# PTSD, Blast TBI, and Changes to the Brain Functional Connectome


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# Disclaimer

*The views, opinions, and/or findings contained in this presentation are those of the authors and should not be construed as an official US Department of Veterans Affairs or US Department of Defense position, policy or decision, unless so designated by other official documentation*

*The authors declare no conflicts of interest*

# Post Deployment Conditions

## Measurement

- Mid-Atlantic MIRECC Assessment of TBI (MMA-TBI)
- Salisbury Blast Interview (SBI)

## Symptoms

- Blast and PTSD affect self-reported symptoms independently
- Blast exposure is more relevant than TBI in psychiatric symptom presentation

## Cognitive Function

- Blast TBI results in poorer attention than TBI or blast alone

## Structural Neuroimaging

- Blast is related to increases in white matter hyperintensities over time
- Blast is related to lower hippocampal volume

Rowland et al., 2020a; Rowland et al., 2020b; Martindale et al., 2021a; Martindale et al., 2020; Taber et al., 2015; Martindale et al., 2018; Martindale et al., 2021b;

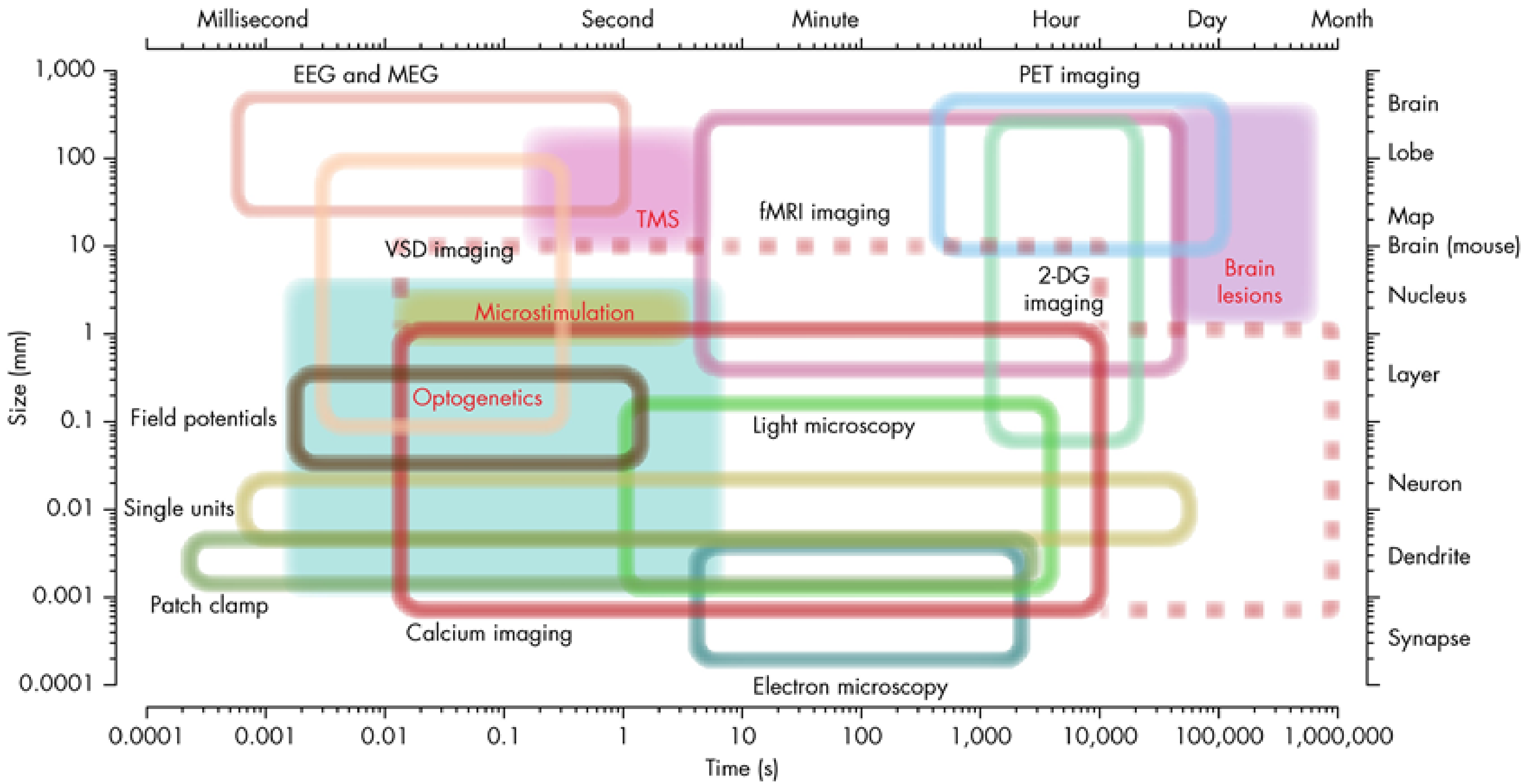
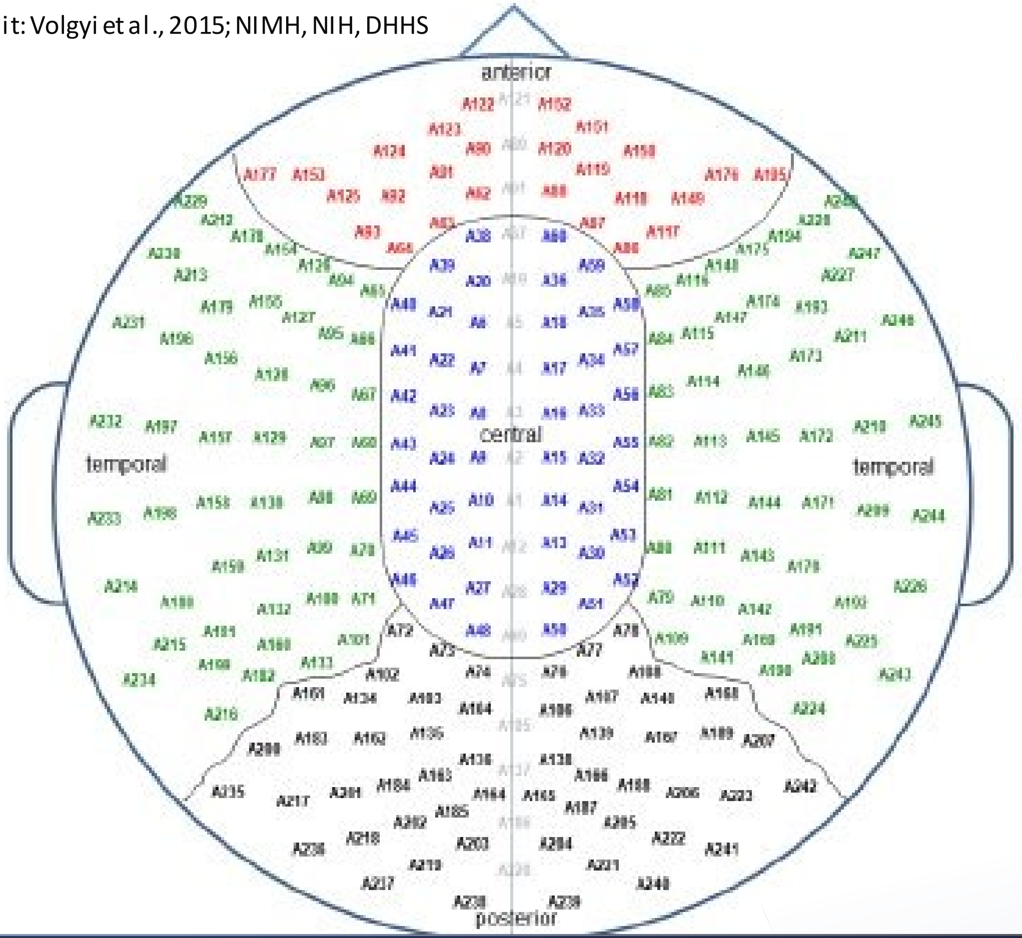



Image Credit: Biafra Ahanonu, based on Sejnowski, 2014

# Functional Neuroimaging

Image Credit: Volgyi et al., 2015; NIMH, NIH, DHHS



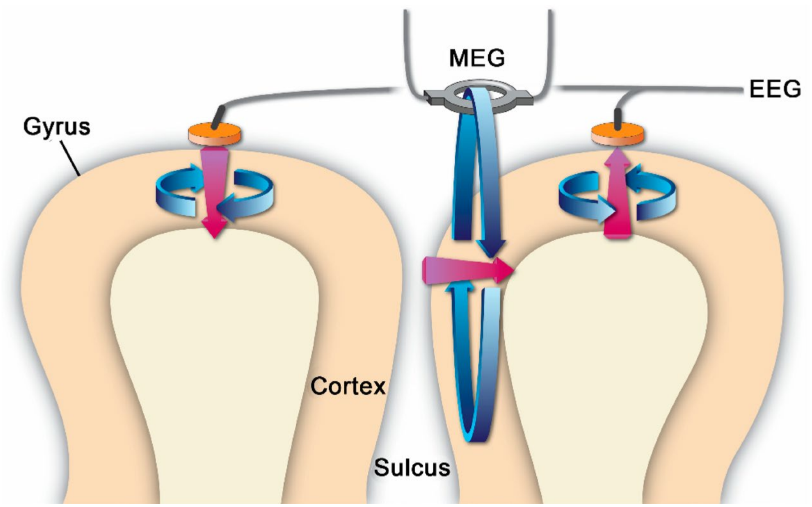

# Magnetoencephalography (MEG)

# Poll Question

**How familiar are you with magnetoencephalography (MEG)?**

A. **None** – Unaware of MEG
B. **Minimal** – Familiar with MEG (e.g., heard of, read about)
C. **Moderate** – Have worked with MEG clinically or as part of research
D. **Strong** – Work with MEG often

# Magnetoencephalography



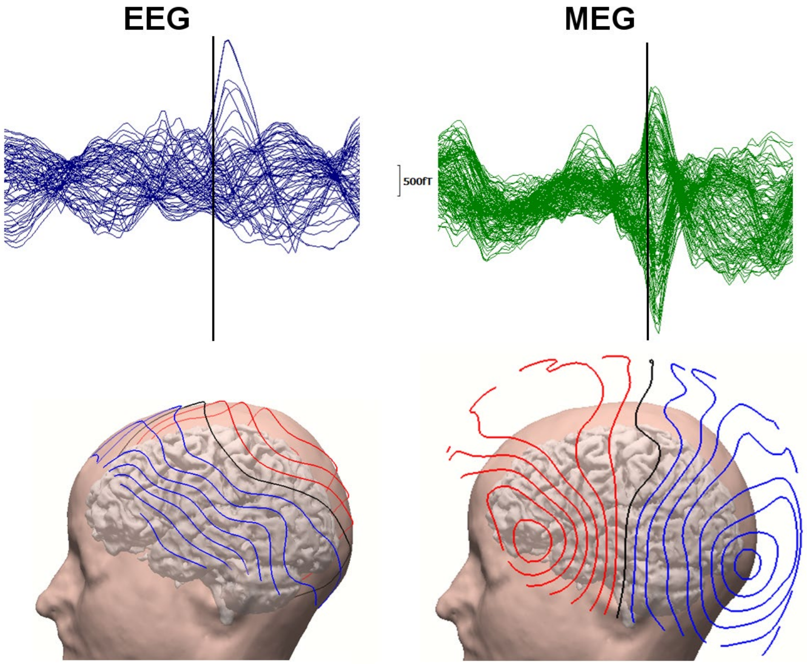




Image Credit: Aydin et al., 2014; Peitz et al., 2021

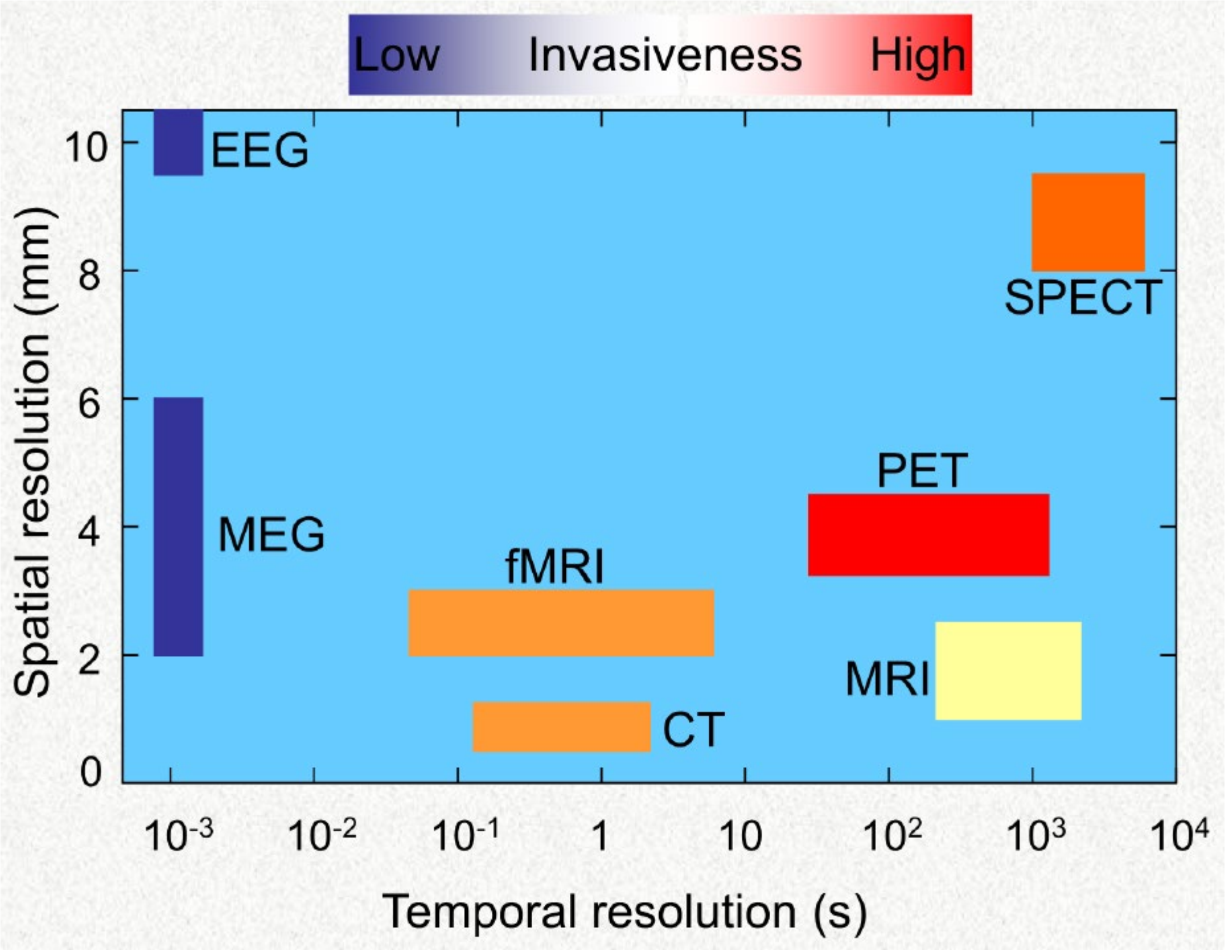



Image Credit: Ashrafulla, 2013

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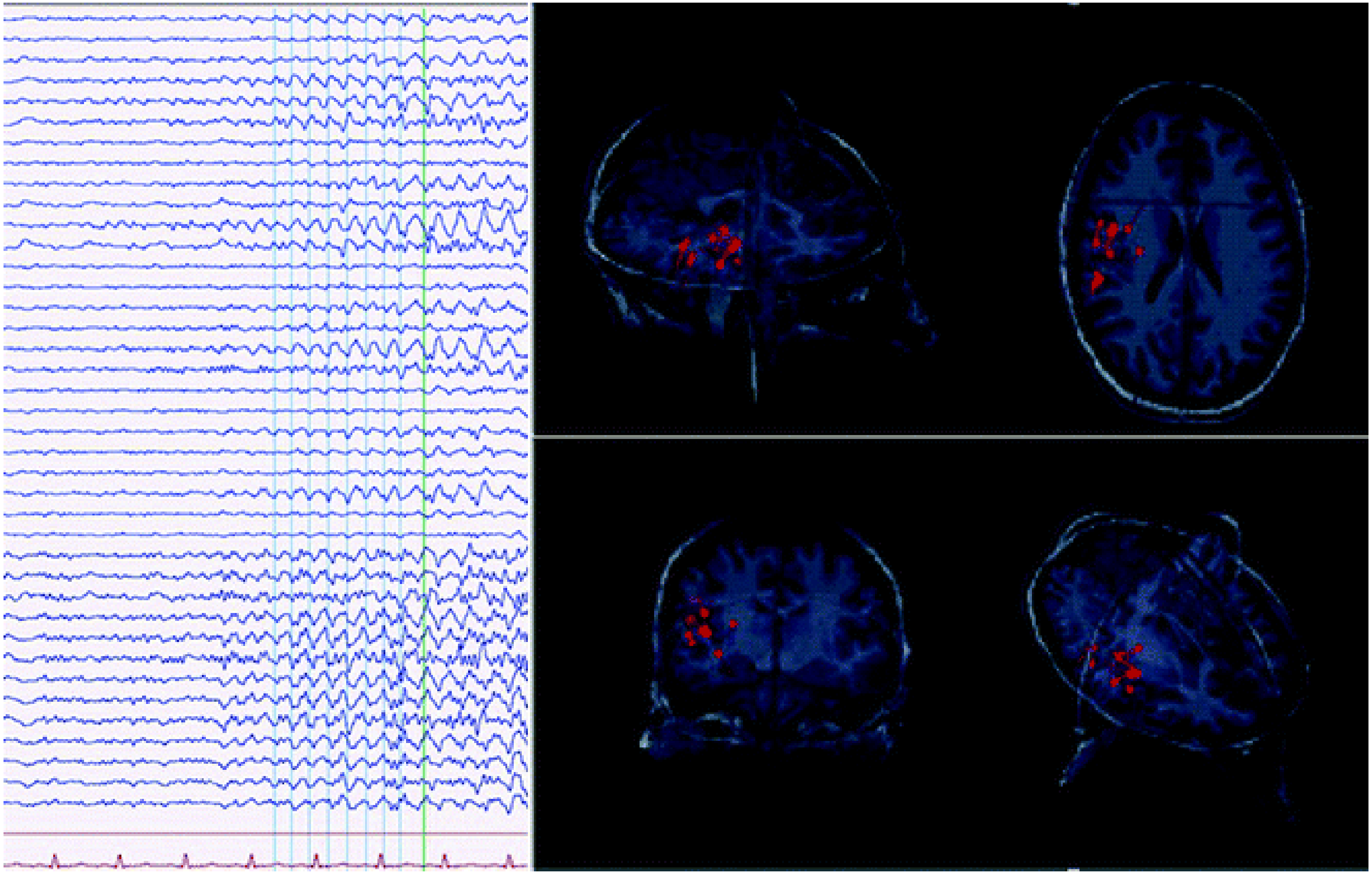

Image Credit: Neupsy Key

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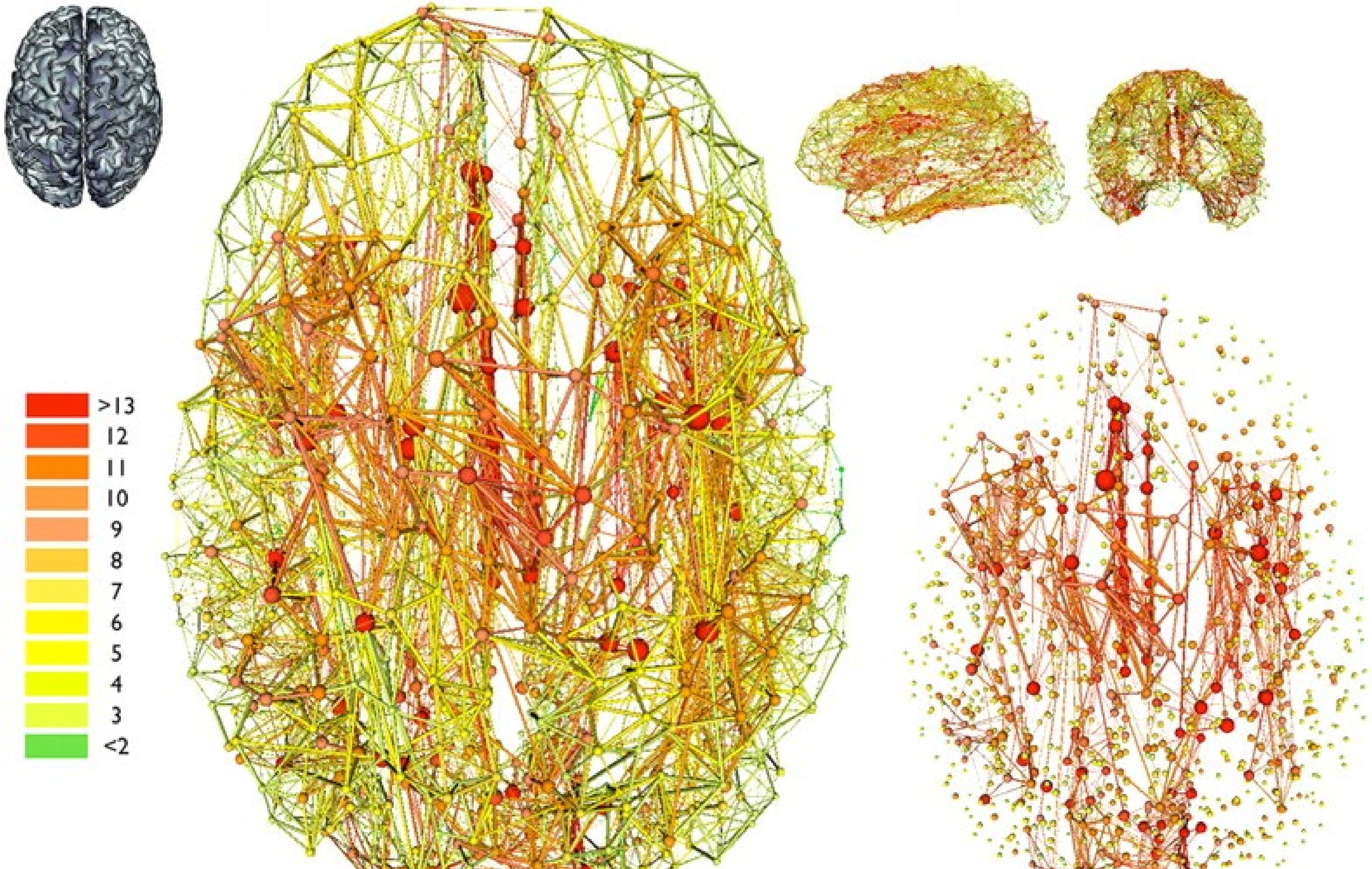


Image Credit: van den Heuvel & Sporns, 2011

# Network Analysis

# Network Analysis

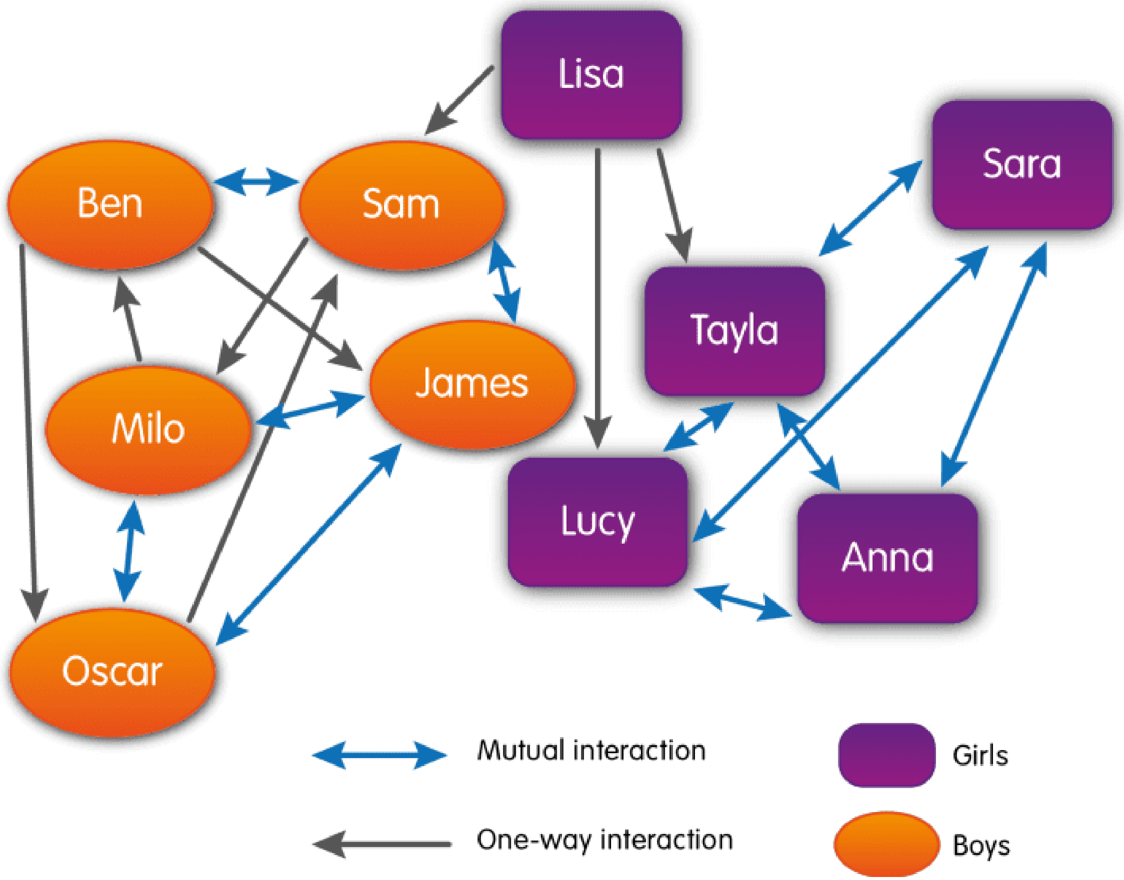


Image Credit: The Emotional Intelligence Network

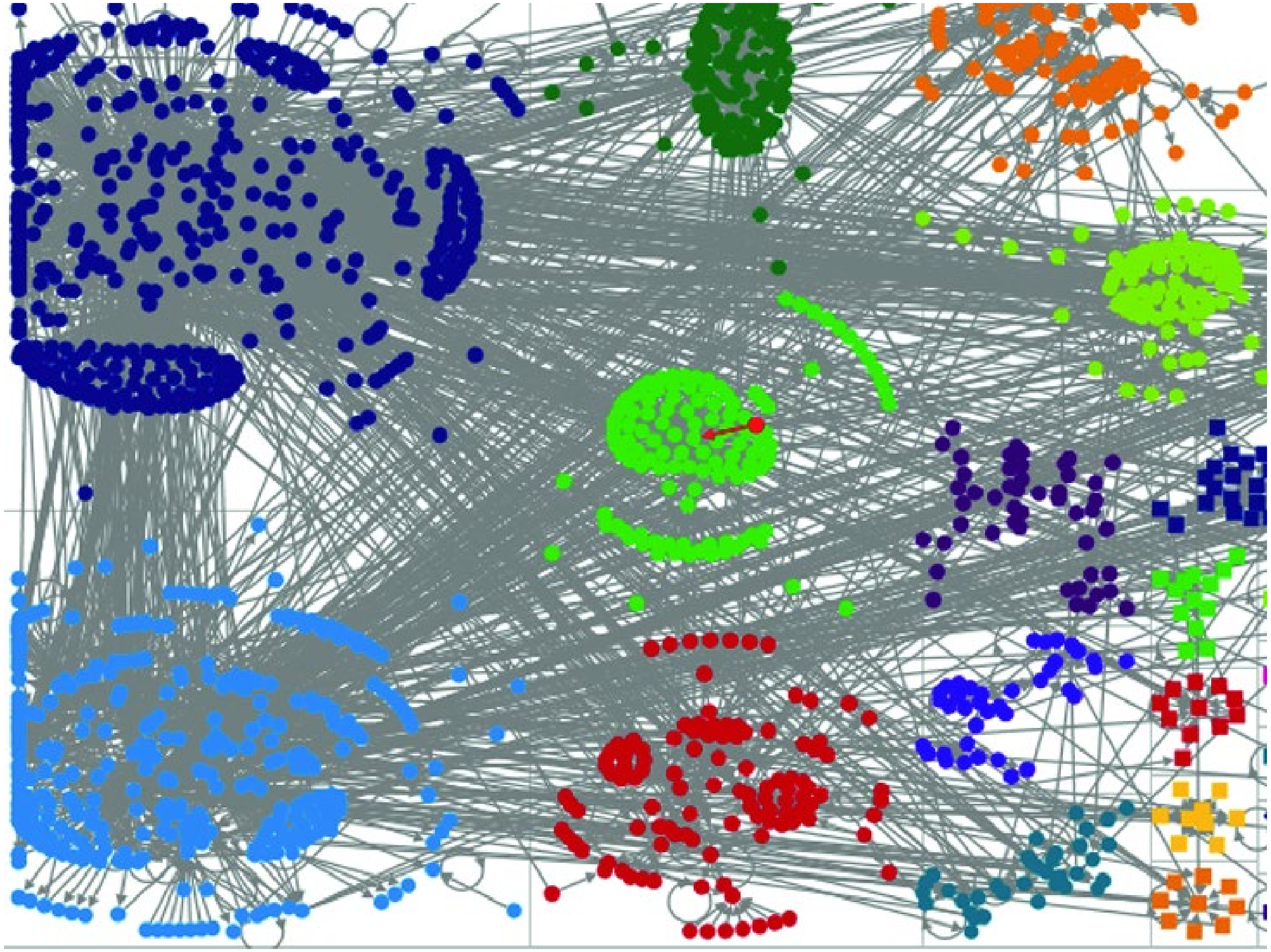

Image Credit: Struweg, 2020

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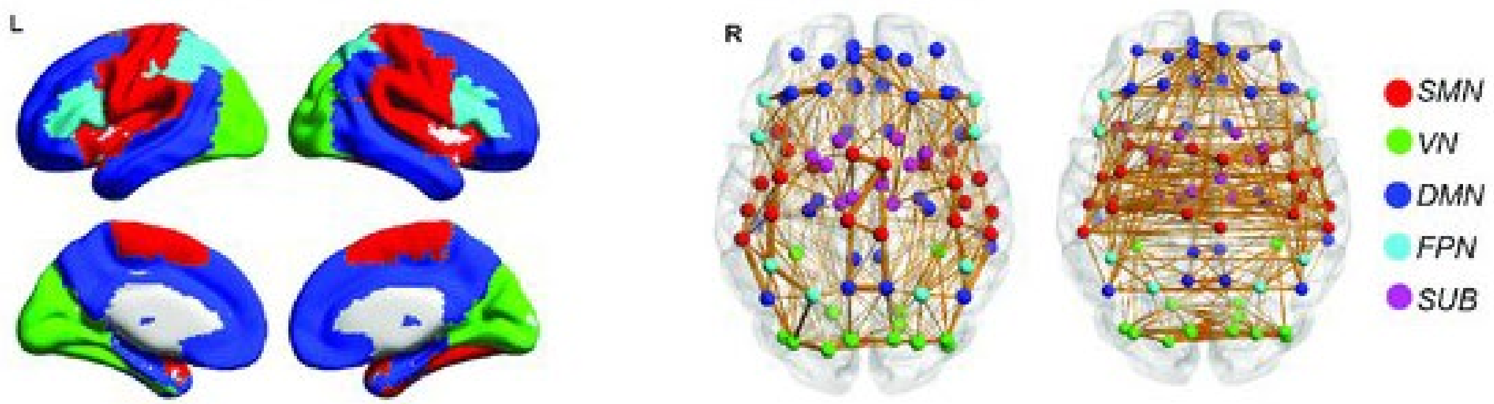


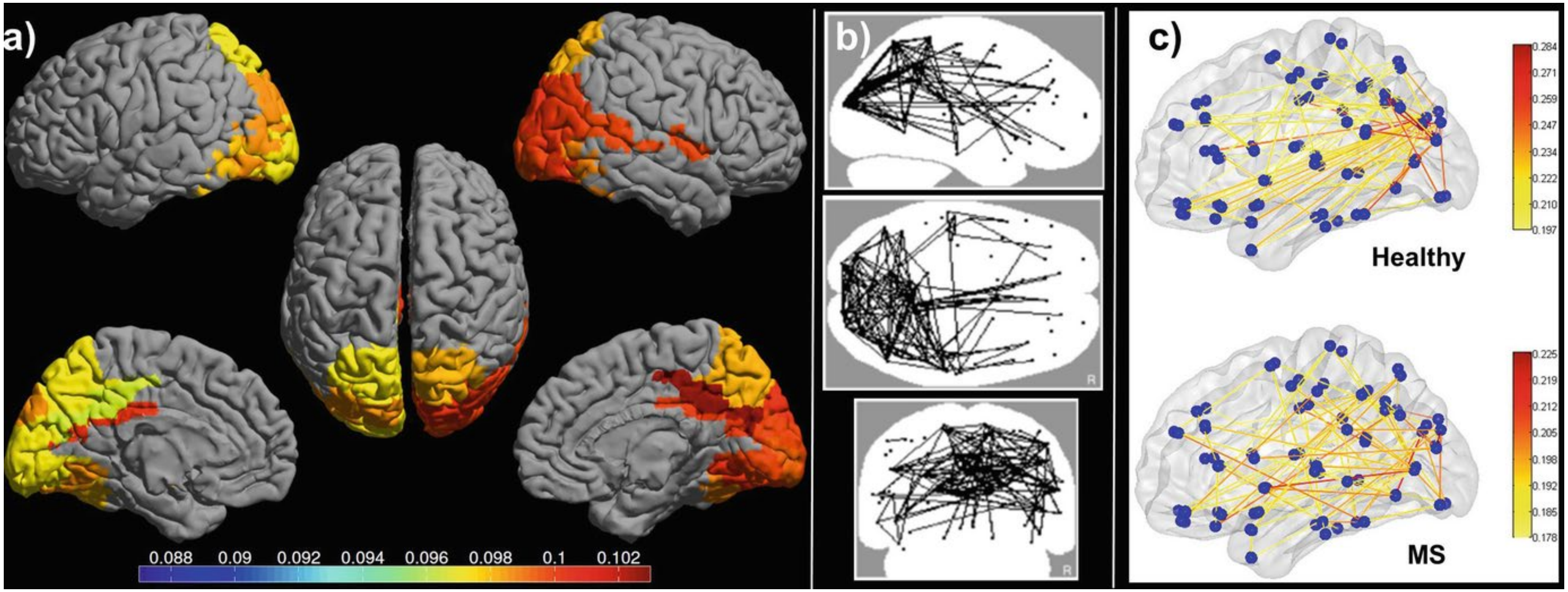
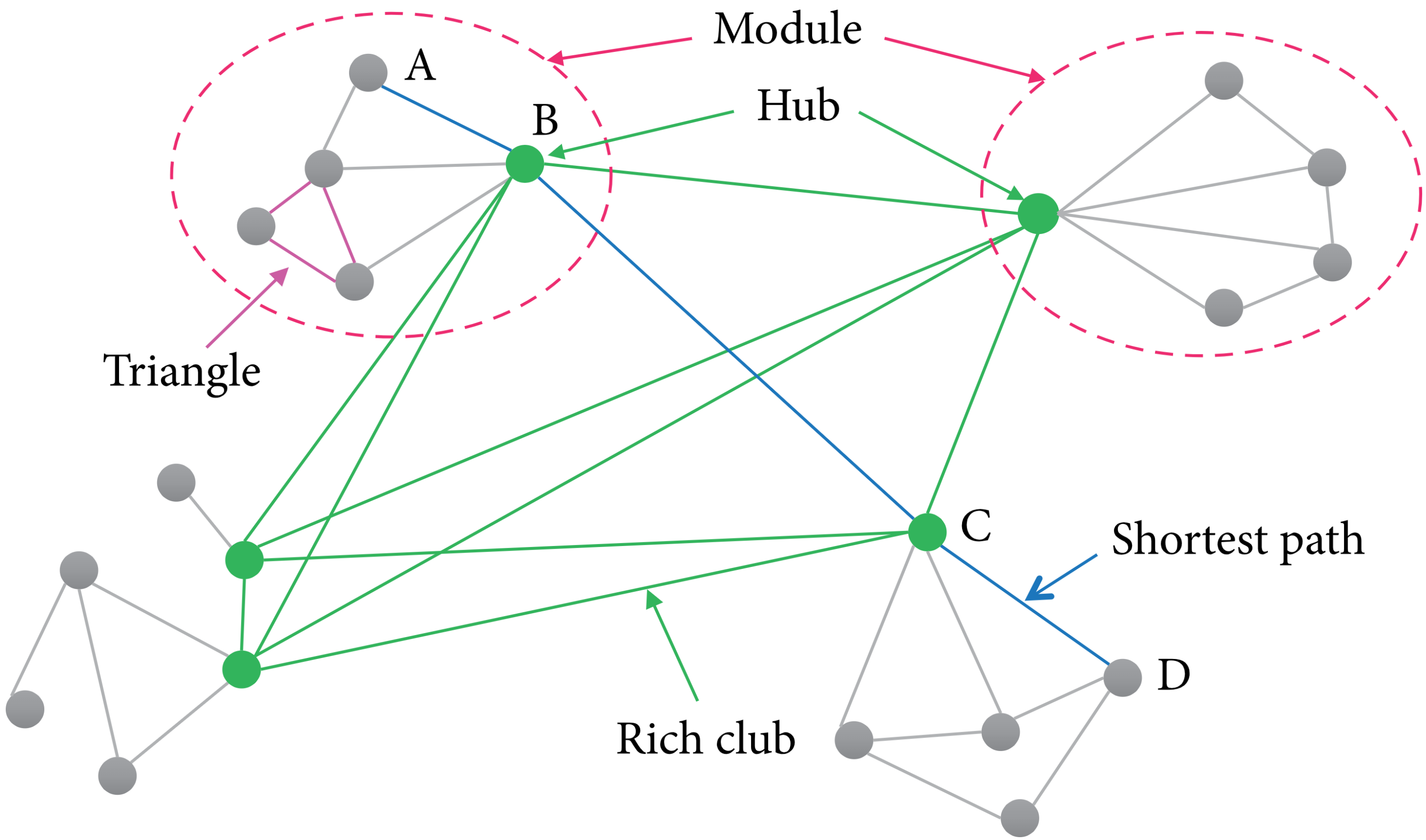




Image Credit: Liu et al., 2018; Hillebrand & Stam, 2019

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# Network Analysis

# Veteran TBI Research Connectome

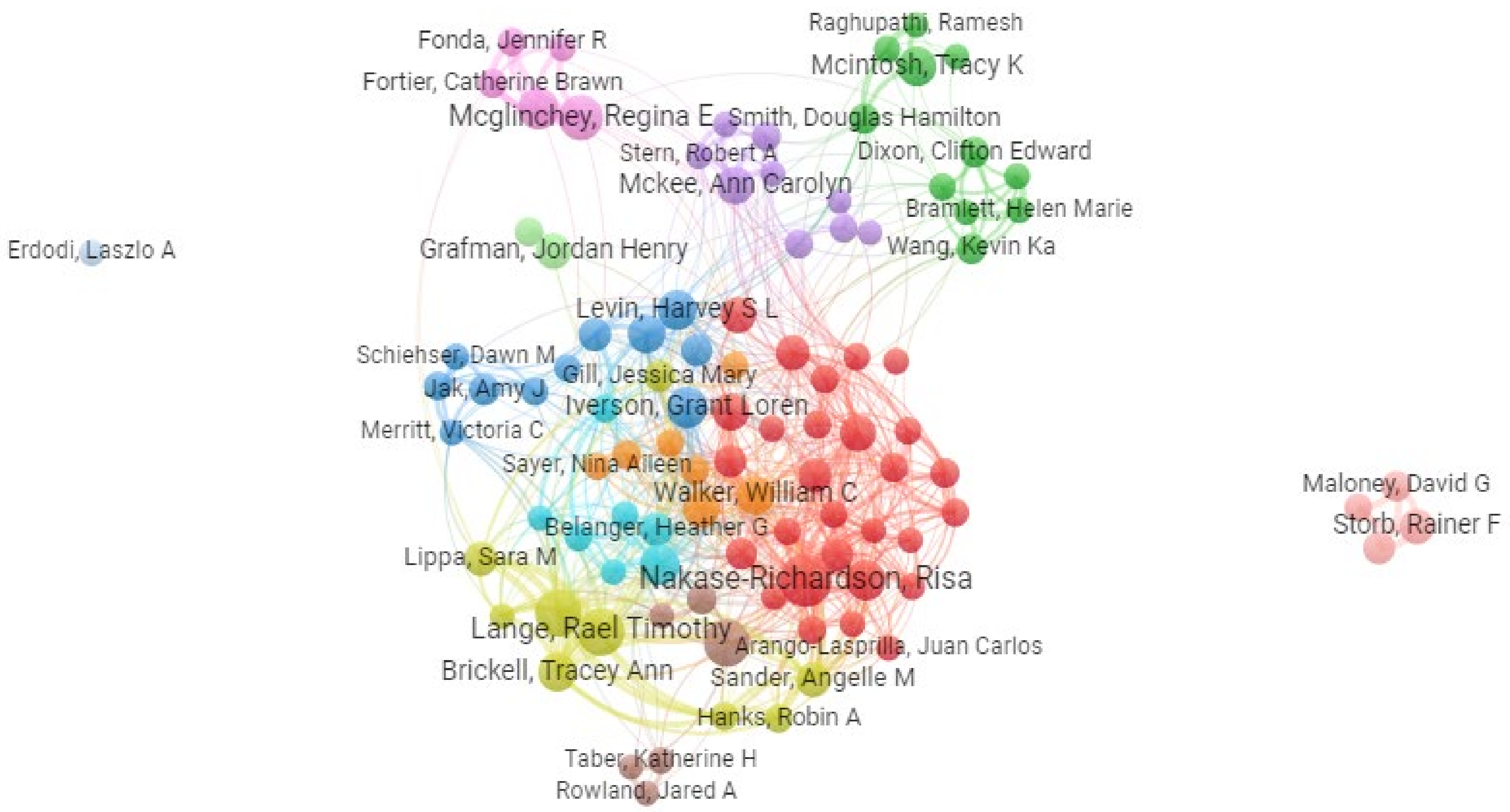
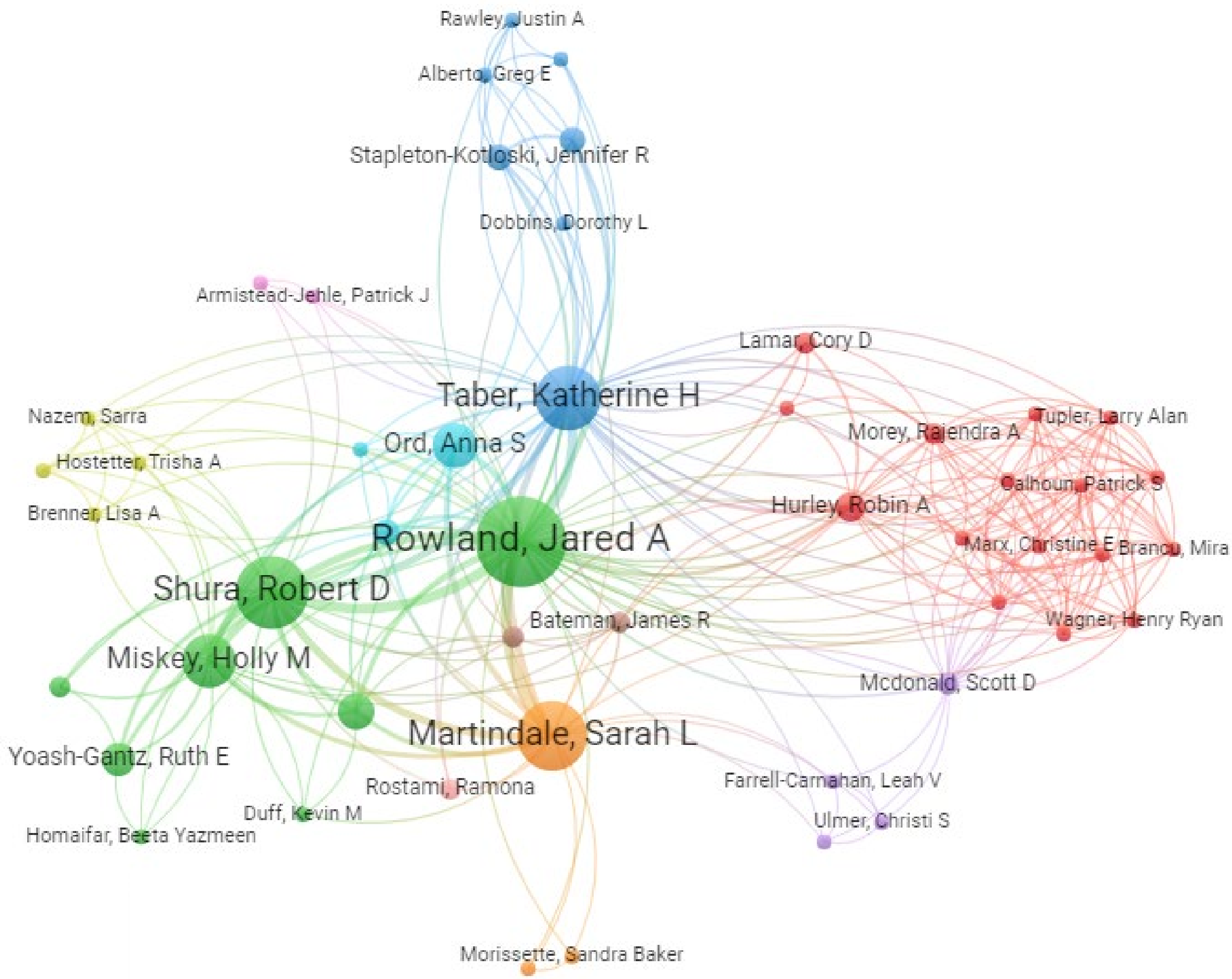



Image Credit: VOS Viewer

# Veteran TBI Subnetwork

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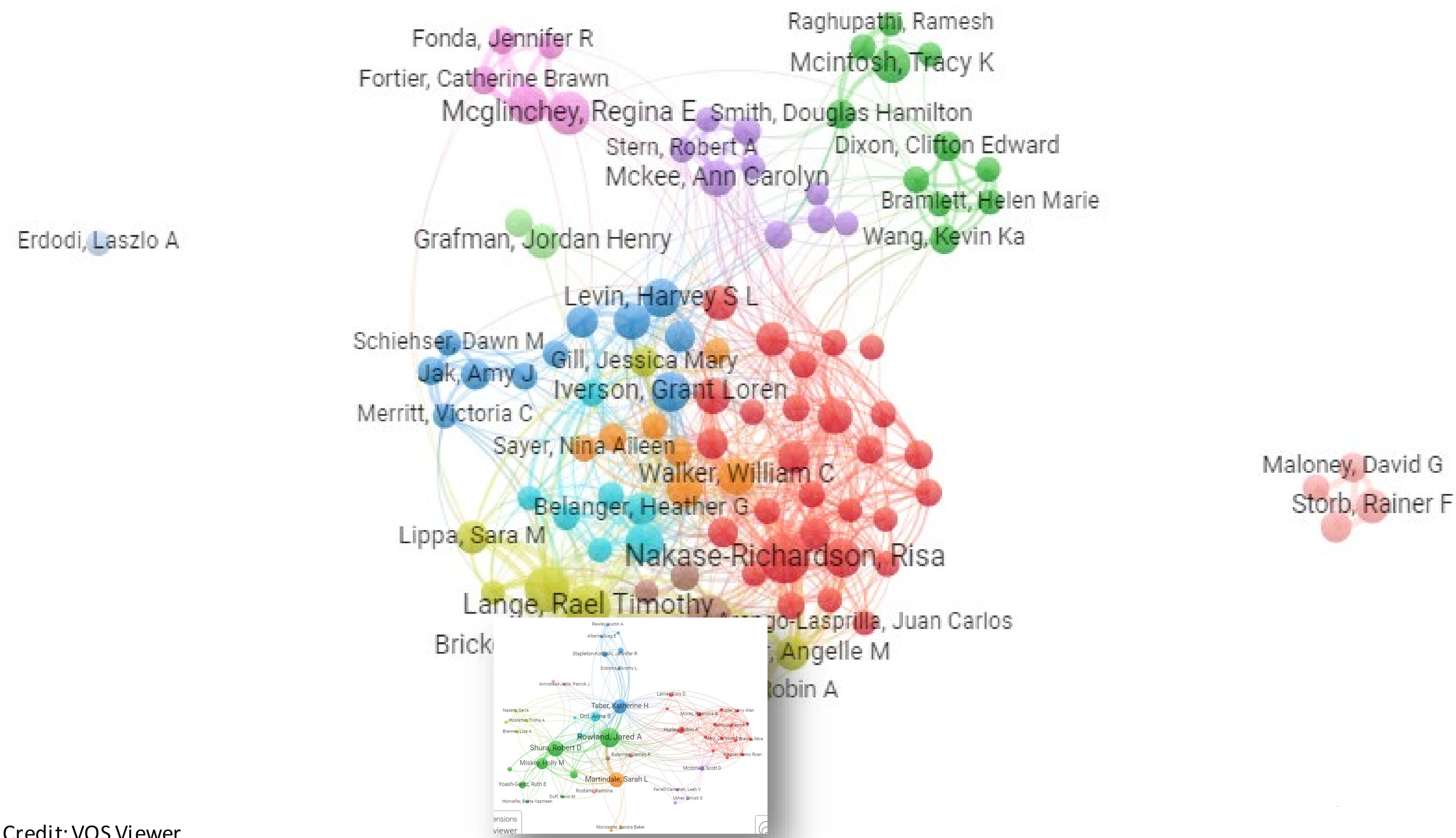


Image Credit: VOS Viewer

# Functional Connectome in PTSD and TBI

## PTSD

Connectivity Strength

- ↓ connectivity

Organization and Topology

- ↓ small-worldness (veterans; MEG)
- ↓ clustering coefficient (veterans; MEG)
- ↑ clustering coefficient (civilian; fMRI)
- ↑ global efficiency (civilian; fMRI)

## TBI

Connectivity Strength

- ↑ connection strength in DMN and Rich Club

Organization and Topology

- ↑ small-worldness (veterans; MEG)
- ↑ clustering coefficient (veterans; MEG)
- ↓ modularity (civilian; fMRI)
- ↓ local efficiency in DMN (civilians)
- Hyperconnectivity

# Objective

**Purpose**

Clarify variability in connectivity strength as well as organization and topology of the functional connectome in Veterans with PTSD, mild TBI, and/or blast exposure

**Hypotheses**

- ↑ Connection strength in TBI
- ↓ Connection strength in PTSD
- ↑ Organization in TBI
- ↓ Organization in PTSD

# Method

# Sample

**Study 34, Chronic Effects of Neurotrauma Consortium (CENC)**

- **Inclusion:** deployed after 9/11/2001, combat exposure
- **Exclusion:** moderate to severe TBI, major neurologic disorder, serious mental illness, dementia, current substance use disorder, psychosis, ferrous metal, electrical implant, pregnancy, performance or symptom validity failure
- ***N* = 181** (neuroimaging sample)

**Measures**

- Salisbury Blast Interview (SBI)
- Mid-Atlantic MIRECC Assessment of TBI (MMA-TBI)
- Structured Clinical Interview for DSM-IV (SCID)
- Clinician Administered PTSD Scale (CAPS-5)
- Magnetoencephalography (MEG)

Rowland et al., 2020a; Rowland et al., 2020b; First et al., 1991; Weathers et al., 2013

# Sample Characteristics

**Table 1. Descriptive Statistics of Characterizing Variables**

| | |
|---|---|
| Age | 41.6 (10.2) |
| Female, *n* (%) | 22 (12%) |
| Minority, *n* (%) | 81 (45%) |
| Years education | 15.3 (2.2) |
| Estimated pre-morbid IQ | 99.4 (12.1) |
| Number of deployments | 2.8 (3.9) |
| Time since deployment (years) | 9.4 (3.7) |
| Deployment TBI, *n* (%) | 74 (41%) |
| Number of deployment TBI | 0.7 (1.1) |
| Time since injury (years) | 11.0 (4.1) |
| PTSD diagnosis, *n* (%) | 51 (28%) |
| Time since traumatic event (years) | 12.6 (7.7) |
| Branch of service | |
| Army, *n* (%) | 128 (71%) |
| Marines, *n* (%) | 17 (9%) |
| Navy, *n* (%) | 21 (12%) |
| Air Force, *n* (%) | 15 (8%) |

Values are presented as mean (standard deviation) unless otherwise indicated.

$N = 181$.

PTSD, post-traumatic stress disorder; TBI, traumatic brain injury; IQ, intelligence quotient.

Rowland et al., 2021

d) Pressure Change/Gradient

0 **none**
1 **slightly**, noticeable but not uncomfortable
2 noticeable and uncomfortable
3 **moderately**, results in minor pain or alteration in function
4 resulted in minor injury
5 **strongly**, resulted in greater than minor injury

# Measures

- **Current and Lifetime PTSD Diagnosis** were determined using the CAPS-5 and represented with mutually exclusive variables.
- **Deployment TBI** was determined using the MMA-TBI. The presence of blast related Deployment TBI and the presence of non-blast related Deployment TBI were used in analyses.
- **Blast Characteristics** were evaluated using the Salisbury Blast Interview (SBI). This included frequency of blast exposure and severity of blast exposure.
- **Covariates**: age, sex, minority status and time since deployment acquired TBI.

Weathers et al., 2018; Rowland et al., 2020a; Rowland et al., 2020b

# Functional Connectome

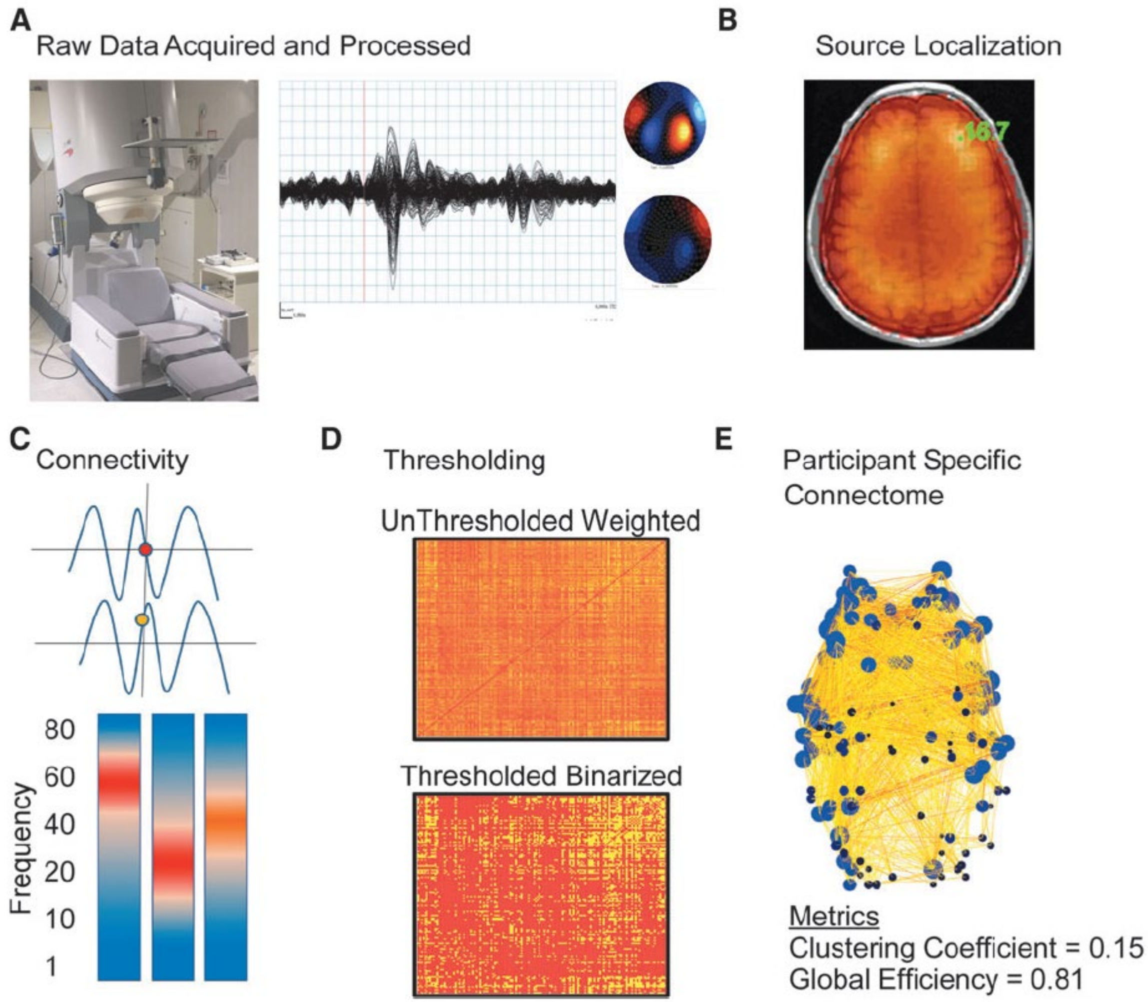


Image Credit: Rowland et al., 2021

# Data Analysis

| | Initial Model |
|---|---|
| Covariates | Age<br>Sex<br>Minority Status<br>Time Since TBI |
| Main Effects | PTSD<br>Blast TBI<br>Non-Blast TBI<br>PTSD*Blast TBI<br>PTSD*Non-Blast TBI |

Rowland et al., 2021

# Data Analysis

d) Pressure Change/Gradient

0 **none**
1 **slightly**, noticeable but not uncomfortable
2 noticeable and uncomfortable
3 **moderately**, results in minor pain or alteration in function
4 resulted in minor injury
5 **strongly**, resulted in greater than minor injury

| | Initial Model | Blast Frequency |
|---|---|---|
| Covariates | Age<br>Sex<br>Minority Status<br>Time Since TBI | Age<br>Sex<br>Minority Status<br>Time Since TBI |
| Main Effects | PTSD<br>Blast TBI<br>Non-Blast TBI<br>PTSD*Blast TBI<br>PTSD*Non-Blast TBI | PTSD<br>**TBI**<br>**PTSD*TBI**<br>**Blast Frequency**<br>**TBI*Blast Frequency** |

Rowland et al., 2021

# Data Analysis

d) Pressure Change/Gradient

| | |
|---|---|
| 0 | **none** |
| 1 | **slightly**, noticeable but not uncomfortable |
| 2 | noticeable and uncomfortable |
| 3 | **moderately**, results in minor pain or alteration in function |
| 4 | resulted in minor injury |
| 5 | **strongly**, resulted in greater than minor injury |

| | Initial Model | Blast Frequency | Blast Severity |
|---|---|---|---|
| Covariates | Age<br>Sex<br>Minority Status<br>Time Since TBI | Age<br>Sex<br>Minority Status<br>Time Since TBI | Age<br>Sex<br>Minority Status<br>Time Since TBI |
| Main Effects | PTSD<br>Blast TBI<br>Non-Blast TBI<br>PTSD*Blast TBI<br>PTSD*Non-Blast TBI | PTSD<br>**TBI**<br>**PTSD*TBI**<br>**Blast Frequency**<br>**TBI*Blast Frequency** | PTSD<br>TBI<br>PTSD*TBI<br>**Blast Severity**<br>**TBI*Blast Severity** |

Rowland et al., 2021

# Results

# Blast TBI

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38:3086–3096 (November 15, 2021)
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ORIGINAL ARTICLE IMAGING

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**Abstract**

**Table 3. Parameter Estimates for Connectome Metrics Significantly Predicted by the Model including Blast and Non-Blast Deployment TBI**

| | *PTSD* | *Blast deployment TBI* | *PTSD- blast TBI interaction* | *Non-blast deployment TBI* | *PTSD- non-blast TBI interaction* | *Time since injury (days)* |
|---|---|---|---|---|---|---|
| Nodes | 9.52* | -0.56 | -12.47* | -6.68 | -18.03* | 0.002* |
| Average degree | -0.02 | -0.02 | 0.054* | -0.02 | -0.04 | 0.000 |
| Connection Strength | -0.01 | -0.028* | 0.048* | 0.01 | -0.02 | 0.000 |
| Minimum Threshold | -0.15 | -0.25* | 0.42 | -0.06 | -0.04 | 0.000 |
| K-Core Degree | -0.19 | -0.59 | 0.77 | -0.54 | 0.44 | 0.0002* |
| K-Core Nodes | -1.54 | 1.55 | -3.72 | 5.53 | -4.04 | -0.0014* |
| Alpha Connections | 60.69 | -41.31 | -36.33 | 34.85 | -128.50 | -0.035* |
| Gamma Connections | -95.84 | -8.25 | 54.53 | 3.03 | 104.12 | 0.034* |

*N* = 181.
*Parameter estimate significant at $p < 0.05$.
Parameter estimates are not standardized. Models presented are significant following false discovery rate correction at $p < 0.05$.
PTSD, post-traumatic stress disorder; TBI, traumatic brain injury.

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| | Model R^2 | Deployment TBI | PTSD | PTSD-TBI interaction | Blast exposure frequency | Frequency-TBI interaction | Time since injury (days) |
|---|---|---|---|---|---|---|---|
| Nodes | 0.17 | -2.58 | 9.23* | -14.39* | 0.00 | 0.00 | 0.00 |
| K-core Degree | 0.33 | -0.66* | -0.19 | 0.63 | -0.00 | 0.00 | 0.0002* |
| K-core Nodes | 0.13 | 2.49 | -1.49 | -3.63 | -0.00 | -0.00 | -0.001* |
| Number of modules | 0.12 | -1.61 | -2.30 | 1.83 | -0.00 | 0.00 | 0.0007* |
| Theta Connections | 0.23 | -1.03 | 21.30 | 17.01 | 0.03* | 0.00 | -0.001 |
| Alpha Connections | 0.27 | -12.39 | 62.74 | -44.26 | -0.02 | -0.08 | -0.032* |
| Gamma Connections | 0.22 | -9.46 | -95.60 | 64.51 | -0.00 | 0.02 | 0.035* |

$N = 181$. Parameter estimates are not standardized. Models presented are significant following false discovery rate correction at $p < 0.05$.
*Parameter estimate significant at $p < 0.05$.
PTSD, post-traumatic stress disorder; TBI, traumatic brain injury.

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| K-core Nodes | 0.13 | 2.49 | -1.49 | -3.63 | -0.00 | -0.00 | -0.001* |
| Number of modules | 0.12 | -1.61 | -2.30 | 1.83 | -0.00 | 0.00 | 0.0007* |
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| | Model R^2 | Deployment TBI | PTSD | PTSD-TBI interaction | Blast exposure severity | Severity-TBI interaction | Time since injury (days) |
|---|---|---|---|---|---|---|---|
| Nodes | 0.18 | -7.13 | 9.47* | -14.74* | -0.44 | 2.09 | 0.002 |
| Average degree | 0.99 | -0.06* | -0.02 | 0.03 | -0.00 | 0.01 | -0.000 |
| Mean connection frequency | 0.10 | -4.63 | -2.92 | 2.87 | -2.02 | 2.38 | 0.002* |
| K-core Degree | 0.32 | -0.53 | -0.22 | 0.73 | 0.07 | -0.06 | 0.0002* |
| K-core Nodes | 0.14 | 6.39 | -2.18 | -2.67 | 1.16 | -2.20 | -0.001* |
| Alpha Connections | 0.26 | 45.36 | 46.56 | -37.62 | 24.95 | -41.40 | -0.04* |
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Blast TBI

Connections / Communication

Blast TBI + PTSD

Connections / Communication

Structure

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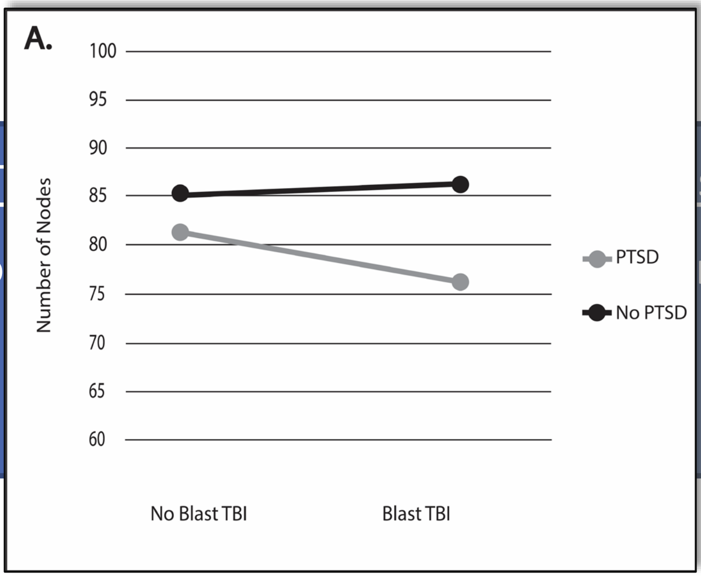
Blast T

Connections / Co




st TBI + PTSD

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Deployment TBI

Blast

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Deployment TBI

X

Blast

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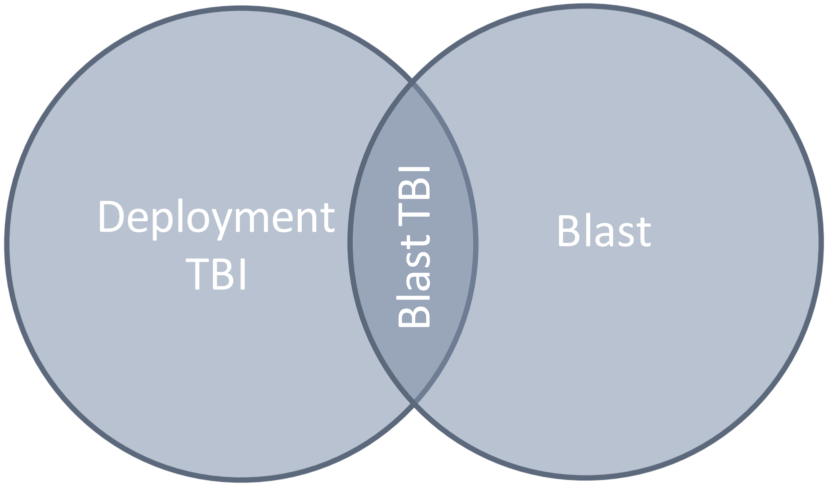

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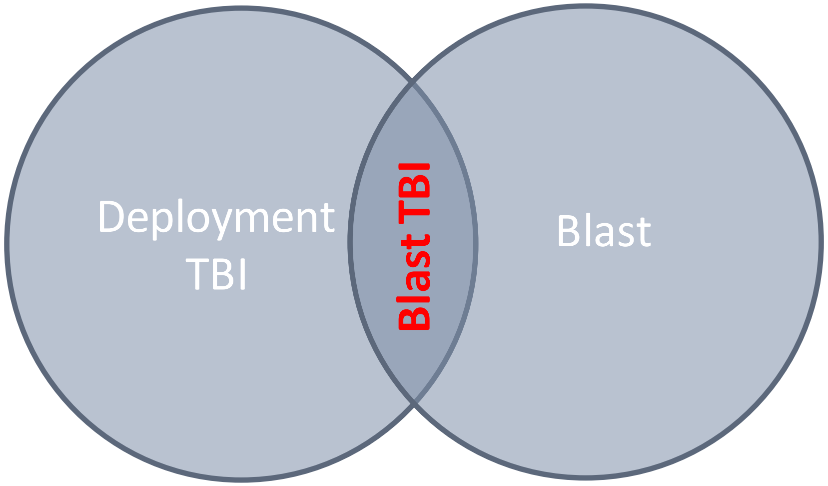

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Time since injury is an important consideration

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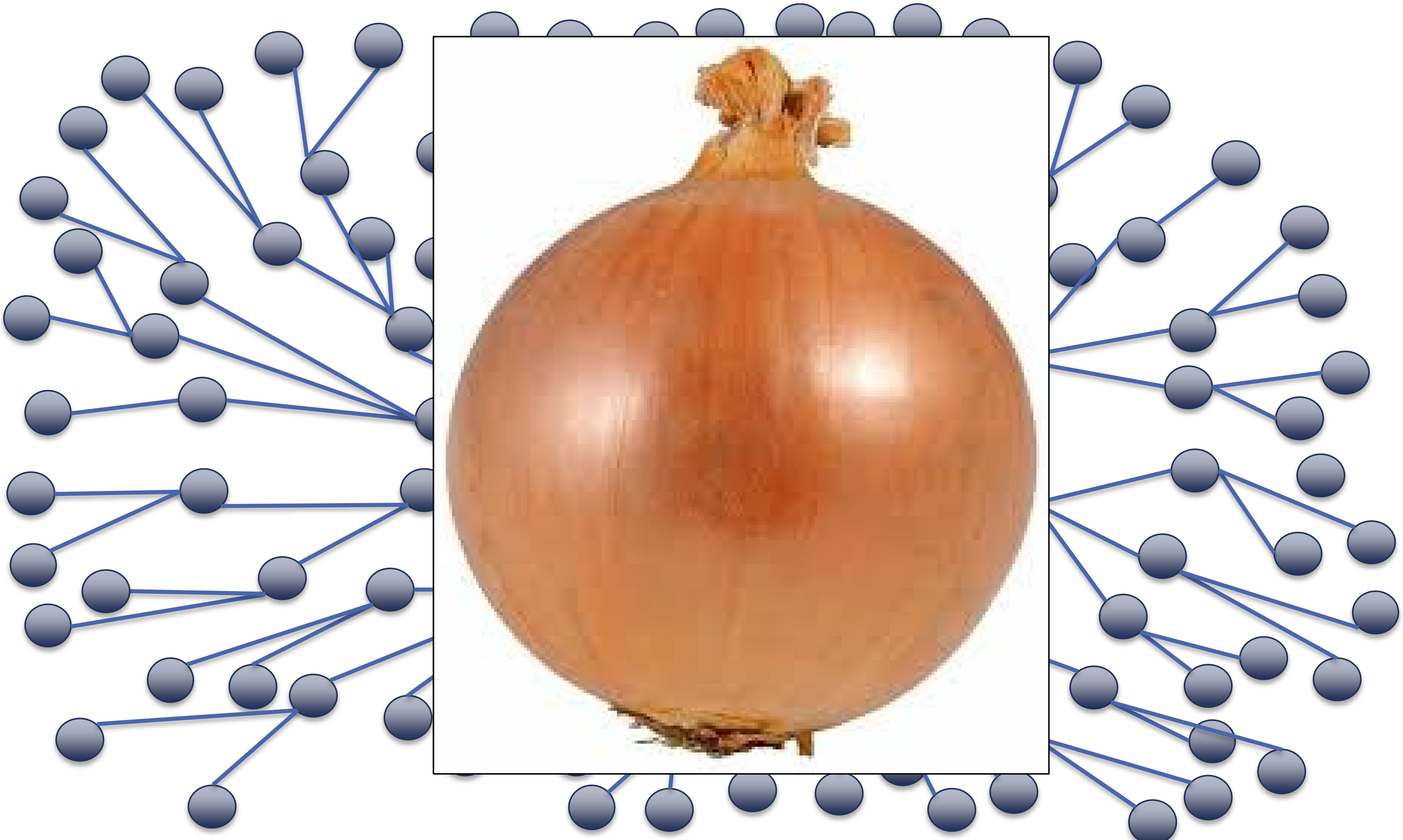

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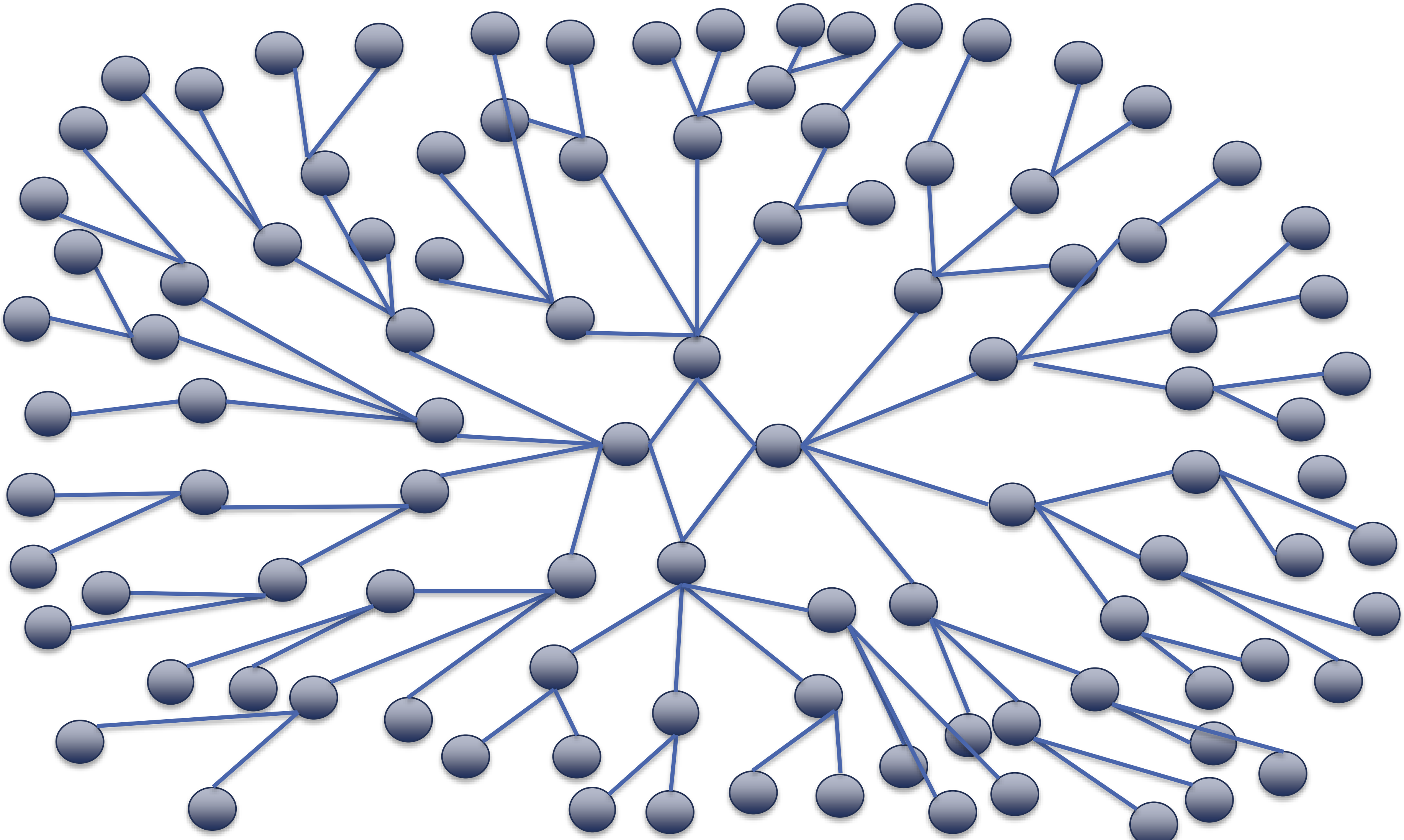

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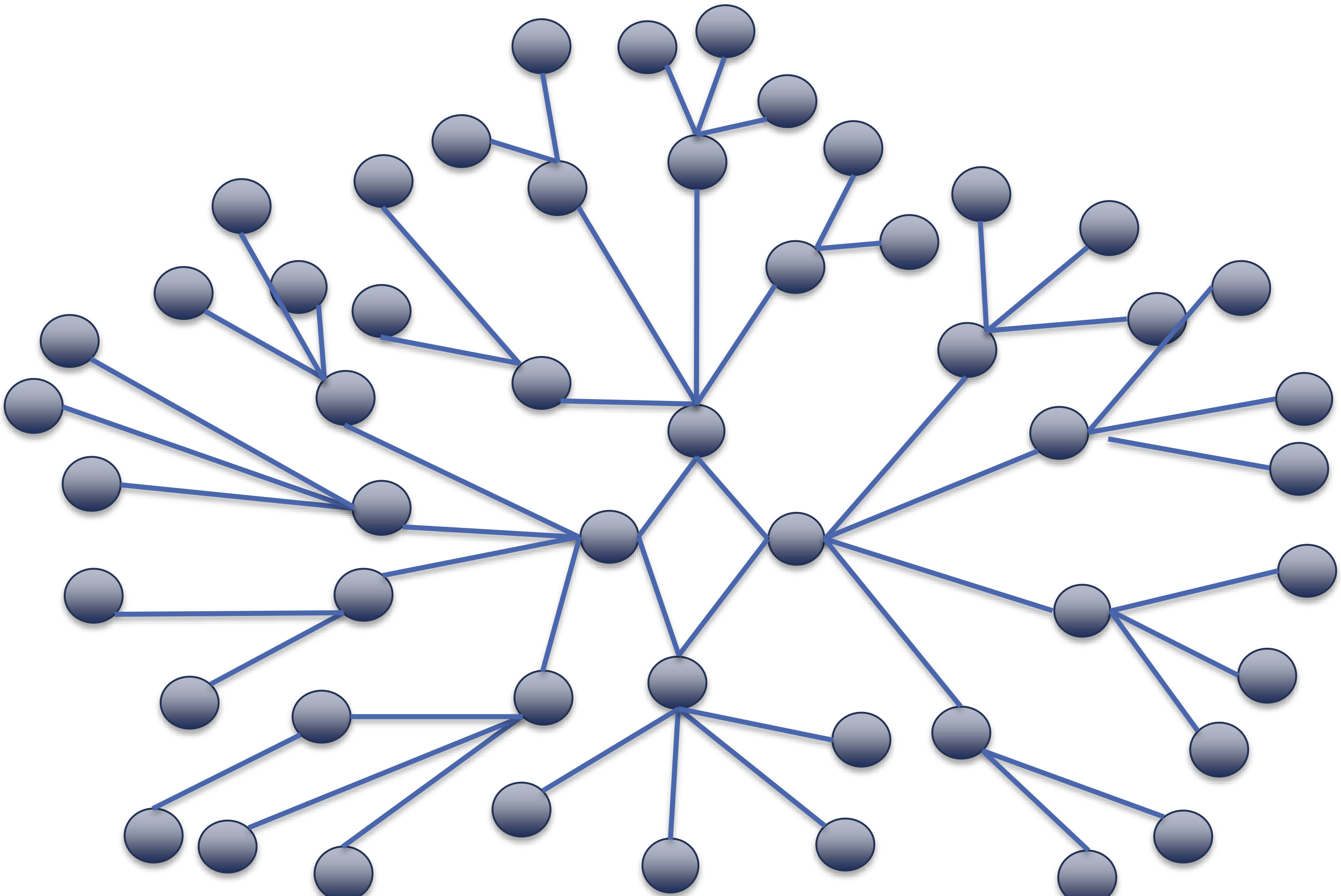

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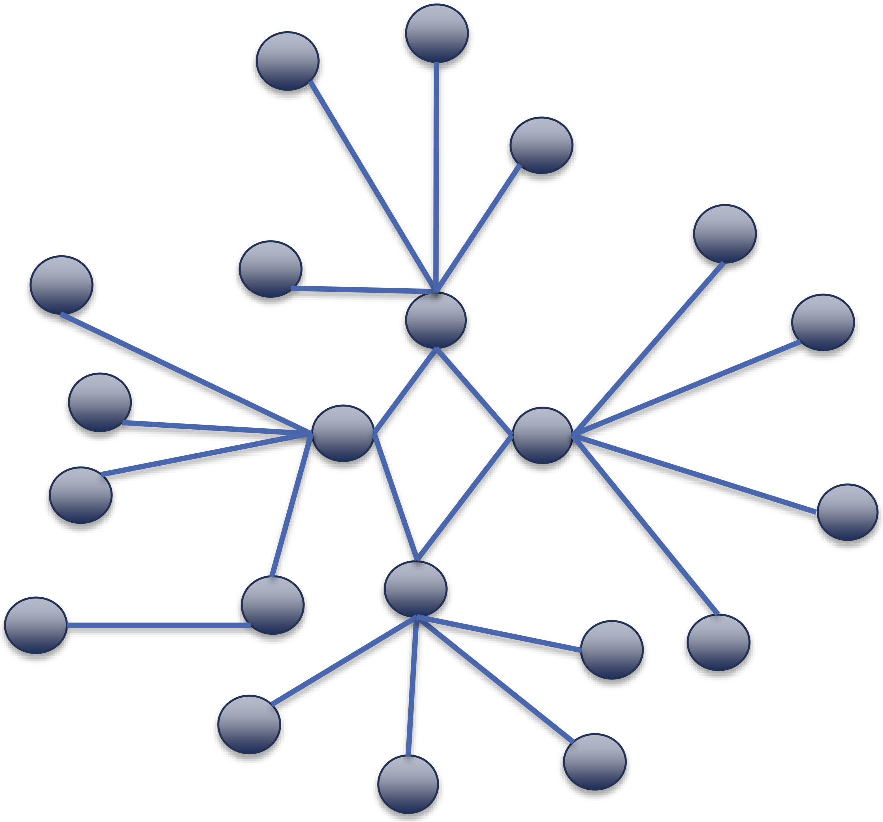

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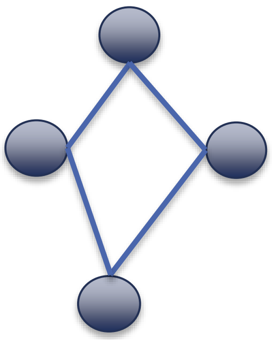

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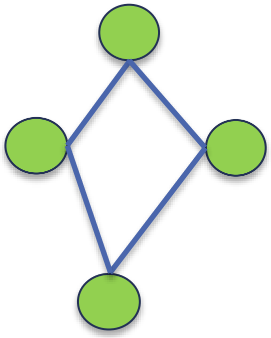
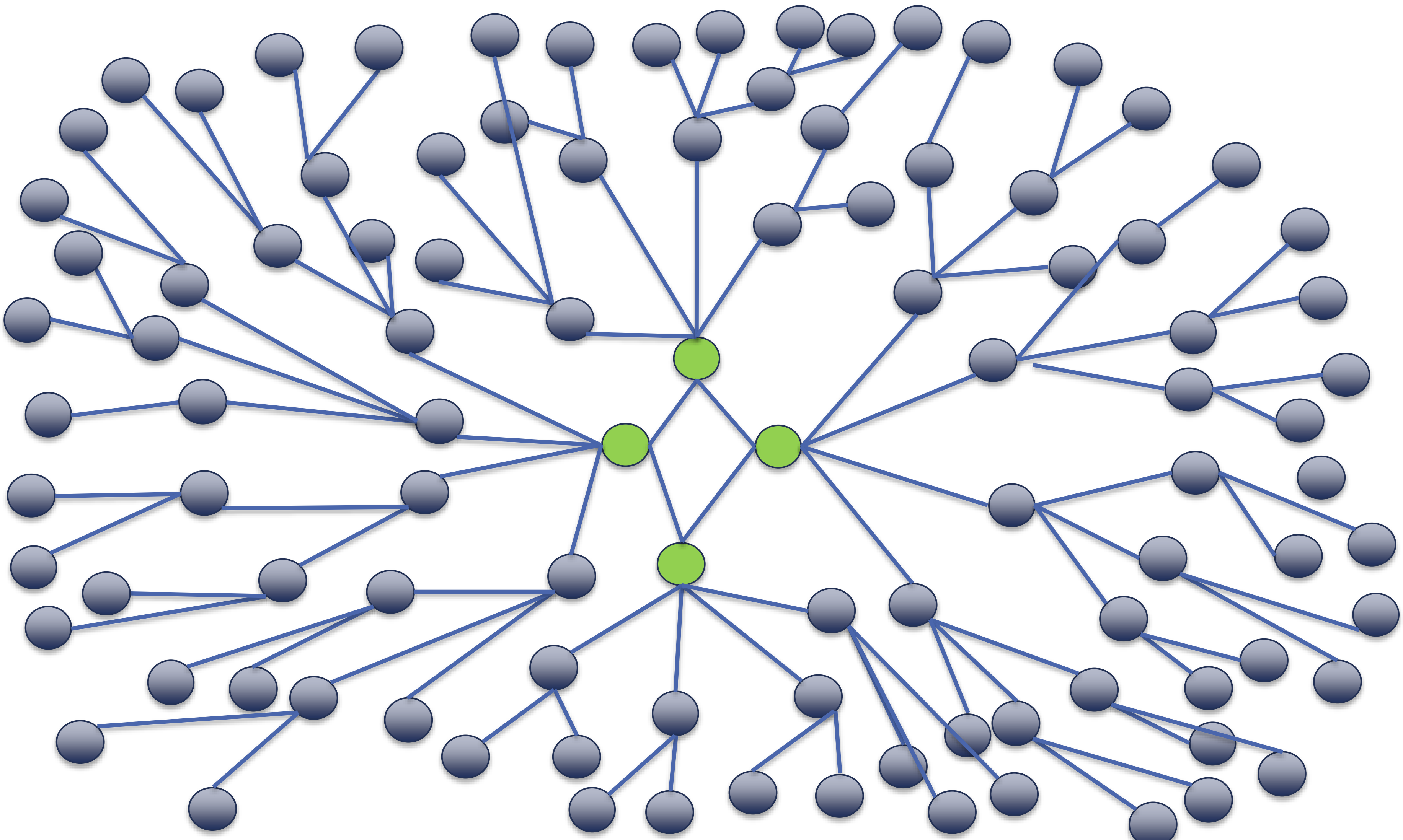


# Discussion



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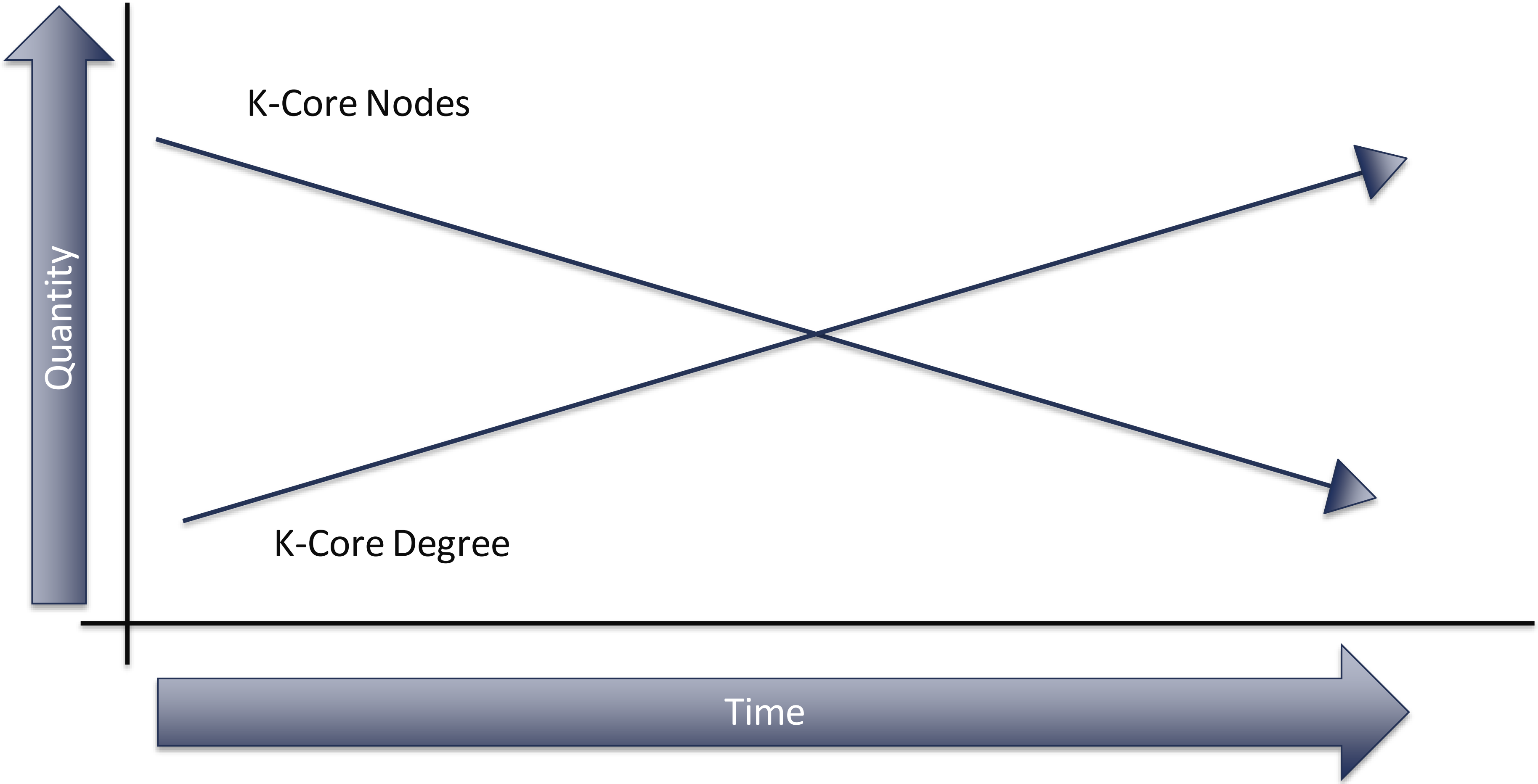

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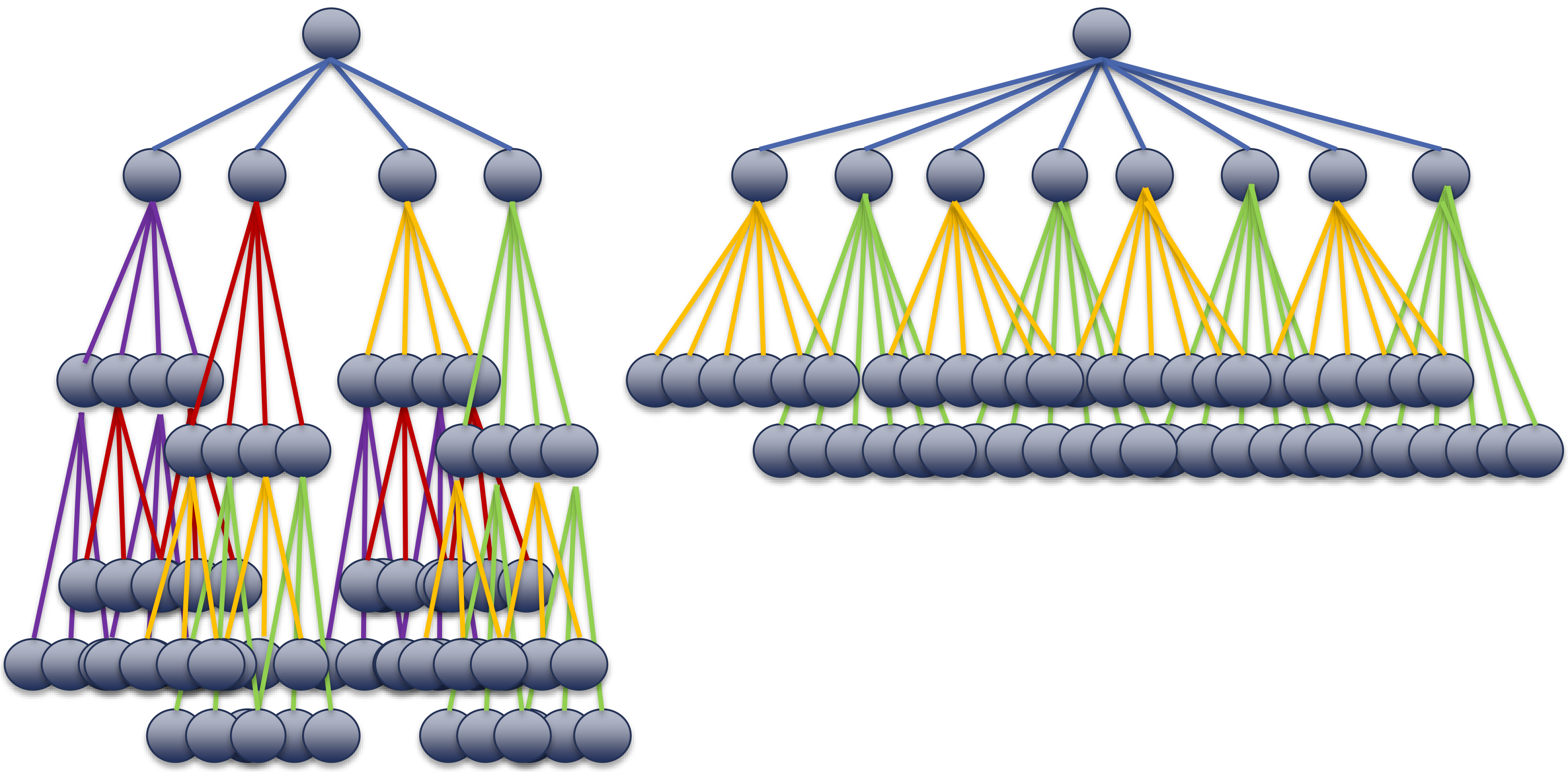

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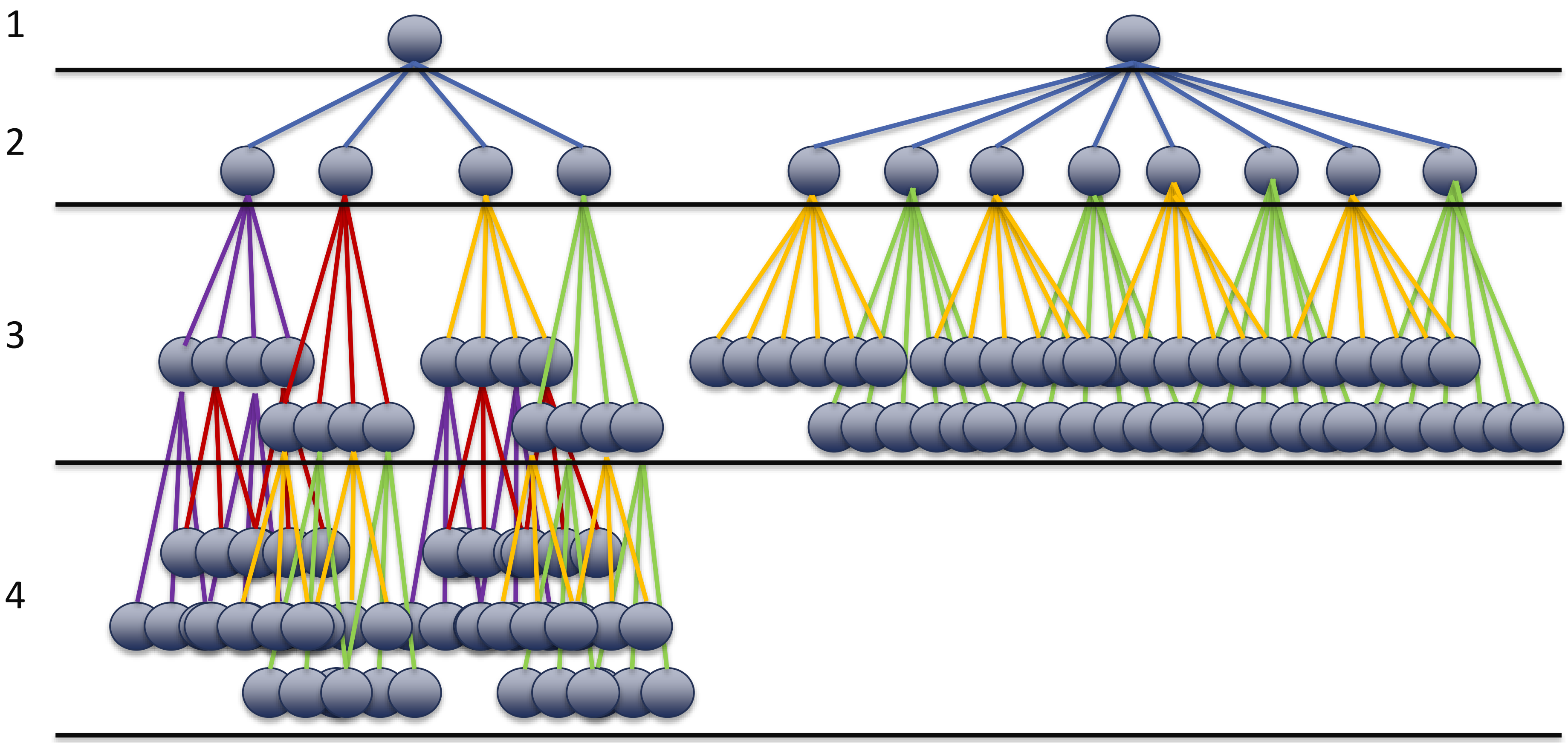

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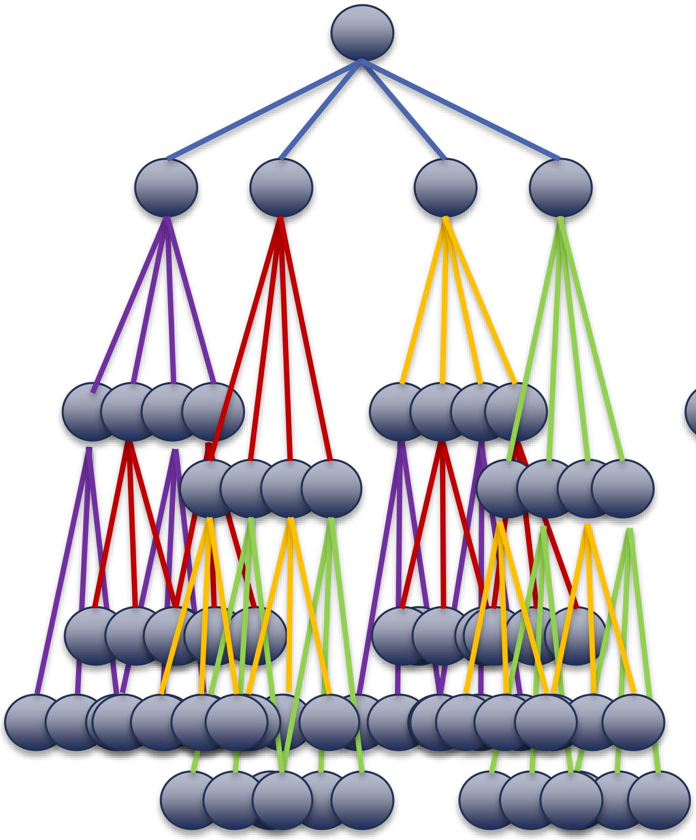

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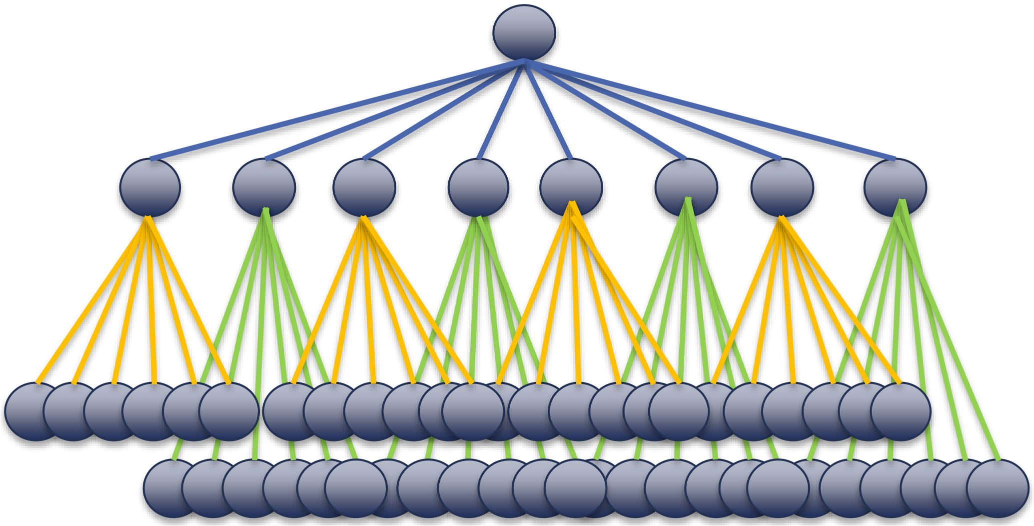

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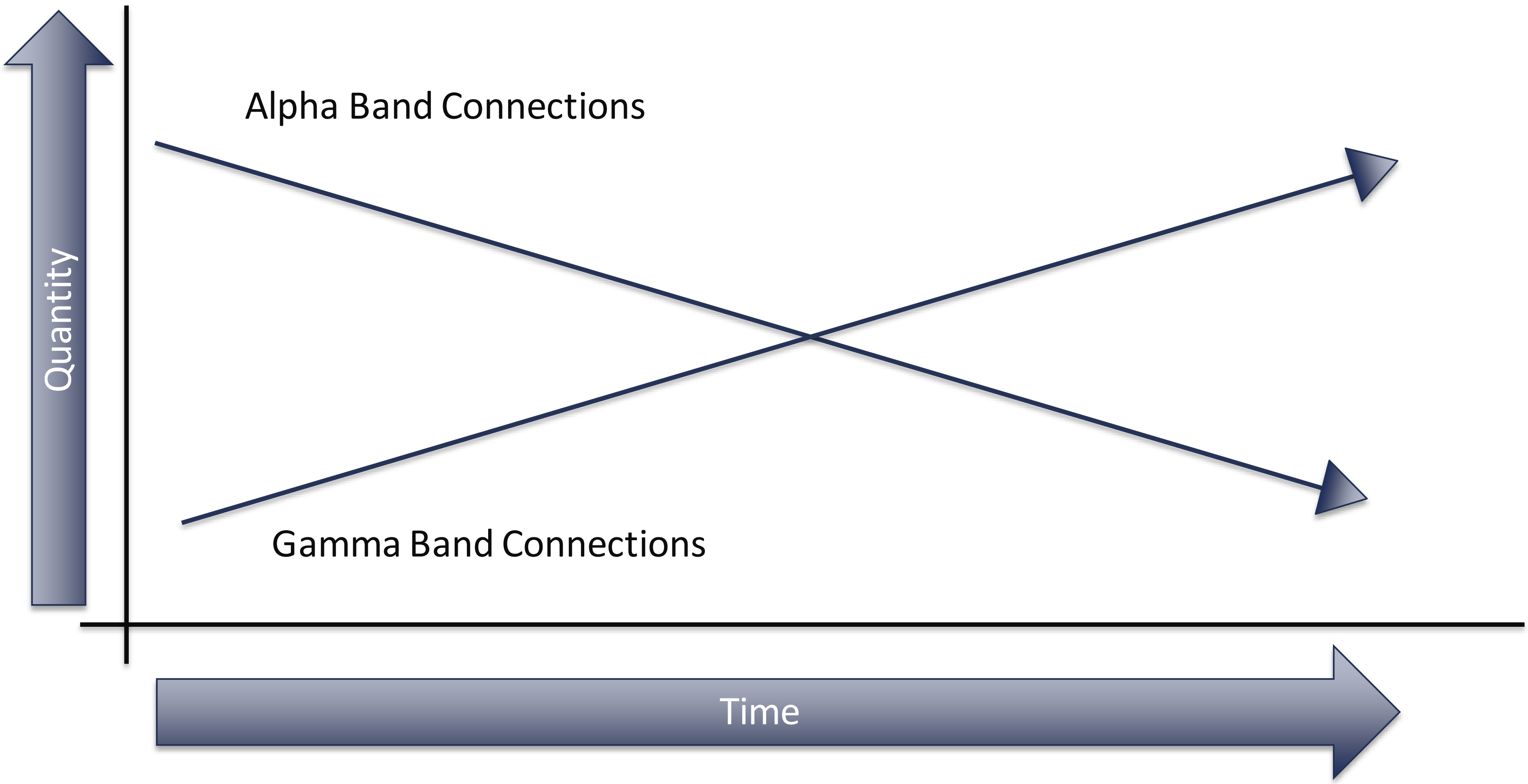
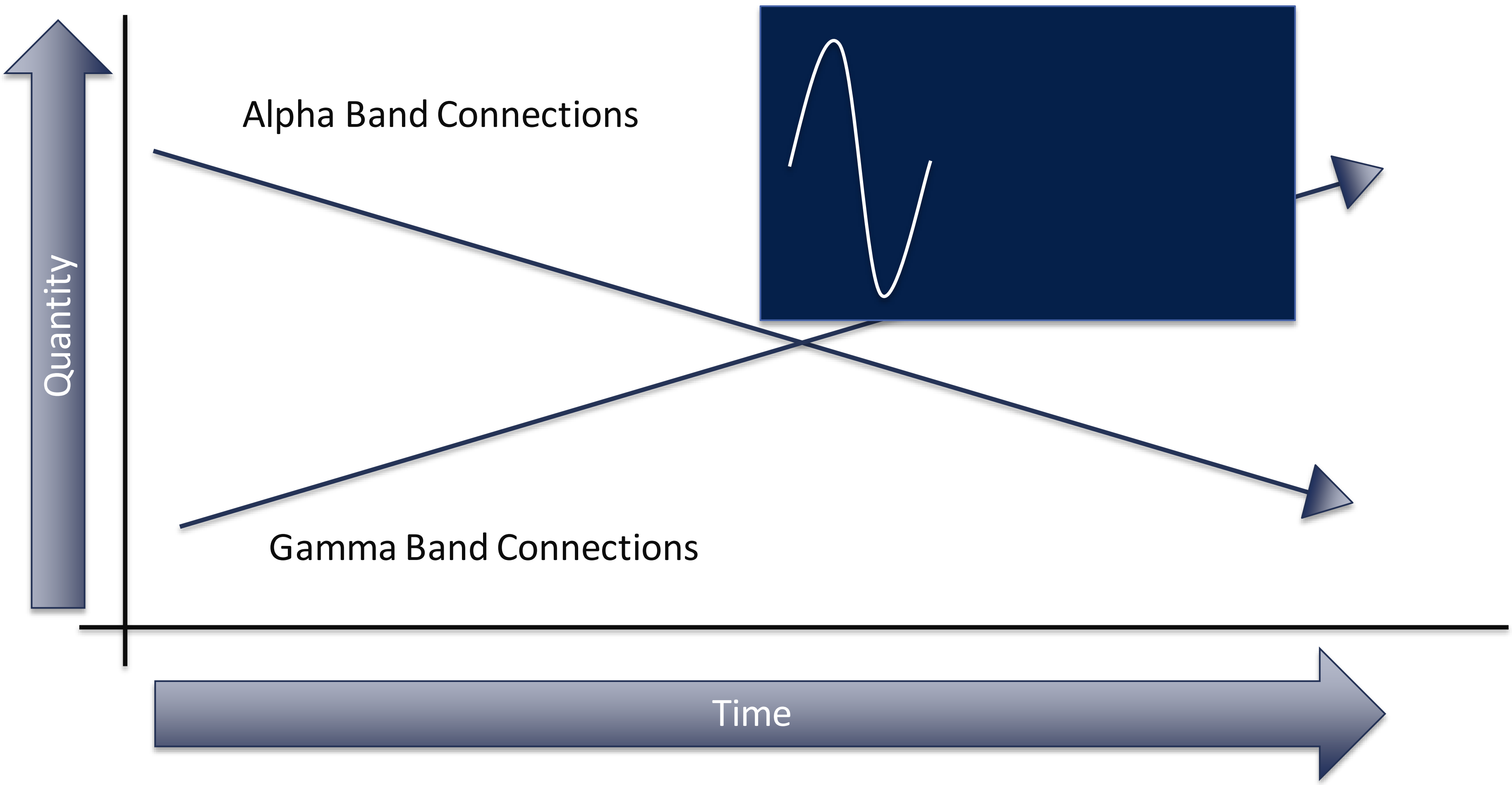
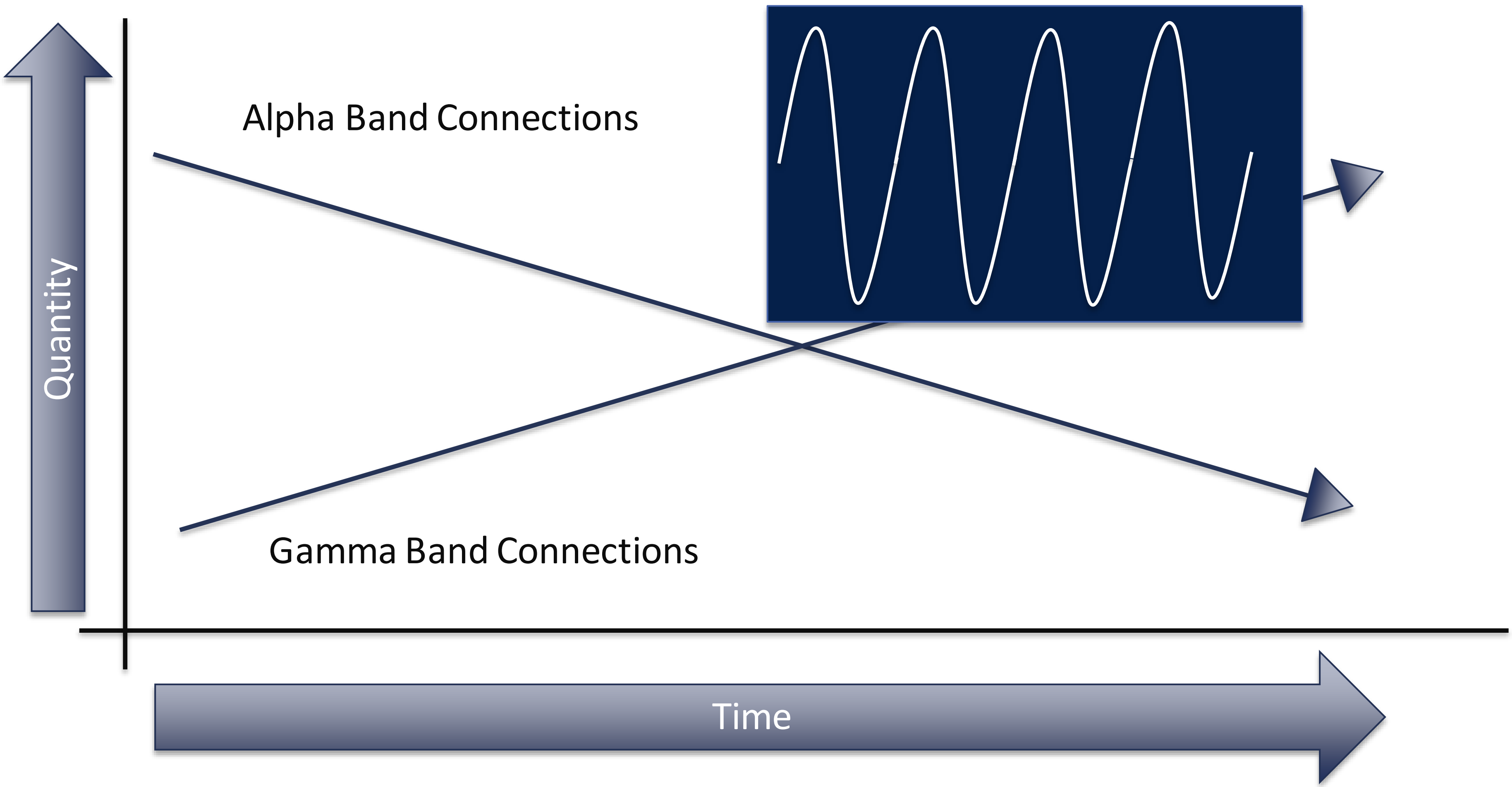

Alpha Band Connections
Gamma Band Connections
Quantity
Time

# Discussion



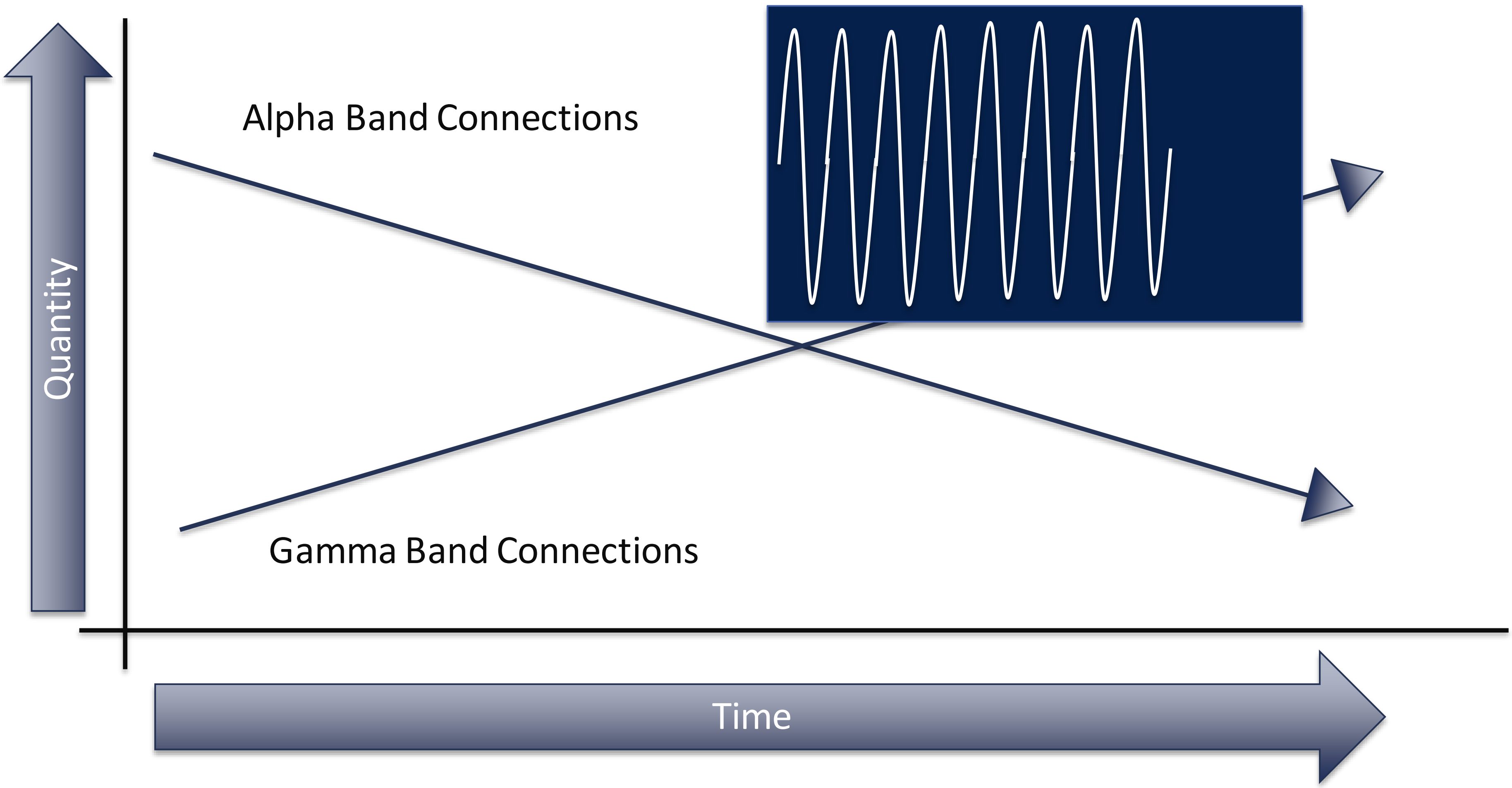
Alpha Band Connections
Gamma Band Connections
Quantity
Time

# Discussion

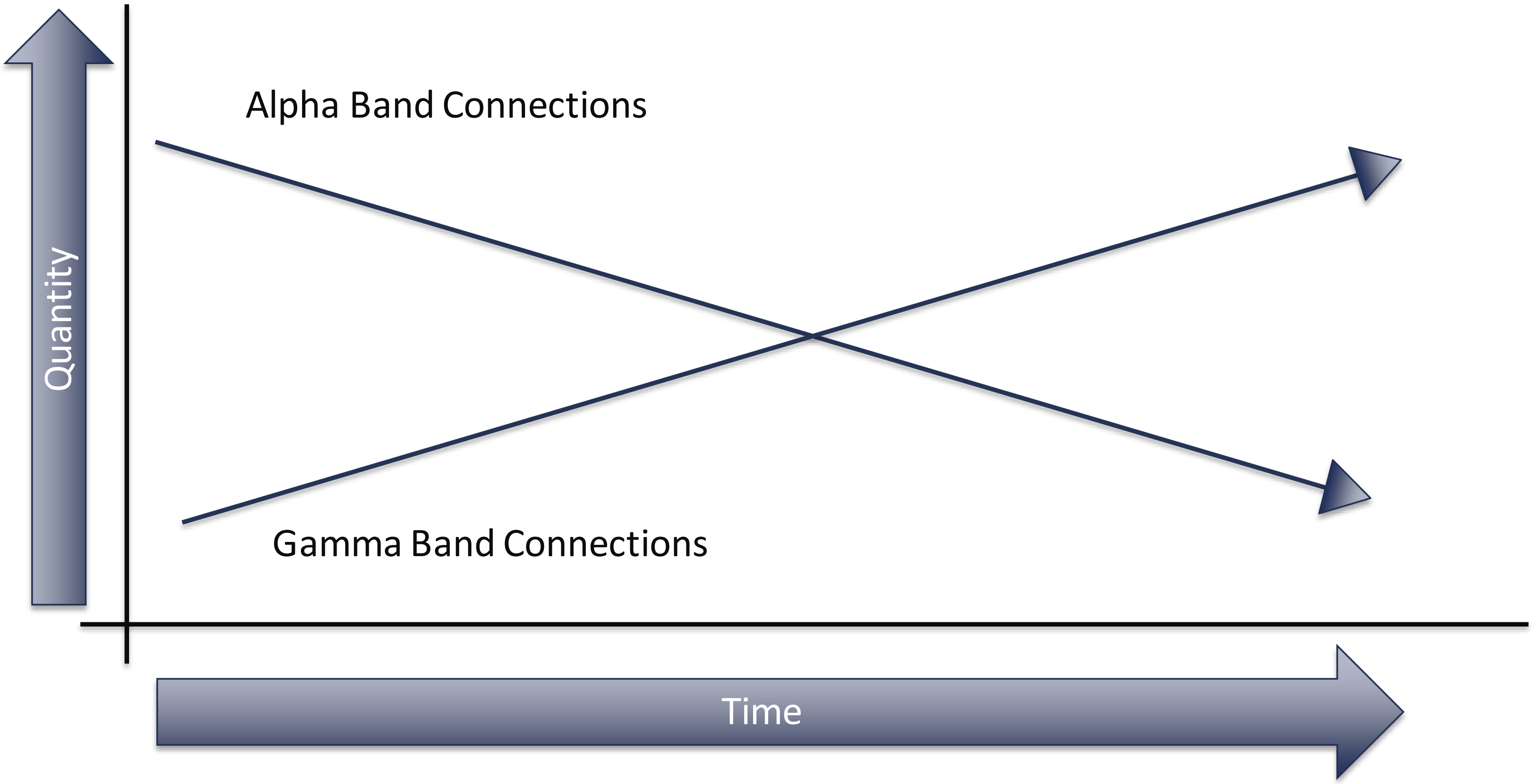


Quantity
Alpha Band Connections
Gamma Band Connections
Time

# Discussion


Alpha Band Connections
Gamma Band Connections
Quantity
Time

# Discussion



Quantity
Alpha Band Connections
Gamma Band Connections
Time

# Discussion

**Deployment TBI increases risk for developing PTSD**

- Fear learning
- Changes in brain structure

Yurgil et al., 2014; Stein et al., 2015; Glenn et al., 2017; Terrio et al., 2009; Rowland et al., 2020

# Discussion

**Deployment TBI increases risk for developing PTSD**

- Fear learning
- Changes in brain structure

**Blast is an important characteristic for TBI**

# Discussion

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Published in final edited form as:
*Brain Imaging Behav.* 2017 August ; 11(4): 1129–1138. doi:10.1007/s11682-016-9593-7.

## White Matter Abnormalities are Associated With Overall Cognitive Status in Blast-Related mTBI

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### Abstract

Blast-related mild traumatic brain injury (mTBI) is a common injury of the Iraq and Afghanistan Wars. Research has suggested that blast-related mTBI is associated with chronic white matter abnormalities, which in turn are associated with impairment in neurocognitive function. However, findings are inconsistent as to which domains of cognition are affected by TBI-related white matter disruption. Recent evidence that white matter abnormalities associated with blast-related mTBI are spatially variable raises the possibility that the associated cognitive impairment is heterogeneous. Thus, the goals of this study were to examine (1) whether mTBI-related white matter abnormalities are associated with overall cognitive status and (2) whether white matter abnormalities provide a mechanism by which mTBI influences cognition. Ninety-six Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans were assigned to one of three groups: no-TBI, mTBI without loss of consciousness (LOC) (mTBI−LOC), and mTBI with LOC (mTBI+LOC). Participants were given a battery of neuropsychological tests that were selected for their sensitivity to mTBI. Results showed that number of white matter abnormalities was associated with the odds of having clinically significant cognitive impairment. A mediation analysis revealed that mTBI+LOC was indirectly associated with cognitive impairment through

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ORIGINAL RESEARCH
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## Blast Exposure, White Matter Integrity, and Cognitive Function in Iraq and Afghanistan Combat Veterans

Iliyan Ivanov, Corey Fernandez, Effie M. Mitsis, Dara L. Dickstein, Cheuk Y. Tang, Jessie Simantov, Charlene Bang, Erin Moshier, Gregory A. Elder and Erin A. Hazlett

OPEN ACCESS

The long-term effects of blast exposure are a major health concern for combat veterans returning from the recent conflicts in Iraq and Afghanistan.

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## White Matter Compromise in Veterans Exposed to Primary Blast Forces

*Katherine H. Taber, PhD; Robin A. Hurley, MD; Courtney C. Haswell, MS; Jared A. Rowland, PhD; Susan D. Hurt, PhD; Cory D. Lamar, MD; Rajendra A. Morey, MD*

**Objective:** Use diffusion tensor imaging to investigate white matter alterations associated with blast exposure with or without acute symptoms of traumatic brain injury (TBI). **Participants:** Forty-five veterans of the recent military conflicts included 23 exposed to primary blast without TBI symptoms, 6 having primary blast with mild TBI, and 16 unexposed to blast. **Design:** Cross-sectional case-control study. **Main Measures:** Neuropsychological testing and diffusion tensor imaging metrics that quantified the number of voxel clusters with altered fractional anisotropy (FA) radial diffusivity, and axial diffusivity, regardless of their spatial location. **Results:** Significantly lower FA and higher radial diffusivity were observed in veterans exposed to primary blast with and without mild TBI relative to blast-unexposed veterans. Voxel clusters of lower FA were spatially dispersed and heterogeneous across affected individuals. **Conclusion:** These results suggest that lack of clear TBI symptoms following primary blast exposure may not accurately reflect the extent of brain injury. If confirmed, our findings would argue for supplementing the established approach of making diagnoses based purely on clinical history and observable acute symptoms with novel neuroimaging-based diagnostic criteria that "look below the surface" for pathology. **Key words:** *diffusion tensor imaging (DTI), diffusivity, fractional anisotropy, mild traumatic brain injury (mTBI), military veterans, primary blast, subconcussive blast exposure, white matter*

ALTHOUGH EXPOSURE to explosive forces emanating from bombs and other devices is increasing among civilians and is common in veterans of recent military conflicts in Iraq and Afghanistan, relatively little is known about the consequences to the brain.

DOI: 10.1097/HTR.0000000000000030

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# Discussion

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]

**Abstract**

Combat military and civilian law enforcement personnel may be exposed to repetitive low-intensity blast event[s …] training and operations. Persons who use explosives to gain entry (i.e., breach) into buildings are known as "breac[hers …] dynamic entry personnel. Breachers operate under the guidance of established safety protocols, but despite these pre[cautions …] breachers who are exposed to low-level blast throughout their careers frequently report performance deficits and symp[toms …] healthcare providers. Although little is known about the etiology linking blast exposure to clinical symptoms in […] animal studies demonstrate network-level changes in brain function, alterations in brain morphology, vascular and [inflam]matory changes, hearing loss, and even alterations in gene expression after repeated blast exposure. To explore […] similar effects occur in humans, we collected a comprehensive data battery from 20 experienced breachers exposed […] throughout their careers and 14 military and law enforcement controls. This battery included neuropsychological asse[ssments …] blood biomarkers, and magnetic resonance imaging measures, including cortical thickness, diffusion tensor imaging […] matter, functional connectivity, and perfusion. To better understand the relationship between repetitive low-le[vel …] exposure and behavioral and imaging differences in humans, we analyzed the data using similarity-driven multi-vie[w …] reconstruction (SiMLR). SiMLR is specifically designed for multiple modality statistical integration using dimens[ionality] reduction techniques for studies with high-dimensional, yet sparse, data (i.e., low number of subjects and many […] subject). We identify significant group effects in these data spanning brain structure, function, and blood biomark[ers …]

**Keywords:** breachers; cortical thickness; diffusion tensor imaging; functional MRI; perfusion imaging; SiMLR

**Introduction**

Traumatic brain injury (TBI), particularly mild TBI, resulting from exposure to improvised explosive devices (IEDs) may be linked to long-term post-concussive sequelae and neuropathology.[1,2] These observations have fueled intensive research efforts to understand the underlying acute and cumulative injury mechanisms of blast exposure. A significant component of these efforts has been to assess the effects of repeated low-inten[sity …] exposure in populations, such as military and civilian […] forcement "breachers" who use explosives to gain (brea[ch …]) to buildings. One of the earliest studies of breachers […] Marine Corps personnel participating in a breacher trainin[g …] at Quantico, Virginia. Course instructors with extensive […] exposure to low-intensity blast events and students with sig[…] lower blast exposures were included in the analysis. F[…]

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Brain Imaging and Behavior (2014) 8:102–109
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ORIGINAL RESEARCH

## Preliminary findings of cortical thickness abnormalities in blast injured service members and their relationship to clinical findings

D. F. Tate · G. E. York · M. W. Reid · D. B. Cooper · L. Jones · D. A. Robin · J. E. Kennedy · J. Lewis

[…]w York 2013

[…]alities have been demon[strated …] [trau]matic brain injured (TBI) […]dies examining cortical […]ld TBI (mTBI). The pur[pose …] the effects and functional […] thickness in a small cohort […]S Service Members (SM). […]hrough blast injury were […]tched control SM without […]pants were active duty and […]nent. Subjects underwent […]ted anatomic images were […]e of tools. Cortical thick[ness …] groups and examined for […]y (TSI). Utilizing a large […]ts (BrainMap), significant […] used to determine the behavioral profiles most consistently associated with the specific ROI. In addition, clinical variables were examined as part of post-hoc analysis of functional relevance. Group comparisons controlling for age demonstrated several significant clusters of cortical thinning for the blast injured SM. After multiple comparisons correction (False Discovery Rate (FDR)), two left hemisphere clusters remained significant (left superior temporal (STG) and frontal (SFG) gyri). No clusters were significantly correlated with TSI after FDR correction. Behavioral analysis for the STG and SFG clusters demonstrated three significant behavioral/cognitive sub-domains, each associated with audition and language. Blast injured SMs demonstrated distinct areas of cortical thinning in the STG and SFG. These areas have been previously shown to be associated with audition and language. Post-hoc analyses of clinical records demonstrated significant abnormal audiology reports for the blast injured SM suggesting that the thinning in these ROIs might be related to injury to the external auditory system rather than direct injury to the brain from the blast. It is clear that additional replication is needed in much larger cohorts. Importantly, the combination of imaging tools and methods in this study successfully demonstrated the potential to define unique ROIs and functional correlates that can be used to design future studies.

**Keywords** TBI · Blast Injury · Mild TBI · Cortical thickness · Cognition · Behavior · FreeSurfer · MANGO

[…]er · J. E. Kennedy
[…], Contractor for the Henry […]ent of Military Medicine, […] (SAMMC), […]
[…] Center, San Antonio, TX, […]

*J Head Trauma Rehabil*
Vol. 36, No. 6, pp. 424–428


## Research Letter: Blast Exposure and Brain Volume

*Sarah L. Martindale, PhD; Robert D. Shura, PsyD, ABPP; Ramona Rostami, PhD; Katherine H. Taber, PhD; Jared A. Rowland, PhD*

**Objective:** To determine whether blast exposure is associated with brain volume beyond posttraumatic stress disorder (PTSD) diagnosis and history of traumatic brain injury (TBI). **Setting:** Veterans Affairs Medical Center. **Participants:** One hundred sixty-three Iraq and Afghanistan combat veterans, 86.5% male, and 68.10% with a history of blast exposure. Individuals with a history of moderate to severe TBI were excluded. **Main Measures:** Clinician-Administered PTSD Scale (CAPS-5), Mid-Atlantic MIRECC Assessment of TBI (MMA-TBI), Salisbury Blast Interview (SBI), and magnetic resonance imaging. Maximum blast pressure experienced from a blast event represented blast severity. **Methods:** Hierarchical regression analysis evaluated effects of maximum pressure experienced from a blast event on bilateral volume of hippocampus, anterior cingulate cortex, amygdala, orbitofrontal cortex, precuneus, and insula. All analyses adjusted for effects of current and lifetime PTSD diagnosis, and a history of deployment mild TBI. **Results:** Maximum blast pressure experienced was significantly associated with lower bilateral hippocampal volume (left: $\Delta R2 = 0.032$, $P < .001$; right: $\Delta R2 = 0.030$, $P < .001$) beyond PTSD diagnosis and deployment mild TBI history. Other characteristics of blast exposure (time since most recent exposure, distance from closest blast, and frequency of blast events) were not associated with evaluated volumes. **Conclusion:** Exposure to a blast is independently associated with hippocampal volume beyond PTSD and mild TBI; however, these effects are small. These results also demonstrate that blast exposure in and of itself may be less consequential than severity of the exposure as measured by the pressure gradient. **Key words:** *blast, concussion, explosion, hippocampus, military, posttraumatic stress disorder, traumatic brain injury, veteran*

***Author Affiliations:*** *Mid-Atlantic Mental Illness Research, Education, and Clinical Center (MA-MIRECC), Research & Academic Affairs Service Line (Drs Martindale, Shura, Taber, and Rowland), and Mental Health & Behavioral Sciences Service Line (Dr Rostami), W. G. (Bill) Hefner VA Healthcare System, Salisbury, North Carolina; Departments of Physiology & Pharmacology (Dr Martindale), Neurology (Dr Shura), and Neurobiology & Anatomy (Dr Rowland), Wake Forest School of Medicine, Winston-Salem, North Carolina; Division of Biomedical Sciences, Edward Via College of Osteopathic Medicine, Blacksburg, Virginia (Dr Taber); and Department of Physical Medicine & Rehabilitation, Baylor College of Medicine, Houston, Texas (Dr Taber).*

*This work was supported by grant funding from Department of Defense, Chronic Effects of Neurotrauma Consortium (CENC) Award W81XWH-13-2-0095 and Department of Veterans Affairs CENC Award I01 CX001135. The authors thank the veterans and service members who contributed their time and effort to this research. The authors also thank Mary Peoples, David J. Curry, MSW, Christine Sortino, MS, Alana M. Higgins, MA, and G. Melissa Evans, MA, for their contributions to this project.*

*The views, opinions, and/or findings contained in this article are those of the authors and should not be construed as an official US Department of Veterans Affairs or US Department of Defense position, policy or decision, unless so designated by other official documentation.*

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*The authors declare no conflicts of interest.*

***Corresponding Author:*** *Sarah L. Martindale, PhD, MA-MIRECC, Research & Academic Affairs Service Line, W. G. (Bill) Hefner VA Healthcare System, 1601 Brenner Ave (11M), Salisbury, NC 28144 (Sarah.Martindale-Supak@va.gov).*

EXPOSURE to blast forces is a common experience that is relatively unique to service members and is a leading cause of mild traumatic brain injuries (TBIs) in military personnel deployed to a combat zone. Although many blast exposures do not result in a TBI, there is growing evidence that subconcussive blast exposure has effects on brain structure and function. Several studies have described alterations to brain volume in veterans with other common postdeployment conditions such as posttraumatic stress disorder (PTSD) and TBI. PTSD is associated with smaller hippocampal, rostral anterior cingulate cortex, and insula volume.[1] Mild TBI has been similarly associated with structural differences in the anterior cingulate cortex, precuneus, and hippocampus.[2,3] The current study extends prior work to understand the potential role of blast exposure on brain volume beyond PTSD and mild TBI.

Research on the effects of blast exposure in human subjects is severely limited by measurement of blast exposure, which is either conducted without a validated instrument or evaluated within the context of a TBI. The latter limitation precludes determination

*DOI: 10.1097/HTR.0000000000000660*

# Discussion

JOURNAL OF NEUROTRAUMA 34:S-53–S-61 (Supplement 1, 2017)

DOI: 10.1089/neu.2016.4709

## Characterization of Differences in Functional Connectivity Associated with Close-Range Blast Exposure

Meghan E. Robinson,[1–3] Dustin C. Clark,[1] William P. Milberg,[2,4,5]
Regina E. McGlinchey,[2,4,5] and David H. Salat[1,2,6]

**Abstract**

Despite the prevalence of blast injuries in recent overseas conflicts, knowledge of their impact on neural health is lacking. We have recently published work demonstrating differences in functional magnetic resonance imaging (fMRI) connectivity that were specific to close-range blast exposure (CBE), as opposed to other prevalent military-related factors. Here, we replicate this finding in an independent sample of 135 veterans, again finding that CBE, regardless of concussion, is predictive of persistent changes in brain physiology. Although there was weak overlap anatomically, in both samples, the group differences could be described as spreading of anticorrelation. Using the combined sample, we now seek to identify likely mechanisms that could bring about this effect. We compared participants with ($n = 116$) and without ($n = 153$) CBE by analyzing two networks through group difference maps and correlation distributions to assess spatially homogenous and heterogeneous effects. As boundaries between positive and negative correlations in fcMRI are determined by noise covariates, we compared analyses with and without global signal regression. We found evidence of widespread altered connectivity that was spatially heterogeneous across participants, and that the role of global signal regression was network dependent. These findings are not consistent with expected results from damaged white matter or impaired neural function. Rather, potential biological interpretations include disrupted cerebral blood flow or impaired neurovascular coupling, which have each been observed in animal models of blast exposure. Further targeted work will be necessary to distinguish the contribution of each of these mechanisms to producing changes in brain function associated with CBE.

**Keywords:** adult brain injury; military injury; MRI

### Introduction

Combat-related blast exposures are common in service members who served in Afghanistan and Iraq; over 50% of soldiers returning from Iraq reported being near two or more improvised explosive devices (IEDs), in many cases being exposed to high energy explosives, now survivable because of advanced vehicle and body armor.[1] Hence, the prevalence of survivable blast-related injuries is unprecedented; therefore, it is not surprising that there are critical gaps in knowledge regarding the neurobiological consequences of exposure to these blasts. Animal and human research suggests that blast exposure is associated with a number of pathological changes in brain tissue. In animal models, primary blast exposure, without accompanying blunt trauma, is associated with altered gene expression,[2] brain chemistry,[3] and neuroimaging findings.[4] Neuroimaging work in humans[5–7] has demonstrated that exposure to blast, even without diagnostic symptoms of concussion, results in measurable changes in the brain, and may even alter brain aging trajectories.[8]

Our recent work[6] revealed differences in functional connectivity magnetic resonance imaging (fcMRI) in veterans of Operations Enduring Freedom, Iraqi Freedom, and New Dawn (OEF/OIF/OND) reporting exposure to blast, regardless of whether the blast was associated with concussion. Specifically, we found that in the group reporting close-range blast exposures (CBE) (self-reported to be within 10 m), areas of anticorrelation (i.e., negative correlation) to the default mode network (DMN) extended into the somatomotor cortex, unlike the no-CBE group. Critically, changes in fcMRI were specific to CBE, and were not dependent on associated concussion symptoms; that is: fcMRI alterations for veterans with CBE were

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[3]Department of Neurology, Boston University School of Medicine, Boston, Massachusetts.
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[6]A. A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts.



♦ Human Brain Mapping 36:911–922 (2015) ♦

## Close-Range Blast Exposure is Associated With Altered Functional Connectivity in Veterans Independent of Concussion Symptoms at Time of Exposure

**Meghan E. Robinson,[1,2]* Emily R. Lindemer,[1,2] Jennifer R. Fonda,[2] William P. Milberg,[2,3,4] Regina E. McGlinchey,[2,3,4] and David H. Salat[1,2,5]**

*[1]Neuroimaging Research for Veterans Center (NeRVe), VA Boston Healthcare System, Boston, Massachusetts*
*[2]Translational Research Center for TBI and Stress Disorders (TRACTS), VA Boston Healthcare System, Boston, Massachusetts*
*[3]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts*
*[4]Geriatric Research, Education, and Clinical Center, (GRECC), VA Boston Healthcare System, Boston, Massachusetts*
*[5]A. A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts*

**Abstract:** Although there is emerging data on the effects of blast-related concussion (or mTBI) on cognition, the effects of blast exposure itself on the brain have only recently been explored. Toward this end, we examine functional connectivity to the posterior cingulate cortex, a primary region within the default mode network (DMN), in a cohort of 134 Iraq and Afghanistan Veterans characterized for a range of common military-associated comorbidities. Exposure to a blast at close range (<10 meters) was associated with decreased connectivity of bilateral primary somatosensory and motor cortices, and these changes were not different from those seen in participants with blast-related mTBI. These results remained significant when clinical factors such as sleep quality, chronic pain, or post traumatic stress disorder were included in the statistical model. In contrast, differences in functional connectivity based on concussion history and blast exposures at greater distances were not apparent. Despite the limitations of a study of this nature (e.g., assessments long removed from injury, self-reported blast history), these data demonstrate that blast exposure per se, which is prevalent among those who served in Iraq and Afghanistan, may be an important consideration in Veterans' health. It further offers a clinical guideline for determining which blasts (namely, those within 10 meters) are likely to lead to long-term health concerns and may be more accurate than using concussion symptoms alone. *Hum Brain Mapp 36:911–922, 2015.* **Published 2014. This article is a U.S. Government work and is in the public domain in the USA.**

Additional Supporting Information may be found in the online version of this article.
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# Discussion

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**Original Articles**

## Functional Status after Blast-Plus-Impact Complex Concussive Traumatic Brain Injury in Evacuated United States Military Personnel

Christine L. MacDonald,[1] Ann M. Johnson,[1] Elliot C. Nelson,[1] Nicole J. Werner,[1] Col. Raymond Fang,[2,3] Col. (ret) Stephen F. Flaherty,[2,4] and David L. Brody[1]

questions remain unanswered about the longitudinal impact of blast-plus-impact complex traumatic brain
from wars in Iraq and Afghanistan. This prospective, observational study investigated measures of clinical
JS military personnel evacuated to Landstuhl Regi
concussive TBIs. Glasgow Outcome Scale-Extende
lerate overall disability in 41/47 (87%) blast-plus TB
8) of demographically similar US military contro
ction assessed with a neuropsychological test batter
ormance of both groups was generally in the normal
ever, 29/47 (57%) of blast-plus subjects with TBI m
28%) of controls ($p = 0.014$). PTSD was highly asso
patients who did not meet full PTSD criteria had m
ere also more severe in the TBI group ($p = 0.05$)
Thus, in summary, high rates of PTSD and depressi
observed 6–12 months after concussive blast-plus-in
ypically reported in civilian non-blast concussive (
etween these clinical outcomes and specific blast-
s remains unknown.

last; clinical outcomes; PTSD; TBI

TED TRAUMATIC BRAIN INJURY (TBI) has been a
ccurrence in US military personnel during the wars
hanistan. Based on the Defense and Veterans Brain
website, there have been 266,810 physician diag-
m 2000–2012, of which approximately 80% have
d as concussive or "mild" (http://www.dvbic.org/
-numbers-tbi). The RAND report survey[1] indicated
rs could be substantially higher if the self-report
re accurate. Based on a survey of US Army soldiers
approximately 75% of concussive (mild) TBIs are

University School of Medicine, St Louis, Missouri.
gional Medical Center, Landstuhl, Germany.
ss: US Air Force Center for Sustainment of Trauma and Read
ore, Maryland.
ss: Cape Fear Valley Medical Center, Fayetteville, North Caroli



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## Effects of blast exposure on psychiatric and health symptoms in combat veterans

Sarah L. Martindale[a,b,*], Anna S. Ord[a,b], Lakeysha G. Rule[a], Jared A. Rowland[a,b]

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*Keywords:*
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Depression
Neurobehavioral symptoms
Sleep
Quality of life
Traumatic brain injury

ABSTRACT

Blast exposure is common among service members, but the chronic psychiatric effects associated with blast exposure are not well-characterized independent of a resulting mild traumatic brain injury (TBI). This analysis evaluated whether blast exposure severity was independently associated with or exacerbated symptom report beyond posttraumatic stress disorder (PTSD) and mild TBI. Participants were Iraq and Afghanistan combat veterans ($N = 275$; 86.55% male), 71.27% with history of blast exposure, 29.82% current diagnosis of PTSD, and 45.45% with mild TBI. All participants completed diagnostic interviews for PTSD, lifetime TBI, and lifetime blast exposure. Self-reported psychiatric and health outcomes included posttraumatic stress symptoms, depressive symptoms, neurobehavioral symptoms, sleep quality, pain interference, and quality of life. Blast severity was associated with PTSD ($B = 2.00$), depressive ($B = 0.76$), and neurobehavioral ($B = 1.69$) symptoms beyond PTSD diagnosis and mild TBI history. Further, blast severity accounted entirely (i.e., indirect/mediation effect) for the association between TBI and posttraumatic stress ($B = 1.62$), depressive ($B = 0.61$), and neurobehavioral ($B = 1.38$) symptoms. No interaction effects were present. Exposure to blast is an independent factor influencing psychiatric symptoms in veterans beyond PTSD and mild TBI. Results highlight that blast exposure severity may be a more relevant risk factor than deployment mild TBI in combat veterans and should be considered in the etiology of psychiatric symptom presentation and complaints. Further, severity of psychological distress due to the combat environment may be an explanatory mechanism by which blast exposure mediates the relationship between mild TBI and symptom outcomes.

### 1. Introduction

Exposure to blast and explosive events is common for military service members during training and deployment. However, relatively little is known about how exposure to these events affects symptom presentation, particularly outside the context of mild traumatic brain injury (TBI) (Belding et al., 2021a). This is in part due to lack of an agreed-upon definition of what constitutes the state of having been *blast exposed*. Though physical injury characteristics of blast exposure are well-defined (i.e., primary, secondary, tertiary, quaternary), many blasts that service members experience do not result in injuries that fall within these categories. In addition, exposure to a blast or explosive event does not always result in symptoms congruent with a mild TBI (Carr et al., 2016; Rowland et al., 2020b; Taber et al., 2015). Recent work has just begun to propose empirical definitions of blast exposure and comprehensively evaluate experience of blast events outside of mild TBI (Belding et al., 2021a; Rowland et al., 2020b). Because of this, it is unclear what effects exposure to a blast may have on behavioral health outcomes independent from mild TBI, and what characteristics of blast exposure are associated with psychiatric (e.g., PTSD, depression, neurobehavioral) and health (e.g., sleep, pain) symptoms as well as overall quality of life.

The majority of our foundational knowledge of behavioral health effects of blast exposure is within the context of blast as a TBI mechanism (Belding et al., 2021b; Greer et al, 2016, 2018; Mac Donald et al., 2017). Specifically, a significant portion of human research on blast exposure evaluates consequences of primary blast mild TBI (i.e., mild TBI resulting from blast exposure without contribution of non-blast forces), compared to non-blast mild TBI (i.e., blunt mild TBI) (Belding

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## Relation of Repeated Low-Level Blast Exposure With Symptomology Similar to Concussion

*Walter Carr, PhD; Elena Polejaeva, BS; Anna Grome, MS; Beth Crandall, BA; Christina LaValle, MS; Stephanie E. Eonta, BS, BA; Lee Ann Young, MA*

**Objective:** To investigate anecdotal reports suggesting that repeated exposure to low-level explosive blast has myriad health impacts, including an array of neurological effects. **Participants:** A total of 184 anonymous survey respondents from military and nonmilitary law enforcement populations (135 exposed to occupational blast and 49 controls). **Design:** Survey of self-reported history of occupational exposure to repeated low-level blast (breaching blast) and symptomology similar to concussion. **Results:** Findings suggest that number and severity of symptoms increase with history of chronic blast exposure ($F = 18.26$, $P < .001$) and that symptoms can interfere with daily activity ($t = 2.60$, $P = .010$). **Conclusion:** Given the prevalence of repeated exposure to blast among some military and civilian law enforcement occupations, the results of this survey study support a role for blast surveillance programs as well as continued research on health impacts of low-level repeated blast exposure. **Key words:** *blast*, *concussion*, *military*, *survey*, *symptoms*

TRAUMATIC BRAIN INJURY (TBI) remains a principal concern in recent conflicts.[1,2] Within a sample of these injuries, 78% were from explosive mechanisms,[3] with as many as 88% of military personnel treated at a medical unit in Iraq because of injury from an improvised explosive device (IED) or mortar.[4,5] Traumatic brain injury associated with blast is not a new phenomenon in the scope of warfare; however, blast-related TBI has become relatively more common for military medicine as protective gear, and treatment of other injuries has improved and as blast has become a primary weapon for adversaries in asymmetric warfare. In comparison with TBI from non-blast-related causes, blast waves present risk for diffuse injury to the brain rather than an isolated injury.[5] Several studies have examined the effects of blast-related head injury in comparison with blunt head trauma.[6,7] The study presented here examines effects of blast that may be occurring beneath the threshold for entry into the medical system.

Injuries caused by blast are classified into 4 categories: primary blast injury occurs when the injury is caused by the high-force blast waves themselves, and secondary, tertiary, and quaternary blast injuries occur when the mechanical aftermath of the explosion causes the injury (eg, being hit by debris, being forcefully moved by blast, or being crushed by collapsing object).[5,6] In a combat setting, secondary, tertiary, and quaternary blast injuries can be expected to co-occur with cases of primary blast injury, obscuring the attribution of effects to any single category of blast injury. Also, when injury associated with blast is presented in the military medical system, it is typically polytrauma.[8,9] As with co-occurring categories of blast injury, polytrauma has made it difficult for studies to focus solely on TBI.

Professions that make regular use of explosive breaching present a unique opportunity to study effects of blast exposure without co-occurring injury. Breachers are military and civilian law enforcement tactical personnel

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*The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Army, Department of the Navy, Department of Defense, nor the US Government.*



*The authors declare no conflicts of interest.*

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# Discussion

Emerging work on blast

- White matter
- Brain volume
- Brain function
- Psychiatric presentation

**Most of this work is limited by its cross-sectional nature**

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## Effects of blast exposure on psychiatric and health symptoms in combat veterans

Sarah L. Martindale [a,b,*], Anna S. Ord [a,b], Lakeysha G. Rule [a], Jared A. Rowland [a,b]

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ABSTRACT

Blast exposure is common among service members, but the chronic psychiatric effects associated with blast exposure are not well-characterized independent of a resulting mild traumatic brain injury (TBI). This analysis evaluated whether blast exposure severity was independently associated with or exacerbated symptom report beyond posttraumatic stress disorder (PTSD) and mild TBI. Participants were Iraq and Afghanistan combat veterans ($N = 275$; 86.55% male), 71.27% with history of blast exposure, 29.82% current diagnosis of PTSD, and 45.45% with mild TBI. All participants completed diagnostic interviews for PTSD, lifetime TBI, and lifetime blast exposure. Self-reported psychiatric and health outcomes included posttraumatic stress symptoms, depressive symptoms, neurobehavioral symptoms, sleep quality, pain interference, and quality of life. Blast severity was associated with PTSD ($B = 2.00$), depressive ($B = 0.76$), and neurobehavioral ($B = 1.69$) symptoms beyond PTSD diagnosis and mild TBI history. Further, blast severity accounted entirely (i.e., indirect/mediation effect) for the association between TBI and posttraumatic stress ($B = 1.62$), depressive ($B = 0.61$), and neurobehavioral ($B = 1.38$) symptoms. No interaction effects were present. Exposure to blast is an independent factor influencing psychiatric symptoms in veterans beyond PTSD and mild TBI. Results highlight that blast exposure severity may be a more relevant risk factor than deployment mild TBI in combat veterans and should be considered in the etiology of psychiatric symptom presentation and complaints. Further, severity of psychological distress due to the combat environment may be an explanatory mechanism by which blast exposure mediates the relationship between mild TBI and symptom outcomes.

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## Research Letter: Blast Exposure and Brain Volume

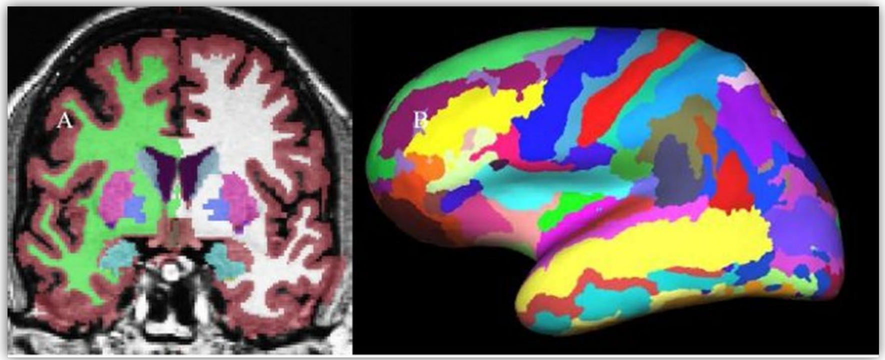
*Sarah L. Martindale, PhD; Robert D. Shura, PsyD, ABPP; Ramona Rostami, PhD; Katherine H. Taber, PhD; Jared A. Rowland, PhD*

**Objective:** To determine whether blast exposure is associated with brain volume beyond posttraumatic stress disorder (PTSD) diagnosis and history of traumatic brain injury (TBI). **Setting:** Veterans Affairs Medical Center. **Participants:** One hundred sixty-three Iraq and Afghanistan combat veterans, 86.5% male, and 68.10% with a history of blast exposure. Individuals with a history of moderate to severe TBI were excluded. **Main Measures:** Clinician-Administered PTSD Scale (CAPS-5), Mid-Atlantic MIRECC Assessment of TBI (MMA-TBI), Salisbury Blast Interview (SBI), and magnetic resonance imaging. Maximum blast pressure experienced from a blast event represented blast severity. **Methods:** Hierarchical regression analysis evaluated effects of maximum pressure experienced from a blast event on bilateral volume of hippocampus, anterior cingulate cortex, amygdala, orbitofrontal cortex, precuneus, and insula. All analyses adjusted for effects of current and lifetime PTSD diagnosis, and a history of deployment mild TBI. **Results:** Maximum blast pressure experienced was significantly associated with lower bilateral hippocampal volume (left: $\Delta R2 = 0.032$, $P < .001$; right: $\Delta R2 = 0.030$, $P < .001$) beyond PTSD diagnosis and deployment mild TBI history. Other characteristics of blast exposure (time since most recent exposure, distance from closest blast, and frequency of blast events) were not associated with evaluated volumes. **Conclusion:** Exposure to a blast is independently associated with hippocampal volume beyond PTSD and mild TBI; however, these effects are small. These results also demonstrate that blast exposure in and of itself may be less consequential than severity of the exposure as measured by the pressure gradient. **Key words:** *blast, concussion, explosion, hippocampus, military, posttraumatic stress disorder, traumatic brain injury, veteran*

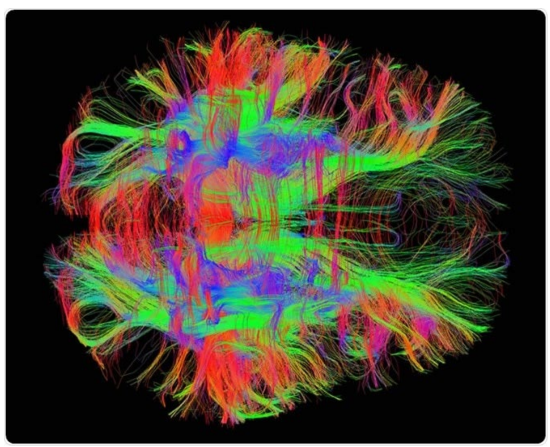
# Discussion

Deployment
Blast TBI

# Discussion




Deployment
Blast TBI



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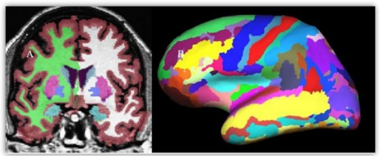

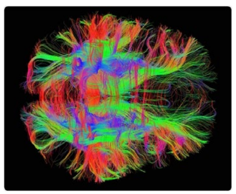

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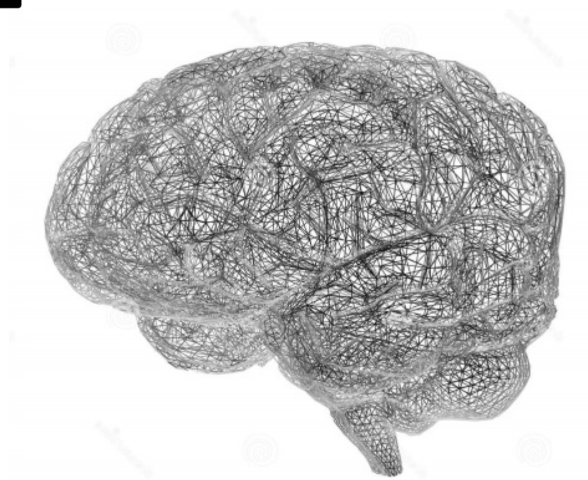
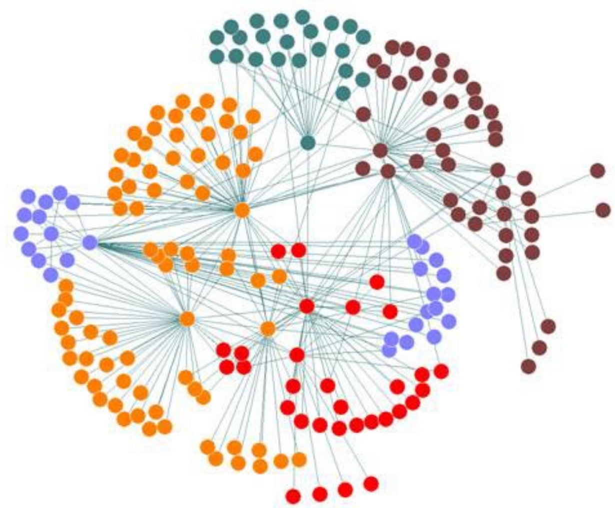
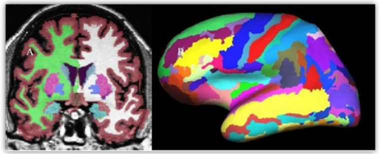
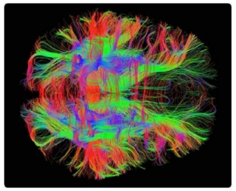


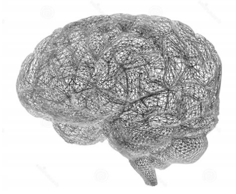


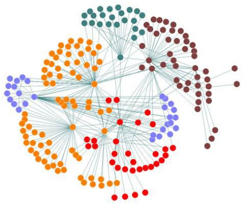
# Discussion

Deployment Blast TBI





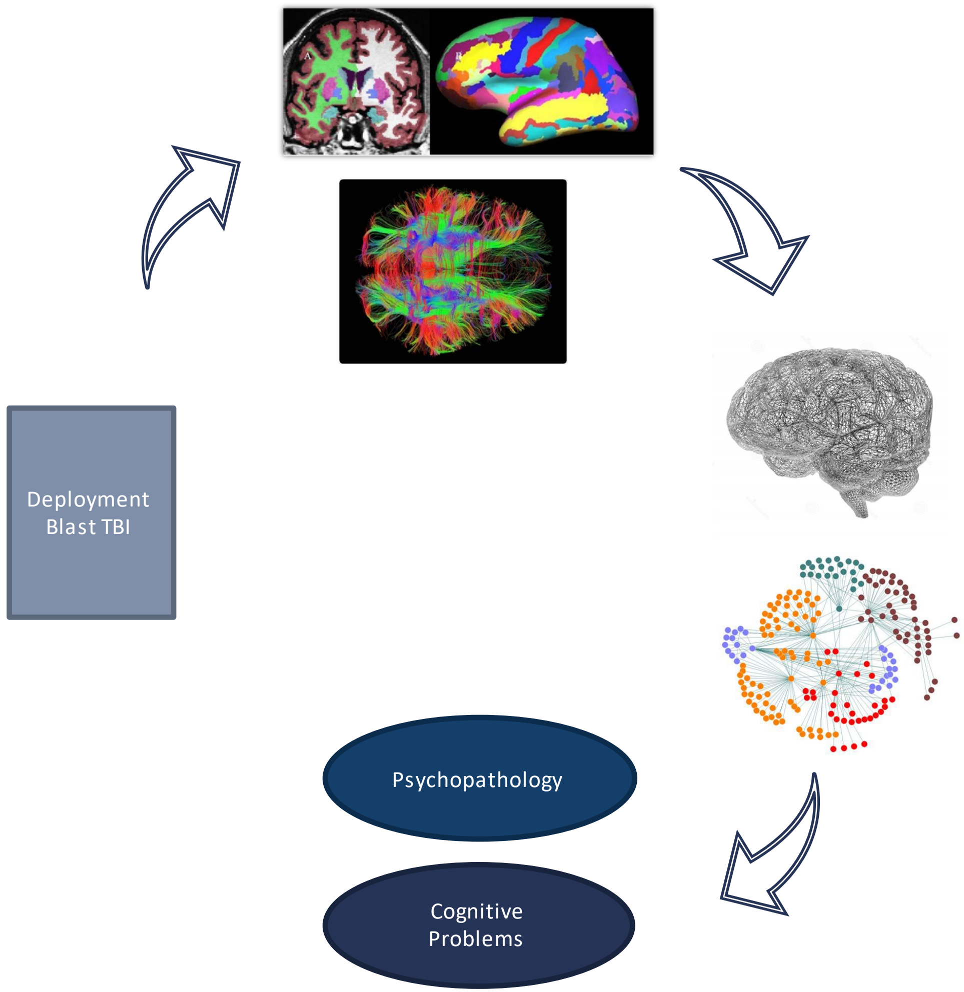




Psychopathology

Cognitive Problems

# Discussion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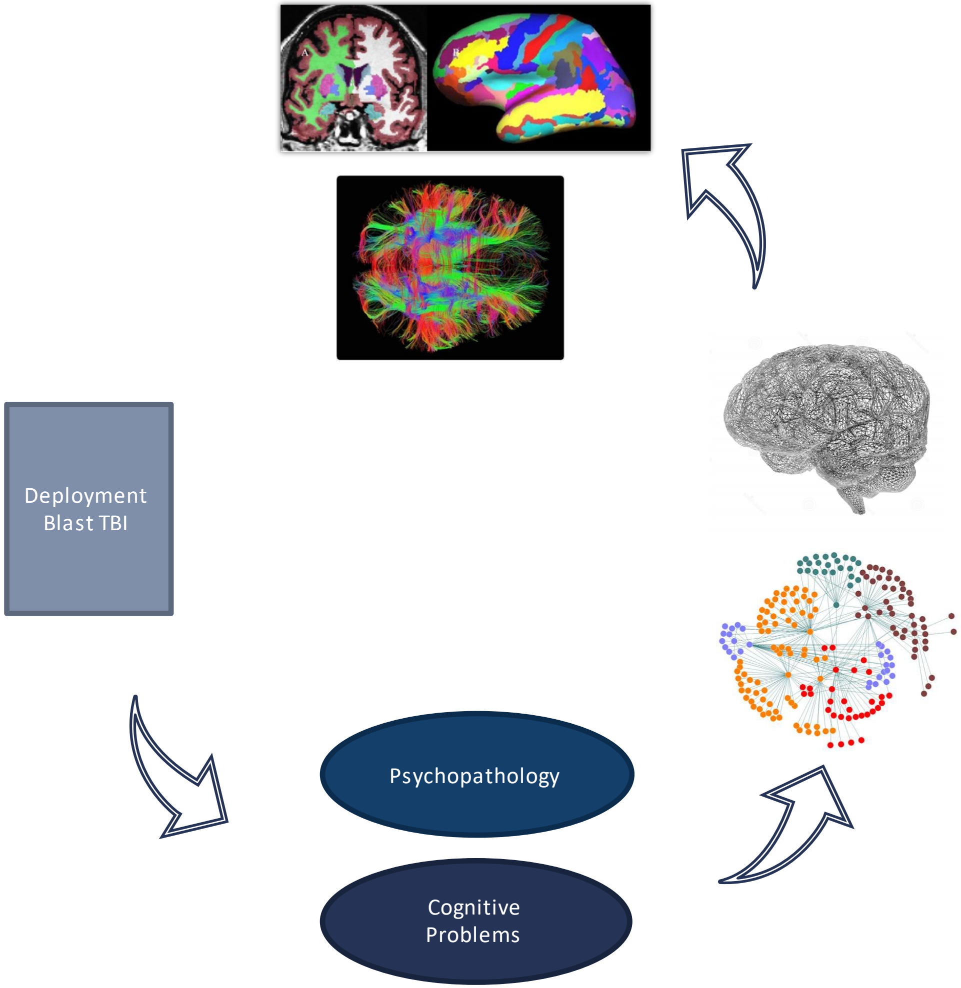
# Discussion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Psychopathology
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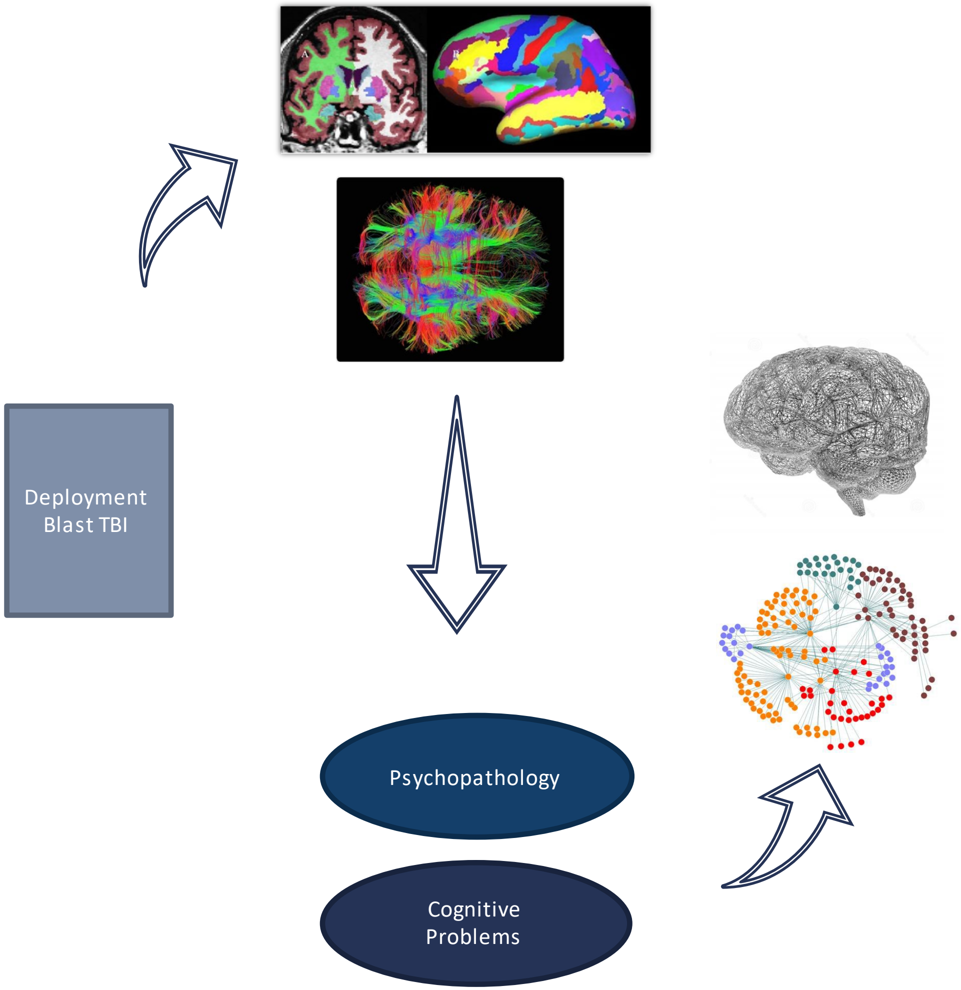
# Discussion


Deployment Blast TBI
Psychopathology
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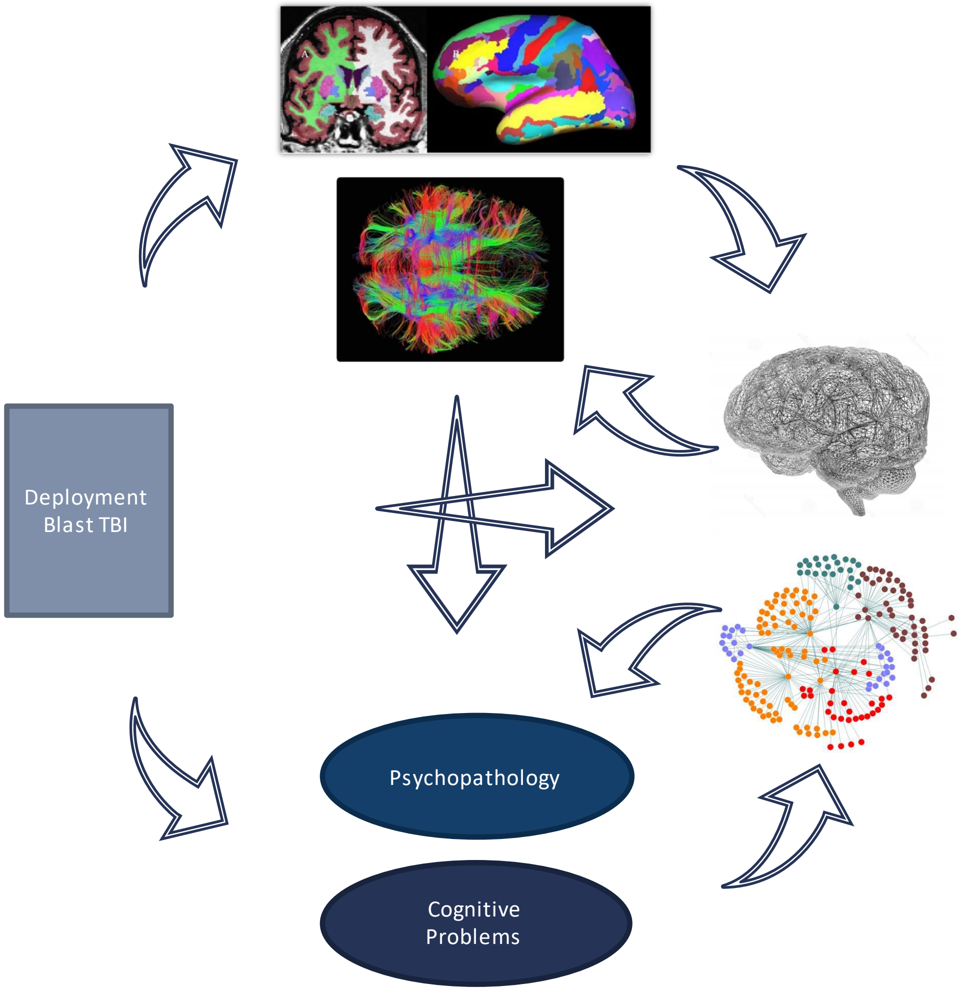
# Discussion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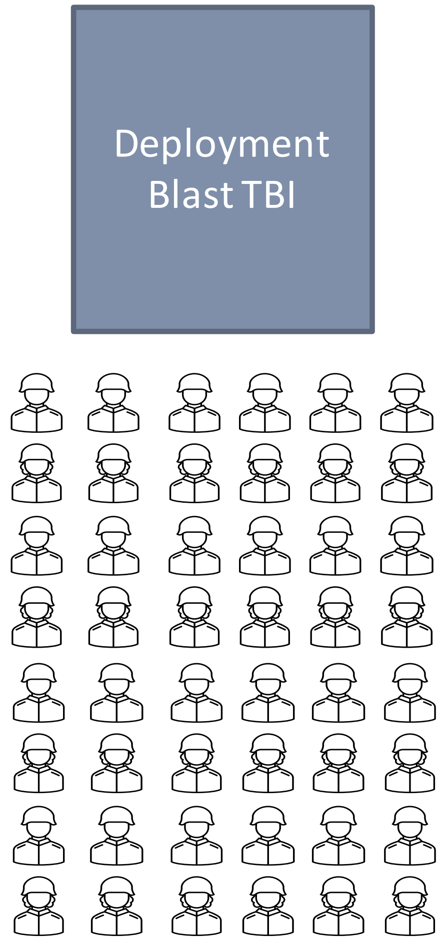
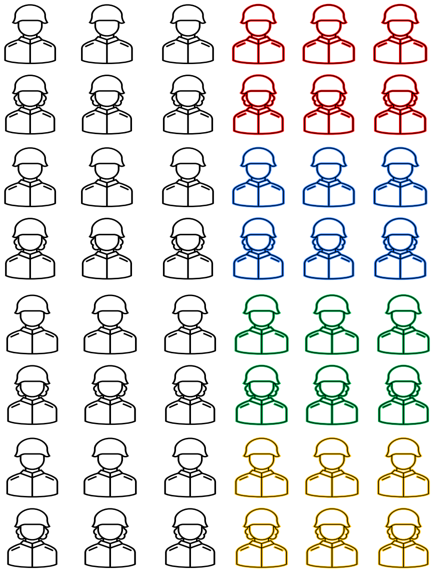
# Discussion

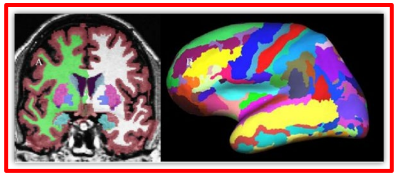


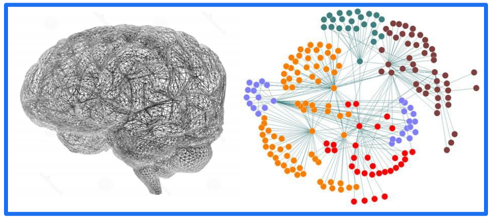
# Discussion

Deployment
Blast TBI

No Negative
Outcomes







Psychopathology

Cognitive Problems

# TBI in PTSD Recovery

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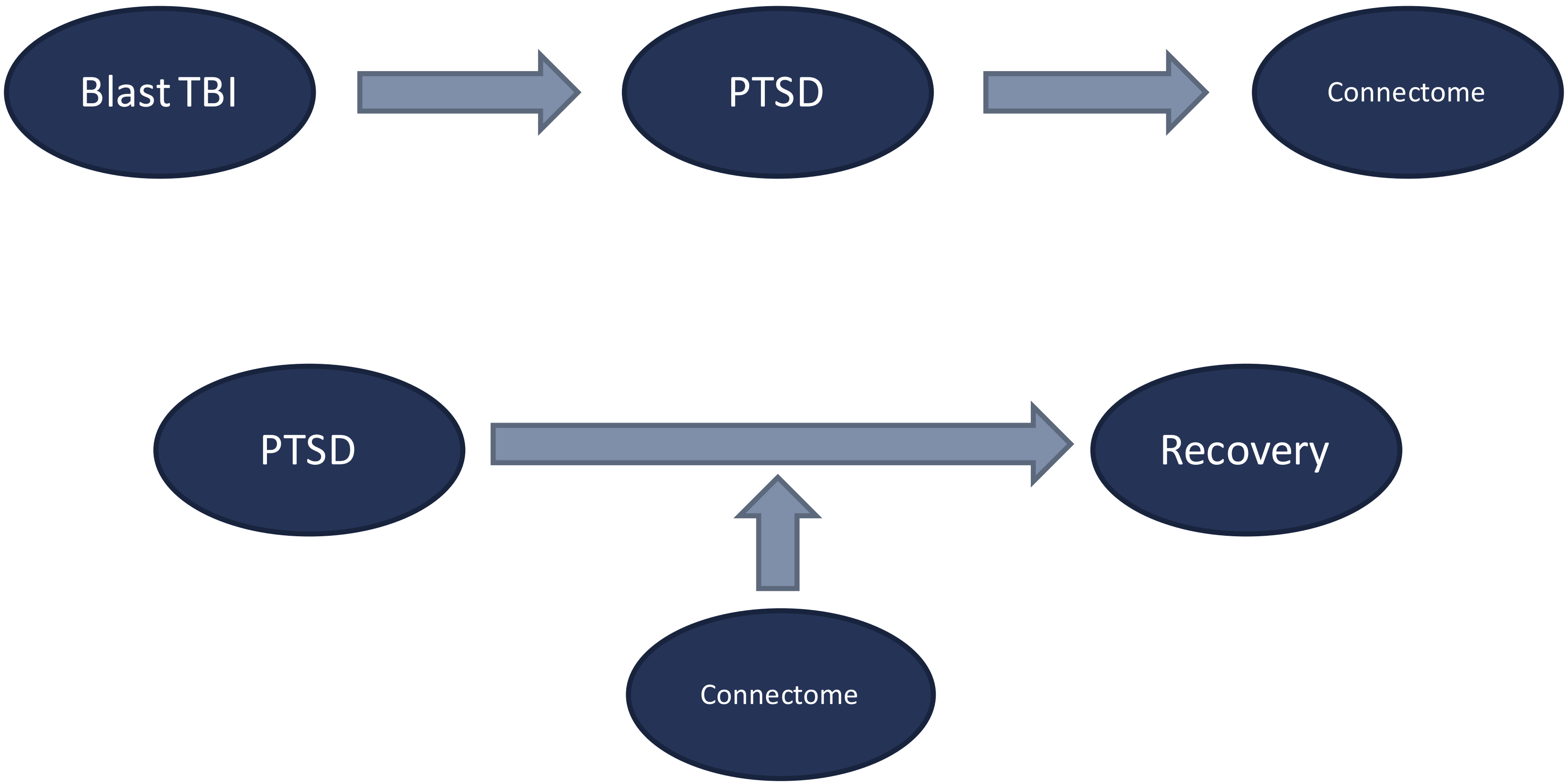
# TBI in PTSD Recovery



# Discussion


# Discussion


## The Invisible Wounds of War

# Future Directions & Clinical Implications

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## Blast is important to consider

- Unique effects across multiple domains
- Clarify when and how

# Future Directions & Clinical Implications

Blast is important to consider

- Unique effects across multiple domains
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Biomarkers of Blast

- Functional Neuroimaging shows changes
- How is everything connected?

# Future Directions & Clinical Implications

## Blast is important to consider

- Unique effects across multiple domains
- Clarify when and how

## Biomarkers of Blast

- Functional Neuroimaging shows changes
- How is everything connected?

## Time matters

- Time since injury changes presentation
- Acute versus chronic

MID★ATLANTIC MIRECC POST DEPLOYMENT MENTAL HEALTH

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CENC Chronic Effects of Neurotrauma Consortium

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MID ATLANTIC MIRECC POST DEPLOYMENT MENTAL HEALTH

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