Long term risks associated with mild traumatic brain injuries: why do we need to protect our children?

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McGill University
Montreal Children’s Hospital
Over last decade, lots of attention given to returning children to activities post-concussion
Always on the lookout for successful strategies for optimal recovery

Rest initially, but don’t stay in bed!
1. Children need to rest after an mTBI
Disruption of functioning in the acute period

**Evidence that there are large effect sizes on cognition and balance immediately post-injury**

(Iverson, Gagnon, Griesbach, 2012)
Temporal window of vulnerability (animal studies)

FIGURE 1. Bar graphs showing effect of single and repetitive concussion on learning performance of mice in the MWM. Testing began at 1 day after the surgery/injury. A, animals subjected to repetitive CBI (RCBI) with an interval of 3 or 5 days between the two concussions exhibited significant learning impairment compared with sham-injured mice and mice receiving a single CBI. However, when the interval between the two injuries was 7 days, mice subjected to repetitive CBI showed no significant deficit. B, mice subjected to RCBI with an interval of 3 days when tested beginning 7 days after the second concussion performed significantly worse than sham and single CBI groups. #, P < 0.05 compared with sham; *, P < 0.05 compared with single CBI; **, P < 0.01 compared with single CBI. Data are presented as mean ± standard error of the mean.

Longhi 2008
Temporal window of vulnerability (animal studies)

Increasing Recovery Time Between Injuries Improves Cognitive Outcome After Repetitive Mild Concussive Brain Injuries in Mice

BACKGROUND: Although previous evidence suggests that the cognitive effects of concussions are cumulative, the effect of time interval between repeat concussions is largely unknown.

OBJECTIVE: To determine the effect of time interval between repeat concussions on the cognitive function of mice.

METHODS: We used a weight-drop model of concussion to subject anesthetized mice to 1, 3, 5, or 10 concussions, each a day apart. Additional mice were subjected to 5 concussions at varying time intervals: daily, weekly, and monthly. Morris water maze performance was measured 24 hours, 1 month, and 1 year after final injury.

RESULTS: After 1 concussion, injured and sham-injured mice performed similarly in the Morris water maze. As the number of concussions increased, injured mice performed worse than sham-injured mice. Mice sustaining 5 concussions either 1 day or 1 week apart performed worse than sham-injured mice. When 5 concussions were delivered at 1-month time intervals, no difference in Morris water maze performance was observed between injured and sham-injured mice. After a 1-month recovery period, mice that sustained 5 concussions at daily and weekly time intervals continued to perform worse than sham-injured mice. One year after the final injury, mice sustaining 5 concussions at a daily time interval still performed worse than sham-injured mice.

CONCLUSION: When delivered within a period of vulnerability, the cognitive effects of multiple concussions are cumulative, persistent, and may be permanent. Increasing the time interval between concussions attenuates the effects on cognition. When multiple concussions are delivered at short intervals, the cognitive effects are worse than when delivered at longer intervals.
Effect of exercise too early or too late post injury

Fig. 1. Effects of exercise following FPI on BDNF protein. Sham and FPI rats were housed with or without access to a RW from postinjury days 0–6 (acute) or 14–20 (delayed). BDNF protein levels within the hippocampus were measured by ELISA. Mean values were analyzed through a repeated three-way ANOVA [injury: (FPI vs. Sham), time: (acute vs. delayed) and exercise: (RW vs. Sed)]. Interaction effects were further analyzed by performing means comparisons in which desired contrast weights were specified. Graph demonstrates BDNF levels, ipsilateral and contralateral to the injury. Each value represents the mean±S.E.M. Significant comparisons between groups are indicated by brackets (* P<0.05; ** P<0.005). (A) Side ipsilateral to the injury. (B) Side contralateral to the injury.

Griesbach 2004
Is Rest After Concussion “The Best Medicine?”: Recommendations for Activity Resumption Following Concussion in Athletes, Civilians, and Military Service Members

Noah D. Silverberg, PhD; Grant L. Iverson, PhD

Journal of Head Trauma Rehabilitation, 2012

### TABLE 2  Recommendations for activity resumption following MTBI

1. Bed rest exceeding 3 days is not recommended. (Strength of recommendation = D)
2. Gradual resumption of preinjury activities should begin as soon as tolerated. (Strength of recommendation = B)
3. For contact sports and other activities with a high MTBI exposure risk, a delay of at least 1 week will help reduce the risk of overlapping injuries. (Strength of recommendation = B)
4. The medium- and long-term risks of exertion sufficient to exacerbate symptoms are unknown. In theory, during the acute recovery period (eg, first 2 weeks postinjury), heavy exertion that elicits significant symptoms could be harmful. We simply do not know. In response to symptom exacerbations, patients should therefore be advised to temporarily reduce their physical and cognitive demands and resume their graduated return to activity at a slower pace. (Strength of recommendation = I)
5. After 1 month, supervised exercise should be considered as part of the treatment plan for individuals who remain symptomatic. (Strength of recommendation = C)
When is it ok for children to return to physical activities
Always on the lookout for successful strategies for optimal recovery

Rest initially, but don’t stay in bed!

Wait to be symptom-free at rest to return fully to activities
2. Children need to be symptom-free before returning to activities
CPS Statement 2012
An athlete with a concussive injury **should not be allowed to return to activity until all signs and symptoms have resolved** and he/she has been cleared to do so by a physician... **Once children and adolescents have been symptom-free for several days**, they should then follow a medically supervised stepwise exertion protocol
Children need to be symptom-free before returning

Essentially, same content as recommendations in Consensus statement 2009

Consensus Statement on Concussion in Sport
3rd International Conference on Concussion in Sport
Held in Zurich, November 2008

Paul McCrory, MBBS, PhD,* Willem Meuwisse, MD, PhD,† Karen Johnston, MD, PhD,‡ Jiri Dvorak, MD,§ Mark Aubry, MD,¶ Mick Molloy, MB,‖ and Robert Cantu, MA, MD§

The cornerstone of concussion management is physical and cognitive rest until symptoms resolve and then a graded programme of exertion prior to medical clearance and return to play. The recovery
RETURN TO SPORTS FOLLOWING A CONCUSSION

If you have sustained a concussion, this action plan is recommended before you put your team jersey back on for the game.

You must complete your recommended period of rest and follow the activity restrictions. You should be symptom-free at rest for a full week before returning to any physical activity. When you are ready to return to play follow these gradual progressive steps.

There should be approximately 24 hours in between each step. If any symptoms return at any time during this action plan, stop working out. Rest until you are symptom-free for 24 hours. Then return to the previous step. If symptoms do not resolve or get worse, you are urged to seek medical attention.

★ STEP 1: Light general conditioning exercises
  • NO CONTACT.
  • Begin with a warm up (stretching/ flexibility) for 5-10 minutes.
  • Start a cardio workout of 15-20 minutes which can include: stationary bicycle, treadmill, fast paced walking, light jog, rowing or swimming.

★ STEP 2: General conditioning and sport specific skill work done individually
  • NO CONTACT.
  • Begin with a warm up (stretching/ flexibility) for 5-10 minutes.
  • Increase intensity and duration of cardio workout to 20-30 minutes.
  • Begin sport specific skill work within the workout, but no spins, dives or jumps.

★ STEP 3: General conditioning, skill work done individually and with a team-mate
  • NO CONTACT.
  • Increase duration of session to 60 minutes. Begin resistance training.
  • Continue practicing sport specific individual skills.
  • May begin general shooting, kicking or passing drills with a partner.
  • May start beginner level spins, dives and jumps.

★ STEP 4: General conditioning, skill work and team drills
  • NO CONTACT. NO SCRIMMAGES.
  • Resume pre-injury duration of practice and team drills.
  • Increase resistance training and skill work as required.
  • Gradually increase skill level of spins, dives and jumps.

★ STEP 5: Full practice with body contact
  • CONTACT. SCRIMMAGES.
  • Participate in a full practice to get yourself back in the lineup. If completed with no symptoms, discuss with the coach about getting back in the game.
  • Coaches must make sure that the athlete has regained their pre-injury skill level and is confident in their ability to return to activity.

★ STEP 6: Return to competition

Guidelines:
★ Consists of 6 steps
★ Sport specific or general
★ To be progressed by 24 hour intervals
★ If symptoms appear:
  Stop
  Rest
  Return to step
Always on the lookout for successful strategies for optimal recovery

Rest initially, but don’t stay in bed!

Wait to be symptom-free at rest to return fully to activities

If slow to recover, don’t wait to get help
3. Children who are slower to recover

- Clinical program with interesting evidence based on following principles
  
  Exercise has a cerebral effect
  May contribute to neural repair and vascular auto-regulation
  Contributes to improve mood and energy level

Gagnon, Galli, Friedman, Grilli, Iverson., Brain Injury, 2009
These strategies usually work and there is a return to usual activities.

But there is often some concern for the future.
What are the long-term consequences?

- The concussion has cleared.
- The athlete’s sport has relatively greater risk for concussion.
- You are asked, “should this athlete risk a subsequent concussion?”
What do we know?

1. Concussion History
   a. Risk of recurrence
   b. Cumulative effects

2. Early developmental concussions

3. Delayed consequences
   a. Chronic Traumatic Encephalopathy
   b. Other preliminary findings
Getting a proper concussion history

“Recognizing the importance of a concussion history, and appreciating the fact that many athletes will not recognize all the concussions they may have suffered in the past, a detailed concussion history is of value.

Such a history may pre-identify athletes that fit into a high risk category and provides an opportunity for the healthcare provider to educate the athlete in regard to the significance of concussive injury.”
Concussion History

Did you ever have concussions before?

Not enough!

How many?
Circumstances?
Which symptoms?
Duration of symptoms?
Injury occurring with less force?
Equipment worn at the time?
Concussion History: Risk of recurrence

Having a previous head injury or concussion leads to an increased risk of sustaining another one.

PEDIATRICS

Previous Head Injury Is a Risk Factor for Subsequent Head Injury in Children: A Longitudinal Cohort Study
Bonnie R. Swaine, Camille Tremblay, Robert W. Platt, Guy Grimard, Xun Zhang and I. Barry Pless

Pediatrics 2007;119:749-758
DOI: 10.1542/peds.2006-1186

Conclusion: This large prospective cohort study indicates the risk of sustaining a cerebral concussion is nearly six times greater for individuals with a history of concussion than for individuals with no such history.
“So what?”
There could be cumulative effects of repeated concussions.

<table>
<thead>
<tr>
<th>Length of Symptom Recovery (d)</th>
<th>No. of Previous Concussions†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n = 122)</td>
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<tr>
<td>-------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Rapid (&lt;1)</td>
<td>37 (30.3)</td>
</tr>
<tr>
<td>Gradual (1-7)</td>
<td>76 (62.3)</td>
</tr>
<tr>
<td>Prolonged (&gt;7)</td>
<td>9 (7.4)</td>
</tr>
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</table>

*Data are expressed as No. (%) of players with concussion.
†P = .03 by Fisher exact test.

From: Cumulative Effects Associated With Recurrent Concussion in Collegiate Football Players: The NCAA Concussion Study

There could be cumulative effects of repeated concussions

Neuropsychological performance following a history of multiple self-reported concussions: A meta-analysis

HEATHER G. BELANGER,1,2,4 ERIC SPIEGEL,1 AND RODNEY D. VANDERPLOEG1,2,3,4

Table 2. Effect sizes for six cognitive domains and symptom complaints

<table>
<thead>
<tr>
<th></th>
<th>Number of studies (k)</th>
<th>Sample size Controls</th>
<th>Sample size ≥2 MTBI</th>
<th>d</th>
<th>95% CI</th>
<th>Q</th>
</tr>
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<tbody>
<tr>
<td>Attention</td>
<td>10</td>
<td>926</td>
<td>614</td>
<td>0.05</td>
<td>-0.05 – 0.15</td>
<td>94*</td>
</tr>
<tr>
<td>Executive functions</td>
<td>6</td>
<td>443</td>
<td>247</td>
<td>0.24*</td>
<td>0.08 – 0.40</td>
<td>133*</td>
</tr>
<tr>
<td>Fluency</td>
<td>4</td>
<td>362</td>
<td>220</td>
<td>-0.09</td>
<td>-0.27 – 0.09</td>
<td>46*</td>
</tr>
<tr>
<td>Memory acquisition</td>
<td>5</td>
<td>362</td>
<td>220</td>
<td>0.13</td>
<td>-0.03 – 0.29</td>
<td>43*</td>
</tr>
<tr>
<td>Delayed memory</td>
<td>8</td>
<td>750</td>
<td>405</td>
<td>0.16*</td>
<td>0.04 – 0.28</td>
<td>166*</td>
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<tr>
<td>Visuospatial skill</td>
<td>1</td>
<td>56</td>
<td>45</td>
<td>0.17</td>
<td>-0.22 – 0.56</td>
<td>0</td>
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<tr>
<td>Motor functions</td>
<td>1</td>
<td>129</td>
<td>78</td>
<td>0.10</td>
<td>-0.17 – 0.37</td>
<td>0</td>
</tr>
<tr>
<td>Symptoms</td>
<td>4</td>
<td>349</td>
<td>192</td>
<td>0.13</td>
<td>-0.05 – 0.31</td>
<td>49*</td>
</tr>
</tbody>
</table>

Note. *p < .05.
There could be cumulative effects of repeated concussions

No data available on
- motor outcomes
- social functioning
- sport performance
What do we know?

1. Concussion History
   a. Risk of recurrence
      having one makes you at risk of getting another one
   b. Cumulative effects
      after 3, effects may be more long lasting/permanent?

2. Early developmental concussions

3. Delayed consequences
   a. Chronic Traumatic Encephalopathy
   b. Other preliminary findings
Early developmental injuries

- Clients in substance abuse treatment have higher incidence of childhood TBI’s than general public.
- Prisoners have high prevalence of early childhood TBI’s.
- Birth cohorts show early TBI’s predispose to later behavioral problems.
Early developmental injuries

Adolescent Psychiatric Symptoms
Following Preschool Childhood Mild
Traumatic Brain Injury: Evidence From
a Birth Cohort

McKinlay et al. 2009 Journal of Head Trauma Rehabilitation 24(3)

Psychiatric symptoms at ages 14-16 years based on DSM-III-R

- ADHD
- Conduct Disorder
- Substance Abuse
- Anxiety Disorder
- Mood Disorder

Reference Group
Injury with Fractures
Outpt. Mild TBI
Inpt. Mild TBI
Early developmental injuries

Early concussions could lead to problems only identified later in life

<table>
<thead>
<tr>
<th></th>
<th>Percentage with disorder</th>
<th>Inpatient OR relative to reference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Reference n</td>
<td>Outpatient n</td>
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<tr>
<td>ADHD</td>
<td>49 (6.0)</td>
<td>6 (10.5)</td>
</tr>
<tr>
<td>ODD/CD</td>
<td>72 (8.6)</td>
<td>4 (7.0)</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>95 (11.3)</td>
<td>7 (12.3)</td>
</tr>
<tr>
<td>Mood</td>
<td>188 (12.9)</td>
<td>7 (12.3)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>250 (29.8)</td>
<td>14 (24.6)</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention deficit/hyperactivity disorder; CI, confidence interval; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised); ODD/CD, oppositional defiant disorder/conduct disorder; OR, odds ratio.

⁹⁹ After adjustment for covariates.
⁹ P < .05.
³⁹ P < .01; sample sizes: reference group n = 839, outpatient n = 57, inpatient n = 19.
Early developmental injuries

Early concussions could lead to problems only identified later in life

Long-term behavioural outcomes of pre-school mild traumatic brain injury

A. McKinlay, R. C. Grace, L. J. Horwood, D. M. Fergusson and M. R. MacFarlane

*Figure 4. Comparison of inpatient, outpatient, hospital accidents and reference groups in terms of developmental trajectory from age 7 to 13 for averaged mother and teacher ratings of ADHD. Broken line indicates minimum possible scores. ADHD, attention deficit/hyperactivity disorder; MTBI, mild traumatic brain injury.*
Early developmental injuries

Early concussions could lead to problems only identified later in life

Long-Term Outcome From Childhood Traumatic Brain Injury: Intellectual Ability, Personality, and Quality of Life

Figure 1. IQ distributions across injury severity groups.
Early Developmental injury

Developmental trajectories of infants and toddlers with good initial presentation following moderate or severe traumatic brain injury: A pilot clinical assessment project


Table 3

<table>
<thead>
<tr>
<th></th>
<th>9 month Mean ± SD</th>
<th>18 month Mean ± SD</th>
<th>30 month Mean ± SD</th>
<th>42 month Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 16) 95%</td>
<td></td>
<td>(n = 29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>confidence interval</td>
<td></td>
<td>(n = 28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(n = 31)</td>
<td></td>
</tr>
<tr>
<td>Receptive language</td>
<td>N/A</td>
<td>51.4 ± 33.7</td>
<td>30.9 ± 27.3*</td>
<td>16.2–42.1</td>
</tr>
<tr>
<td>Expressive language</td>
<td>N/A</td>
<td>50.0 ± 5.0</td>
<td>47.8 ± 30.1</td>
<td>28.5–63.5</td>
</tr>
<tr>
<td>Gross motor function</td>
<td>36.3 ± 20.7*</td>
<td>38.3 ± 20.1*</td>
<td>28.0–48.7</td>
<td>41.4 ± 22.3</td>
</tr>
<tr>
<td>Fine motor function</td>
<td>46.4 ± 17.9</td>
<td>38.0 ± 33.5</td>
<td>32.0–53.9</td>
<td>25.4–57.3</td>
</tr>
<tr>
<td>Personal-Social abilities</td>
<td>48.5 ± 26.5</td>
<td>43.8 ± 23.8</td>
<td>32.4–53.9</td>
<td>25.4–57.3</td>
</tr>
<tr>
<td>Adaptive behavior</td>
<td>37.5 ± 34.2</td>
<td>37.1 ± 18.6*</td>
<td>25.3–49.0</td>
<td>0.8–48.6</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01; *** p < 0.001
What do we know?

1. Concussion History
   a. Risk of recurrence
      having one makes you at risk of getting another one
   b. Cumulative effects
      after 3, effects may be more long lasting/permanent?

2. Early developmental concussions
   Having a TBI, even a mild one, can have negative consequences on development

3. Delayed consequences
   a. Chronic Traumatic Encephalopathy
   b. Other preliminary findings
Delayed Consequences in moderate to severe TBI

- Widespread Tau and Amyloid-Beta Pathology Many Years After a Single TBI in Humans—Johnson, Stewart and Smith *Brain Pathology*, in press

- Brain Injury May More Than Double Dementia Risk in Older Veterans—Yaffe et al. Alzheimer’s Association International Conference 2011

- TBI Increases Risk of Parkinson’s Disease—Hutson et al., Journal of Neurotrauma 2011


- TBI Linked with Tenfold Increase in Stroke Risk—Chen, Kang & Lin Stroke 2011
Chronic Traumatic Encephalopathy

- progressive degenerative disease of the brain found in athletes (and others) with a history of repetitive brain trauma

- known to affect boxers, recent reports have been published of neuropathologically confirmed CTE in retired professional football players and other athletes who have a history of repetitive brain trauma.

- triggers progressive degeneration of the brain tissue, including the build-up of an abnormal protein called tau and can begin months or years after the last brain trauma

- The brain degeneration is associated with memory loss, confusion, impaired judgment, impulse control problems, aggression, depression, and, eventually, progressive dementia.
Depression

Delayed Consequences: other findings

Very preliminary and limited to specific populations

**Recurrent Concussion and Risk of Depression in Retired Professional Football Players**

KEVIN M. GUSKIEWICZ, STEPHEN W. MARSHALL, JULIAN BAILES, MICHAEL MCCREA, HERMOND P. HARDING, JR., AMY MATTHEWS, JOHN A. REGISTER MIHALIC, and ROBERT C. CANTU

![Graph showing percentage of retired players with known diagnoses of clinical depression by concussion history.](image)

**FIGURE 1**—Percentage (± 95% CI) of retired players with known diagnoses of clinical depression (N = 269), stratified by number of previous concussions (none; one or two; or three or more). Test for linear trend: $\chi^2 = 63.76$, $df = 1$, $P < 0.005$. 
Cognitive impairments

ASSOCIATION BETWEEN RECURRENT CONCUSSION AND LATE-LIFE COGNITIVE IMPAIRMENT IN RETIRED PROFESSIONAL FOOTBALL PLAYERS

(Guskiewicz, 2005)

FIGURE 3. Percentage of retired players aged 50 years or older with a diagnosis of MCI and memory problems (self-reported and reported by a spouse or close relative) by concussion history (none, one, two, and three or more). Error bars indicate 95% confidence intervals. P < 0.007.
Delayed Consequences

A Major Missing Piece of Information

How does a temporary disruption of brain function become permanent damage?

• Metabolic?
• Genetic or epigenetic?
• Functional (i.e., electrical/neurochemical)?
• Structural?

Does the “spacing” between blows make a difference?
What do we know?

1. Concussion History
   a. Risk of recurrence
      having one makes you at risk of getting another one
   b. Cumulative effects
      after 3, effects may be more long lasting/permanent?

2. Early developmental concussions
   Having a TBI, even a mild one, can have negative consequences on development

3. Delayed consequences
   Some evidence, limited to specific populations and limited number of individuals, that there could be a cognitive impact only observed later in life, linked to the presence of tau protein in the brain
So should your child or adolescent risk another concussion?
So should your child or adolescent risk another concussion?

• For now, we just don’t know enough for a definitive answer

• Must be answered on case by case basis

• More severe mTBI should be cautious

• >3 mTBIs should be cautious

• If child is young, should be cautious

We need to focus on protecting our children
Thank you!
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