Chronic Effects of Traumatic Brain Injury on Psychological Health
Disclaimer

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Overview of Workshop

- Introduction: The interaction between psychological health and traumatic brain injury
- Topic 1: Brain injury as a chronic condition
- Topic 2: Effects post-injury inflammation and stress on psychological health
- Topic 3: Mind, Brain, Body, and environment
- Summary
Introduction:
What does psychological health have to do with brain injury?
Psychological illnesses are behavioral manifestations of underlying disorders in physiological processes of the brain and/or endocrine systems.
Brain-Behavior Relationships and Regional Cortical Vulnerability to TBI

Dorsolateral prefrontal cortex
(executive function, including sustained and complex attention, memory retrieval, abstraction, judgement, insight, problem solving)

Orbitofrontal cortex
(emotional and social responding)

Anterior temporal cortex
(memory retrieval, sensory-limbic integration)

Amygdala
(emotional learning and conditioning, including fear/anxiety)

Ventral brainstem
(arousal, ascending activation of diencephalic, subcortical, and cortical structures)

Hippocampal-Entorhinal Complex
(declarative memory)

Viewed on coronal MRI

(Figure adapted from Arciniegas and Beresford 2001)
Psychological Health Issues After TBI

SOMATIC
Hyperarousal / Hypervigilance
Fatigue

NEUROPSYCHIATRIC
Anxiety Disorders
Depression (>25% with MTBI)
Irritability
Mood Swings
Sleep Disturbances
Flashbacks
Avoidance of triggers

COGNITIVE
Decreased Concentration
Memory Problems

Prevalence:
30% lifetime prevalence of PTSD in male veterans who served in Southeast Asia during the Vietnam war era (1965–1975) compared to 5% for the general male population [33].
The prevalence in the current conflicts is somewhere between 6 and 20%.

Chronic Pain 57.8% all types; 75.3% MTBI
(Nampiaparampil, JAMA. 2008;300(6):711-719.)
The TBI / PTSD Example

Models of mTBI and PTSD
Interface of PTSD and Persistent Postconcussive Symptoms

PTSD
- Reexperiencing symptoms
- Shame
- Guilt

PPCS
- Headache
- Sensitivity to light (and sound)
- Memory deficit
- Dizziness

Depression/anxiety
- Insomnia
- Irritability/anger
- Trouble concentrating
- Fatigue
- Hyperarousal
- Avoidance

Why are PTSD and TBI muddled?

- Common presentations
- Both can have delayed onset of symptoms
- Both have a hypoactive PFC vs. amygdala
- The failure to diagnose mild TBI due to insensitivity of tests or reliance on self-report.
- The misdiagnosis of PTSD for other anxiety orders.
- Complex comorbidities
Self-Reports of Head Injury.
Two studies estimated the prevalence of mild traumatic brain injury.

• The first (Vasterling et al., 2006) asked whether the respondent had suffered a prior head injury with loss of consciousness lasting longer than 15 minutes.

• The other (Hoge et al., 2008) identified respondents as having mild TBI if they reported a head injury and one of the following three conditions: (1) loss of consciousness; (2) being dazed, confused, or “seeing stars”; or (3) not remembering the injury.

• While some preliminary evidence suggests that these screening criteria are valid for identifying cases of mild TBI (Schwab et al., 2007), more thorough validation of these tools is needed.

• False negatives may result from relying upon the inaccurate self-report of brain injured individuals.
Can TBI and PTSD co-exist?

- PTSD following TBI is often difficult to diagnose, because many of the symptoms overlap.

- Compared to non-TBI PTSD, TBI patients reported more greater anxiety and more intrusive memories; the rate of intrusions decreased over time in non-TBI PTSD patients, but increased in those who had sustained a mTBI.

PTSD in TBI

• One of the reasons that it is difficult to diagnose PTSD following TBI is the similarity of symptoms, such as memory deficits, fatigue, and irritability.

• 33% of the sample had shown symptoms of diagnosable PTSD.

• The tools used to measure PTSD symptoms are brought into question Ohry et al., as many of the PTSD symptoms in TBI survivors are also characteristic of post-concussive disorder.

Ohry et. al, Brain Inj. 1996 Sep;10(9):687-95
False Positives in PTSD Diagnosis

86% of subjects with PTSD
5% of healthy controls
43% of subjects with other, non-PTSD, anxiety disorders

Met the PTSD diagnosis criteria using the PTSD Symptom Scale (PSS), a self-report instrument

The Effects of Lost of Consciousness

- LOC may have protective effects against the development of PTSD, as the memory of the traumatic event does not exist.
- PTSD may be less prevalent in patients with LOC, but it does occur.
- No differences in levels of depression were reported between the conscious and unconscious groups.
- The conscious group, however, reported greater levels of anxiety than did the unconscious group.

Prevalence of PTSD after severe TBI

• 18 percent of TBI survivors suffered from moderate to severe symptoms of PTSD
• The trauma itself may have a negative emotional impact and serve as a traumatic psychological stressor, resulting in the development of PTSD symptoms following TBI
• PTSD symptoms are common following severe TBI, although compared to mTBI survivors, PTSD symptoms are less common
• Careful measure must be taken in terms of assessment of PTSD symptoms in TBI survivors; self-reports are not always accurate

Is the Memory of the TBI Event Necessary?

• Findings of the study showed relationship between TBI severity and level of PTSS
• Memory of the traumatic event is not required for the development of PTSS symptoms
• Severity of PTSS symptoms was greater at 12 months, compared to 6 months

Topic 1

Brain injury as a chronic condition
Detecting Post-Concussion Syndrome

fMRI Imaging - Additional activation in posterior brain region. Both mild and moderate PCS groups showed activation peaks in the left temporal lobe (circled in red) during the verbal working memory task, whereas the frontal cortex is deactivated (circled blue). These peaks were not present in the normal control group. J.K. Chen et al. (2007) J. Neurol. Neurosurg. Psychiatry.
Fiber Tractography

Healthy volunteers

DAI patients

TBI: Concussion Vs. Blast

M. Huang et al., J Neurotrauma, (Apr 22, 2009).
The effects of blast on white matter integrity

J. R. Wrathall et al., J Neurotrauma, (Jun 9, 2009).
DTI and Cognitive Performance

6-months Post-Injury

DTI Reveals mTBI Link to Symptoms

Results:
DTI measures revealed several regions of damage including the anterior corona radiata (41%), uncinate fasciculus (29%), genu of the corpus callosum (21%), inf. longitudinal fasciculus (21%), and cingulum bundle (18%).

Conclusion:
Microstructural white matter lesions detected by DTI correlate with persistent cognitive deficits in mild TBI up to 65 months post-injury.
Topic 2

Effects of inflammation and stress on psychological health
TBI and Acute Inflammation

Inflammation During Acute TBI

• Maegele, et al. 2007:
  – Traumatic brain injury often elicits a ‘cytokine-mediated immunoresponse,’ as implicated by increased levels of cytokine production and circulation
  – Additive effects of cytokines in terms of circulating levels and duration as a result of multiple injuries

• Csuka, E., M. C. Morganti-Kossmann, et al. (1999):
  – Inflammation following brain trauma has been associated with adverse outcomes, therefore it may be beneficial to regulate inflammatory responses following TBI
  – Increased levels of proinflammatory cytokines have been shown in both human and animal models

• Wang, C. X. and A. Shuaib (2002).
  – Cytokines IL-1β and TNF are generally considered perpetrators of secondary CNS injury.
Inflammation in the Chronic Phase after TBI

- Holmin and Mathiesen 1999:
  - Persistent major histocompatibility complex (MHC)-II up-regulation, mononuclear phagocytes, IL-1β and TNFα synthesis were detected in large areas of injured hemisphere at 3 months post-injury in rats.

- Gentleman, et al. 2004:
  - Microglial hyperplasia and hypertrophy with both MHC class II upregulation and increased phagocytosis in the white matter of cases of fatal head injury, and continued neuroinflammation for up to 16 years in survivors.
  - This may be due to the consequences of both focal and diffuse pathologies after traumatic brain injury and may form the basis for the cognitive deficits seen in long-term survivors.
Markers of microglia and MHC class II activated cells post-injury

# Cerebral Infarct

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<thead>
<tr>
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<tbody>
<tr>
<td>Evolution of lesion</td>
<td>1 day–53 years</td>
<td>16 h–27 days</td>
<td>2.5 h–16 days</td>
<td>30 min–7 days</td>
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<tr>
<td>Eosinophilic neurons</td>
<td>1–35 days</td>
<td>1–14 days</td>
<td>After 12 h</td>
<td>N/A</td>
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<tr>
<td>Other neuronal injury</td>
<td>1–60 days</td>
<td>2–27 days</td>
<td>1–16 days</td>
<td>30 min–7 days</td>
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<tr>
<td>Neuronal ferrugination</td>
<td>3 days and older</td>
<td>10–27 days</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Spheroids</td>
<td>1 day and older</td>
<td>N/A</td>
<td>1–16 days</td>
<td>12 h–7 days</td>
</tr>
<tr>
<td>Coagulative necrosis</td>
<td>1 day–5 years</td>
<td>N/A</td>
<td>N/A</td>
<td>After 2 days</td>
</tr>
<tr>
<td>Polymorphonuclear leucocytes (6)</td>
<td>1–37 day</td>
<td>1–10 days</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mononuclear cells (7)</td>
<td>3 days–53 years</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Perivascular cuffing (8)</td>
<td>3 days–53 years</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Macrophages</td>
<td>3 days–53 years</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Neuronophagia</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4/127 cases</td>
<td>15/31 cases</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hemosiderin</td>
<td>3 days and older</td>
<td>After 8 days</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Hematoidin</td>
<td>3 days and older</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Spongiosis</td>
<td>1 day and older</td>
<td>1–27 days</td>
<td>1–7 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Astrogliosis</td>
<td>2 days and older</td>
<td>After 10 days</td>
<td>7–16 days</td>
<td>N/A</td>
</tr>
<tr>
<td>Neovascularization</td>
<td>3 days and older</td>
<td>4–27 days</td>
<td>7–16 days</td>
<td>1–24 h</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2/27</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Vasculitis</td>
<td>2/27</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Cavitation</td>
<td>12 days and older</td>
<td>After 13 days</td>
<td>N/A</td>
<td>N/A</td>
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Inflammation and Psychological Health

• Justo, et al. 2008:
  – Chronic inflammation in men is correlated with mental health crises.

• García-Bueno, et al., 2008:
  – Pro-inflammatory cytokines (such as IL-1b) may mediate some of the behavioral responses that occur during stress including “depressive-like” behaviors.
  – Studies showing that acute inhibition of pro-inflammatory mediators prevents these acute and chronic stress-induced behaviors.

• Ford and Erlinger, 2004:
  – C-Reactive Protein levels were higher among men who had a more recent (within 1 yr) episode of depression and who had recurrent depression.
Development of sickness behavior in response to an infection is part of our normal response to fight infection.

During acute inflammation, these behavioral changes are adaptive and allow the body to mobilize necessary resources for the healing process.

In chronic condition microglia become primed by the ongoing pathology and these microglia, respond to a systemic challenge with a heightened reaction.

A normal part of our homeostatic signaling from periphery to brain has the potential to have a profound impact on brain disease initiation or progression.  

(Teeling and Perry in Press)
Dysfunctional PFC in PTSD as Compared to TBI


The Connection Between Inflammation and Stress


<table>
<thead>
<tr>
<th>Human</th>
<th>Animal Models</th>
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<tr>
<td>Exposure to stressors has a causal association with major depression (MD).</td>
<td>Chronic stress induces depressive-like behavioral and physiological symptoms.</td>
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<tr>
<td>A high incidence of depression is associated with various inflammatory conditions.</td>
<td>Exposure to various immune challenges produces depressive-like symptoms, which can be attenuated by chronic antidepressant treatment.</td>
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<tr>
<td>Immunotherapy with cytokines induces MD, which can be reversed by antidepressants.</td>
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<td>Experimental immune stimulation causes depressed mood in normal subjects.</td>
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<tr>
<td>The levels of IL-1 in MD patients are markedly elevated, and IL-1 levels are correlated positively with the severity and duration of MD, and negatively with the age of MD onset.</td>
<td>Peripheral or central administration of IL-1 produces depressive-like symptoms.</td>
</tr>
<tr>
<td>Polymorphisms in IL-1 family genes are associated with MD severity and its responsiveness to antidepressant drugs.</td>
<td>In mice with impaired IL-1 signaling chronic stress does not induce depression.</td>
</tr>
<tr>
<td>MD patients exhibit activation of the HPA axis and hypersecretion of cortisol, which are normalized by antidepressant therapy.</td>
<td>Stress- or immune activation-induced depression is blocked by IL-1ra.</td>
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<tr>
<td>The glucocorticoid antagonist mifepristone can be used as an antidepressant drug.</td>
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<tr>
<td>Hypercortisolemia, as well as treatment with high glucocorticoids doses can induce MD.</td>
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<tr>
<td>In MD patients hippocampal volume is reduced, in association with illness duration.</td>
<td>IL-1 activates the HPA axis and elevates plasma cortisol levels.</td>
</tr>
<tr>
<td>Chronic antidepressant treatment increases hippocampal volume.</td>
<td>Adrenalectomy and mifepristone block stress-induced depressive symptoms.</td>
</tr>
<tr>
<td>Stress decreases hippocampal neurogenesis. Antidepressants increase neurogenesis.</td>
<td>Chronic corticosterone administration induces depressive symptoms, even in IL-1 signaling deficient mice.</td>
</tr>
<tr>
<td>This increase is necessary for the achievement of the therapeutic effect of antidepressants.</td>
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</tr>
<tr>
<td>Antidepressants and IL-1 blockade prevent stress-induced neurogenesis reduction.</td>
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</table>
Chronic Fear and Anxiety Positive Feedback Loop
TOPIC 3

Mind, Brain, Body and Environment
Mind, Body, Environment Interaction

Environmental stressors (work, home, neighborhood)

Major life events

Perceived stress (threat, helplessness, vigilance)

Trauma, abuse

Behavioral responses (fight or flight; personal behavior — diet, smoking, drinking, exercise)

Individual differences (genes, development, experience)

Physiologic responses

Allostasis

Adaptation

Allostatic load

What is an Enriched Environment?

- Environment that promotes optimal development
- Provides stimulation and rest/recovery
- Enriched means better than abuse- and deprivation-free
- In animals:
  - Promotes brain plasticity
  - More robust HPA axis
Environmental Enrichment (EE) Outcomes

- Social environment
- Physical training: acrobatics and aerobics
- Spatial complexity of environment
- Cognitive challenge
- Multi-Sensory stimulation
- Nutrition
- Sleep

Enhanced:
- Cognitive ability
- Motor ability
- Structural complexity

Reduced:
- Social aggression
- Anxiety
**Protective and Therapeutic Effects**

- Higher basal corticosterone but smaller amplitude response to stressful situations and faster return to baseline
- Excessive enrichment may be detrimental; inverted U dose response curve
- Stress inoculation: mild stressors presented in a predictable and controlled manner with opportunities for recovery
- Protects the individual against subsequent sudden, intense, and uncontrolled psychological stress
- EE promotes recovery from brain injury

EE after TBI

EE attenuates cognitive deficits and preserves tissue integrity in a TBI model which causes cerebral contusion and cell death.

Passineau, M., Green, E. and Deitrich, D. Therapeutic Effects of Environmental Enrichment on Cognitive Function and Tissue Integrity Following Severe Traumatic Brain Injury in Rats, Experimental Neurology Volume 168, Issue 2, April 2001, Pages 373-384

EE promotes recovery after brain injury: demonstrated under many conditions over decades of research.

EE and Inflammation

Benefits of EE may be associated with inhibition of the expression of immunity and inflammation-related genes in the brain.

Dong, S, et al., Environment enrichment rescues the neurodegenerative phenotypes in presenilins-deficient mice, European Journal of Neuroscience, Volume 26, Number 1, July 2007, pp. 101-112

EE alters physiological properties within the anterior cingulate cortex which results in enhanced responses to acute and long-term inflammation.

Fanny W.F. Shum, Long-Jun Wu, Ming-Gao Zhao, et al. Alteration of cingulate long-term plasticity and behavioral sensitization to inflammation by environmental enrichment, Learn. Mem. 2007 14: 304-312
EE May Protect Against TBI and Stress

• Animals enriched prior to TBI showed more exploratory behavior in EPM after TBI, compared to non-enriched prior.
• Animals enriched prior to TBI showed improved learning on MWM, compared to non-enriched prior.
• EE attenuates responses to certain anxiety provoking situations, and that these effects persist over time.
• EE attenuates behavioral anxiety-type responses and endocrine responses mediated via the hypothalamic-pituitary-adrenal (HPA) axis evoked by psychogenic and/or neurogenic stressors.
• EE attenuates the enduring or persistent effects engendered by past psychogenic stressor(s) such as prenatal stress or neonatal maternal separation.

Neurorehabilitation as EE

- Design experiences and environments to promote recovery of function
- Consider plasticity promoting effects of specific stressors/enrichments
- Highly individualized response to stressors requires careful case management

Music Therapy

T. Sarkamo et al., Brain 131, 866 (Mar, 2008).
Aerobic activity: Daily high-dose aerobic exercise

- Physiological effects have been found in addition to increased exercise capacity, however.
- For example, regular aerobic exercise has a normalizing effect on the cortisol system.
- ENP draws upon evidence of the importance of motor cortex involvement in recovery from TBI.
- Agility appears to be a stronger promoter of recovery in the animal research.
- EE environments generally offer the opportunity for aerobic exercise in synergy with acrobatic elements.
Virtual Reality and EE

• Efficacy of environmental enrichment in promoting neural plasticity and positive functional outcomes

• The onus to create rehabilitation conditions most conducive to harnessing plasticity falls squarely on the shoulders of clinicians.

• Can the emerging technology of Virtual Reality (VR) provide the means to increase patients' cerebral activation levels via the use of enriched Virtual Environments (VEs)?
Remote Delivery of VR

Problem: Existing VR assistant tools tend to be available in clinical research facilities, but not in patients’ homes.

Solutions:
• Develop affordable high-quality, portable hardware.
• Produce robust hardware.
• Due to the vast amount of 3D data.
• Create new visual displays and input devices.
• Facilitate development and operation of user friendly programs.
• Reduce side effects due to VR usage.
• Making the exercises enticing.