“Cerebral Consequences: The Impact of Concussions in Youth”

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ONGOING PROGRAMMATIC RESEARCH AT THE VCCYF

- **Genetics of Exercise Behavior in Adolescents**: Genetics & epigenetics of exercise benefits for obese, sad, or anxious children (NIDDK)
- **Neurobiology and Genetics in Foster Care Children**: Study of ‘exposome’ (abuse), genetics, epigenetics, structural and functional neuroimaging, EEG, and phenotypic data in abused children (NICHD)
- **Generation R**: 10,000 children followed since 12 weeks in utero. Brain, heart, lung, & gut imaging with genetics, epigenetics & disease outcome on 5000 children (NWO)
- **Genomics of Developmental Trajectories in Twins**: Genome wide SNP & CNV study of 5000 twin pairs followed since birth
- **Sports Concussion**: Effect of concussion in elite youth hockey players combining genetics, epigenetics, MRI, and sports phenotyping (In review at NINDS; 4 papers from pilot work).
- **Vermont Family Based Approach**: Public Health Promotion, illness prevention, family intervention (8 studies and a bill).
- **UVM WE**: Health Promotion for University Students.
The CONCO TEAM

MATT ALBAUGH, JAY GONYEA, SCOTT HIPKO, CATHERINE ORR, AND RICHARD WATTS.

Kristen DeStigter, MD, FACR
Outline

• Sports Related Traumatic Brain Injury (sTBI)
• Why sTBI in children and adolescents should be a major focus of pediatric medicine.
• Our Study
  – Cortical thickness
  – White Matter Hyperintensities
• The future
• Conclusions
Epidemiology

- 3.8 million concussions occurring in sports and recreational activities/yr.
  - Underreported
- Football, ice hockey, soccer, and lacrosse tend to have the highest incidence
- Game incidence higher than practice
- May be as prevalent as ADHD (our data).
Sports Related TBI

- [http://www.youtube.com/watch?v=yY1bUvx3_ao](http://www.youtube.com/watch?v=yY1bUvx3_ao)
Not only hockey
Head trauma in JR hockey

- 2 seasons (74 games)
- Age 17 to 21
- Head impact telemetry system (HITS)
- Dual camera video game analysis
- 5200 head impacts
- Average 185 head hits/player
- 10 diagnosed concussions

Dan Gaz 2013
HITS data

- 7 yr. data
- High school, junior and college hockey
- 100,000 head impacts
- Individual athletes >750 head hits
- Usually impact posterior to anterior
- Males higher linear acceleration
- **120 diagnosed concussions but > 8000 impacts at higher magnitude and not associated with a concussion diagnosis**

Rick Greenwald PhD 2013
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Basic Premise

1. 10-13% of children report having had a concussion.
2. Concussion is associated with increased rates of attention problems, anxiety, aggression, and emotional regulatory problems.
3. The developing brain is at greater risk for negative outcomes than more mature brains.
4. Need to baseline young athletes and follow them longitudinally in order to understand the role that playing has on brain structure and function.
Cerebellar Development for 145 Youths (Ages 4-22) Based on 243 Brain MRI Scans

Castellanos et al, 2004
Developmental Mapping of the Child Cortex

Image courtesy of Paul Thompson, 2007
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Study Design
The Boys
Sample

• Twenty-nine male subjects were recruited from preparatory school and collegiate ice hockey teams, and were between 14 and 23 years of age ($M = 17.8, SD = 2.2$).

• Of the 29 subjects that enrolled in the study, 27 underwent both neuroimaging and cognitive testing (2 subjects were unable to complete cognitive testing).
Follow one team throughout the season:

Preseason:
- Genetics: Obtain genetic samples.
- Imaging: Take baseline MRI scans.

Post-concussion and after the season:
- Repeat protocol and compare to baseline
MRI IMAGING

Preseason-Baseline

Post-injury Follow-up

Postseason Follow-up

delta''

delta'

qBI
MRI PROTOCOL

T1-weighted 3D TFE (MP-RAGE):
This sequence is a standard anatomical scan. Morphometric analyses of the cerebral cortex and subcortical structures will be conducted using T1 data.
MRI PROTOCOL

3D T2-FLAIR:
This sequence is particularly suitable for visualizing small focal lesions, and could be used for quantifying lesion volume.
**Susceptibility-Weighted Imaging:**
This scan enables visualization of blood vessels in the brain, and is helpful in detecting micro-hemorrhages, or “microbleeds,” that could result from sports-related head injuries.
Diffusion Tensor/Kurtosis Imaging:
Diffusion kurtosis has recently been shown to be a biomarker for reactive astrogliosis (Zhuo et al, Neuroimage).
MRI PROTOCOL

Pseudo-Continuous Arterial Spin Labeling (pCASL):
pCASL provides a quantitative measure of regional cerebral blood flow, and is helpful in detecting possible alterations in brain perfusion following injury.
MRI PROTOCOL

**T1rho:**

T1rho acquisitions provide a quantitative measure of amyloid deposition in the brain.

![MRI images showing T1rho maps](image-url)

*Fig. 3. T₁ρ maps obtained in the brains of a control and SAD patients that were categorized by neurological tests. Color bar on the right ranges from 10 ms to 200 ms with red and magenta colors indicating higher T₁ρ values. Pixels with higher T₁ρ are more prominent in AD patients especially in the medial temporal lobe region as indicated by the circle on the 57 year-old AD patient. Also noted was increased sulcal space in AD subjects, especially in the older patients (dashed arrows), suggesting greater brain atrophy.*
Resting state functional MRI:
Resting state analysis enables generation and comparison of functional brain networks based on spontaneous fluctuations in neuronal activity reflected in blood oxygenation level dependent (BOLD) signal.
Findings from Baseline Scans (Post Season Data collected and in QC)

• Incidental findings in 11 of 29 athletes
  – T2 hyperintensities 9/29
  – Cerebral mass 1/29
  – Caudate hemorrhage 2/29
  – Suspected MS 1/29

  – * incidental defined as “serious enough to be called by neuroradiologist as pathology”.
Manual segmentation of cerebral mass located in right dorsomedial prefrontal cortex shown in combination with subject's pial surface reconstruction (generated using the FreeSurfer) (top). Bottom figure depicts cerebral mass segmentation (magenta) in combination with FreeSurfer cortical parcellation.
Suspected Multiple Sclerosis

Figure displays T2-weighted FLAIR data from an asymptomatic male subject (from left to right, coronal slices progress from anterior to posterior). Several areas of increased signal intensity in periventricular white matter can be seen.
Transient Hyperintensity in Splenium

Figure displays coronal cross-section of T2-weighted FLAIR data from an asymptomatic male subject. A large area of increased signal intensity is visible in the posterior portion of the corpus callosum (i.e., splenium).
Caudate Hemorrhage
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Brain Structure and Post-Concussive Symptoms
Concussion History, Concussive Symptoms, and Cortical Structure

• To what extent is concussion history associated with cerebral cortical thickness?

• Is there an association between self-reported post-concussive symptoms and cerebral cortical thickness?
Cortical thickness = distance between pial and white matter surfaces
Our group has demonstrated associations between cortical morphometry and a host of behaviors in developing youths (attention problems, anxious/depressed symptoms, aggressive behavior, aspects of emotion regulation)...
ImPACT Testing

• Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) is a widely used computerized test battery that assesses verbal and visual memory, processing speed, reaction time, and impulse control (Maroon et al., 2000).

• ImPACT also includes the Post-Concussion Symptom Scale, which consists of 22 commonly reported symptoms (e.g., difficulty concentrating, difficulty remembering, difficulty regulating emotion).
**YSR/11-18 - Syndrome Scale Scores for Girls Scored Using T Scores for United States**

**ID:** 200105.003  
**Gender:** Female  
**Date Filled:** 12/04/2000  
**Clinician:** Theresa Lopez  
**Informant:** Self  
**Birth Date:** 06/16/1989  
**Agency:** School  
**Relationship:** Self  
**Verified:** Yes

### Internalizing

<table>
<thead>
<tr>
<th>T Score</th>
<th>Percentile</th>
</tr>
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<tbody>
<tr>
<td>12</td>
<td>65-B</td>
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**T Score Percentile:**

- Anxiety: 93%
- Withdrawn: 79%
- Somatic: 97%
- Social: 92%
- Thought: 92%
- Attention: 92%
- Rule-Breaking: 76%
- Aggressive: 96%

**Symptoms:**

- Headache
- Nausea
- Vomiting
- Balance problems
- Dizziness
- Fatigue
- Trouble falling to sleep
- Excessive sleep
- Loss of sleep
- Drowsiness
- Light sensitivity
- Noise sensitivity
- Irritability
- Sadness
- Nervousness
- More emotional
- Numbness
- Feeling "slow"
- Feeling "foggy"
- Difficulty concentrating
- Difficulty remembering
- Visual problems

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B = Borderline clinical range. C = Clinical range  
Broken lines = Borderline clinical range
Concussion History

• Self-reported concussion history was obtained for all 29 subjects

• A positive concussion history was defined as a self-report of having previously received a diagnosis of a sports-related concussion by a medical professional

• For those participants who reported concussion history (n=16), incidence ranged from 1 to 4 ($M = 2.13$), and, at the time of baseline assessment, all were at least three months removed from their most recent concussion ($M = 40.6$ months)
Structural Imaging Data

• Anatomical data were acquired on Philips Achieva 3T scanner using 3D T1 turbo field echo (TFE) (1 mm × 1 mm × 1 mm) sequence.

• T2-weighted data were acquired using a 3D T2-FLAIR turbo spin echo (TSE) (0.6 mm × 0.6mm × 1.2mm) sequence.
FreeSurfer (Version 5.3)

- T1-weighted anatomical data
- Subcortical segmentation
- Surface reconstruction
Cerebral Cortical Thickness
Cerebral Cortical Thickness

5mm

1mm
Results
Postconcussive Symptoms Are Associated with Cerebral Cortical Thickness in Healthy Collegiate and Preparatory School Ice Hockey Players

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Objective To investigate the degree to which concussion history and postconcussive symptoms are associated with cortical morphology among male hockey players.

Study design Male subjects (n = 29), ranging in age from 14 to 23 years (mean 17.8 years), were recruited from preparatory school and collegiate ice hockey teams and underwent neuroimaging and baseline Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) testing. Cerebral cortical thickness was regressed against ImPACT Total Symptom Score (TSS), concussion history, as well as baseline measures of psychopathology. Reconstruction of surfaces and cortical thickness analysis were conducted with FreeSurfer (version 5.3.0).

Results ImPACT TSS was inversely associated with local cortical thickness in widespread brain areas. Associations were revealed in a host of frontal as well as bilateral temporoparietal cortices. Conversely, concussion history was not associated with cortical thickness. An “Age by Concussion History” interaction was associated with thickness in the right ventrolateral and right parietal cortices. Post-hoc analysis revealed that concussed participants did not exhibit age-related cortical thinning in these regions.

Conclusion We have identified an association between brain structure and postconcussive symptoms among young, otherwise-healthy male athletes. Postconcussive symptoms and related reductions in cortical thickness may be tied to participation in a full-contact sport that involves frequent blows to the head. (J Pediatr 2014; #:#-#).
Relationship Between Cortical Thickness and Baseline Behavior
Attention Problems and Cortical Thickness

Region of left medial prefrontal cortex and left temporal cortex in which Youth Self-Report (YSR)/Adult Self-Report (ASR) Attention Problems score was inversely associated with cortical thickness. Age and intracranial volume have been controlled for in the analysis. Colors correspond to corrected p value (displayed at p < .05 threshold), with cold shades depicting negative associations and warm shades representing positive associations.
Relationship Between Cortical Thickness and Post-Concussive Symptoms
Cortical regions in which ImPACT Total Symptom Score (TSS) and Cognitive Symptom subscore were inversely associated with cortical thickness. Age and intracranial volume have been controlled for in the analysis. Colors correspond to corrected p value (displayed at p < .05 threshold), with cold shades depicting negative associations and warm shades representing positive associations.
Conclusions

• Cortical thickness in frontal, parietal, and temporal regions was inversely associated with self-reported post-concussive symptoms among young, healthy ice hockey players.

• The regions involved play a role in the emotional regulatory, attentional, aggression and affective control processes.
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  – Cortical thickness
  – *White Matter Hyperintensities*

• The future
White Matter
Hyperintensities
TITLE: White matter hyperintensities in young ice hockey players: A reason for concern?

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White Matter Hyperintensities

• White matter hyperintensities (WMHs) are localized regions of high signal intensity on T2-weighted magnetic resonance images.

• WMHs have been associated with bipolar disorder and depression, as well as other psychiatric and neurological conditions.

• Despite the prevalence of WMHs, little is known regarding their etiology and clinical significance, particularly in otherwise healthy individuals participating in full contact sports.
Prevalence of WMHs

• Age and gender-matched controls were taken from the NIH Normal Brain Development study

• Relative to healthy young male ice hockey players, the prevalence of WMHs was significantly lower in similarly aged, typically developing males (37.9% and 11.1%, respectively) ($\chi^2=11.01, p = .0009$)
Figure displays T2-weighted FLAIR data from an asymptomatic male subject (from left to right and top to bottom, coronal slices progress from anterior to posterior). Increased signal intensity is visible in a number of white matter regions (circled for reference).
Research Questions

• To assess the prevalence of WMHs in young, healthy male ice hockey players, and in age- and gender-matched typically developing youths.

• Based on previous literature linking WMHs with depressive symptoms, we tested putative associations between WMH burden and self-reported anxious/depressed symptoms.

• We tested the relationship between WMH volume and cerebral cortical thickness. We hypothesized that WMH burden would be associated with reduced cortical thickness in healthy, young ice hockey players.
On left, cerebral cortical regions in which WMH volume was inversely associated with cortical thickness ($p < .05$, corrected), shown from right lateral (a.), left lateral (b.), dorsal (c.), and anterior (d.) perspectives. On right, WMH segmentations across hockey participants are shown in yellow in combination with translucent cortical surface.
Summary WMHs

• Findings suggest that WMHs may be more prevalent in young ice hockey players relative to typically developing controls.

• Findings also suggest that WMHs in young ice hockey players are associated with internalizing symptoms as well as reduced cortical thickness in bilateral temporal regions.
FLAIR Hyperintensities

• Across subjects, how are these FLAIR hyperintensities distributed throughout the brain?

• Is there any discernible pattern with regard to the location of these lesions?
Distribution of WMHs

Bar graph depicting percentage of total WMH volume per fiber pathway across participants. Error bars represent 95% confidence intervals.
Affected Fiber Pathways

3D Reconstruction of Fiber Pathways from Diffusion-Weighted Data

Connectional Topography of SLF III (from Schmahmann & Pandya)
Hyperintensities were located, bilaterally, in the SLF, uncinate fasciculus, and forceps minor.
FLAIR Hyperintensities
Brain Motion...
Affected Fiber Pathways

- Dorsal, middle, and ventral components of the superior longitudinal fasciculus (SLF)
- Forceps minor (which interconnects right and left frontal lobes)
- Uncinate fasciculus
Affected Fiber Pathways

- The SLF, forceps minor, and uncinate fasciculus are implicated in both voluntary and automatic aspects of affect regulation.

- If hyperintensities reflect compromised structural integrity of the above pathways, one would expect that hyperintensities would be associated with difficulty regulating affect.
WMHs and Behavioral Correlates

- FLAIR WMH volume was not significantly associated with a self-reported concussion history ($p = .19$) when controlling for age, ICV, and self-reported anxious/depressed symptoms.

- Self-reported anxious/depressed symptoms, however, were significantly associated with total WMH volume ($p = .04$).

- Post hoc exploratory analysis revealed that among hockey players possessing WMHs ($N = 11$), the relationship between anxious/depressed symptoms and WMH volume was even more robust ($p = .006$).
A/D symptoms and FLAIR lesion volume

*Relationship between A/D and lesion volume remains significant after controlling for age and intracranial volume

$R^2 = .76$
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  – Other sources of Behavioral Findings
  – Genetics
  – Epigenetics

• The future
Results have undergone cluster-wise correction for multiple comparisons from Monte Carlo z-field simulation (p<.05). Controlling for age and ICV.
Has player ever used marijuana?

- No
- A few times
- Yes

Results have undergone Gaussian random field theory correction ($p<.05$). Controlling for age and ICV.
Aging and Iron Deposition in the Basal Ganglia

Relationship between T2* and age in 28 young hockey players ($p < .05$, corrected)

T2* signal in posterior putamen and pallidum
In Vivo Quantification of Free Iron

R2* signal and basal ganglia mask shown overlaid upon subject’s MRI

3D reconstruction of subject’s basal ganglia

Association between basal ganglia R2* and concussion number
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Current and Proposed Studies

- Young female hockey players
- Hockey versus Soccer in the very young
- Prep and College
- Current Professional
- Retired Professional
What about female athletes

• Same protocol in 30 Elite age matched female high school and college hockey players
• 9 or 30 complete
• Rates of concussions twice what is reported in males.
• More to follow.
Youth Study

• Downward extend our current study to 8, 10, 12, 14, and 16 year old hockey players. (I have commitments from teams).
• N=250 hockey athletes (I am currently imaging 100 soccer players who will be controls).
Extend Prep-College Study

• Extend our current study in male and female prep players to college players. I have the commitments.
• N= 120 subjects
Current Players Study

- Provide current players with individual imaging data to improve their ability to make decisions about return to play decisions.
- N=100 players
Retired Players Study

• Extend our current study to retired players (great interest was generated at the Mayo Summit). AND create an NHL living brain bank in collaboration with Dr. Ann McKee.

• N= 200 (fifty 30, 40, 50, 60 year old former players).
Multimodal MRI

Pathology

2 yrs.  

2 yrs.  

6 mos.  

in vivo  

ex vivo  

Behavioral
In Vivo MRI Biomarkers

Ex Vivo Pathology

Premorbid Emotional and Behavioral Functioning
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Title: Ice Hockey Summit II: Zero Tolerance for Head Hits and Fighting


(Accepted for simultaneous publication in the following: Current Sports Med Reports, Clinical Journal of Sports Medicine, and Physical Medicine & Rehabilitation)
Benefits of Strict Rest After Acute Concussion: A Randomized Controlled Trial

Danny George Thomas, MD, MPH, Jennifer N. Apps, PhD, Raymond G. Hoffmann, PhD, Michael McCrea, PhD, Thomas Hammeke, PhD

OBJECTIVES: To determine if recommending strict rest improved concussion recovery and outcome after discharge from the pediatric emergency department (ED).

METHODS: Patients aged 11 to 22 years presenting to a pediatric ED within 24 hours of concussion were recruited. Participants underwent neurocognitive, balance, and symptom assessment in the ED and were randomized to strict rest for 5 days versus usual care (1–2 days rest, followed by stepwise return to activity). Patients completed a diary used to record physical and mental activity level, calculate energy exertion, and record daily postconcussive symptoms. Neurocognitive and balance assessments were performed at 3 and 10 days postinjury. Sample size calculations were powered to detect clinically meaningful differences in postconcussive symptom, neurocognitive, and balance scores between treatment groups. Linear mixed modeling was used to detect contributions of group assignment to individual recovery trajectory.

RESULTS: Ninety-nine patients were enrolled; 88 completed all study procedures (45 intervention, 43 control). Postdischarge, both groups reported a 20% decrease in energy exertion and physical activity levels. As expected, the intervention group reported less school and after-school attendance for days 2 to 5 postconcussion (3.8 vs 6.7 hours total, \( P < .05 \)). There was no clinically significant difference in neurocognitive or balance outcomes. However, the intervention group reported more daily postconcussive symptoms (total symptom score over 10 days, 187.9 vs 131.9, \( P < .03 \)) and slower symptom resolution.

CONCLUSIONS: Recommending strict rest for adolescents immediately after concussion offered no added benefit over the usual care. Adolescents’ symptom reporting was influenced by recommending strict rest.
Summary

1. Understanding the pathophysiology of concussion will continue to be the focus of study in our lab.

2. However, we need to understand individual variation at the structural, behavioral, genetic, and epigenetic level in order to understand the role of concussion in subsequent pathology.

3. We intend to study the very young (8, 10, 12, 14 and 16 year old athletes), current (18, 20, 25, 30, 35 and 40 athletes), and retired players (40, 45, 50, 55, and 60) in order to understand developmental pathways.

4. Such research will lead to changes in improvements in the way sports are played, in assessment, treatment, and return to play decisions.
CONCUSSION

Look on the Bright side. For one brief, glorious moment, you forgot you were on the Cubs.