Combat exposure, PTSD, and head injuries differentially relate to alterations in cortical thickness in military Veterans.

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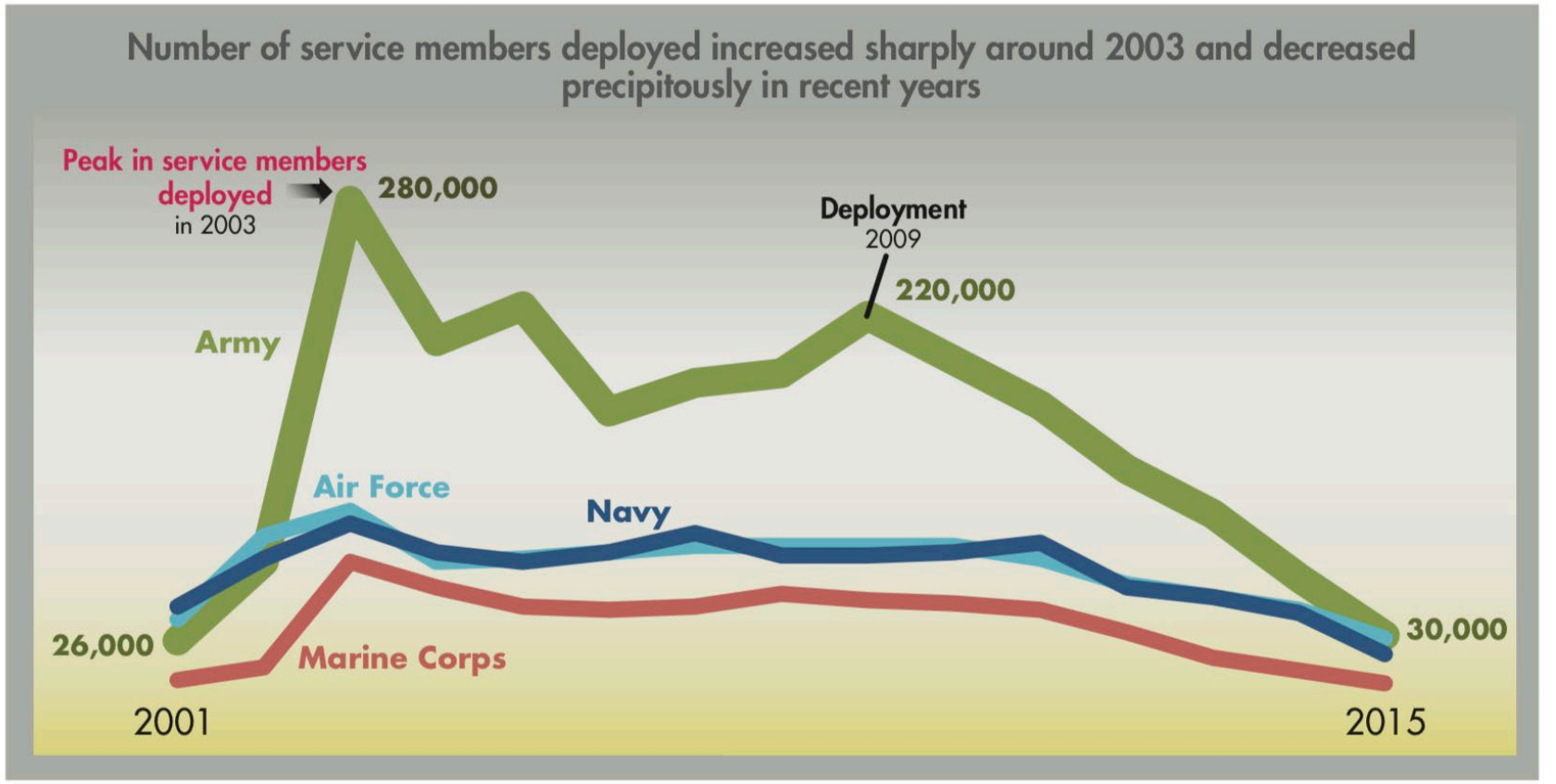
- What is your primary role in VA?
  - student, trainee, or fellow
  - clinician
  - researcher
  - Administrator, manager or policy-maker
  - Other

Poll Question #1

- Approximately of many service members have deployed as part of Operations Iraqi Freedom, Enduring Freedom and/or New Dawn?
  - 1,000,000
  - 500,000
  - 5,400,000
  - 2,800,000

Poll Question #2



Following 9/11, there was a sharp increase in deployments across all four of the armed services, but especially within the Army. Except in the first and last two years shown, the Army provided at least 40 percent of the service members deployed each year.

SOURCE: RAND Arroyo Center Analysis of DMDC's Contingency Tracking System Deployment File.
NOTE: Data include September 2001 through September 2015; 2001 and 2015 represent partial calendar years.

Motivation: High levels of combat exposure

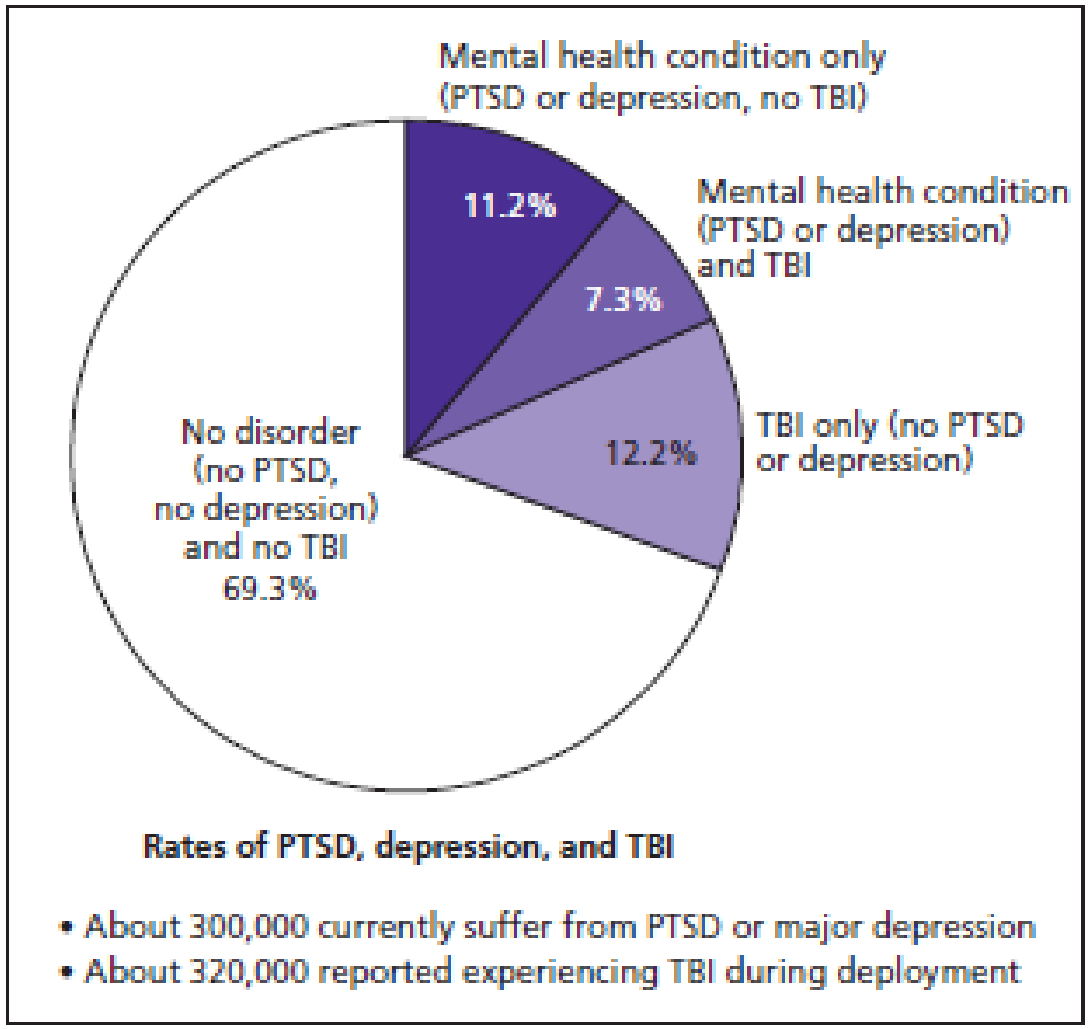
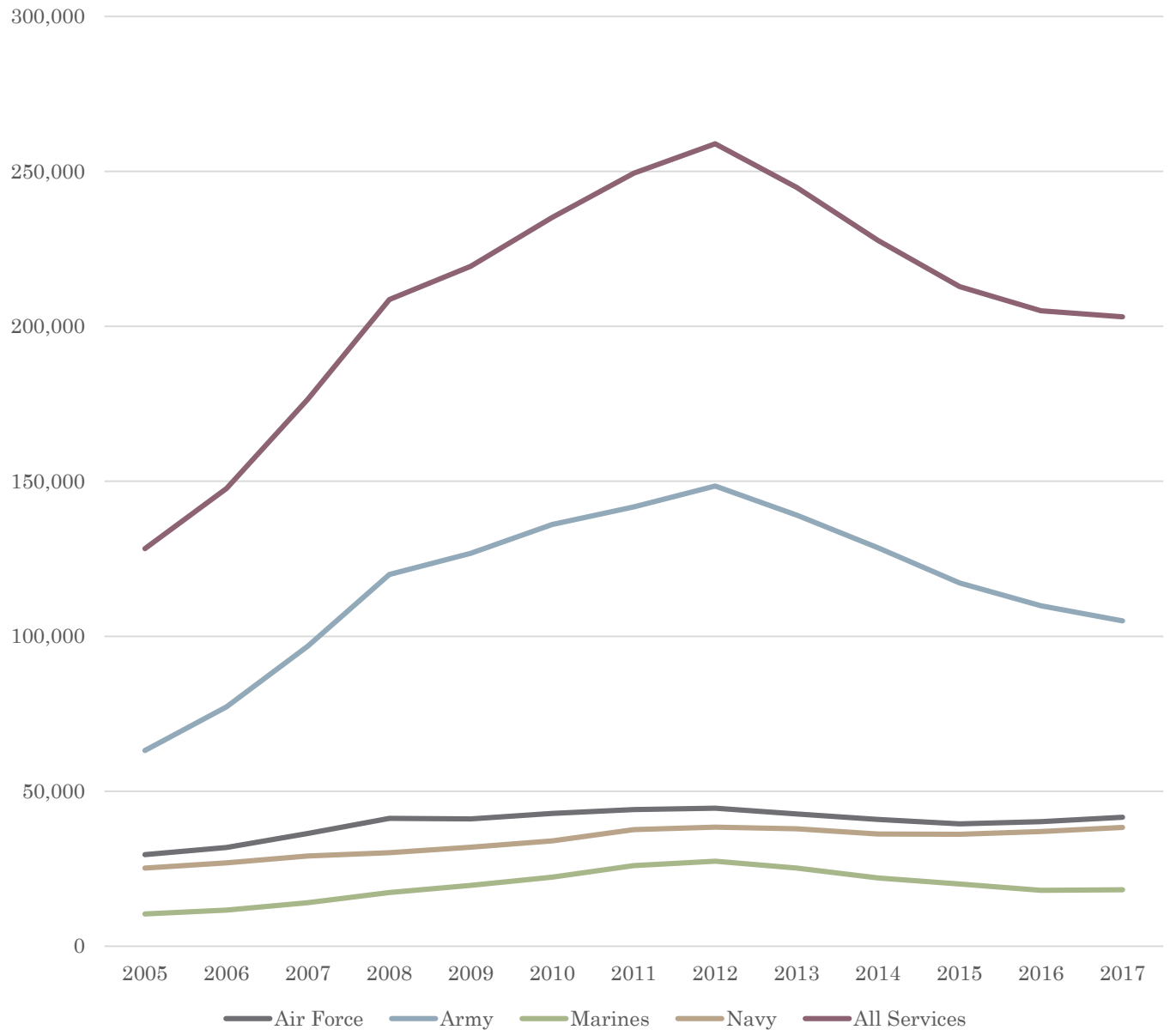


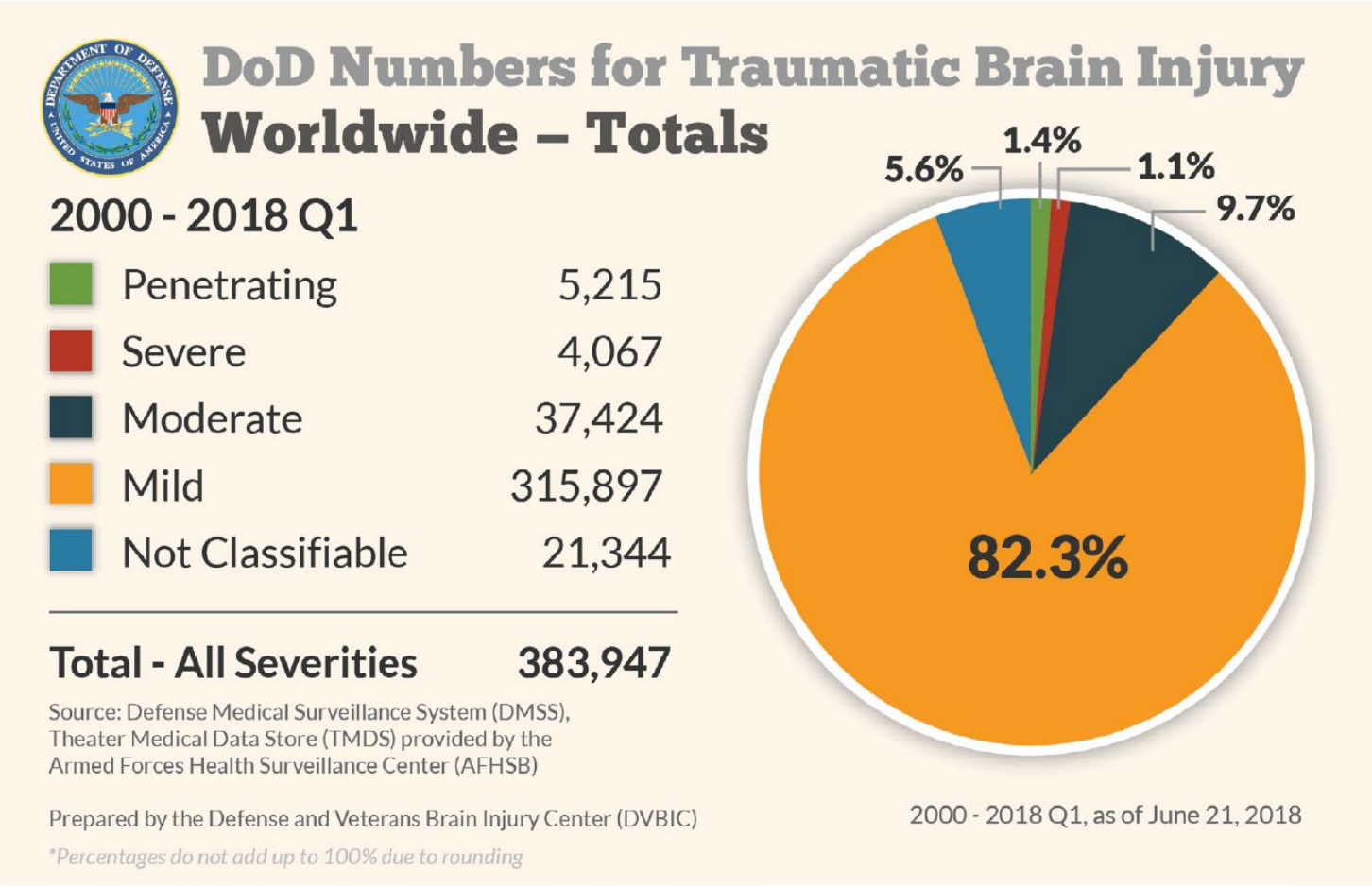
Image from Tanielian et al., 2008

Motivation: 1 in 3 OIF/OEF/OND service members report symptoms of a mental health or cognitive condition.



Mental Health Disorders By Branch

Plot created from data prepared by the Deployment Health Clinic Center, Released 2017



TBI is the "signature injury" of post-9/11 Veterans

- ~ 19% of service members sustain a head injury during a deployment
- The majority of head injuries are classified as mild traumatic brain injuries (30)
- mTBIs are linked with increased PTSD and accelerated brain aging (31), suggesting changes in grey and white matter health.

Mechanistic research linking chronic stress to changes in the brain highlights a critical role for the HPA axis

- Chronic stress → dysregulated cortisol levels, cytokines, glucocorticoid receptors, and CRH levels, increased catecholamine levels, decreased ACH, and increased pro-inflammatory response (Frodl & O'Keane, 2012; de Kloet et al., 2005; Kim & Won2017; Popoli et al., 2011)
- HPA dysregulation → weaken a cells' resilience, lead to cellular atrophy and/or inhibited neurogenesis (Fordl & O'Keane, 2012)

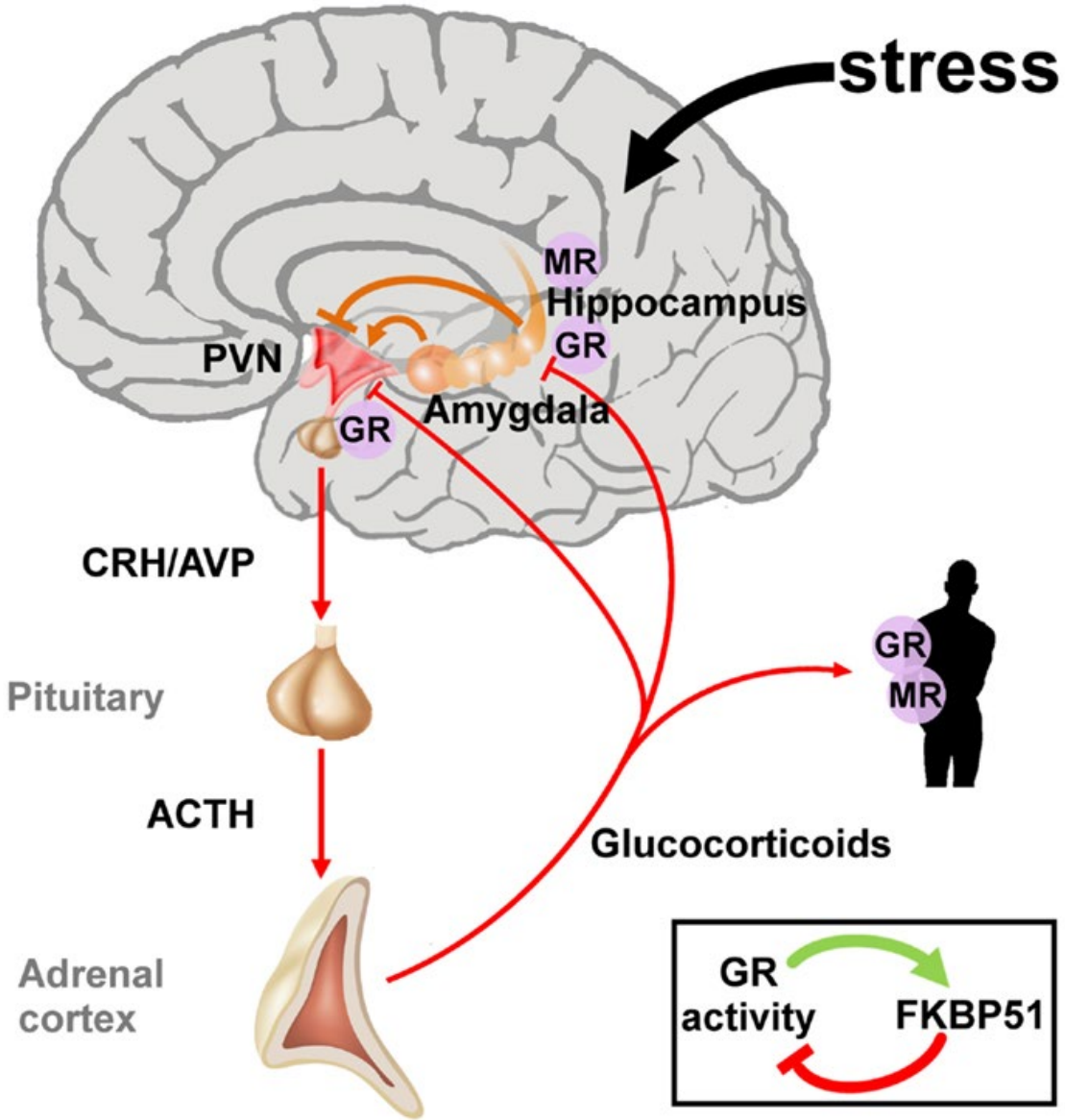
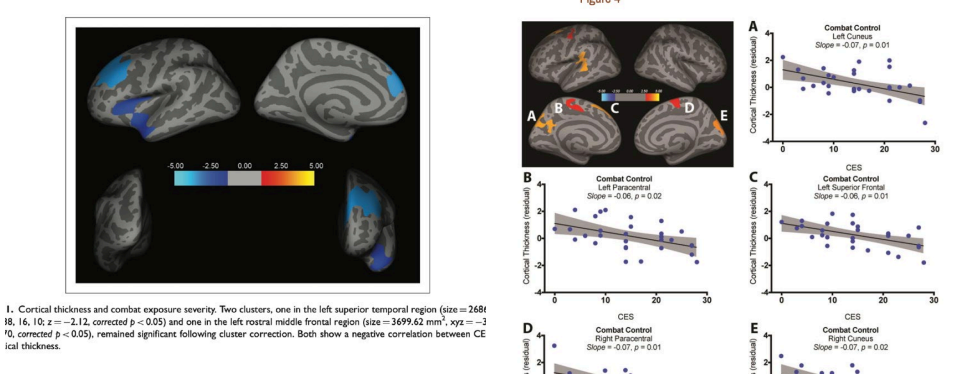


Image from: Joachin Raabe & Spengler 2013

Alterations in Cortical Thickness are Associated with Combat

- In Veterans, combat exposure relates to lower cortical thickness within the left lateral prefrontal cortex, regardless of PTSD diagnosis (Wrocklage et al., 2017; Averill et al., 2017)
- Stronger negative relationships between combat exposure and cortical thickness in Veterans without a PTSD diagnosis than Veterans with PTSD (23, 24)
- ***How do head injuries or mild traumatic brain injuries (mTBI) impact these relationships?***



1. Cortical thickness and combat exposure severity. Two clusters, one in the left superior temporal region (size = 268
8, 16, 10; z = −2.12, *corrected* $p < 0.05$) and one in the left rostral middle frontal region (size = 3699.62 mm^2, xyz = −3
0, *corrected* $p < 0.05$), remained significant following cluster correction. Both show a negative correlation between CE
ical thickness.

European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology

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Cortical Thickness Reduction in Combat Exposed U.S. Veterans with and without PTSD

Kristen M. Wrocklage, Lynnette A. Averill, [...], and Chadi G. Abdallah

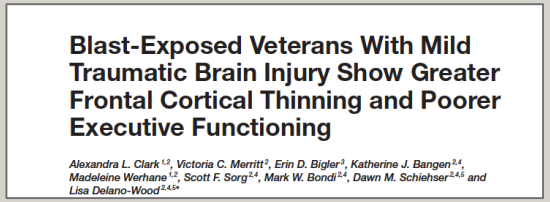
iginal Article

Combat Exposure Severity Is Associated With Reduced Cortical Thickness in Combat Veterans: A Preliminary Report

ynnette A. Averill[1,2], Chadi G. Abdallah[1,2], Robert H. Pietrzak[1,2], hristopher L. Averill[1,2], Steven M. Southwick[1,2], hn H. Krystal[1,2], and Ilan Harpaz-Rotem[1,2]

TBI is associated with cortical thinning in Veterans

- Veterans with mTBI exhibit decreased cortical thickness within the right inferior temporal, right insular, and right inferior frontal gyrus (Michael et al., 2015), as well as changes in the prefrontal cortex (Clark et al., 2018)
- Veterans with both PTSD and mTBI exhibit lower cortical thickness within the postcentral and middle temporal gyri (Lindemer et al., 2013)
- **However, the unique role of combat exposure, vs. PTSD vs. TBI remains unclear**



Blast-Exposed Veterans With Mild Traumatic Brain Injury Show Greater Frontal Cortical Thinning and Poorer Executive Functioning

Alexandra L. Clark[1,2], Victoria C. Merritt[2], Erin D. Bigler[3], Katherine J. Bangen[2,4], Madeleine Werhane[1,2], Scott F. Sorg[2,4], Mark W. Bondi[2,4], Dawn M. Schiehser[2,4,5] and Lisa Delano-Wood[2,4,5]

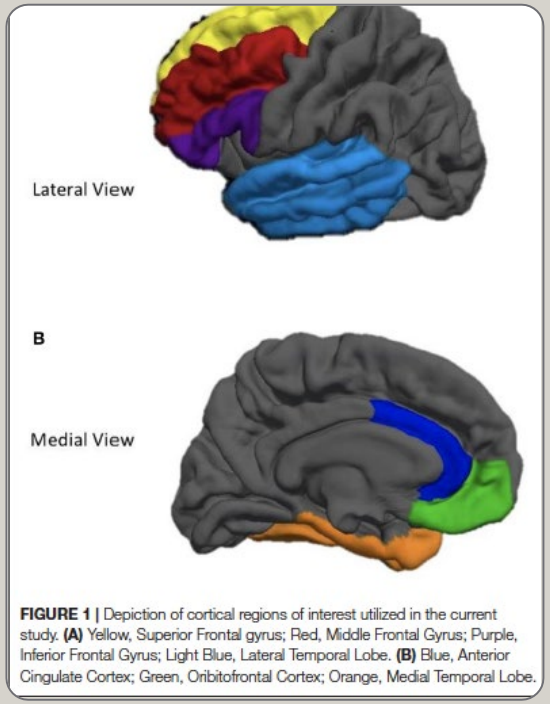


FIGURE 1 | Depiction of cortical regions of interest utilized in the current study. **(A)** Yellow, Superior Frontal gyrus; Red, Middle Frontal Gyrus; Purple, Inferior Frontal Gyrus; Light Blue, Lateral Temporal Lobe. **(B)** Blue, Anterior Cingulate Cortex; Green, Oribitofrontal Cortex; Orange, Medial Temporal Lobe.

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DOI: 10.1089/neu.2015.3918

Evaluation of Cortical Thickness after Traumatic Brain Injury in Military Veterans

Reduced cortical thickness with increased lifetime burden of PTSD in OEF/OIF Veterans and the impact of comorbid TBI

Emily R. Lindemer [a], David H. Salat [a, b], Elizabeth C. Leritz [a, b, d], Regina E. McGlinchey [a, c], William P. Milberg [a, c]

01

Previous focus on diagnostic-specific investigations

02

Difficulty assessing unique impact of comorbid conditions given small sample sizes

03

ROI-based vs. whole-brain approaches

Gaps in the literature

Neuropsychopharmacology

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ARTICLE

Combat exposure, posttraumatic stress disorder, and head injuries differentially relate to alterations in cortical thickness in military Veterans

Ashley N. Clausen[1,2], Emily Clarke[1,2], Rachel D. Phillips[1,2], Courtney Haswell[1,2], VA Mid-Atlantic MIRECC Workgroup[1] and Rajendra A. Morey[1,2,3,4]

Examine the unique impact of combat exposure, PTSD and prior head injuries on cortical thickness in Veterans.

Overarching Aim

Sample

Table 1 Demographics

From: Combat exposure, posttraumatic stress disorder, and head injuries differentially relate to alterations in cortical thickness in military Veterans

	Mean	SD
Age	38.3	10.1
Combat exposure scale total	10.5	10.5
BDI-II total severity score	10.8	11.6
AUDIT total severity score	3.8	4.5
TLEQ non-combat trauma severity score	2.1	2.8
Education	3.9	1.7
	Endorsed (%)	Endorsed (*N*)
Sex (% male)	80.1%	270
Head injuries (% with ≥1 injury)	10.7%	36
PTSD diagnosis (% with PTSD)	28.2%	95

BDI-II Beck Depression Inventory–II, *AUDIT* Alcohol Use Identification Test, *TLEQ* Traumatic Life Exposure Questionnaire, *SD* Standard Deviation, *PTSD* Posttraumatic Stress Disorder

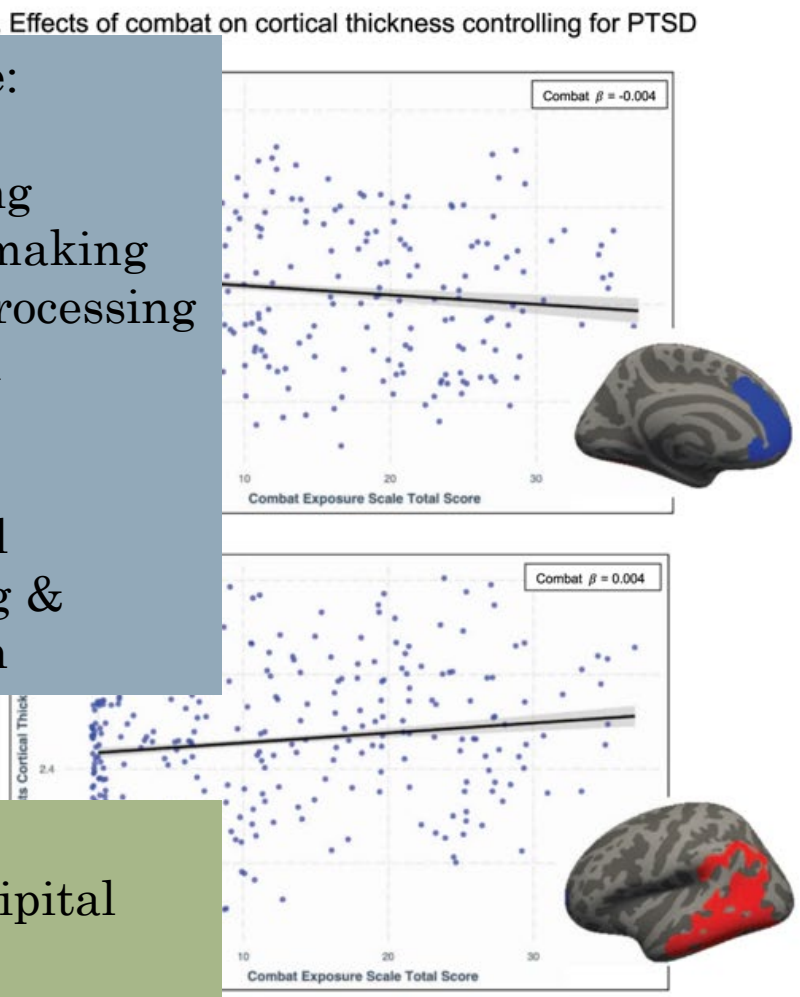
- 341 Veterans
- Recruited between 2005 - 2018 from a post-deployment mental health repository (Brancu et al., 2017)
- Served since 9/11/2001
- Ages 18 - 59
- Important exclusion criteria: penetrating head injury, LOC≥30 min, history of neurological disorders, severe chronic medical conditions, neurosurgery, and Axis I psychiatric disorders other than PTSD and co-morbid Major Depression

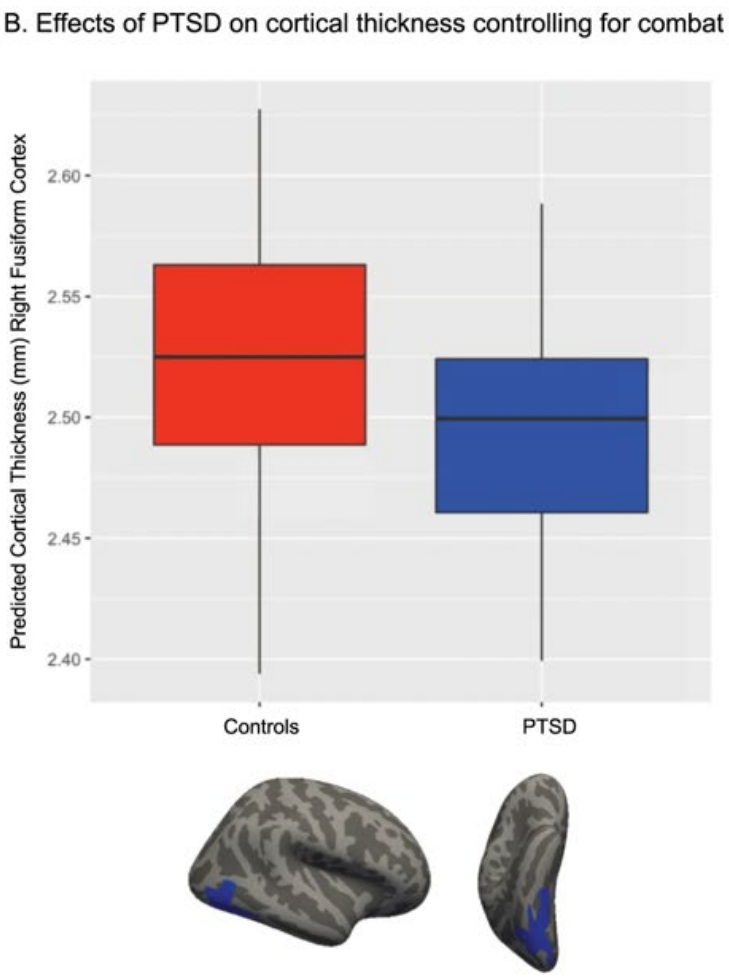
Data-driven methodology

- Clinical Assessment
  - PTSD
  - Depression
  - Combat
  - Alcohol Use
  - Trauma exposure
- Neuroimaging Assessment
  - Structural T-1 weighted image
- Statistical Analysis
  - FreeSurfer QDEC – whole brain approach examining cortical thickness
  - All models were adjusted for the following covariates:
    - Age, sex, education, prior diagnosis of a head injury, depression, non-military trauma, and alcohol use

Frontal Lobe:

- Executive functioning
- Decision making
- Reward processing
- Sustained attention
- Memory
- Emotional processing & regulation





Right Fusiform:

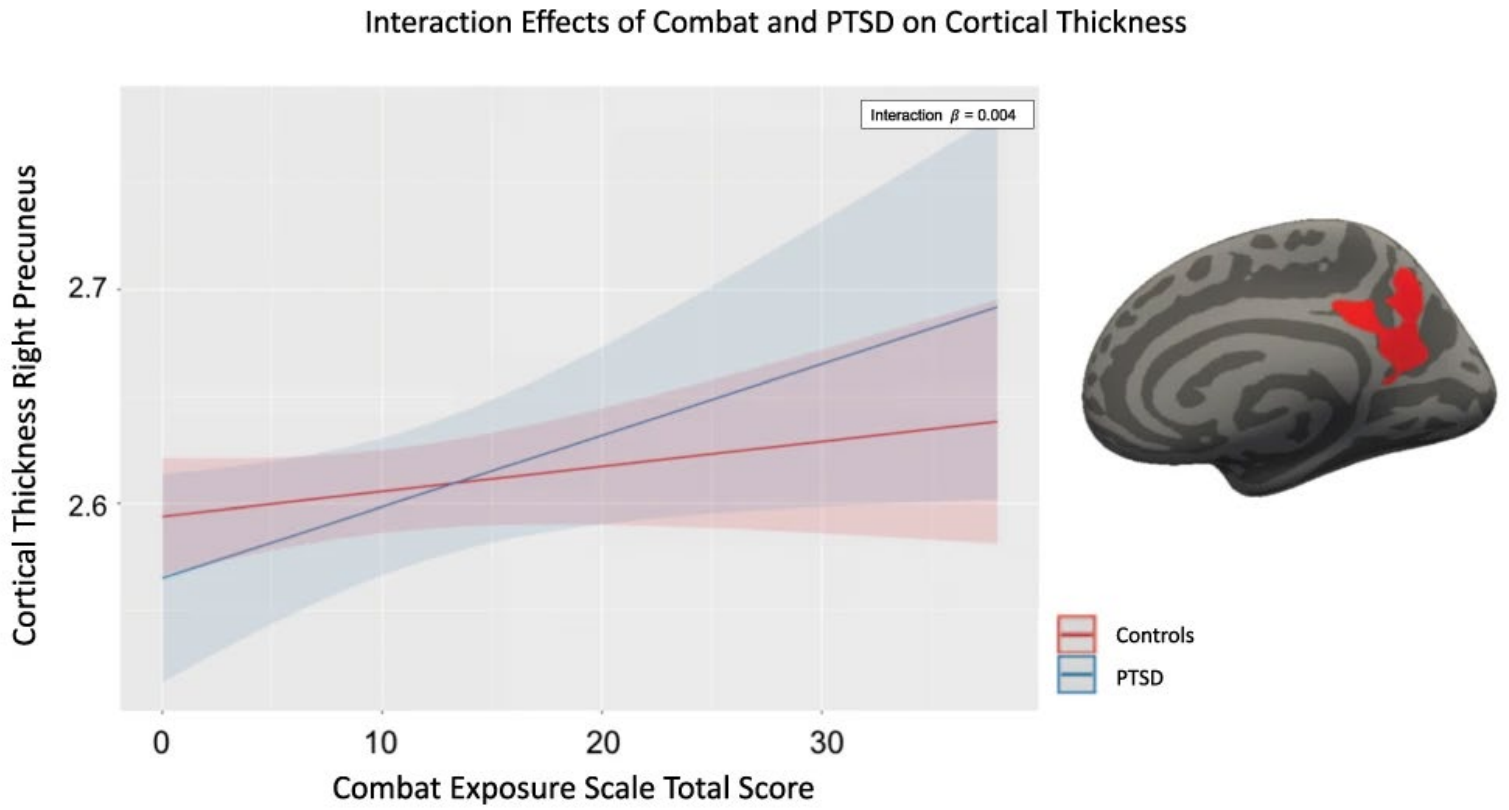
- Pattern, object and facial recognition

Inferior temporal/occipital cortex:

- Multisensory processing
- Object recognition

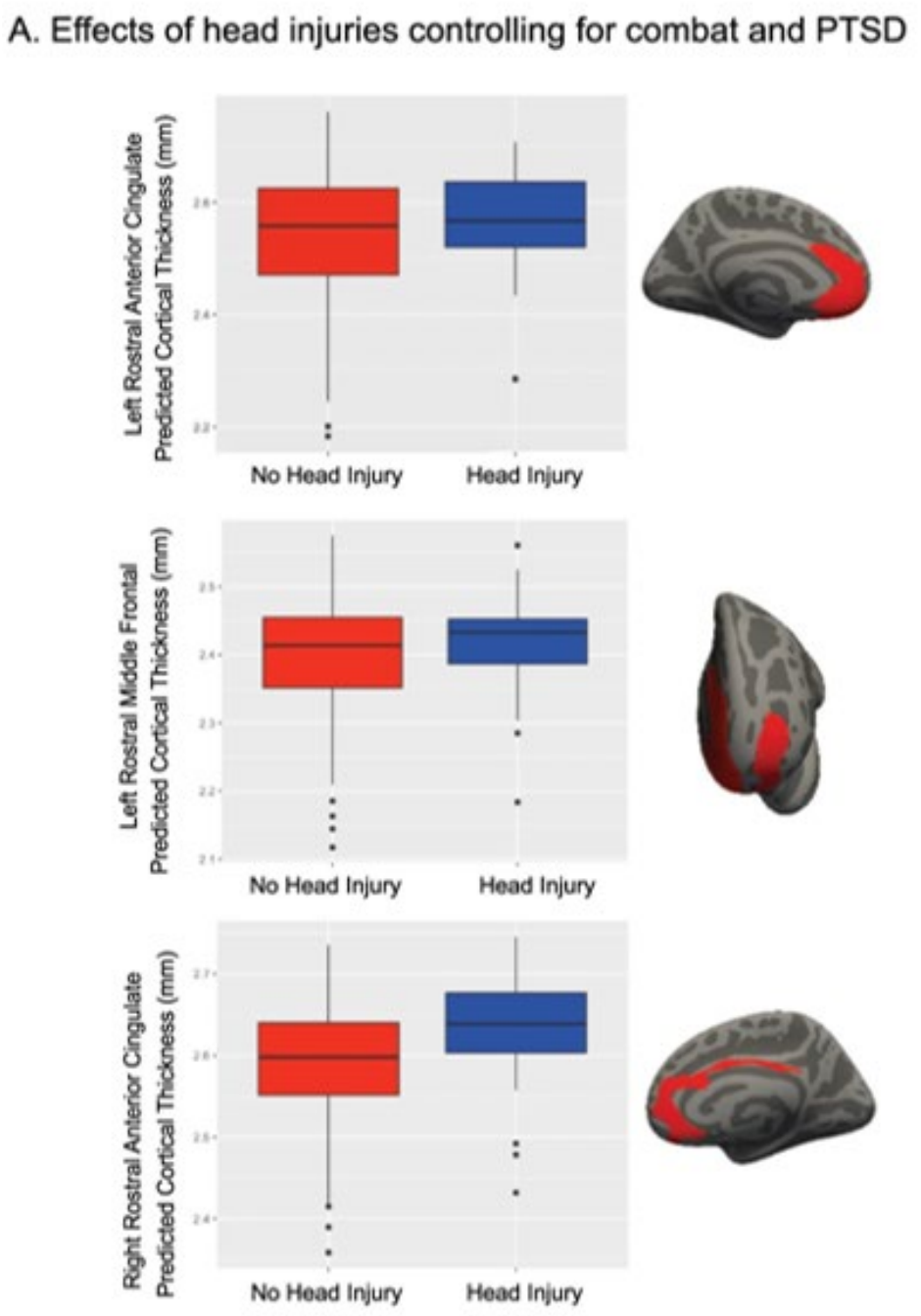
When controlling for PTSD, **combat exposure** is associated with lower cortical thickness in the prefrontal cortex and increased cortical thickness in the left middle and inferior temporal lobe. **PTSD**, controlling for combat relates to lower cortical thickness in the right fusiform cortex.

Interaction of PTSD and Combat



Precuneus
- visuospatial imagery
- episodic memory
- self-referential processing

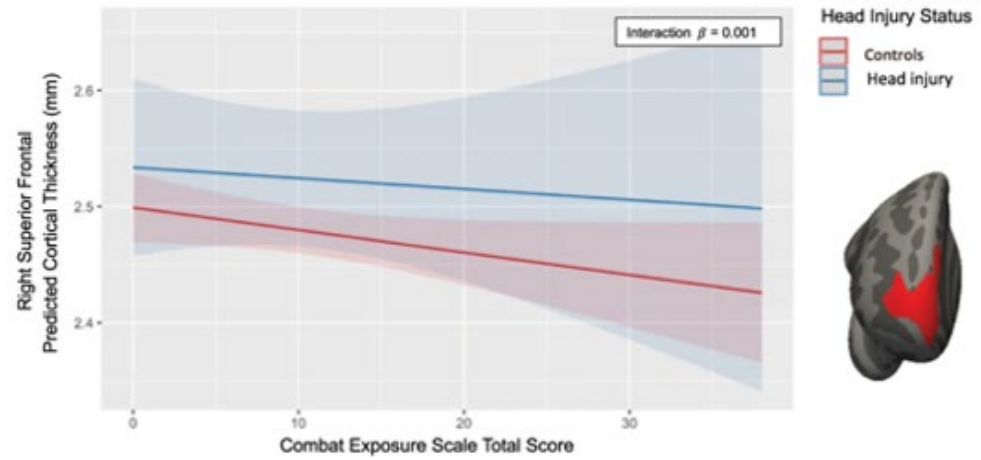
Veterans with PTSD and higher levels of combat exhibited steeper increases in cortical thickness within the right precuneus, a region implicated in visuospatial imagery, episodic memory and self-referential processing



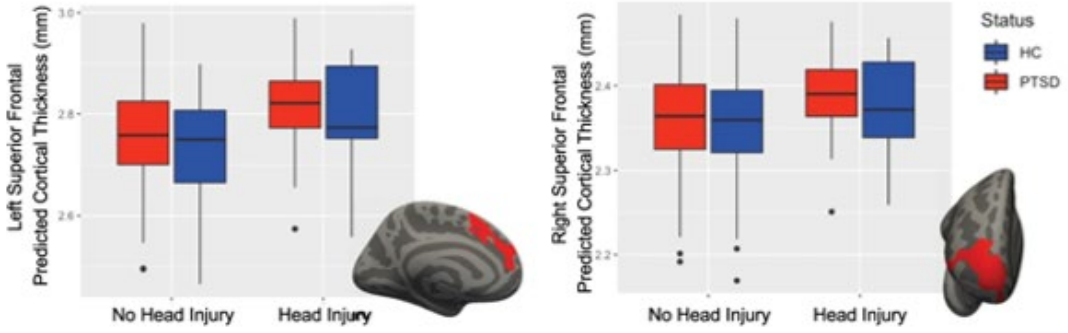
Impact of Head Injuries…

- Prior diagnosis of a head injury in this study significantly related to increased cortical thickness within bilateral rostral anterior cingulate and left rostral middle frontal cortices
- Regions involved in higher order functions:
  - executive functioning
  - decision-making
  - emotional processing

B. Interaction of head injuries and combat on cortical thickness



C. Interaction of head injuries and PTSD on cortical thickness



Head Injuries interact with combat and PTSD

- Veterans with head injuries plus higher levels of combat or PTSD exhibited increased cortical thickness in the superior frontal cortex.

Further examination of head injuries

- A subset of Veterans completed a semi-structured traumatic brain injury interview developed at the VA VISN 6 MIRECC (Martindale et al., 2017, 2018; Epstein et al., 2019).
- Index of the type of injury (blast, land-based or air-based vehicular accident, fall, fragment, physical confrontation, accident, or other), number of head injuries, the severity of injuries (none, mild, moderate/severe), and the presence of loss of or altered consciousness.
- Examination of number of head injuries occurring during deployment

Number of deployment-related injuries relates to increased cortical thickness in the left rostral middle frontal region.

Limitations and next steps

- Dichotomous, self-reported head injuries
- Lower levels of head injuries in the present sample relative to Veteran population
- No direct assessment of blast exposure
- Co-linearity between combat, PTSD and depression
- Effects of psychotropic medication

Conclusion

- Examination of combat on neural health by assessing the contributions of various sources of heterogeneity in a large sample of combat Veterans ($N = 337$).
- Combat exposure severity, significantly relates to lower cortical thickness within the left prefrontal lobe and increased cortical thickness within the left middle and inferior temporal cortex.
- PTSD relates to lower cortical thickness within the right fusiform extending into the lateral occipital and inferior temporal cortex.
- Veterans who sustained a head injury exhibit increased cortical thickness bilaterally in the medial prefrontal cortex.
- This may indicate combat exposure severity, PTSD, and prior head injuries have differential impacts on cortical thickness in Veteran populations.

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