CANADA NORTH
CONCUSSION NETWORK

The Role of Neuroimaging in the Clinical Management of Concussion and Traumatic Brain Injury: Current Status and Future Directions

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Neurosurgery
Pan Am Concussion Program

2017 UHN TBI Meeting

panam

Health Sciences Centre Winnipeg

University of Manitoba

Children's Hospital Health Sciences Centre Winnipeg
Celebrating children: 100 years of care

the Children's Hospital Research Institute of Manitoba
a division of the Children's Hospital Foundation of Manitoba

Disclosures

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- No additional disclosures.

Objectives

- To discuss the clinical role of conventional neuroimaging in the evaluation and management of concussion and TBI
- To review the potential role of novel neuroimaging assessment tools in the evaluation and management of concussion and TBI
- To identity obstacles that must be overcome for novel neuroimaging tools to bridge the gap between understanding and managing concussion

Case

- 15 year old female athlete
- Cycling accident
- +LOC, post-traumatic amnesia
- 5 months later presents with global headaches, dizziness, and fatigue
- Physical examination:
  - Normal: no evidence of vestibulo-ocular dysfunction or cervical spine injury
- Management? Neuroimaging?

Neuroimaging

Conventional neuroimaging:

- Computerized tomography
- Magnetic resonance imaging

Advanced neuroimaging

- Diffusion tensor imaging
- Functional MRI
- Cerebrovascular imaging

CT

<u>Computerized tomography (CT):</u>

Strengths

- Widely available
- Short acquisition time
- Easy to interpret

Limitations

- Exposure to radiation
- Poorer contrast resolution compared to MRI

Common Findings in TBI

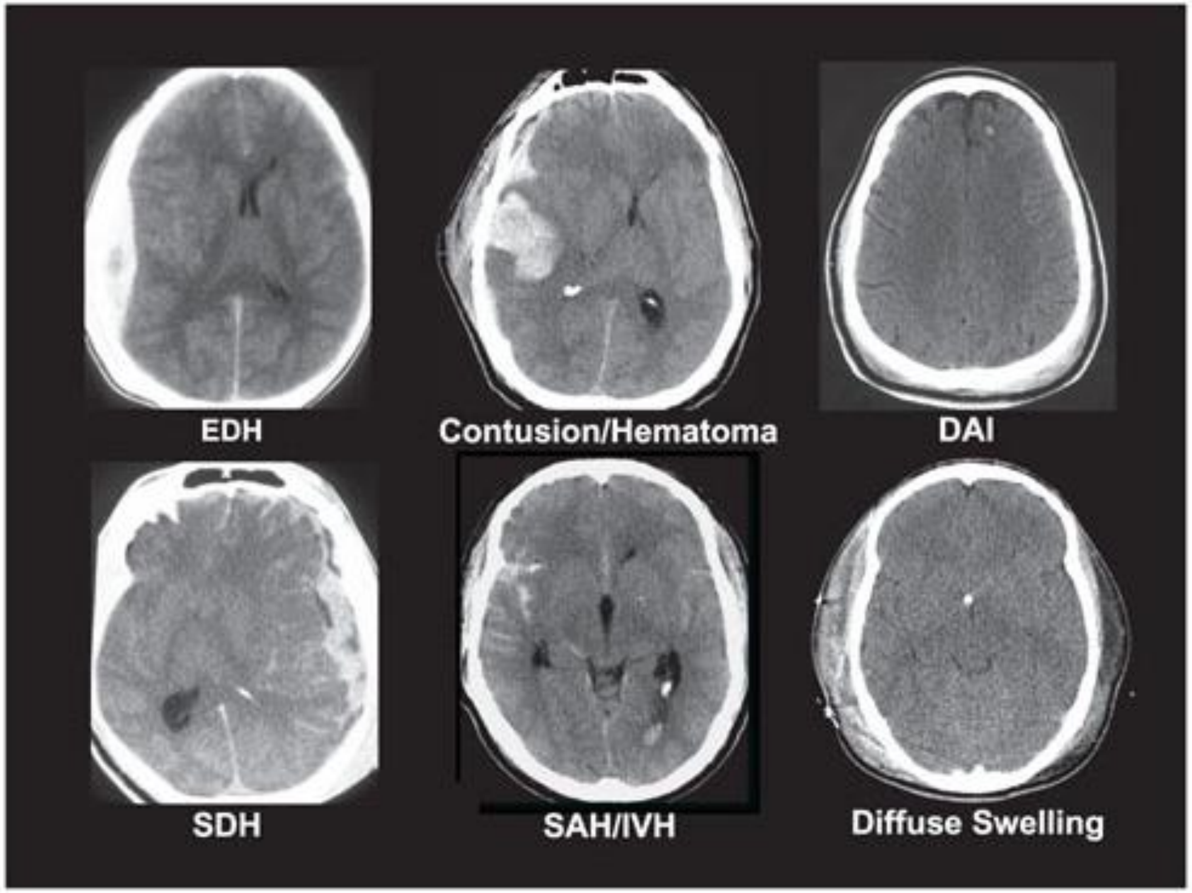


FIG. 1. Heterogeneity of severe traumatic brain injury (TBI). Computed tomography (CT) scans of six different patients with severe TBI, defined as a Glasgow Coma Scale score of <8, highlighting the significant heterogeneity of pathological findings. CT scans represent patients with epidural hematomas (EDH), contusions and parenchymal hematomas (Contusion/Hematoma), diffuse axonal injury (DAI), subdural hematoma (SDH), subarachnoid hemorrhage and intraventricular hemorrhage (SAH/IVH), and diffuse brain swelling (Diffuse Swelling).

Saatman, K. E., Duhaime, A. C., Bullock, R., Maas, A. I., Valadka, A., & Manley, G. T. (2008). Workshop Scientific Team and Advisory Panel Members. Classification of traumatic brain injury for targeted therapies. Journal of Neurotrauma, 25 (7), 719–738

CT

Marshall CT Classification of Brain Injury

Diffuse Injury Grade	CT Findings	Mortality
I	Normal	9.6%
II	Cisterns present, midline shift< 5mm	13.5%
III	Cisterns compressed/absent, midline shift< 5mm	34%
IV	Midline shift> 5mm	56.2%

Rotterdam CT Classification

TABLE 1. Rotterdam Computed Tomography Classification[a]

Predictor	Score
Basal cisterns	
Normal	0
Compressed	1
Absent	2
Midline shift	
No shift or shift ≤5 mm	0
Shift >5 mm	1
Epidural mass lesion	
Present	0
Absent	1
Intraventricular blood or subarachnoid hemorrhage	
Absent	0
Present	1
Sum score	+1

[a]In the Rotterdam scoring system, 1 point is added as a sum score to make the Rotterdam grade numerically total 6 points, consistent with the motor score of the Glasgow Coma Scale and the Marshall classification. From Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery*. 2005;57(6):1173–1182.[7]

TABLE 3. Rotterdam Computed Tomography Score vs Mortality and Unfavorable Outcome[a]

Rotterdam CT Score	No. of Patients	Mortality, No. (%)	Unfavorable Outcome, No. (%)
2	6	0 (0)	1 (16.7)
3	13	1 (7.7)	4 (30.8)
4	25	5 (20.0)	11 (44.0)
5	47	11 (23.4)	29 (61.7)
6	36	24 (66.7)	33 (91.7)

[a]CT, computed tomography.

Mild TBI

CMAJ RESEARCH

CATCH: a clinical decision rule for the use of computed tomography in children with minor head injury

Martin H. Osmond MD CM, Terry P. Klassen MD, George A. Wells PhD, Rhonda Correll RN, Anna Jarvis MD, Gary Joubert MD, Benoit Bailey MD, Laurel Chauvin-Kimoff MD CM, Martin Pusic MD, Don McConnell MD, Cheri Nijssen-Jordan MD, Norm Silver MD, Brett Taylor MD, Ian G. Stiell MD; for the Pediatric Emergency Research Canada (PERC) Head Injury Study Group

- GCS 13-15, LOC, amnesia, disorientation, vomiting or irritability
- 3866 pediatric patients enrolled
- 159 (4.1%) had CT evidence of brain injury
- 24 (0.6%) underwent a neurosurgical intervention

Osmond et al., CMAJ, 2010

Mild TBI

Prevalence of abnormal CT-scans following mild head injury

GRANT L. IVERSON†,
MARK R. LOVELL‡, STANLEY SMITH§
and MICHAEL D. FRANZEN§

- GCS 13-15
- 912 adult patients enrolled
- 59% MVA
- 16-21% had positive CT findings

BRAIN INJURY, 2000, VOL. 14, NO. 12, 1057–1061

Clinicial Prediction Rules

Children

CT of the head is required only for children with minor head injury* and any one of the following findings:

High risk (need for neurologic intervention)

1. Glasgow Coma Scale score < 15 at two hours after injury
2. Suspected open or depressed skull fracture
3. History of worsening headache
4. Irritability on examination

Medium risk (brain injury on CT scan)

5. Any sign of basal skull fracture (e.g., hemotympanum, “raccoon” eyes, otorrhea or rhinorrhea of the cerebrospinal fluid, Battle’s sign)
6. Large, boggy hematoma of the scalp
7. Dangerous mechanism of injury (e.g., motor vehicle crash, fall from elevation ≥ 3 ft [≥ 91 cm] or 5 stairs, fall from bicycle with no helmet)

Note: CT = computed tomography.
*Minor head injury is defined as injury within the past 24 hours associated with witnessed loss of consciousness, definite amnesia, witnessed disorientation, persistent vomiting (more than one episode) or persistent irritability (in a child under two years of age) in a patient with a Glasgow Coma Scale score of 13–15.

Osmond et al., CMAJ, 2010

Adults

Canadian CT Head Rule

CT head is only required for minor head injury patients with any one of these findings:

High Risk (for Neurological Intervention)

1. GCS score < 15 at 2 hrs after injury
2. Suspected open or depressed skull fracture
3. Any sign of basal skull fracture*
4. Vomiting ≥ 2 episodes
5. Age ≥ 65 years

Medium Risk (for Brain Injury on CT)

6. Amnesia before impact ≥ 30 min
7. Dangerous mechanism ** *(pedestrian, occupant ejected, fall from elevation)*

*Signs of Basal Skull Fracture
- hemotympanum, 'racoon' eyes, CSF otorrhea/ rhinorrhea, Battle's sign

** Dangerous Mechanism
- pedestrian struck by vehicle
- occupant ejected from motor vehicle
- fall from elevation ≥ 3 feet or 5 stairs

Rule Not Applicable If:
- Non-trauma cases
- GCS < 13
- Age < 16 years
- Coumadin or bleeding disorder
- Obvious open skull fracture

Stiell IG, et al. The Canadian CT Head Rule for Patients with Minor Head Injury. Lancet 2001;357:1391-96.

Summary

<u>Computerized tomography:</u>

- Most commonly used neuroimaging tool used in initial evaluation of TBI patients
- Abnormal findings observed in 4-30% of mTBI patients
- Use of CT should be restricted to the emergency room setting
- Recommended use according to evidence-based clinical decision-making rules

MRI

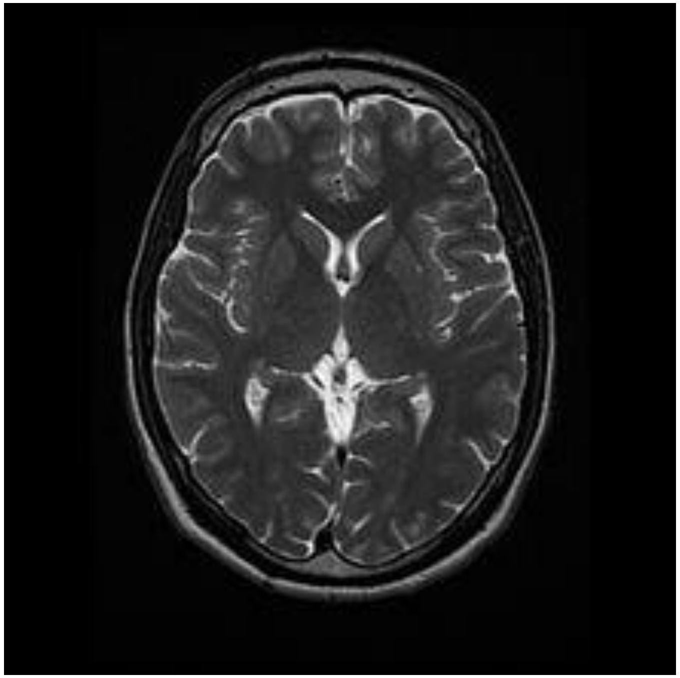
Magnetic resonance imaging (MRI):

Strengths

- Superior resolution

Limitations

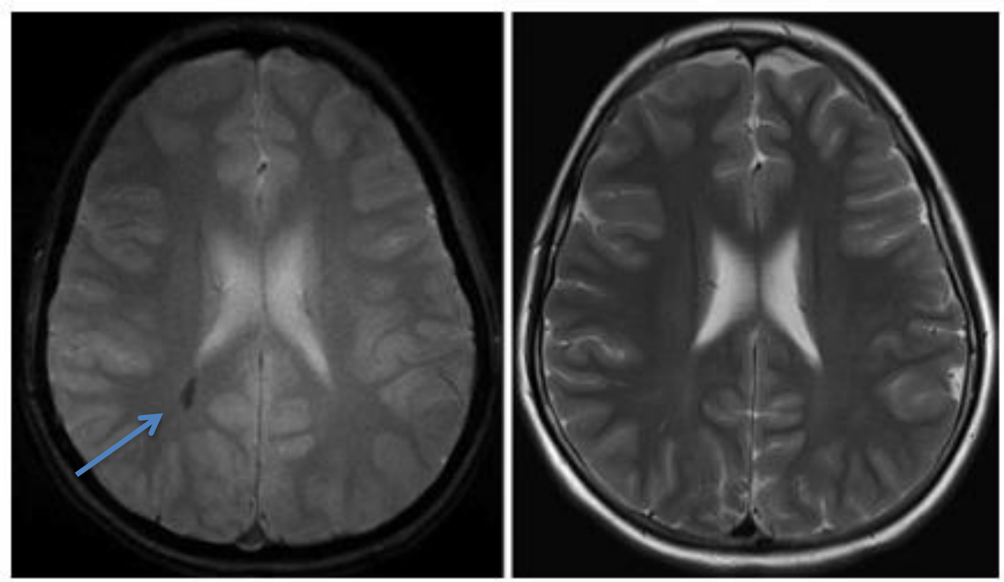
- Less accessible
- Longer acquisition time
- Contraindications
- Greater cost



MRI

Gradient recalled echo & susceptibility-weighted imaging:

- Enhanced sensitivity to cerebral micro-hemorrhages previously undetected on conventional sequences

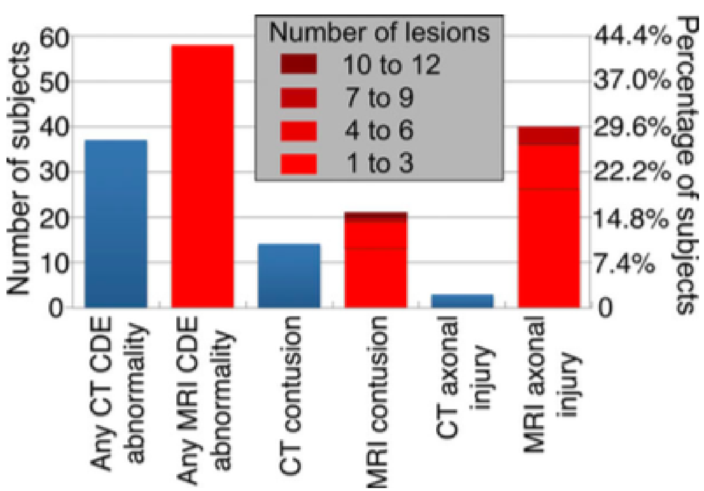


GRE T2

Magnetic Resonance Imaging Improves 3-Month Outcome Prediction in Mild Traumatic Brain Injury

Esther L. Yuh, MD, PhD,[1,2] Pratik Mukherjee, MD, PhD,[1,2] Hester F. Lingsma, PhD,[3] John K. Yue, BS,[1,4] Adam R. Ferguson, PhD,[1,4] Wayne A. Gordon, PhD,[5] Alex B. Valadka, MD,[6] David M. Schnyer, PhD,[7] David O. Okonkwo, MD, PhD,[8] Andrew I. R. Maas, MD, PhD,[9] Geoffrey T. Manley, MD, PhD,[1,4] and the TRACK-TBI Investigators

- GCS 13-15
- 135 adult patients enrolled
- Day of injury CT, early MRI (mean= 12 days)



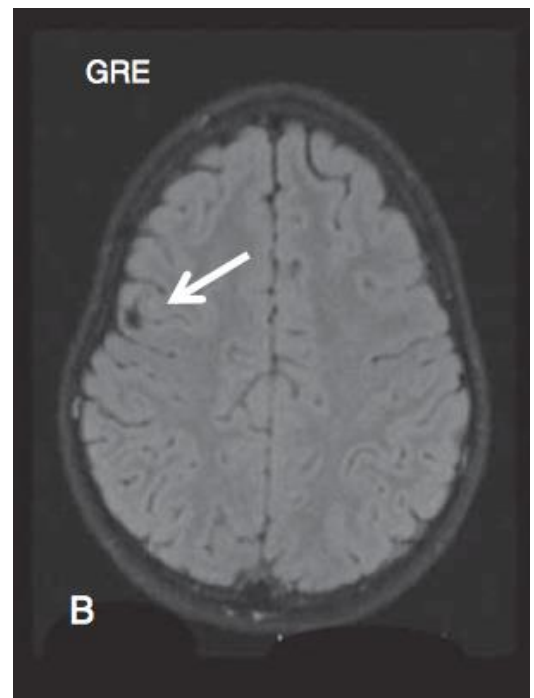
- More sensitive than CT for DAI and contusions
- Presence of any contusion or ≥ 4 hemorrhagic foci on MRI associated with multivariate odd ratio of 3.5 for poorer 3-month outcome after controlling for demographic, clinical, and socioeconomic factors

Ann Neurol, 2013

Structural Neuroimaging Findings in Mild Traumatic Brain Injury

Erin D. Bigler, PhD,† Tracy J. Abildskov,* Naomi J. Goodrich-Hunsaker, PhD,*
Garrett Black, BS,* Zachary P. Christensen, BS,*† Trevor Huff, BS,*†
Dawn-Marie G. Wood, MS,† John R. Hesselink, MD,‡
Elisabeth A. Wilde, PhD,§ and Jeffrey E. Max, MBBCh‡||*

- Pediatric mTBI Study
- 131 mTBI: GCS 13-15; 66 Orthopedic injured controls
- MRI at 6 month post-injury
- Hemosiderin deposition (3 patients), encephalomalacia (2 patients), white matter changes (4 patients), prominent Virchow-Robin spaces (5 patients)



Sports Med Arthrosc, 2016

SRC

- Conventional CT and MR-imaging is typically normal in SRC patients, and therefore, “contributes little to concussion evaluation.”

Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012

Paul McCrory,[1] Willem H Meeuwisse,[2,3] Mark Aubry,[4,5,6] Bob Cantu,[7,8] Jiří Dvořák,[9,10,11] Ruben J Echemendia,[12,13] Lars Engebretsen,[14,15,16] Karen Johnston,[17,18] Jeffrey S Kutcher,[19] Martin Raftery,[20] Allen Sills,[21] Brian W Benson,[22,23,24] Gavin A Davis,[25] Richard G Ellenbogen,[26,27] Kevin Guskiewicz,[28] Stanley A Herring,[29,30] Grant L Iverson,[31] Barry D Jordan,[32,33,34] James Kissick,[6,35,36,37] Michael McCrea,[38] Andrew S McIntosh,[39,40,41] David Maddocks,[42] Michael Makdissi,[43,44] Laura Purcell,[45,46] Margot Putukian,[47,48] Kathryn Schneider,[49] Charles H Tator,[50,51,52,53] Michael Turner[54]

▸ Additional material is published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/bjsports-2013-092313).

For numbered affiliations see end of article.

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PREAMBLE

This paper is a revision and update of the recommendations developed following the 1st (Vienna 2001), 2nd (Prague 2004) and 3rd (Zurich 2008) International Consensus Conferences on Concussion in Sport and is based on the deliberations at the 4th International Conference on Concussion in Sport held in Zurich, November 2012.[1–3]

The new 2012 Zurich Consensus statement is designed to build on the principles outlined in the previous documents and to develop further conceptual understanding of this problem using a formal consensus-based approach. A detailed description of the consensus process is outlined at the end of this document under the Background section. This document is developed primarily for use by physicians and healthcare professionals who are involved in the care of injured athletes, whether at the recreational, elite or professional level.

While agreement exists pertaining to principal messages conveyed within this document, the authors acknowledge that the science of concussion is evolving, and therefore management and return to play (RTP) decisions remain in the realm of clinical judgement on an individualised basis. Readers are encouraged to copy and distribute freely the Zurich Consensus document, the Concussion Recognition Tool (CRT), the Sports Concussion Assessment Tool V3 (SCAT3) and/or the Child SCAT3 card and none are subject to any restrictions, provided they are not altered in any way or converted to a digital format. The authors request that the document and/or the accompanying tools be distributed in their full and complete format.

This consensus paper is broken into a number of sections

1. A summary of concussion and its management, with updates from the previous meetings;
2. Background information about the consensus meeting process;
3. A summary of the specific consensus questions discussed at this meeting;
4. The Consensus paper should be read in conjunction with the SCAT3 assessment tool, the Child SCAT3 and the CRT (designed for lay use).

To cite: McCrory P, Meeuwisse WH, Aubry M, et al. *Br J Sports Med* 2013;47:250–258.

SECTION 1: SPORT CONCUSSION AND ITS MANAGEMENT

The Zurich 2012 document examines the sport concussion and management issues raised in the previous Vienna 2001, Prague 2004 and Zurich 2008 documents and applies the consensus questions from section 3 to these areas.[1–3]

Definition of concussion

A panel discussion regarding the definition of concussion and its separation from mild traumatic brain injury (mTBI) was held. There was acknowledgement by the Concussion in Sport Group (CISG) that although the terms mTBI and concussion are often used interchangeably in the sporting context and particularly in the US literature, others use the term to refer to different injury constructs. Concussion is the historical term representing low-velocity injuries that cause brain ‘shaking’ resulting in clinical symptoms and that are not necessarily related to a pathological injury. Concussion is a subset of TBI and will be the term used in this document. It was also noted that the term *commotio cerebri* is often used in European and other countries. Minor revisions were made to the definition of concussion, which is defined as follows:

> Concussion is a brain injury and is defined as a complex pathophysiological process affecting the brain, induced by biomechanical forces. Several common features that incorporate clinical, pathologic and biomechanical injury constructs that may be utilised in defining the nature of a concussive head injury include:

1. Concussion may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an “impulsive’ force transmitted to the head.
2. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, symptoms and signs may evolve over a number of minutes to hours.
3. Concussion may result in neuropathological changes, but the acute clinical symptoms

Neuroimaging

Childs Nerv Syst (2015) 31:2305–2309
DOI 10.1007/s00381-015-2916-y

ORIGINAL PAPER

Post-concussion syndrome (PCS) in a youth population: defining the diagnostic value and cost-utility of brain imaging

Clinton D. Morgan[1] · Scott L. Zuckerman[1] · Lauren E. King[2] · Susan E. Beaird[2] · Allen K. Sills[1] · Gary S. Solomon[1]

- 52 PCS patients (imaging obtained in 23 patients)
- 77% sports-related concussion
- 1/8 (13%) CT studies demonstrated skull fracture
- 1/19 (5.3%) MRI studies demonstrated multiple punctate foci within the bilateral frontal, temporal, and parietal lobes
- Clinical indication for imaging- persistent symptoms

Neuroimaging

JNS PEDIATRICS

CLINICAL ARTICLE

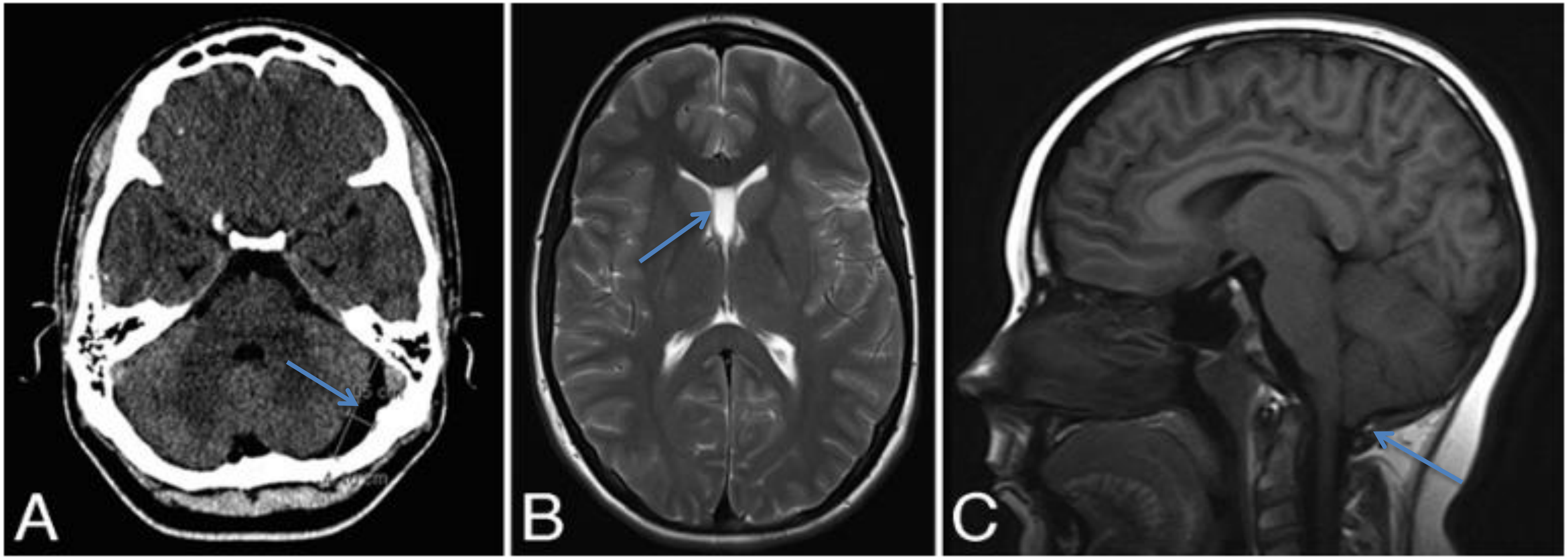
Neuroimaging findings in pediatric sports-related concussion

Michael J. Ellis, MD,[1,2,4,6,7] Jeff Leiter, PhD,[1,6] Thomas Hall, BSc,[6] Patrick J. McDonald, MD, MHSc,[1,2,4,6,7] Scott Sawyer, MD,[2,5] Norm Silver, MD,[2,5] Martin Bunge, MD,[3] and Marco Essig, MD[3]

- 151 patients (mean age=14 years, 59% female) were included this study. Overall, 24% of patients underwent neuroimaging studies (CT,MRI) of which 78% were normal.
- 11% of neuroimaging studies demonstrated traumatic abnormalities.

J Neurosurg Pediatr June 2, 2015

Neuroimaging



Arachnoid cyst

Cavum septum pellucidum

Chiari I malformation

Neurosurg Focus 40 (4):E8, 2016

Retirement

NEUROSURGICAL FOCUS

Neurosurg Focus 40 (4):E8, 2016

Retirement-from-sport considerations following pediatric sports-related concussion: case illustrations and institutional approach

Michael J. Ellis, MD, FRCSC,[1,2,6–9] Patrick J. McDonald, MD, MHSc, FRCSC,[8–11]
Dean Cordingley, MSc,[7,9] Behzad Mansouri, MD, PhD, FRCP(C),[4,7,9]
Marco Essig, MD, PhD, FRCP(C),[3,7,9] and Lesley Ritchie, PhD[5,7,9]

- Abnormalities on neuroimaging
- Focal neurological deficits and abnormalities on clinical exam
- Cumulative or prolonged effects of concussion

Retirement

NEUROSURGICAL FOCUS

Neurosurg Focus 40 (4):E8, 2016

TABLE 1. Summary of our current institutional approach to RTP and retirement considerations in children and adolescents with structural brain abnormalities

Clinical Indication	Institutional Approach/RTP Consideration
Traumatic structural brain injury	Retirement from future contact & collision sports participation
Skull fractures & prior craniotomy for nontraumatic brain lesions	Individualized approach. RTP considered following radiographic evidence of bone healing
Craniotomy for traumatic lesions (e.g., subdural hematoma, intraparenchymal hemorrhage, second-impact syndrome)	Retirement from future contact & collision sports participation
Transsphenoidal, endovascular, endoscopic approaches to intracranial lesions	Individualized approach
Cavum septum pellucidum	No contraindication to safe RTP
Arachnoid cyst	Individualized approach. Patient must be informed of risk of intracystic hemorrhage, subdural hematoma/hygroma. RTP considered in patients w/ small, asymptomatic, or incidental arachnoid cysts (<5 cm) w/ no or minimal mass effect
Hydrocephalus	Individualized approach. Patient must be informed of risk of shunt malfunction, hard-ware damage, subdural hematoma/hygroma. RTP considered in patients treated w/ endoscopic third ventriculostomy
Chiari Type I malformation	Individualized approach. RTP considered for patients w/ asymptomatic or minimal tonsillar herniation w/ no syrinx. RTP considered in patients w/ foramen magnum decompression w/o associated spinal malformation & instability

Summary

Magnetic resonance imaging:

Considered in patients with..

- Focal neurological deficits (weakness, numbness, monocular visual deficits)
- Post-traumatic seizures
- Abnormalities on initial CT
- Persistent symptoms that do not respond to conservative management or treatment
- Deficits on formal neuropsychological testing

Future Directions

Future studies are needed…

- To identify which patients benefit from neuroimaging (i.e clinical indications)
- To evaluate the prognostic value of MRI findings on patient outcomes
- Evidence-based recommendations regarding sports participation in patients with abnormalities detected on conventional MRI

MRI

Remember..

- Just because an MRI study is normal does not mean it doesn’t provide value to the patient, their family, and the treating physician.

Case

- 15 year old female athlete
- Cycling accident
- +LOC, post-traumatic amnesia
- PMHx: 3 previous concussions
- 5 months later presents with global headaches, dizziness, and fatigue
- Physical examination:
  - Normal: no evidence of vestibulo-ocular dysfunction or cervical spine injury
- Management? Neuroimaging?

Neuroimaging

<u>Conventional neuroimaging:</u>

- Computerized tomography
- Magnetic resonance imaging

<u>Advanced neuroimaging</u>

- Diffusion tensor imaging
- Functional MRI
- Cerebrovascular imaging

Case

- 15 year old female athlete
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Clinical Value

Advanced neuroimaging

- Must be able to provide clinically meaningful information that can not otherwise be obtained by clinical history & physical examination
- Must provide information about an individual patient basis
- Ideally, provides reliable quantitative biomarkers that can be used in cross-sectional and longitudinal assessment

Clinical Value

Potential uses of advanced neuroimaging in concussion and mTBI:

- Assist diagnosis
- Confirm recovery
- Quantify extent of injury
- Prediction of outcomes

Neuroimaging

<u>Conventional neuroimaging:</u>

- Computerized tomography
- Magnetic resonance imaging

<u>Advanced neuroimaging</u>

- Diffusion tensor imaging
- Functional MRI
- Cerebrovascular imaging

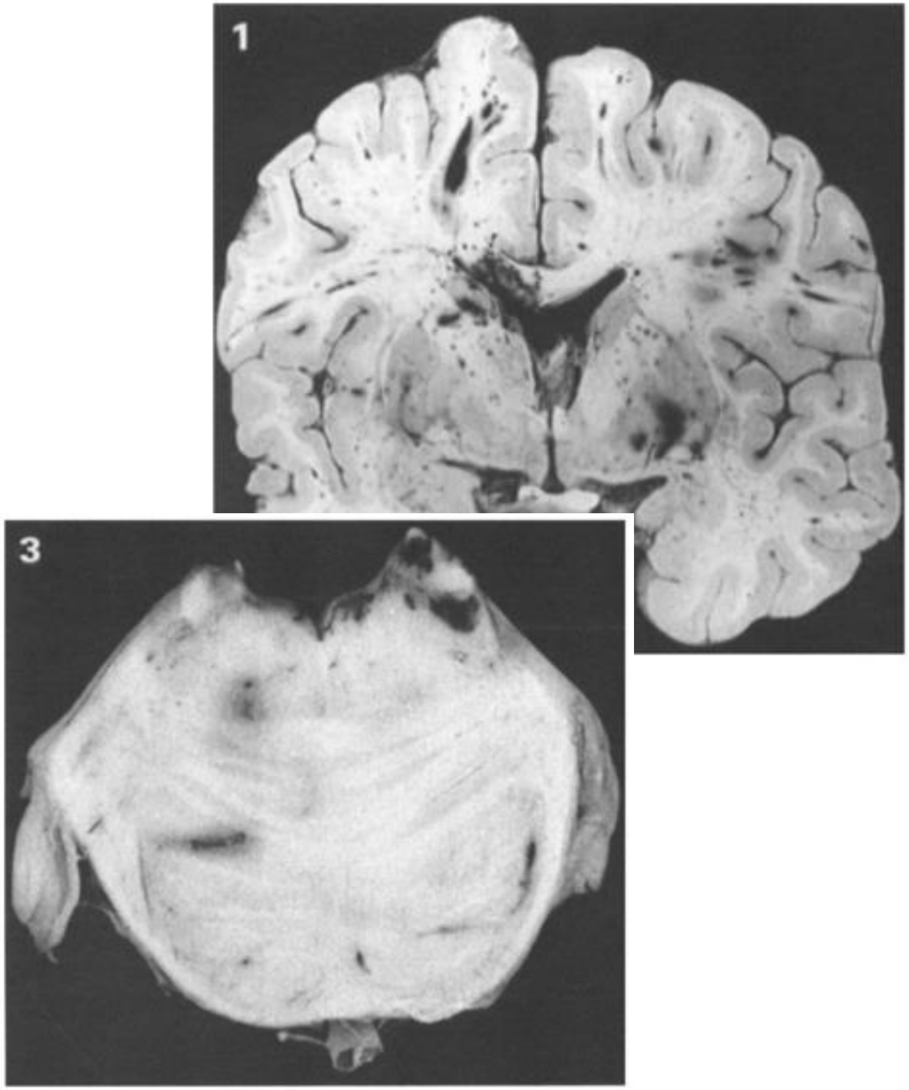
DTI

Diffusion tensor imaging (DTI):

- Diffusion is constrained by tissues in the brain and that assessment of this diffusion can provide information about the white matter microstructure.
- Based on assessment of diffusion, a number of quantitative biomarkers can be calculated.
- Fractional aniostropy (FA), radial diffusivity (RD), mean diffusivity (MD), axial diffusivity (AD), trace.

DTI

- One of key pathophysiological mechanisms underlying TBI is shear injury to white matter tracts and resultant cerebral micro-hemorrhages, termed diffuse axonal injury.
- DAI has been found in TBI patients of all severities



Adams et al., Histopathology, 1989

DTI

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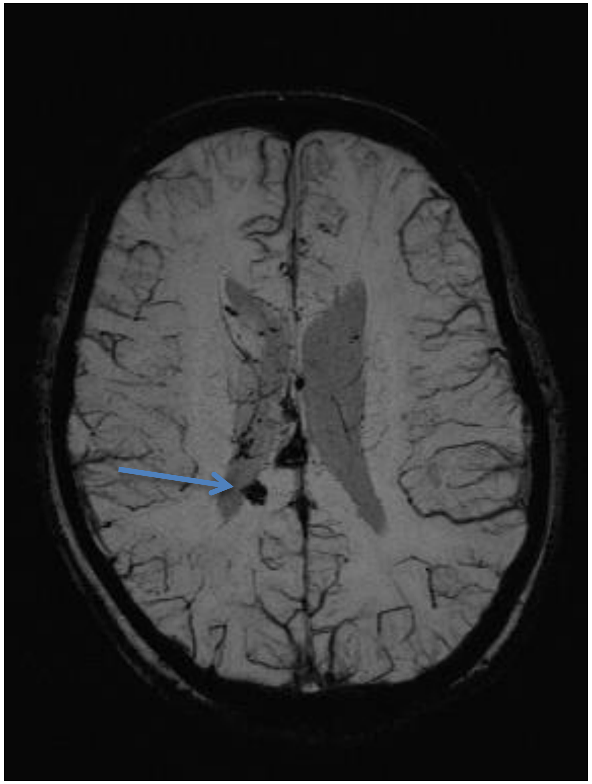


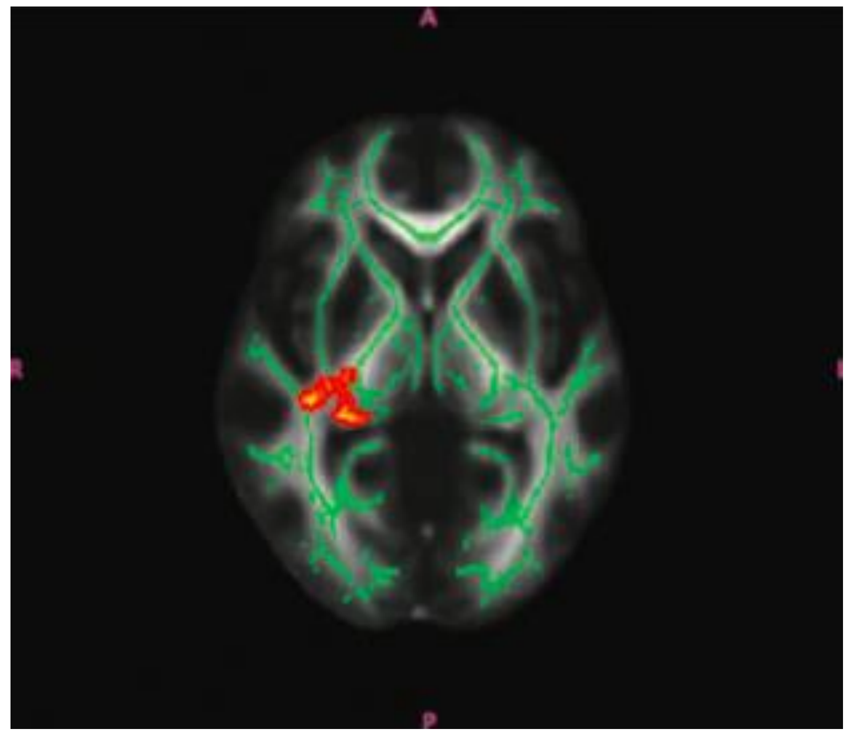
JOURNAL OF NEUROTRAUMA 31:1860–1871 (November 15, 2014)

DOI: 10.1089/neu.2014.3368

A Longitudinal Diffusion Tensor Imaging Study Assessing White Matter Fiber Tracts after Sports-Related Concussion

Murali Murugavel,[1] Valerie Cubon,[2] Margot Putukian,[3] Ruben Echemendia,[4]
Javier Cabrera,[5] Daniel Osherson,[6] and Annegret Dettwiler[1,7]

- Varsity athletes with SRC vs. normal controls
- DTI within 2 days, 2 weeks, and 2 month post-injury
- ↑ RD and ↓ FA within right hemisphere WMT within 72 hours of injury followed by recovery that may extend beyond 2 weeks.



JOURNAL OF NEUROTRAUMA 28:2049–2059 (October 2011)

DOI: 10.1089/neu.2011.1836

Acute and Chronic Changes in Diffusivity Measures after Sports Concussion

Luke C. Henry,[1] Julie Tremblay,[2] Sebastien Tremblay,[1] Agatha Lee,[6] Caroline Brun,[4]
Natasha Lepore,[5] Hugo Theoret,[1,2] Dave Ellemberg,[1,3] and Maryse Lassonde[1,2]

- Collegiate athletes with SRC vs. normal controls
- DTI within 6 days of injury and at 6 months post-injury
- ↑ FA and AD ↓ MD within the corpus callosum and right corticospinal tract and right hemisphere WMT compared to controls.
- ↑ FA was found to persist at 6 months

Neurometabolic and microstructural alterations following a sports-related concussion in female athletes

Emilie Chamard[1], Maryse Lassonde[1], Luke Henry[2], Julie Tremblay[3], Yvan Boulanger[4], Louis De Beaumont[5], & Hugo Théoret[1]

[1]Centre de Recherche en Neuropsychologie et Cognition, Department of Psychology, University of Montreal, Montréal, Québec, Canada, [2]UPMC Sports Concussion Clinic, Pittsburgh, PA, USA, [3]Hôpital Ste. Justine, Montréal, Québec, Canada, [4]Department of Radiology, University of Montreal and Hôpital Saint-Luc, Montréal, Québec, Canada, and [5]Centre de Recherche en Neuropsychologie et Cognition, Department of Psychology, University du Québec à Trois-Rivières (UQTR), Montréal, Québec, Canada

- Female athletes with SRC vs. normal controls
- DTI at 7 months post-injury
- ↑ MD within diffuse white matter tracts but no differences in FA.

Brain Inj, 2013; 27(9): 1038–1046

DTI

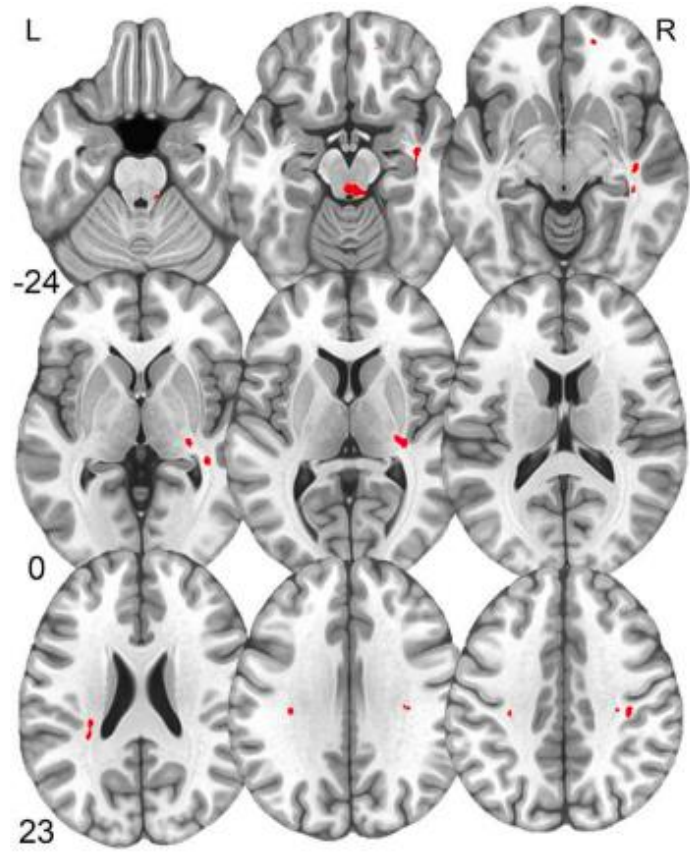
Diffusion tensor imaging findings are not strongly associated with postconcussional disorder 2 months following mild traumatic brain injury.(Lipton et al., J Head Trauma Rehabil, 2012)

- mTBI patients vs. orthopedically injured controls
- DTI of the corpus callosum at 6-8 weeks post-injury
- No group differences any DTI measures
- No group differences between mTBI patients meeting the ICD-10 criteria for post-concussion syndrome

Longitudinal Assessment of White Matter Abnormalities Following Sports-Related Concussion

Timothy B. Meier,[1,2,3] Maurizio Bergamino,[3] Patrick S. F. Bellgowan,[4]
T. K. Teague,[5,6,7] Josef M. Ling,[2] Andreas Jeromin,[8] and Andrew R. Mayer[2,9,10]

- Longitudinal DTI in collegiate SRC patients vs controls
- Imaged at mean 1.64, 8.33, & 32.15 days
- Group and subject-specific analysis demonstrated ↑ FA within several WMT
- No evidence of longitudinal recovery



Human Brain Mapping 37:833–845 (2016)

J Head Trauma Rehabil
Vol. 30, No. 2, pp. E32–E42

Diffusion Tensor Imaging Alterations in Patients With Postconcussion Syndrome Undergoing Exercise Treatment: A Pilot Longitudinal Study

Paul Polak, MASc; John J. Leddy, MD, FACSM, FACP; Michael G. Dwyer, PhD; Barry Willer, PhD; Robert Zivadinov, MD, PhD, FAAN

- 8 patients with PCS, 15 controls
- 4 treated with sub-maximal exercise prescription and 4 treated with stretching
- ↓ FA and ↑ RD and MD within the corpus callosum among PCS group compared to controls
- Despite clinical improvements in exercise tolerance and symptoms in patients treated with exercise there were no longitudinal group differences in DTI indices.

Neuroimaging

Michael L. Lipton, MD, PhD
Namhee Kim, PhD, PhD
Molly E. Zimmerman, PhD
Mimi Kim, ScD
Walter F. Stewart, PhD
Craig A. Branch, PhD
Richard B. Lipton, MD

Soccer Heading Is Associated with White Matter Microstructural and Cognitive Abnormalities[1]

Radiology

- Observed ↓ FA within the temporo-occipital white matter in amateur soccer players that were associated with poorer memory scores and a soccer "heading" threshold of 1800/year.

Radiology: Volume 268: Number 3—September 2013

Neuroimaging

White matter microstructure abnormalities in pediatric migraine patients

Cephalalgia
2015, Vol. 35(14) 1278–1286

DOI: 10.1177/0333102415578428
cep.sagepub.com
SAGE

Roberta Messina[1,2], Maria A Rocca[1,2], Bruno Colombo[2], Elisabetta Pagani[1], Andrea Falini[3], Giancarlo Comi[2] and Massimo Filippi[1,2]

- Observed ↓ MD, RD, AD and ↑ FA among pediatric migraine patients compared to controls

Summary

- DTI is capable of demonstrating group (and more recently individual) changes in white matter tracts following mTBI and concussion.
- The anatomical distribution of these changes are variable across studies.
- Natural history of quantitative biomarkers changes following concussion remains unclear.
- Similar changes have been observed in athletes with exposure to sub-clinical head impacts and in other neurological conditions to commonly co-exist among SRC patients.

Case

- 15 year old female athlete
- Cycling accident
- +LOC, post-traumatic amnesia
- PMHx: 3 previous concussions
- 5 months later presents with global headaches, dizziness, and fatigue
- Physical examination:
  - Normal: no evidence of vestibulo-ocular dysfunction or cervical spine injury
- Management? Neuroimaging?

Clinical Questions

<u>Conventional neuroimaging:</u>

- Computerized tomography
- Magnetic resonance imaging

<u>Advanced neuroimaging</u>

- Diffusion tensor imaging
- Functional MRI
- Cerebrovascular imaging

fMRI

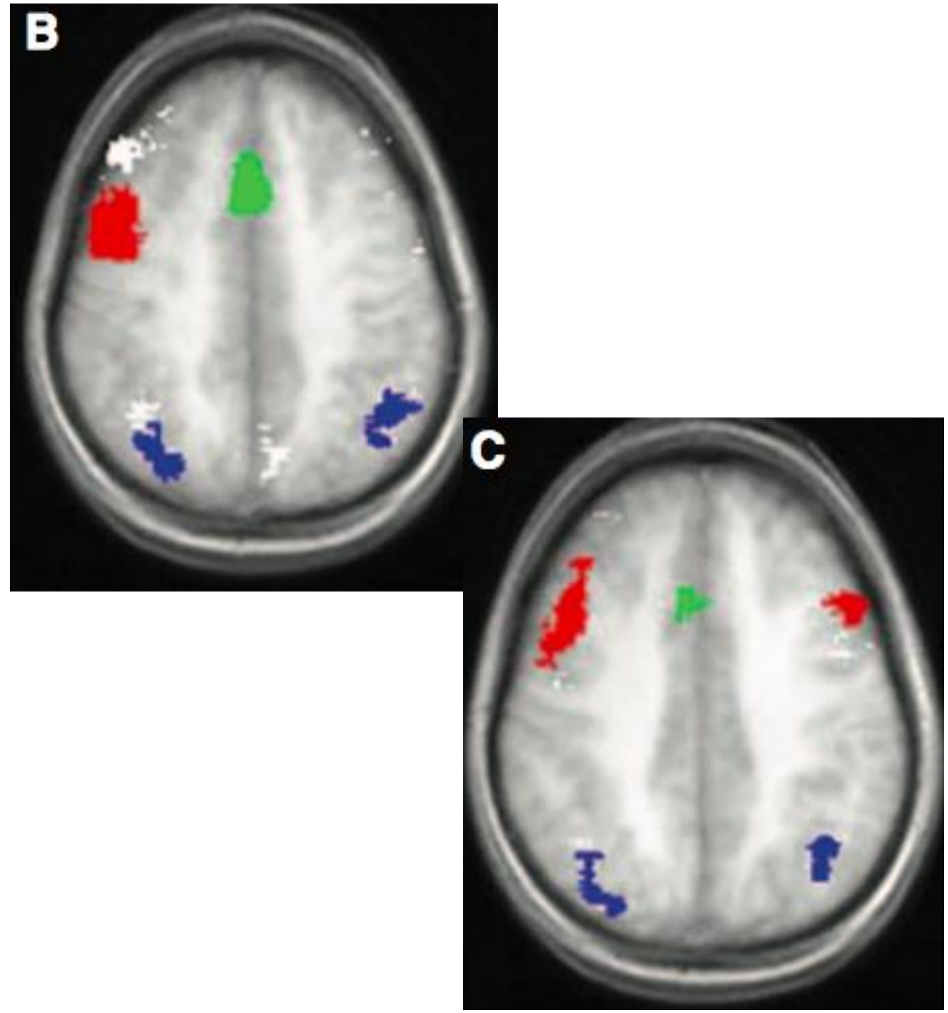
<u>Functional MRI (fMRI):</u>

- Spatial measurements of blood oxygen level-dependent (BOLD) MRI signal throughout the brain.
- Task-based: assessing activation patterns within networks that govern performance on behavioral and cognitive tasks
- Resting-state: spontaneous signal fluctuations and connectivity within brain networks

Mark R. Lovell, Ph.D.
Department of Orthopedic Surgery,
University of Pittsburgh
School of Medicine,
Pittsburgh, Pennsylvania

Functional Brain Abnormalities Are Related to Clinical Recovery and Time to Return-to-play in Athletes

- High school SRC patients
- fMRI during N-back working memory task within 1 week of injury and again following clinical recovery
- Decreased activation within posterior parietal network correlated with increased symptoms
- Activity within the medial premotor and supplementary motor region was associated with time to recovery



Neurosurgery 61:352–360, 2007

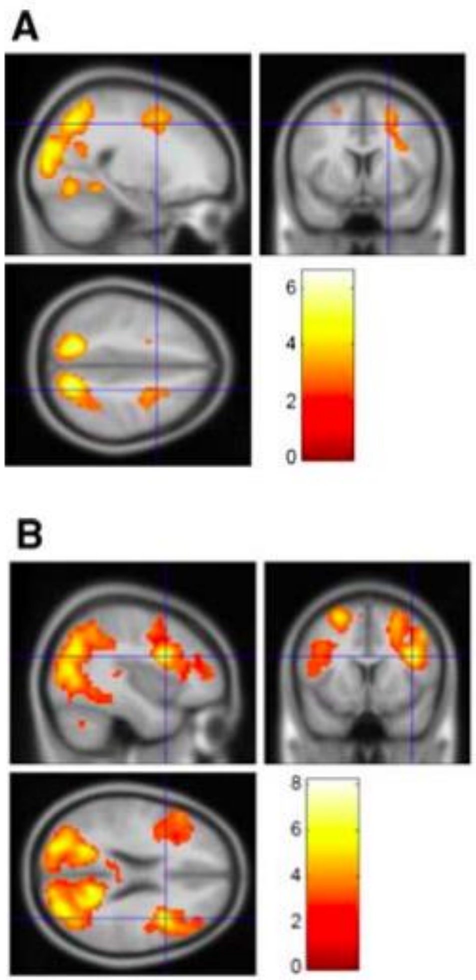
Exp Brain Res (2010) 202:341–354
DOI 10.1007/s00221-009-2141-6

RESEARCH ARTICLE

Functional abnormalities in normally appearing athletes following mild traumatic brain injury: a functional MRI study

Semyon M. Slobounov · K. Zhang · D. Pennell · W. Ray · B. Johnson · W. Sebastianelli

- Collegiate SRC patients imaged 30 days post-injury and normal controls
- “virtual corridor” spatial memory task
- No differences in task performance between groups
- SRC patients demonstrated larger activations involving the right dorsolateral prefrontal cortex and cerebellum.



Controls

MTBI

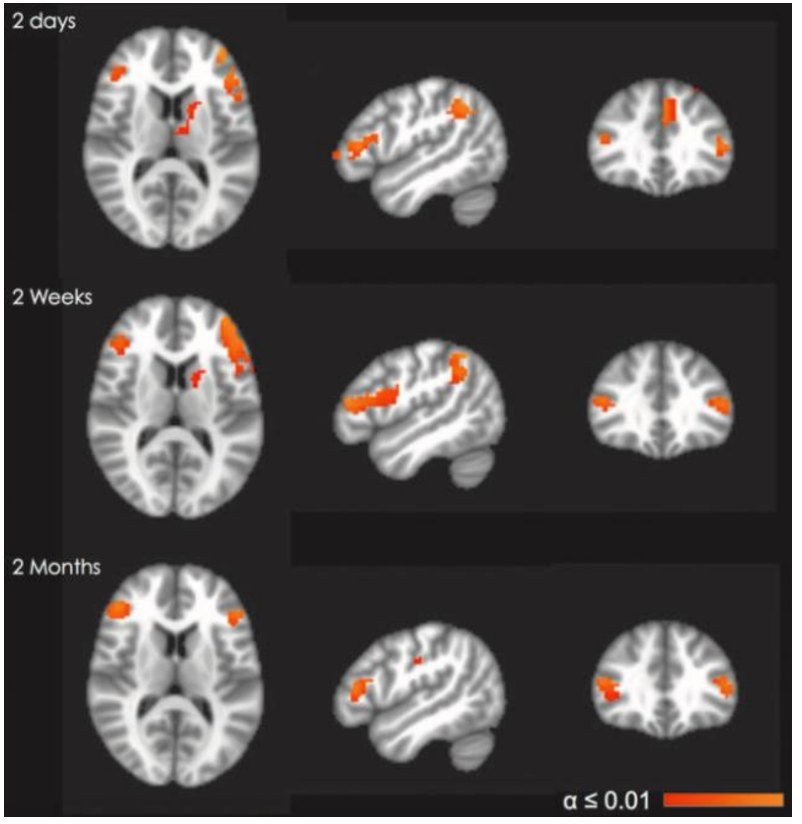
JOURNAL OF NEUROTRAUMA 31:180–188 (January 15, 2014)

DOI: 10.1089/neu.2013.2983

Persistent Differences in Patterns of Brain Activation after Sports-Related Concussion: A Longitudinal Functional Magnetic Resonance Imaging Study

Annegret Dettwiler,[1] Murali Murugavel,[1] Margot Putukian, Valerie Cubon,[3]
John Furtado,[2] and Daniel Osherson[4]

- Varsity athletes and controls
- fMRI during N-back working memory task within 72 hours, at 2 weeks and at 2 months of injury injury
- Persistent hyperactivation within the inferior parietal lobe for two weeks and within the dorsolateral prefrontal cortices for two months among SRC patients



Tb-fMRI

JOURNAL OF NEUROTRAUMA 31:327–338 (February 15, 2014)

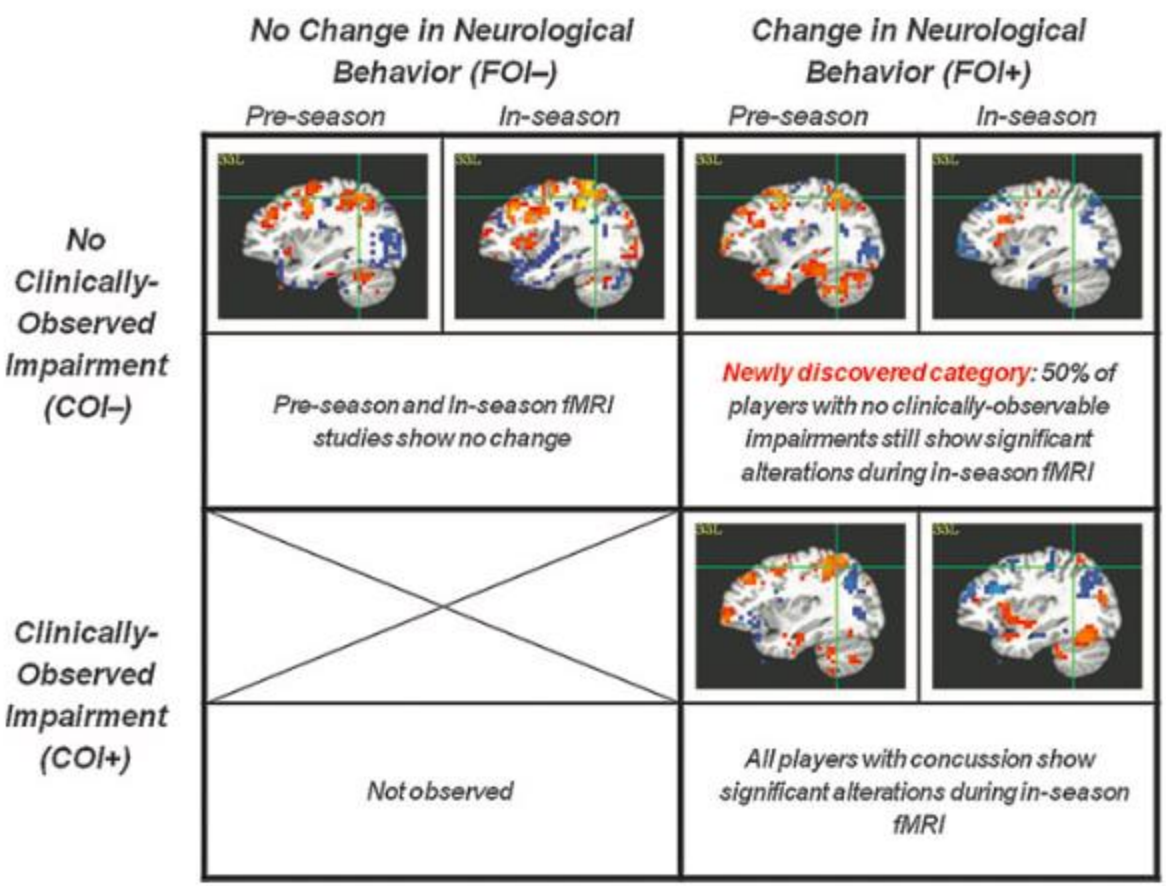
DOI: 10.1089/neu.2010.1512

Functionally-Detected Cognitive Impairment in High School Football Players without Clinically-Diagnosed Concussion

Thomas M. Talavage,[1,2] Eric A. Nauman,[1,3,4] Evan L. Breedlove,[1] Umit Yoruk,[2] Anne E. Dye,[3]
Katherine E. Morigaki,[5] Henry Feuer,[6] and Larry J. Leverenz[5]

- 11 male highschool football players
- Collision events (HIT system), neurocognitive testing (ImPACT) and fMRI during N-back task
- Baseline and in-season testing

Tb-fMRI



- Alterations in fMRI activation patterns among those with concussion and those without a concussion but with neurocognitive deficits

Tb-fMRI

Exercise Treatment for Postconcussion Syndrome: A Pilot Study of Changes in Functional Magnetic Resonance Imaging Activation, Physiology, and Symptoms

John J. Leddy, MD, FACSM, FACP; Jennifer L. Cox, PhD; John G. Baker, PhD; David S. Wack, PhD; David R. Pendergast, EdD; Robert Zivadinov, MD, PhD; Barry Willer, PhD

- FMRI activation patterns during a math processing task examined in healthy controls, PCS patients assigned to stretching, and PCS patients assigned to aerobic exercise prescription.
- Exercise prescription resulted in improved resting HR and concussion symptoms, increased exercise tolerance, and normalization of activation patterns compared to PCS patients assigned to stretching.

J Head Trauma Rehabil
Vol. 28, No. 4, pp. 241–249

Summary

- fMRI is capable of demonstrating group changes in brain activation patterns following mTBI and concussion.
- Differences in study samples and imaging paradigms limit comparisons between studies
- Changes have been observed in athletes with exposure to sub-clinical head impacts and in other neurological conditions to commonly co-exist among SRC patients.
- Use for longitudinal assessment shows promise

Case

- 15 year old female athlete
- Cycling accident
- +LOC, post-traumatic amnesia
- PMHx: 3 previous concussions
- 5 months later presents with global headaches, dizziness, and fatigue
- Physical examination:
  - Normal: no evidence of vestibulo-ocular dysfunction or cervical spine injury
- Management? Neuroimaging?

Clinical Questions

Conventional neuroimaging:

- Computerized tomography
- Magnetic resonance imaging

Advanced neuroimaging

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- Functional MRI
- Cerebrovascular imaging

Cerebrovascular imaging

- The maintenance of CBF is one of the most important processes responsible for maintaining brain function during health, disease, and injury.

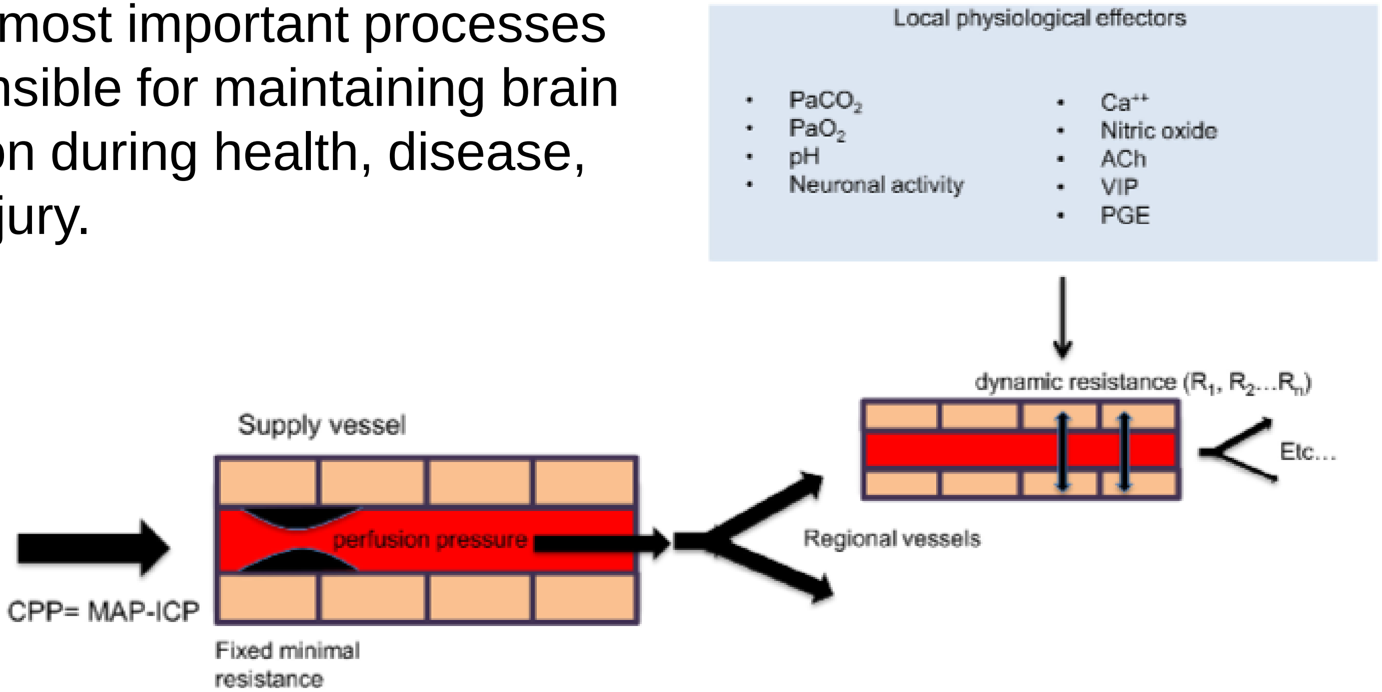


FIGURE 1 | General schema of cerebral perfusion. Intracranial vessels are perfused in parallel in a fractal branching pattern. The net flow in each region is dynamically determined by the net flow resistance of each branch. Under normal conditions, the inflow from major extracranial vessels is not limiting. The flow to each vascular region is controlled by its local factors as shown in the figure. The net effect of regional vascular resistances determines the total cerebral blood flow. However, with a strong global vasodilatory stimulus, the drop in resistance in the collective downstream branches can be reduced to the point where the blood flow in the larger supply vessels is limiting ("fixed minimal resistance" in supply vessel in the figure). Abbreviation: CPP, cerebral perfusion pressure; MAP, mean arterial pressure; ICP, intracranial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; Ca^{++}, calcium ions; ACh, acetylcholine; VIP, vasoactive intestinal polypeptide; PGE, prostaglandins.

Ellis et al., Front of Neurol, 2016

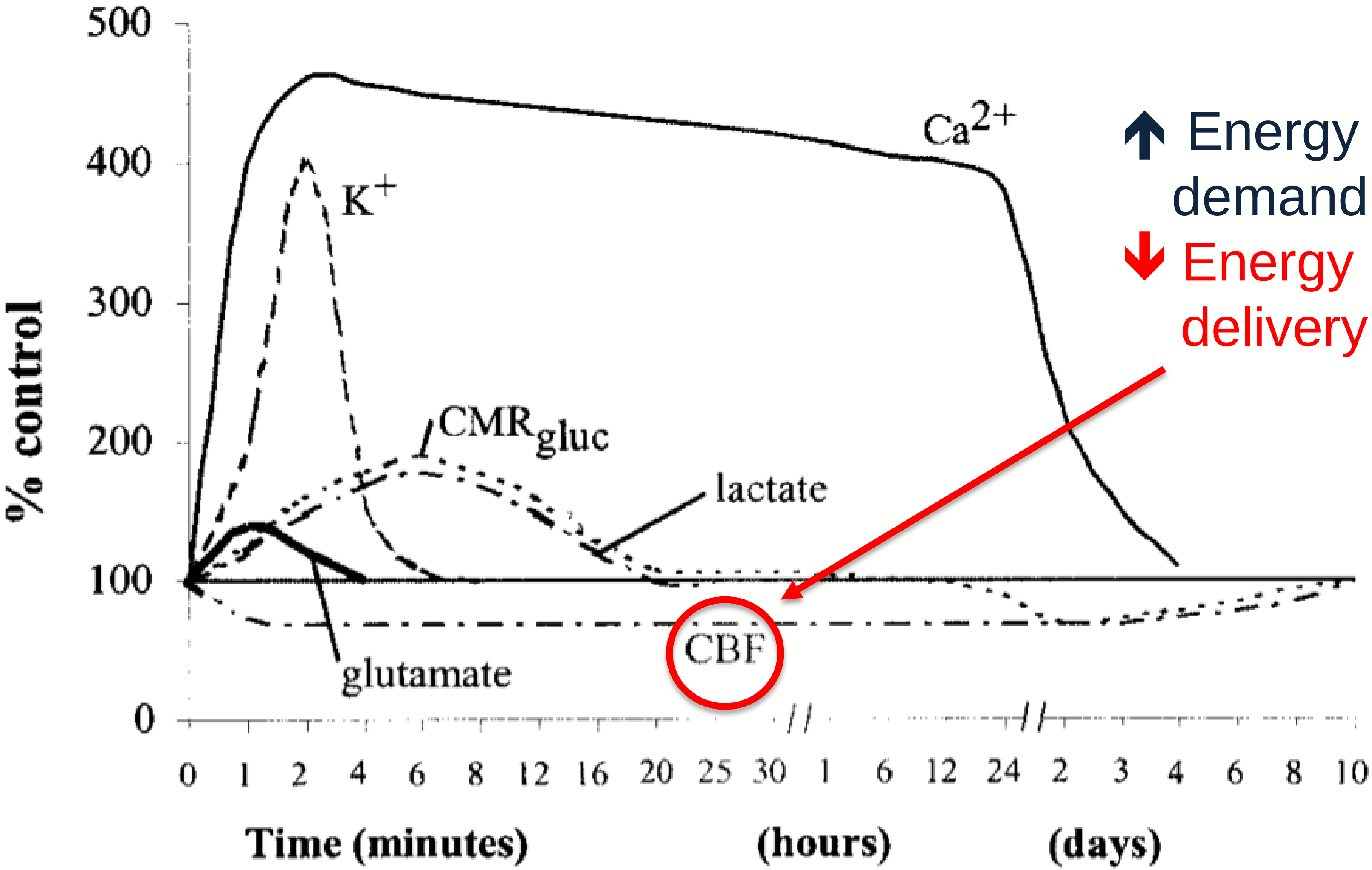
Cerebrovascular imaging

- Primary brain injury: biomechanical disruption of brain tissue at the time of injury
- Secondary brain injury: cellular, metabolic, inflammatory processes that result in further tissue edema, injury, and resultant neurological deterioration

Cerebrovascular imaging

- 90% of autopsy specimens from patients with fatal TBI show evidence of ischemia (Graham et al., 1971, 1989)
- Clinical studies in moderate and severe TBI demonstrate that alterations in resting global CBF are predictive of poor outcomes (Bouma et al., 1991; Coles et al., 2004; Wintermark et al., 2004).

Cerebrovascular imaging



↑ Energy demand

↓ Energy delivery

Giza & Hovda, Journal of Athletic training 2001

Cerebrovascular imaging

Measurement of cerebral blood flow:

- Quantify global and regional cerebral blood flow.
- *Direct CBF measurement:* arterial spin labeling (ASL), pseudo-continuous ASL (pCASL)
- *Indirect CBF measurement:* blood oxygen level-dependent (BOLD) MRI

Cerebrovascular imaging

Pediatric Sports-Related Concussion Produces Cerebral Blood Flow Alterations

AUTHORS: Todd A. Maugans, MD,[a,b] Chad Farley, MD,[b]
Mekibib Altaye, PhD,[c,d] James Leach, MD,[c,e] and
Kim M. Cecil, PhD[c,e]

- 12 SRC patients (11-15 years) vs controls
- ASL & DTI MRI and ImPACT testing <72 hours, 2 weeks, and >30 days post-injury
- No group differences in DTI indices over any time point or within any regions of interest
- Impaired mean resting CBF in the acute phase that persisted at 1 month despite resolution of symptoms and normalization of neurocognitive testing scores.

Pediatrics 2012;129:28–37

Cerebrovascular imaging

Recovery of Cerebral Blood Flow Following Sports-Related Concussion

Timothy B. Meier, PhD; Patrick S. F. Bellgowan, PhD; Rashmi Singh, PhD; Rayus Kuplicki, PhD;
David W. Polanski, MS, ATC, LAT; Andrew R. Mayer, PhD

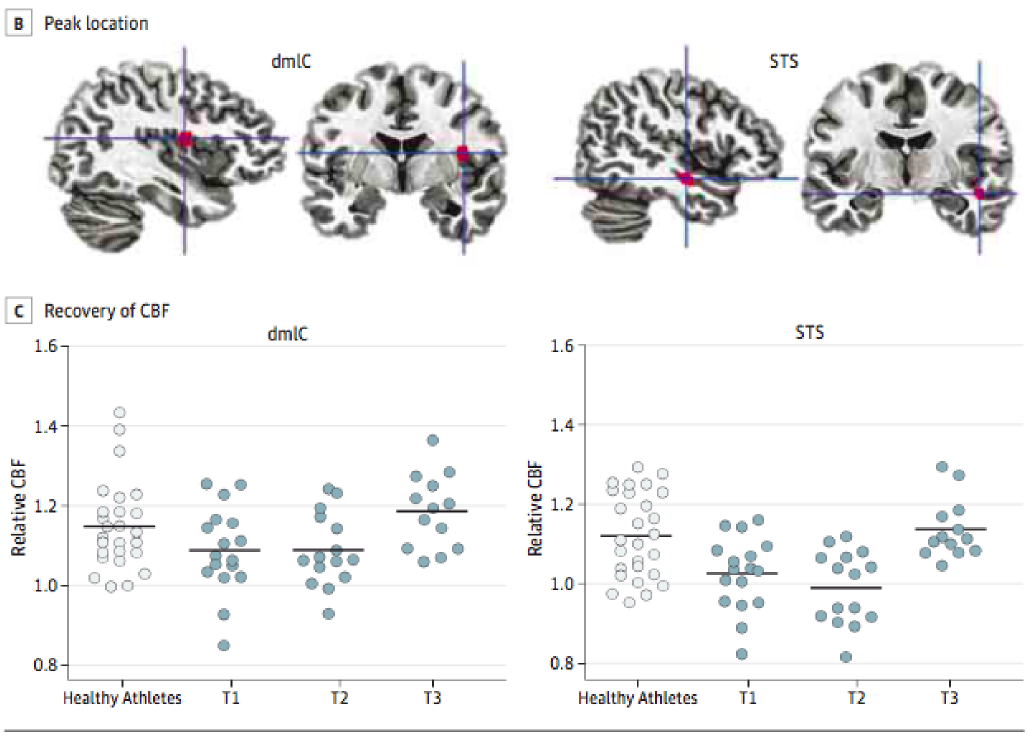
- 44 collegiate football players including 13-15 with a SRC
- Completed ASL MRI and depression and anxiety rating scales at T1(0-3 d), T2(6-13d), and T3(30 d) post-injury.

JAMA Neurology Published online March 2, 2015

Cerebrovascular imaging

Recovery of Cerebral Blood Flow Following Sports-Related Concussion

Timothy B. Meier, PhD; Patrick S. F. Bellgowan, PhD; Rashmi Singh, PhD; Rayus Kuplicki, PhD; David W. Polanski, MS, ATC, LAT; Andrew R. Mayer, PhD



A, Regions exhibiting a significant main effect of time for the longitudinal analysis. The highlighted regions indicate the location of the clustered volume that had a significant main effect of time. B, Five-mm-radius spherical regions of interest created at the 2 peak regions for the main effect of time including the right dorsal midinsular cortex (dmIC) and right superior temporal sulcus (STS). The red indicates the location of the regions of interest used in subsequent post hoc analyses. C, Scatterplots of relative CBF are displayed for all healthy athletes (open circles) as well as concussed athletes (filled circles) at the 3 recovery points (T1 = 1 day; T2 = 1 week; T3 = 1 month) postinjury.

Cerebrovascular imaging

Cerebral blood flow alterations in acute sports-related concussion (Wang et al. J of Neurotrauma, 2016)

- 18 football players with SRC and 19 normal controls
- Completed ASL MRI and SCAT3 within 24 hours of injury and at 8 days post-injury.
- Significant reduction in resting CBF at 8 days compared to 24 hours post-injury despite normalization of SCAT3 scores.

Cerebrovascular imaging

- *Cerebrovascular reactivity:* unit change in cerebral blood flow in response to a unit change in a vasodilatory (stress)

CVR

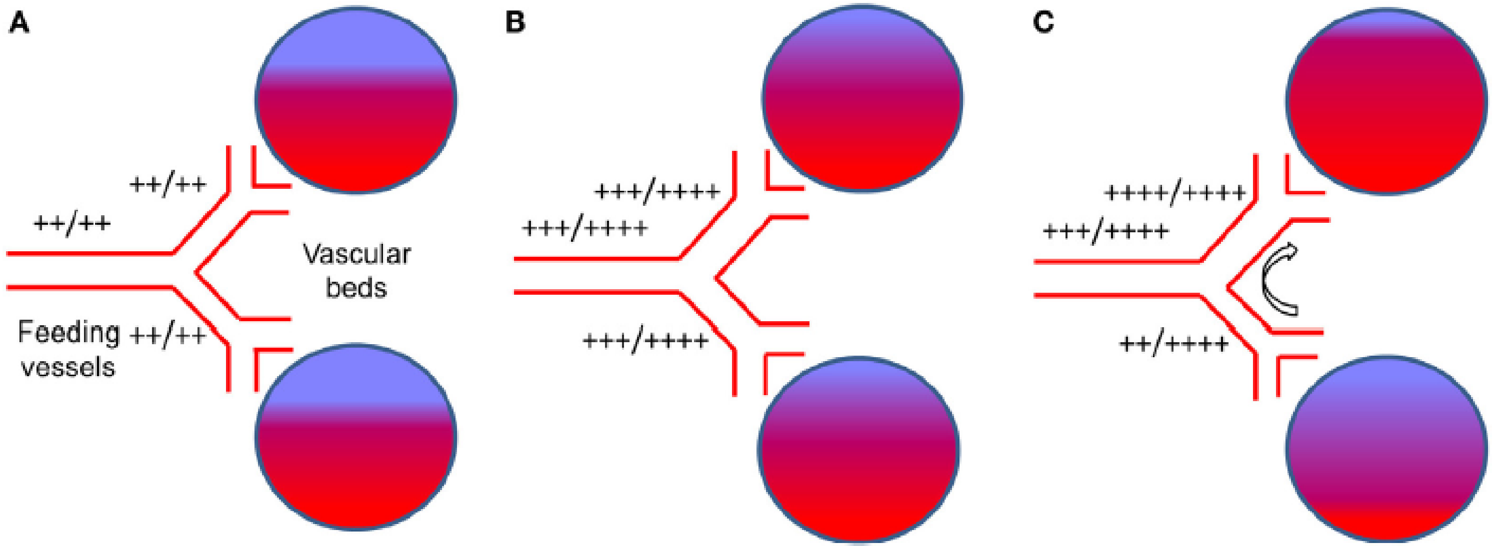
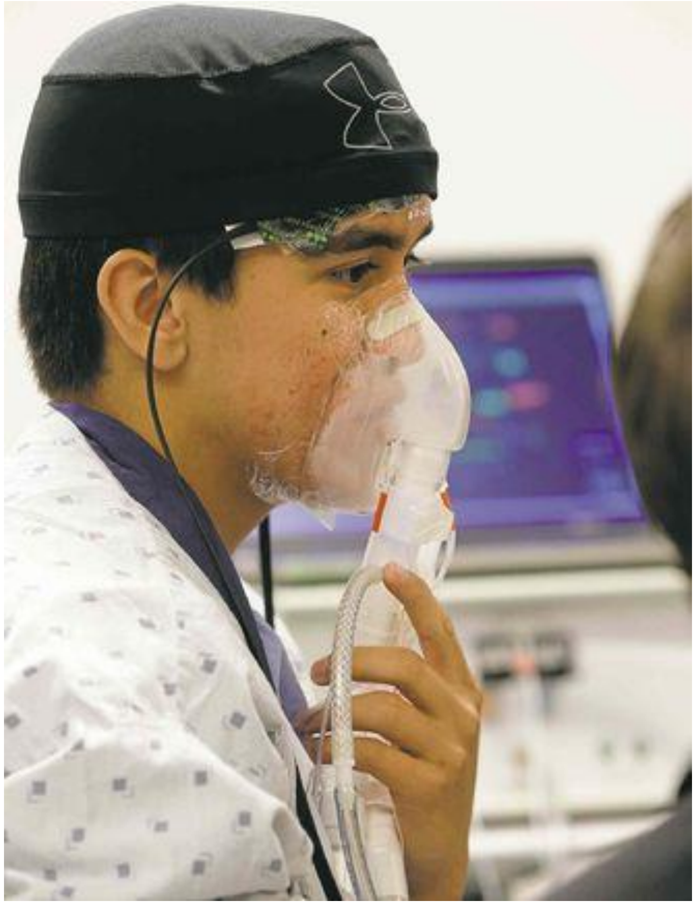
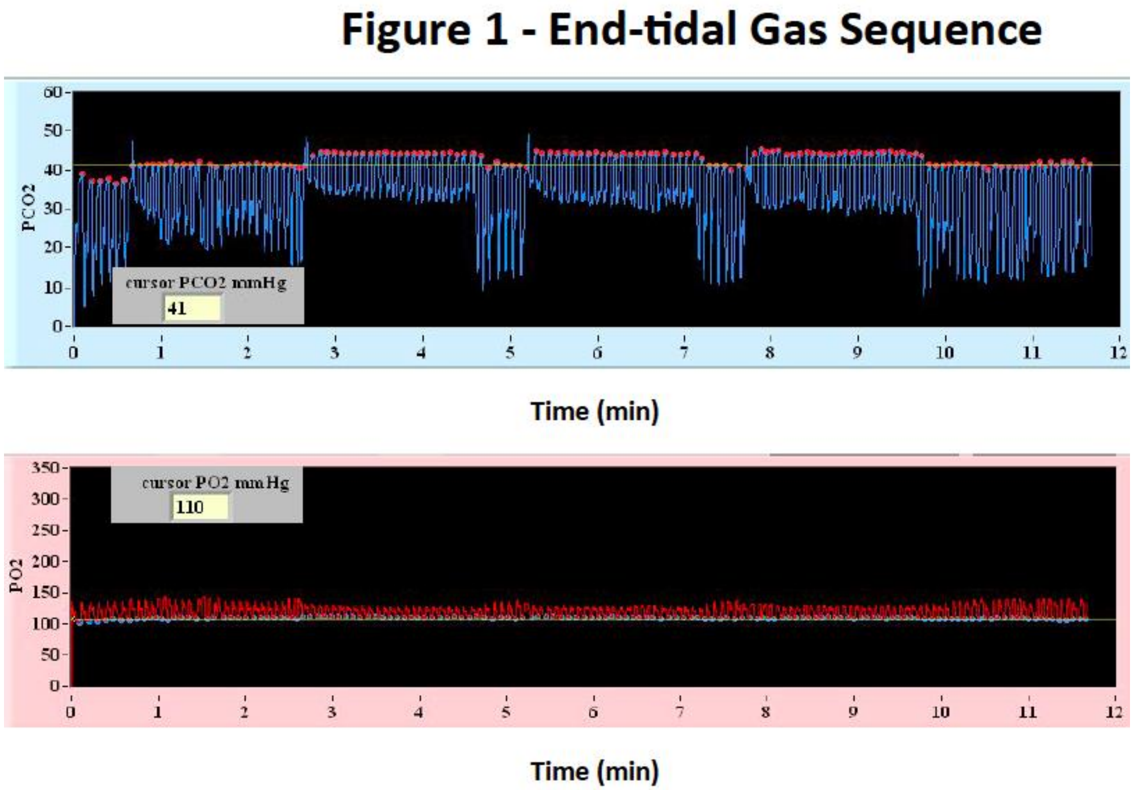


FIGURE 2 | The effect of a global vasodilatory stimulus on regional blood flow with normal vasculature and with impaired regional vascular response. (A) The normal state at normocapnia. The extent of red color in the vascular beds represents actual blood flow and blue color represents potential blood flow. "++/++" beside vessels represents normal blood flow at rest (++) compared to the flow demand (++). This would be the case for normal vasculature and for vasculature that has branches with reduced vasodilatory capacity. **(B)** With normal vasculature, hypercapnia stimulates increase blood demand by the vascular beds. The vasodilatory demand of the vascular beds combined exceed that of the main feeding vessel (23), which is limiting, i.e., their flow (+++) does not meet demand (++++). However, the dilatory response capability of each feeding vessel is symmetrical and so is their flow. **(C)** In the presence of a dysfunctional vessel, a hypercapnic stimulus results in the same demand in the healthy and dysfunctional vessel (i.e., ++++). There is a strong vasodilation in the healthy (upper) branch and a weaker vasodilation in the dysfunctional (lower) branch. The inflow from the main vessel is still limiting (i.e., +++/++++). The direct competition for flow between the vascular beds results in an increased proportion of the flow through the normal vessel (++++) "at the expense of the dysfunctional vessel [flow reduced from +++ in **(B)**, to ++]. This is referred to as vascular 'steal.'"

Ellis M, Ryner L, Sobczyk O, Fierstra J, Mikulis D, Fisher J, Duffin J, Mutch WAC: Neuroimaging assessment of cerebrovascular reactivity in concussion: current concepts, methodological considerations and review of the literature. Frontiers of Neurology- Neurotrauma (published online) 2016

Cerebrovascular imaging





Cerebrovascular imaging

JNS
CLINICAL ARTICLE

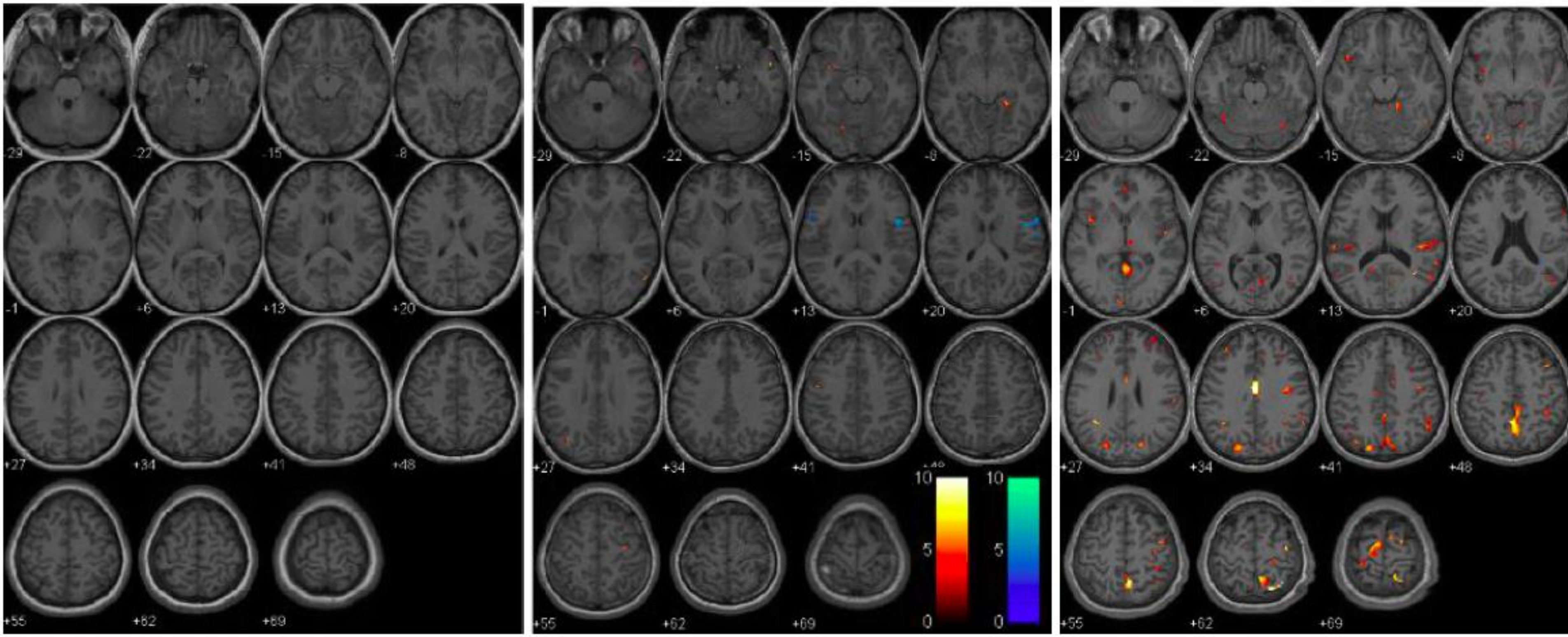
Brain magnetic resonance imaging CO_2 stress testing in adolescent postconcussion syndrome

*W. Alan C. Mutch, MD,[1,6,10] Michael J. Ellis, MD,[2,3,5,7,8,10] Lawrence N. Ryner, PhD,[4,6,10] M. Ruth Graham, MD,[1,10] Brenden Dufault, MSc,[9,10] Brian Gregson, MD,[1,10] Thomas Hall, BSc,[10] Martin Bunge, MD,[4,10] and Marco Essig, MD,[4,6,10] for the Canada North Concussion Network, and Joseph A. Fisher, MD,[11,12,14] James Duffin, PhD,[11,12,14] and David J. Mikulis, MD,[13,14] for the University Health Network Cerebrovascular Reactivity Research Group

- 15 symptomatic adolescent PCS patients and 17 normal controls
- CVR assessment using model-based prospective end-tidal CO_2 targeting and BOLD MRI
- Patient-specific alterations in resting regional CBF and CVR

J Neurosurg December 18, 2015

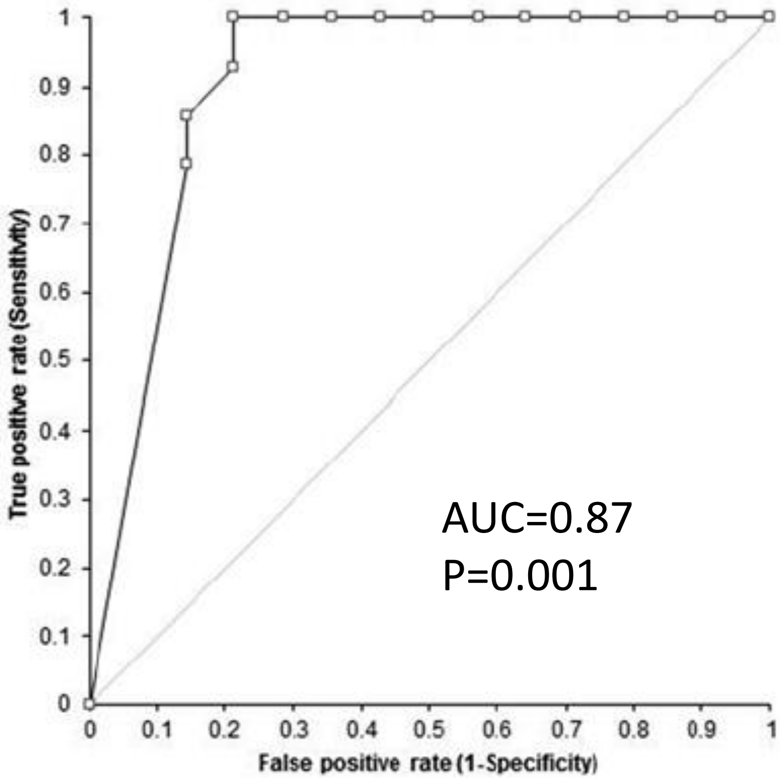
Cerebrovascular imaging



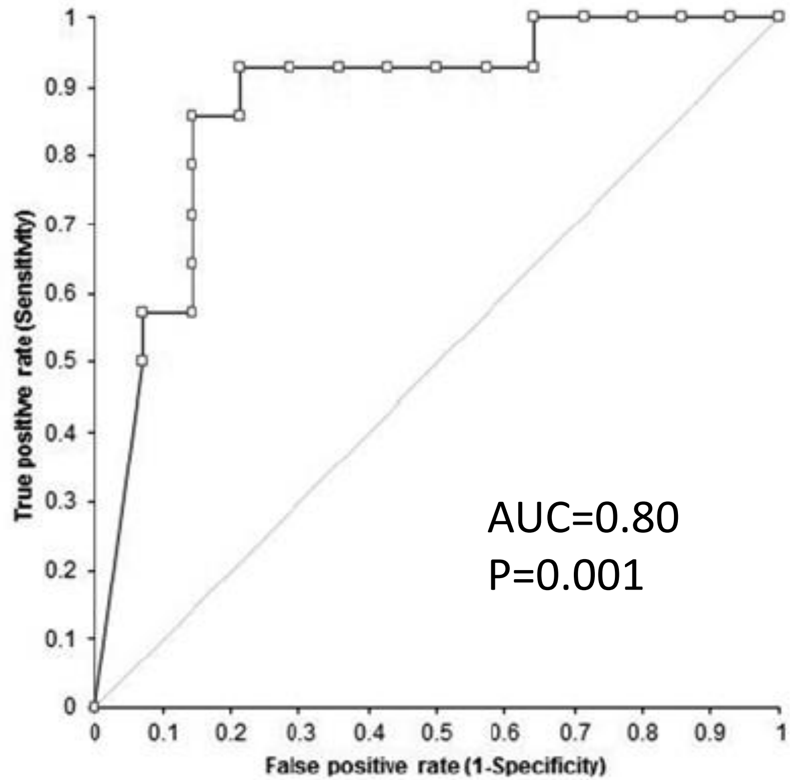
PCSS=0	PCSS=73	PCSS=42
>Voxels=0	>Voxels=708	>Voxels=9391
<Voxels=0	<Voxels=744	<Voxels=192

J Neurosurg December 18, 2015

Cerebrovascular imaging



Voxel Counts > Control Group



Voxel Counts < Control Group

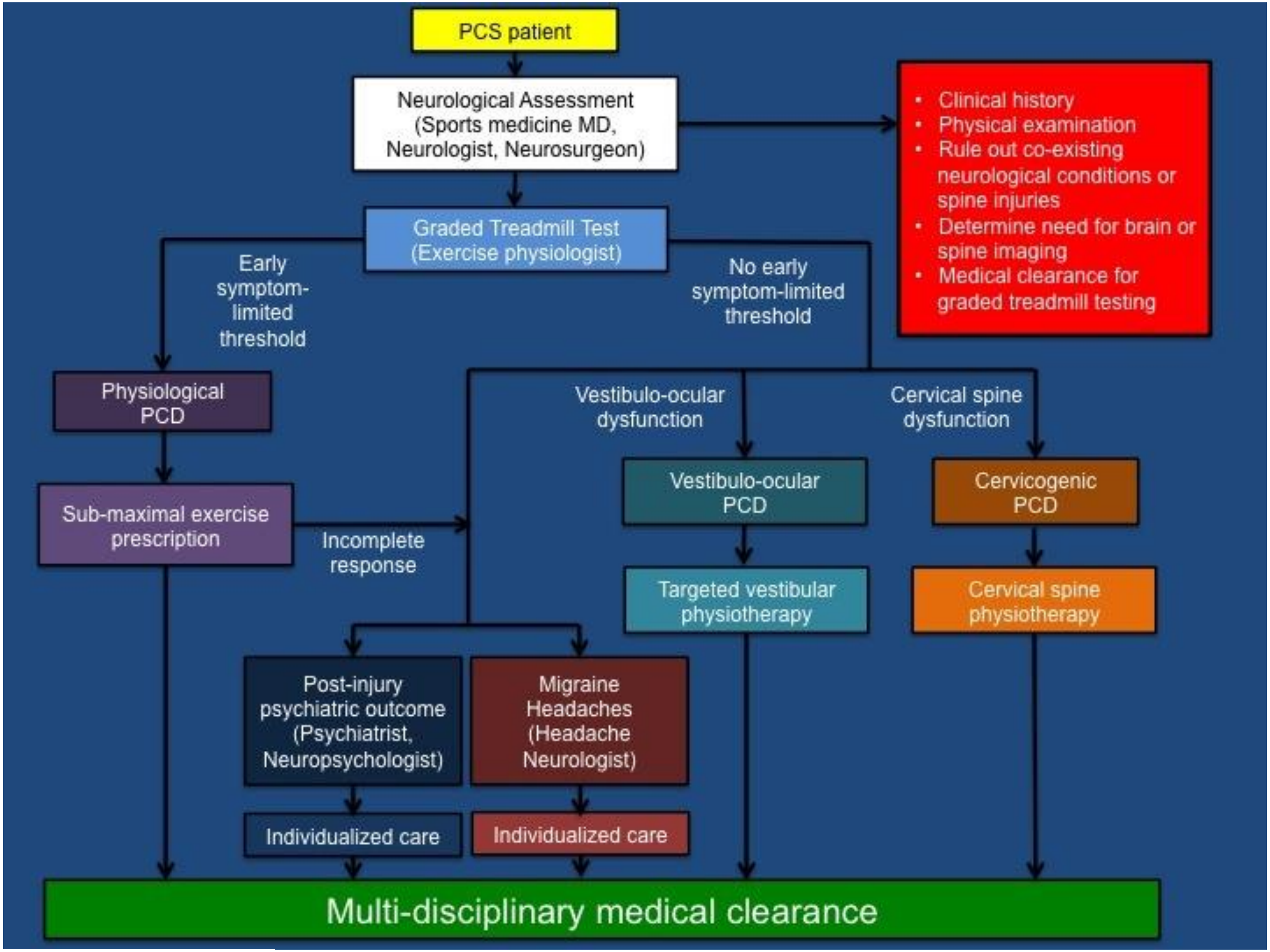
FIG. 5. The ROC curves for the greater-than **(left)** and less-than **(right)** responses to the control atlas at the p = 0.001 level for significant abnormal voxel counts.

Summary

- MRI-based techniques are capable of demonstrating group and individual differences in resting CBF and CVR following mTBI and concussion.
- Limited studies with small sample sizes published to date.
- Natural history of CBF and CVR changes following concussion require further study.
- CVR studies require rigorous methodological considerations to generate reliable results

Case

- 15 year old female athlete
- Cycling accident
- +LOC, post-traumatic amnesia
- PMHx: 3 previous concussions
- 5 months later presents with global headaches, dizziness, and fatigue
- Physical examination:
  - Normal: no evidence of vestibulo-ocular dysfunction, cervical spine injury
- Management? Neuroimaging?

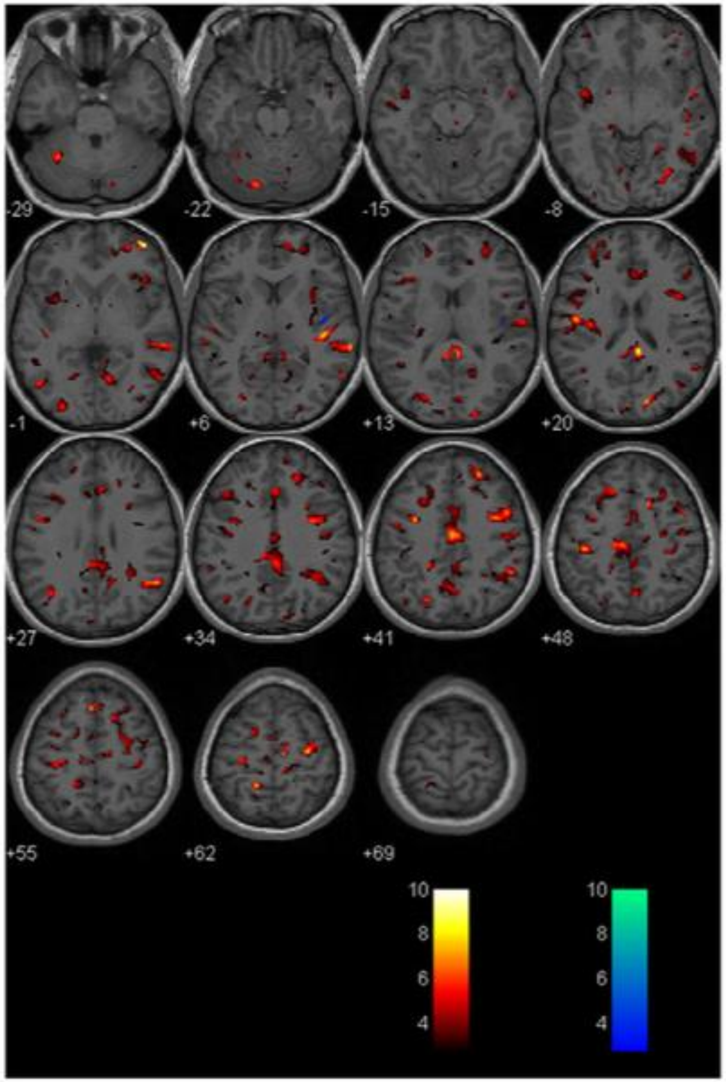


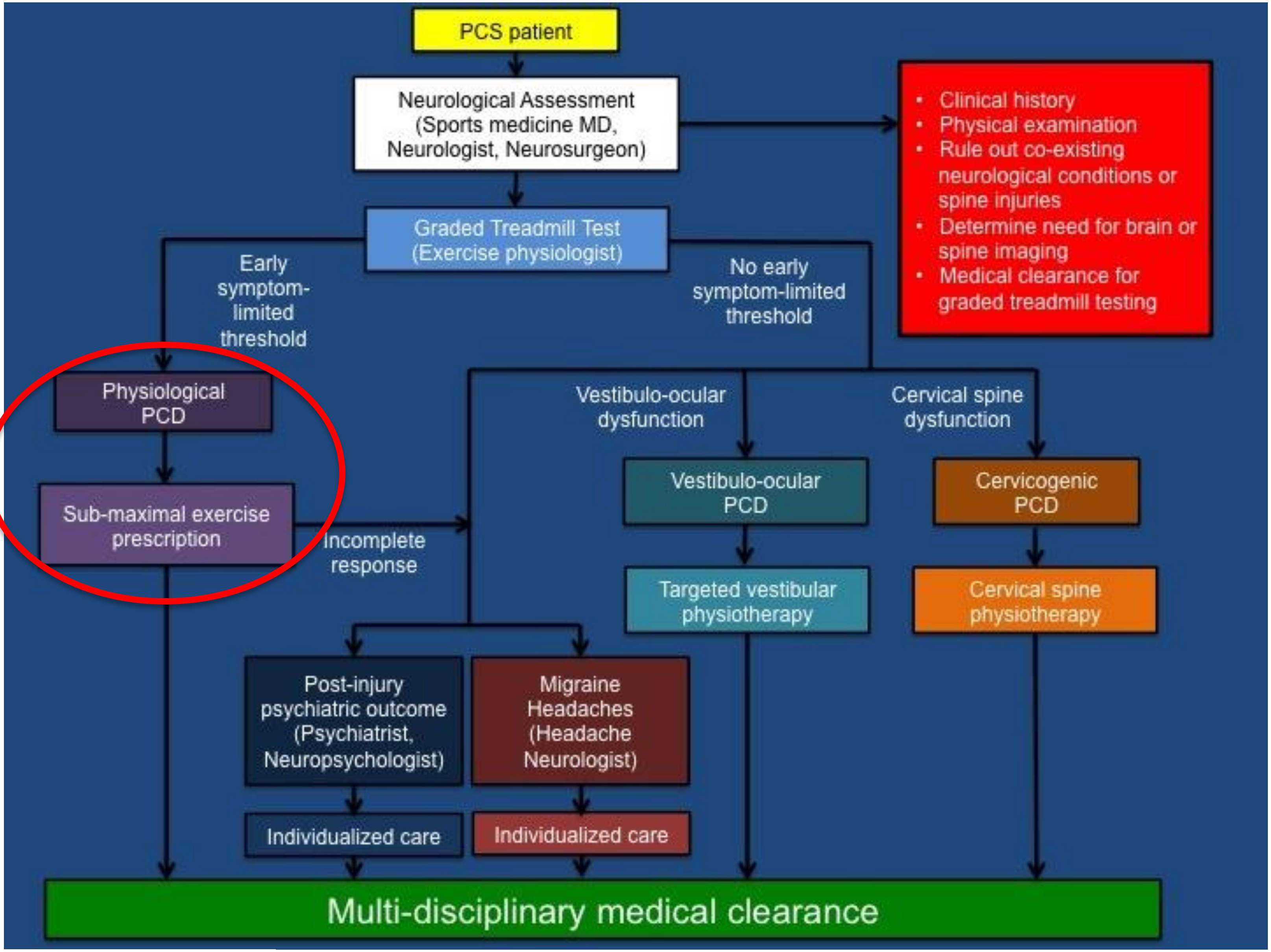
frontiers in Neurology

HYPOTHESIS AND THEORY
published: 24 August 2016
doi: 10.3389/fneur.2016.00136

Case Illustration

- Graded aerobic treadmill testing
- Symptom limiting threshold= Physiological PCD
- MRI normal
- Brain stress test= abnormal





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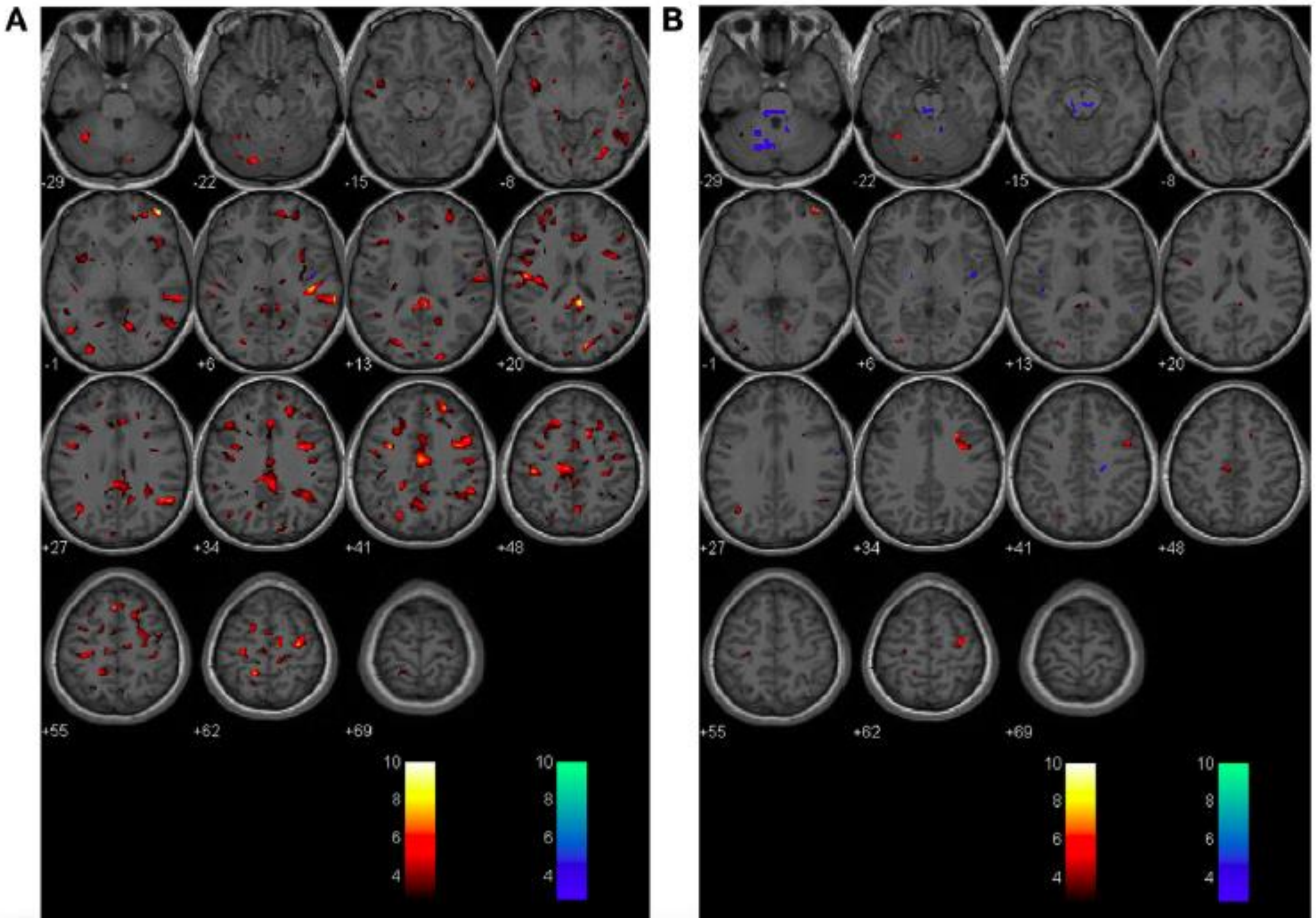
Case

- Sub-maximal aerobic exercise program
- 2 month later, transition to sports-specific RTP program
- 1 month later, cleared for return to full sports activities

Neuroimaging



Symptomatic

Clinically recovered

Mutch WAC, et al.: Longitudinal brain magnetic resonance imaging CO2 stress testing in individual adolescent sports-related concussion patients. Frontiers of Neurology- Neurotrauma (published online) 2016

JNS

CLINICAL ARTICLE

Brain magnetic resonance imaging CO_2 stress testing in adolescent postconcussion syndrome

*W. Alan C. Mutch, MD,[1,6,10] Michael J. Ellis, MD,[2,3,5,7,8,10] Lawrence N. Ryner, PhD,[4,6,10]
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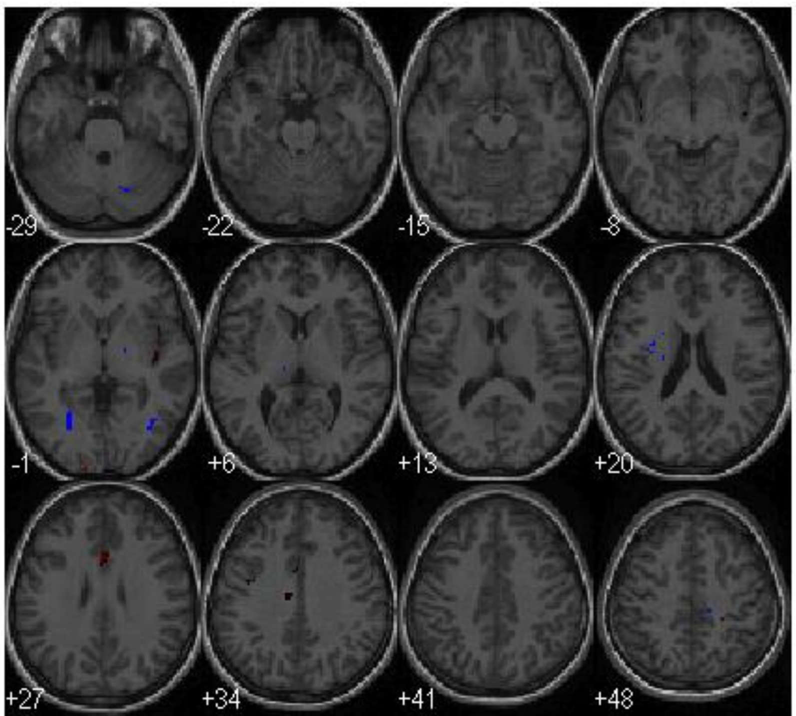
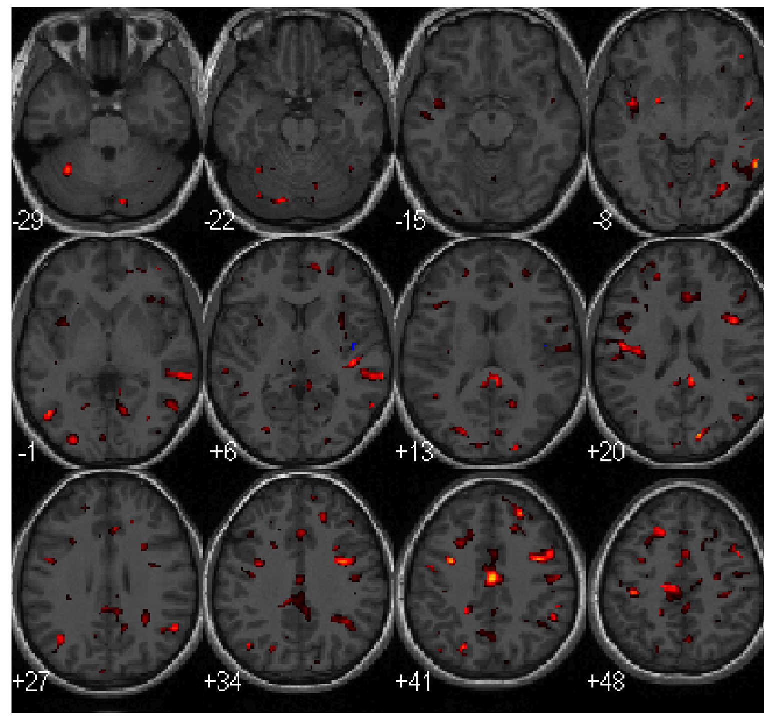
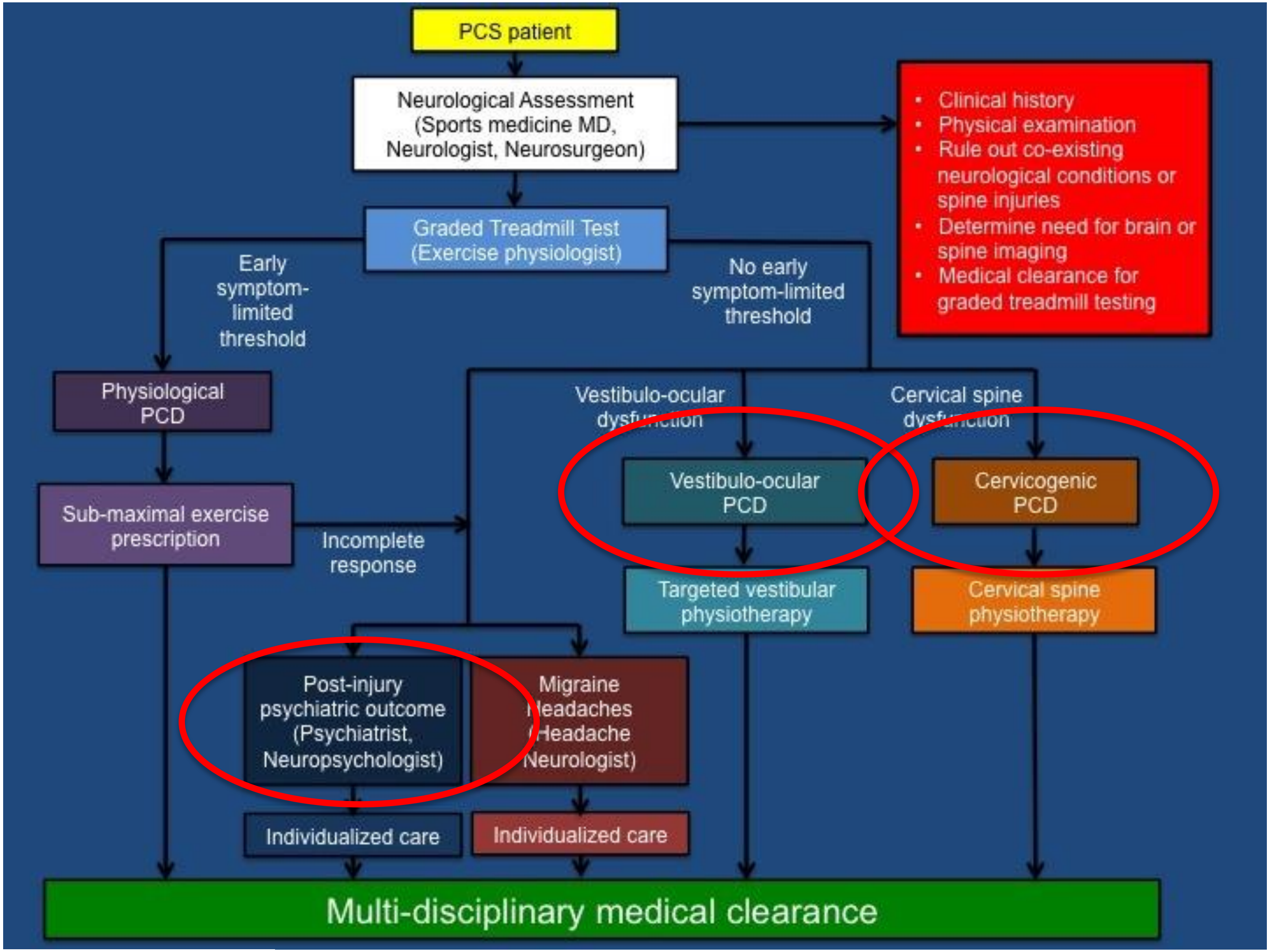


Vestibulo-ocular PCD



Physiological PCD



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Conclusions

- Conventional neuroimaging plays an important role in clinical management of moderate and severe TBI patients and selected patients with mild TBI and concussion.
- At present, there is no role for advanced neuroimaging techniques in the clinical management of concussion patients.

Conclusions

- For advanced neuroimaging techniques to contribute value to the clinical care of concussion patients in the future they must provide biomarkers:
  - Reliable
  - Disease-specific
  - Must provide information on an individual patient basis
  - Must provide information that is otherwise clinically unavailable

Thanks