippocampus</td>
<td>6550.6 ± 770.4</td>
<td>5154.9 ± 917.7</td>
<td>4460.6 ± 1285.2*</td>
</tr>
</tbody>
</table>

* p<0.05 compared to controls

ERC, entorhinal cortex; CA1-2 transition, CA1-CA2 transition zone (definition see text); CA3B/CA5, CA3 and CA5 together with dentate gyrus

AD: Alzheimer’s disease
MCI: Mild cognitive impairment, a transitional condition to AD
Cortical Thickness In Relation To Subfields in PTSD

In PTSD, negative correlation between smaller hippocampus and thicker orbitofrontal cortex.

ASL-MRI shows hyperperfusion of orbitofrontal cortex in the same subjects.

Automated measurements of cortical thickness
http://surfer.nmr.mgh.harvard.edu/

Diffusion Tensor Imaging

Model of fractional anisotropy

\[ 0 < FA > 1 \]

White Matter Abnormalities In PTSD

Positive correlation between FA and CA3&Dentate volume

Negative correlation between FA and PTSD severity

FA decrease ~ CAPS increase in PTSD+ (p<0.01)

MRI in TBI

- Pilot Study – findings are preliminary
- All TBI are combat veterans
- Comparison with veterans positive or negative for PTSD
- Use of DTI
- No data yet of subfields and cortical thickness in TBI
White Matter Alterations In TPI

**TBI +**
N = 10 all male
Age: 33 ± 8 yrs
DOI > 2 Years

**PTSD –**
N=14 all male
Age matched
CAPS: 7 ± 7

Comparison: Alterations In PTSD

**PTSD +**
N = 19 all male
Age: 40 ± 12 yrs
CAPS: 61 ± 13

**PTSD –**
N=19 all male
Age matched
CAPS: 7 ± 7
*includes 5 not exposed to trauma
Challenges For MRI in TBI

- Heterogeneity of brain damage
  - Conventional group analyses may lack sensitivity
  - Individual tests could be more effective but require robust single subject statistics
  - Multivariate MRI, using structural perfusion, diffusion and spectral imaging together should improve statistical power

- Scale variability of damage
  - Large versus small scale dilemma in detecting alterations
  - Image analysis on a variable scale may be necessary

PTSD

- Reduction of dentate/CA3 in PTSD is consistent with suppressed neurogenesis under chronic stress
- Dentate/CA3 reductions are not seen in normal aging, MCI and AD and therefore might be specific for PTSD
- Correlations between dentate/CA3, thickness of cortical regions, and white matter degradation suggests that PTSD impacts brain networks

TBI

- Findings of abnormal FA values suggest damage of motor fibers
- Includes regional increase of FA – underlying mechanism unknown
- Differences in DTI patterns between TBI and PTSD still inconclusive

MORE STUDIES, REPLICATING THE PRELIMINARY FINDINGS ARE WARRANTED!

Conclusions
Impact

• MRI of hippocampal subfields might
  ‣ yield a marker of PTSD
  ‣ differentiate between PTSD from TBI
  ‣ be useful in assessing efficacy of pharmacologic interventions, specifically those that target proliferation of neurogenesis
  ‣ advance our understanding of neural mechanisms in PTSD

• DTI of white matter alterations might
  ‣ yield an index for TBI
  ‣ differentiate between TBI and PTSD

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