

# Impact of Repeated Blast Exposure on Active-Duty United States Special Operations Forces

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# Funding and Disclosures

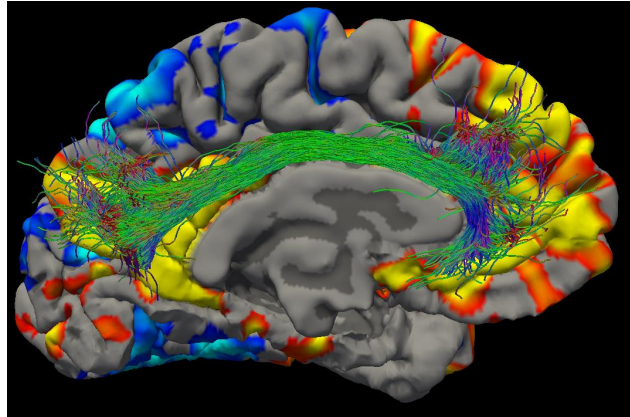
## Funding:

- USSOCOM: Contract No. H9240520D0001
- Navy SEAL Foundation

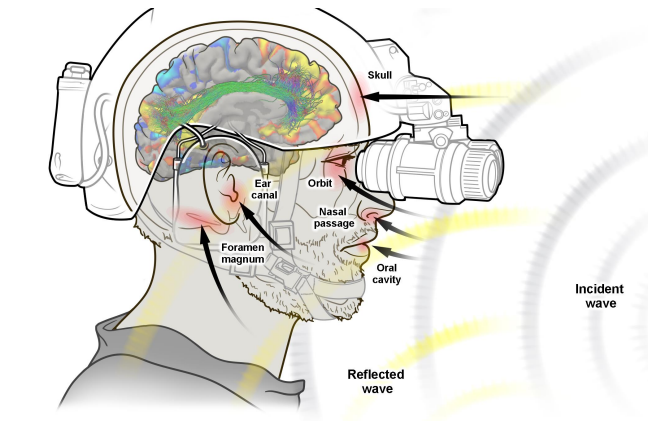
## Financial Disclosures and Conflicts of Interest:

- None

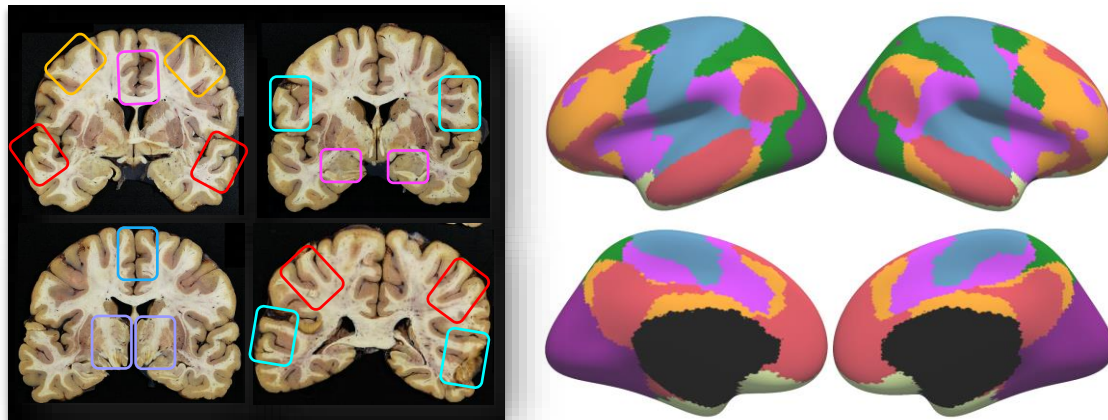
# Objectives



State of the Science



Gaps in Knowledge



Future Directions



Supporting Operators *Now*

# Background

- U.S. SOF are frequently exposed to explosive blasts in training and combat.
- Repeated blast exposure is associated with cognitive, psychological & physical symptoms.
- There is **no diagnostic test** for repeated blast brain injury (rBBI).

## Individuals

- Return to training or combat when brain is **vulnerable**
- **Exacerbation** of symptoms
- Misdiagnosis may cause **despair** and **moral injury**

## Force

- Undermine readiness and performance
- Barrier to recruitment
- Compromise retention

# Mission Driven

Those who perform at the highest level and sacrifice the most for our country deserve the best medical care.

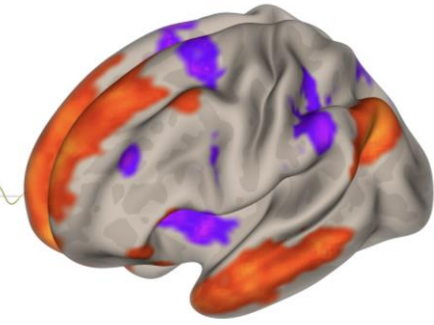
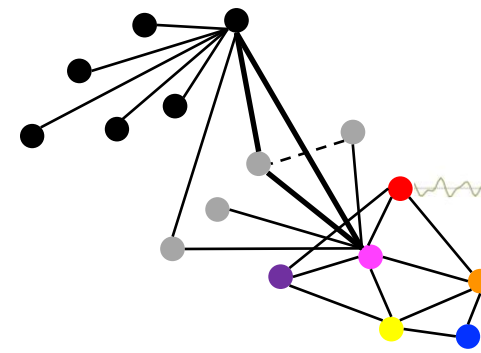
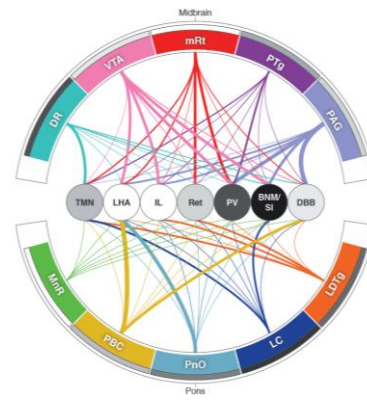
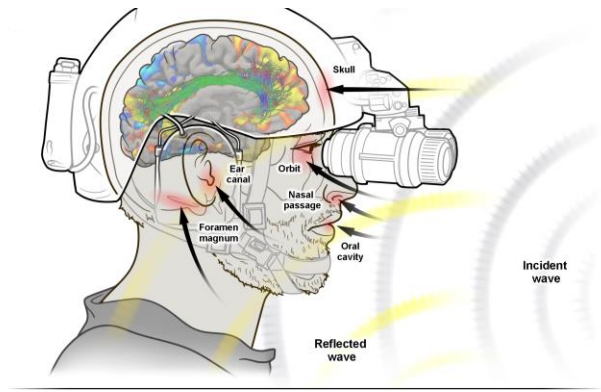
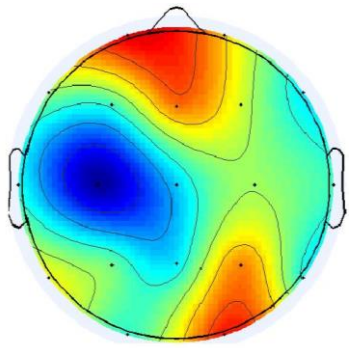
Optimize **combat readiness**, increase **career longevity** and improve **quality of life**.

Develop a **diagnostic test** for early detection of **repeated blast brain injury (rBBI)** in active-duty SOF.

# Repeated Blast Exposure



Navy SEAL Foundation  
2021 IMPACT FORUM

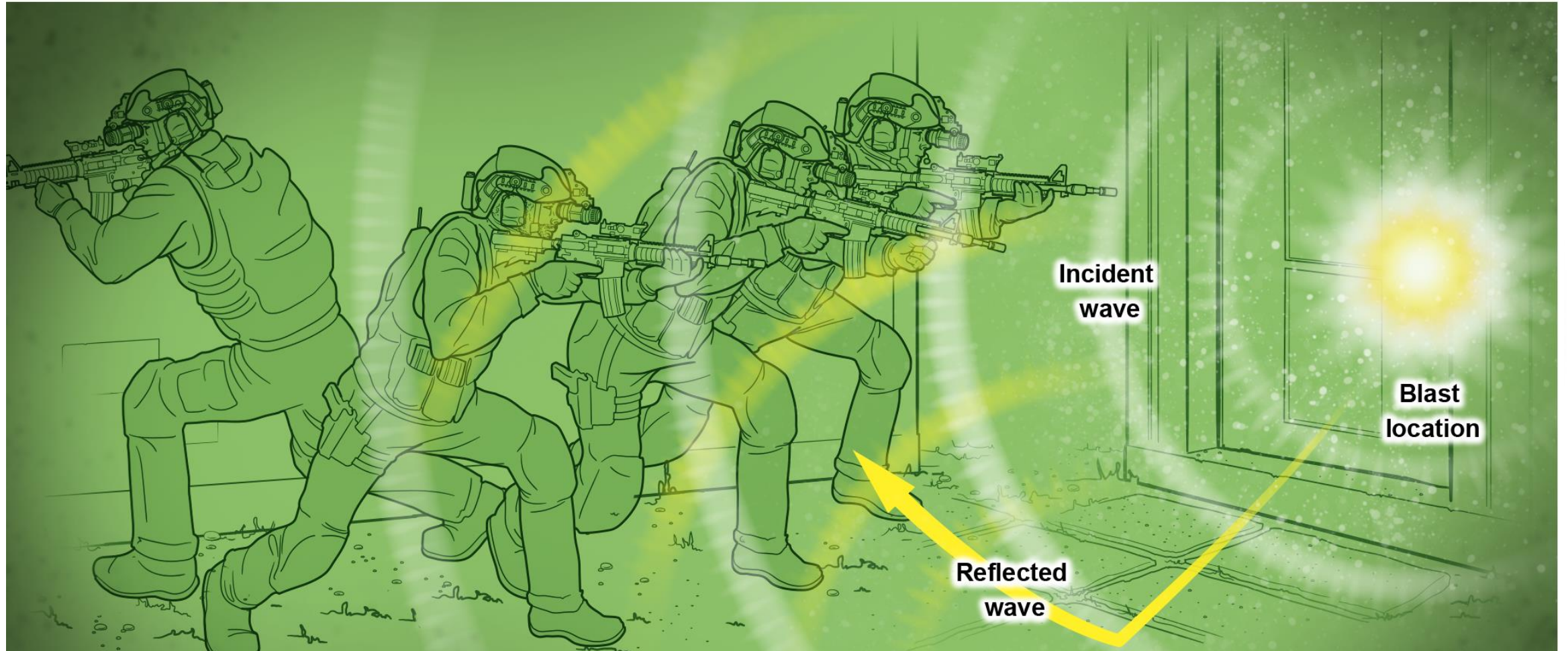


# State of the Science

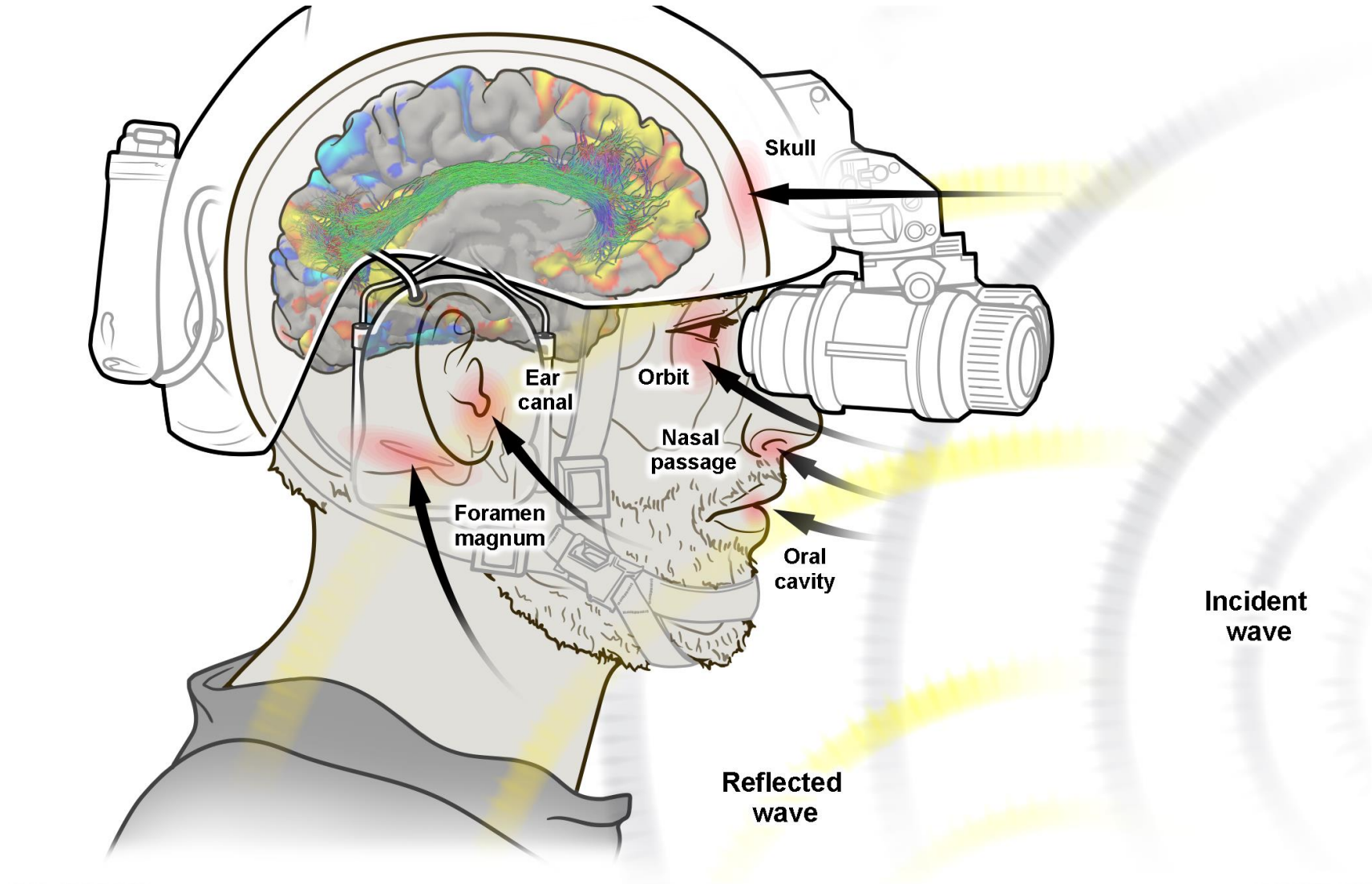




# Repeated Blast Exposure



# Blast Biomechanics



# rBBI is *not* CTE

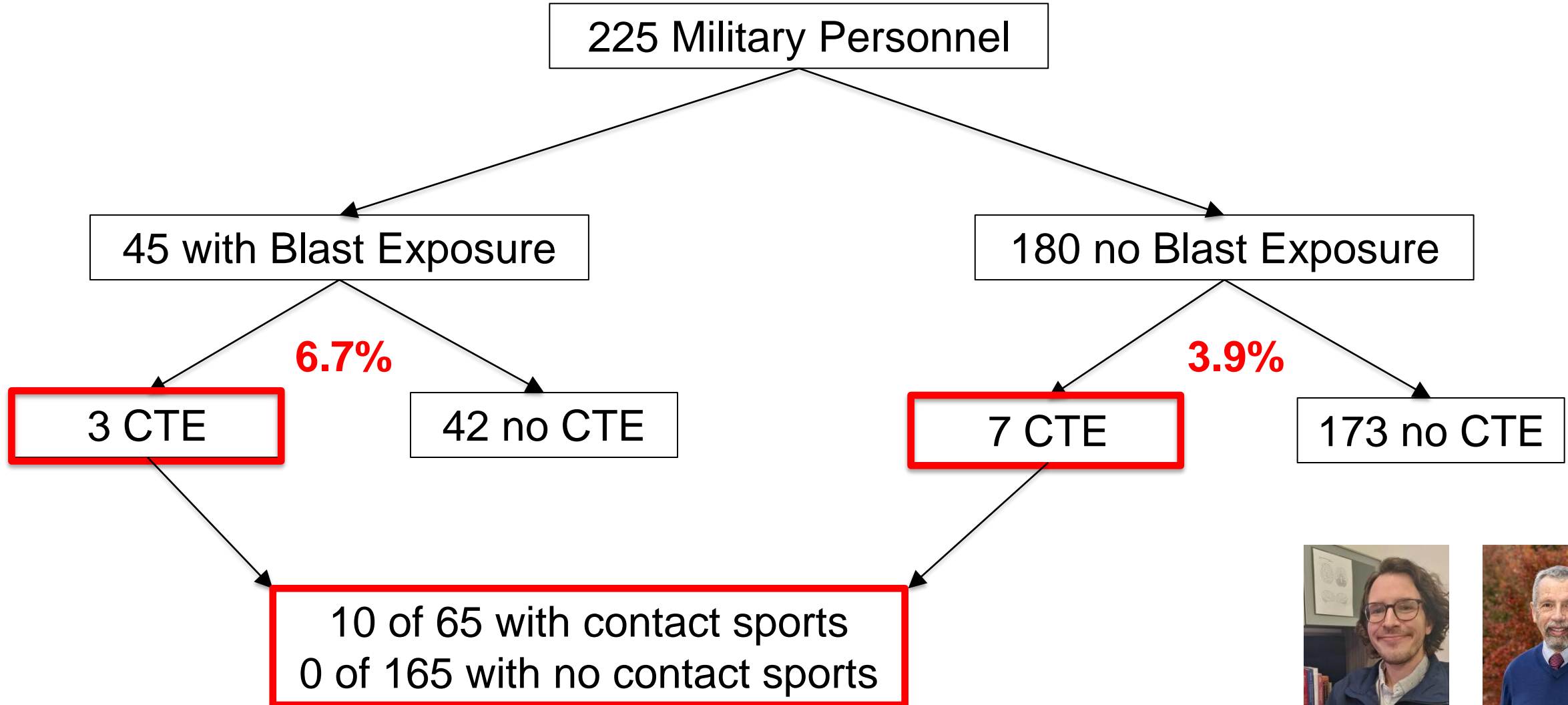


Risk for CTE



Risk for rBBI

# rBBI is *not* CTE



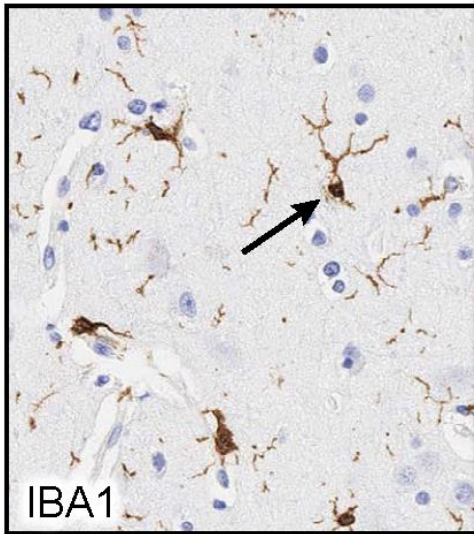
David Priemer, MD



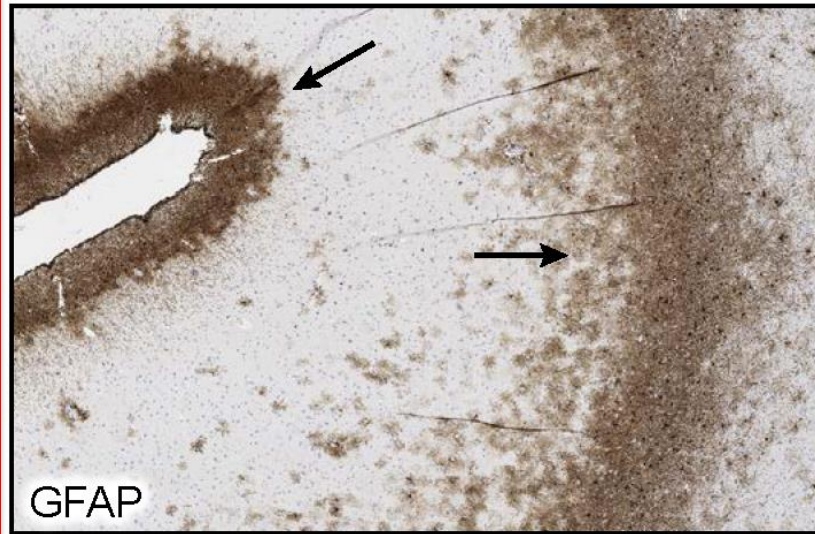
Dan Perl, MD

# Blast Pathology Spectrum

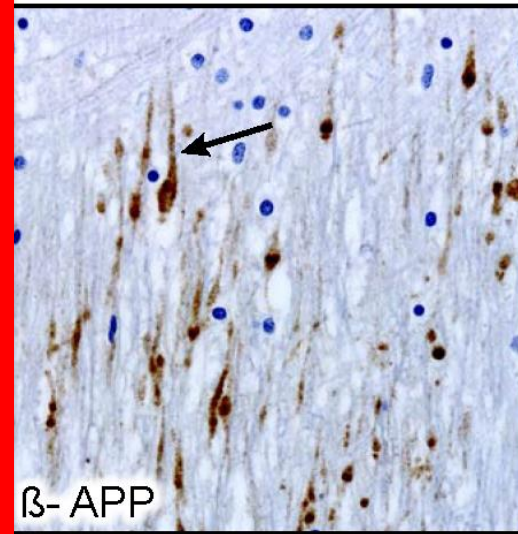
Inflammation



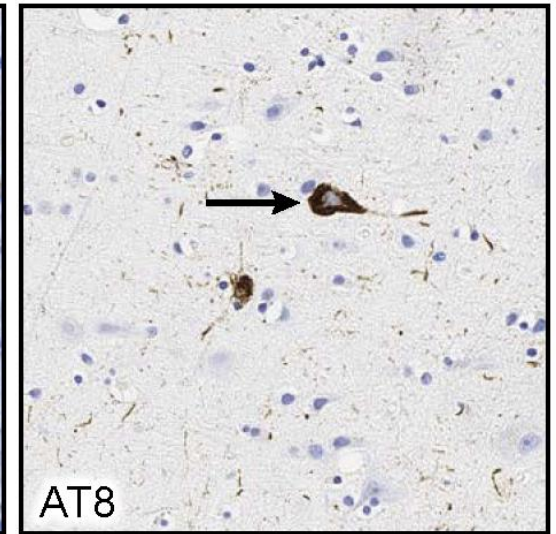
Astroglial Scarring



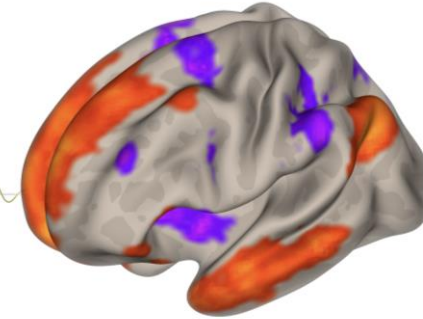
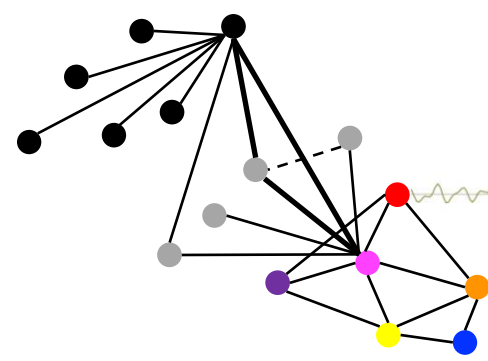
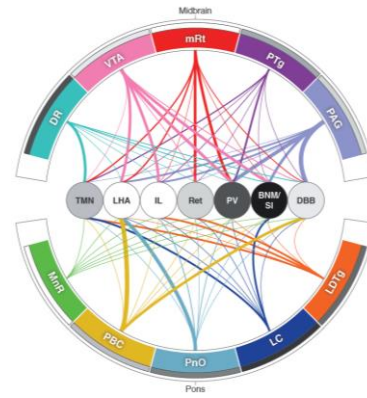
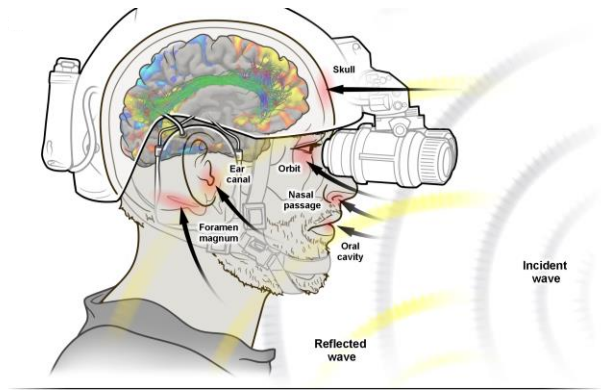
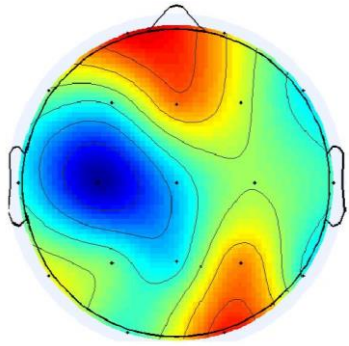
Axonal Injury



Tau Deposition



Histopathology data from Dan Perl, M.D. and David Priemer, M.D.  
Uniformed Services University  
Center for Neuroscience and Regenerative Medicine



# ReBlast Study

## 2021 – 2023



# MGH-USSOCOM Collaboration



June 2021

# Study Design Overview

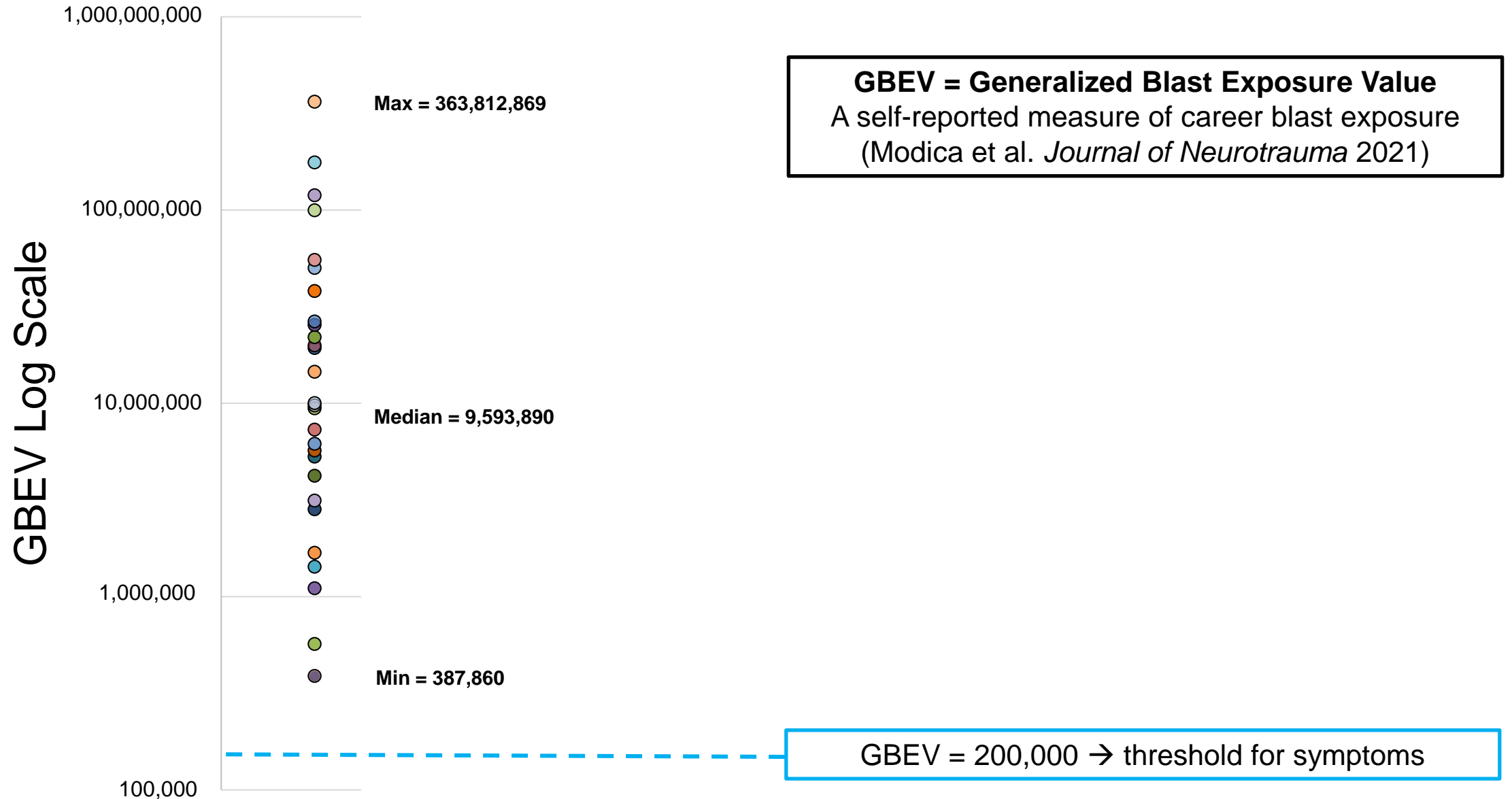
Assessment	Study Activity (time to complete)	Day 1	Day 2
Advanced Neuroimaging	Connectome MRI (1 – 2 hours)	X	
	7 Tesla MRI (1 – 2 Hours)		X
	TSPO PET (3 – 4 hours)	X	
	Tau PET (3 – 4 hours)		X
Blood Biomarker	Blood Draw (10 minutes)	X	
Neurocognitive Assessment	ANAM, WAIS-IV Arithmetic/Digit Span, TOPF, Grooved pegboard, DKEFS Color-Word Interference, ACT, Pupillometry Test (2 – 3 hours)	X	
Blast Exposure and TBI History	GBEV, BISQ, DVBIC, DRRI Combat Experiences (1 hour)		X
Clinical Symptom and Global Function, Self-report	Completed in-person & via REDCap survey pre-visit, PSQI, STOP BANG, PHQ-9, PCL-5, TBI-QOLs, AUDIT-C, MSVT, DAST-10, GOSE, GBEV, MOS, CES, FrSBE, PROMIS Pain Interference and Intensity, HIT-6, WHO-DAS, SBQ-R, Brown-Goodwin, Buss-Perry, NSI/mBIAS, NIH TBI Common Data Elements Medical History (1 – 2 hours)	X	
Philips IntelliSpace Cognitive Testing	RAVLT, Trail Making Test, Letter Fluency, Star-Cancellation, Clock Drawing/Copy Test, Rey-Osterrieth Complex Figure Test, Category Fluency and Digit Span (45 minutes)		X



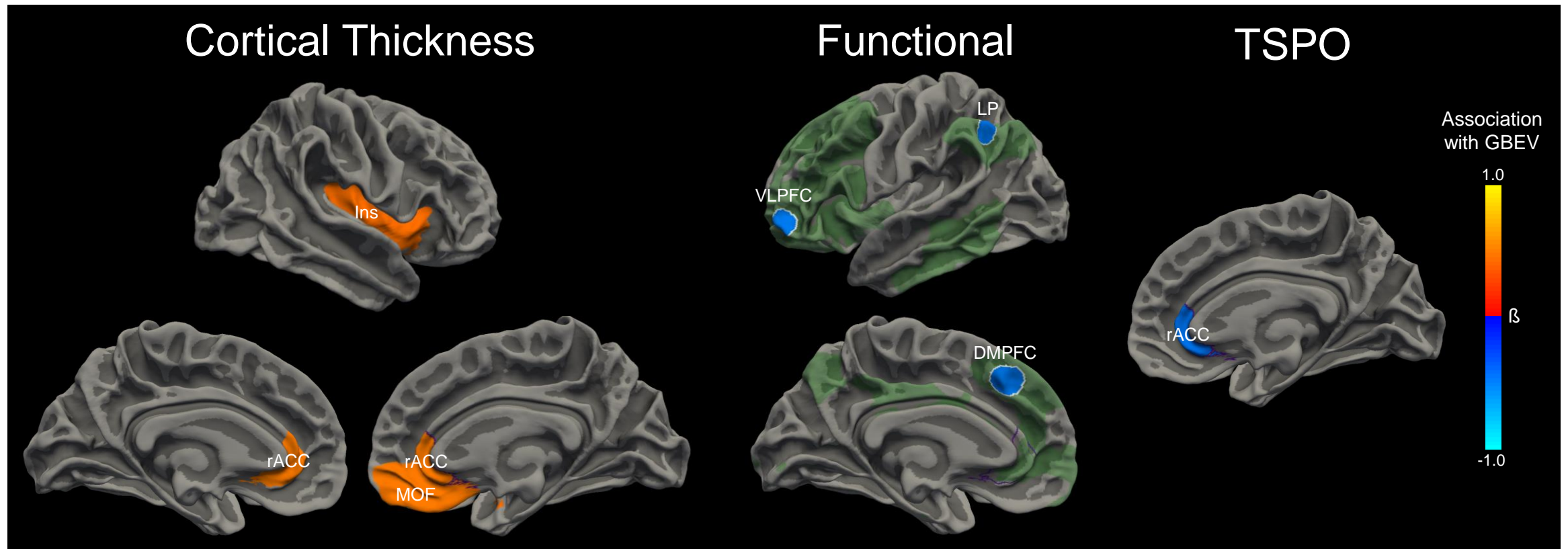
# Demographics and Exposures

Characteristic	ReBlast Cohort (n=30)
<b>Age (yr)</b>	37.1 ± 3.9
<b>Sex: Male</b>	30
<b>Race: White</b>	30
<b>Ethnicity: Non-Hispanic</b>	27
<b>Education (yr)</b>	16.9 ± 2.0
<b>Years in Service</b>	17.2 ± 4.4
<b>Military Branch</b>	20 Army, 4 Navy, 4 Air Force, 2 Marines
<b>Rank</b>	
Officer	1
Warrant Officer	4
Enlisted	25
<b>CES Score</b>	33 ± 5.0
<b>Combat Exposure (CES)</b>	
Moderate	2
Moderate-Heavy	10
Heavy	18
<b>Surrounded by Enemy</b>	
0 times	1
1-2 times	1
3-12 times	6
13-25 times	3
26+ times	19
<b>Blows to the Head (BISQ)</b>	
Low (could remember exact number of blows to the head)	9
High (had more blows to the head than could be remembered)	21
<b>Cumulative Blast Exposure (GBEV)</b>	9,593,890 (387,860 – 363,812,869)

# Cumulative Blast Exposure

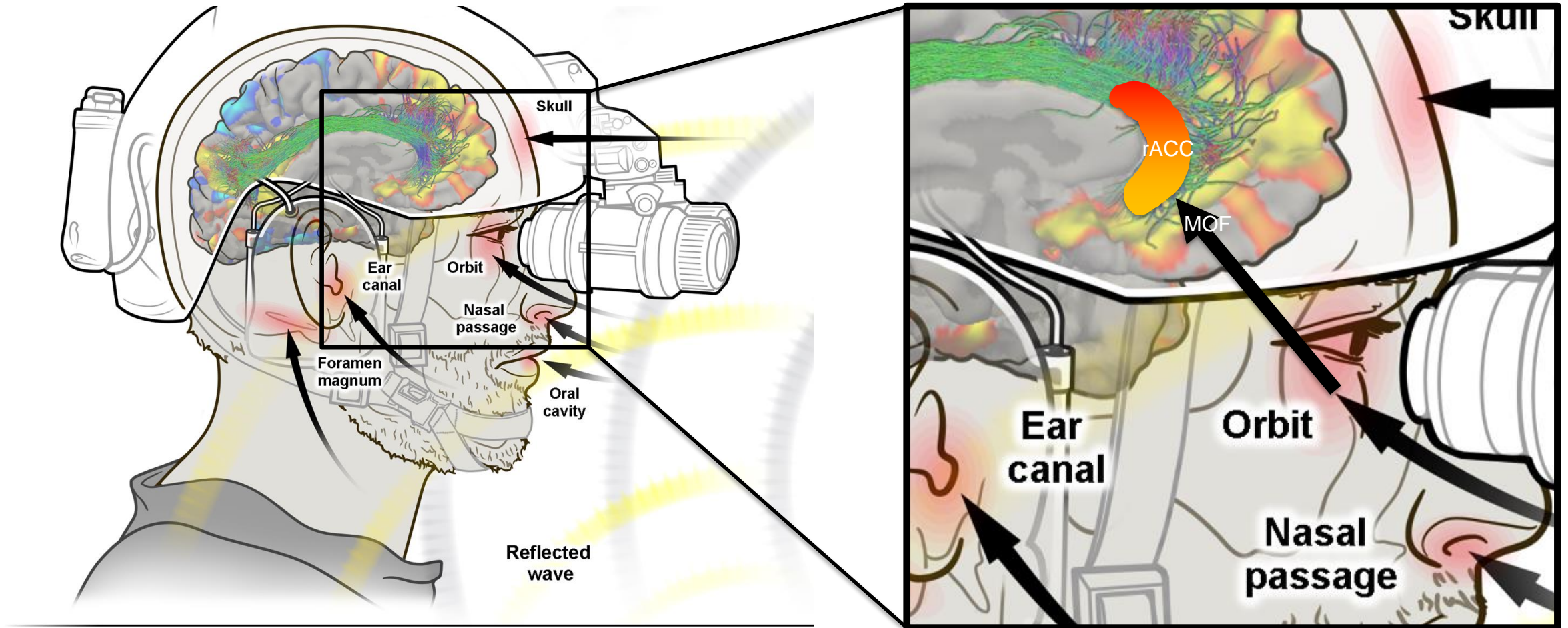
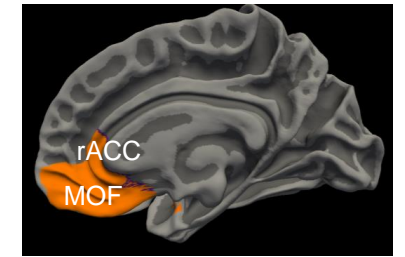


# Multimodal Evidence for Frontal Lobe Injury



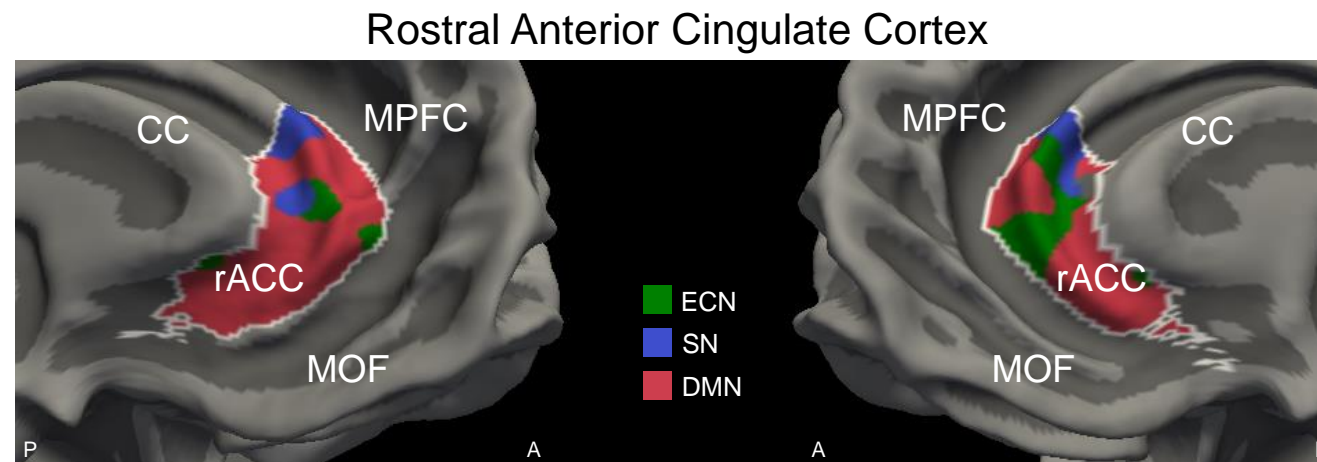
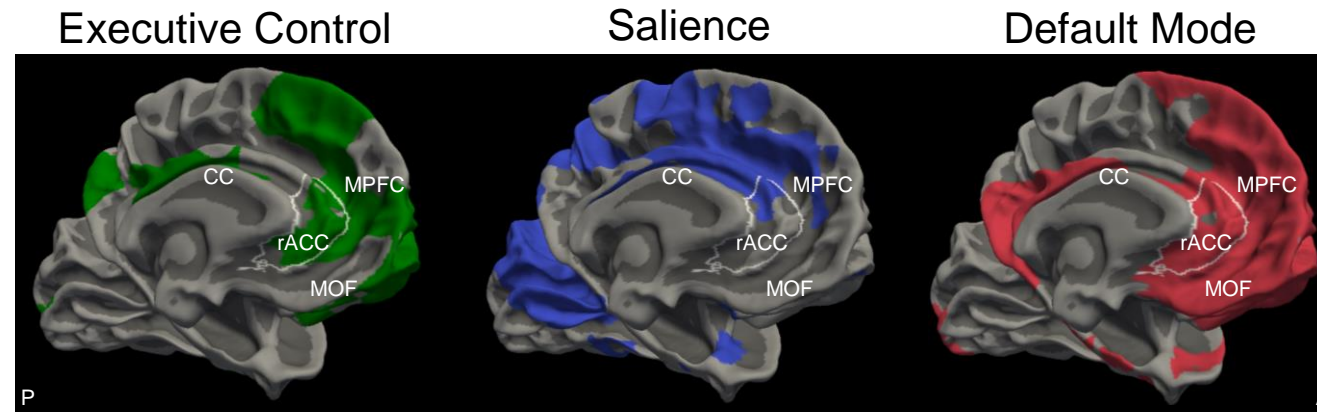
**rACC = rostral Anterior Cingulate Cortex**

# Biomechanical Plausibility

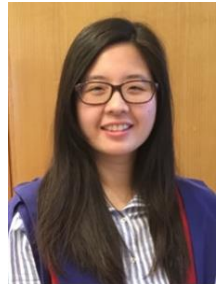


rACC = rostral Anterior Cingulate Cortex

# Disruption of a Network Hub (rACC) Linking Cognition and Emotion



Natalie Gilmore, PhD



Jane Tseng, PhD



Chiara Maffei, PhD

# Biological Basis for Behavioral Changes

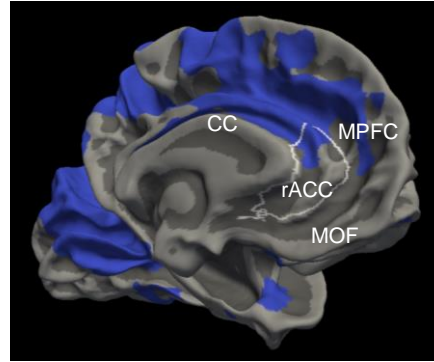


Natalie Gilmore, PhD

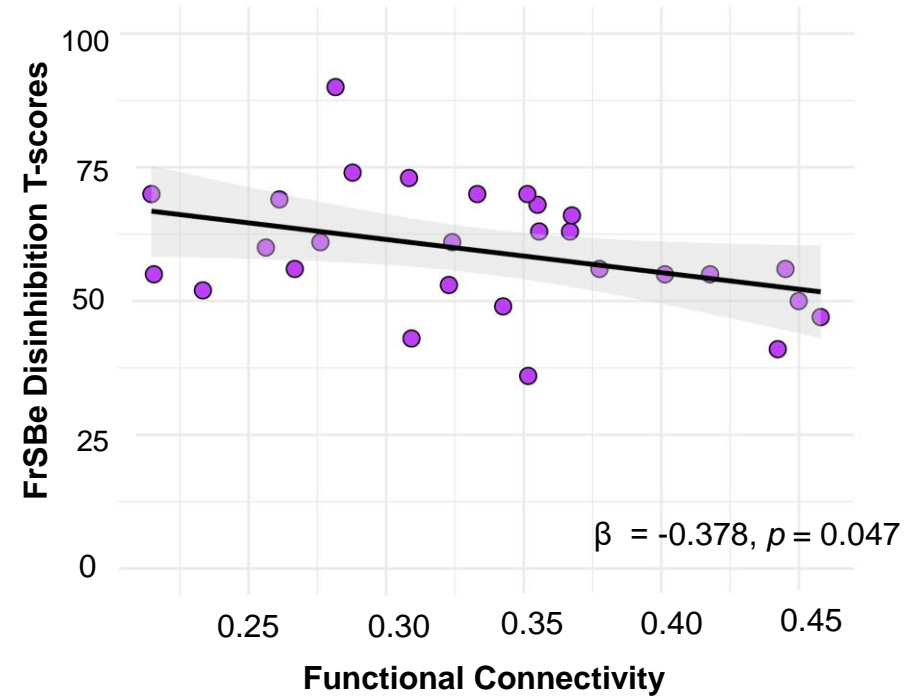
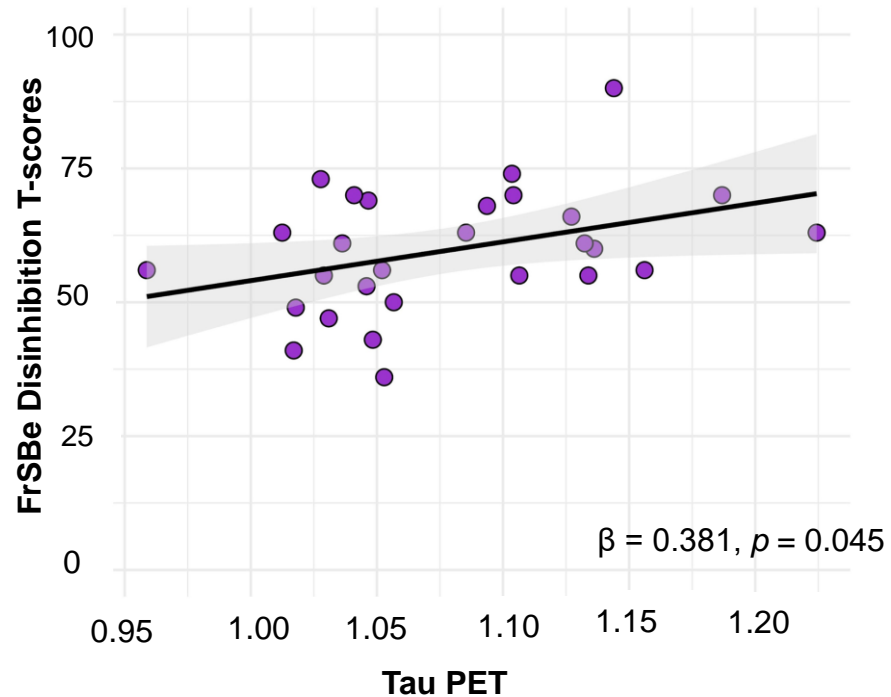


Yelena Bodien, PhD

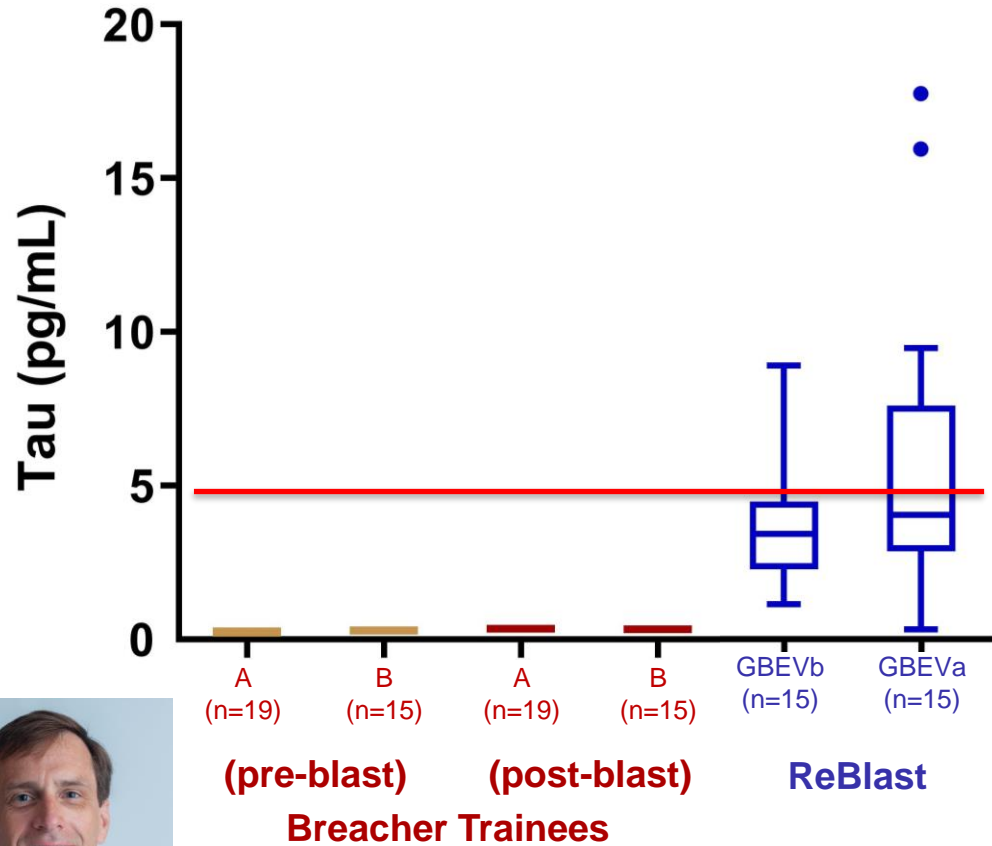
Saliience



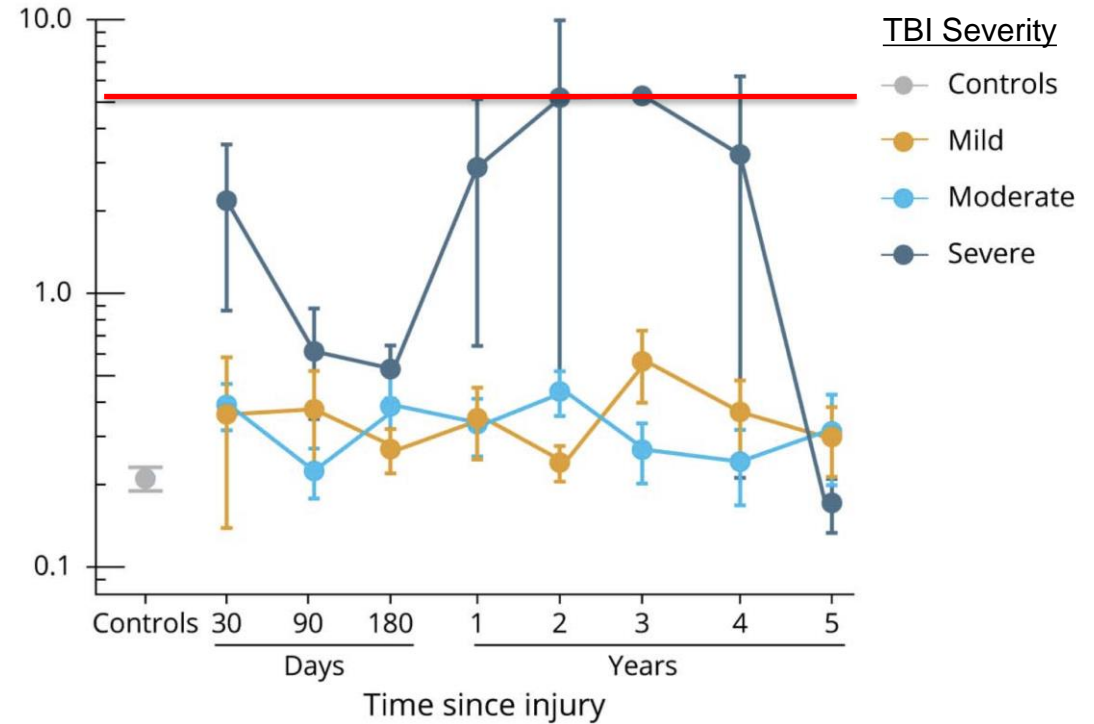
Emotional control  
Behavioral regulation



# Blood Tau >10x Higher in ReBlast Cohort than in Breacher Trainees

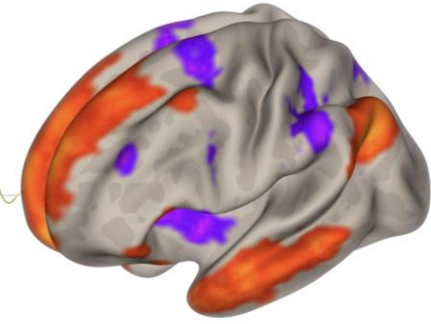
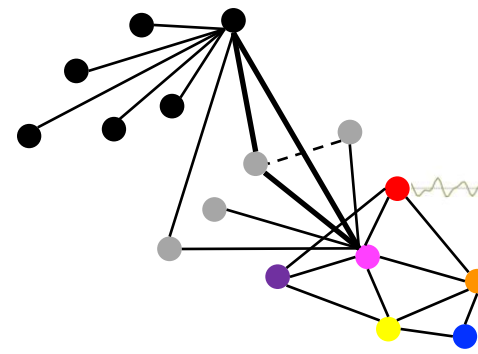
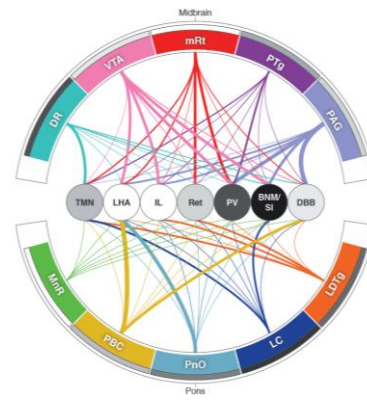
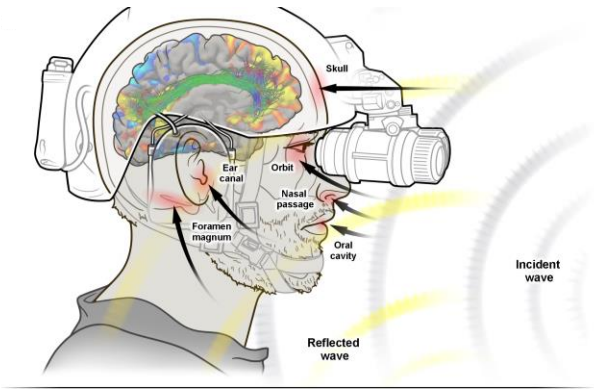
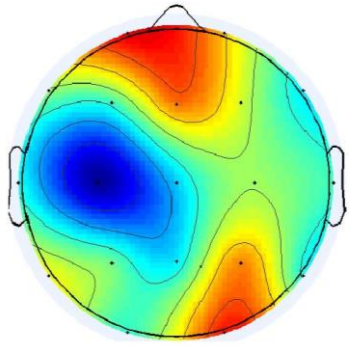


Vorn et al. *Front Neurol* 2022



Shahim et al. *Neurology* 2020





# The Future of SOF Brain Health





# Developing a Diagnostic Test

## - Principles -

Time (years)



Exposure

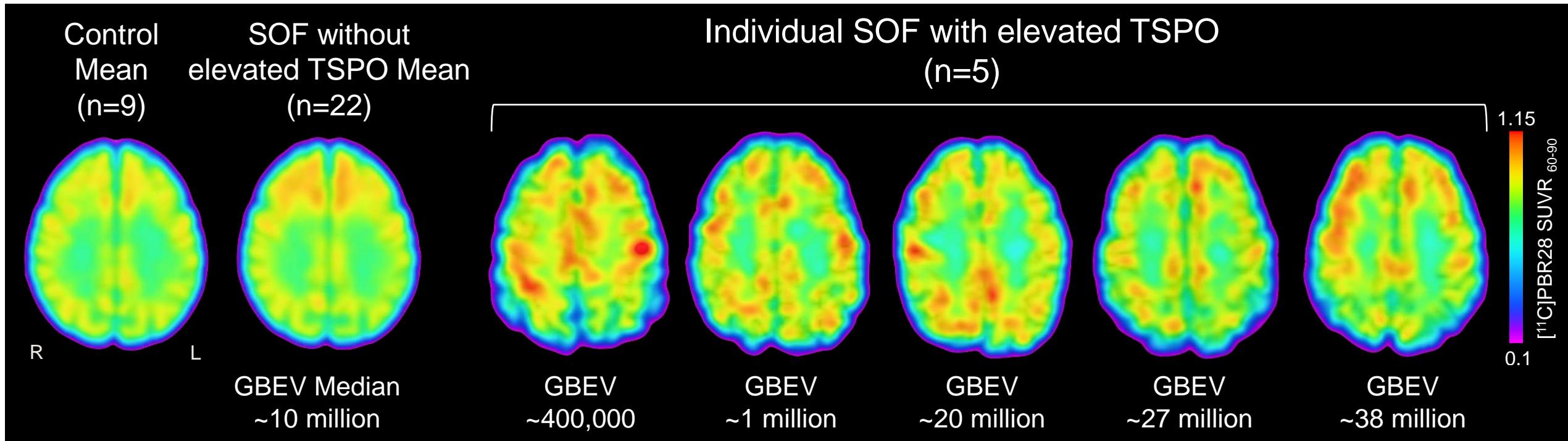


Active-duty  
Operator

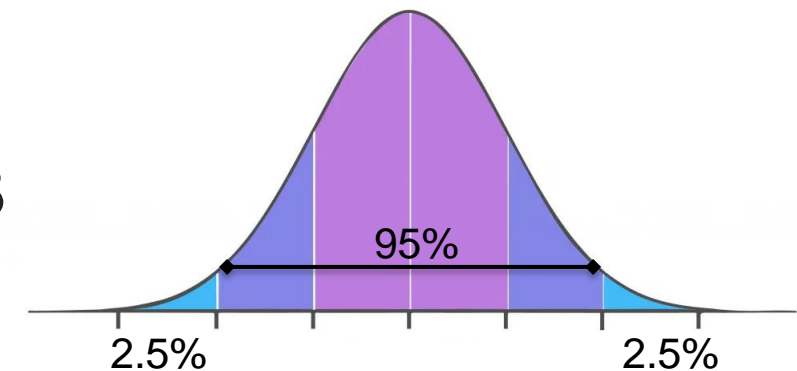


Symptoms

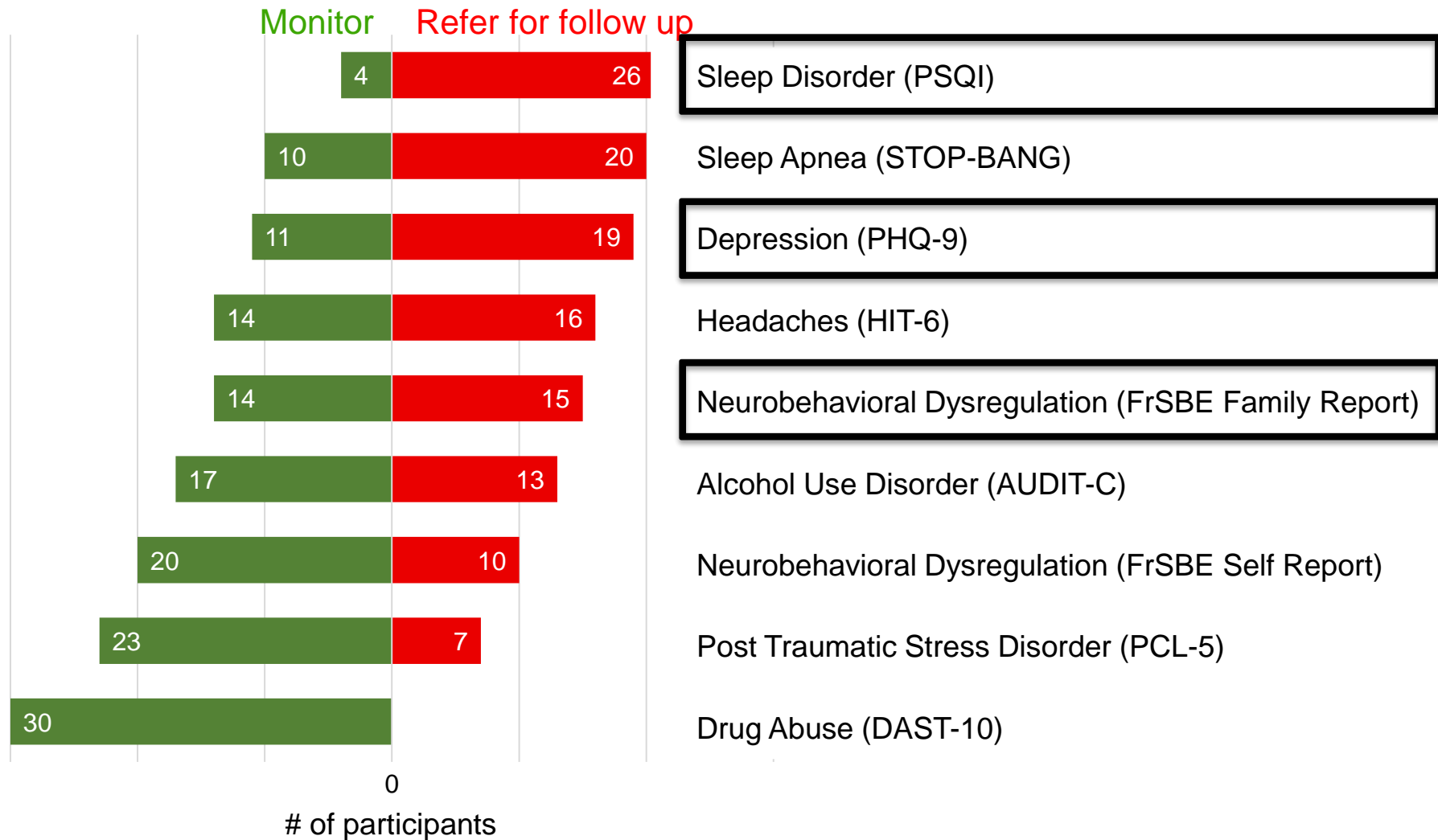
# Is Measuring Exposure Sufficient for Diagnosis?



- Expected rate for healthy controls = 2.5%
- Observed rate for Operators = 18.5%,  $p = 0.0003$



# Is Measuring Symptoms Sufficient for Diagnosis?



# Linking Pathology to Imaging



Dan Benjamini, PhD



Peter Basser, PhD



Dan Perl, MD

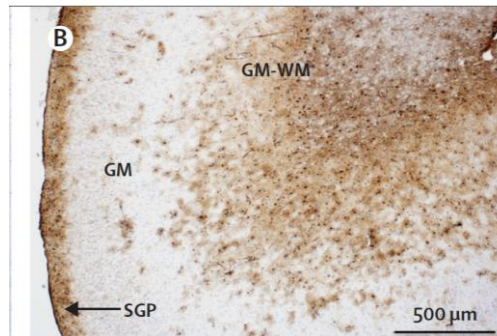
Benjamini...Basser. *Brain* 2022

**Diagnose rBBI and intervene early**

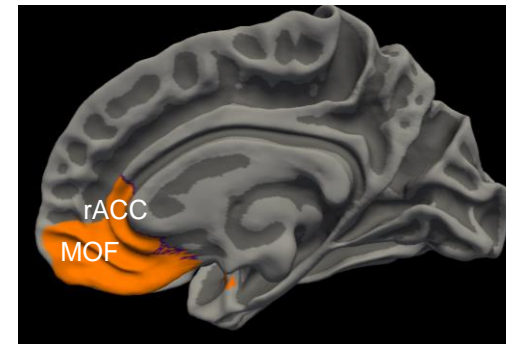
# Implications for Operator Brain Health

- **Complex relationship** between blast exposure and biomarkers.
- Repeated blast exposure has **heterogeneous manifestations**.
- No single test is sufficient – a multimodal diagnostic protocol is needed.

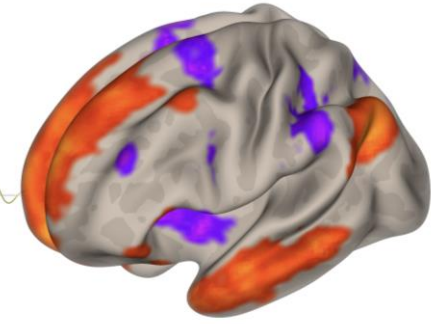
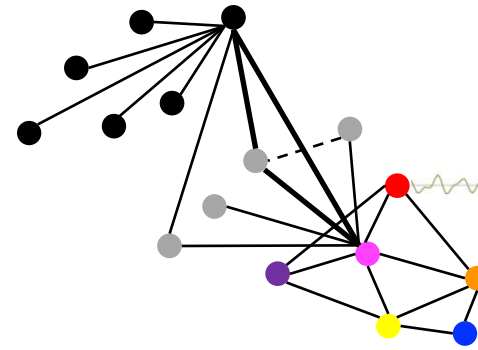
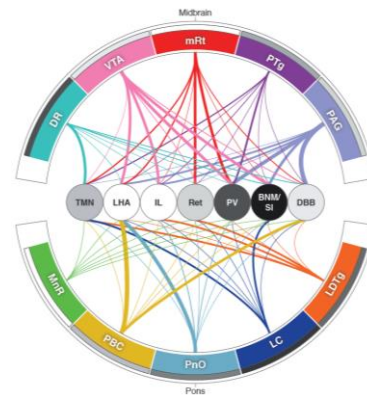
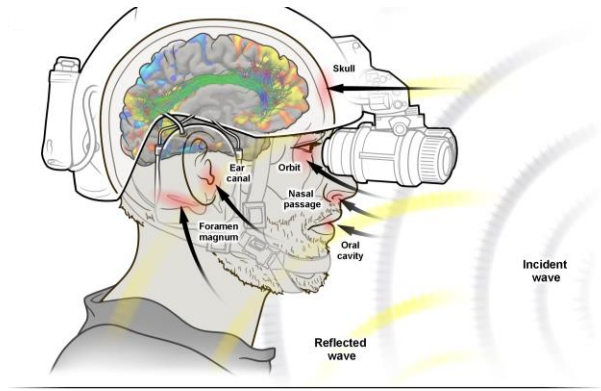
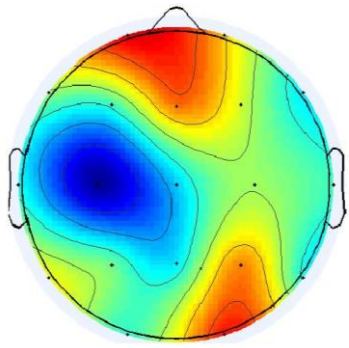
**A normal conventional MRI scan does not rule out repeated blast brain injury.**



Shively et al. *Lancet Neurol* 2016



Gilmore, Tseng, Maffei et al. *PNAS* 2024



# Supporting Operators *Now*



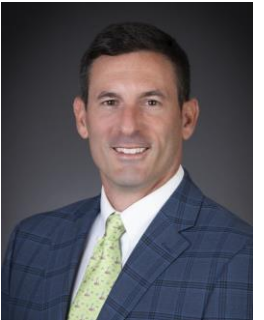
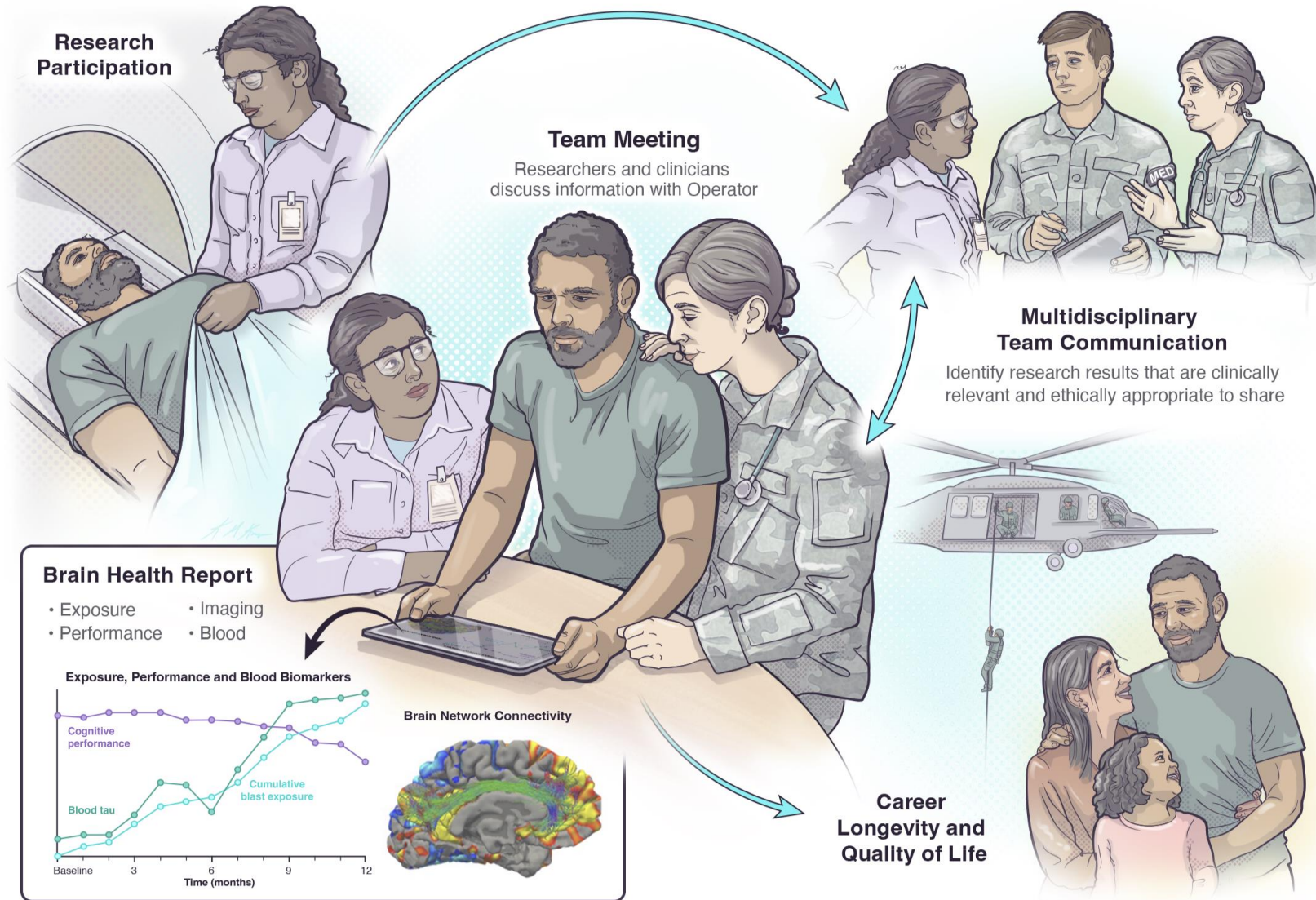
# Risk Matrix

	rBBI	No rBBI
Symptomatic	High (treat)	Uncertain (monitor)
Asymptomatic	Moderate (frequent monitoring)	Low (monitor)

rBBI = repeated Blast Brain Injury

What is the risk to **combat readiness** and **operational performance**?

# Real-Time Communication



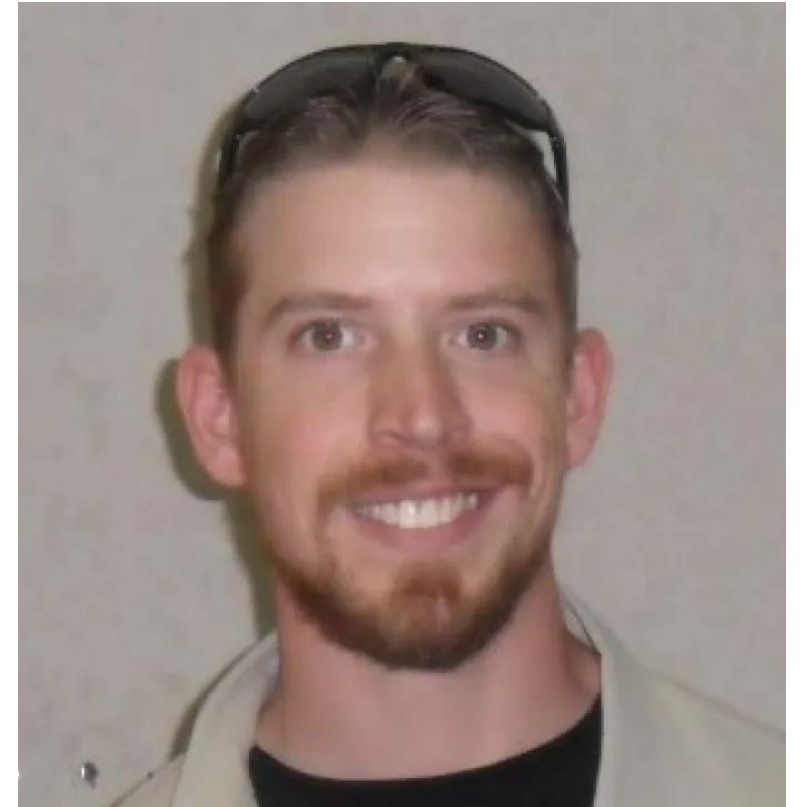
John Tramazzo, JD, LL.M.



Michael Young, MD, MPhil



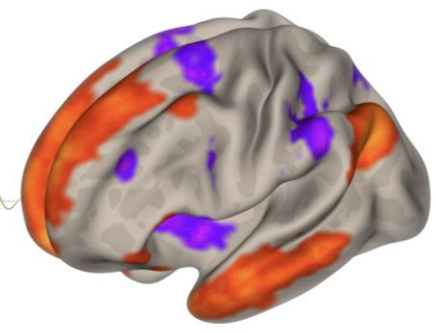
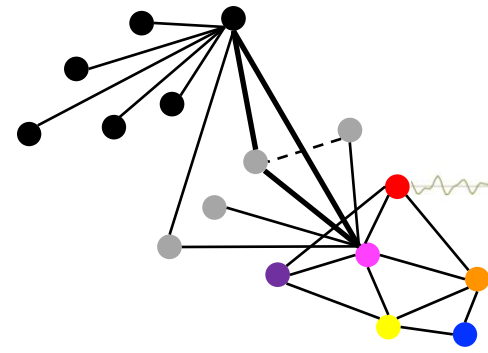
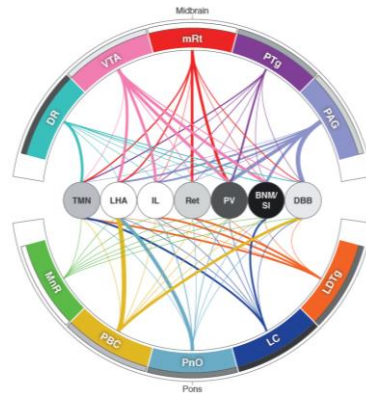
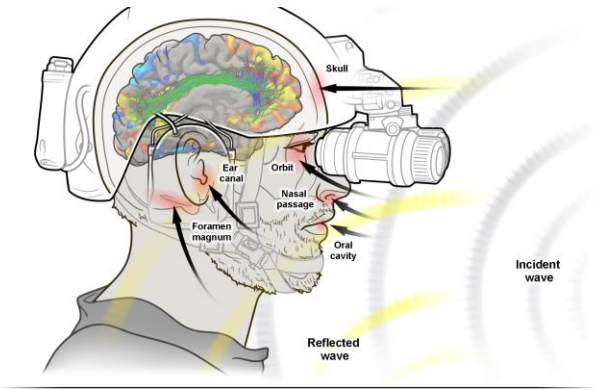
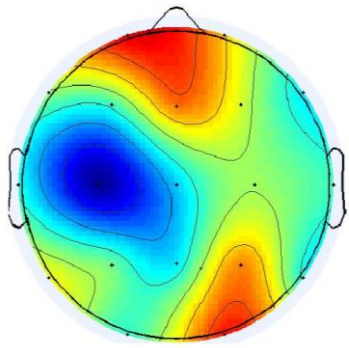
# In honor of



and the many others  
whose sacrifices will not be forgotten.



# Our Why

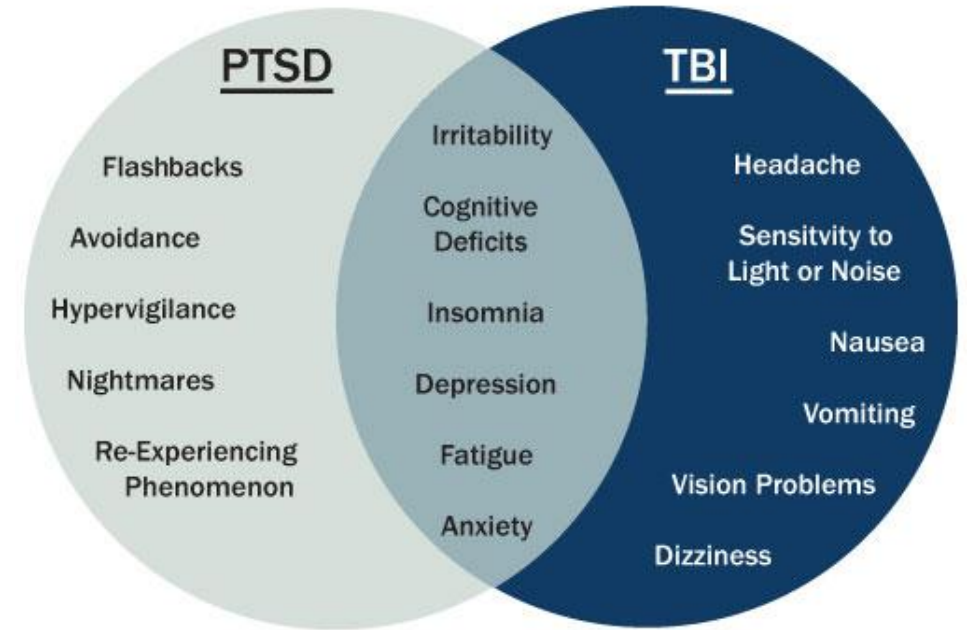


# INVISIBLE WOUNDS<sup>®</sup> FOUNDATION



# Is this PTSD?

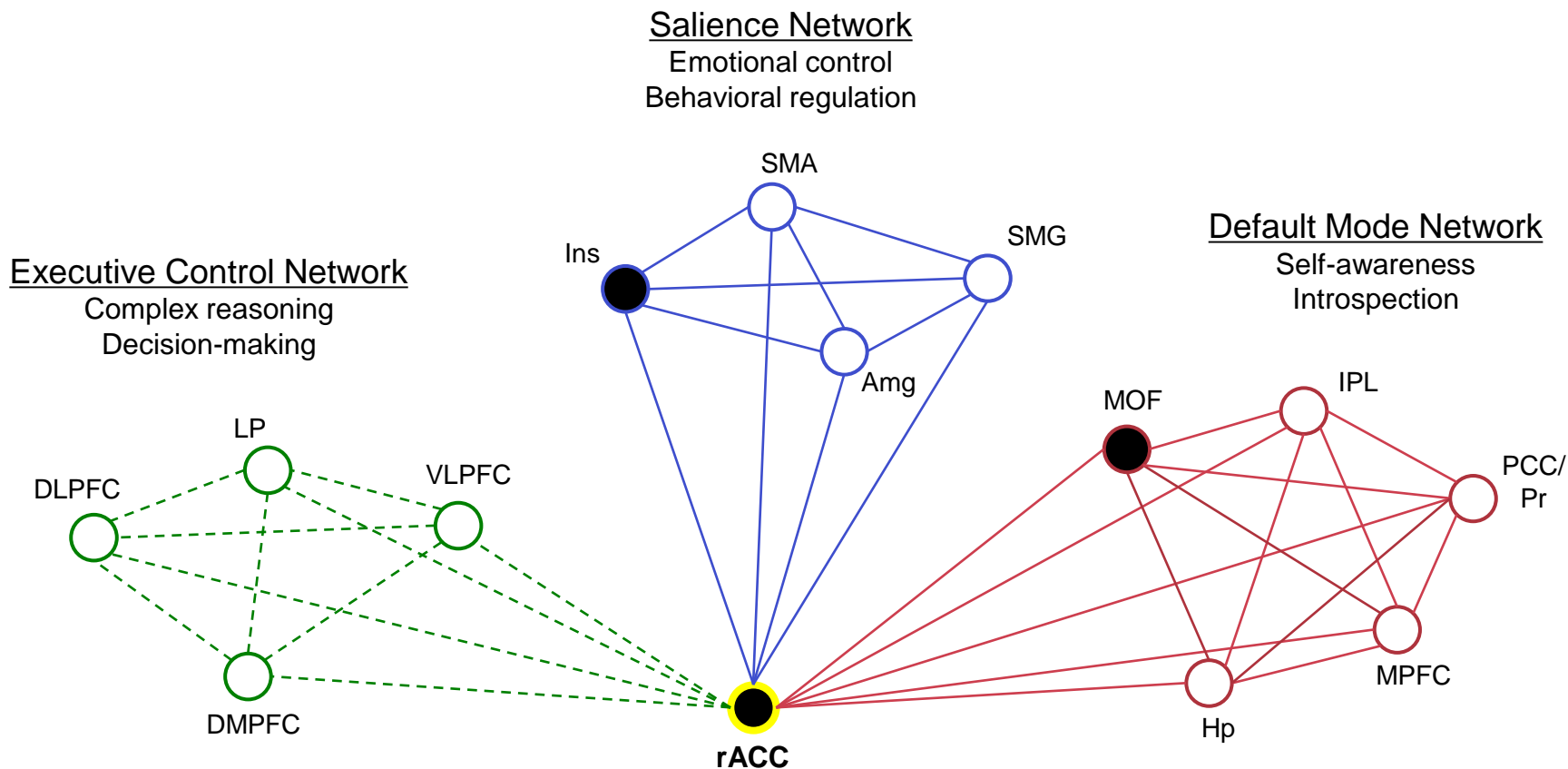
- Venn diagrams overlap
- PTSD can cause structural changes in brain *without* TBI (Kunimatsu et al. *J MRI* 2020)
- Blast exposure in combat associated with PTSD (Belding et al. *Front Neurol* 2023)



Stein et al. *Am J Psychiatry* 2009

- Rat model of blast under anesthesia
  - Fear & anxiety without a psychological stressor (Elder et al. *J Neurotrauma* 2012)
- ReBlast Study
  - No association between blast exposure and PTSD symptoms
  - No change in any results when PTSD symptoms included in the models

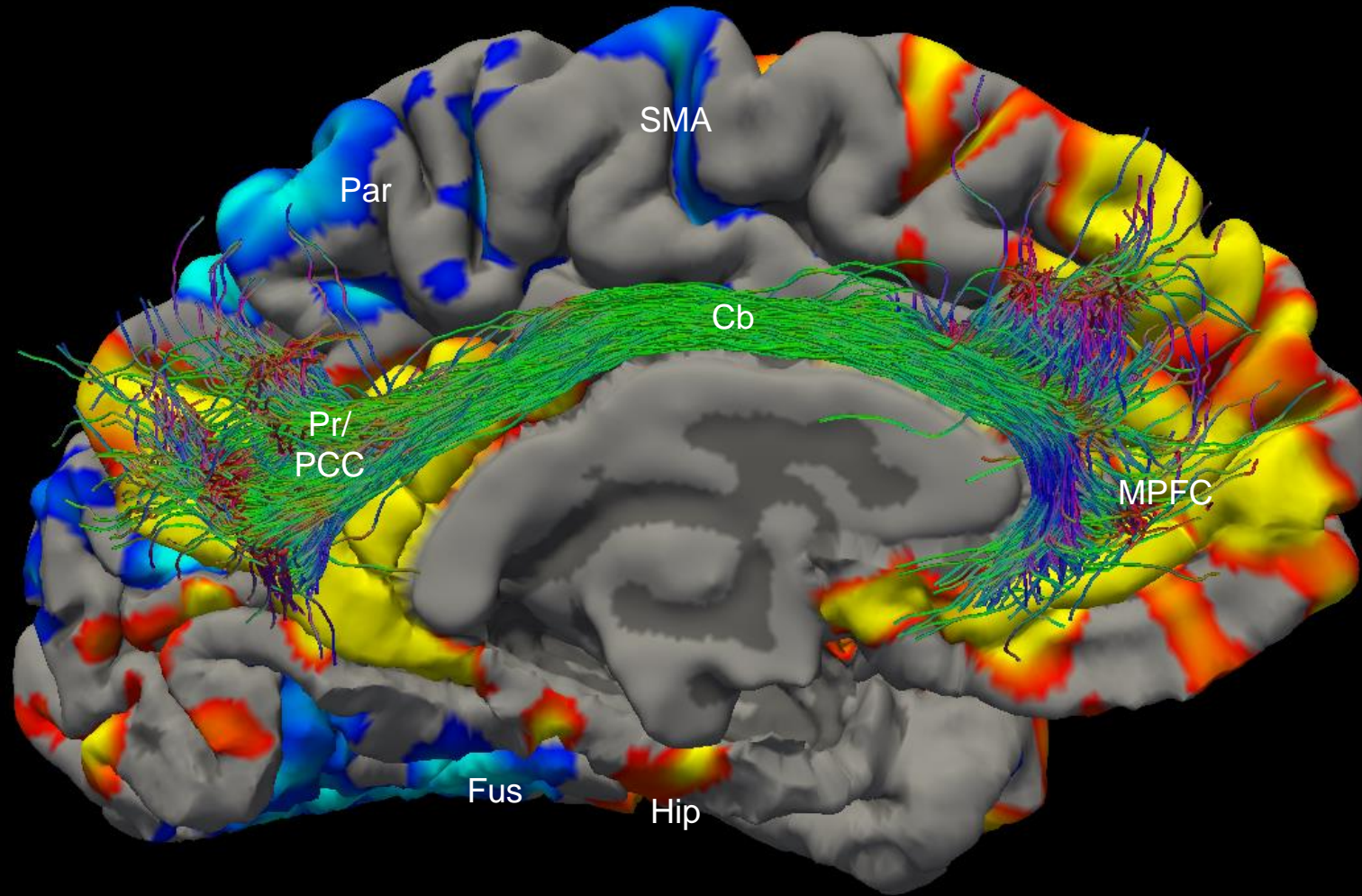
# Convergence of Structural and Functional Network Disruption at rACC



**rACC = rostral Anterior Cingulate Cortex**

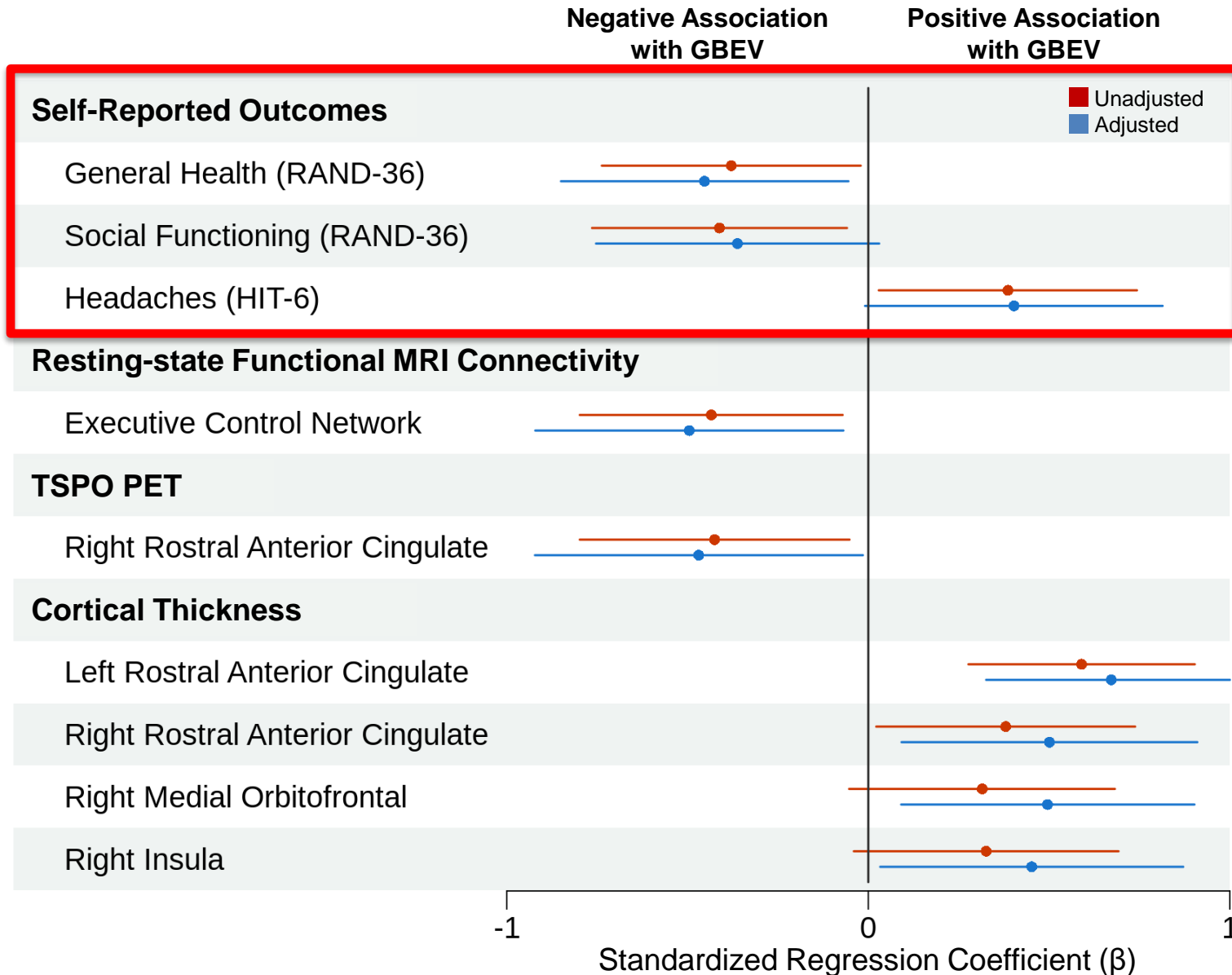


# Network-based Brain Mapping

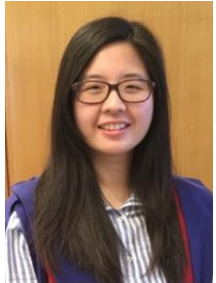


Doug Greve, PhD

# Summary of ReBlast Results



Natalie Gilmore, PhD

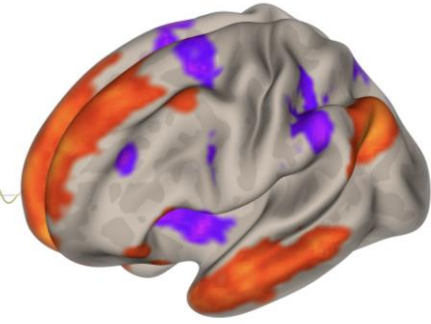
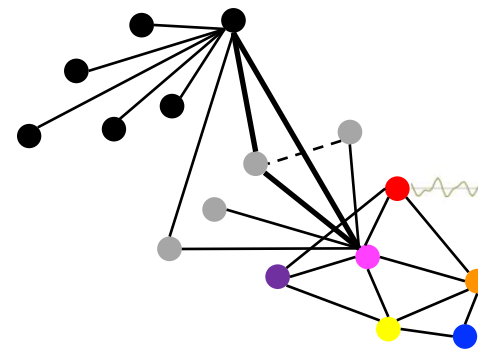
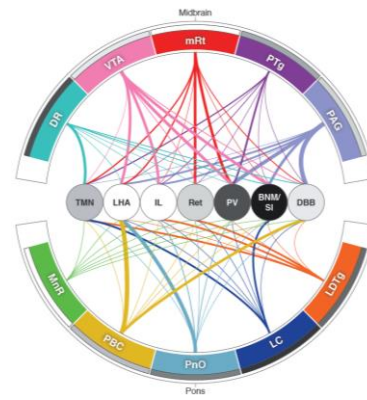
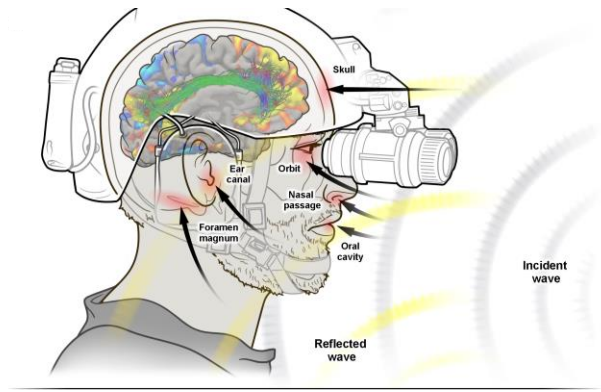
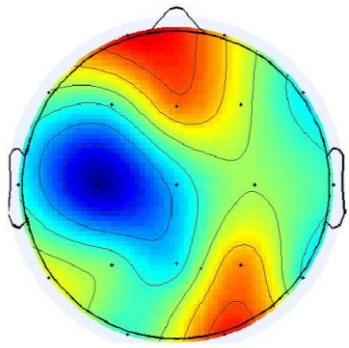


Jane Tseng, PhD



Chiara Maffei, PhD





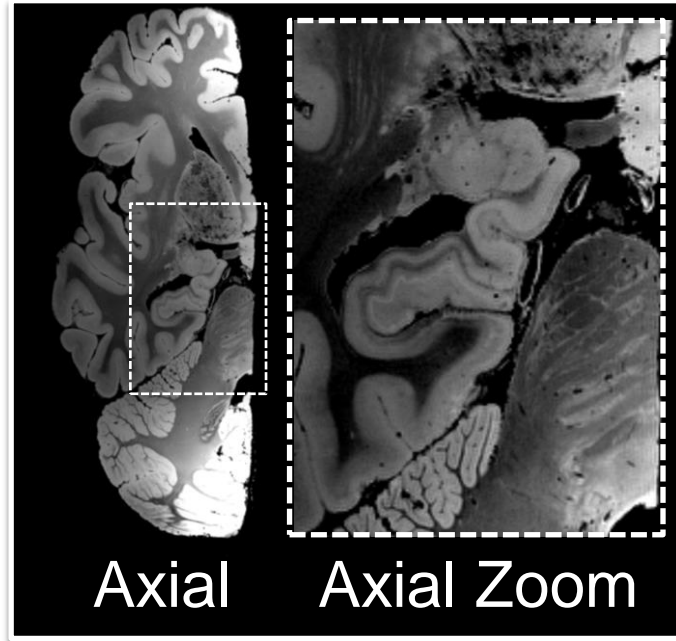
# Future Directions

- Linking Pathology to Imaging-

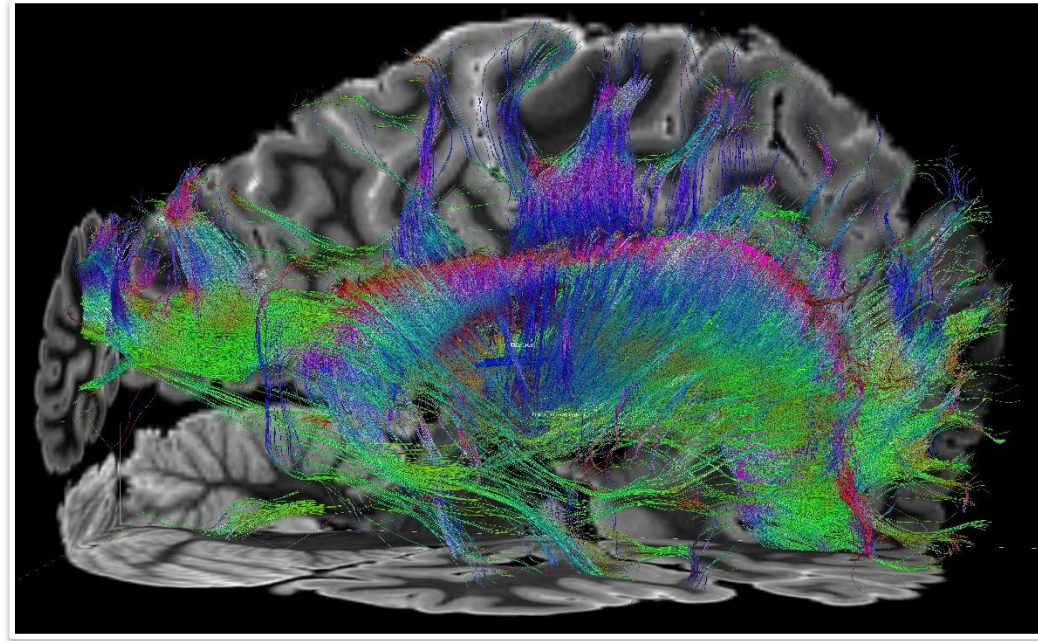


# Network-Based Autopsy

7T MEF 200  $\mu\text{m}$



3T HARDI 750  $\mu\text{m}$



Edlow...Dams-O'Connor. *J Neurotrauma* 2018.

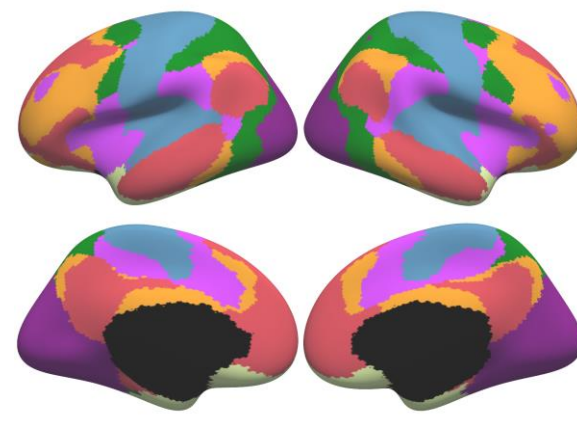
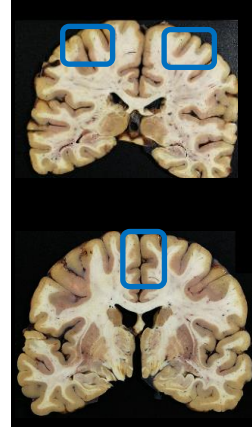
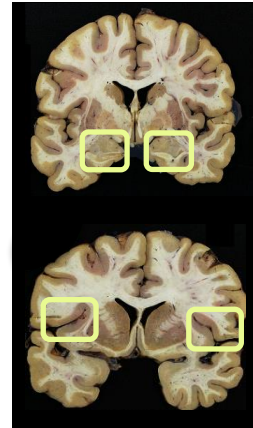


R. Folkerth



D. Perl

## Nodal Pathology



K. Dams-O'Connor



A. Nolan

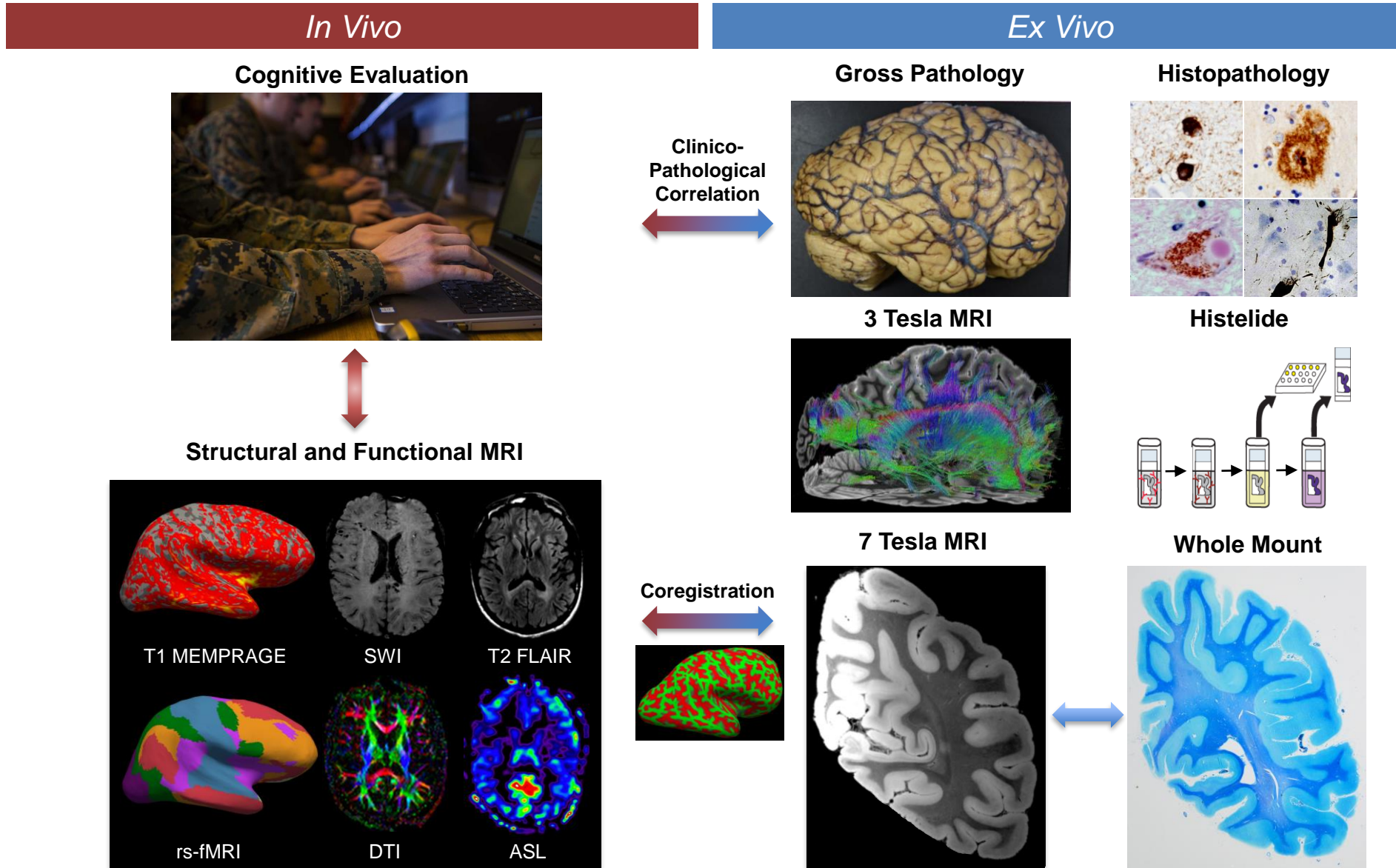


C.D. Keene

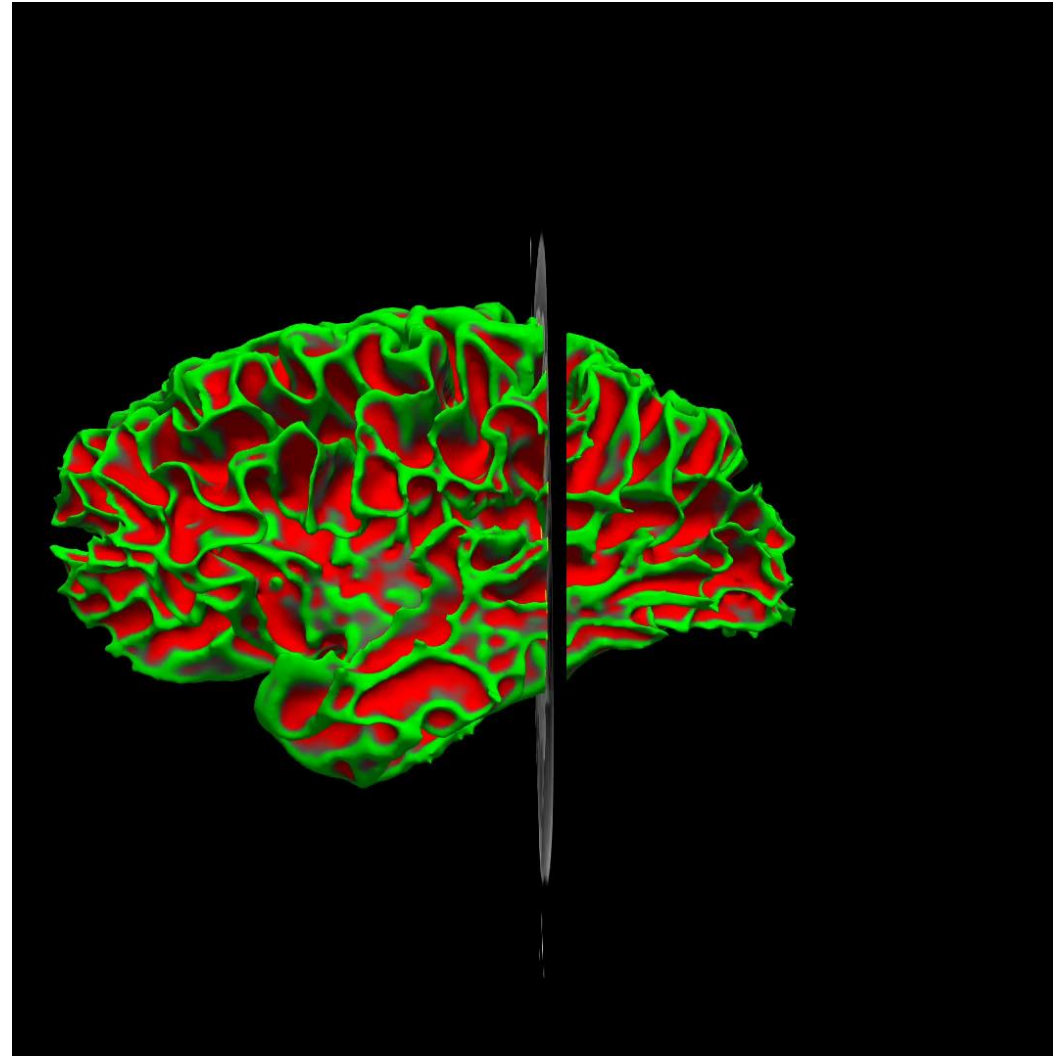


C. Mac Donald

# Conceptual Framework



# Integration of MRI and Pathology



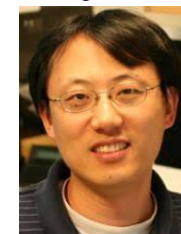
C. Magnain



E. Iglesias



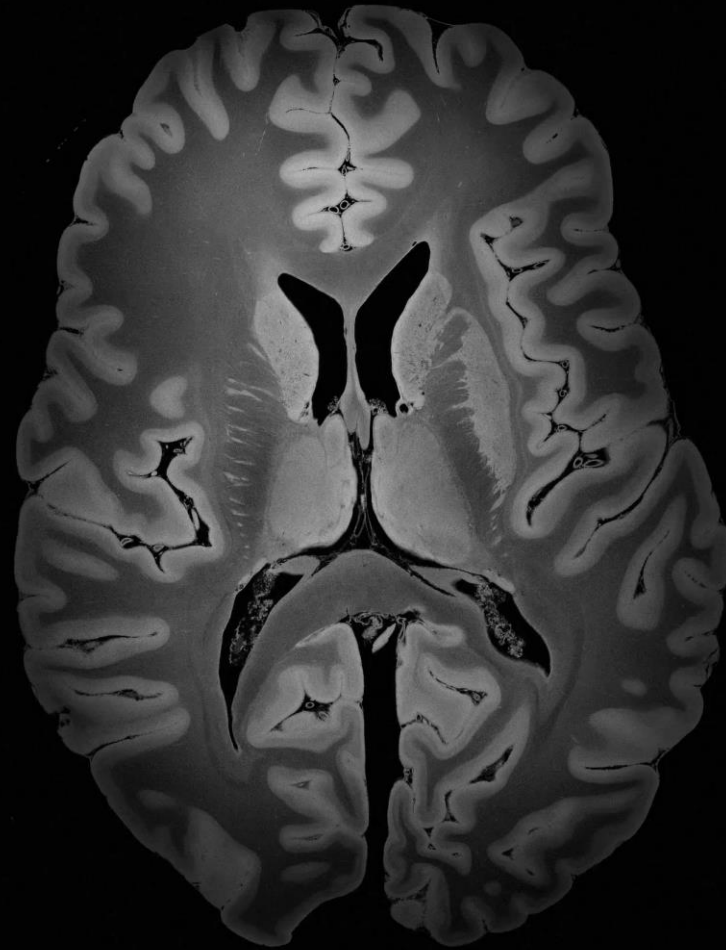
B. Fischl



R. Wang

Video by Bruce Fischl, Caroline Magnain, Eugenio Iglesias, and Ruopeng Wang.

# 100 Micron MRI



Edlow et al. *Scientific Data* 2019



A. van der Kouwe



B. Fischl



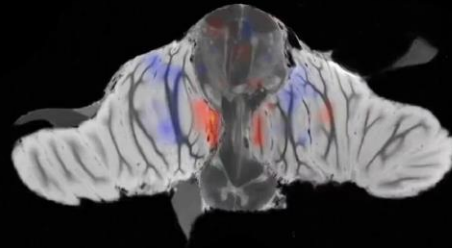
A. Mareyam



L. Wald

Data available at [www.datadryad.org](http://www.datadryad.org), [www.OpenNEURO.org](http://www.OpenNEURO.org),  
[www.lead-dbs.org](http://www.lead-dbs.org), <https://histopath.nmr.mgh.harvard.edu>, [www.youtube.com](http://www.youtube.com)

# Mapping Brain Networks

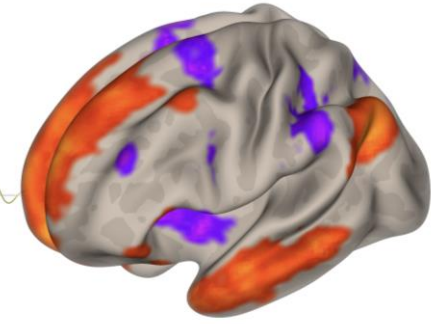
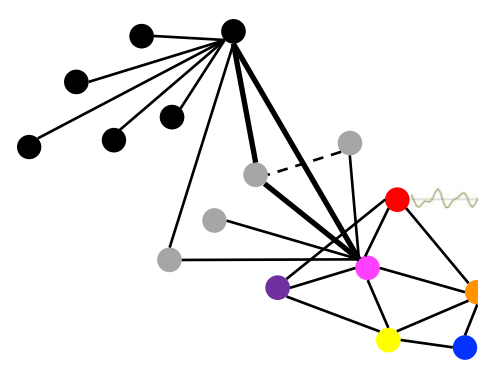
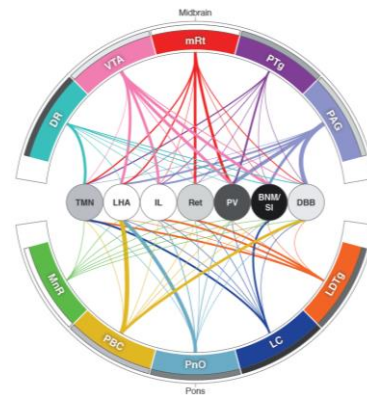
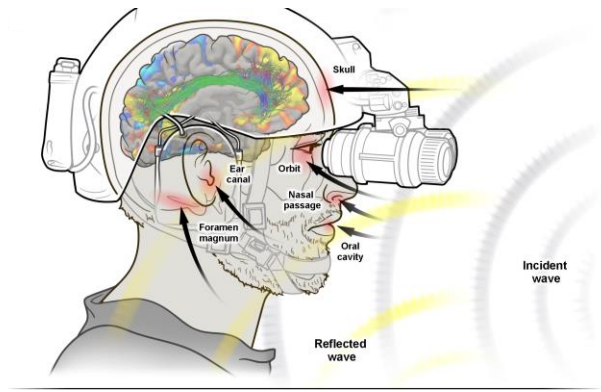
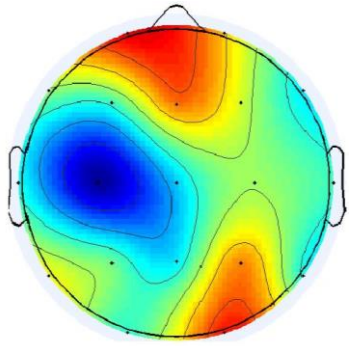


Li et al. *NeuroImage* 2021

Data available at [www.OpenNEURO.org](http://www.OpenNEURO.org),  
[www.lead-dbs.org](http://www.lead-dbs.org), <https://histopath.nmr.mgh.harvard.edu>.



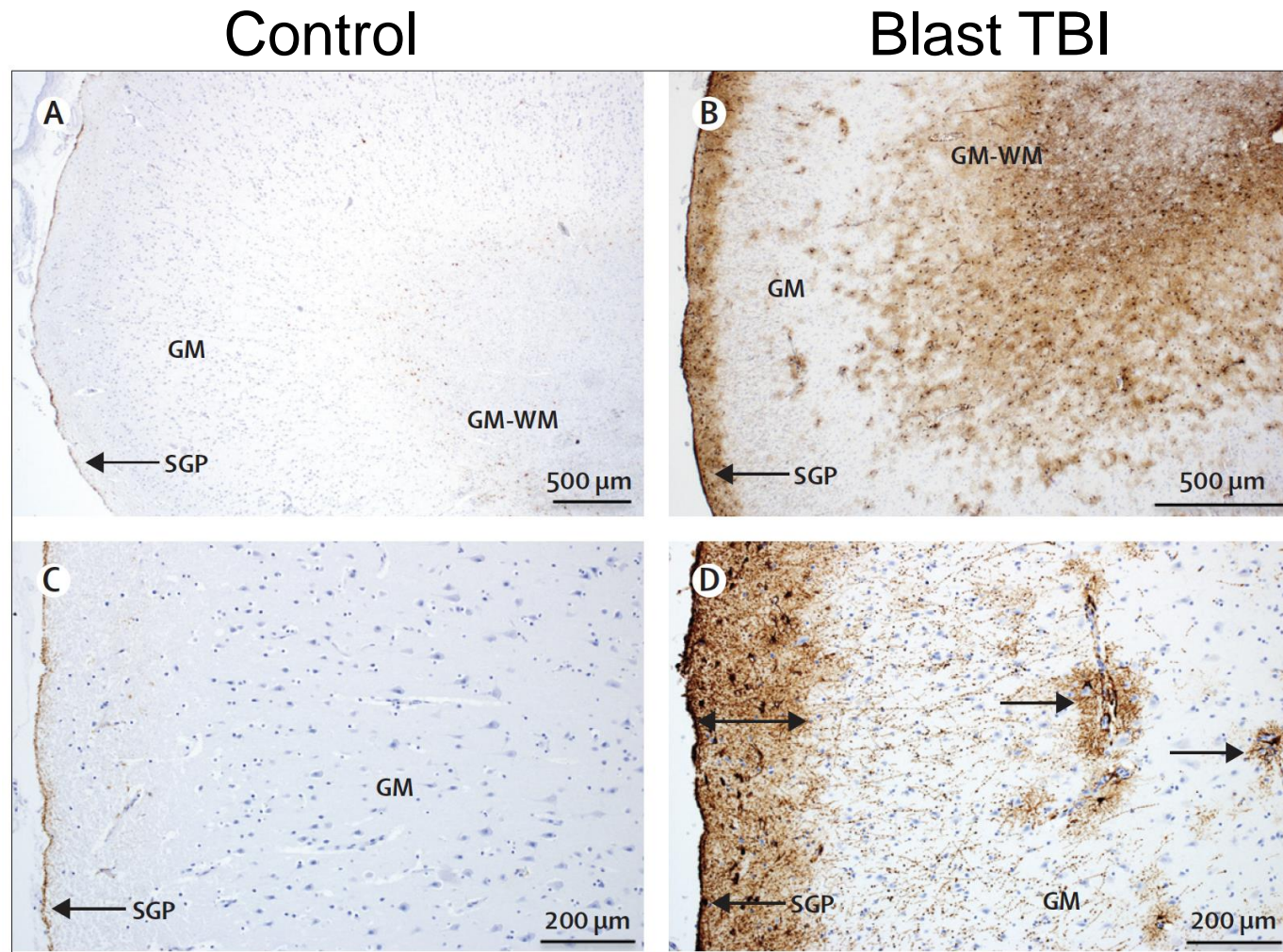
Andrew Li, PhD



# Gaps in Knowledge



# There is No Gold Standard... ...and the Silver Standard is Inaccessible





# How Do We Accurately Measure Cumulative Blast Exposure?



Blast Gauge

<p>2a. Large arms, often shoulder-fired, that can be carried on a person?            O Rocket-propelled weapon systems, such as: RPG, LAW, SMAW, Dragon            O Recoilless rifles and launchers, such as: GUSTAV, AT4, Javelin, grenade launcher</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	(Mark with X)
<p>2b. Approximately how many years were you exposed?            (If you recall years in which only 1 exposure occurred, also count those.)</p>	<input type="text" value="14"/>	(Whole number, round up)
<p>2c. On average, how many months per year?            (Or, if 1 year, how many months in that year?)            (If you recall months in which only 1 exposure occurred, also count those.)</p>	<input type="text" value="3"/>	(Whole number, 1-12)
<p>2d. On average, how many days per month?            (Or, if 1 month, how many days in that month?)            (If you recall days in which only 1 exposure occurred, also count those.)</p>	<input type="text" value="10"/>	(Whole number, 1-31)
<p>2e. On average, how many rounds per day?            (Or, if 1 day, how many rounds in that day?)</p>	<input type="text" value="3000"/>	(Whole number, round up)
<p>2f. Over the course of your life, approximately how often did exposures occur two days in a row? (or more than two days in a row)?</p> <p style="text-align: center;"> <input type="checkbox"/> Not at all         Almost never         Some of the time         All of the time         </p> <p style="text-align: center;">(Mark with X)</p>		

GBEV Questionnaire

# Unmeasured Exposures



Special Warfare Combatant-craft Crewmen

<https://www.navy.com/>

# Unmeasured Exposures



SOAR 160th  
U.S. Military News

# Centers of Excellence

## - Home Base -



# Real-Time Communication



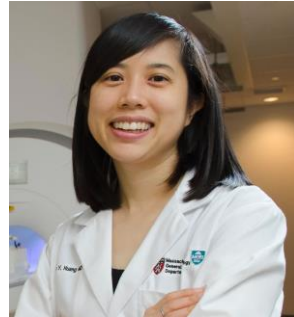
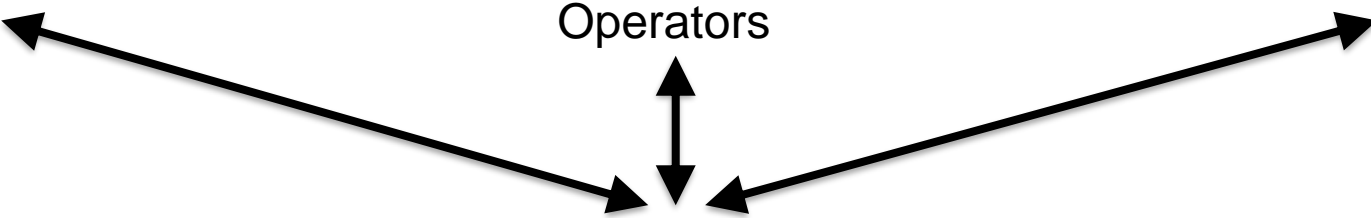
SOF Medics



Operators



SOF Doctors



Clinician-Investigators

John Tramazzo, JD, LLM

Michael Young, MD, MPhil

# Career Longevity and Quality of Life



# Demographics and Exposures

Characteristic	ReBlast Cohort (n=30)
Age (yr)	37.1 ± 3.9
Sex: Male	30
Race: White	30
Ethnicity: Non-Hispanic	27
Education (yr)	16.9 ± 2.0
Years in Service	17.2 ± 4.4
Military Branch	20 Army, 4 Navy, 4 Air Force, 2 Marines
Rank	
Officer	1
Warrant Officer	4
Enlisted	25
CES Score	33 ± 5.0
Combat Exposure (CES)	
Moderate	2
Moderate-Heavy	10
Heavy	18
Surrounded by Enemy	
0 times	1
1-2 times	1
3-12 times	6
13-25 times	3
26+ times	19
Blows to the Head (BISQ)	
Low (could remember exact number of blows to the head)	9
High (had more blows to the head than could be remembered)	21
Cumulative Blast Exposure (GBEV)	9,593,890 (387,860 – 363,812,869)



Samantha Tromly, BS



Kat Deary, NP

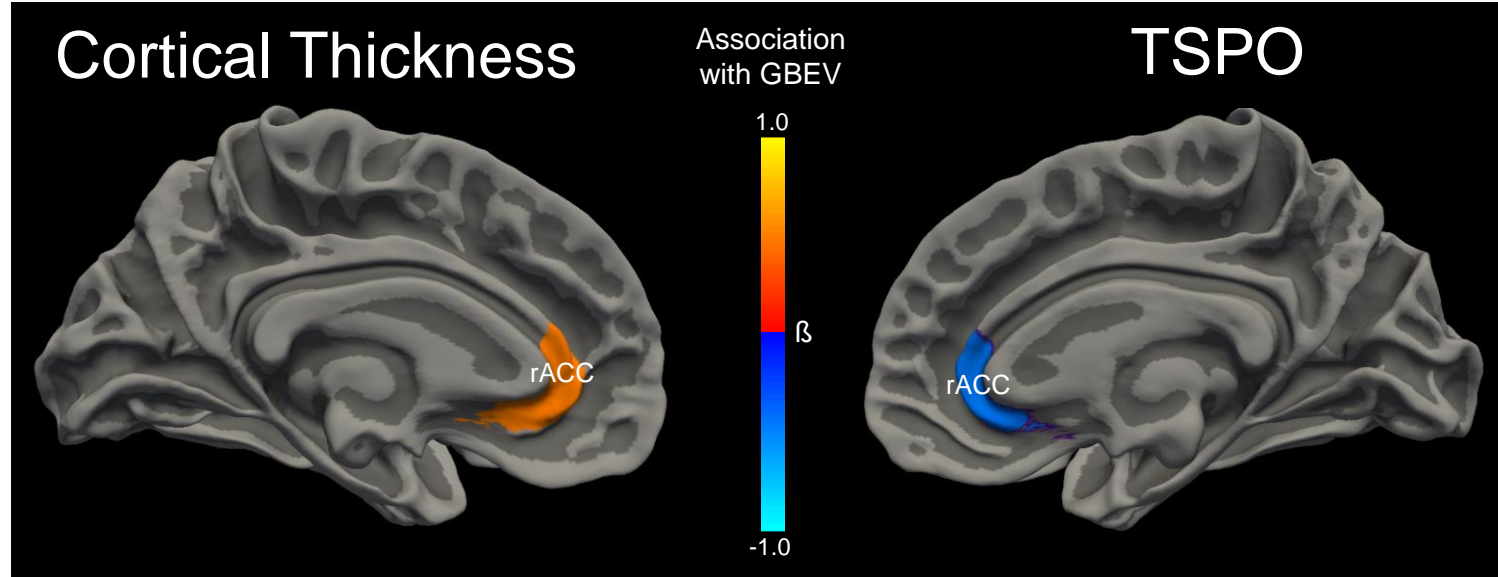


Collin Hu, DO

# Call to Action



# Pathophysiologic Plausibility

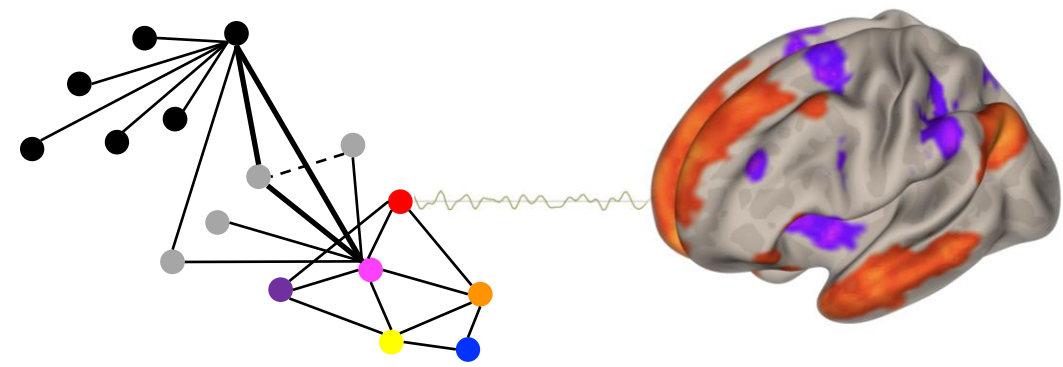
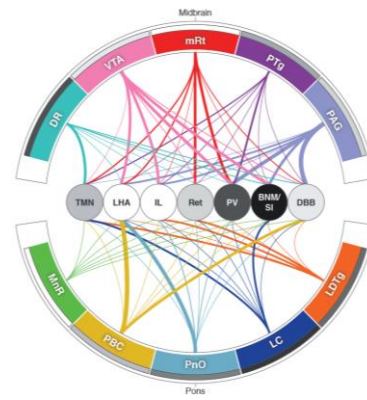
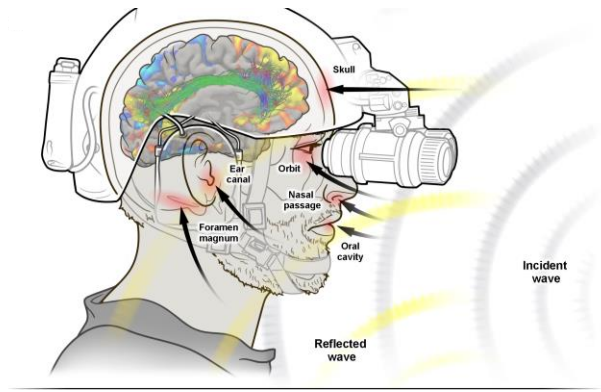
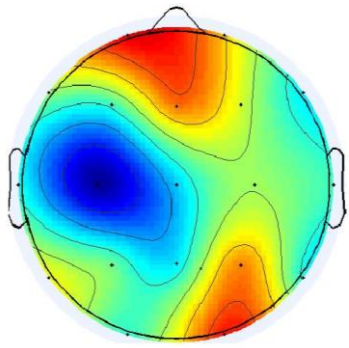


## Increased cortical thickness:

- Breachers  
(Stone et al. *J Neurotrauma* 2021)

## Decreased TSPO:

- PTSD (Bhatt et al. *Nature Comm* 2020)
- Schizophrenia (Plaven-Sigra et al. *Biol Psych* 2018)
- Autism (Zurcher et al. *Mol Psych* 2021)
- Alcohol use disorder (Hillmer et al. *Mol Psych* 2017)

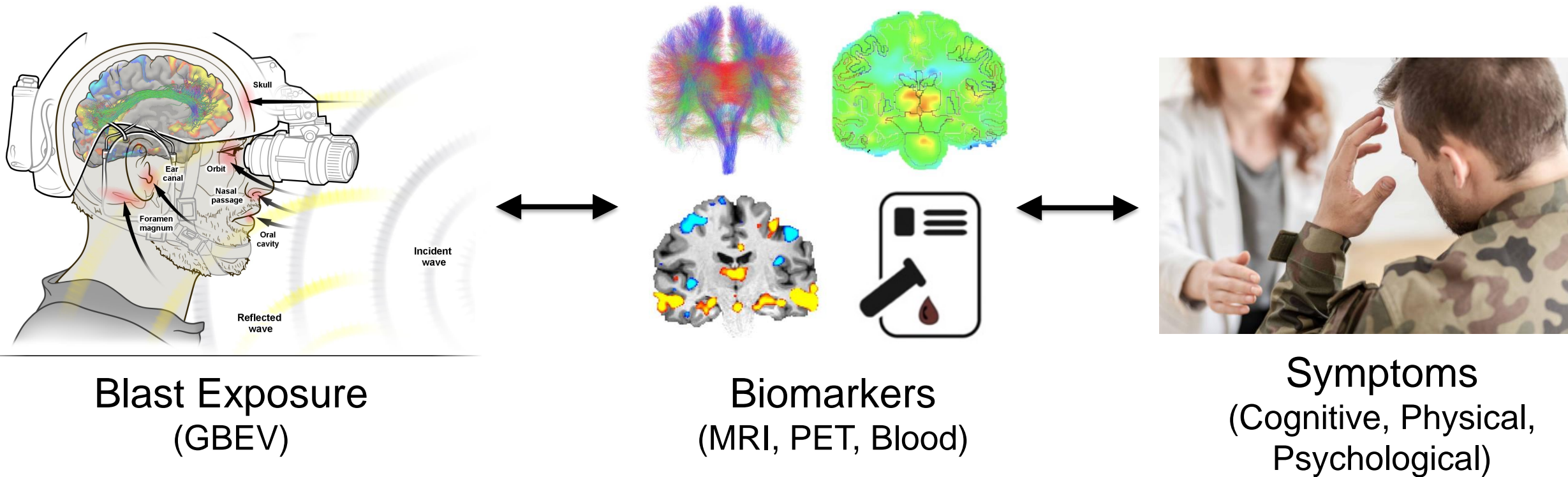


# ReBlast Continuum



# ReBlast Continuum

- Filling the Gap in Diagnostic Testing -

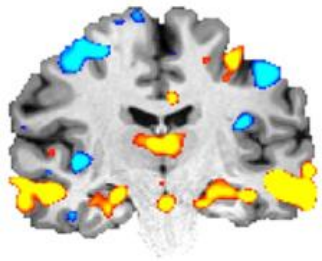


**Diagnostic Biomarkers Link Blast Exposure to Symptoms**

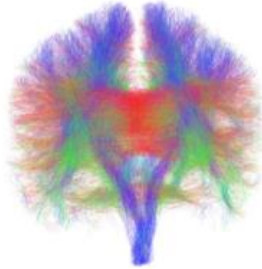
# ReBlast Continuum

## - Longitudinal Study Design -

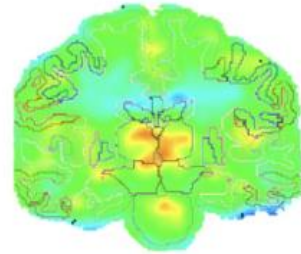
**Travel Cohort** – 75 SOF assessed 2 times in Boston, MA and 5 times remotely



Function



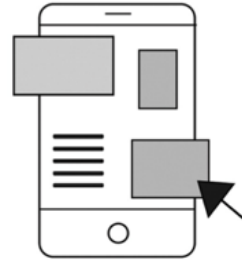
Structure



Inflammation

Baseline and Study Completion

**Remote Cohort** – 150 SOF assessed 7 times remotely



Cognitive Performance



Physical Symptoms



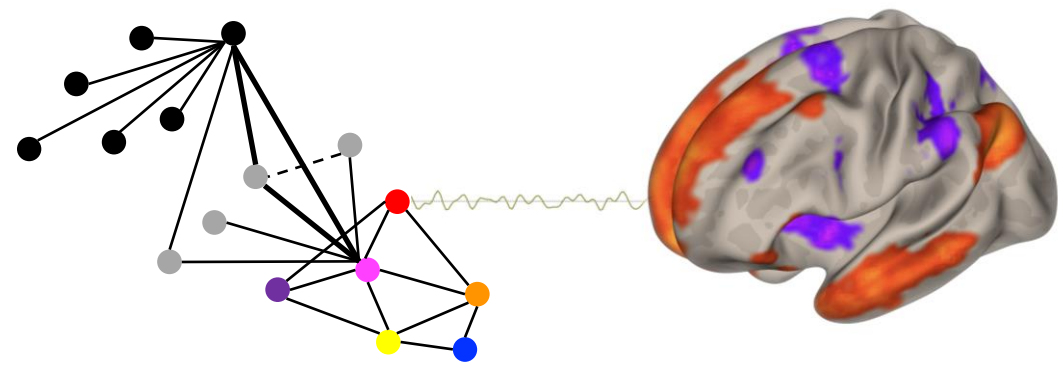
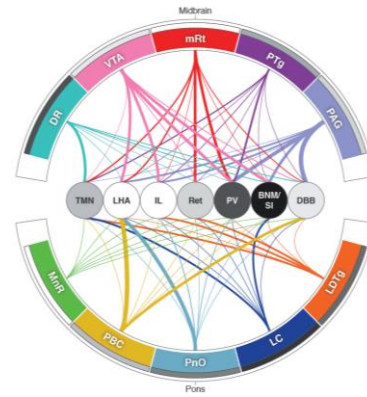
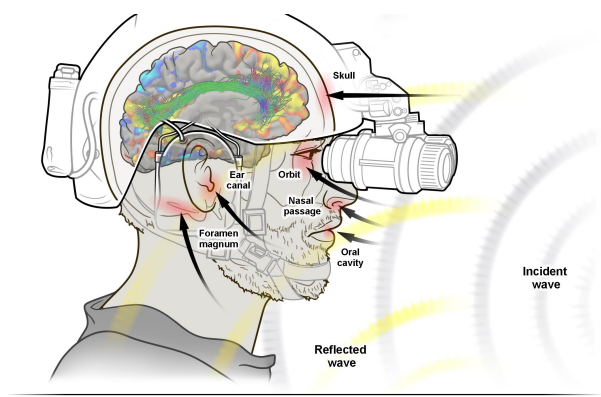
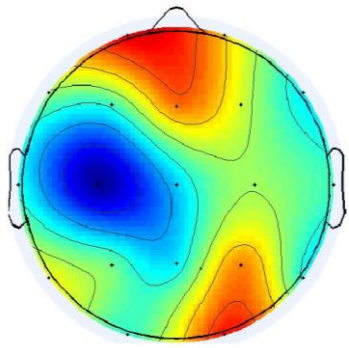
Psychological Health



Blood Biomarkers

Baseline and Every 6 Months

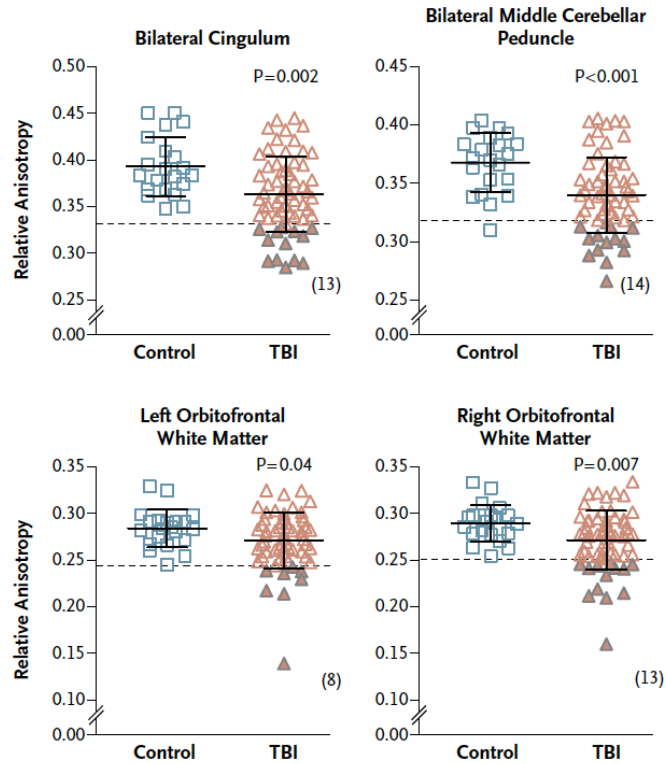
- 1) **Larger sample size**
- 2) **Longitudinal design** to characterize trajectory of biomarker changes
- 3) Account for **additional exposures**
- 4) **Personalized measurements** of change from baseline



# Personalized Precision Medicine



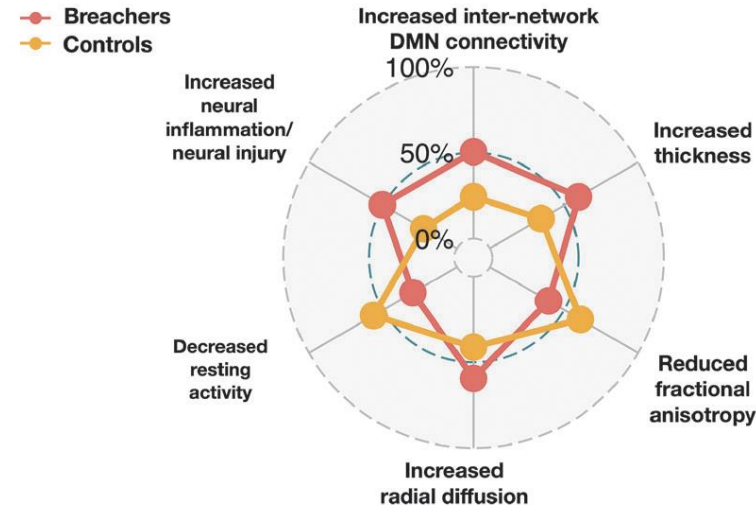
# Limitations of Group-Level Analysis



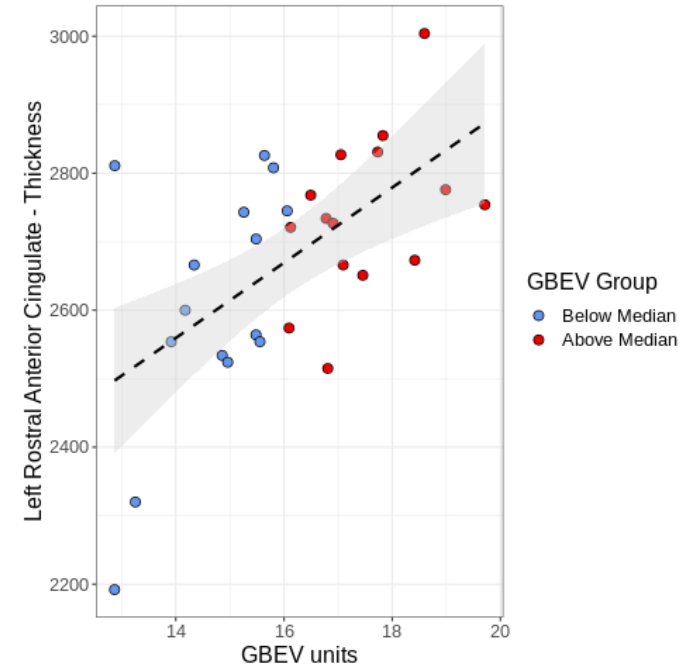
Mac Donald et al. *NEJM* 2011

## Breacher effects over all modalities relative to controls

Only results that survive Bonferroni correction are shown

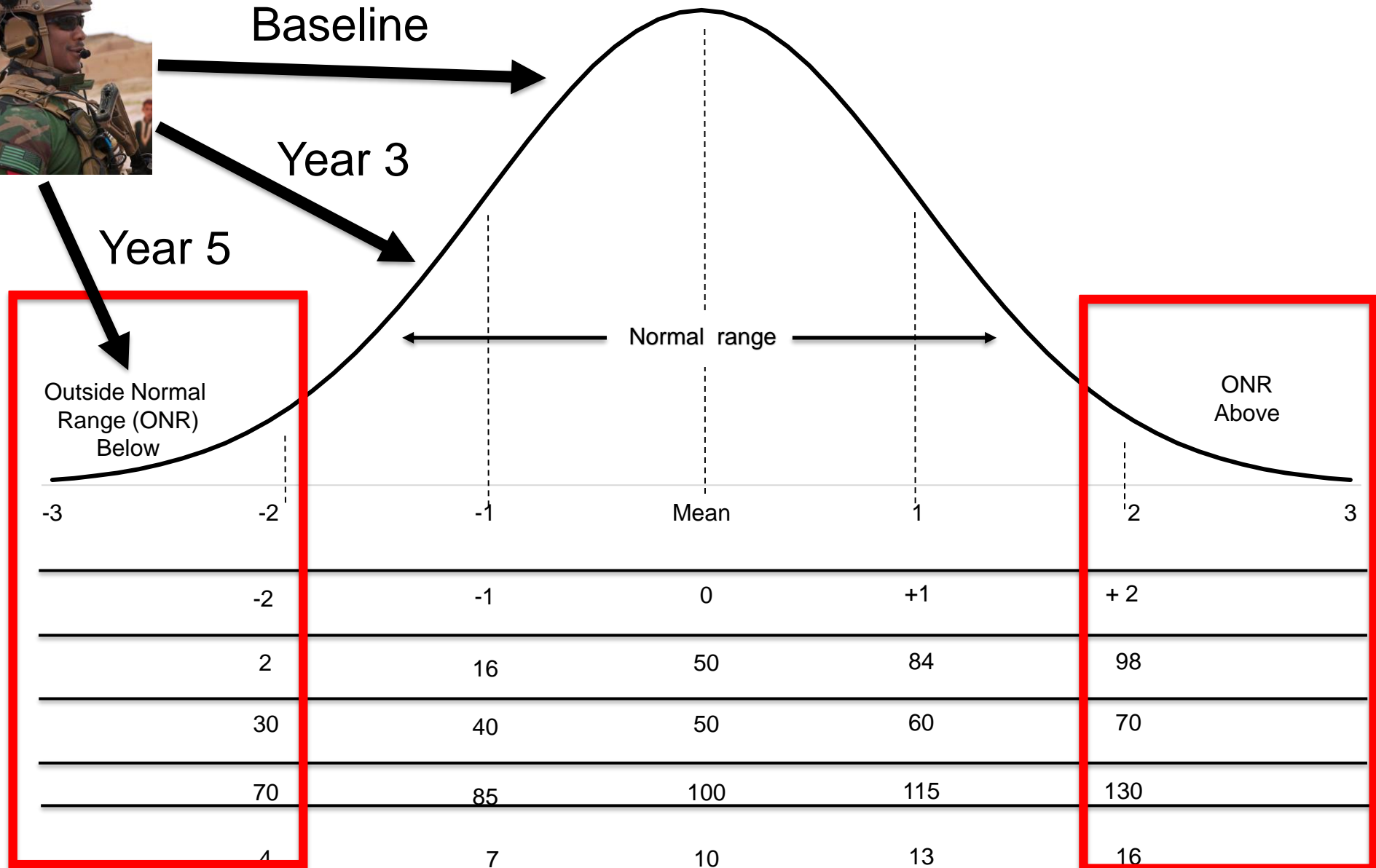


Stone et al. *Journal of Neurotrauma* 2020

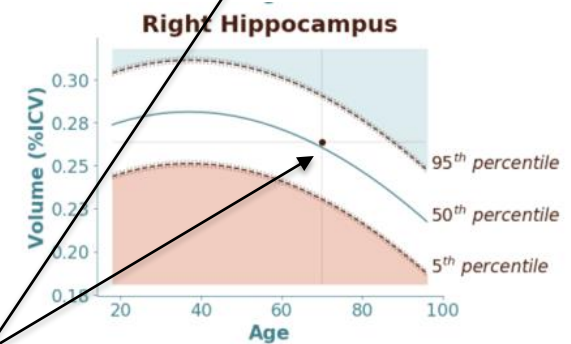
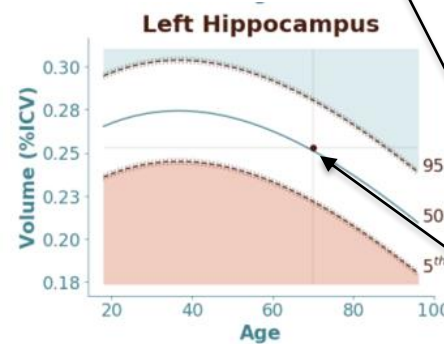
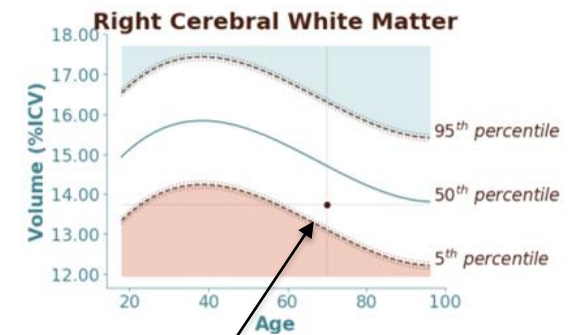
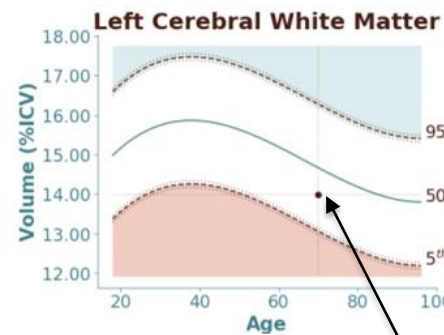
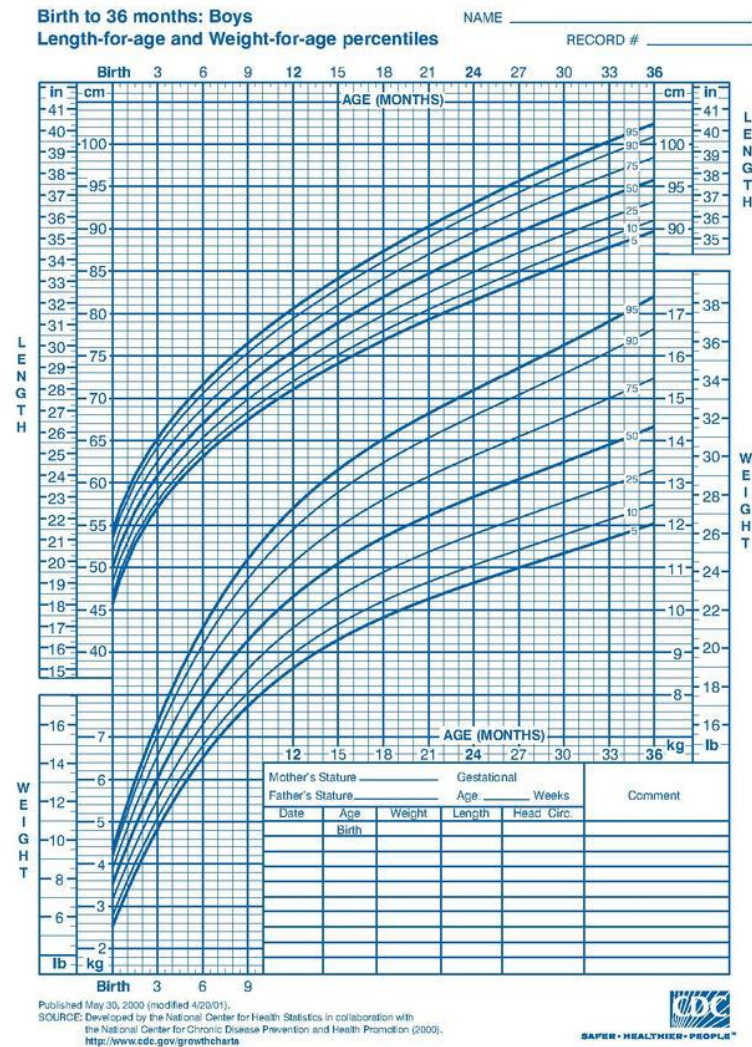


Gilmore et al. *PNAS* 2024

# Benefits of Personalized Analysis



# Personalized Precision Medicine



Bruce Fischl, PhD Paul Wighton, PhD



# Who are the Controls?

- Civilians
- Conventional military with less blast exposure
- Operators at the time of selection
- Elite performers (e.g., neurosurgeons, Olympic athletes)

# What are We Diagnosing?

## ▶ 2024 ICD-10-CM Diagnosis Code S06.8A1A 📄 🇺🇸

**Primary blast injury of brain, not elsewhere classified with loss of consciousness of 30 minutes or less, initial encounter**

2023 - New Code

2024

Billable/Specific Code

- S06.8A1A is a billable/specific ICD-10-CM code that can be used to indicate a diagnosis for reimbursement purposes
- Short description: **Primary blast inj brain, NEC LOC of 30 minutes or less, init**
- The 2024 edition of ICD-10-CM S06.8A1A became effective on October 1, 2023.

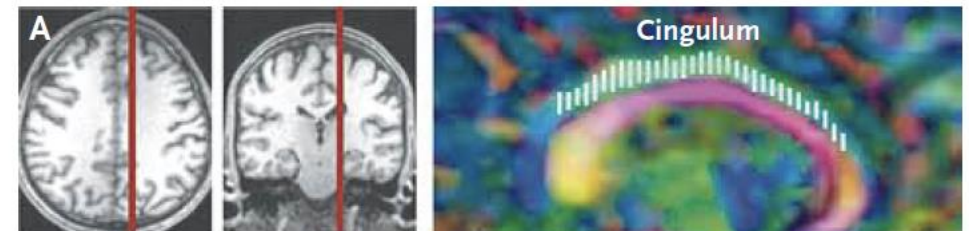


[www.aoav.org.uk](http://www.aoav.org.uk)



### Detection of Blast-Related Traumatic Brain Injury in U.S. Military Personnel

Christine L. Mac Donald, Ph.D., Ann M. Johnson, Dana Cooper, B.S., Elliot C. Nelson, M.D.,  
Nicole J. Werner, Ph.D., Joshua S. Shimony, M.D., Ph.D., Abraham Z. Snyder, M.D., Ph.D., Marcus E. Raichle, M.D.,  
John R. Witherow, M.D.,\* Raymond Fang, M.D., Stephen F. Flaherty, M.D., and David L. Brody, M.D., Ph.D.



Mac Donald et al. *NEJM* 2011

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  - Department of Defense: W81XWH-21-S-TBIPH2
- Foundation:
  - **Navy SEAL Foundation**
  - Chen Institute MGH Research Scholar
  - James S. McDonnell Foundation
- Departmental:
  - MGH Department of Neurology and Division of Neurocritical Care
  - MGH Martinos Center for Biomedical Imaging

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- None