Vulnerability to Post Traumatic Stress Disorder after TBI
Chronic Stress and Aging

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Disclosures

• None relevant
Let’s start with a case

- Right handed man
- Age: 31
- Army veteran
  - Combat exposure
  - Dishonorable discharge – drug and alcohol use
- Presented with severe PTSD,
  - PCLM = 66,
  - SCL-90-R – (T score >80)
    - depression, anxiety, hostility, paranoia
- Mild TBI, 17 years old
  - LOC 10 seconds
  - No pre or post traumatic amnesia
  - No residual symptoms

- Cigarettes
  - ½ pack per day
- Alcohol
  - 15 drinks a week, 10 years
- Marijuana
  - 6 joints a week, 10 years
- No meds
- Sleep problems
  - Difficulty falling asleep
  - Difficulty staying asleep
  - Nightmares
  - Daytime fatigue
Cognitive performance

• TOMM = 50, 49
• WTAR = 94
• Phonemic fluency = 29 words (10, 9 and 10)
• RBANS total = 79
• Immediate = 81
• Visuospatial = 69
• Language = 82
• Attention = 103
• Delayed memory = 83
What’s going on?

• Cognitive dysfunction?
• What is fueling the chronic PTSD?
• Substance use?
• Is the mild TBI relevant?

Key points:
- TOMM = WNL
- WTAR = 94
- RBANS = 79
  - Visuospatial = 69
  - Imm, Lan, delay = low 80s
- TBI history
- Severe PTSD
Overview

• Mild TBI and PTSD linked
• Is there a mechanistic contribution of mild TBI to PTSD development, type, and severity?
  • Difficult signal, lots of noise
• Neurophysiology of TBI
  • Animal work
  • Human work
• Chronic Stress, cumulative injury
Mild Traumatic Brain Injury

- Alteration or loss of consciousness 30 min or less
- Post traumatic amnesia <24 hours
- Focal neurological deficits may or may not be present
- No evidence of injury on conventional imaging
Interesting points from VA/DOD guidelines for diagnosis and management of mild TBI

• From practice guidelines
  • Recommend using term “history of mild TBI” rather than any variant of “damage” or “patients with mild TBI”
    • Implies ongoing problem, could contribute to persistent symptoms

• Against using the following tests to establish the diagnosis of mTBI
  • Neuroimaging past 7 days from event.
    • Notes DTI not sensitive enough indicatory because only 40% show measurable differences.
  • Serum biomarkers, including:
    • S100 calcium-binding protein B (S100-B),
    • glial fibrillary acidic protein (GFAP),
    • ubiquitin carboxyl-terminal esterase L1 (UCH-L1),
    • neuron specific enolase (NSE), and
    • α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) peptide

• Electroencephalogram (EEG)
• Neuropsych testing within 30 days of injury and only in specific incidences after (emotional issues/effort, and as prep for cognitive rehab) or
• We suggest that patients with a history of mTBI who report cognitive symptoms that do not resolve within 30-90 days and have been refractory to treatment for associated symptoms (e.g., sleep disturbance, headache) be referred as appropriate for a structured cognitive assessment or neuropsychological assessment to determine functional limitations and guide treatment.

https://www.healthquality.va.gov/guidelines/Rehab/mtbi/mTBI
CPGFullCPG50821816.pdf
Pathophysiology of mild TBI

- White matter changes
  - Diffuse axonal injury

- Heterogeneous
  - Injury type (closed head injury or blast)
  - Forces involved (vector of injury)
  - Number of injuries
  - Context of injury
  - Severity of injury
Effect of Mild TBI on Behavior

• Symptoms often transient
• There is a chronic population, unclear if related to TBI
• ADHD, conduct disorder, substance abuse, discharge rates from military, criminal behavior (Ommaya et al., 1996)
• Large study of military members with TBI
  • 42% PTSD, 74% anxiety, 66% depression, 76% mood swings, 84% irritability
    • Some evidence that these issues are independent of premorbid psychiatric status
    • Lew et al. 2007

Ommaya AK, Salazar AM, Dannenberg AL et al. J Trauma 1996
Anatomic changes and Mood

• 42 political detainees, 26 TBI, 16 without
  • Thinner prefrontal cortices, left dorsolateral pfc, bilateral superior temporal
    • correlated with depression scores
      • Mollica et al, 2009

• Blast, mTBI, 11 with MDD, 11 without MDD
  • Lower DTI-FA values in left and right anterior corona radiata in group with MDD
  • fMRI, TBI w MDD = greater amygdala activation
But wait. . .

- mTBI = 37, 15 w/o.
  - No relationship between mood measures, cognitive performance and FA
    - Levin et al., 2010

- Why different results?
  - Previous study used emotional induction/reactivity
  - Levin used mood scales
  - Previous study selected for major depression
  - Levin study did not

- Why does sample selection matter?
  - Example – MS, memory, donepezil
Post Traumatic Stress Disorder DSM V criteria

- No longer an anxiety disorder
- New conceptualization
  - Primarily a disorder of reactivity
- Criterion A: Stressor
- Criterion B: Intrusive Symptoms
- Criterion C: Avoidance
- Criterion D: Negative alterations in cognition and mood
- Criterion E: Alterations in Arousal and reactivity
- Criterion F: Persistence > 1 month
- Criterion G: Functional significance
- Criterion H: Exclusion
Situational overlap?

• N = 2714 Army combat infantry
  • Assessed 3 to 4 months after return from year long Iraq deployment

• Measures
  • Combat Experiences Scale
  • Questionnaire for injury characterization, customized
  • Patient Health Questionnaire
  • PTSD Checklist

• Results
  • 5% LOC and 10% AOC
  • 44% LOC = PTSD, 27% AOC = PTSD, sig even controlling for combat intensity

• Key takeaways
  • Reflects exposure to a very intense traumatic event that threatens loss of life and significantly increases the risk of PTSD
  • High rates of physical health problems reported by soldiers with mild traumatic brain injury 3 to 4 months after deployment are mediated largely by PTSD or depression

Hoge CW, McGurk D, Thomas JL et al. NEJM 2008
Link between PTSD severity, TBI history and cognitive performance

- Neurocognition Deployment Health Study
- N = 315 Army Soldiers
  - Measured before and after deployment to Iraq, and again 7.6 years later
  - TBI n = 60, 89% mild
  - PSTD n = 54
- Measures
  - PCL-C
  - DRRI
  - CES
  - TBI structured interview
  - WMS-III, VPA I VPA2; VR
  - ANAM Simple Reaction Time
  - NES3 Continuous Performance Test
- Primary conclusions
  - Cognitive performance both a predictor and outcome of PTSD severity
  - TBI associated with more severe PTSD, independent of combat stress (contrast to Hoge et al., 2008)
  - TBI not associated with cognitive performance

Vasterling JJ, Aslan M, Lee LO, et al., JINS 2017
Military mild TBI increased PTSD Risk

- ARMY STARRS
- N = 4,645 soldiers, Afghanistan
  - Measured 3 months and 9 months post-deployment
  - 18% mild TBI
  - 1.2% more than mild

- Methods to measure TBI, PTSD, depression, anxiety, and irritability
  - CIDI-SC
  - Modified PCL and full PCL
  - Columbia Suicided Severity Rating Scale
  - Study specific deployment stress inventory
  - Study specific TBI interview and Army TBI surveillance component of pre and post deployment health reassessment

- Primary conclusions
  - Mild TBI increased risk of PTSD
  - Severity of mild TBI was associated with greater risk, “dose-response”
  - TBI also was associated with major depressive episodes and generalized anxiety disorder

Stein M., Kessler RC., Heeringa SG. Et al., Am J Psychiatry 2015
Heterogeneity of injury

• mTBI vs mTBI/outcome vs outcome
• Premorbid brain and injury differences may contribute to variability in results
• N = 34 mTBI adults, 26 health controls
• Injury
  • 41% anterior corona radiata
  • 29% uncinate fasciculus
  • 21% genu of the corpus collossum
  • 21% inferior longitudinal fasciculus
  • 18% cingulum bundle
• White matter injury associated with cognitive performance

Specific white matter injury and cognition

- N = 33 mild TBI, 5 moderate TBI, 17 controls
  - Average 4 year post injury
- Measures
  - WRAT-4 reading
  - CVLT-2
  - Rey CFT
  - WCST, DKEFS Fluency switching and Trails, Wechsler Digit symbol
  - TOMM
  - 3T, DTI UCSDm, Excite HDx platform and 10 on MR750 platform
    - (inconvenient scanner upgrade occurred)
- Results:
  - TBI = more PTSD and depression
  - More TBI = more AIC damage
  - No association between TBI and PCLM severity
  - No association between PCLM and cognition
  - TBI predicted poorer memory and coding performance
  - Processing speed associated with white matter injury

Sorg SF, Schiehser DM, Bondi MW, et all. *Journal of Head Trauma Rehabilitation* 2016
Fronto-limbic connections, TBI, emotional dysregulation

- Could damage to fronto-limbic connections affect manifestation of PTSD symptoms?
- Key emotional control networks
- Critical for autonomic regulation
  - Central autonomic network
- Vulnerability?
- Ongoing facilitator?

mTBI reduces sound density of projection neurons in mPFc and impairs fear extinction

- N – 16 male Sprague-Dawley rats
  - 8 Lateral fluid percussion injury, 8 sham
    - Causes white matter injury but no visible brain damage on conventional imaging
- Footshock, fear stimulus
- Freezing behavior DV
- Decrease spine density in layer II/III pyramidal neurons in infralimbic cortex (IL neurons projecting to amygdaloid complex are here)
- Impaired fear extinction learning

Mild TBI increases GABA in PFC, modified fear learning and extinction

• Mouse model of mild TBI

Schneifer, Ghodoussi, Charlton et al., 2016, Journal of Neurotrauma
Skin conductance

- Measures sweat response
- Measure of sympathetic nervous system activity
- Relationship between emotion and sympathetic nervous system activity

Figure from Combe and Fuji, 2011, Frontiers in Psychology
TBI and sympathetic nervous system

• More severe TBIs can result in paroxysmal sympathetic hyperreactivity
  • Can persist for weeks or months
  • Periodic episodes or increased heart rate and blood pressure, sweating, hyperthermia
  • 1st described by Wilder Penfield
• Thought to be a disconnection syndrome, loss of inhibitory control
• Mild TBI not associated with acute sympathetic nervous system effects

## Limbic inputs and PTSD

### PCLM and Right and Left Uncinate Correlations

<table>
<thead>
<tr>
<th></th>
<th>Disturbing memories</th>
<th>Disturbing Dreams</th>
<th>Military Re-exp</th>
<th>Reminded of mil exp</th>
<th>Physical reaction</th>
<th>Avoidance</th>
<th>Angry Outbursts</th>
<th>Jumpy, startle</th>
<th>Total</th>
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<tbody>
<tr>
<td><strong>Left Uncinate</strong></td>
<td>-167</td>
<td>-.263*</td>
<td>-.114</td>
<td>-.161</td>
<td>-.130</td>
<td>-.185</td>
<td>.028</td>
<td>-.018</td>
<td>-.097</td>
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<tr>
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<td>-.303*</td>
<td>-.329*</td>
<td>-.144</td>
<td>-.250*</td>
<td>-.200</td>
<td>-.251*</td>
<td>-.295*</td>
<td>-.304*</td>
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### SCL90-R and Right and Left Uncinate Correlations

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<tr>
<th></th>
<th>Depression</th>
<th>Anxiety</th>
<th>Hostility</th>
<th>Phobic</th>
<th>Paranoia</th>
<th>Psychoticism</th>
<th>Positive Symptom</th>
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<td>-.198</td>
<td>-.278*</td>
<td>-.342*</td>
<td>-.094</td>
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<td>-.178</td>
<td>-.205</td>
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<td></td>
<td>TBI</td>
<td>TBI/PTSD</td>
<td>PTSD</td>
<td>Combat controls</td>
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<tr>
<td>NSI total</td>
<td>13.4+-11</td>
<td>30.3+- 20</td>
<td>26+-16</td>
<td>8.2+-7</td>
<td></td>
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<tr>
<td>WTAR</td>
<td>102.6+-7</td>
<td>100.2+-10</td>
<td>103.6+-12</td>
<td>103.3+-14</td>
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<td>PCLM</td>
<td>27.6+-23</td>
<td>49.2+-18</td>
<td>49.4+-11</td>
<td>23.6+-13</td>
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<tr>
<td>TOMM Trial 2</td>
<td>49.5+-1.1</td>
<td>49.7+-0.8</td>
<td>50+-0</td>
<td>50+-0</td>
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<td>RBANS Coding</td>
<td>58.3</td>
<td>54.6</td>
<td>60.8</td>
<td>65.9</td>
<td></td>
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<tr>
<td>RBANS Digit Span</td>
<td>11.9</td>
<td>10.9</td>
<td>14.4</td>
<td>12.9</td>
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<td>17</td>
<td>24</td>
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Data from VA CDA-2, Williamson PI
Heart rate variability

• Index of vagal tone
  • Vagal contribution to heart rate variability
• Variability in r-r interbeat intervals
• Many different calculation methods
• Typically seen in literature
  • High frequency
    • Respiratory frequency (RSA)
  • Low frequency
    • Sympathetic and para
  • Very low frequency
    • Thermoregulation, hormonal mechanisms
Neurovisceral integration

Autonomic dysfunction is brain dysfunction, lessons from prairie voles
RSA reflects behavior of central control

Regulation of HPA axis altered during post-injury period

• 216 male Sprague-Dawley rats
  • Mild FPI n = 81 sham = 81

• Methods
  • Restraint stress, 30 minutes
  • Measures
    • plasma corticosterone
    • Adrenocorticotropic hormone
  • first two weeks post TBI

• Results
  • > Stress response

Autonomic responses to exercise following mild TBI

• 63 Sprague-Dawley rats
  • 19 sham, 19 FPI
• Measured sub-acutely
  • Forced and voluntary wheel exercise
  • Similar DVs to prior study
• Results
  • Decreased activity levels after FPI
  • Circadian rhythm disruption
  • Increased HR as a result of voluntary exercise

Autonomic recovery after exercise post-acute TBI

• 57 Sprague-Dawley rats
  • 29 FPI, 28 sham

• Measures
  • Voluntary and forced exercise
  • Autonomic/stress response assessment
    • BDNF, CORT, ACTH, HR, temperature
  • Sleep quantification

• Results
  • Stress response via ACTH and CORT recovers with delay in voluntary exercise by 28 days
  • However, BDNF elevations to voluntary exercise remain in FPI group
  • Circadian cycles normal post acute
  • Trend to fatigue
  • FPI rats exposed to forced exercise remained more response dto experimental manipulations

Abuse history related to autonomic recovery from non emotional tasks

• N = 49
  • 27 remote child/adult abuse, 22 no abuse challenge = exercise bike, 5 min

Combat exposure, subclinical trauma, PTSD

- N = 2430 Marines
  - Assessed pre and post deployment
- Measures
  - Photoplethysmograph derived IBI
    - 5 minutes
  - CAPS
  - BDI-2
  - TBI interview
- Results
  - TBI related to lower HRV
  - PTSD related to lower HRV even when controlling for TBI in model
  - Combat exposure associated with lower HRV
  - Subclinical PTSD associated with lower HRV

PTSD and autonomic features

• N = 57 patients with PTSD, 41 healthy controls
  • TBI not assessed, non-military population

• Measures
  • CAPS and SCID, childhood trauma questionnaire
  • BDI-2, Multiscale Dissociation Inventory, STAI,
  • Response to Script Driven Imagery
  • Resting state fMRI
  • Seed based approach, central autonomic network regions
    • vmPFC, amygdala, periaqueductal gray
  • Heart rate variability

• Results
  • Lack of HRV variation with CAN-related brain connectivity in chronic PTSD group

Aversive imagery response

• 49 PTSD, 76 healthy control

• Measures
  • Anxiety disorder Interview Schedule DSM IV

• Approach
  • 24 narrative imagery texts used
  • Eyes closed, instructed to imagine events
  • Startle probe (50 ms 95 dB white noise)

Marijuana may impair fear extinction

- Marijuana use common in PTSD/TBI population
- Some discussion of medical marijuana use for PTSD
  - Mizrach et al., 2016
- N = 40, 20 chronic marijuana users, 20 controls
- Fear conditioning and extinction paradigm
  - UCS = loud sound burst
- Compared, within session extinction between session extinction and extinction generalization
- Measured GSR
- Chronic marijuana use associated with impaired extinction

Autonomic disruptions and health consequences
Autonomic features predict health outcomes

• Framingham heart study
• 1028 ambulatory ECG recordings
  • 2 hour duration
• Heart rate variability
  • SDNN
  • pNN50
  • R-MSSD
  • Total Power (.01 and 4 hz)
  • High frequency power (.15 and .4 hz)
  • Very low frequency power (.01 to .04 hz)
  • Low frequency/high frequency ratio
• All five Frequency domain measures associated with all-cause mortality, unadjusted
• SDNN also predicted.
• Low frequency power had the highest hard ratios of 1.7 to 1.87
  • 1 SD decrement in natural log-transformed LF = 70% increase in mortality, accounting for age, sex and clinical risk factors
• Including mean heart rate in model had little or no impact on the results
Personality traits associated with HRV and blood pressure reactivity increase risk of heart disease

• Hostility, aggressiveness, etc. . . Associated with cardiovascular disease.

• Rumination over an anger stressor prolongs cardiovascular response to stress.
  • Busch et al., 2017, Psychological Bulletin
PTSD and \textbf{Fight or Flight}

- High rates of aggression and anger
  - Navaco and Chemtob, 2002 \textit{Journal of Trauma and Stress}

- Trauma exposure population
  - N = 232
  - 24\% met criteria for lifetime intermittent explosive disorder
  - PTSD severity was a significant predictor of intermittent explosive disorder diagnosis
    - Reardon et al., 2014 \textit{Journal of anxiety disorders}
PTSD and Fight or Flight

• High rates of depression and anxiety
• In ~ 21K World Trade Center area survivors
  • Depression was more common:
    • in people with PTSD (56.1%)
    • Than those without (~5%)
    • Jacobson et al., 2017

• Elevated rates of social anxiety co-morbidity
  • McMillan et al., 2017, *Journal of Trauma Stress*

• Veterans with PTSD show higher rates of perceived social isolation
  • Ahmadian et al., 2015, *Neuropsychiatric Disease and Treatment*
Subclinical hostility

• Even subclinical levels of trait hostility are associated with differential physiological response
  • Williamson and Harrison 2003, *Brain and Cognition*, sympathetic response
  • Resting RSA is lower
    • Sloan et al, 2001, *Psychosom Med*

• High frequency heart rate variability stability response to stress mitigates cortisol sensitivity
  • Individual differences in risk?
  • Murdock, et al 2017
    • *Psychoneuroendocrinology*
Lower HRV associated with anxiety

- Pet dog behavioral problems were assessed by owner questionnaire

Wormald et al., 2017, *Physiology & Behavior*

Black = affected by behavioral problems
Loneliness, it’s about perception

- Perceived social connectedness rather than objective social support, associated with cardiovascular risk factors including:
  - Lower blood pressure
  - Better immune response
  - Lower basal levels of stress hormones
  - Lower risk of atherosclerosis
    - Knox et al., 2000
  - Coronary artery bypass surgery survival 30 days and 5 years after surgery
    - Herlitz et al., 1998
  - History of loneliness show acceleration of blood pressure increases with age.
    - Cacioppo et al., 2002
• The driver of health outcomes after trauma
  • not necessarily the categorical presence of PTSD
  • reaction to trauma that perturbs the dynamic homeostasis of the social engagement system such that some aspect of chronic defensive disposition is elicited.

• Symptoms that manifest primarily as anger, sadness, isolation or a constellation of these states and dispositions may result in a more severe presentation of symptoms, chronic stress, and deleterious health outcomes.
Autonomic nervous system and state

• ANS is hierarchical
  • Concept: Dissolution
    • Higher nervous system arrangements inhibit/control the lower, and thus, when the higher are impaired, the lower rise in activity

• Regulates adaptation to safe, dangerous, and life threatening environments

Polyvagal Theory, Porges, 2007
Social engagement

Safe  →  Social Engagement

Danger  →  Fight/Flight

Life threat  →  Shutdown

Porges, Polyvagal
Polyvagal response strategies

• Removal of ventral vagal complex tone
• Increase in sympathetic tone
• Surge in dorsal vagal complex tone
Neuroception

• The detection of features in others or the environment – *without awareness* – that dampens defensive systems and facilitates social behavior OR promotes defensive strategies of mobilization (fight/flight) or immobilization (shutdown, dissociation).
  • Polyvagal concept

Challenges may:

• Shift physiological and behavioral state
• Distort social awareness
• Displace ‘appropriate’ spontaneous social behaviors with asocial behavior or defensive reactions

Porges, Polyvagal
Neuroception
Safe

FFA/STS

Amygdala
(central nucleus)

Motor Cortex

Medulla
(source nuclei V, VII, IX, X, XI)

Social Engagement System

Somatomotor
(muscles of face & head)

Visceromotor
(heart, bronchi)

Inhibitory pathways

Excitatory pathways

Porges, Polyvagal
Neuroception
Danger

Amygdala
(central nucleus)

dorsolateral and lateral
Periaqueductal Gray
Rostral Caudal

Fight
(pyramidal tracks)

Flight
(pyramidal tracks)

Autonomic State
(sympathetic)

Inhibitory pathways
Excitatory pathways

Porges, Polyvagal
Functional connectivity fMRI, PTSD

Data from VA, CDA-2, Williamson, PI
Functional connectivity, mild TBI

- 22 mTBI
- 22 healthy controls
- Resting state
- Primary findings
  - Hypoperfusion frontal poles

Chronic PTSD associated with systemic impairment

- Cardiovascular disease
  - Hypertension
  - Heart failure
- Diabetes
- Obesity
- Asthma
- Cancer
- Back pain
- Peripheral vascular disease
- Gastrointestinal problems
- Thyroid disorders
- Alzheimer’s disease
PTSD and Obesity

- Meta-analysis
- 13 studies
- 589,781 people with PTSD
- Odds ratio = 1.55

Bartoli et al., 2015. The Journal of Clinical Psychiatry
PTSD, elevated metabolic syndrome severity

- N = 971 Veterans from project VALOR (Veterans After-Discharge Longitudinal Registry) with PTSD
  - Mental health registry including PTSD and non-PTSD
- Age = 37 (+-10)
- 29% METs PTSD
  - vs 20% US pop
  - Between 20-39

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tr>
<td>Central obesity</td>
<td>BMI ≥ 25³</td>
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<tr>
<td>Dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>&lt;40 (men)</td>
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<tr>
<td></td>
<td>&lt;50 (women)</td>
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<tr>
<td>Triglycerides (mg/dl)</td>
<td>≥150</td>
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<tr>
<td>Elevated blood sugars</td>
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<td>Fasting glucose (mg/dl)</td>
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<td>Systolic blood pressure (mmHg)</td>
<td>≥130</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>≥85</td>
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</table>

Or taking cholesterol-lowering medication
Or taking medication for elevated triglycerides
Or taking medication for diabetes or elevated glucose
Or taking medication for hypertension

Wolf et al., 2016, *Psychological Medicine*
PTSD severity ➔ metabolic syndrome

Wolf et al., 2016, *Psychological Medicine*
• Poor sleep quality
Sleep disturbance in mild TBI and PTSD

• Very common after TBI
  • Insomnia, hypersomnia, apnea

• Also common in people with PTSD

• Sleep apnea in Veterans presents w insomnia more often than obesity
  • This is different than non-PTSD
  • Razaeitalab et al., 2018 *Sleep Breath*
Poor sleep quality and amyloid pathology

- N = 101 people from Wisconsin Registry for Alzheimer’s prevention
- CSF collection, cognitively normal
- Medical Outcomes Sleep Quality Scale
- CSF assayed
  - amyloid 42 [Aβ42]), tau pathology (phosphorylated tau [p-tau] 181), neuronal/axonal degeneration (total tau [t-tau], neurofilament light [NFL]), neuroinflammation/astroglial activation (monocyte chemoattractant protein–1 [MCP-1], chitinase-3-like protein 1 [YKL-40]), and synaptic dysfunction/degeneration (neurogranin)
- Worse subjective sleep quality, more sleep problems, and daytime somnolence were associated with greater AD pathology, indicated by lower CSF Aβ42/Aβ40 and higher t-tau/Aβ42, p-tau/Aβ42, MCP-1/Aβ42, and YKL-40/Aβ42.

Sprecher et al., 2017 *Neurology*
Chronic stress impacts hippocampal characteristics

• Numerous replications of various stress models in humans and rate demonstrating changes in hippocampal characteristics

• Neurogenesis has been demonstrated in adults in the hippocampus and is thought to be involved in learning and memory
  • E.g., Deng et al., 2009, *J Neurosci*

• Acute and chronic stressors reduce:
  • Cell proliferation
  • Differentiation
    • Egeland et al., 2015, *Nat Rev Neurosc*
  • Survival of new neurons in hippocampus
    • Shoenfeld at al 2012, *Experimental Neuro*
Stressed even when sleeping

- 13 Veterans with PTSD
- 17 trauma exposed controls
- 15 healthy controls
- Sleep study, 2 nights
- Patients with PTSD woke up more frequently
- Heart rate higher
- Adrenocorticotropic hormone and cortisol levels inversely related to slow wave sleep

Van Liempt et al., 2013 *Psychoneuroendocrinology*
RSA during sleep, PTSD

- 14 Panic Disorder, 14 PTSD, 13 PTSD+PD, 9 healthy controls

Woodward et al., 2009 Biological Psychiatry
Experimental evaluation of new neurons in hippocampus and stress

Experiment 1

De Miguel et al., 2018, Molecular Psychiatry
Experimental evaluation of new neurons in hippocampus and stress

Experiment 2

De Miguel et al., 2018, Molecular Psychiatry
Experimental evaluation of new neurons in hippocampus and stress

Experiment 3

De Miguel et al., 2018, Molecular Psychiatry
APOE4, PTSD and TBI recovery

• Limited long term data.

• Meta-analysis (only 12 studies, small n) of APOE4, TBI recovery shows:
  • No short term effect of APOE4
  • Possible medium to long term effect (>6 months out)
  • Li et al., 2015

• Several studies indicate APOE4 + combat exposure > PTSD
  • Eg., Kimbrel et al., 2015
    • N = 1624
Mild TBI, PTSD, genetic risk for AD, cortical thickness in AD related areas

  - Translational Research Center for TBI and Stress Disorders (TRACTS)
    - Veterans Affairs Boston Healthcare System.
  - Mean age = 31
  - 105 lifetime mild TBI, 85 PTSD
    - 27 APOE 4
  - 55 No TBI, 28 PTSD
    - 10 APOE 4

Hayes et al., 2017, *Brain*
From: Mild traumatic brain injury is associated with reduced cortical thickness in those at risk for Alzheimer's disease
Brain | Published by Oxford University Press on behalf of the Guarantors of Brain 2017. This work is written by US Government employees and is in the public domain in the United States
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DNA methylation and age predictions

• Epigenetic clock

• Measure DNA methylation levels to estimate biological age of a tissue, cell type or organ

• Steve Horvath – UCLA, DNA Methylation Age of Human Tissues and Cell Types
  • Genome Biol 2013

• Genome-wide Methylation Profiles Reveal Quantitative Views of Human Aging Rates
  • Hannum et al., 2013, Molecular Cell
Evidence of physiological aging in PTSD

• 241 Veterans screen followed 6.5 years
• DNA methylation analysis
• Hyperarousal symptoms associated with DNA methylation age
• Trauma exposure and total severity were not
• DNA methylation age also associated with 13% increase for all-cause morality

Wolf et al., 2017 *Psychosomatic Medicine*
Treatment and interrupting the cycle

• Monozygotic twin study
  • 20 pairs, one with PTSD one without
  • Decreased RSA in twin with PTSD at baseline

• Successful treatment associated with normalized RSA

• Negative health consequences may be reversible and preventable if treated before cumulative damage from chronic stress.

• Early resolution of PTSD critical to avoid cascade

• Promising potential treatments
  • Transcutaneous vagal nerve stimulation
Summary

- Mild TBI, especially multiple may increase vulnerability to PTSD acquisition
- Animal and human data demonstrate potential damage to prefrontal/limbic circuitry
- Behavioral effects of this damage associated with changes in processes relevant to poor resolution of PTSD (e.g., fear extinction learning decrements)
- PTSD is associated with many health related issues that may accelerate aging and poor aging outcomes
- Autonomic issues may be most impactful to these processes and seem to be pervasive in poor outcome categories
- Some preliminary data suggest that intervention may normalize autonomic features
- Unclear if mild TBI/multiple mild TBIs increase chronic PTSD severity or alter treatment success trajectories
Thank you!

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