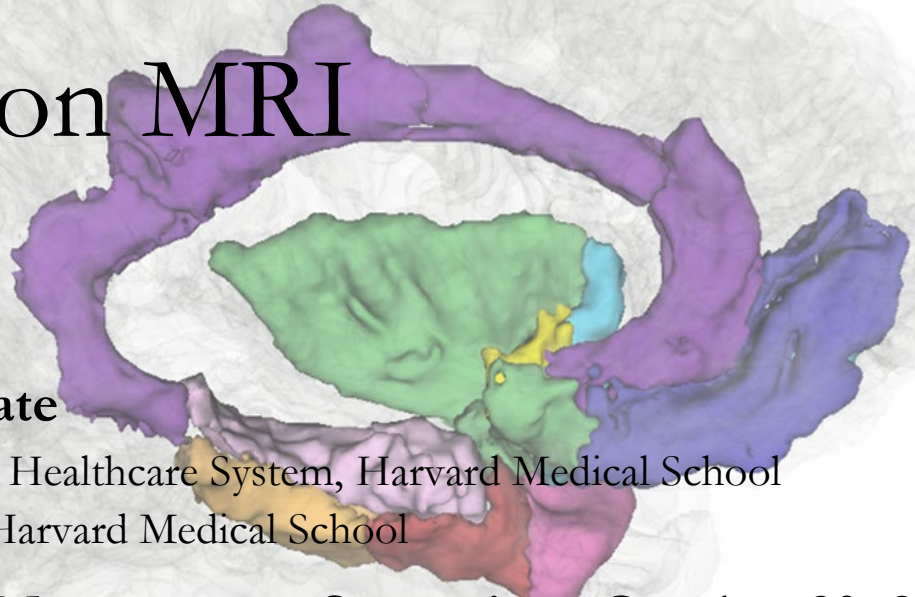
Understanding the Neurobiology of Deployment-Related Traumatic Co-morbidities with Diffusion MRI



William Milberg, PhD & Valerie Sydnor, PhD Candidate

Translational Research Center for TBI and Stress Disorders, VA Boston Healthcare System, Harvard Medical School

Psychiatry Neuroimaging Laboratory, Brigham and Women's Hospital, Harvard Medical School

VA HSR&D Cyberseminar: Mild TBI Diagnosis and Management Strategies • October 20, 2020

TRACTS Mission:

- To conduct multidisciplinary, clinical research aimed at understanding the complex pathophysiology associated with co-occurring TBI and related stress disorders.

- To develop effective treatment opportunities for OEF/OIF/OND Veterans with multiple co-occurring conditions.

TRACTS is a VA Rehabilitation Research and Development Traumatic Brain Injury National Network Research Center (B9254-C)

Inclusion Criteria

- Veteran of OEF/OIF (deployed at least one time to either Afghanistan or Iraq)
- Active duty Service Member (SM) not yet deployed to post-9/11 operation
- Age range 18-65 years at baseline visit

Exclusion Criteria

- History of neurological illness (Huntington's, Parkinson's, dementia, MS, etc)
- History of Seizure Disorders, unrelated to head injuries
- Current diagnosis of schizophrenia, bipolar or other psychotic disorder
- Severe depression or anxiety, current active homicidal and/or suicidal ideation with intent requiring crisis intervention
- Cognitive disorder due to general medical condition other than TBI
- Unstable psychological diagnosis that would interfere with accurate data collection, determined by consensus of at least two doctorate-level psychologists

TRACTS LONGITUDINAL COHORT STUDY:

Site	Baseline	*Time 2 (+1-2 yrs)	Time 3 (+5 yrs)	Deployed
Boston (2010)	669	397	64	618
Houston (2015)	191	79	0	191
Total	860	476	64	809

*Return rate = 66%

TRACTS Assessment Core

Medical/Blood-based Biomarkers	Neuropsych Domains	Affective/Psychosocial	Blast/TBI	Neuroanatomy S/F MRI
Blood Chemistry	Simple/Divided Attention	PTSD: CAPS & PCL-C	Boston Assessment of TBI-Lifetime	Cortical Volume
GWAS/Methylation	Information Processing Speed	DSM-IV AXIS I: SCID	Ohio State University TBI ID	Cortical Thickness
Neuro-steroids/hormones	Executive Function	Traumatic Life Events Questionnaire	Neurobehavioral Symptom Inventory	Diffusion Tensor
Inflammatory Markers	Declarative/Procedural Memory	Deployment Risk & Resiliency Inventory		Resting-State Networks
Quanterix SIMOA (NFL, T-Tau, AB40, AB42 BDNF, pNF-heavy, IL-6, IL-10, TNF alpha, NSE)	Pre-morbid Function	Depression, Anxiety & Stress Scale-21		Functional Connectivity
	Perception	Pittsburgh Sleep Quality Index		Task-Based fMRI
	Symptom Validity	McGill Pain Questionnaire		
	Psychomotor Speed	Alcohol, Nicotine		
		Sickness Impact Profile		

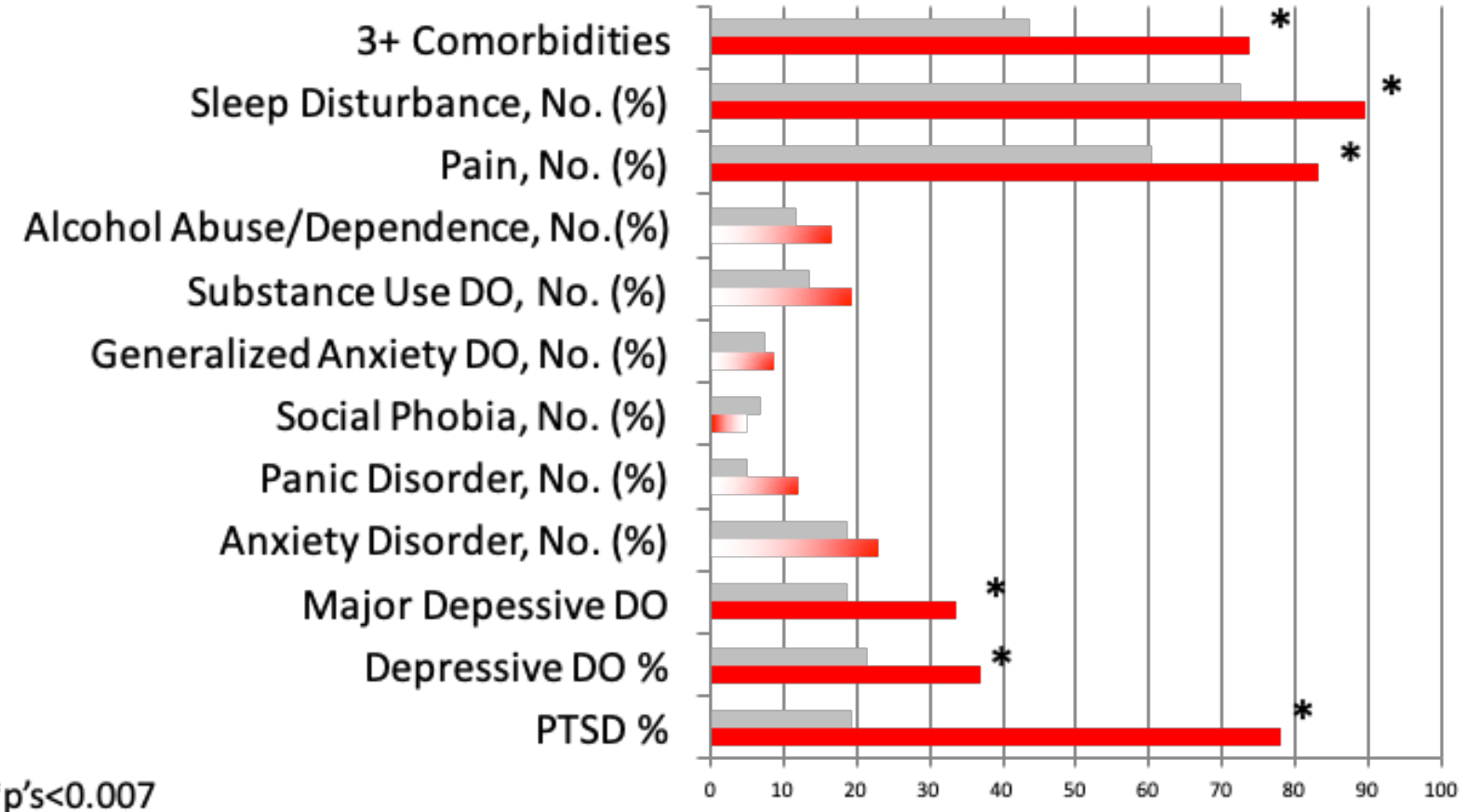
Blast exposure in first 456 deployed TRACTS participants (BATL-Assessment)

	< 10 meters	**11 – 25 meters**	**26-100 meters**	**Total Blast Exposures < 100 meters**
Number of Service Members Exposed (%)	211 (46.3%)	213 (46.7%)	342 (75.0%)	380 (83.3%)
Mean Blasts per Service Member (SD)	3.0 (21.6)	3.3 (12.4)	27.9 (104.6)	34.2 (115.4)
Median Blasts per Service Member (IQR)	0 (0, 2)	0 (0, 2)	2 (1, 10)	4 (1, 18)
Range of Blasts per Service Member	0 – 416	0 – 204	0 – 999	0 – 1102

Longitudinal Cohort Study (analysis n=511)

•mTBI is a polymorbid condition in Post 9/11 Veterans.
•Very few (8% of TRACTS cohort) have mTBI without a co-occurring clinical condition

•When a mTBI is diagnosed (red; n=241), there is a significantly greater percentage of cases* with co-occurring conditions compared to when no mTBI is diagnosed (gray; n=270)



*p's<0.007

Journal of Traumatic Stress
February 2015, *28*, 25–33

ISTSS International Society for Traumatic Stress Studies

Deployment-Related Psychiatric and Behavioral Conditions and Their Association with Functional Disability in OEF/OIF/OND Veterans

Sara M. Lippa,[1,2] Jennifer R. Fonda,[1,3] Catherine B. Fortier,[1,4] Melissa A. Amick,[1,5] Alexandra Kenna,[1] William P. Milberg,[1,4] and Regina E. McGlinchey[1,4]

[1]Translational Research Center for TBI and Stress Disorders (TRACTS) and Geriatric Research, Education and Clinical Center (GRECC), VA Boston Healthcare System Boston, Massachusetts, USA
[2]Defense and Veterans Brain Injury Center, Walter Reed National Military Medical Center, Bethesda, Maryland, USA
[3]Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts, USA
[4]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA
[5]Department of Psychiatry, Boston University Medical School, Boston, Massachusetts, USA

Understanding the factors that influence veterans' functional outcome after deployment is critical to provide appropriately targeted care. Mild traumatic brain injury (mTBI) and posttraumatic stress disorder (PTSD) have been related to disability, but other psychiatric and behavioral conditions are not as well examined. We investigated the impact of deployment-related psychiatric and behavioral conditions on disability among 255 OEF/OIF/OND service members and veterans. Structured clinical interviews assessed TBI and the psychiatric conditions of depression, PTSD, anxiety, and substance use. Self-report questionnaires assessed disability and the behavioral conditions of sleep disturbance and pain. Over 90% of participants had a psychiatric and/or behavioral condition, with approximately half presenting with $\geq$ 3 conditions. Exploratory factor analysis revealed 4 clinically relevant psychiatric and behavioral factors which accounted for 76.9% of the variance: (a) depression, PTSD, and military mTBI (deployment trauma factor); (b) pain and sleep (somatic factor); (c) anxiety disorders, other than PTSD (anxiety factor); and (d) substance abuse or dependence (substance use factor). Individuals with the conditions comprising the deployment trauma factor were more likely to be substantially disabled than individuals with depression and PTSD, but no military mTBI, $OR = 3.52$; 95% CI [1.09, 11.37]. Depression, PTSD, and a history of military mTBI may comprise an especially harmful combination associated with high risk for substantial disability.

Psychiatric and Behavioral Clusters (n=255)

	Factor 1	Factor 2	Factor 3	Factor 4
mTBI	**0.431**	0.349	-0.093	-0.532
Mood Di			0.01	0.049
PTSD	**0.692**	0.405	0.153	-0.004
Pain	-0.001	**0.863**	-0.102	-0.02
Sleep				0.136
Alcohol Abuse/Dependence	0.322	-0.05	**0.659**	-0.041
Other Abuse/Dependence	-0.147	0.085	**0.833**	0.023
Anxiety Disorder	0.142	0.173	-0.053	

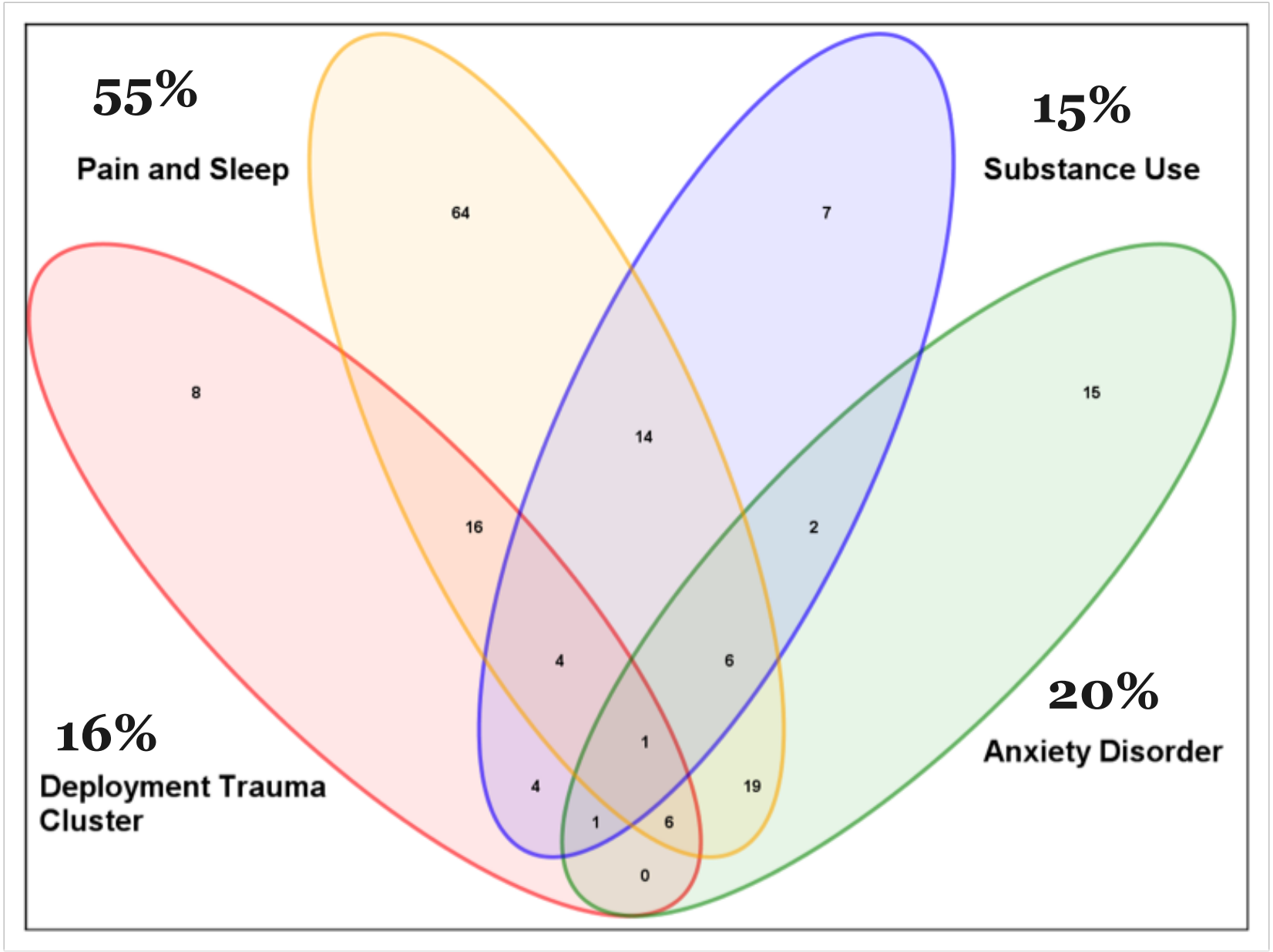
Deployment Trauma Phenotype

Pain/Sleep Factor

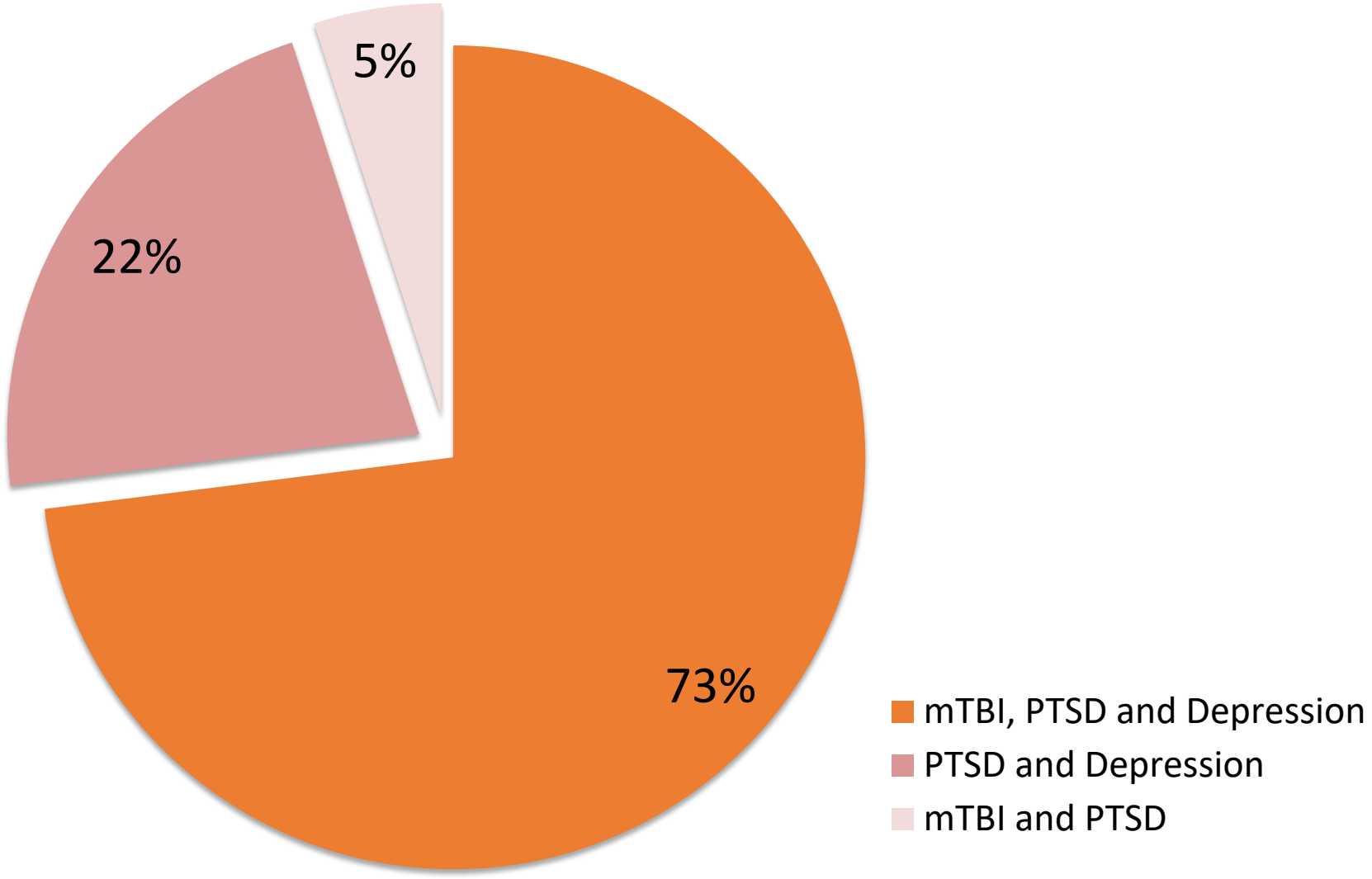
Substance Abuse Cluster

Anxiety Cluster

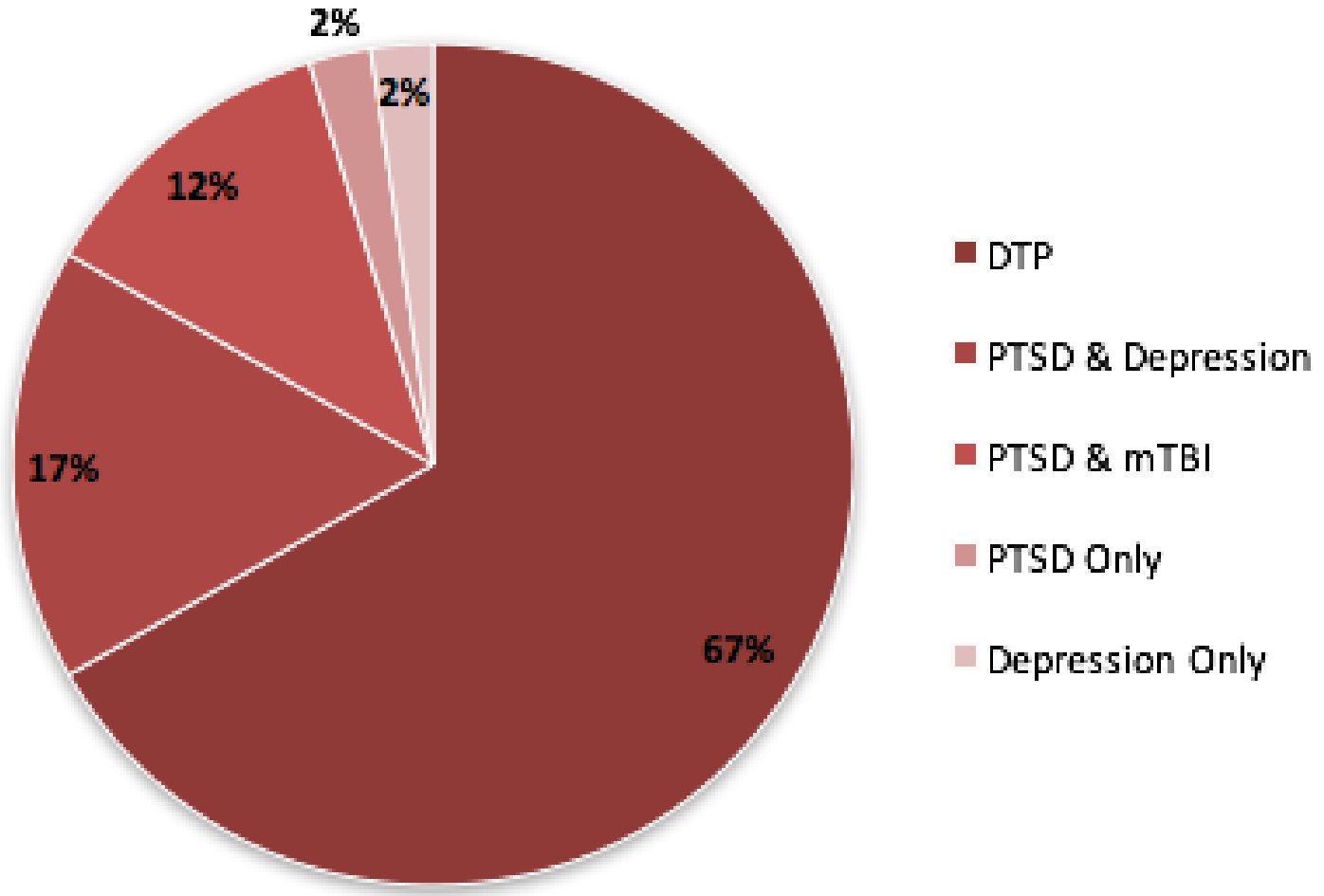
Psychiatric and Behavioral Clusters (n=255)



Deployment Trauma Phenotype Associated with Substantial Disability (WHODAS overall score of ≥45 =22; 73%=16/22)



Current Total TRACTS n=435
Deployment Trauma Phenotype Associated with Substantial Disability (WHODAS overall score of ≥45 =42; 67%=28/42)



TRANSLATIONAL RESEARCH CENTER FOR TBI AND STRESS DISORDERS
VA RR&D TBI NATIONAL NETWORK RESEARCH CENTER
VA BOSTON HEALTHCARE SYSTEM

https://www.researchgate.net/project/Translational-Research-Center-for-Traumatic-Brain-Injury-and-Stress-Disorders-TRACTS

https://heartbrain.hms.harvard.edu/

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Mild traumatic brain injury impacts associations between limbic system microstructure and post-traumatic stress disorder symptomatology

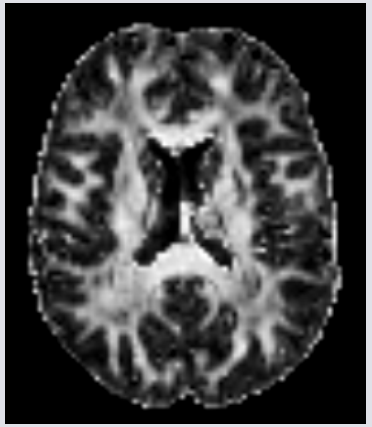
Valerie J. Sydnor[a], Sylvain Bouix[a], Ofer Pasternak[a], Elisabeth Hartl[a,b], Laura Levin-Gleba[a,c], Benjamin Reid[a], Yorghos Tripodis[d], Jeffrey P. Guenette[a,e], David Kaufmann[a,f], Nikos Makris[a,g], Catherine Fortier[c,h], David H. Salat[c,i], Yogesh Rathi[a], William P. Milberg[c,h,j], Regina E. McGlinchey[c,h,j], Martha E. Shenton[a,e,k,1], Inga K. Koerte[a,f,1,*]

[a] Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States
[b] Department of Neurology, University Hospital, LMU Munich, Munich, Germany
[c] Translational Research Center for TBI and Stress Disorders (TRACTS), VA Boston Healthcare System, Boston, MA, United States
[d] Boston University School of Public Health, Boston University, Boston, MA, United States
[e] Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States
[f] Department of Child and Adolescent Psychiatry, Psychosomatic, and Psychotherapy, Ludwig-Maximilian University, Munich, Germany
[g] Center for Morphometric Analysis, Departments of Psychiatry and Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States
[h] Department of Psychiatry, Harvard Medical School, Boston, MA, United States
[i] Neuroimaging Research for Veterans (NeRVe) Center, VA Boston Healthcare System, Boston, MA, United States
[j] Geriatric Research, Education and Clinical Center (GRECC), VA Boston Healthcare System, Boston, MA, United States
[k] VA Boston Healthcare System, Brockton Division, Brockton, MA, United States

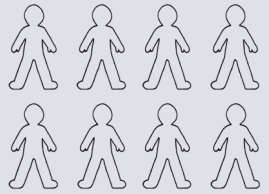
Study Goals

1. To understand potential neurological contributors to PTSD symptom severity

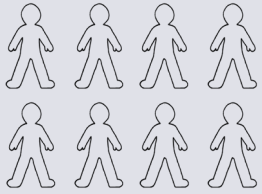
2. To investigate whether mild TBI affects the clinical and neurological presentation of PTSD



PTSD Only



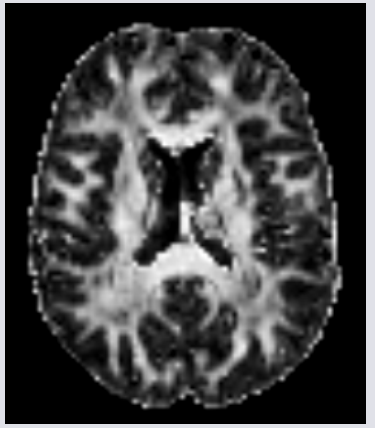
PTSD+TBI



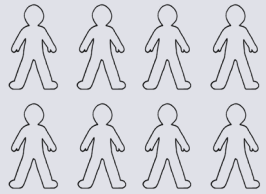
Study Goals

1. To understand potential neurological contributors to PTSD symptom severity

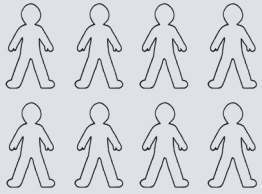
2. To investigate whether mild TBI affects the clinical and neurological presentation of PTSD



PTSD Only



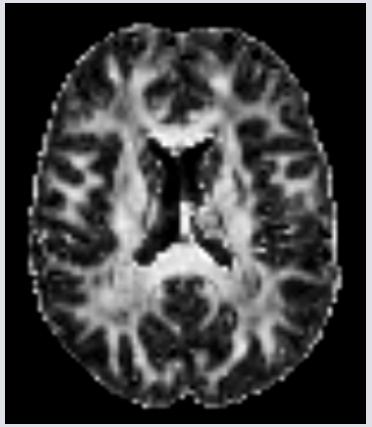
PTSD+TBI



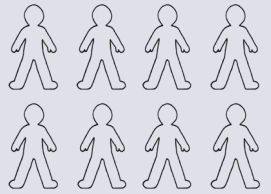
Study Goals

1. To understand potential neurological contributors to PTSD symptom severity

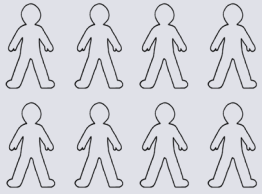
2. To investigate whether mild TBI affects the clinical and neurological presentation of PTSD



PTSD Only

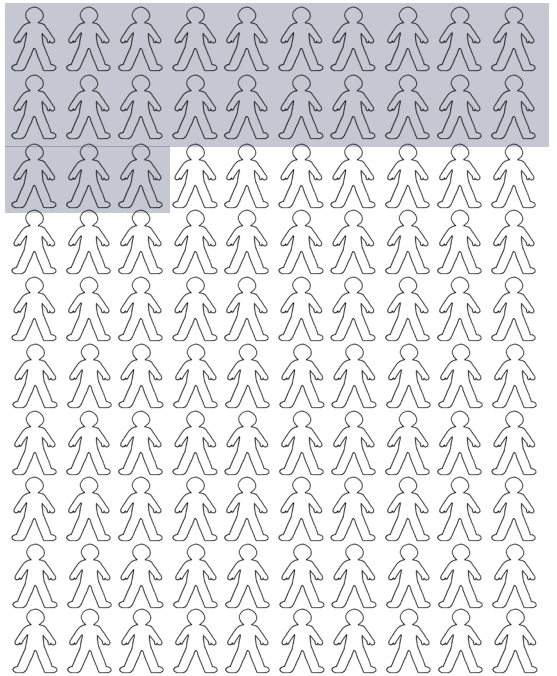


PTSD+TBI



PTSD and mTBI: Prevalence & Consequences

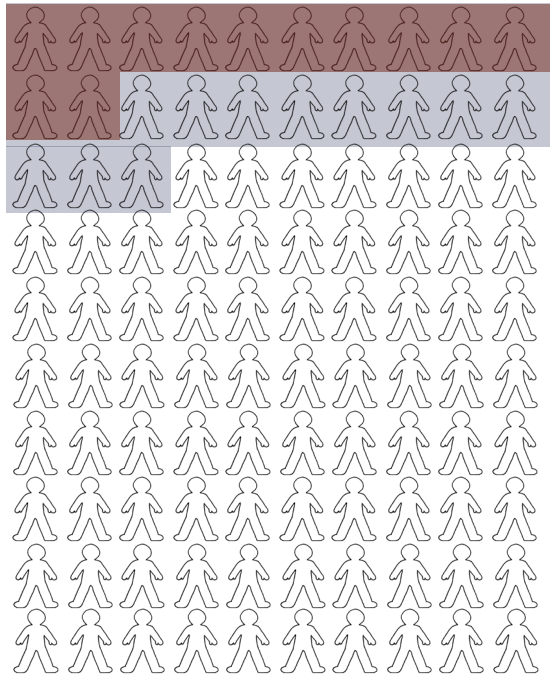
- ~23% of OEF/OIF Veterans are diagnosed with PTSD[1]



1. Fulton et al., 2015, J Anxiety Disord; 2. Stojanovic et al., 2016, Pain Med; 3. Combs et al., 2015, J Neurotrauma; 4. Lippa et al., 2015, J Trauma Stress;
5. Vanderploeg et al., 2009, Arch Phys Med Rehabil

PTSD and mTBI: Prevalence & Consequences

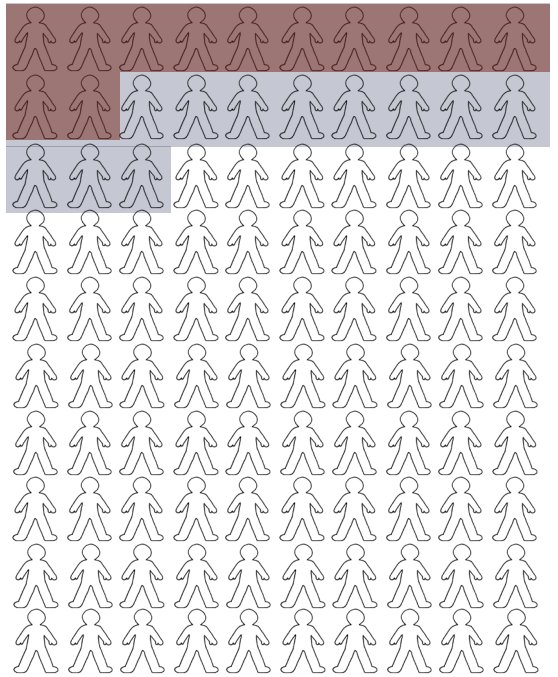
- ~23% of OEF/OIF Veterans are diagnosed with PTSD[1]
- ~50% with PTSD have a military-related mTBI[2]



1. Fulton et al., 2015, J Anxiety Disord; 2. Stojanovic et al., 2016, Pain Med; 3. Combs et al., 2015, J Neurotrauma; 4. Lippa et al., 2015, J Trauma Stress; 5. Vanderploeg et al., 2009, Arch Phys Med Rehabil

PTSD and mTBI: Prevalence & Consequences

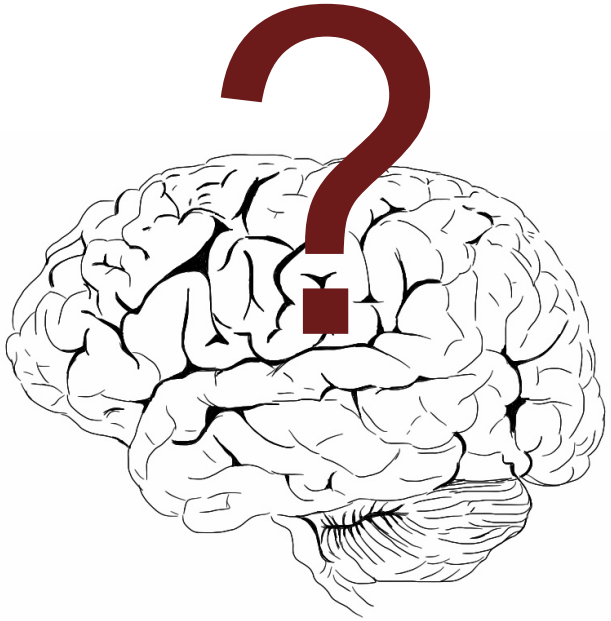
- ~23% of OEF/OIF Veterans are diagnosed with PTSD[1]
- ~50% with PTSD have a military-related mTBI[2]
- Compared to PTSD, individuals with PTSD+mTBI:
  - Endorse more severe PTSD symptoms[3]
  - Exhibit poorer neurocognitive functioning[3]
  - Are more functionally disabled[4]
  - Experience worse long-term recovery[5]



1. Fulton et al., 2015, J Anxiety Disord; 2. Stojanovic et al., 2016, Pain Med; 3. Combs et al., 2015, J Neurotrauma; 4. Lippa et al., 2015, J Trauma Stress; 5. Vanderploeg et al., 2009, Arch Phys Med Rehabil

PTSD and mTBI: Prevalence & Consequences

- ~23% of OEF/OIF Veterans are diagnosed with PTSD[1]
- ~50% with PTSD have a military-related mTBI[2]
- Compared to PTSD, individuals with PTSD+mTBI:
  - Endorse more severe PTSD symptoms[3]
  - Exhibit poorer neurocognitive functioning[3]
  - Are more functionally disabled[4]
  - Experience worse long-term recovery[5]



1. Fulton et al., 2015, J Anxiety Disord; 2. Stojanovic et al., 2016, Pain Med; 3. Combs et al., 2015, J Neurotrauma; 4. Lippa et al., 2015, J Trauma Stress;
5. Vanderploeg et al., 2009, Arch Phys Med Rehabil

Previous Studies of PTSD Pathomechanisms

Neuroimaging

Alterations in limbic/paralimbic macrostructure

- Reduced hippocampal volume[1,2,3]
- Reduced amygdala volume[1,2,3]
- Reduced cingulate cortex volume/thickness[1,3]
- Reduced temporal lobe gray matter[1]

1. Bromis et al., 2018, AJP; 2. Logue et al., 2018, Biol Psychiatry; 3. O'Doherty et al., 2015, Psychiatry Res

Previous Studies of PTSD Pathomechanisms

Neuroimaging

Alterations in limbic/paralimbic macrostructure

- Reduced hippocampal volume[1,2,3]
- Reduced amygdala volume[1,2,3]
- Reduced cingulate cortex volume/thickness[1,3]
- Reduced temporal lobe gray matter[1]

Emotion
Appetitive/aversive conditioning
Motivation
Learning
Memory
Reward responding

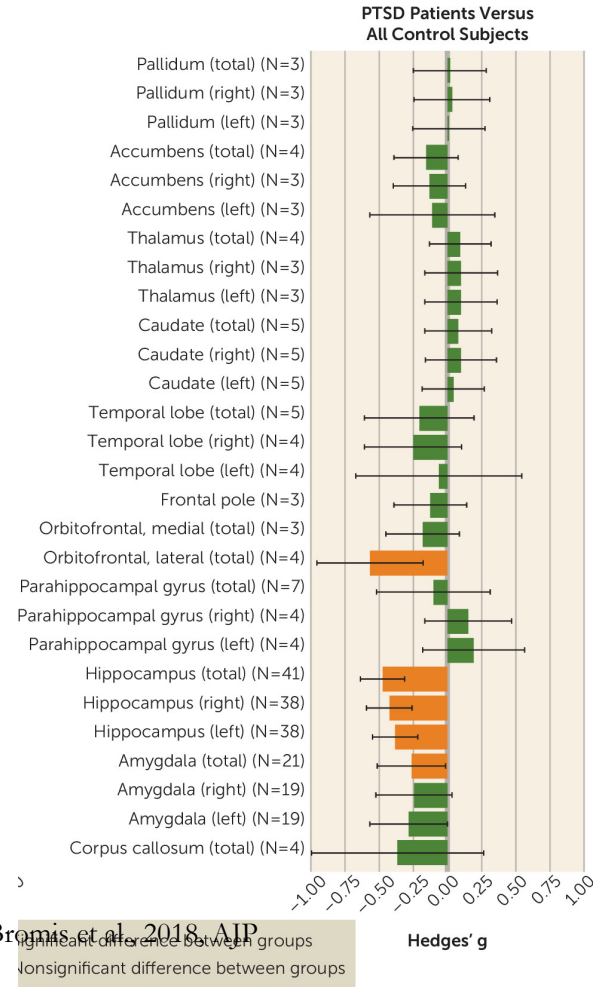
1. Bromis et al., 2018, AJP; 2. Logue et al., 2018, Biol Psychiatry; 3. O'Doherty et al., 2015, Psychiatry Res

Previous Studies of PTSD Pathomechanisms

Neuroimaging

Alterations in limbic/paralimbic macrostructure

- Reduced hippocampal volume[1,2,3]
- Reduced amygdala volume[1,2,3]
- Reduced cingulate cortex volume/thickness[1,3]
- Reduced temporal lobe gray matter[1]



Bromis et al., 2018, AJP

1. Bromis et al., 2018, AJP; 2. Logue et al., 2018, Biol Psychiatry; 3. O'Doherty et al., 2015, Psychiatry Res

Previous Studies of PTSD Pathomechanisms

Neuroimaging

Alterations in limbic/paralimbic macrostructure

- Reduced hippocampal volume[1,2,3]
- Reduced amygdala volume[1,2,3]
- Reduced cingulate cortex volume/thickness[1,3]
- Reduced temporal lobe gray matter[1]

1. Bromis et al., 2018, AJP; 2. Logue et al., 2018, Biol Psychiatry; 3. O'Doherty et al., 2015, Psychiatry Res

Magnitude of volumetric and thickness changes correlates with PTSD symptom severity

Lindemer et al., 2013, Neuroimage Clin; O'Doherty et al., 2017, Psychiatry Res Neuroimaging; Wrocklage et al., 2017, Eur Neuropsychopharmacol

↓

PTSD is a dimensional disorder, wherein symptoms and correlated neurobiological changes occur on a continuum

Ruscio et al., 2002, J Abnorm Psychol; Fobers et al., 2005, J Trauma Stress

Previous Studies of PTSD Pathomechanisms

Neuroimaging

Alterations in limbic/paralimbic macrostructure

- Reduced hippocampal volume[1,2,3]
- Reduced amygdala volume[1,2,3]
- Reduced cingulate cortex volume/thickness[1,3]
- Reduced temporal lobe gray matter[1]

Animal Models

Microstructural effects of stress

- Dendritic atrophy in the hippocampus[4]
- Loss of glia cells in limbic cortex[5]

1. Bromis et al., 2018, AJP; 2. Logue et al., 2018, Biol Psychiatry; 3. O'Doherty et al., 2015, Psychiatry Res

4. Magariños & McEwen, 1995, Neuroscience; 5. Averill et al., 2017, Neurosci Lett

Previous Studies of PTSD Pathomechanisms

Neuroimaging

Animal Models

Alterations in limbic/paralimbic macrostructure ⟷ Microstructural effects of stress

Harnessing microstructural diffusion imaging to study the relationship between PTSD severity and limbic microstructure

Conceptual and Technical Advances

- Dimensional approach to studying PTSD symptomatology

Conceptual and Technical Advances

- Dimensional approach to studying PTSD symptomatology
- Examined associations between brain microstructure and dimensional PTSD symptom severity in Veterans with PTSD only and PTSD and mTBI

1. Is dimensional PTSD symptom severity associated with the microstructure of limbic and paralimbic gray matter, as evinced by diffusion MRI?

2. Does mild TBI impact associations between PTSD symptom severity and brain microstructure?

1. Is dimensional PTSD symptom severity associated with the microstructure of limbic and paralimbic gray matter, as evinced by diffusion MRI?

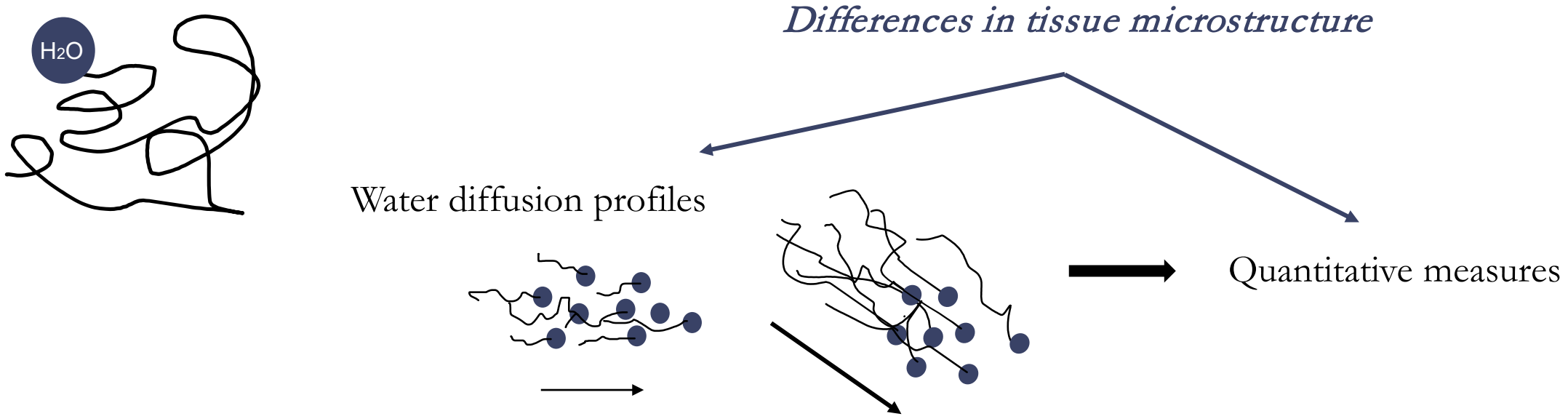
2. Does mild TBI impact associations between PTSD symptom severity and brain microstructure?

Conceptual and **Technical** Advances

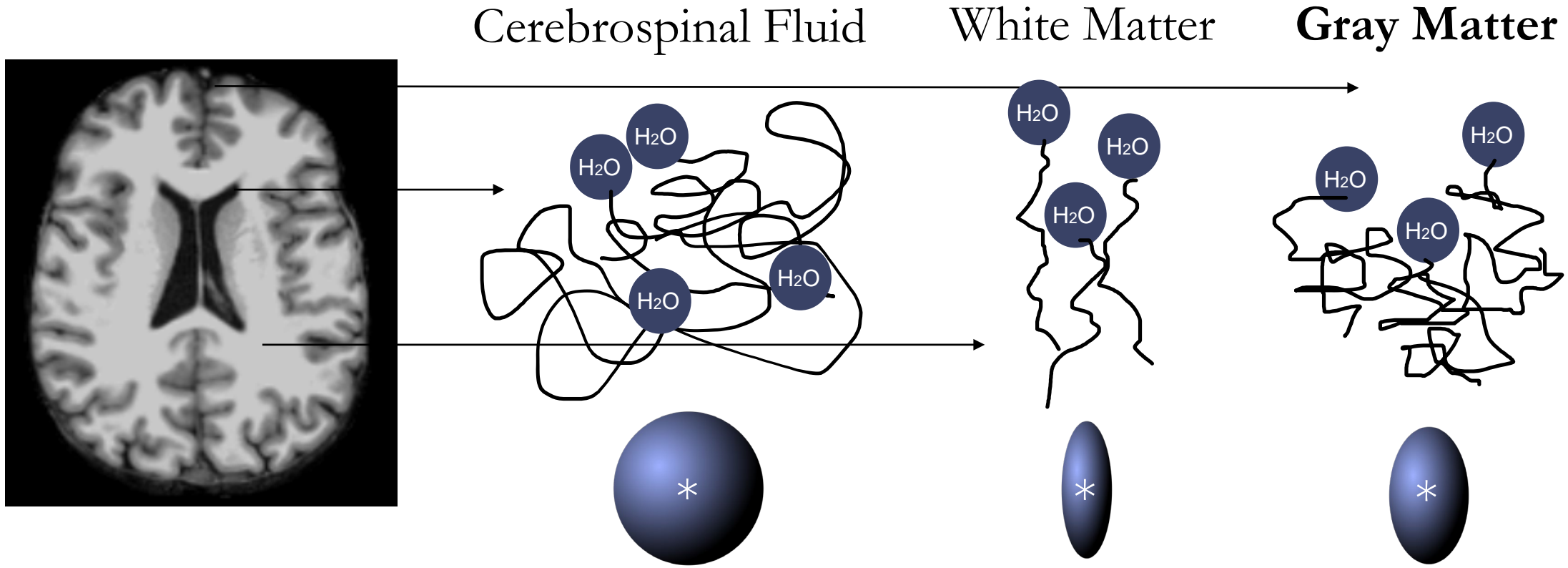
- Dimensional approach to studying PTSD symptomatology
- Examined associations between brain microstructure and dimensional PTSD symptom severity in Veterans with PTSD only and PTSD and mTBI
- Harnessed an advanced, multi-compartment diffusion modeling approach

Diffusion Imaging

An MR-based neuroimaging method that allows us to study brain tissue microstructure by characterizing the diffusion of water molecules in the brain

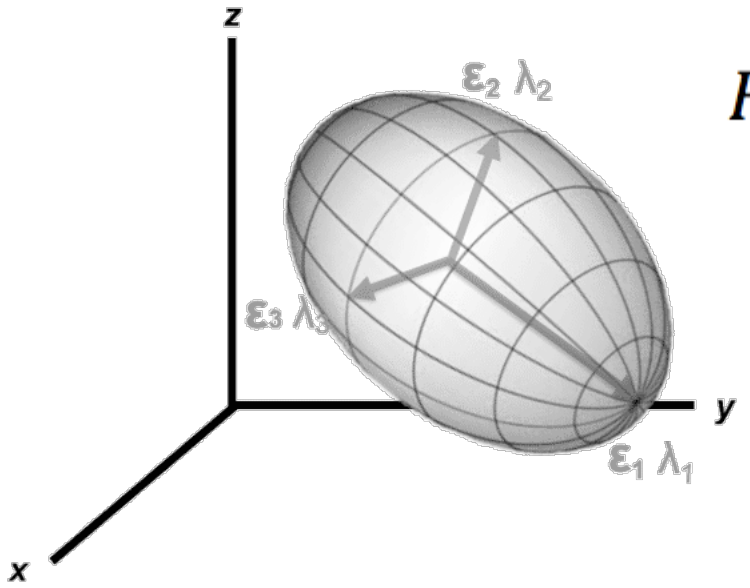


Diffusion Imaging

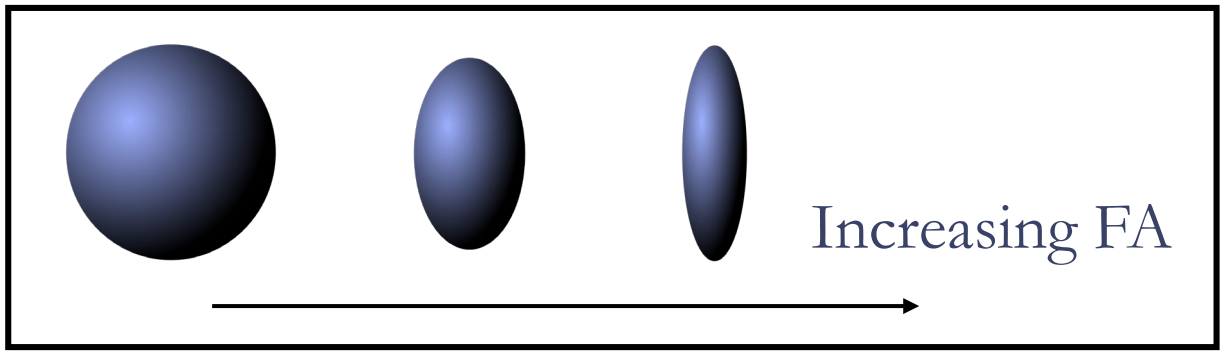


Diffusion Imaging Quantitative Measure

FRACTIONAL ANISOTROPY

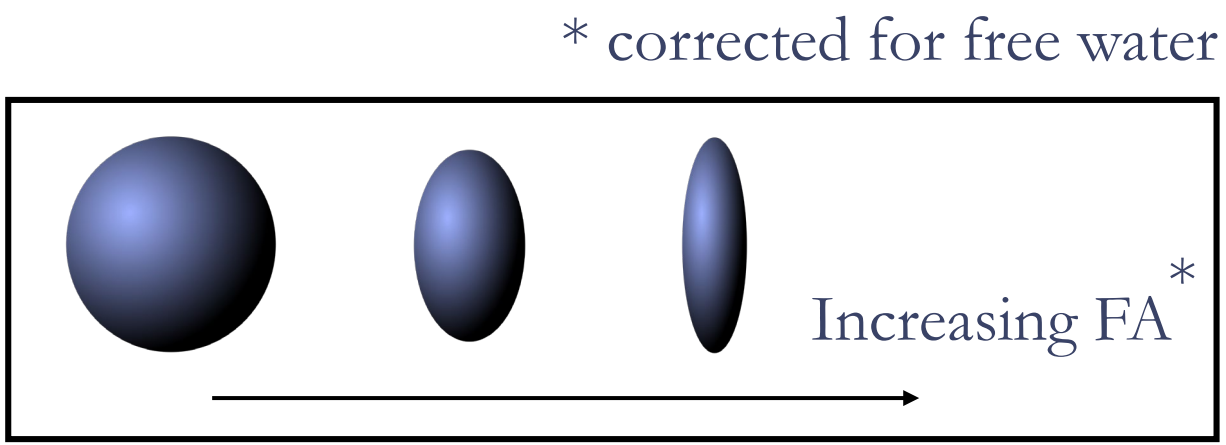


$$FA = \sqrt{\frac{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_1-\lambda_3)^2}{2(\lambda_1{}^2+\lambda_2{}^2+\lambda_3{}^2)}}$$



Free Water Imaging

- A two-compartment diffusion model
- Models extracellular free water (isotropic compartment) and tissue (diffusion tensor)
- Mitigates partial voluming
- FA more specific to tissue



Pasternak et al., 2009, Magn Reson Med.

Gray Matter Fractional Anisotropy

- Differences in tissue composition or complexity can affect FA
- Studies combining diffusion and histology have shown:
  - Dendritic atrophy ↑ FA
  - Increased intracortical myelin ↑ FA
  - Glia loss ↓ FA
  - Reduced cell density ↓ FA
- Diffusion MRI/FA is not cell type specific

1. Is dimensional PTSD symptom severity associated with the microstructure of limbic and paralimbic gray matter, as evinced by diffusion MRI?

2. Does mild TBI impact associations between PTSD symptom severity and brain microstructure?

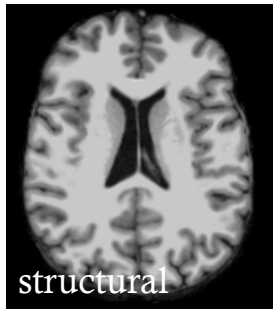
Study Design Overview

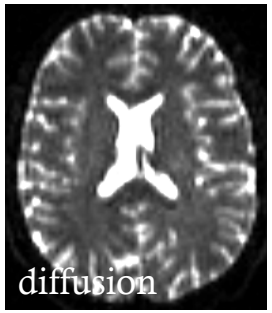
Study Sample

102 male TRACTS participants
All diagnosed with current PTSD

Neuroimaging

Diffusion MRI scan
Structural MRI scan





Clinical Measures

frequency + severity of 17 symptoms

CAPS-Diagnostic Version: PTSD symptom severity
Boston Assessment of TBI Lifetime: mTBI/blasts

Study Sample

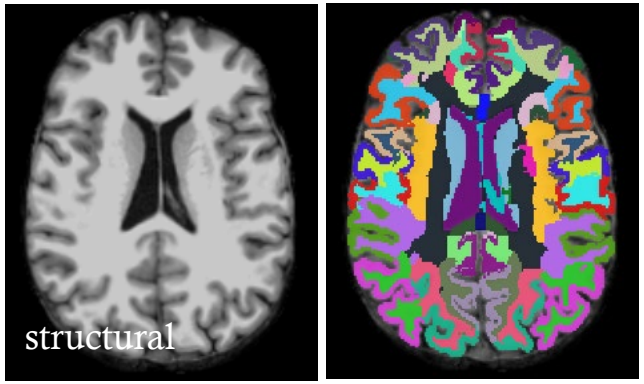
PTSD Only: N=48
PTSD+TBI: N=54

PTSD+TBI group endorsed significantly more severe PTSD symptoms than the PTSD Only group

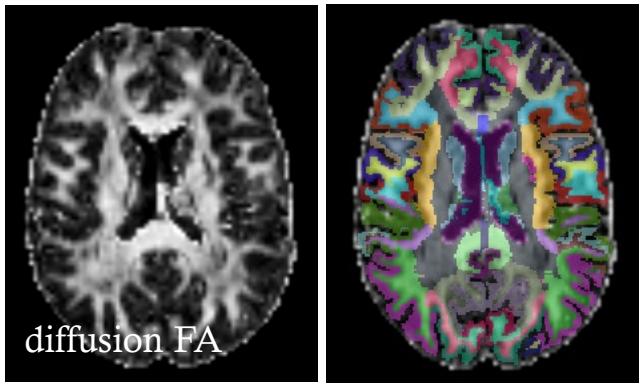
Years of Education	13.6 (± 1.9)	13.7 (± 1.8)	0.923
Race (Caucasian)	77.8%	83.3%	0.619^{+}
Branch of Service (Army)	53.7%	54.2%	1.000^{+}
Branch of Service (Marines)	31.5%	37.5%	0.539^{+}
CAPS-DX Current Symptom Severity Score	60.2 (± 18.8)	69.6 (± 15.0)	0.007^*
Current Mood Disorder	27.8%	29.6%	0.216^{+}
Current Anxiety Disorder	16.7%	18.8%	0.801^{+}
Current Substance Use Disorder	14.8%	22.9%	0.320^{+}
DASS21 Anxiety Symptoms Total Score	6.6 (± 7.2)	9.5 (± 7.6)	0.054^
DASS21 Depression Symptoms Total Score	9.9 (± 9.2)	13.0 (± 8.8)	0.081^
LDH Weight-Corrected Lifetime Drinking Score	2109.6 (± 2391.4)	1917.4 (± 1829.3)	0.651^
Number of Military Mild TBIs	0.0 (± 0.0)	1.9 (± 2.3)	<0.001^*
Number of Close Range Blasts (<10 m)	1.8 (± 7.6)	12.3 (± 59.8)	0.232^

Analysis Overview

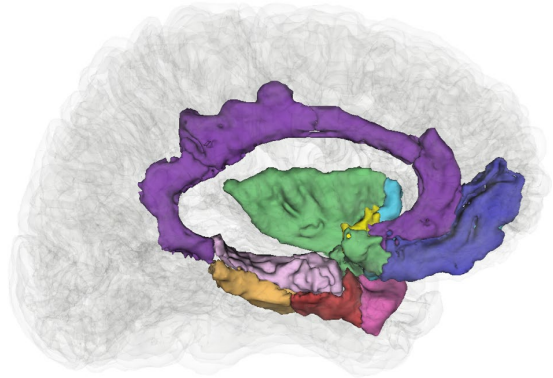
Anatomical Parcellation



Register to Free-Water Corrected FA Maps



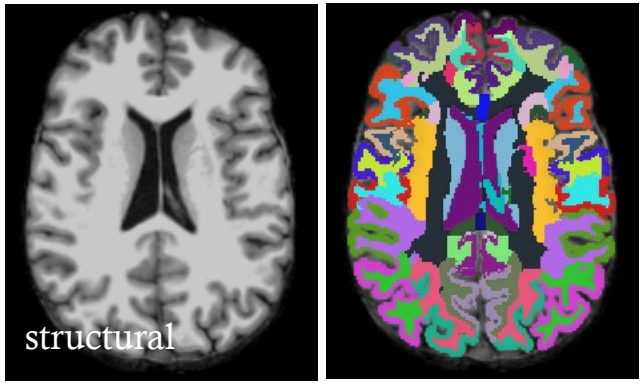
Quantified Average FA in 9 Bilateral Regions of Interest



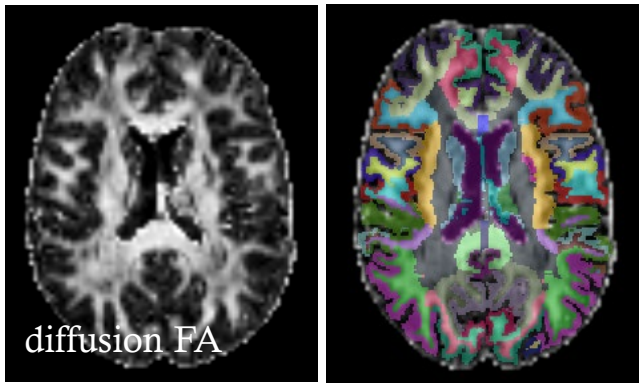
- Amygdala-hippocampus
- Cingulate cortex
- Entorhinal cortex
- Insula
- Lateral orbitofrontal
- Medial orbitofrontal
- Nucleus accumbens
- Parahippocampal
- Temporal pole

Analysis Overview

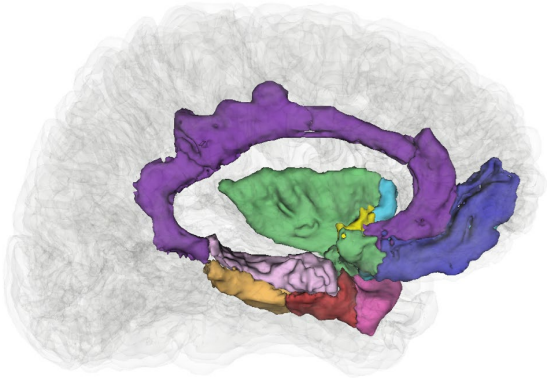
Anatomical Parcellation



Register to Free-Water Corrected FA Maps



Quantified Average FA in 9 Bilateral Regions of Interest

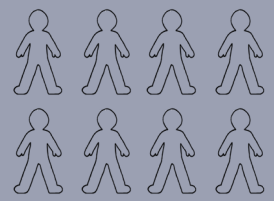


PTSD Only PTSD+TBI

Examined associations between PTSD symptom severity and regional FA with repeated measures linear fixed effects models controlled for age and close-range blast exposure

Findings: PTSD Only Group

PTSD Only



Associations between limbic/paralimbic FA and CAPS PTSD symptom severity

PTSD ONLY COHORT

Brain Region	Partial R	FDR-corrected *p*-value
Right amygdala-hippocampus complex	0.426	0.027
Right cingulate cortex	−0.442	0.027

- More severe PTSD symptoms were associated with higher RH amygdala-hippocampus FA and lower RH cingulate cortex FA

- **Amygdala-hippocampus functions**: memory encoding/retrieval, threat detection, aversive conditioning, emotional learning
- **Cingulate functions**: emotion/cognitive/reward processing

Findings:

PTSD Only

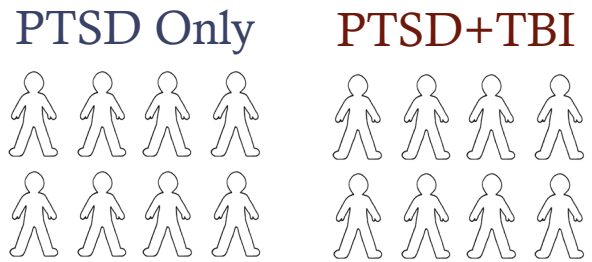
vs.

PTSD+TBI

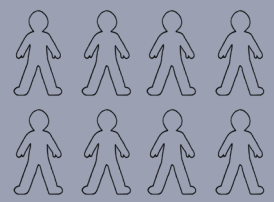
Region FA

Group differences in limbic/paralimbic FA

- No significant group differences in regional FA between Veterans with and without a history of military mild TBI
- More severe psychiatric symptoms in PTSD+TBI group not due to differences in tissue microstructure alone



PTSD+TBI



Associations between limbic/paralimbic FA and CAPS PTSD symptom severity

PTSD + TBI COHORT

Brain Region	Partial R	FDR-corrected *p*-value
Right amygdala-hippocampus complex	0.651	< 0.0001
Left amygdala-hippocampus complex	0.695	< 0.0001
Right cingulate cortex	−0.356	0.018
Left cingulate cortex	−0.394	0.018
Right nucleus accumbens	0.429	0.007
Left nucleus accumbens	0.445	0.006

- More severe PTSD symptoms were associated with higher RH and LH amygdala-hippocampus FA, lower RH and LH cingulate cortex FA, and higher RH and LH accumbens FA
- Mild TBI strengthens brain FA-symptom associations
- Individuals with co-morbid PTSD and mTBI may be more sensitive to the microstructural environment of the brain

Findings: Sensitivity/ Specificity Analyses

- No significant associations between regional FA and in-scanner head motion
- No significant associations between regional FA and depression symptom severity, anxiety symptom severity, or lifetime drinking history score
- **Head motion, co-morbid psychiatric symptoms, and alcohol use were not driving study results**

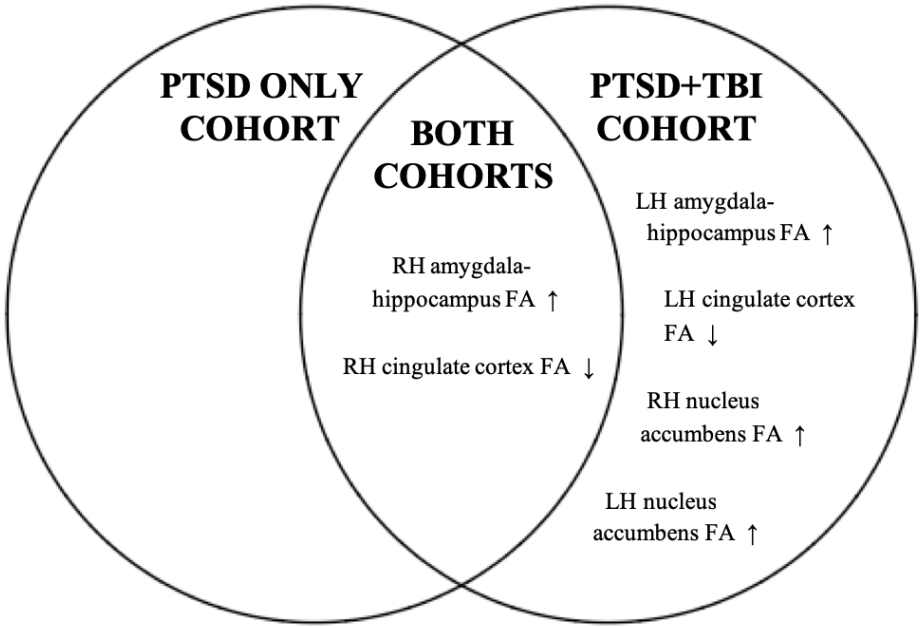
1. Is dimensional PTSD symptom severity associated with the microstructure of limbic and paralimbic gray matter, as evinced by diffusion MRI?

2. Does mild TBI impact associations between PTSD symptom severity and brain microstructure?

1. Dimensional PTSD symptom severity is associated with FA, a diffusion measure sensitive to tissue microstructure, in the amygdala-hippocampus, cingulate cortex and accumbens

- Bridges human neuroimaging and animal histology studies

1. Dimensional PTSD symptom severity is associated with FA, a diffusion measure sensitive to tissue microstructure, in the amygdala-hippocampus, cingulate cortex and accumbens

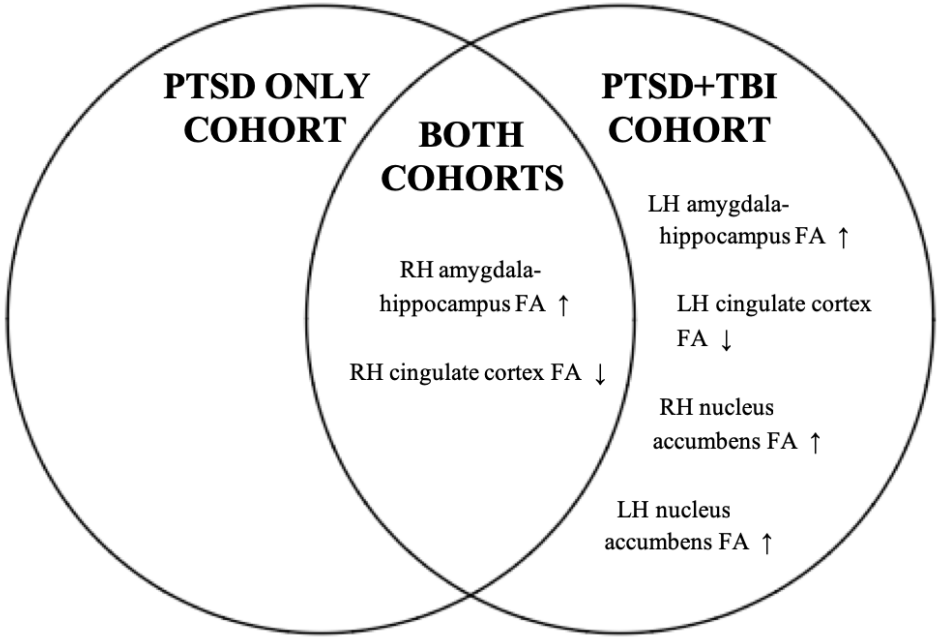


1. Dimensional PTSD symptom severity is associated with FA, a diffusion measure sensitive to tissue microstructure, in the amygdala-hippocampus, cingulate cortex and accumbens

2. Mild TBI affects PTSD symptomatology, and relationships between PTSD symptom severity and brain microstructural diffusion measures

Interpreting Symptom-FA Associations

- Measurable differences in a diffusion MRI measure sensitive to tissue microstructure are related to clinical differences in PTSD



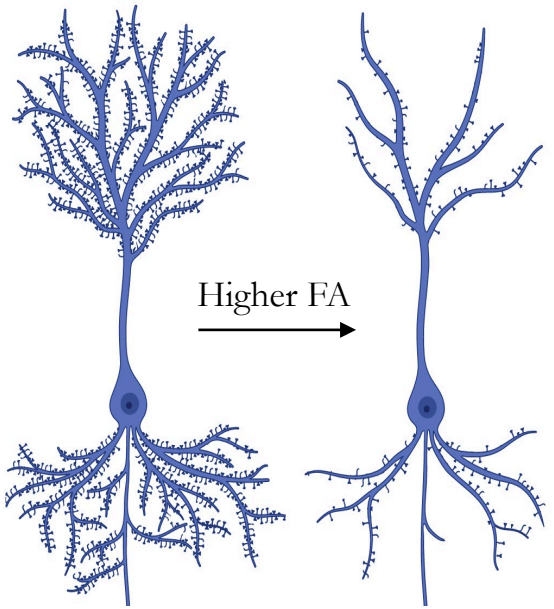
Interpreting Symptom-FA Associations

- Measurable differences in a diffusion MRI measure sensitive to tissue microstructure are related to clinical differences in PTSD
- Hypothesized evidence-based cellular interpretations:

  Increased FA in the amygdala-hippocampus complex in Veterans with more severe PTSD could be linked to heightened dendritic atrophy

  Exposure to stress causes hippocampal dendritic atrophy[1,2]

  Reduced dendritic branch number/length linked to increased FA[3-7]



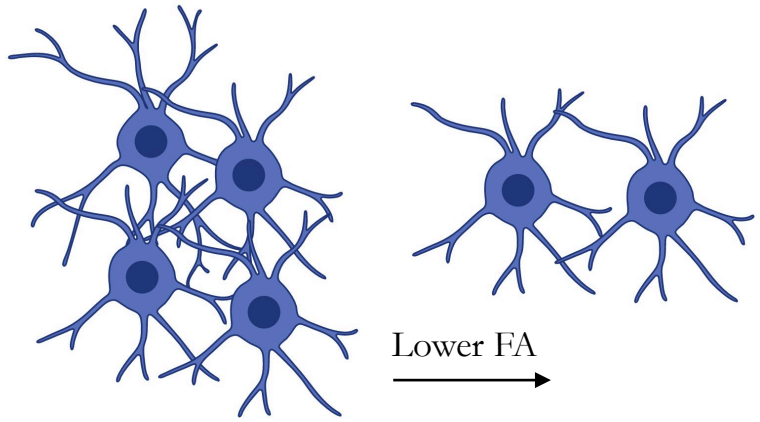
1. Magariños & McEwen, 1995, Neuroscience; 2. Woolley et al., 1990, BrainRes; 3. Bock et al., 2010, Front. Syst. Neurosci; 4. Dean et al., 2013, 5. Sci Transl Med; 6. Leigland & Kroenke, 2011, Animal Models of Behavioral Analysis; 7. Yu et al., 2016, Cereb Cortex

Interpreting Symptom-FA Associations

- Measurable differences in a diffusion MRI measure sensitive to tissue microstructure are related to clinical differences in PTSD
- Hypothesized evidence-based cellular interpretations:

  Any cellular effects likely different in the amygdala-hippocampus and cingulate

  Lower FA in the cingulate cortex in individuals with more severe PTSD may potentially be underlied by a loss of glial cells[1-4]



1. Averill et al., 2017, Neurosci Lett; 2. Sanacora & Banasr, 2013, Biol Psychiatry; 3. Budde et al., 2011, Brain; 4. Stolp et al., 2018, Sci Rep

Interpreting Symptom-FA Associations

- Measurable differences in a diffusion MRI measure sensitive to tissue microstructure are related to clinical differences in PTSD
- Hypothesized evidence-based cellular interpretations:

  Potential cellular determinants of increased FA in the accumbens in Veterans with more severe PTSD and mTBI unclear

Understanding the Impact of mild TBI

Why does mild TBI increase PTSD symptom severity?

1. PTSD with and without military mTBI are distinct disorders

Understanding the Impact of mild TBI

Why does mild TBI increase PTSD symptom severity?

~~1. PTSD with and without military mTBI are distinct disorders~~

Understanding the Impact of mild TBI

Why does mild TBI increase PTSD symptom severity?

~~1. PTSD with and without military mTBI are distinct disorders~~

2. Enduring a military mild TBI worsens PTSD neuropathology

Understanding the Impact of mild TBI

Why does mild TBI increase PTSD symptom severity?

~~1. PTSD with and without military mTBI are distinct disorders~~

~~2. Enduring a military mild TBI worsens PTSD neuropathology~~

Understanding the Impact of mild TBI

Why does mild TBI increase PTSD symptom severity?

~~1. PTSD with and without military mTBI are distinct disorders~~

~~2. Enduring a military mild TBI worsens PTSD neuropathology~~

3. Military TBI makes individuals more vulnerable to the microstructural environment of the brain, and thus to the effects of PTSD neuropathology

Understanding the Impact of mild TBI

Why does mild TBI increase PTSD symptom severity?

Military mild TBI may effectively decrease cognitive/brain reserve, such that the same level of microstructural pathology is associated with more severe PTSD symptoms

Mild TBI may decrease ability to cope with other psychiatric and neurological conditions as well

Implications for Treatment

- Supports that therapies such as TMS that can modulate hippocampus, amygdala, cingulate, or nucleus accumbens will be beneficial for PTSD

Implications for Treatment

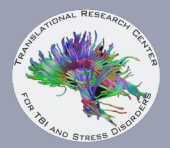
- Supports that therapies such as TMS that can modulate hippocampus, amygdala, cingulate, or nucleus accumbens will be beneficial for PTSD

- Diffusion MRI may provide insight into microstructural effects and clinical efficacy of ketamine for PTSD

Implications for Treatment

- Supports that therapies such as TMS that can modulate hippocampus, amygdala, cingulate, or nucleus accumbens will be beneficial for PTSD
- Diffusion MRI may provide insight into microstructural effects and clinical efficacy of ketamine for PTSD
- Treating cognitive/neural effects of military mTBI may improve PTSD treatment

ACKNOWLEDGEMENTS



People

Sylvain Bouix, Ofer Pasternak, Elisabeth Hartl, Laura Levin-Gleba, Benjamin Reid, Yorghos Tripodis, Jeffrey P. Guenette, David Kaufmann, Nikos Makris, Catherine Fortier, David H. Salat, Yogesh Rathi, **William P. Milberg, Regina E. McGlinchey, Martha E. Shenton, Inga K. Koerte**

Labs and Centers

Psychiatry Neuroimaging Laboratory, Brigham and Women's Hospital, Harvard Medical School
Translational Research Center for TBI and Stress Disorders (TRACTS), VA Boston Healthcare System
Geriatric Research, Education and Clinical Center (GRECC), VA Boston Healthcare System

Funding

VA Rehabilitation Research and Development National Network Research Center for Traumatic Brain Injury Grant (B9254-C) to Regina McGlinchey
VA Merit Award I01RX000928-01A2 to Martha E. Shenton (supporting MES, VJS, SB, YR)
National Institutes of Health Neuroimage Analysis Center Grant NIH P41EB015902 (OP)