MRI In TBI And PTSD

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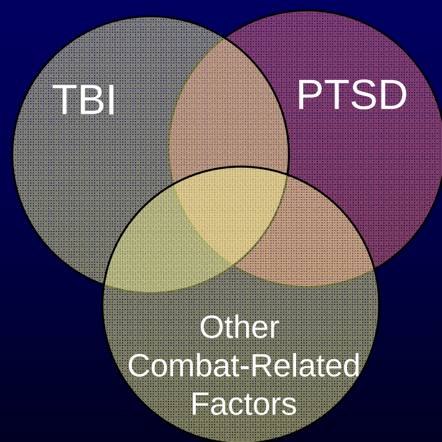
TBI - Problem Statement

- 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



Overall Goal For MRI

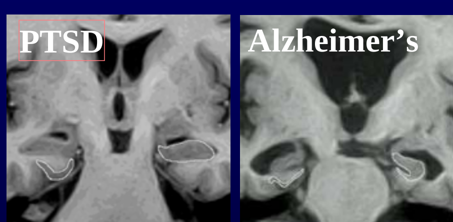
- Objective detection of TBI and PTSD
- Improve differential diagnosis
- Predict progression
- Assess efficacy of therapeutic interventions
- Monitor treatments
- Elucidate mechanisms

MRI In PTSD: The Hippocampus

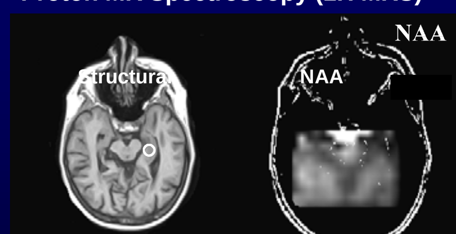
- Plays an important role in
  - Memory (declarative, spatial, and contextual)
  - Perception of chronic pain
- Susceptible to stress hormones (animal studies)
  - Suppressed neurogenesis in the dentate gyrus
  - Remodeling of dendrites in the CA3 region
  - Elevated excitability of hippocampal neurons
- **Problems**
  - Findings of hippocampal atrophy in PTSD have been inconsistent
  - Alterations are subtle
  - Normal aging and many brain disorders affect the hippocampus too

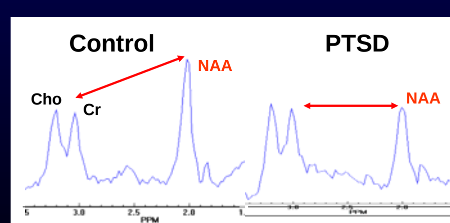
MRI Of Hippocampus in PTSD

Structural MRI



Proton MR Spectroscopy (1H MRS)





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

Schuff et al. Psychiatry Res. 2008;162(2):147-57.

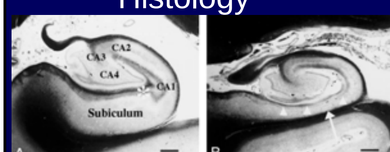
MRI Of Hippocampal Subfields

- 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

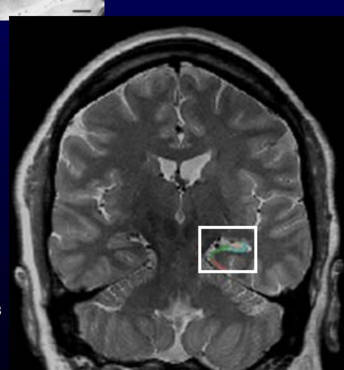
High-Field MRI of Subfields

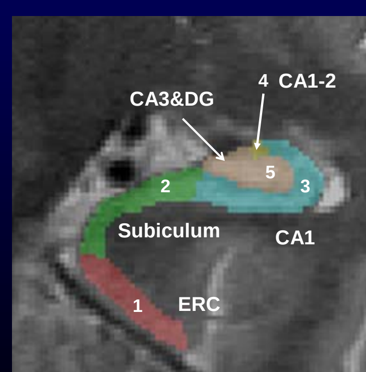
Histology



4 Tesla MRI

Resolution
0.4 x 0.5 x 2mm^3

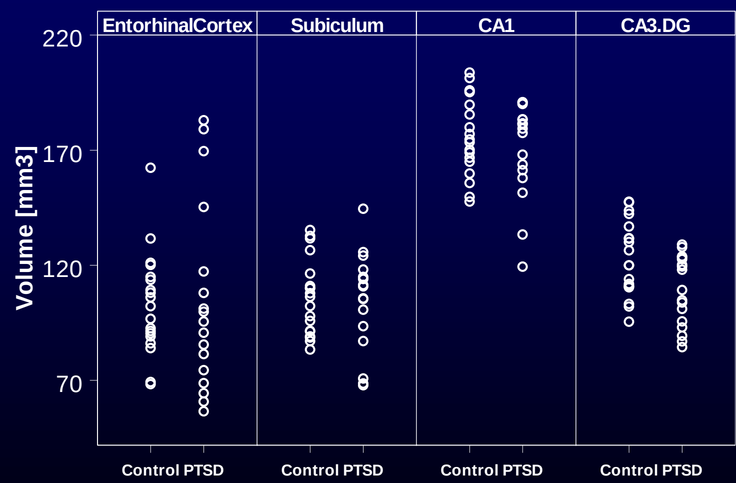




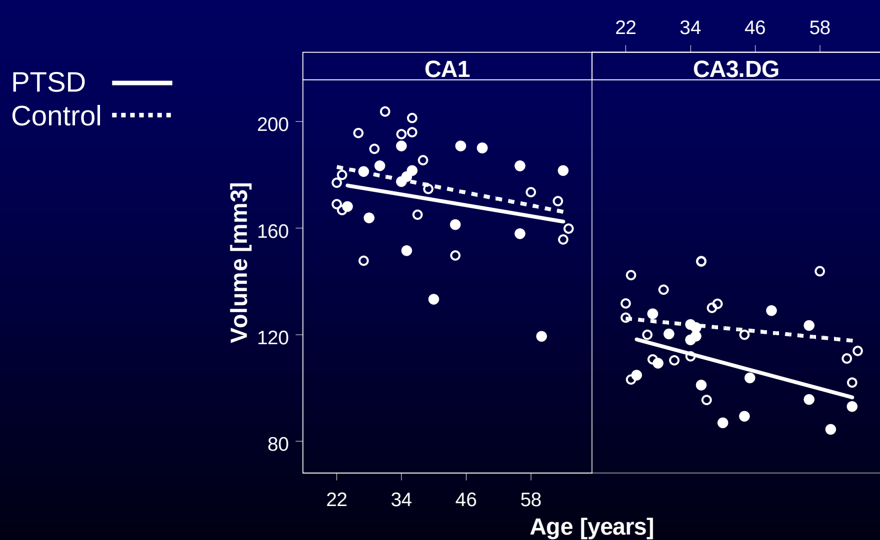
Subfield Volumes In PTSD

17 PTSD +
CAPS: 61 ± 14

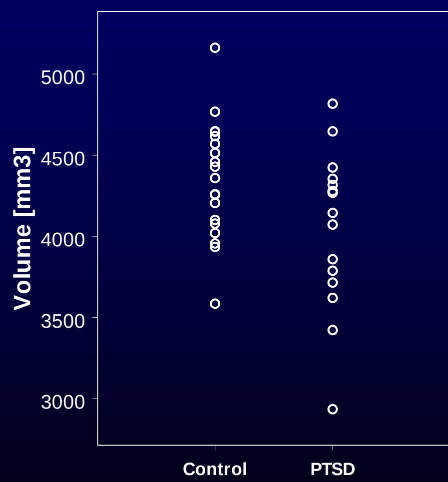
19 Control
CAPS: 8 ± 7



Differential Effects Of PTSD And Age



Total Hippocampal Volume



Subfields In Other Conditions

By Susanne Mueller et al. Neuroimage. 2008;42(1):42-8

Table 1. Subfield and Total Hippocampal Volumes in mm3

	Control N = 47	MCI N = 14	AD N = 14
ERC	202.4 ± 54.0	168.4 ± 48.0	145.0 ± 53.4*
Subiculum	200.2 ± 36.1	184.7 ± 38.1	154.2 ± 44.9*
CA1	331.4 ± 47.0	285.1 ± 42.5*	264.4 ± 63.1*
CA1-2 transition	20.5 ± 5.5	15.1 ± 3.4 *	14.1 ± 3.8*
CA3&DG	224.4 ± 37.7	227.2 ± 24.3	230.3 ± 54.7
Total Hippocampus	5520.6 ± 770.4	5154.9 ± 817.7	4450.8± 1285.2*

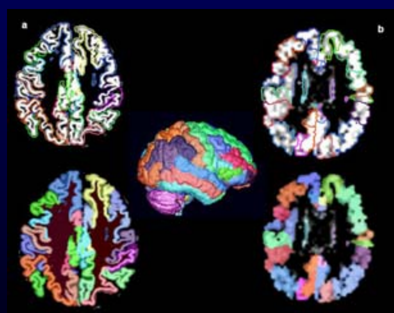
* p<0.05 compared to controls

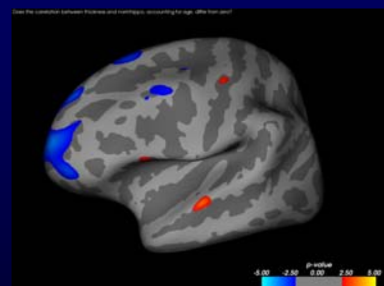
ERC, entorhinal cortex; CA1-2 transition, CA1-CA2 transition zone (definition see text); CA3&DG, CA3 and CA4 together with dentate gyrus

AD : **Alzheimer's disease**
MCI: **Mild cognitive impairment, a transitional condition to AD**

Cortical Thickness In Relation To Subfields in PTSD

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





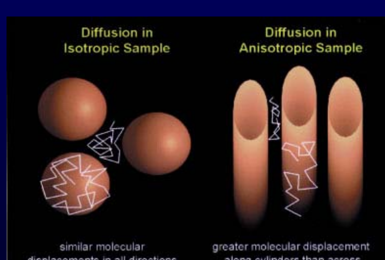
In PTSD, negative correlation between smaller hippocampus and thicker orbitofrontal cortex

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

Diffusion Tensor Imaging

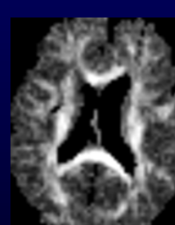
Model of fractional anisotropy

0 < FA > 1

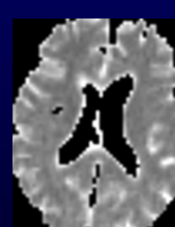


Beaulieu, NMR Biomed. 2002;15:435–455

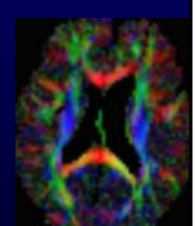
FA



Diffusivity



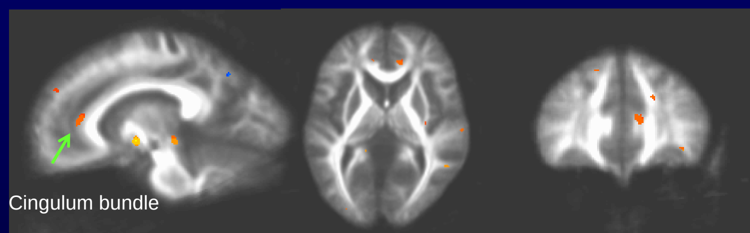
Directionality



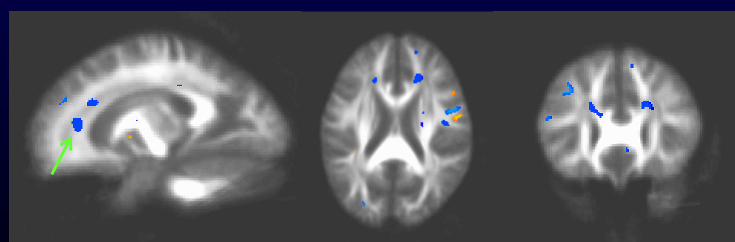
Left-right
Up-down
Front-back

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

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

White Matter Alterations In TPI

TBI +

N = 10 all male

Age: 33 ± 8 yrs

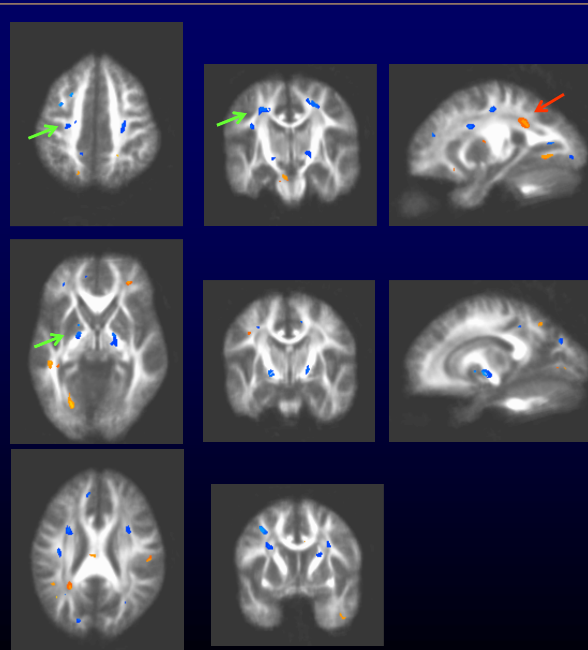
DOI > 2 Years

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

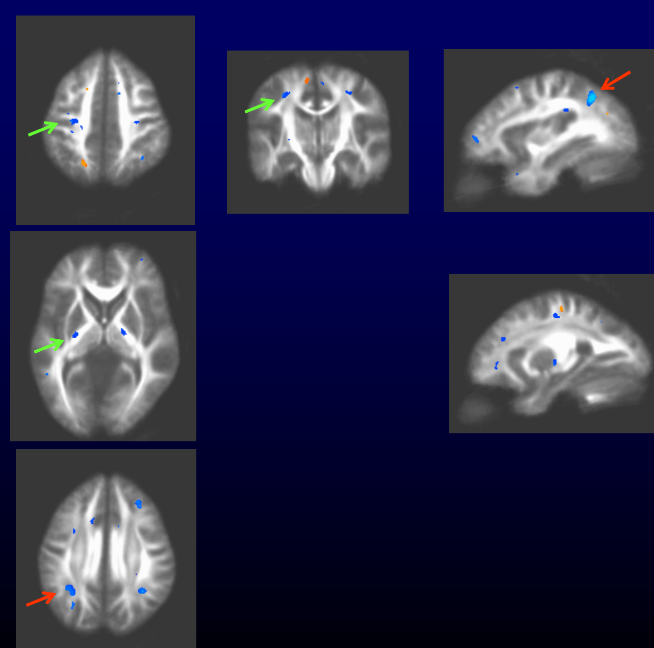
PTSD –

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 a 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**

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

Conclusions

- **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!**

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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