Mind Blasting Effects
Chronic Traumatic Encephalopathy

“It is no longer debatable whether or not there is a problem in football — there is a problem”
NEWS: UCLA STUDY FINDS CTE IN LIVING FORMER NFL PLAYERS.

Go ahead - you take a knee... I'll take a brain...


**CTE MARKERS**

**TAU**

- Proteins present in nerve cells
- Function: stabilize and maintain shape of microtubules (responsible for transport of nutrients between axon and cell body)

**NFTs**

(neurofibrillary tangles)

- Product of hyperphosphorylated tau, a condition in which tau is overly present
- Prevent passage to/from synapse resulting in synaptic dysfunction and degeneration
Causes

Key Variables:
Concentration of tau buildup
Force of blow impact
Starting age
Length of exposure

Repeated, heavy blows to the head over extended periods of time cause tau proteins to fall off
Clump together and form NFTs

Uncertain findings, but connecting the formation of NFTs to damage inflicted by traumatic brain injuries may provide path to better understanding of CTE

sub-concussive impacts equally if not more responsible than concussions
SYMPTOMS

Behavior and Mood
- “Out-of-control” and “explosive”
- Increased rage, aggression, irritability, and impulsivity
- Physically and emotionally violent
- Depressive/suicidal thoughts

Cognitive Ability
- Memory impairment
- Executive dysfunction (planning, organization, multitasking, and judgment)
- Difficulty learning and retaining new information
The Science of Head Trauma
Ann Mckee - Boston University
- studied 85 brains and spinal cords of athletes, military veterans, and civilians
- compared these to 18 people without history of brain trauma
- history of brain trauma and cognitive and behavioral changes determined by interview with closest relative
- neuropathological features of CTE include
  - withering of the cerebral cortex, medial temporal lobe, diencephalon and mammillary bodies with enlarged ventricles
  - cavum septum pellucidum, often with fenestrations
  - extensive neurofibrillary tangles and astrocytic tangles in the frontal and temporal cortices
  - neurofibrillary tangles in limbic regions, diencephalon and brainstem nuclei
  - extensive degeneration of axons and white matter fiber bundles
  - a relative absence of amyloid-β peptide deposits

“The spectrum of disease in chronic traumatic encephalopathy”
<table>
<thead>
<tr>
<th>Pathological features</th>
<th>Alzheimer's disease</th>
<th>CTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tau protein</td>
<td>All six isoforms present</td>
<td>All six isoforms present&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Six isoforms</td>
<td>3 repeat and 4 repeat tau present</td>
<td>3 repeat and 4 repeat tau present</td>
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<tr>
<td>3 or 4 repeat tau</td>
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<tr>
<td>Cell origin</td>
<td></td>
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<tr>
<td>Neuronal</td>
<td>NFTs and pre-tangles</td>
<td>NFTs and pre-tangles</td>
</tr>
<tr>
<td>Astrocytic</td>
<td>Not present&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Prominent astrocytic tangles</td>
</tr>
<tr>
<td>Neuronal domain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell body</td>
<td>Prominent</td>
<td>Prominent</td>
</tr>
<tr>
<td>Dendrite</td>
<td>Prominent</td>
<td>Prominent</td>
</tr>
<tr>
<td>Axon</td>
<td>Sparse</td>
<td>Prominent</td>
</tr>
<tr>
<td>Cell Pattern</td>
<td></td>
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</tr>
<tr>
<td>Perivascular</td>
<td>Not present</td>
<td>Prominent NFTs and astrocytic tangles</td>
</tr>
<tr>
<td>Foci at depths of cerebral sulci</td>
<td>Not present</td>
<td>Prominent NFTs and astrocytic tangles</td>
</tr>
<tr>
<td>Irregular, patchy cortical distribution</td>
<td>Not present</td>
<td>Prominent</td>
</tr>
<tr>
<td>Cortical laminae</td>
<td>NFTs predominantly in laminae III and V</td>
<td>NFTs predominantly in laminae II–III</td>
</tr>
<tr>
<td>Subpial astrocytic tangles</td>
<td>Not present</td>
<td>Prominent</td>
</tr>
<tr>
<td>Periventricular astrocytic tangles</td>
<td>Not present</td>
<td>Present</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
<td></td>
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<tr>
<td>Mild pathology</td>
<td>Braak stages I–III:</td>
<td>CTE stages I–II:</td>
</tr>
<tr>
<td></td>
<td>NFTs in entorhinal cortex, amygdala and hippocampus</td>
<td>NFTs in focal epicentres in cerebral cortex, usually frontal lobe</td>
</tr>
<tr>
<td>Advanced pathology</td>
<td>Braak stages IV–VI:</td>
<td>CTE stages III–IV:</td>
</tr>
<tr>
<td></td>
<td>High density of NFTs in widespread cortical areas and medial temporal lobe, uniform distribution</td>
<td>High density of NFTs in widespread cortical areas and medial temporal lobe, patchy irregular distribution</td>
</tr>
<tr>
<td></td>
<td>Low densities of NFTs in basal ganglia and brainstem; none in mammillary bodies. White matter tracts relatively uninvolved</td>
<td>High densities of NFTs in thalamus, hypothalamus, mammillary bodies, brainstem. Moderate densities of NFTs in basal ganglia, especially nucleus accumbens. Prominent p-tau pathology in white matter tracts.</td>
</tr>
</tbody>
</table>
- A-O: Alzheimer's Disease
- P-FF: CTE

- A-C: NFTs in laminae III and IV
- P-R & U-W: NFTs in laminae II-III, more prominent

- D,E,I,J vs S,T,X,Y small blood vessels at sulci depths—clustering of NFTs

- K vs Z: astrocytic tangles in depth of sulci

- L vs AA: NFTs in periventricular region of third ventricle

- M vs BB: amyloid-β plaques (red), neurofibrillary tangles (brown)

- N: moderate neurofibrillary change in substantia nigra; CC: astrocytic tangles & NFTs in substantia nigra

- O vs DD: astrocytic tangle & NFTs in mammillary bodies
Stage 1

- p-tau neurofibrillary and astrocytic tangles, most prominent in the sulci depths and typically affecting superior and dorsolateral frontal cortices
- symptoms reported
  - headache
  - Loss of attention and concentration
  - Short-term memory loss

Stage 2

- p-tau pathology found most commonly in frontal, anterior, inferior and lateral temporal, inferior parietal, insular and septal cortices. Neurofibrillary tangles were also found in the superficial layers of cortex
- symptoms reported
  - headache
  - loss of attention and concentration
  - explosivity
  - short-term memory loss
  - depression
Stage 3
• Shrinking of the mammillary bodies and thalamus, thinning of corpus callosum
• Neurofibrillary tangles throughout frontal, temporal and inferior parietal cortices, hippocampus, entorhinal cortex, amygdala, nucleus basalis of Meynert and locus coeruleus, hypothalamus, mammillary bodies, substantia nigra and dorsal and median raphe nuclei
• Symptoms
  • memory loss, executive dysfunction, difficulty with attention and concentration, depression or mood swings, visuospatial difficulties and aggression

Stage 4
• Shrinking of the cerebral cortex, medial temporal lobe, thalamus, hypothalamus and mammillary body
• Neuronal loss in the cortex, hippocampal sclerosis affecting CA1 and subiculum and astrocytic p-tau pathology
• Severe p-tau abnormalities were found widely distributed throughout the cerebrum, diencephalon, basal ganglia, brainstem and spinal cord
• Symptoms
  • severe memory loss, profound loss of attention and concentration, executive dysfunction, language difficulties, aggressive tendencies, paranoia, depression, gait and visuospatial difficulties.
<table>
<thead>
<tr>
<th>Location</th>
<th>Stages I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal epicenters</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
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<tr>
<td>Adjacent cortex</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
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<tr>
<td>Amygdala</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
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<tr>
<td>Hippocampus</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
<td><img src="image16.png" alt="Image" /></td>
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<tr>
<td>Nucleus basalis of Meynert</td>
<td><img src="image17.png" alt="Image" /></td>
<td><img src="image18.png" alt="Image" /></td>
<td><img src="image19.png" alt="Image" /></td>
<td><img src="image20.png" alt="Image" /></td>
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<tr>
<td>Substantia nigra</td>
<td><img src="image21.png" alt="Image" /></td>
<td><img src="image22.png" alt="Image" /></td>
<td><img src="image23.png" alt="Image" /></td>
<td><img src="image24.png" alt="Image" /></td>
</tr>
<tr>
<td>Locus coeruleus</td>
<td><img src="image25.png" alt="Image" /></td>
<td><img src="image26.png" alt="Image" /></td>
<td><img src="image27.png" alt="Image" /></td>
<td><img src="image28.png" alt="Image" /></td>
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</tbody>
</table>

**Brain Diagram**

- Neocortex
- Thalamus
- Hypothalamus
- Amygdala
- Locus coeruleus
- Hippocampus
- Spinal Cord
- Substantia Nigra
- Spinal Cord
- Nucleus basalis of Meynert
- Septum pellucidum
- Hippocampus
Diagnosis

The only definitive way to identify CTE is through autopsy

However...
Punch Drunk
(dementia pugilistica)
Degenerated Brain Regions

the frontal lobes
medial temporal lobes
Hippocampus
Amygdala
brainstem
Immune Response and Inflammatory Agents

Maroon and Baylock theorize: “if you get repetitive blows to the head before the brain has healed, this normal repair process gets stuck in the accelerated mode and continues to pour out inflammatory agents, which leads to neurodegeneration and CTE.”
CTE and Suicide
Bennet Omalu

Published in Journal Neuroscience - Mike Webster (2005) and Terry Long (2006)

Officially - Chronic Traumatic Encephalopathy
Terry Long
Dave Duerson
Junior Seau
Conclusion?

Inconclusive:

Relationship between CTE and suicide rate very low on the GRADE criteria

Not enough case studies

Fairly new research
How Blasts Affect the Brain

Blast exposure associated with cerebellum

Reduced glucose metabolism in cerebellum of blast-exposed veteran

More blast exposure directly correlated with suppressed neuronal activity
Glucose Metabolism: Fueling the Brain

Brain demands high amount of glucose

Glucose metabolism is the foundation of cellular maintenance and neurotransmitter generation
In the Battlefield

—

Blast related head injury
Because we are the Orange Turtles and it’s time to talk about some shells
“shell shock”

-first appeared in February 1915 in an article in the Lancet
-the case studies of three British soldiers exposed to blast events who complained of
  1. Sleeplessness
  2. reduced visual field
  3. and loss of taste, hearing, and memory.

Initially their affliction was believed to be a “commotional disorder,” referring to agitation of the brain caused by a blast shock wave.
Who is Affected??

Blast-related traumatic brain injury (TBI) is among the most frequent injuries sustained by soldiers and other personnel who have served in recent wars in Iraq and Afghanistan (Eskridge et al., 2012; McCrea et al., 2009; MacGregor et al., 2011).
Battlefield Head Trauma

The soldiers, whose ages ranged between 22 and 45
All experienced **cognitive, emotional, and impulse-control problems** prior to their deaths.

But **unlike the CTE** pathology described in American football players and wrestlers, which is primarily observed in the brain’s frontal lobes, the damage to the veterans’ brains was **more evenly distributed**.
Why is it different?

-explosive blast is accompanied by an extraordinary change in atmospheric pressure that involves an initial period of peak overpressure, and then a subsequent negative blast phase (under-pressure) that may cause various forms of physical injury, including TBI. Theoretically, blast may result in four types of independent mechanisms of injury: primary, secondary, tertiary, and quaternary effects (DePalma et al., 2005; Mayorga et al., 1997; Taber et al., 2006).
Four Stages
Primary blast injury refers to the direct effect of the blast itself.

- Affects Air-filled organs, such as the lungs
- Not uncommon for primary blast exposure to cause **pulmonary hemorrhages or other forms of internal bleeding**. The tympanic membrane (TM) is also regarded as especially vulnerable to primary blast
- Been identified as a potential proxy for concussive injury (Xydakis et al., 2007)
There are several theorized means by which concussion might result from primary blast exposure, such as *thoracic, translational/rotational, and direct cranial entry mechanisms* (Courtney and Courtney, 2011).
Secondary

Refer to injuries that are sustained as a result of *debris being projected toward the body*, include such injuries as penetrating injuries from projectiles or fragments (DePalma et al., 2005)
Tertiary

A result of the body being displaced as a result of blast, and in the case of TBI, may occur when an individual is thrown against a wall or other stationary object.
Quatemary

The blast effects are everything else—fire that burns, chemicals that sear, dust that asphyxiates.
The Study:

Chronic Traumatic Encephalopathy in Blast-Exposed Military Veterans and a Blast Neurotrauma Mouse Model

Findings: The contribution of blast wind to injurious head acceleration may be a primary injury mechanism leading to blast-related TBI and CTE.
1. exposed mice to a single shock-tube blast that simulated the effects of a moderate-size explosive.
2. High-speed cameras captured the results—a rapid bobble-head effect, as the heads of the mice shook back and forth in reaction to the force.
3. In 30 milliseconds, far less than the blink of an eye, the oscillating wind had spiked and dipped nine times.
4. Two weeks after exposure to the blast, the mice brains showed an accumulation of chemically modified tau protein and other damage.
In Vivo Blast-Induced Traumatic Brain Injury Model

Compressed Driver Gas

Shock Tube

Pressure Transducers

Shock Wave Propagation

Mouse Holder

Adjustable Nose Bar

Main Critique
The mystery lies in the effects of the primary blast.

Theories range wildly: Is it the shock wave’s entry to the brain through cranial orifices—eyes, nose, ears, mouth—that causes injury, and if so, how? Or is external shock pressure on the chest channeled inside vasculature up through the neck and into the brain? Does the transmission of complex wave activity by the skull into the semiliquid brain cause an embolism? Does pressure deform the skull, causing it to squeeze the brain? Is the explosive noise damaging? The flash of light? The majority of soldiers diagnosed with blast-induced neurotrauma have also been hurled or rattled by blast wind. Is military neurotrauma, than, simply an exotic form of concussion?
Estimates of the prevalence of blast-related TBI in military personnel deployed to Iraq (Operation Iraqi Freedom, OIF; now Operation New Dawn) and Afghanistan (Operation Enduring Freedom; OEF) have been as high as 19%–23% (Tanielian and Jaycox, 2008; Terrio et al., 2009; Polusny et al., 2011).
# Testing for a Concussion

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural imaging</td>
<td>Normal</td>
<td>Normal or abnormal</td>
<td>Normal or abnormal</td>
</tr>
<tr>
<td>Loss of consciousness (LOC)</td>
<td>0–30 minutes</td>
<td>&gt;30 minutes and &lt;24 hours</td>
<td>&gt;24 hours</td>
</tr>
<tr>
<td>Alteration of consciousness/mental state*</td>
<td>A moment up to 24 hours</td>
<td>&gt;24 hours; severity based on other criteria.</td>
<td>&gt;24 hours; severity based on other criteria.</td>
</tr>
<tr>
<td>Posttraumatic amnesia</td>
<td>0–1 day</td>
<td>&gt;1 and &lt;7 days</td>
<td>&gt;7 days</td>
</tr>
<tr>
<td>Glasgow Coma Scale (best available score in first 24 hours)</td>
<td>13–15</td>
<td>9–12</td>
<td>&lt;9</td>
</tr>
</tbody>
</table>

*Alteration of consciousness/mental state: A moment up to 24 hours; >24 hours; severity based on other criteria.*
Why This is Not Working

Relying on self reporting

- Reported after the fact
- Highly nonspecific quality of the physical, cognitive, and emotional symptoms that may be reported in the postacute phase of recovery
- Factors other than concussion itself often better account for the symptoms/impairments that individuals report/exhibit in the months and years after concussions are sustained.
In the future, **photonic crystalline materials** that change color when exposed to blast waves, worn as stickers on uniforms and helmets, may provide an objective measurement of blast exposure.
Citations


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“Brain Imaging: Tackling CTE”

“The Differences Between Blast-Induced and Sports-Related Brain Injuries”
http://journal.frontiersin.org/article/10.3389/fneur.2013.00119/full#

“Clinicopathological Evaluation of CTE in Players of American Football”
http://jamanetwork.com/journals/jama/fullarticle/2645104
Citations Cont’d


“Head to Head: The NFL & Brain Injury” https://med.nyu.edu/highschoolbioethics/briefs/head-to-head