The Neurophysiology of Concussion, Electrophysiology, and Chronic Traumatic Encephalopathy

He’s seeing stars.
When can he safely return to being a star?

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Overview

• Physics of injury
• Pathophysiology
• EEG, Evoked potentials (EPs), and Event-related potentials (ERPs)
• Chronic Traumatic Encephalopathy (CTE)
• A model to address post-career CTE symptoms
Recent reference material

The Oxford Handbook of Sports-related Concussion (2014)

Electroencephalography

Michael B. Gaetz Ph.D. and Kelly J. Jantzen Ph.D.
Ruben Echemendia and Grant L. Iverson (Eds)

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Physics of injury

• Concussion is caused by acceleration-deceleration forces sustained by the brain
• The brain moves within the cranium
• The axons of neurons stretch
• This occurs in a diffuse pattern
• Neurons can become temporarily disabled or permanently injured
• Most neurons “recover” – some die.
Acceleration-Deceleration forces

Hockey Concussions
Shear forces

- Rapid head rotations generate shear forces throughout the brain
- Rotational accelerations have a high potential to cause shear-induced tissue damage
- This should not to be confused with the physical “shearing” or cutting of axons—a common misconception that persists today
- Lateral (coronal) plane accelerations have the greatest likelihood for producing damage within the deep internal structures of the human brain
Lateral rotational forces cause the greatest damage.

Damage maximally occurs to fronto-temporal grey-white interface.
Axons can be stretched by acceleration-deceleration forces.
White matter tracts in the brain
White matter tracts are stretched
White matter tracts are stretched
Stretch results in ionic influx

Neuronal stretching:

- Human neurons have a remarkable capacity for stretch with no primary axotomy observed with strains below 65% of their length.

Injury occurs to the neuron’s cytoskeleton

Stage 1 Injury: 5% strain or less.

Result: Failure of the generation and propagation of action potentials. Normal ionic balance is restored in a matter of minutes, and the damaged axon recovers its function completely.
Injury occurs to the neuron’s cytoskeleton

Stage 2 Injury: 5-10% strain.

Swelling and enlargement with mild impairment of axoplasmic flow.

Result: Very few of these injured cells undergo secondary axotomy and most recover electrophysiologically.
In neurons that recover from stretching:

- There is evidence for persistent metabolic dysfunction and even a change in DNA in “recovered” neurons.

• Roughly 10–15% of the acceleration experienced when heading a soccer ball causes considerable brain movement.

FIG. 5. Reference (a; 0 msec after tagging) and deformed (b; 78 msec post-tagging) phase contours (deformation 5× actual) from pairs of tagged sagittal MR images. (c) Maximum principal Lagrangian strain field, $\epsilon_1$, for the deformed sagittal image. Reference (d) and deformed (e) phase contours from pairs of tagged axial images. (f) Maximum principal Lagrangian strain, $\epsilon_1$, field for the deformed axial image. The value $\epsilon_1$ describes the maximum elongation of an element, relative to its original length, when the element is oriented so it experiences only elongation and shortening. In principal strain figures, the length of each line reflects the magnitude of $\epsilon_1$; the direction of each line shows the orientation of principal strain.
Dendrites

- Animal models show a decrease in dendritic branching and length following mTBI.

Dendritic spines

- mTBI leads to dendritic spine degeneration affecting both spine number and quality.

Glial cells

- Non-injured astrocytes clear glutamate from the extracellular space via the glutamate aspartate transporter (GLAST), and glutamate transporter-1 (GLT-1).
- High extracellular glutamate (i.e. neurometabolic cascade that occurs post-mTBI) induces a decline in GLT-1 and GLAST expression in cultured cortical astrocytes.
- Inflammation in the CNS is driven by the microglia, astrocytes, and peripheral macrophages via cytokine release – this is also affected post-injury.
Vascular injury

• Neurons are injured in a diffuse manner
• This is typically not detectable using CT or MRI
• There is usually no damage to arterioles or venules
• When vascular damage occurs, this is often detectable using CT and MRI.
Electrophysiology

• Electroencephalography (EEG)
• Evoked potentials (EP)
• Event-related potentials (ERP)
Neural basis of electrophysiology:

• Potential fluctuations recorded in the EEG reflect ionic capacitance currents flowing across neuronal membranes resulting in extracellular field potentials.

• EEG signals of interest primarily reflect the spatiotemporal summation of excitatory and inhibitory synaptic activity originating from ensembles of cortical pyramidal cells.
Electroencephalography

- Beta ($\beta$) 13-30 Hz
  - Frontally and panetically

- Alpha ($\alpha$) 8-13 Hz
  - Occipitally

- Theta ($\theta$) 4-8 Hz
  - Children, sleeping adults

- Delta ($\delta$) 0.5-4 Hz
  - Infants, sleeping adults

- Spikes
  - 3 Hz

- Epilepsy - petit mal
  - 200 $\mu$V
  - 100 $\mu$V

- Time [s]

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Figure 2. RSOI of resting 4 using electrodes concentrated over right posterior scalp region. Symmetrical eye movements were recorded on channel 1 and RSOI using a referenced montage to the opposite hemispherical region (FPZ) was recorded on channels 2 to 6. The first quick phase of the sleepless (A) was associated with the development of sharp activity in leads 12 to 18 located in the region enclosed by the dashed line. Within this region, the maximum voltage occurred in channels 14 and 20, which is indicated by the dark bar. Each major division on the trace is 1 sec.
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Advanced EEG paradigms

McCrea et al. 2010 reported increased power in the beta band during balance challenge

Slobounov et al. 2002 have reported a reduction in the ability to produce gamma activity recorded during a balance task

Teel et al. 2014; Thompson et al. 2005: a reduction in amplitude for all frequencies in those with a history of concussion

Summary: the most consistent pattern to emerge from analysis of the EEG is the observation of slow frequencies with the reduction, alteration, or absence of faster frequencies
Evoked potentials (EPs)

• Averaged EEG epochs that are initiated by the onset of a stimulus that activates processing in one of the sensory modalities or via activation of primary motor cortex with the potential recorded at a related muscle
Pattern visual evoked potentials
Pattern visual evoked potentials
Concussion and PVEP

• A single case study has been published from an 8-year-old girl who suffered a concussion when falling backwards and hitting the back of her head on the ground during a soccer game.

• When compared to baseline, there was a marked reduction in the response amplitude of the P100 waveform immediately after the injury that continued until 32 weeks with notable improvement by 1 year (Boutin et al., 2008).
Prospective PVEP study in hockey players

Significant changes in PVEP latency following concussion

Baseline 1st 2nd
Latency in msec
Time

Conc - RMonFFOz
Conc - RMonRHOz
Conc - RMonRH02
Control - RMonFFOz
Motor evoked potentials (MEPs)

- A motor-related response can be elicited, either from the cerebral cortex following challenges to posture or balance, or from the distal musculature, following magnetic excitation of motor cortex via transcranial magnetic stimulation (TMS).
Motor evoked potentials (MEPs)
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<th>MEP amplitude</th>
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Event-related potentials (ERPs)

- One of the ERPs commonly used in sport TBI studies is the N2/P3 or P300 response.
- The N2/P3 response is a series of averaged EEG responses time-locked to a stimulus, with positive or negative peaks associated with different cognitive processes.
- P3 peak amplitude is believed to index allocation of attention, while latency is related to stimulus evaluation and categorization time, transfer of information to consciousness and memory systems, and stimulus saliency.
Stimuli examples:

Counting a high tone vs. ignoring low tone

Counting a square and ignoring a triangle

4:1 ratio frequent:infrequent
# Auditory N2/P3

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Auditory P3 amplitude changes present at 1 month

Auditory N2/P3 Grand Average from baseline to one-month follow-up at Cz.

Amplitude in microvolts

Time in milliseconds
# Visual N2/P3

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# Cumulative effects N2/P3

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<td>Moore et al., 2014</td>
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Significant increases in P3 latency for 3+ concussion group.

Grand average N2/P3 responses for word stimulation at Pz for the 0 and 3+ concussion groups. Positive voltages are plotted as upward deflections.
Self-reports of symptoms for the 0 and 3+ concussion groups.
Relationship between symptoms and brain responses

• The “poor memory” and “taking longer to think” variables were significantly correlated with brain response latency.
• These athletes had their last concussion a minimum of one year prior to assessment.
EEG/ERP Conclusions

• **Prospective studies**

• Future studies focus on how to improve the clinical utility of these techniques so that they can be used to **manage individual cases** rather than to be applied to group data

• Newer techniques such as the measurement of **regional functional connectivity** associated with concussion are likely to be of critical importance

• **Computational modeling** can advance our **theoretical** understanding of concussion by allowing for a more direct investigation of how pathophysiological changes to axons that characterize concussion result in altered EEG amplitude, latency, and connectivity.
December 6, 2011

BOSTON UNIVERSITY RESEARCHERS REPORT NHL PLAYER DEREK BOODequeard HAD EVIDENCE OF EARLY CHRONIC TRAUMATIC ENCEPHALOPATHY
January 11, 2013

(CNN) -- Star NFL linebacker Junior Seau -- just 43 years old when he took his own life last May -- suffered from chronic traumatic encephalopathy, a neurodegenerative brain disease that can follow multiple hits to the head, the National Institutes of Health said Thursday.
August 2013

PHILADELPHIA - A federal judge says the NFL and more than 4,500 former players want to settle concussion-related lawsuits for $765 million.
In the theatres...

Concussion – The movie
What is Chronic Traumatic Encephalopathy (CTE)?

- CTE has been known to affect boxers since the 1920s
- Boston University: CTE is a progressive degenerative disease of the brain found in athletes (and others) with a history of repetitive brain trauma.
What is Chronic Traumatic Encephalopathy (CTE)?

• This brain trauma triggers progressive degeneration of the brain tissue, including the build-up of an abnormal protein called tau.

• These changes in the brain can begin months, years, or even decades after the last brain trauma or end of active athletic involvement.
Protein tau aggregation

- Gavett et al. reported that the stretching of axons results in alterations in axonal membrane permeability, calcium influx, and caspase and calpain release.

- Caspases and calpains may in turn trigger tau abnormalities (e.g., misfolding, truncation, aggregation), as well as dissolution of microtubules and neurofilaments.
Protein Tau Aggregation (non-athlete left; retired athletes centre and right)
CTE Symptomatology example:

- Ronnie Jenkins, former NFL running back:
- "My mood has changed," said Jenkins, 36
- "Sometimes I think I'm going crazy."
- Jenkins began to suspect CTE several years ago when an uncharacteristic dark mood and, occasionally, deep anger began to bubble up at unexpected times.
CTE Symptomatology case example 2:

- Became isolated after retirement
- Was depressed and attempted suicide (e.g. consuming prescription drugs and by deliberate carbon monoxide exposure)
- Feared financial ruin but less restrained and discreet with his spending
- Paranoid ideations
- This case committed suicide in his home via gunshot wound approximately 11 years after his retirement from the NFL.
CTE Symptomatology

• Headache
• Depression/Suicidality
• Impulsivity
• Explosivity/Aggression
• Memory problems
• Confusion
• Progressive dementia
A revised CTE definition

• CTE is the term applied to chronic neurodegeneration and symptomatology following a single episode of severe traumatic brain injury or (more commonly) repeated episodes of mild traumatic brain injury.

• Are these typical ex-athletes?

• Is neurotrauma the only potential cause of CTE symptomatology?
Other possibilities...?

• Athlete career transition stress
• Chronic pain
• Substance abuse including the effects of steroids
Other possibilities...?

• “They say athletes die twice” Brian Kingman, pitcher for the Oakland A’s in the 1980s.
Athletic Career Transition Stress:

- McKnight et al., 2009: Because athletes spend much of their time dedicated to their sport at an early age, time has not been allocated to acquiring interests and skills in other areas.
- This may disrupt normal identity development and young athletes may form a foreclosed identity.
Athletic Career Transition Stress:

• Grove et al. (1997):
  • A strong athletic identity (foreclosed) at the time of retirement was positively related to:
    • venting of emotions
    • mental disengagement
    • behavioral disengagement
    • reliance on denial
Chronic pain

• People with significant chronic pain have higher rates of depression, anxiety, drug and alcohol abuse, and suicide

• Sleep disturbance and insomnia are commonly experienced

• Symptoms are exacerbated by personality type.
Drug, alcohol, and steroid use

• It is well known that chronic drug and alcohol use can also cause various forms of neurodegeneration.

• Anabolic-androgenic steroid (AAS) abuse has been reported to result in aggressiveness, anxiety, and depression linked to functional change in monoamine and peptidergic systems.

• This pattern of symptomatology has been demonstrated in non-contact sport athletes and patients groups receiving long-term steroid treatment (HIV).
Hypothetical Model for CTE Symptomatology

CTE Symptoms

Neuro-trauma

Athletic Career Transition Stress

Substance Use/Abuse

Chronic Pain
Hypothetical Model for CTE Symptomatology

- Neurotrauma
- CTE Symptoms
- Chronic Pain
- Substance Use/Abuse
- Athletic Career Transition Stress

Necessary but not a sufficient condition
How much of a problem is a concussion in sport?

• It is a problem, but a manageable one
• The CTE clinical case studies are selective examples of atypical athletes
• Future research must investigate other potentially important factors and not attribute all problems to brain injury alone
• Thanks for your attention – questions?
Cumulative effects of concussion

- Research suggests that athletes who sustain 3 or more concussions may have the following:
  - Measurable changes in brain function
  - Increased and persistent self-reported symptoms
  - Worse neuropsychological test performance
Cumulative effects of concussion

These athletes may be at increased risk for:
• A future concussion that is easier to sustain
• Have worse on-field presentations of their next concussion
• Are more likely to have slowed recovery
• Have greater acute changes in memory performance
Significant increases in P3 latency for 3+ concussion group.

Grand average N2/P3 responses for word stimulation at Pz for the 0 and 3+ concussion groups. Positive voltages are plotted as upward deflections.
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