Neurological correlates of repeated low-intensity blast exposure in operational personnel

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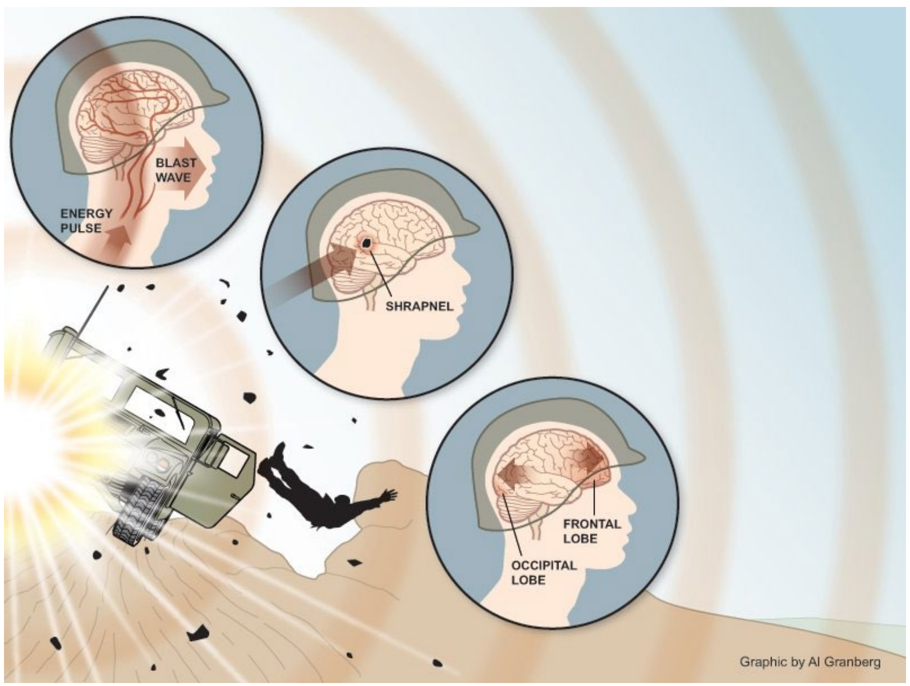
Blast-related Traumatic Brain Injury vs. repeated exposure to low-intensity blast.



Blast Neurotrauma

Dimension	Moderate-Severe TBI	Mild TBI	Subclinical/Cumulative
Blast Frequency	single event		multiple events
Blast Peak Pressure (psi)	20+	11-20 ?	4-11 ?
Physical Forces	1^{o}, 2^{o} & 3^{o}	1^{o} & 3^{o}	1^{o}
Acute Clinical Manifestations (GCS)	LOC, closed & penetrating head trauma, polytrauma GCS $\leq$12	closed head injury, LOC/AOC GCS 13-15	none
Clinical Onset	event-related		gradual emergence after multiple exposures
Conventional radiographic findings	CAT/MRI, obvious hemorrhage, edema	negative	negative
Pathology	obvious hemorrhage, edema, damage to white & gray matter, vasospasm	diffuse	unknown
Biomarkers	N/A	GFAP, UCH-L1	serum biomarkers, MRI, ?PET
Major Studies	TRACK TBI/TED	TED, TRACK TBI, CENC	Exp. Standards, ESiT, others

DIAGNOSED

Adapted from Ahlers et. al., 2012

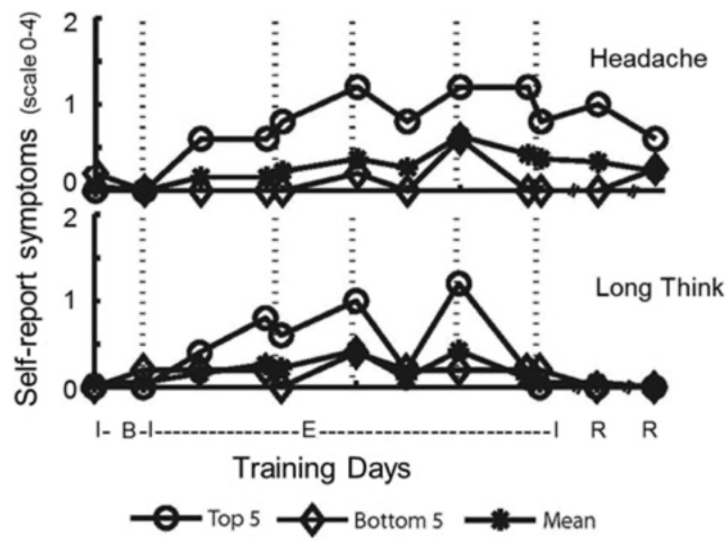
History

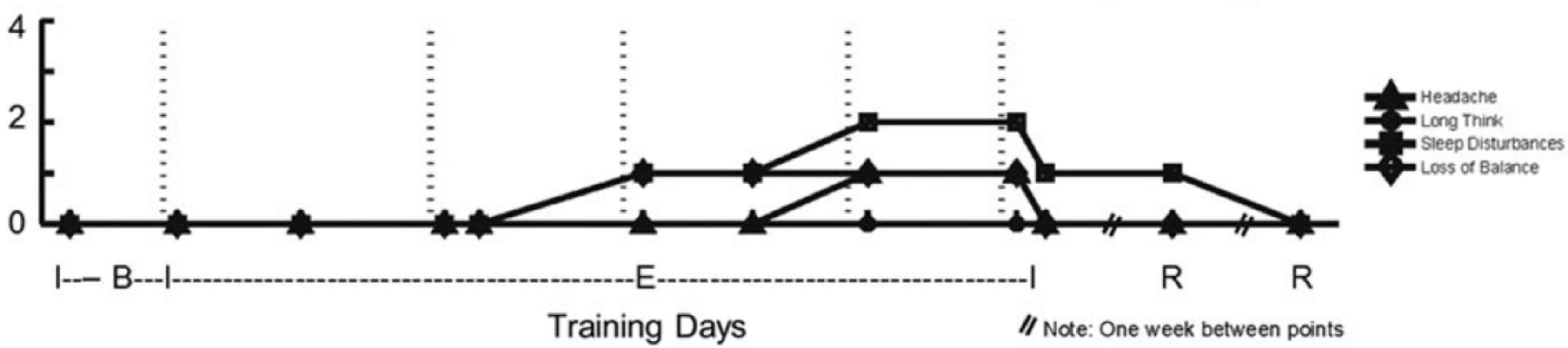
- In 2005 and 2006, military and law enforcement Breachers began expressing some sensitivity to the risk for injury resulting from blast exposure.

- Anecdotal reports from Breacher Instructors included:
  - Sleep pattern disruption
  - Short term memory loss
  - Headaches
  - Mood changes

- Questions raised by these reports included:
  - Whether Breachers demonstrated evidence of injury following training.
  - What blast exposure levels were associated with any observed abnormalities.

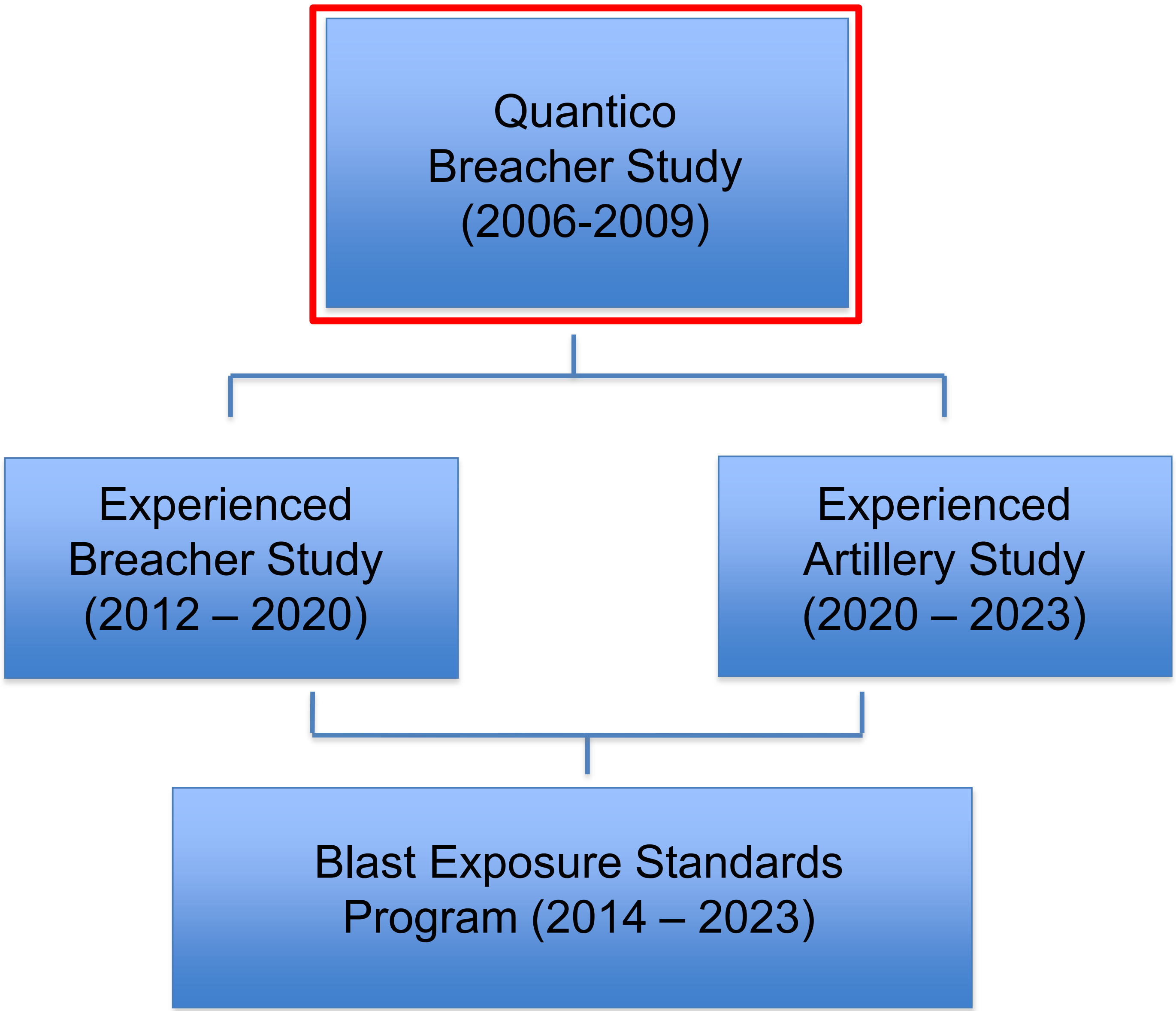
History





Tate et al, 2013

Studies exploring subclinical/cumulative brain changes in blast exposed personnel



Quantico Breacher Study

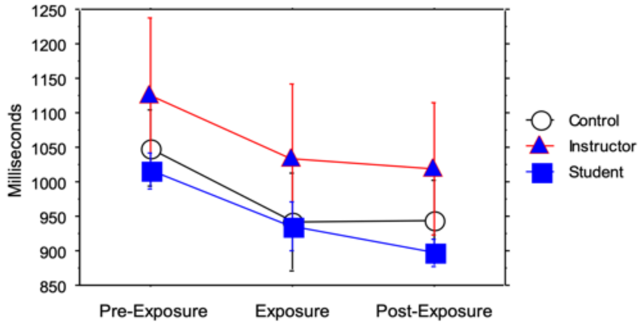
Primary Objective: Determine Whether Breachers Are At Risk of Injury During Standard Training Exercises

Motivation – Experienced breachers report symptoms of sleep pattern disruption, memory loss, word recall, etc.

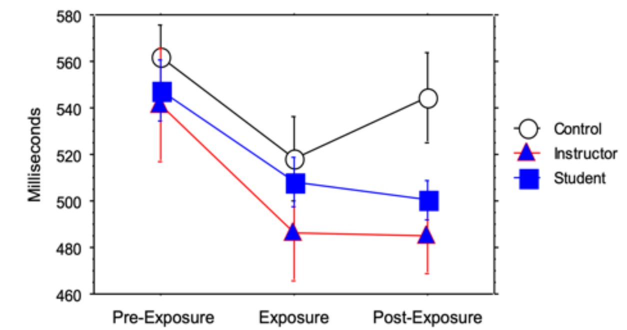
Secondary Objective: Assess instructors of training course with same tools used for Breachers participating in standard training exercises.

Quantico Breacher Study - NeuroCognitive Results

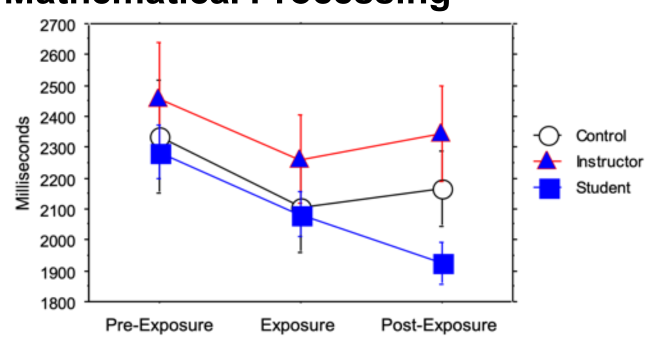
Code Substitution



Procedural Reaction Time



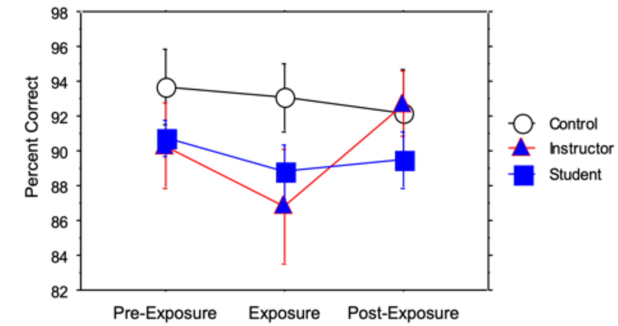
Mathematical Processing



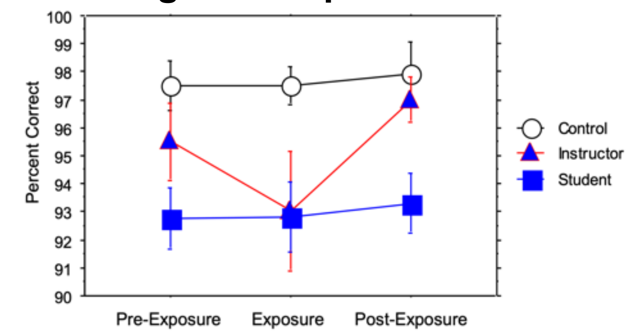
Response times on computer-based tests. These are tests ***without*** demand on memory. Downward sloping line means faster, means "better." Everyone got better.

Accuracy on computer-based tests. These are tests ***with*** demand on memory. Downward sloping line means less accurate, means "worse." Small sample size; mean effect is not statistically significant.

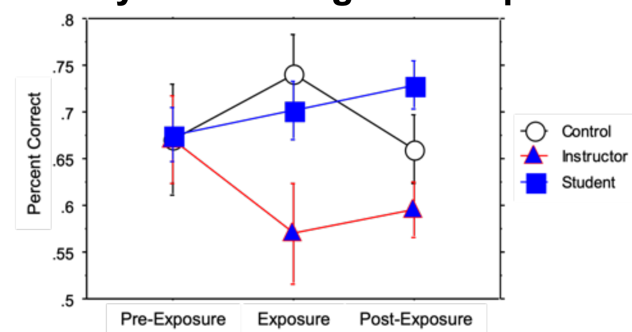
Code Substitution Delayed



Matching To Sample



Delayed Matching-To-Sample

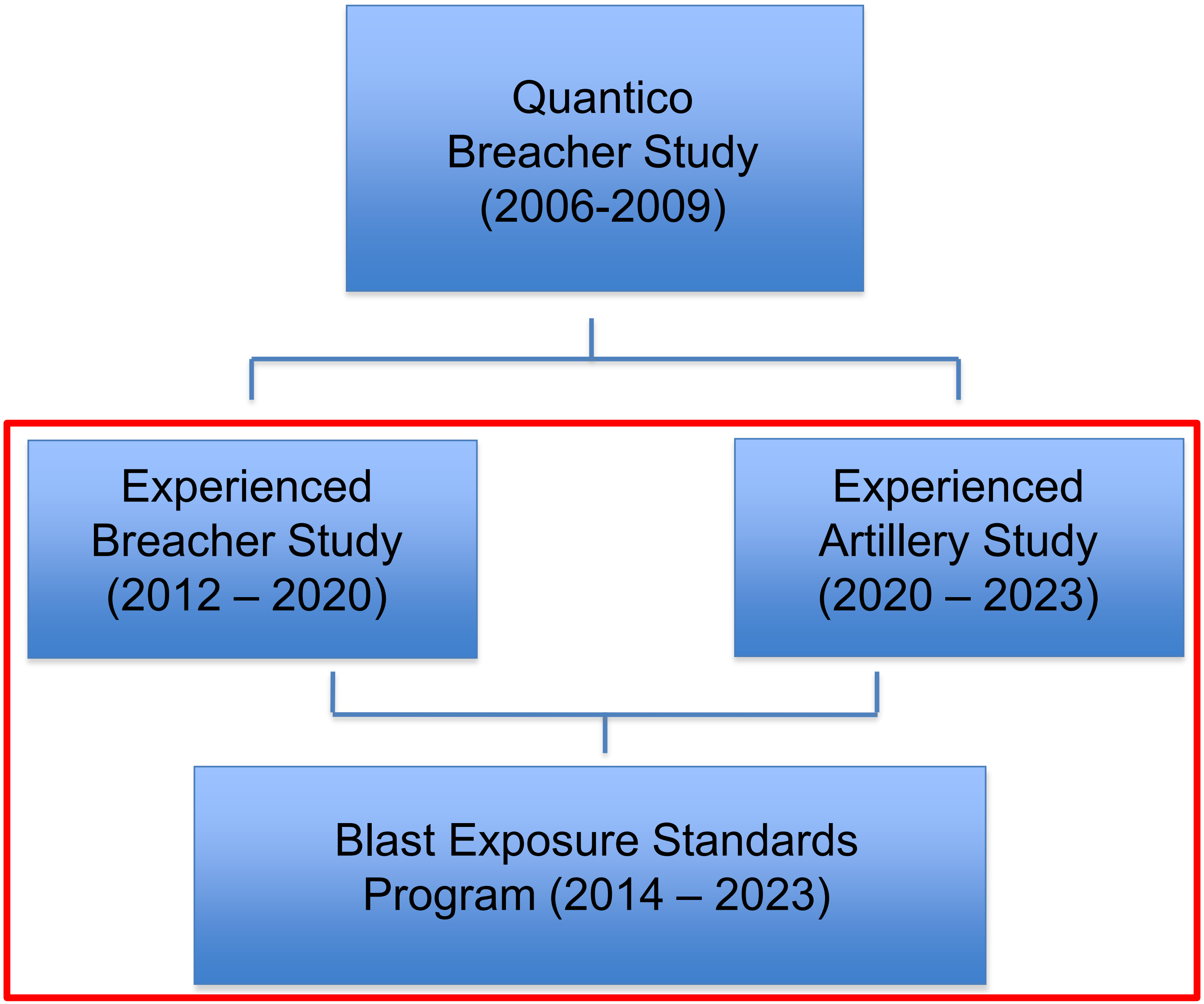


MILITARY MEDICINE, 181, 5:28, 2016

Repeated Low-Level Blast Exposure: A Descriptive Human Subjects Study

MAJ Walter Carr, MS USA; James R. Stone, MD, PhD†; Tim Walilko, PhD‡; Lee Ann Young, MS§; Tianlu Li Snook, MD†; Michelle E. Paggi, MA‖; CAPT Jack W. Tsao, MC USN¶; CAPT Christopher J. Jankosky, MC USN (Ret.)**; LTC Robert V. Parish, MS USA††; CAPT Stephen T. Ahlers, MSC USN (Ret.)‡‡*

Studies exploring subclinical/cumulative brain changes in blast exposed personnel



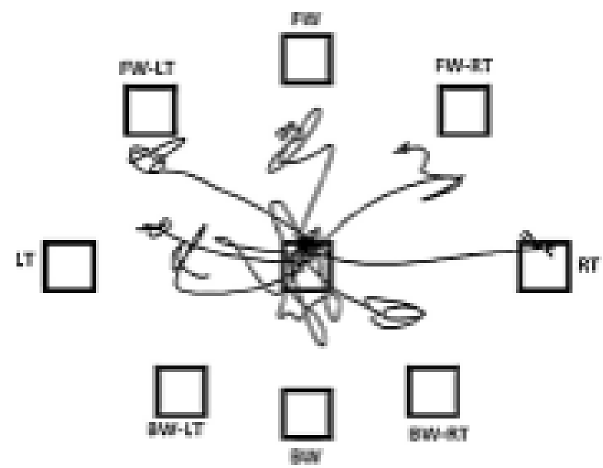
EBS: Neuropsychological Assessments

Neuropsychological Battery	
Given to Participants	Given to their Companions
Demographic and service information	Demographic information
Interview of 46 clinical health and well-being questions	Caregiving Hassles and Uplifts Scale (CHS)
Automated Neuropsychological Assessment Metrics (ANAM)	Functional Status Questionnaire (FSQ)
Beck Depression Inventory (BDI)	Katz Adjustment Scale (KAS-R)
Booklet Category Test (BCT)	Zarit Burden Interview (ZBI)
Brief Symptom Inventory 18 (BSI-18)	Frontal Systems Behavior Scale (FrSBe) (focusing on participant)
California Verbal Learning Test (CVLT)	Interpersonal Reactivity Index (IRI) (focusing on participant)
Combat Exposure Checklist (CEC)	NEO-Five Factor Inventory (NEO-FFI) (focusing on participant)
Delis-Kaplan Executive Function System (DKEFS) Sorting and Verbal subtests	Revised Self-Monitoring Scale (RSMS) (focusing on participant)
Frontal Systems Behavior Scale (FrSBe)	
Immediate Post-Concussion Assessment and Cognitive Test (ImPACT)	
Interpersonal Reactivity Index (IRI)	Clincal Interview
Iowa Gambling Task (IGT)	Example questions
Medical Symptom Validity Test (MSVT)	Do you have any of the following?
NEO-Five Factor Inventory (NEO-FFI)	...Meningitis
Paced Auditory Serial Addition Test (PASAT)	...Troublesome headaches
Post-Traumatic Checklist – Military version (PCL-M)	...Ringing in ears
Revised Self-Monitoring Scale (RSMS)	...Motion or travel sickness
Rey Complex Figure Test (RCFT)	...Memory problems
Rivermead Postconcussive Questionnaire (RPQ)	...Difficulty falling or staying asleep
Satisfaction with Life Scale (SWLS)	...Sensistivity to light/noise
Trail Making Test (TMT)	
Wechsler Abbreviated Scale of Intelligence II (WASI-II)	How many alcohol drinks per week?
Wechsler Memory Scale III Logical Memory subtests (WMS-III LM I & II)	How many hours of exercise per week?
Wechsler Test of Adult Reading (WTAR)	How many hours of sleep per night?

EBS: Balance Assessments

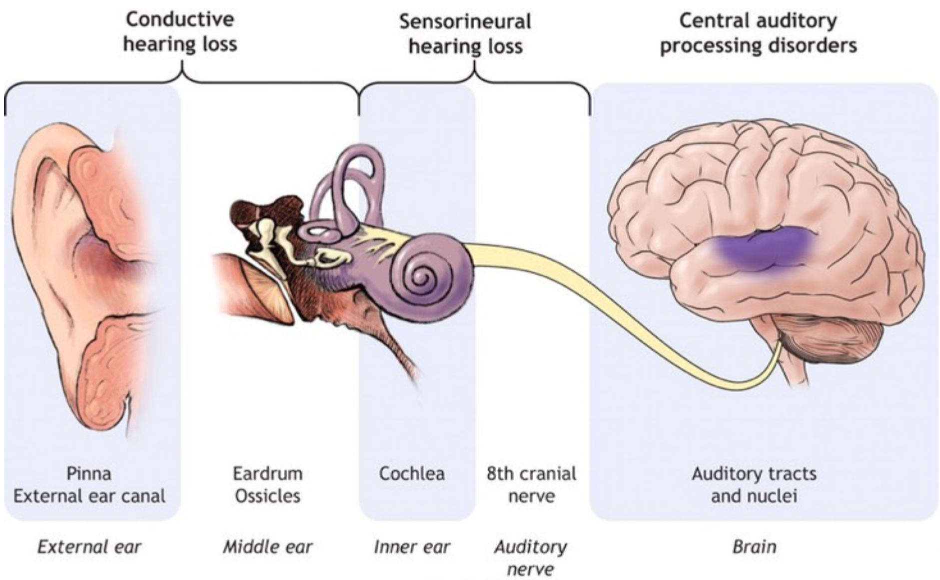
- A limits of stability (LOS) test was used to identify abnormalities in an individual's voluntary control posture

- Participants are to transfer their center of gravity (COG) toward 8 targets spaced at 45 degree angular intervals around the body's COG, as represented on a computer monitor.



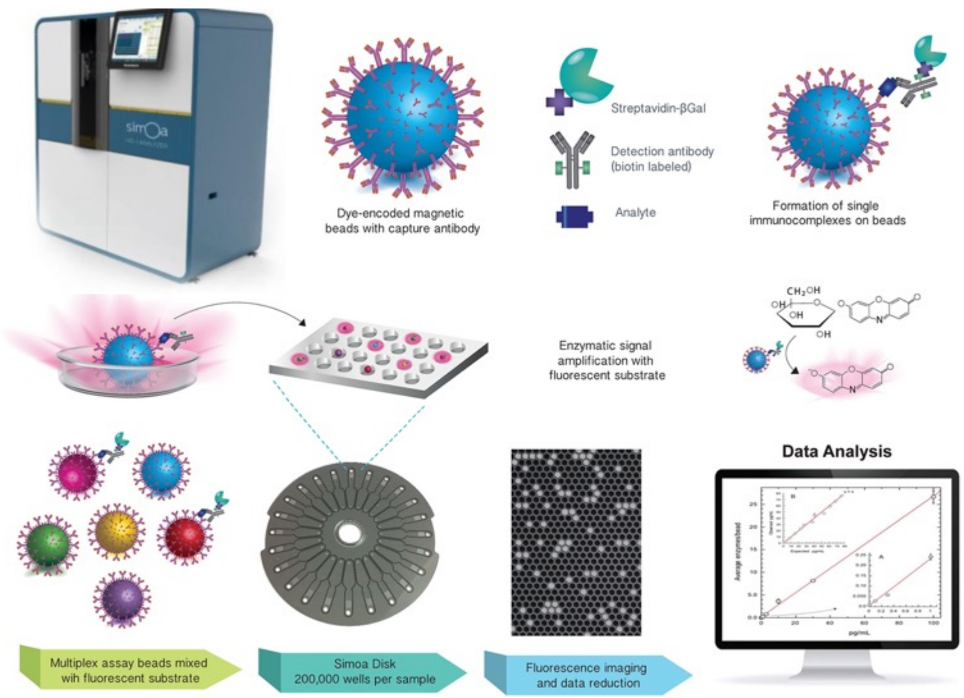
EBS: Audiological Assessments

- Auditory testing, tympanometry, & rotary chair testing were performed to assess the auditory, oculomotor, and vestibular systems



EBS: Biomarker Assessments

SIMOA – High-throughput and ultra sensitivity

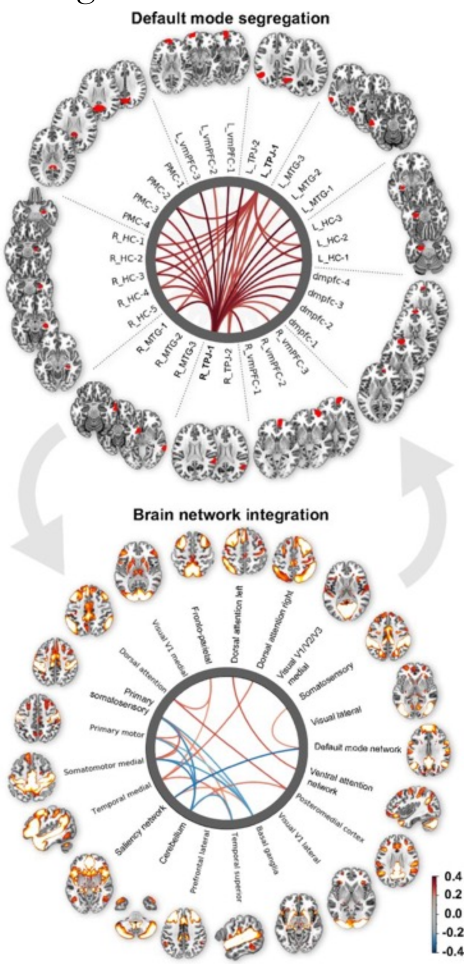


<u>Biomarkers Assessed</u>

- Amyloidβ 40
- Amyloidβ 42
- Tau
- Neurofilament Light Chain (NFL)
- Interleukin-6
- Tumor Necrosis Factor α (TNFα)

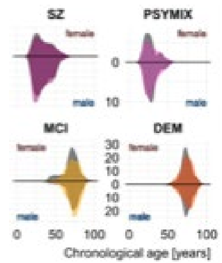
EBS: Neuroimaging Assessments

Default mode connectivity indexes network integration, cognition



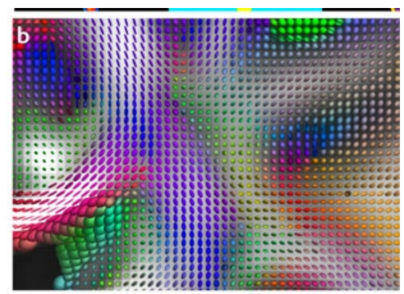
Kernbach et al PNAS 2018

Cortical morphometry is related to overall brain health/brain age

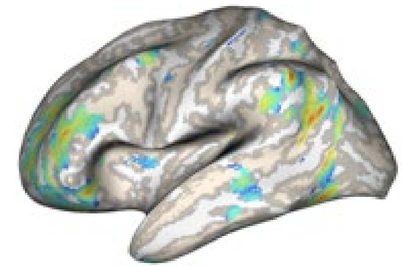


Kaufmann et al., Genetics of brain age, 2018

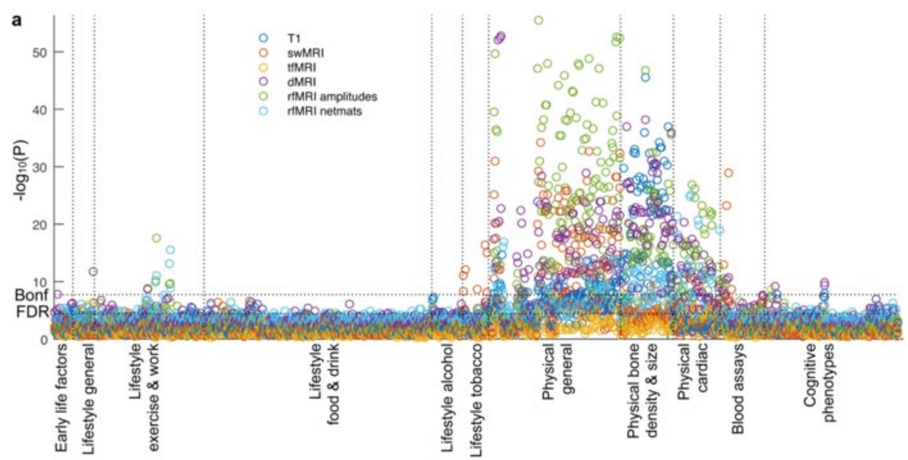
White matter structure often disrupted with brain injury



Brain perfusion/ activity may reflect vascular and functional changes



Multimodality neuroimaging exhibits sensitivity across risks overs the lifespan



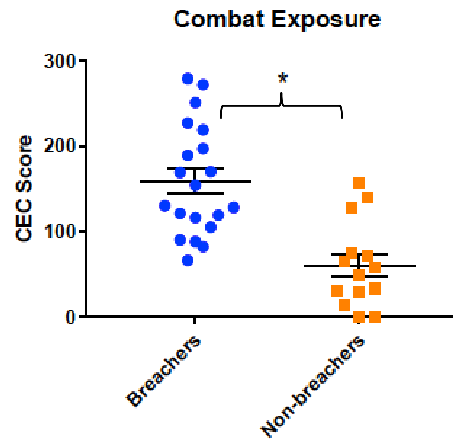
Multimodal population brain imaging in the UK Biobank prospective epidemiological study, Miller et al, 2016

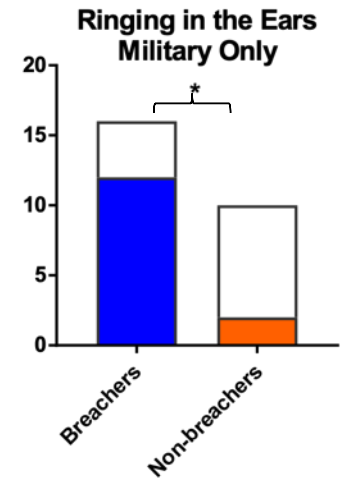
Experienced Breacher Study

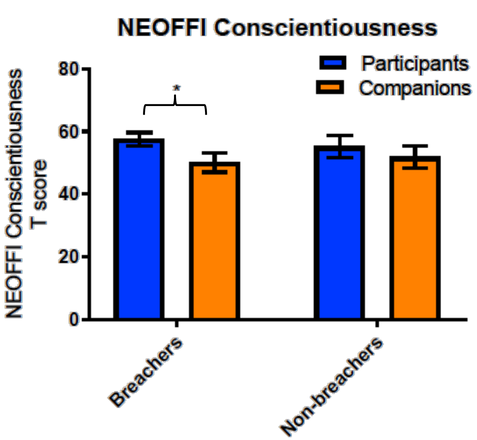
	Breacher	Control	Significance
N	20	14	N/A
Age	39.65 (26-54)	38.85 (27-53)	p=0.59
Ethnicity	Caucasian = 17; American Indian = 1; Asian = 1; Other = 1.	Caucasian = 12; African America = 1; Asian = 1.	N/A
Handedness	Right handed = 18; Left handed = 2	Right handed = 12; Left handed = 2	N/A
Service	Army = 13; Navy = 1; Law Enforcement = 6.	Army = 10; Law Enforcement = 4	N/A
Duration of Service	16.8 (8-27)	13.8 (5-24)	p=0.55
Concussion	Yes=13; No=7	Yes=6; No=8	N/A
Explosive Breaches	>400=18; 200-399=1; 100-199=1	10-39=1; None=13	N/A
Breaches in past year	>400=3; 200-399=5; 100-199=3; 40-99=1; 10-39=2; 1-9=4; None=2.	None=14	N/A

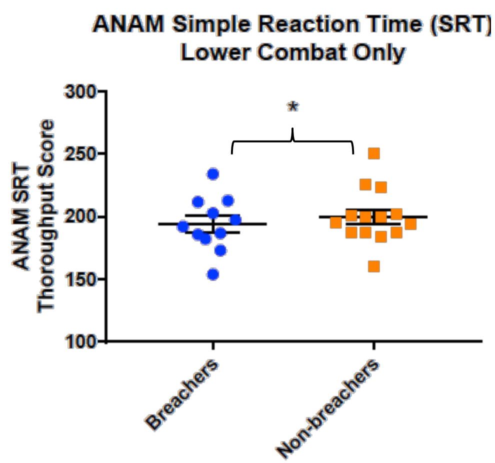
Neuropsychological Results

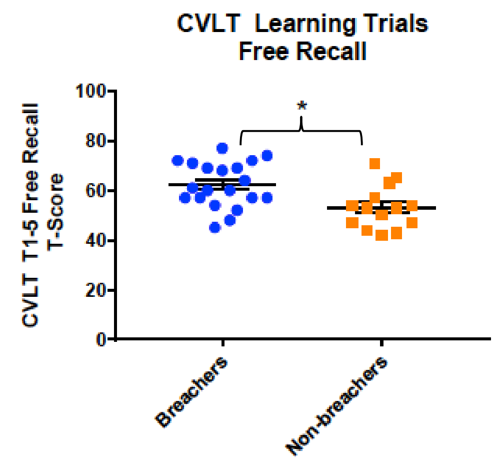
- 5/69 comparisons were found to be significant
- Experienced Breachers:
  - ↑ combat exposure
  - ↑ Ringing in ears (MIL only)
  - ↑ NEOFFI conscientiousness compared to companion score
  - ↓ ANAM SRT (throughput)
  - ↑ CVLT





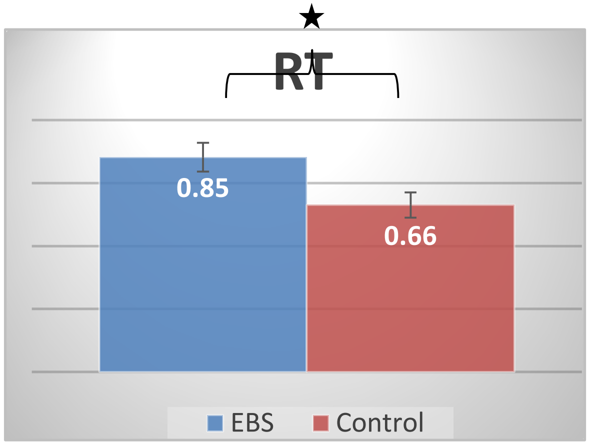


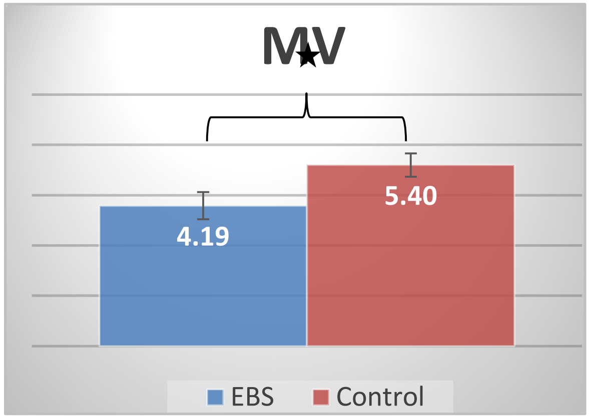




Balance Results

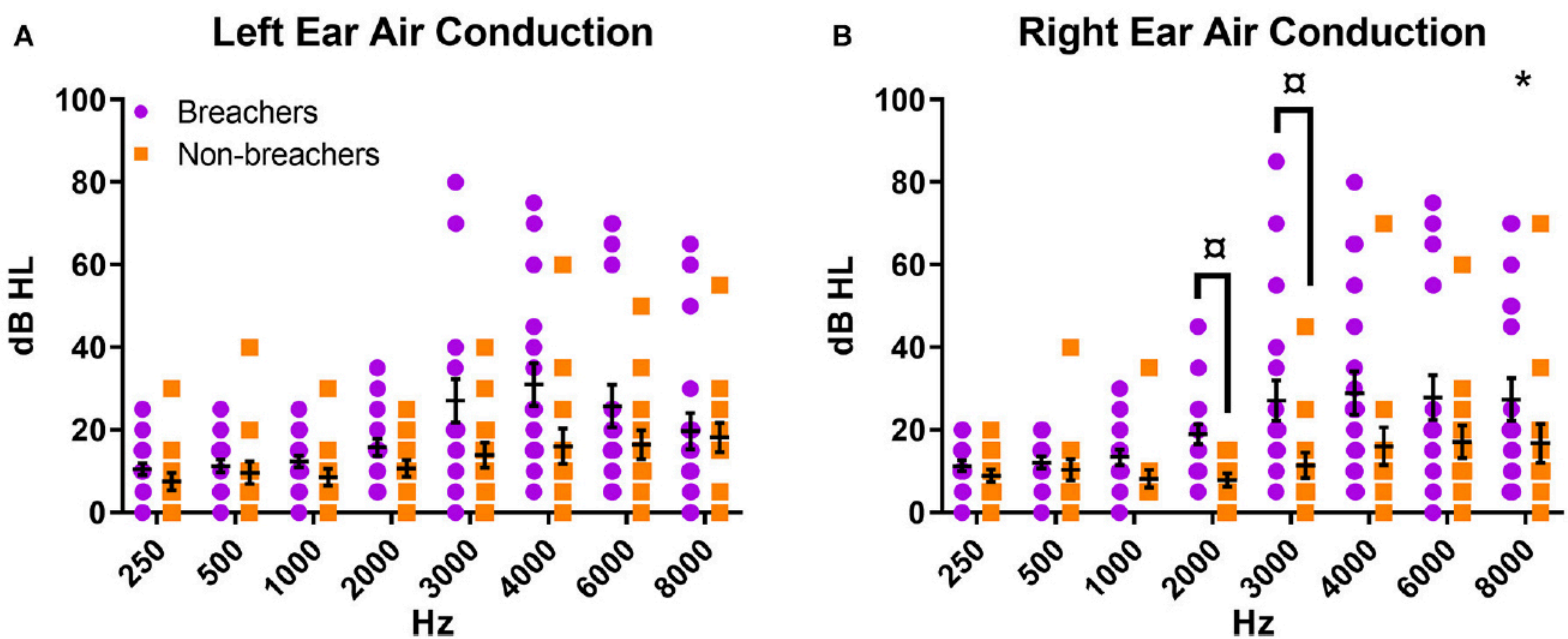
- Metrics of interest were **movement velocity** (MV; the average speed of the COG movement, in deg/s) and **reaction time** (RT; time between the signal to move and the initiation of the movement, in seconds).
- Experienced breachers exhibited:
  - ↑ RT
  - ↓ MV





Audiological Results

- Auditory testing, tympanometry, & rotary chair testing were performed to assess the auditory, oculomotor, and vestibular systems
- Experienced Breachers exhibited:
  - ↑ tinnitus
  - ↑ % hearing loss



frontiers in Neurology

BRIEF RESEARCH REPORT
published: 16 December 2020
doi: 10.3389/fneur.2020.588377

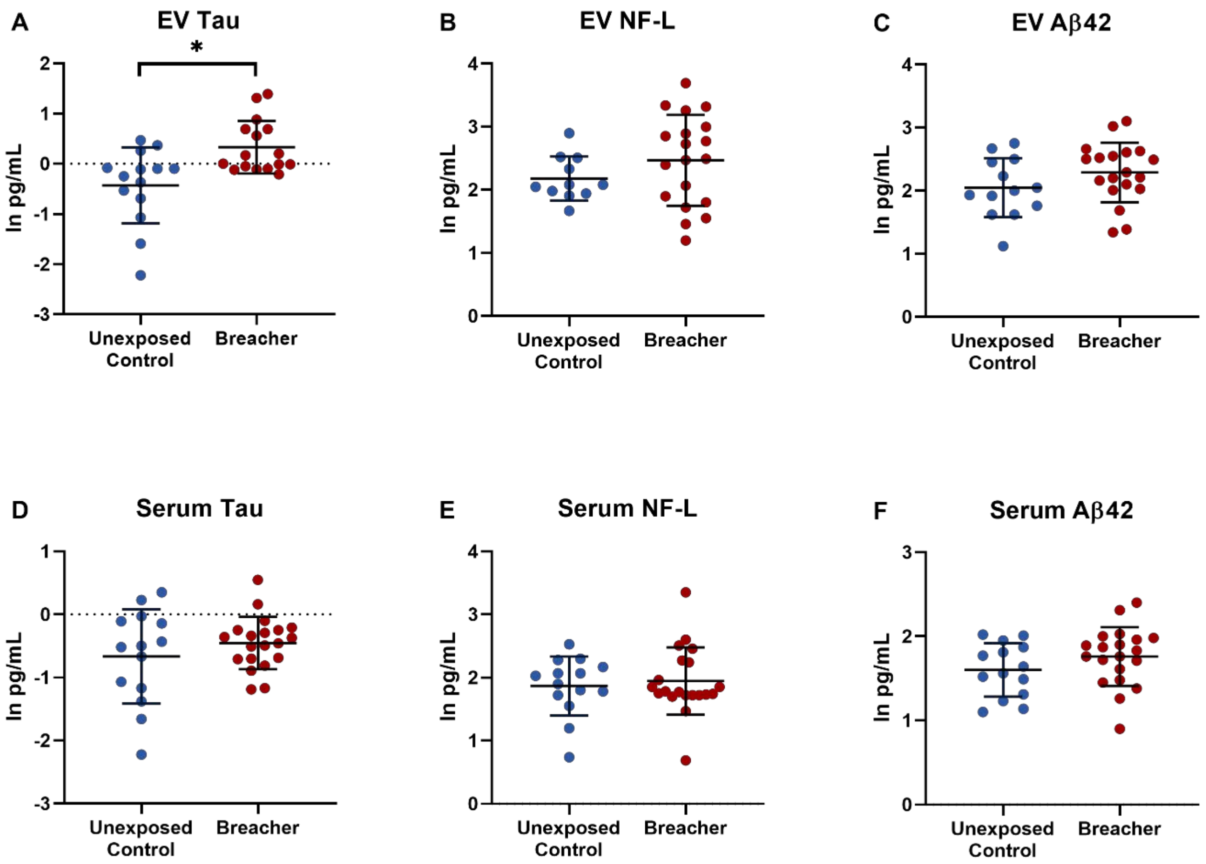
Check for updates

Hearing Loss and Irritability Reporting Without Vestibular Differences in Explosive Breaching Professionals

Claire M. Modica[1], Brian R. Johnson[2*], Christopher Zalewski[3], Kelly King[3], Carmen Brewer[3], John E. King[4], Angela M. Yarnell[5], Matthew L. LoPresti[2], Peter B. Walker[6], Kristine C. Dell[7,8], Elena Polejaeva[7,9], Alycia Quick[7,10,11], Bobby Arnold[1,7,11], Eric M. Wassermann[7], James R. Stone[12], Stephen T. Ahlers[1] and Walter Carr[2,13]*

Changes in Proteins Following in Experienced Breachers

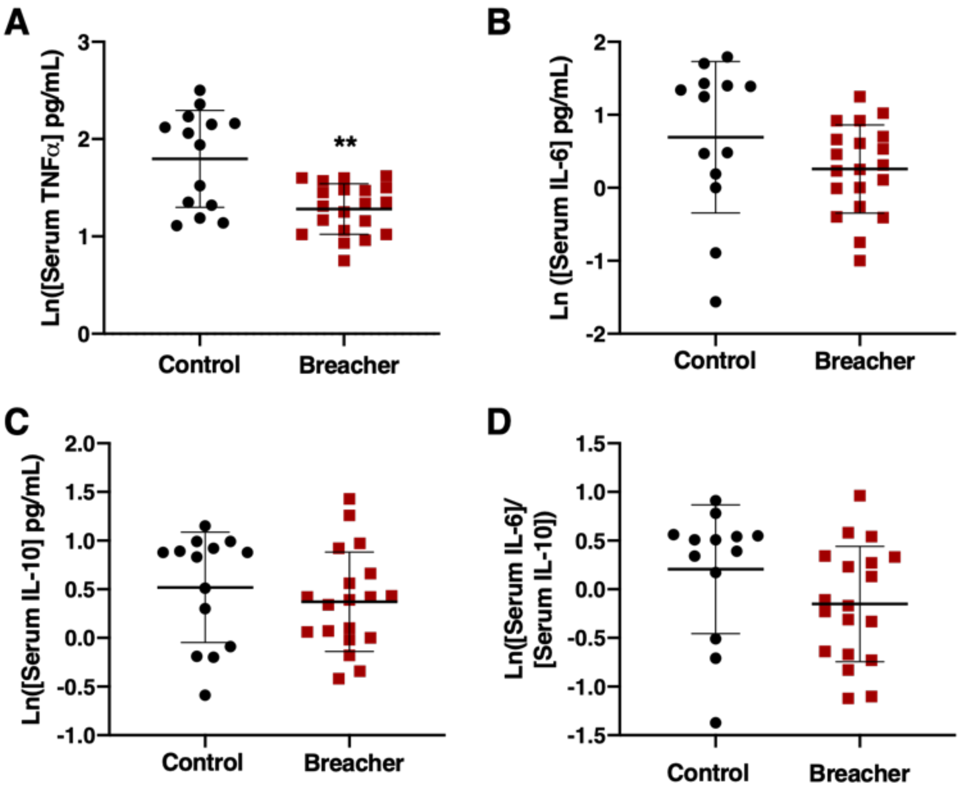
- Neuronal-derived extracellular vesicles (EVs), tau distinguishes experienced breachers from controls



Edwards et al., Scientific Reports, (accepted pending revisions)

Changes in Proteins Following Blast in Experienced Breachers

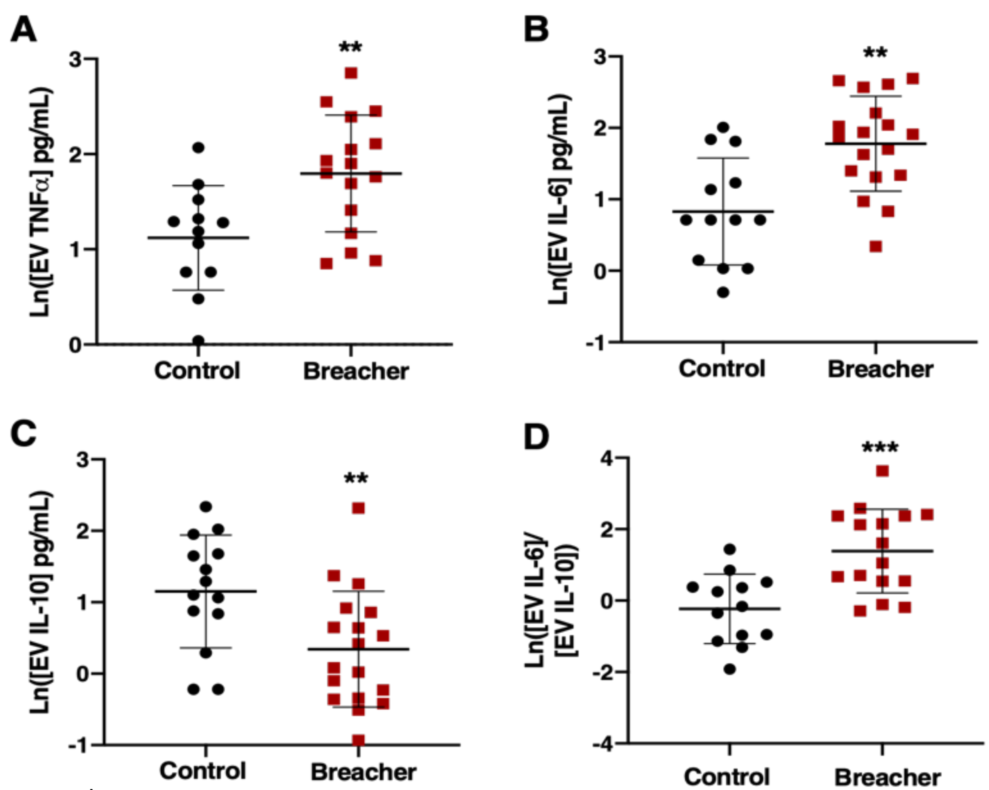
- Serum levels of the pro-inflammatory cytokine TNFα was decreased in Breachers (A)
- No change in serum IL-6, IL-10 between groups (B/C) and no change in the IL-6/IL-10 ratio between groups (D).



Greer et al., Neurology (under revision)

Changes in Proteins Following Blast in Experienced Breachers

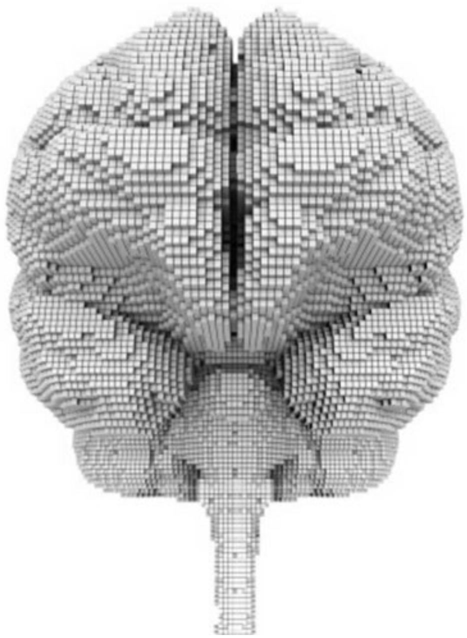
- Neuronal-derived EV pro-inflammatory TNFα and IL-6 propagate were increased in the brain of experienced Breachers (A/B).
- The anti-inflammatory cytokine IL-10 was decreased. (C).
- The ratio of pro/anti-inflammatory cytokines IL-6/IL-10 is higher.

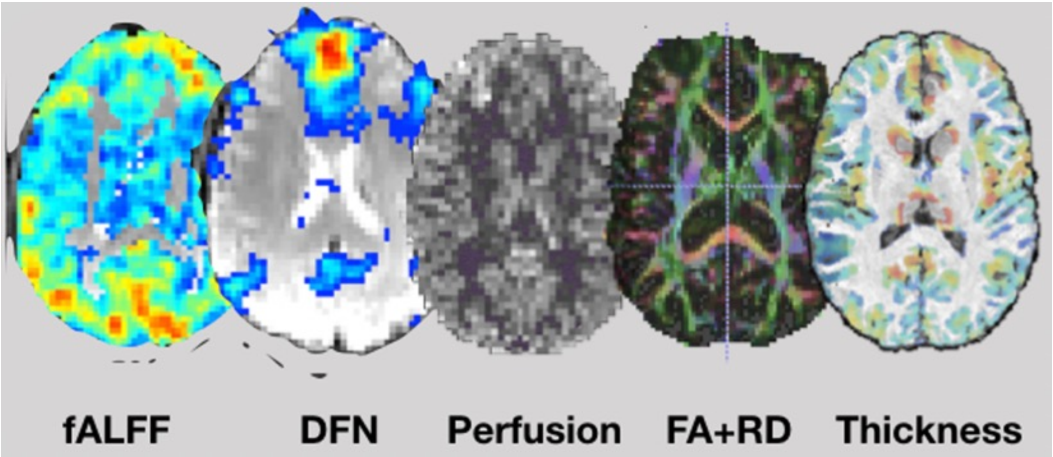


Greer et al., Neurology (under revision)

Problem Statement

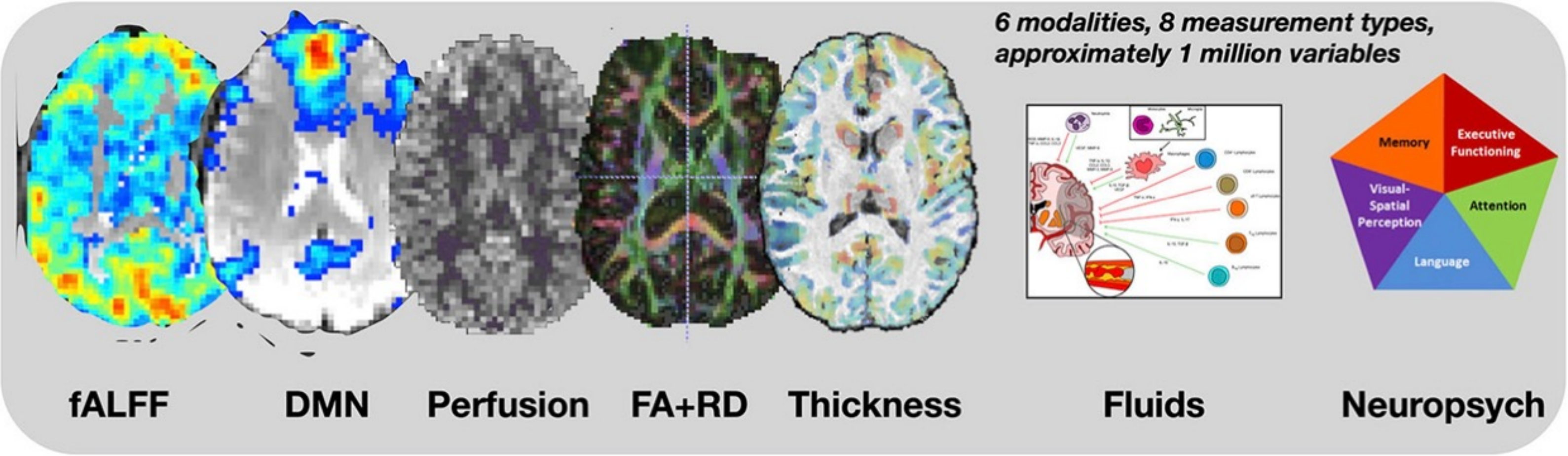
- Brain imaging problems:
  - typical 3-D image > 1e6 voxels (or "dimensions")
  - multiple modalities (DTI, fMRI, thickness, etc.)





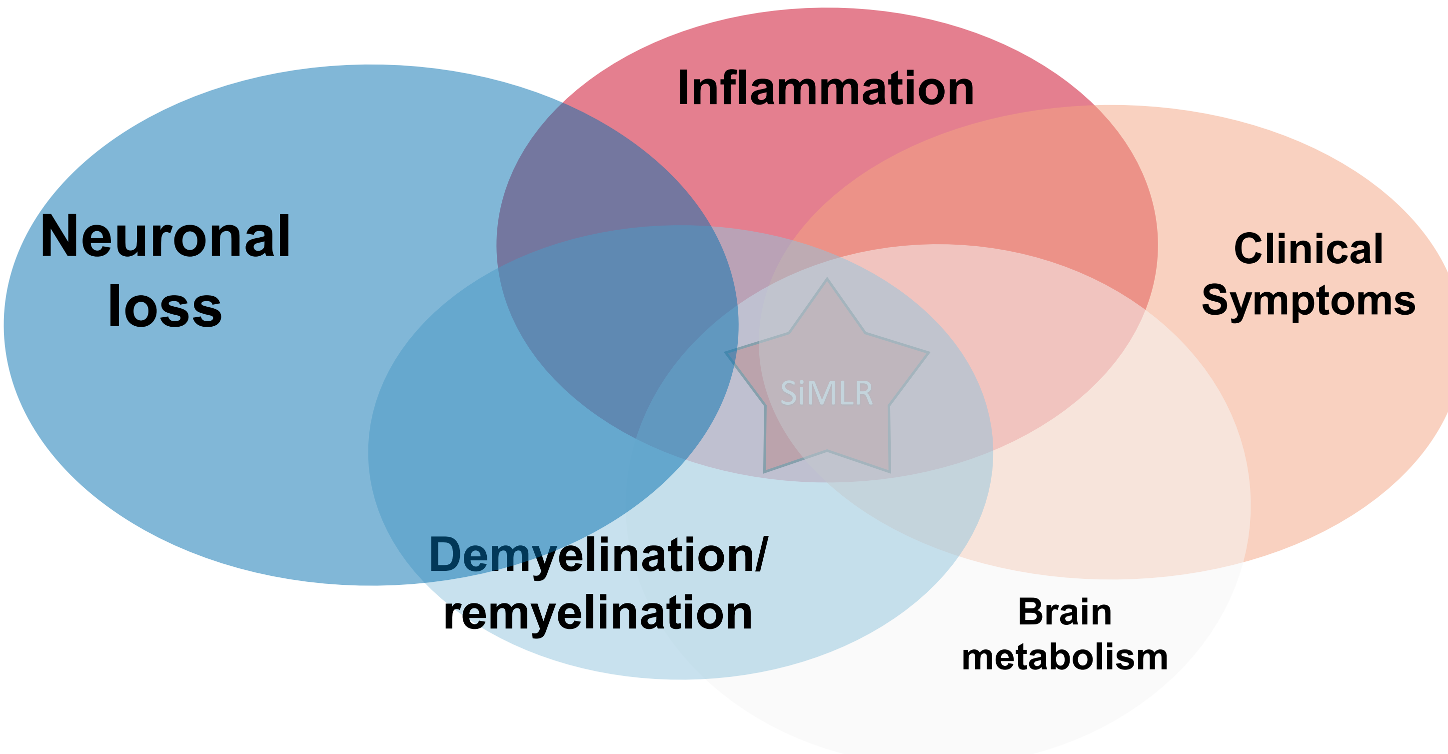
Problem Statement

- For these studies, how do we:
  - include non-imaging data and multiple modalities?
  - integrate all data sources in a statistically principled way?



Similarity-driven multi view linear reconstruction (SiMLR)

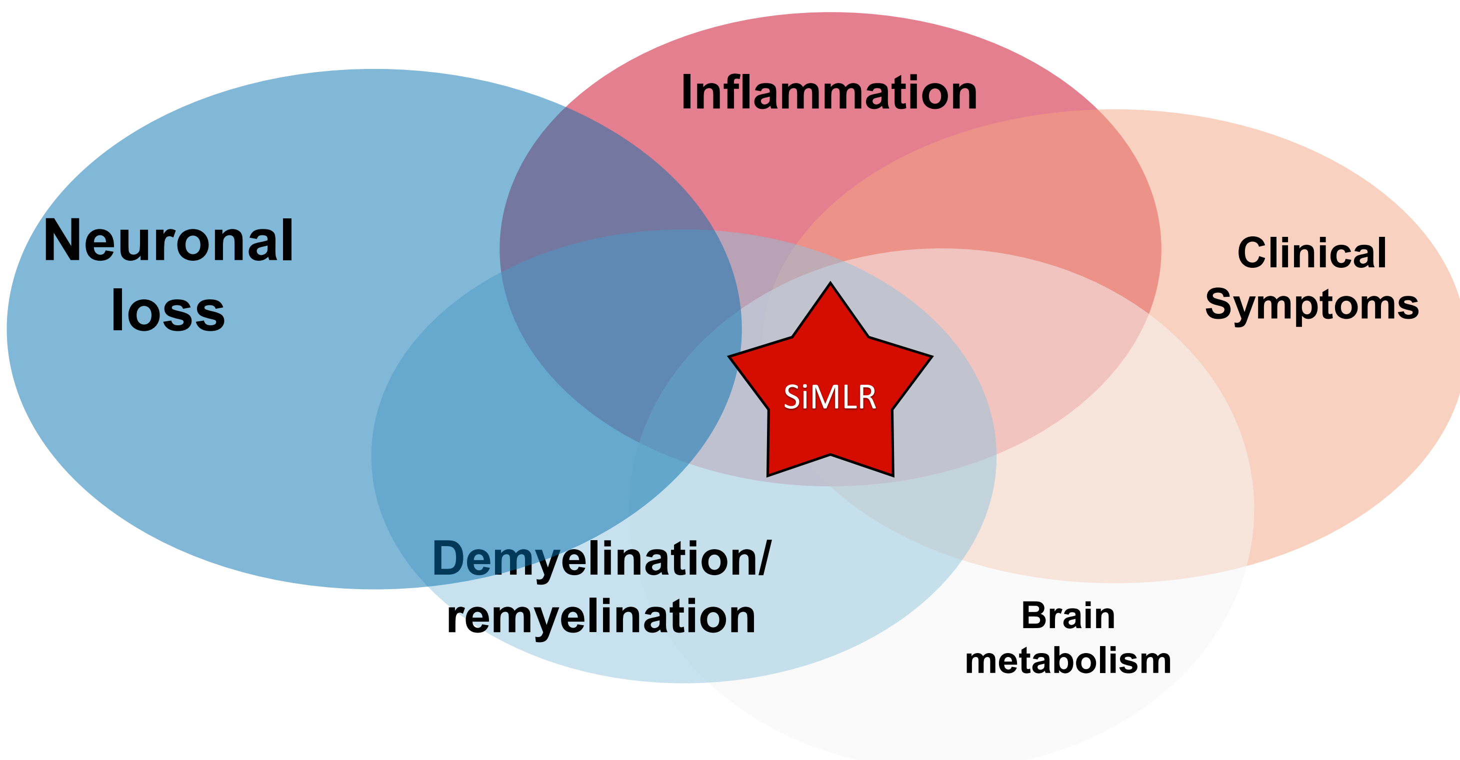
An efficient statistical integration method that can identify hidden signal embedded within high-dimensional multiple modality datasets



Avants, Brian B., Nicholas J. Tustison, and James R. Stone. "Similarity-driven multi-view embeddings from high-dimensional biomedical data." *Nature Computational Science* 1.2 (2021): 143-152.

Similarity-driven multi view linear reconstruction (SiMLR)

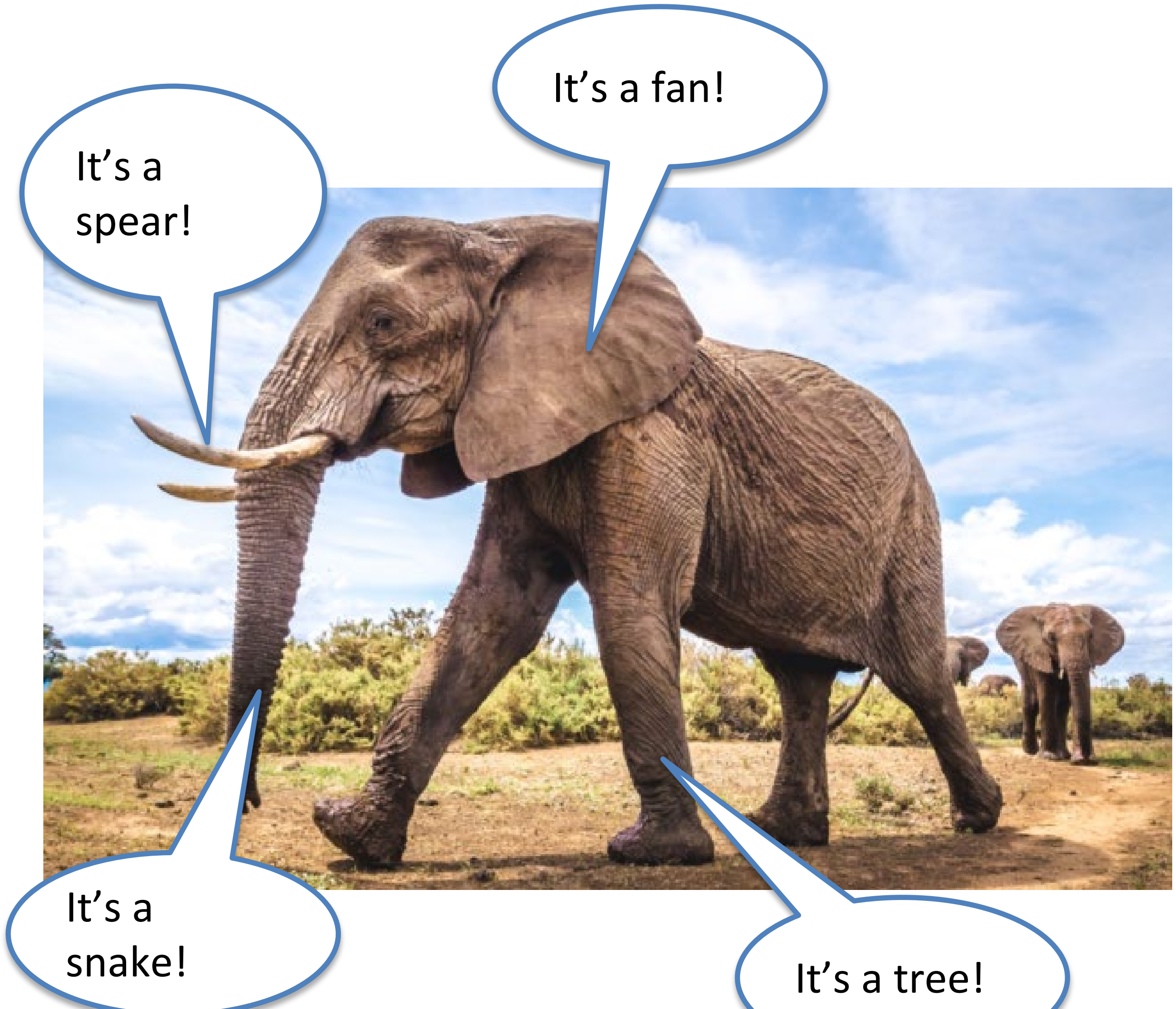
A statistical “hub” linking disparate measurement modalities.



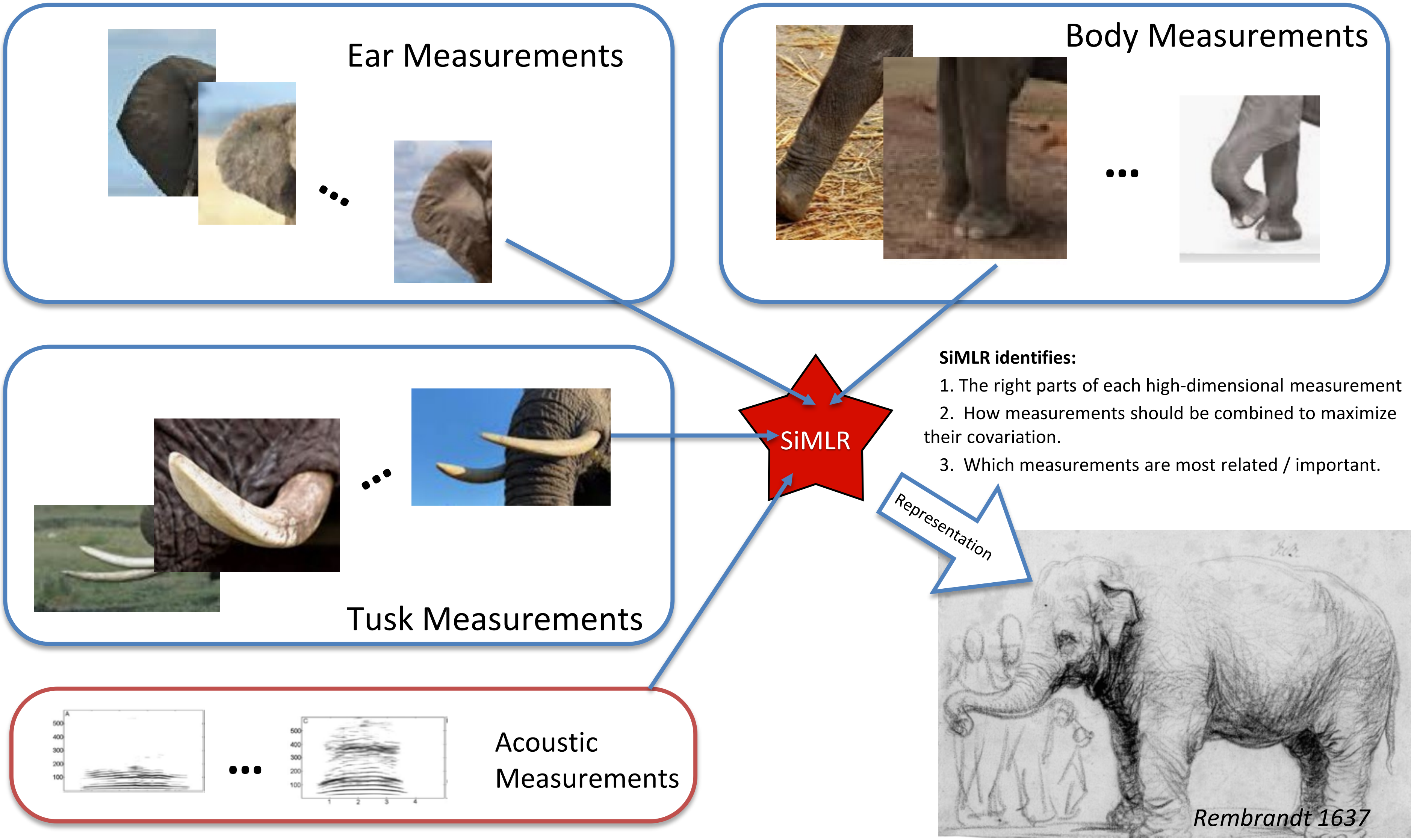
Avants, Brian B., Nicholas J. Tustison, and James R. Stone. "Similarity-driven multi-view embeddings from high-dimensional biomedical data." *Nature Computational Science* 1.2 (2021): 143-152.

SiMLR: Scientific intuition via "the blind men and the elephant"

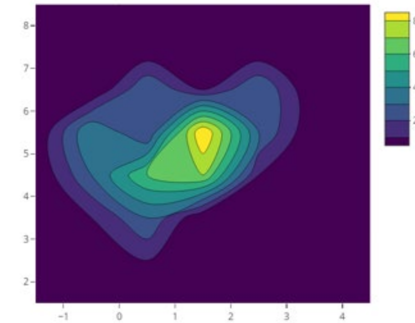
- The elephant represents hidden etiology.
- Each blind person represents a type of data or measurement.
- SiMLR puts these pieces together allowing us to link these independent but related measurements.



SiMLR: Scientific intuition via "the blind men and the elephant”



SiMLR technical context



- SiMLR is an intuitive multi-view (or multi-omic) extension of regression, principal component analysis (PCA) and canonical correlation analysis (CCA).
- SiMLR leverages both blind source separation and data similarity terms.
- Specific variations of SiMLR simplify to:
  - linear regression in the case of two modalities where one is a univariate outcome;
  - PCA when there is only one modality;
  - CCA when there are two modalities.
- SiMLR exploits deep regularization methods and efficient implementations that allow it to be applied to datasets with many more predictors than subjects (*p* >> *n)*

Avants, Brian B., Nicholas J. Tustison, and James R. Stone. "Similarity-driven multi-view embeddings from high-dimensional biomedical data." *Nature Computational Science* 1.2 (2021): 143-152.

SiMLR technical context
In multivariate analysis

$\mathbf{X}_j$ of dimension $n \times p_j$

$\mathbf{V}_j^T$ of dimension $k \times p_j$

Linear regression:

Univariate outcome

Small multivariate predictor data e.g. Age, gender, educational level

$$y_i \approx \mathbf{X}_i v_i + \epsilon$$

Vector solution "Beta weights"

Principal component:

Potentially large multivariate data e.g. MRI

$$\mathbf{X_j} \approx \mathbf{U_j V_j^T}$$

Lower dimensional representation spaces

Canonical Correlation:

$$\mathbf{X_j V_j^T} \approx \mathbf{X_k V_k^T}$$

SiMLR:

A source separated representation of the other modalities

$$\forall\ j\ \mathbf{X_j V_j^T} \approx \mathbf{X_{k \neq j} V_{k \neq j}^T}$$

This is shorthand notation - for full details, see https://doi.org/10.1038/s43588-021-00029-8

SiMLR is a statistical framework

A general formulation allows different incarnations of SiMLR:

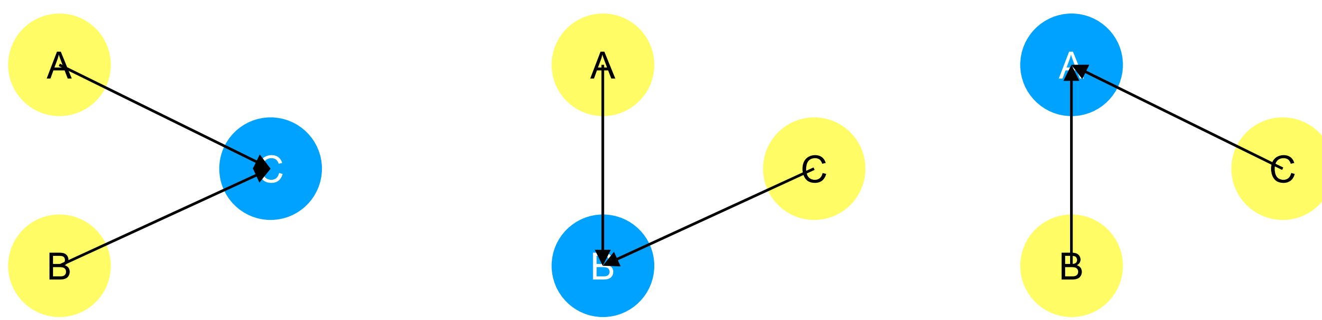
$$\Pr(X_1|X_2,\cdots,X_n)\star\cdots\star\Pr(X_n|X_1,\cdots,X_{n-1})$$

The variational formulation when we assume a Euclidean distance between modalities:

$$\sum_i \|X_i - f_a(U_{j\neq i})V_i^T\|^2 + \sum_i\sum_l \gamma_i \|G_\sigma^i \star v_{il}\|_{\ell_1}^+,$$

data term *regularization/network interactions*

3-modality example: each modality is reconstructed from the other two



Additional constraints: $U_i = X_iV_i$ and $\|U_i\| = 1$.

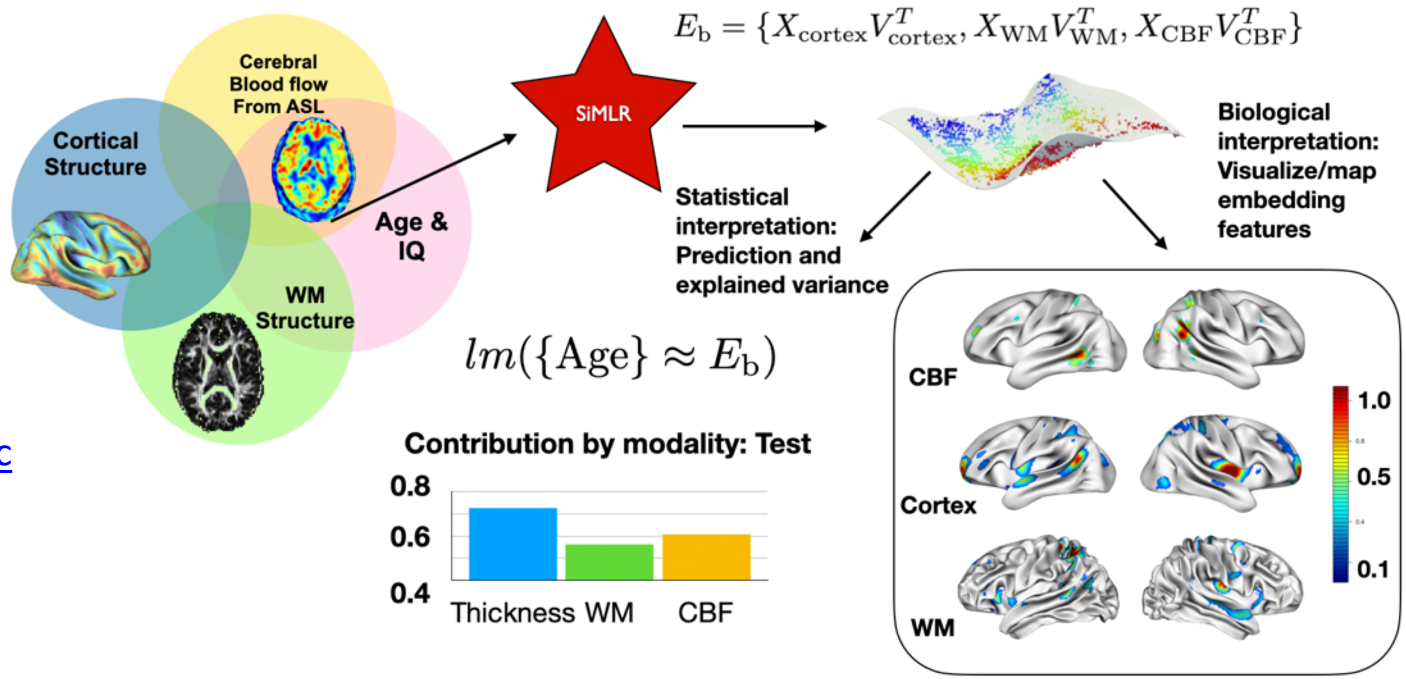
SiMLR evaluation results

1. Improve recovery of known hidden signal (*statistically generated data*).
2. More accurate survival prediction based on gene expression, transcriptomics and methylomics in glioblastoma (*multi-omic cancer benchmark data*).
3. More statistically powerful inference from neuroimaging + genetic risk to clinical scores of depression (*PING data*).
4. Better joint prediction of polygenic hazard scores in Alzheimer's disease from structure, cognition and molecular predictors (*ADNI data*).

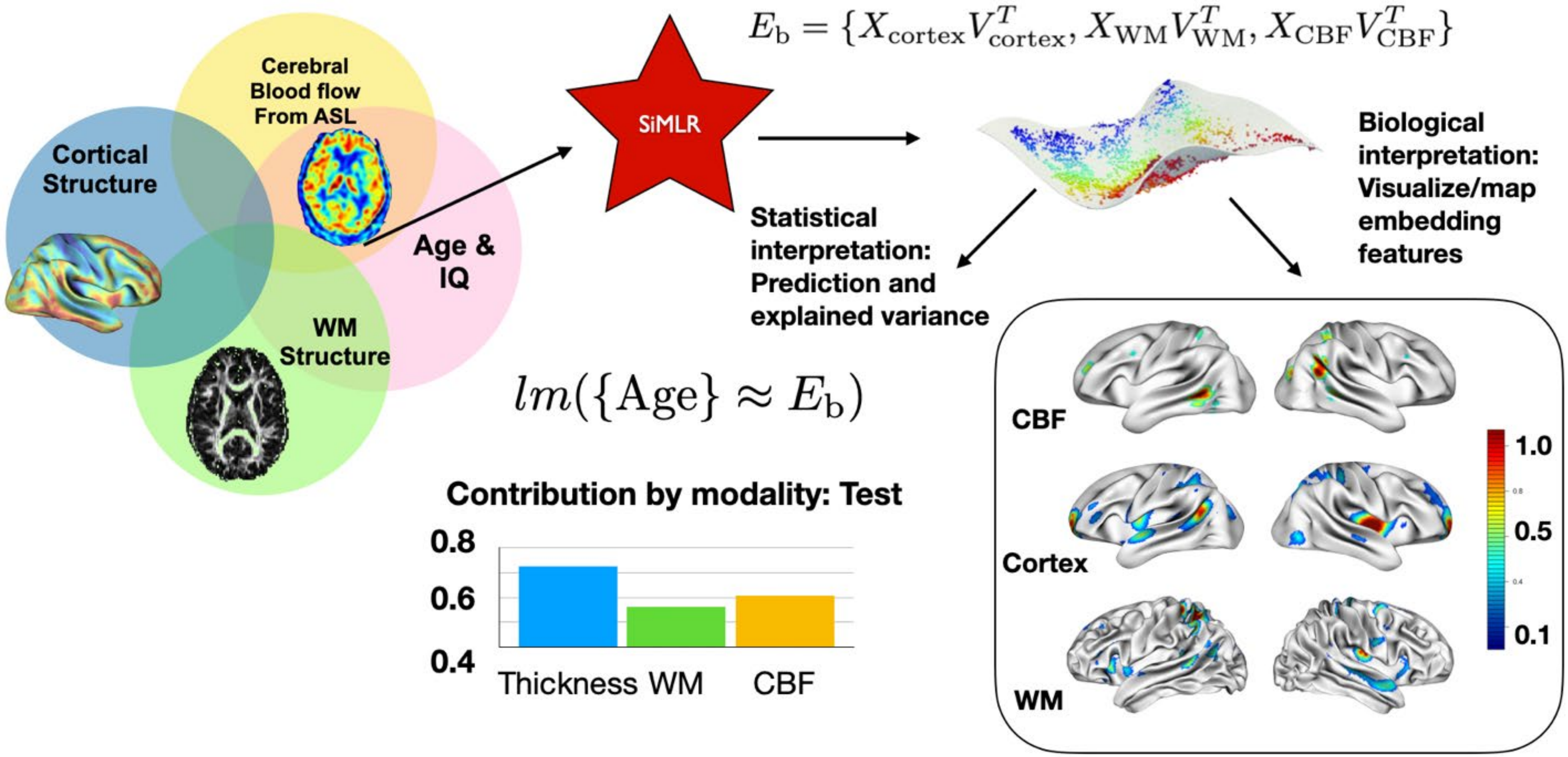
5. More reproducible brain age prediction (right from multiple modality neuroimaging.

These evaluation studies are covered in detail in a reproducible computing platform:

https://codeocean.com/capsule/9877797/tree/v2

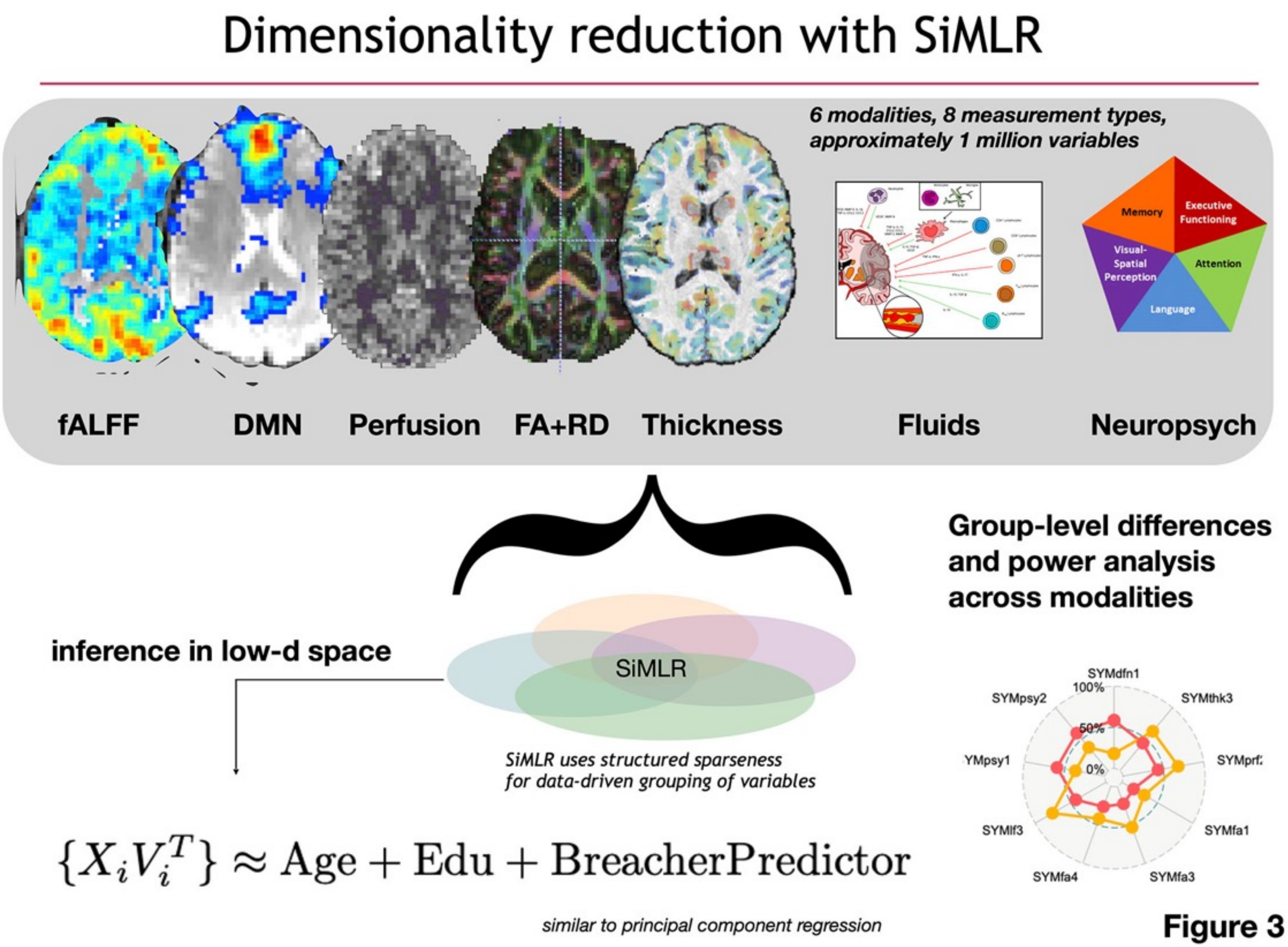


SiMLR evaluation results: Brain Age



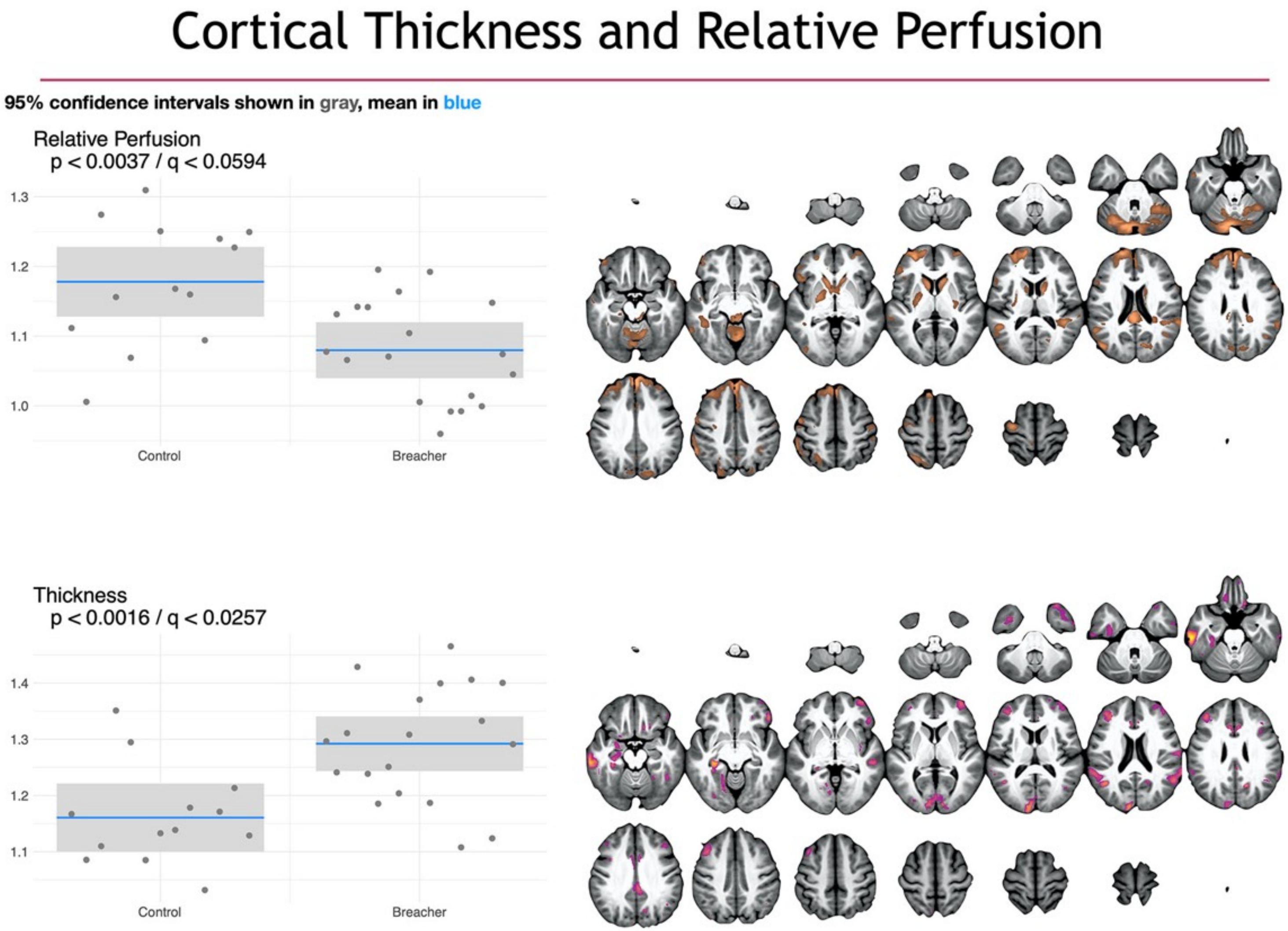
These are the interpretable predictors that are produced by SiMLR.
Like PCA, we can produce several components for each modality.
They are sparse and smooth and can be used for inference or prediction.

Analysis Approach



Stone et al., J Neurotrauma, 2020

Neuroimaging Results

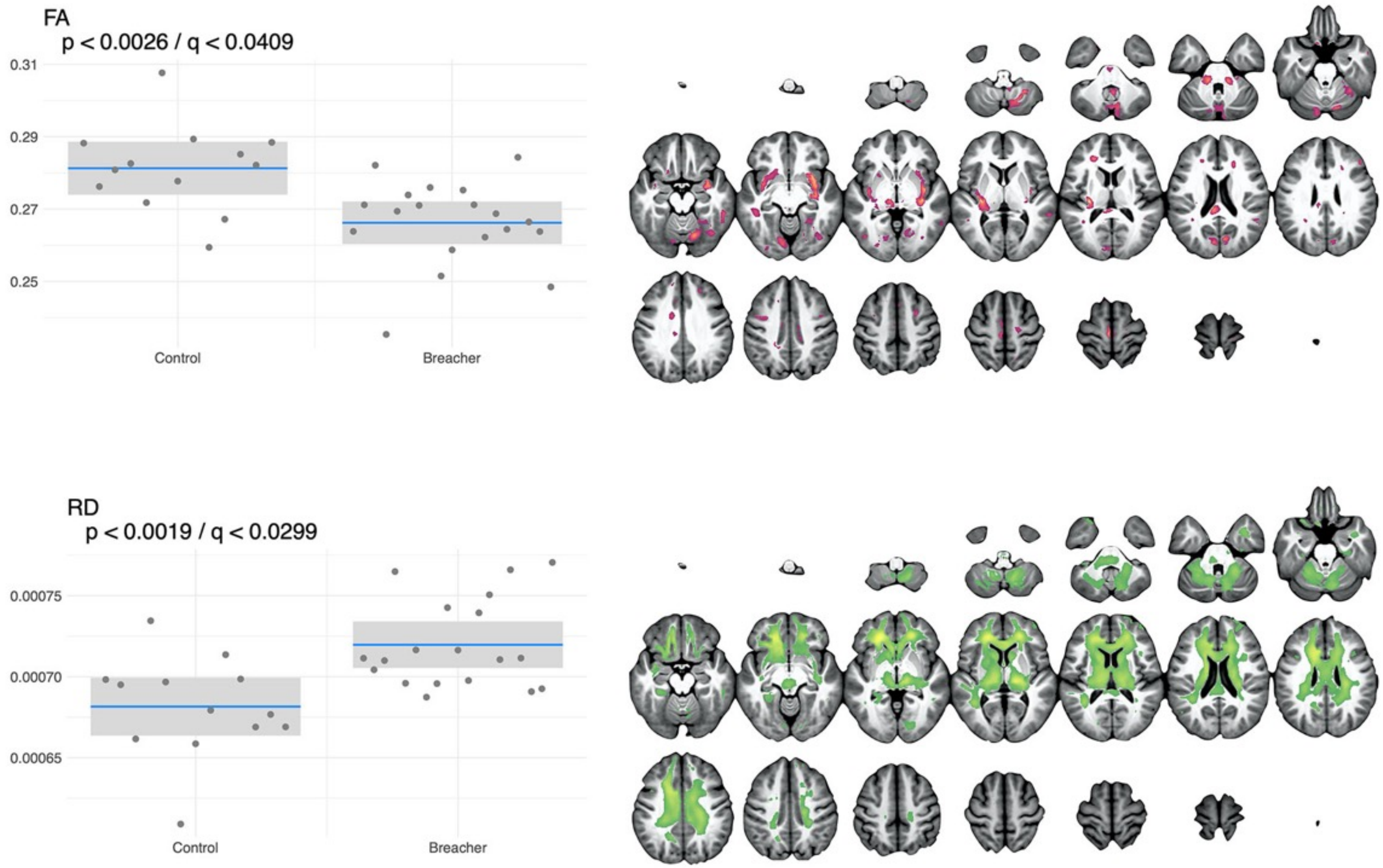


Stone et al., J Neurotrauma, 2020

Neuroimaging Results

White Matter Effects: FA & RD

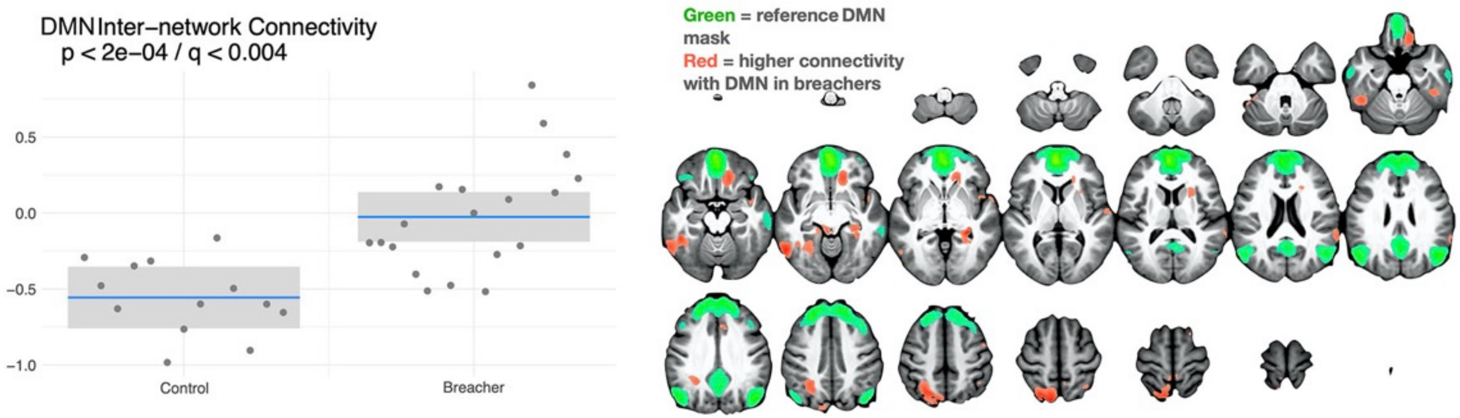
95% confidence intervals shown in gray, mean in blue

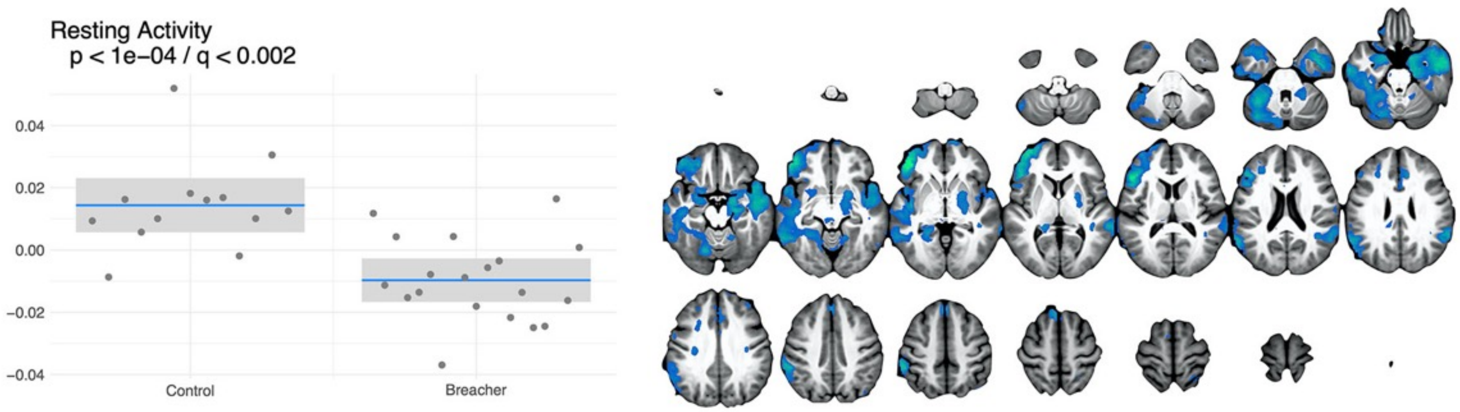


Stone et al., J Neurotrauma, 2020

Neuroimaging Results

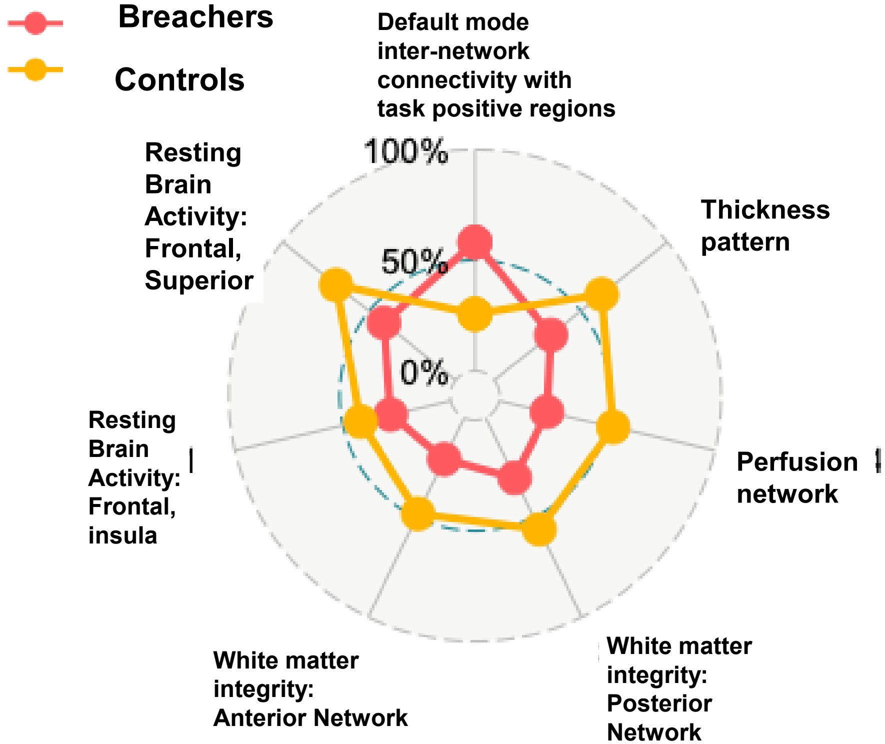
Default mode inter-network connectivity and resting activity



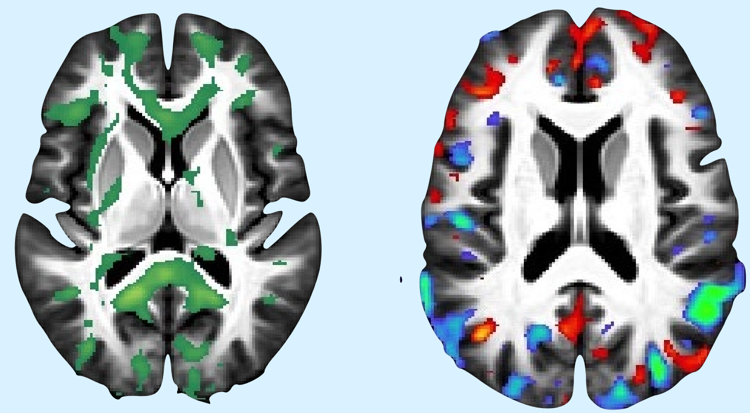


Stone et al., J Neurotrauma, 2020

Effects of breaching on brain structure and function



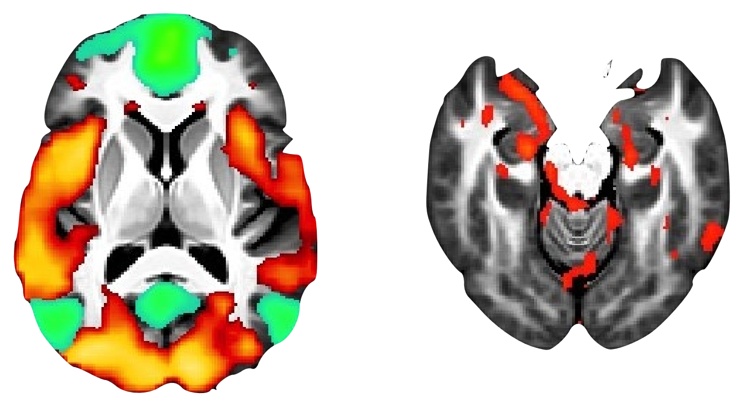
Structural imaging



Reduced white matter integrity in corpus callosum.

Altered pattern of cortical thickness.

Functional imaging



Higher inter-network connectivity / less default mode activity.

Distributed network of reduced frontal and temporal activity.

Structural imaging: sensitive to number of breaches in career and levels of blast exposure

Functional imaging: sensitive to number of breaches in last year and levels of blast exposure.

Fluid biomarkers: ~constant difference independent of career levels of breaching

JOURNAL OF NEUROTRAUMA XX:XX:1–14 (Month XX, 2020)
Mary Ann Liebert, Inc.
DOI: 10.1089/neu.2020.7141

Original Article

Functional and Structural Neuroimaging Correlates of Repetitive Low-Level Blast Exposure in Career Breachers

James R. Stone,[1] Brian B. Avants,[1] Nicholas J. Tustison,[1] Eric M. Wassermann,[2] Jessica Gill,[3] Elena Polejaeva,[4] Kristine C. Dell,[5] Walter Carr,[6,8] Angela M. Yarnell,[7] Matthew L. LoPresti,[8] Peter Walker,[9] Meghan O'Brien,[1] Natalie Domeisen,[1] Alycia Quick,[10] Claire M. Modica,[11] John D. Hughes,[12] Francis. J. Haran,[13] Carl Goforth,[13] and Stephen T. Ahlers[13]

Summary

- Quantico Breacher Study showed significant findings specific to more experienced instructions.
- Experienced Breacher study demonstrates significant differences with structural and functional imaging as compared to matched controls.
- Experienced Breacher study shows brain-derived exosomes with higher content of inflammatory markers compared with matched controls.
- Experience Breacher study is the first study to perform a comprehensive analysis demonstrating differences between populations exposed to repetitive low-intensity blast and well-matched controls.

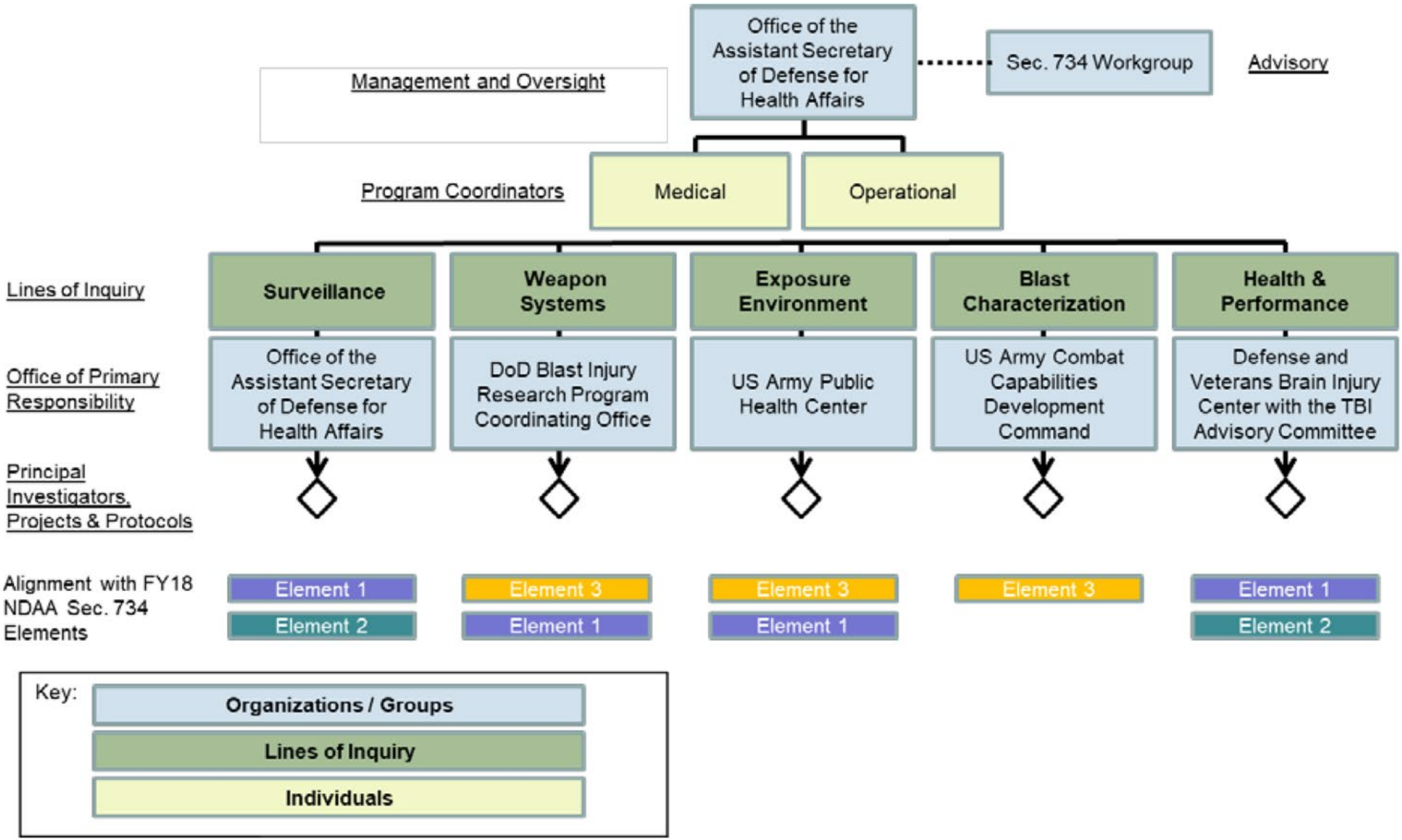


Figure 1. Program Structure Developed to Support Section 734

Gaps

- What are the limits of safe exposure to repetitive low-intensity blast? Is this defined by total loading over a lifetime or some combination of frequency and intensity?

- Are chronic neurological changes seen in other populations exposed to repetitive low-intensity blast exposure? (e.g. artillery/heavy weapons, EOD)

- What are the molecular mechanisms of the brain response to repetitive low-intensity blast exposure?

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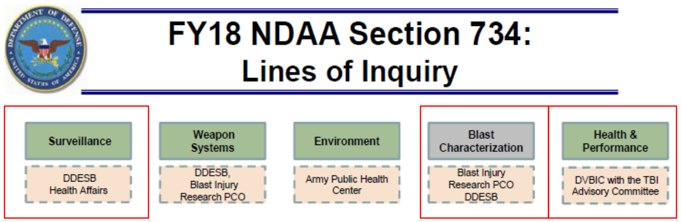
- What are the molecular mechanisms of the brain response to repetitive low-intensity blast exposure?

Operational Blast Exposure Survey



<u>Question</u>: When do chronic symptoms appear in career operators? Which blast exposed communities are most at risk?

Issue:

- The cumulative # of career blast exposures may be informative.
- Number of exposures in contact sports is predictive of long-term neurological consequences.

Approach:

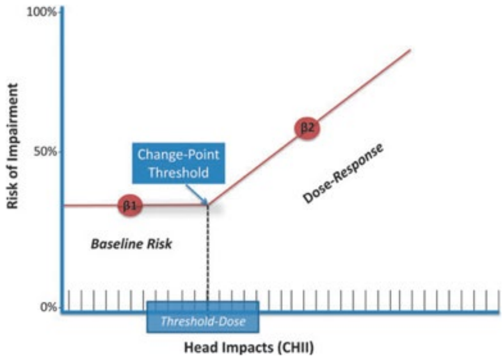
- Survey all DoD blast communities to determine:
  - When during career self-reported symptoms emerge.
  - Symptom differences as a function of weapons system(s).
  - Relationship of number of cumulative blasts and symptoms.
  - The online survey is a blast event counting tool.
- Two complimentary approaches:
  - 5-minute online DoD-approved anonymous survey.
  - In depth interview.

Online Survey Results

- 984 respondents across a wide swath of blast exposed and non-blast exposed communities.
- Significant age diversity.
- Reported symptoms that reached significance:
  - Hearing loss
  - Ringing in ears
  - Forgetfulness
  - Change in taste/smell
- Symptoms were evident in groups with exposure to higher intensity weapons and tended to be evident in older (32+ yrs.) of age.

Generalized Blast Exposure Value (GBEV)

- Analogous to CHII
  - Characterize population
  - Identify and associate with outcomes
  - Identify threshold for risk



Montenigro et al., 2017

- $GBEV = 0.976 * 1\,BEC + 0.751 * (383 * 2\,BEC) + 0.753 * (55 * 3\,BEC) + 77 * 4\,BEC * (4freq) + 75 * 5\,BEC * (5freq)$

BEC (blast exposure count) = years of experience with a weapon * months of experience per year * days of experience per month * number of exposures per day.

Gaps

- What are the limits of safe exposure to repetitive low-intensity blast? Is this defined by total loading over a lifetime or some combination of frequency and intensity?

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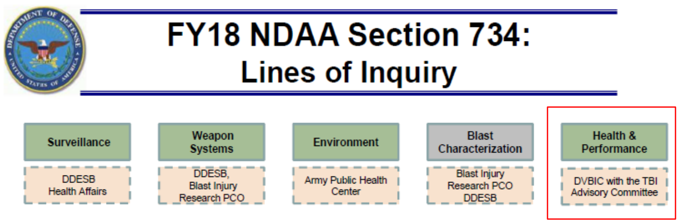
Going Forward



Question: Is there evidence of injury in personnel after a career of repetitive exposures?

Approach:

- Assess "experienced" Artillery service members

Subjects:

- Military
  - 50 experienced artillery
  - Matched controls

Assessment
Demographics and symptom questionnaires
Neuropsychological testing
Audiology/vestibular testing
Postural stability testing
MRI – volumetric imaging, white matter hyperintensity/perivascular spaces assessments, diffusion tensor imaging, resting state functional connectivity, perfusion weighted imaging.
Fluid biomarkers – brain-based exosomes for proteins of interest, gene analyses.

Gaps

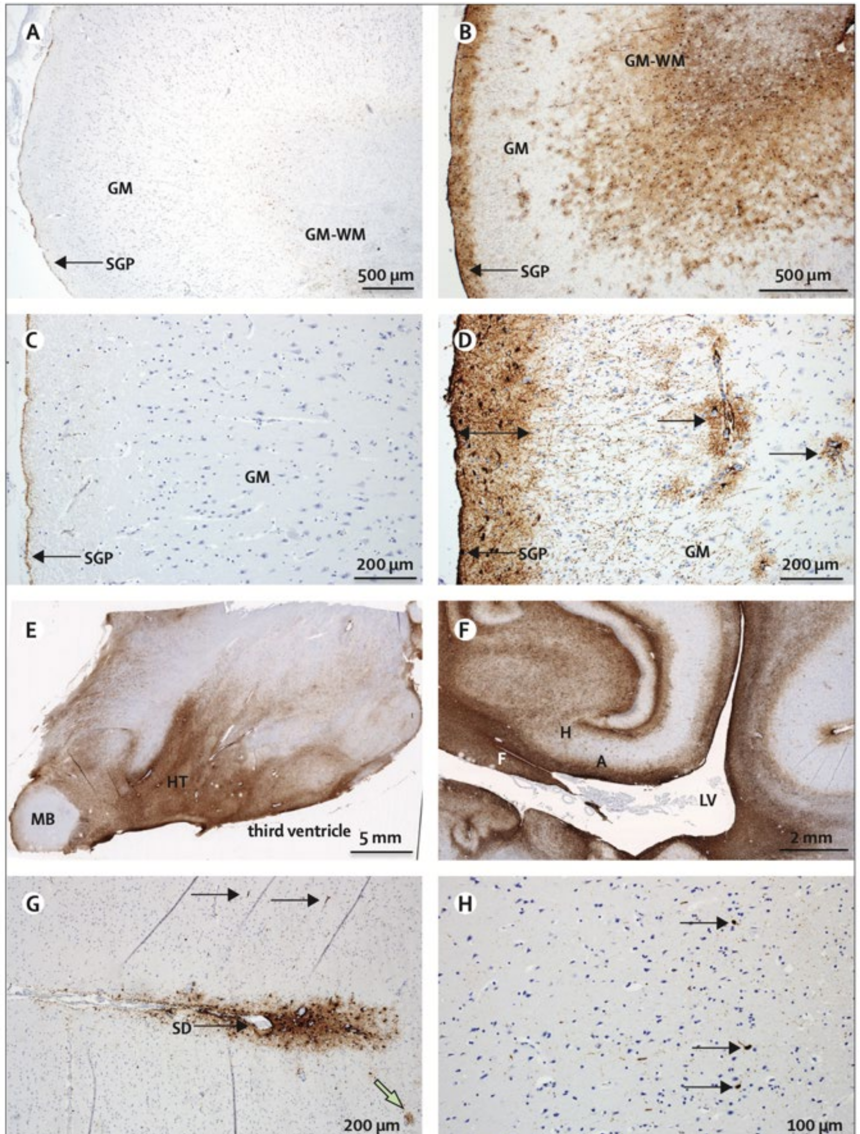
- What are the limits of safe exposure to repetitive low-intensity blast? Is this defined by total loading over a lifetime or some combination of frequency and intensity?

- Are chronic neurological changes seen in other populations exposed to repetitive low-intensity blast exposure? (e.g. artillery/heavy weapons, EOD)

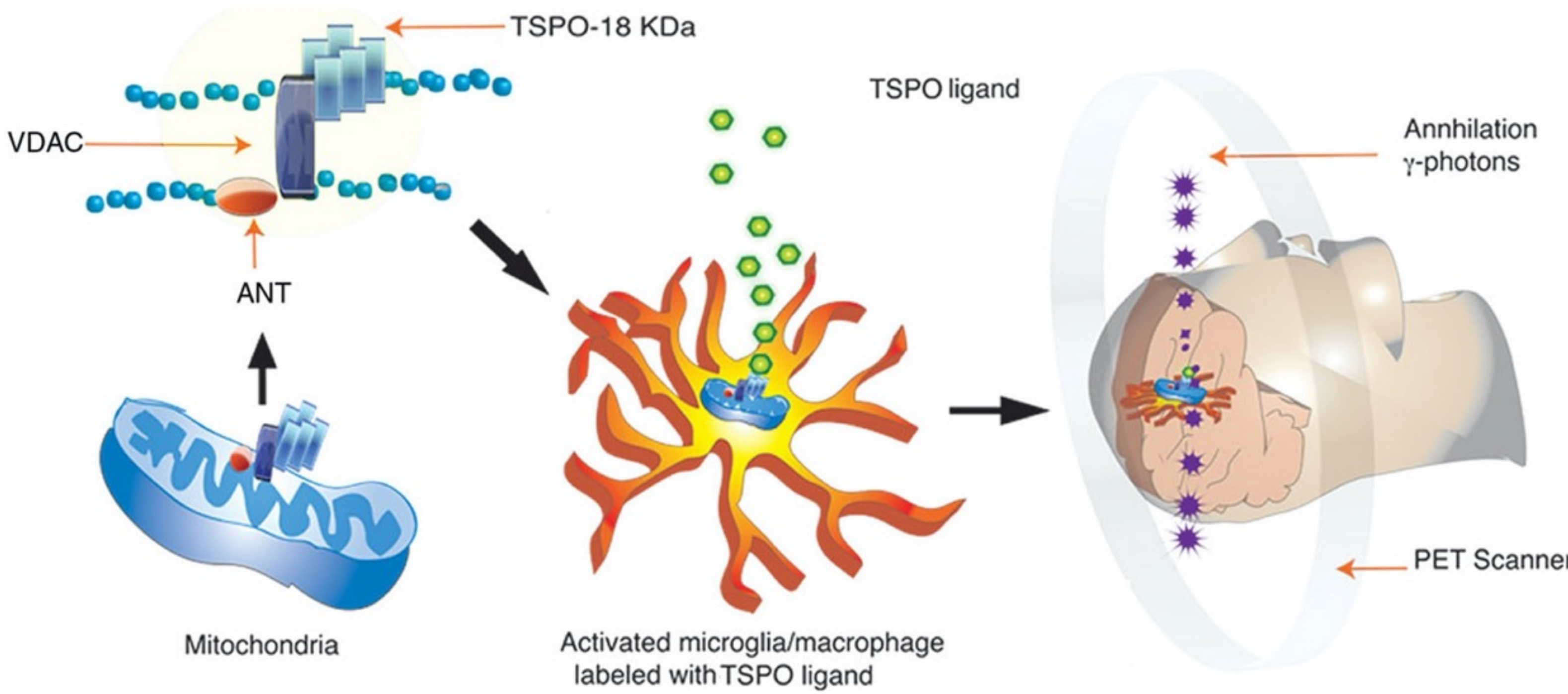
- What are the molecular mechanisms of the brain response to repetitive low-intensity blast exposure?

Characterisation of interface astroglial scarring in the human brain after blast exposure: a post-mortem case series

Sharon Baughman Shively*, Iren Horkayne-Szakaly*, Robert V Jones, James P Kelly, Regina C Armstrong, Daniel P Perl



Molecular Imaging of Inflammation in TBI: TSPO ligands

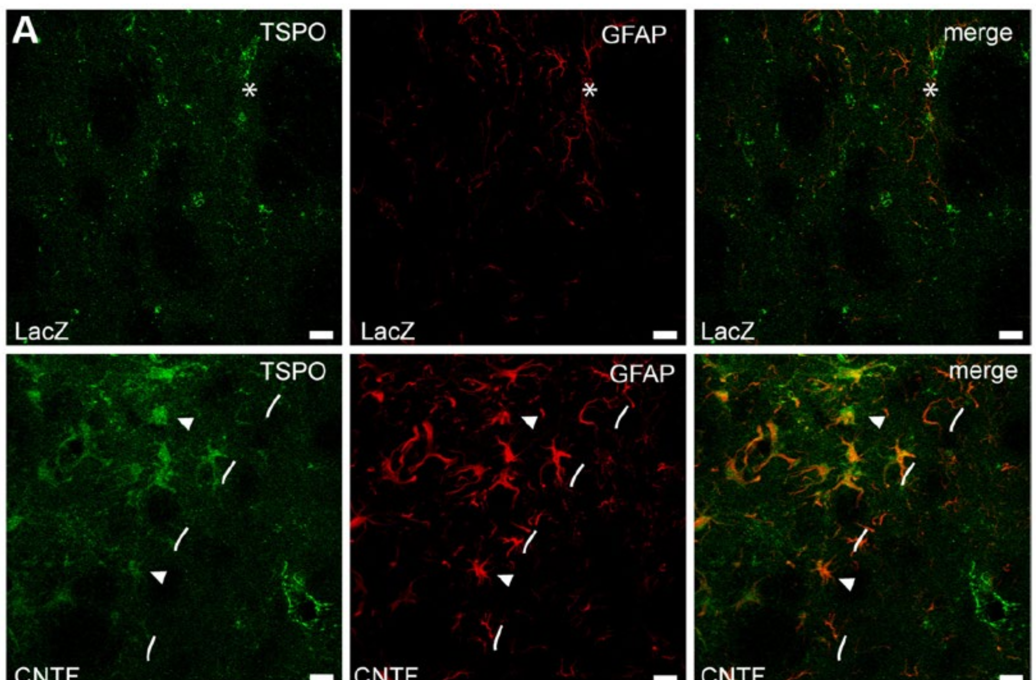


Venneti et al, 2013

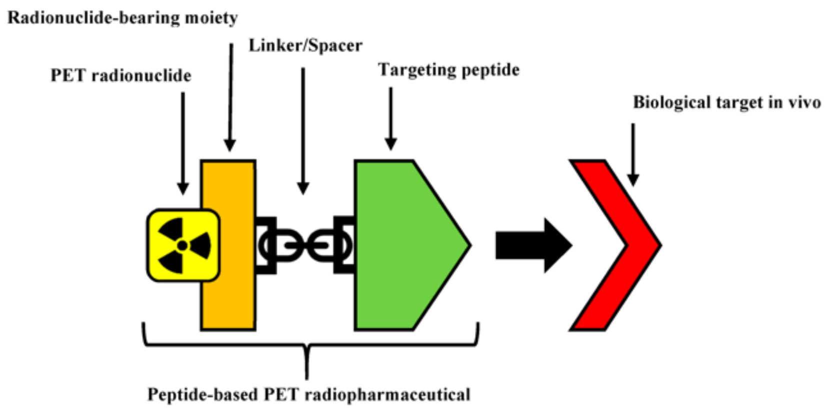
Neurobiology of Disease

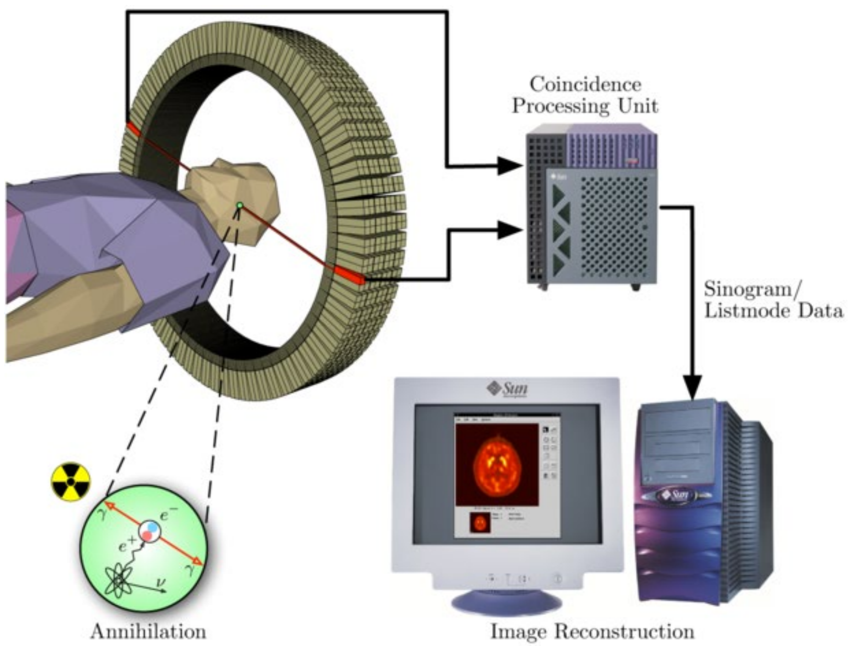
Reactive Astrocytes Overexpress TSPO and Are Detected by TSPO Positron Emission Tomography Imaging

Sonia Lavisse,[1] Martine Guillermier,[1*] Anne-Sophie Hérard,[1*] Fanny Petit,[1*] Marion Delahaye,[1] Nadja Van Camp,[1] Lucile Ben Haim,[1] Vincent Lebon,[1] Philippe Remy,[1,2] Frédéric Dollé,[3] Thierry Delzescaux,[1] Gilles Bonvento,[1] Philippe Hantraye,[1] and Carole Escartin[1]
[1]Commissariat à l'Energie Atomique et aux Energies Alternatives (CEA), Département des Sciences du Vivant (DSV), Institut d'Imagerie Biomédicale, MIRCen and CNRS, URA2210 (I2BM), 92260 Fontenay-aux-Roses, France, [2]Neurology Department, Henri Mondor University Hospital, 94000 Créteil, France, and [3]CEA, DSV, I2BM, Service Hospitalier Frédéric Joliot, 91400 Orsay, France

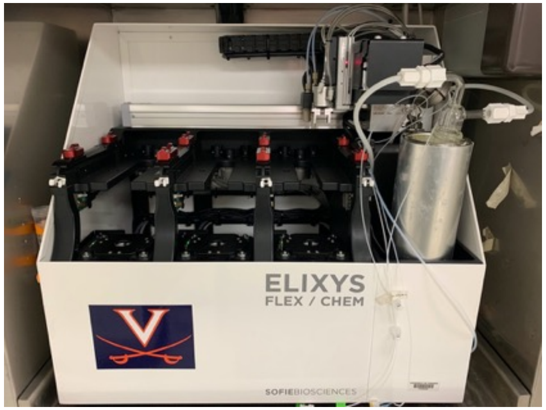


Molecular Imaging with PET

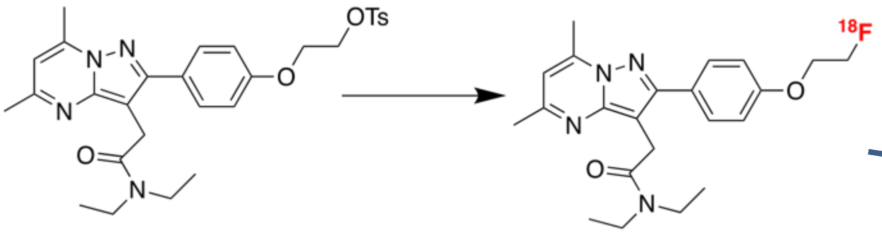


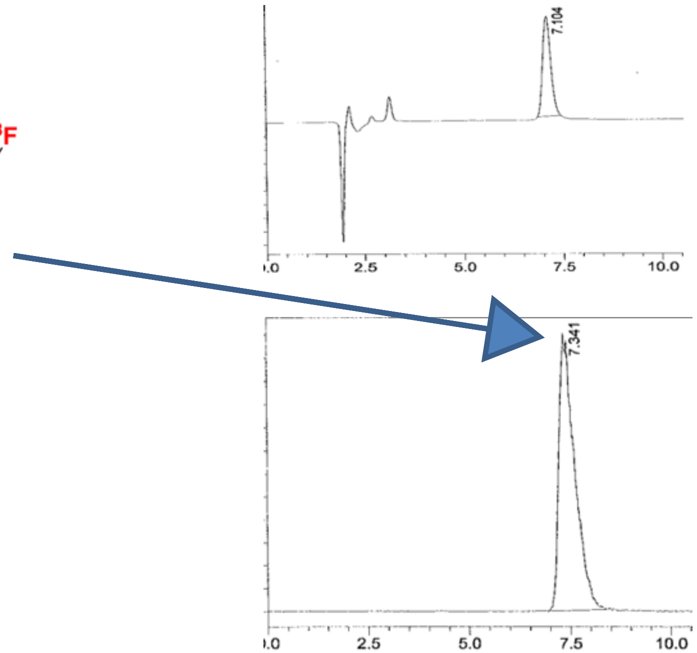


Molecular Imaging of Inflammation in TBI: [^{18}F]DPA-714 TSPO ligand synthesis



- Automated Radiosynthesizer
- Performs all [^{18}F]DPA-714 productions remotely



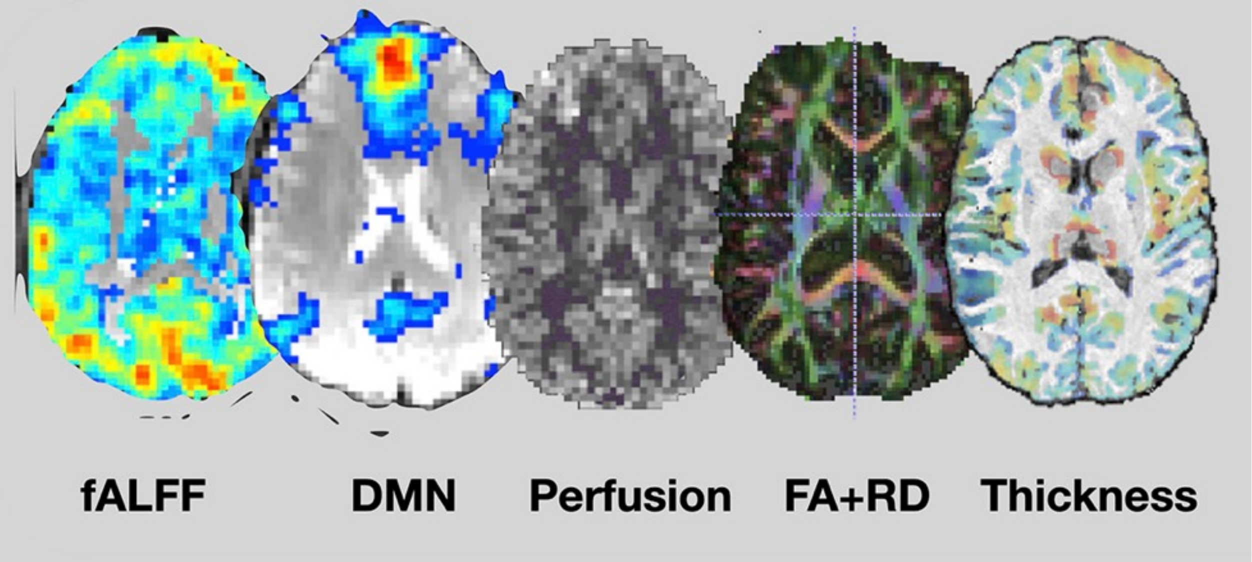


- Synthesized in >99% radiochemical purity
- High yielding and robust synthesis
  - 11 ± 3% yield (>25 syntheses)
- High molar activity product
  - Critical for neuroimaging studies

SOCOM Blast Study Design

- Pilot study involving 10 blast exposed individuals vs. 10 matched controls
- Demographics, head injury questionnaire, ANAM 4 TBI-MIL, PSQI, PCL-5, PGWI, NSI
- PET-CT neuroimaging using [^{18}F]DPA-714
- Fluid biomarkers, focusing upon brain derived measures of inflammation as well as inflammation-related gene polymorphisms.

Study Design



A. Volumetric sequences (e.g. MPRAGE)
B. T2-weighted imaging and fluid attenuation inversion recovery (FLAIR) sequences
C. Susceptibility weighted imaging (SWI)
D. Resting state blood oxygen level dependent (BOLD) sequences to allow for connectivity analyses
E. Arterial spin labeling
F. Diffusion tensor/kurtosis imaging (DTI/DKI)

Generalized Blast Exposure Value (GBEV)

- Analogous to CHII
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  - Identify and associate with outcomes
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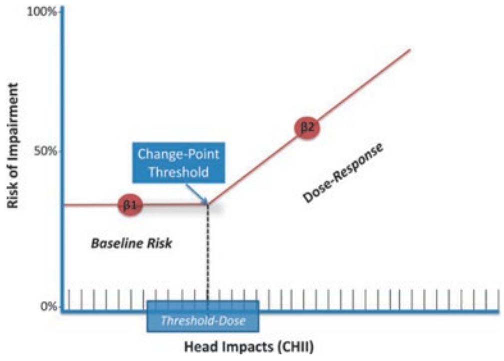

Montenigro et al., 2017

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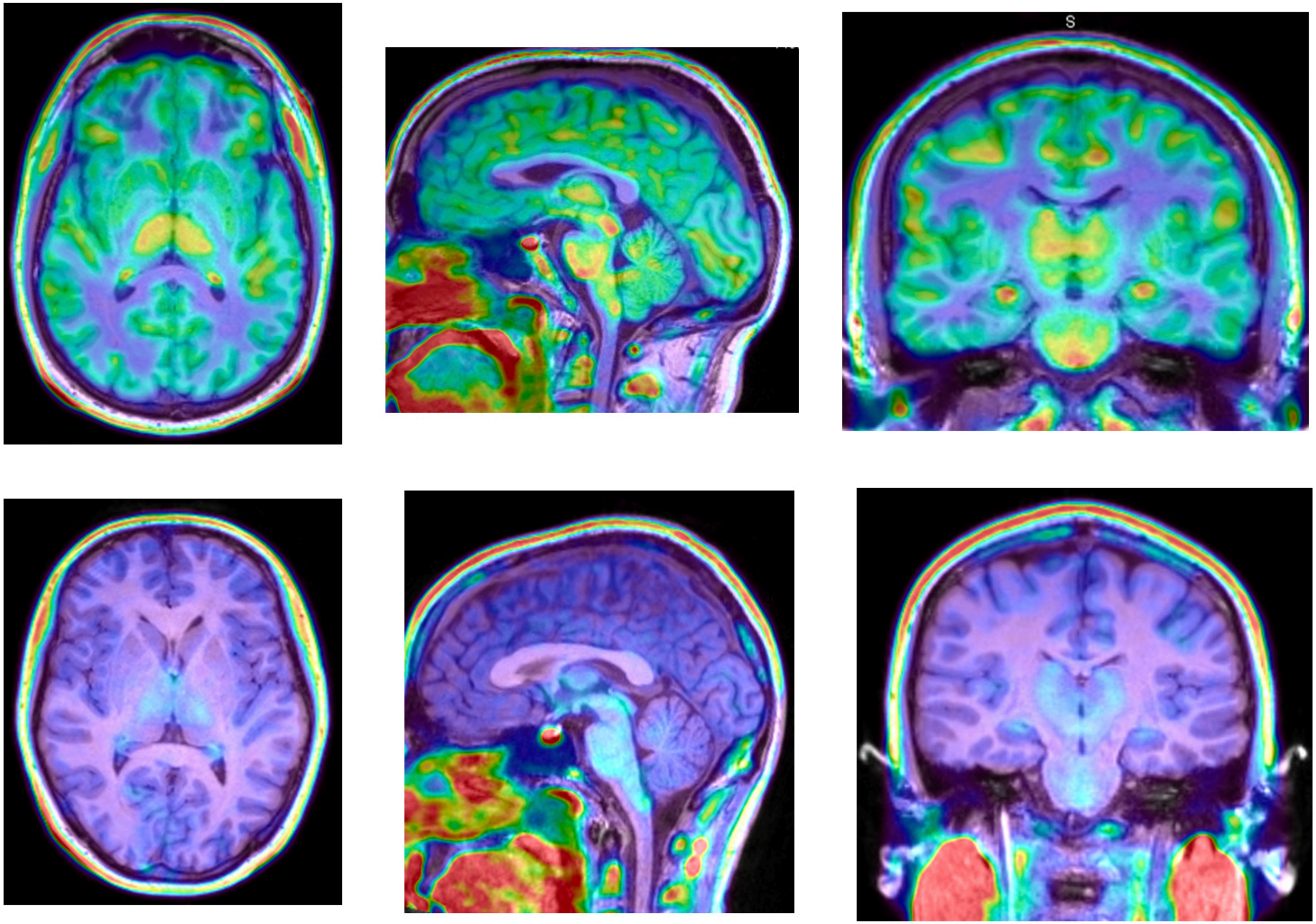
BEC (blast exposure count) = years of experience with a weapon * months of experience per year * days of experience per month * number of exposures per day.

Preliminary Results

[^{18}F]DPA-714 TSPO Imaging in Blast-exposed subject vs. normal subject

Blast exposed

Normal Subject

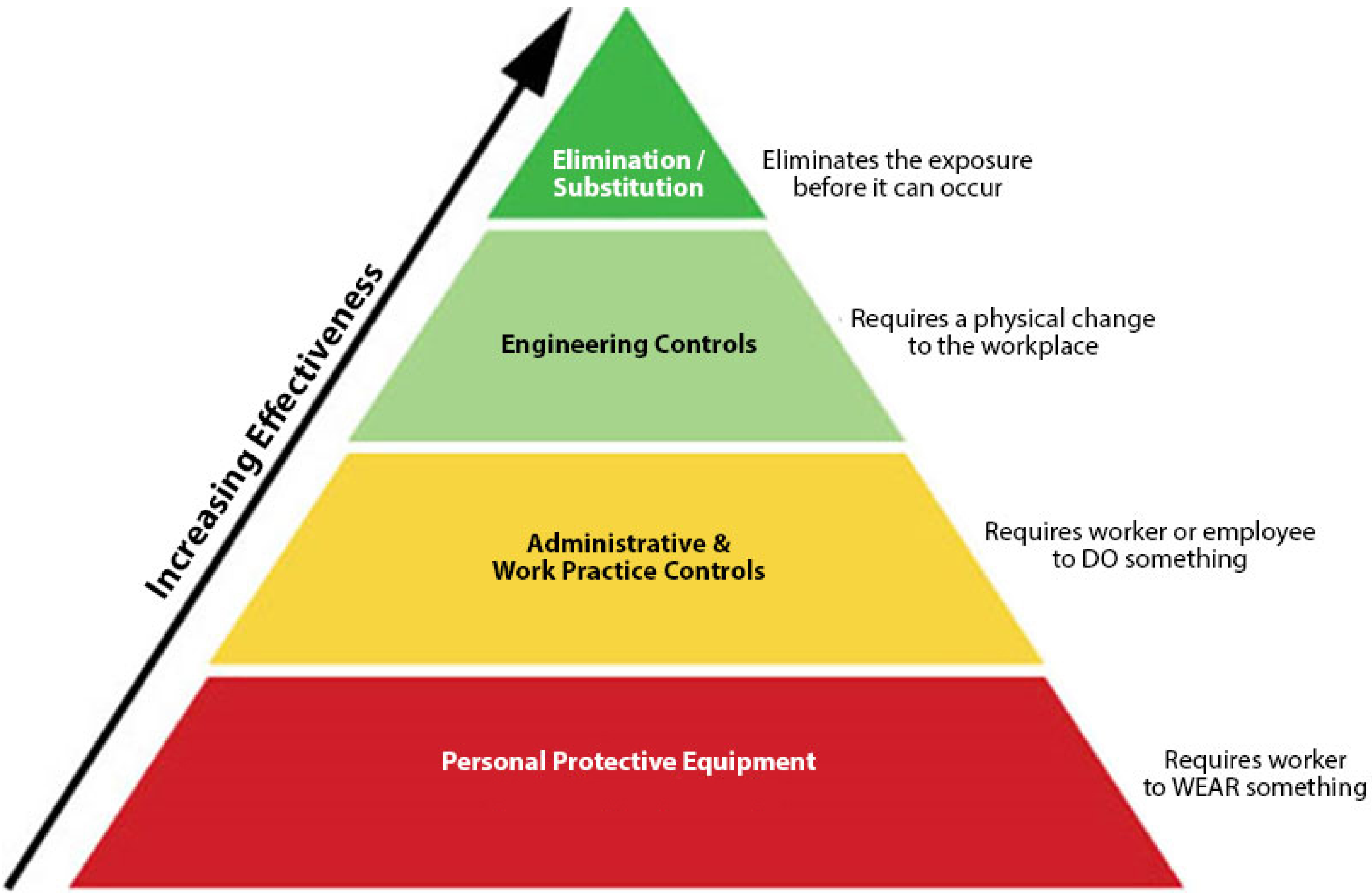


Presented with SOCOM permission

Conclusions

- Building evidence confirms repetitive low-intensity blast exposure is an occupational risk for operational personnel in training and operations.
- Ongoing work is assessing the neurological effects of low-intensity blast exposure in other populations such as those exposed to artillery/heavy weapons.
- Initial work being performed exploring the molecular mechanisms involved in repetitive low-intensity blast exposure in special operations – setting the stage for further targeted study that will identify key knowledge needed to inform optimal diagnostics and mitigation strategies.
- Standardized assessments to determine blast history have been created which will be critical to defining safe loading parameters now rather than relying upon potential future prospective longitudinal studies that could take years to decades to execute.

Conclusions



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Questions?