Imaging in Concussion

CANADIAN CONCUSSION CENTRE
Research | Diagnosis | Solutions

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Healthcare | REVOLUTIONIZED

Disclosures

- None

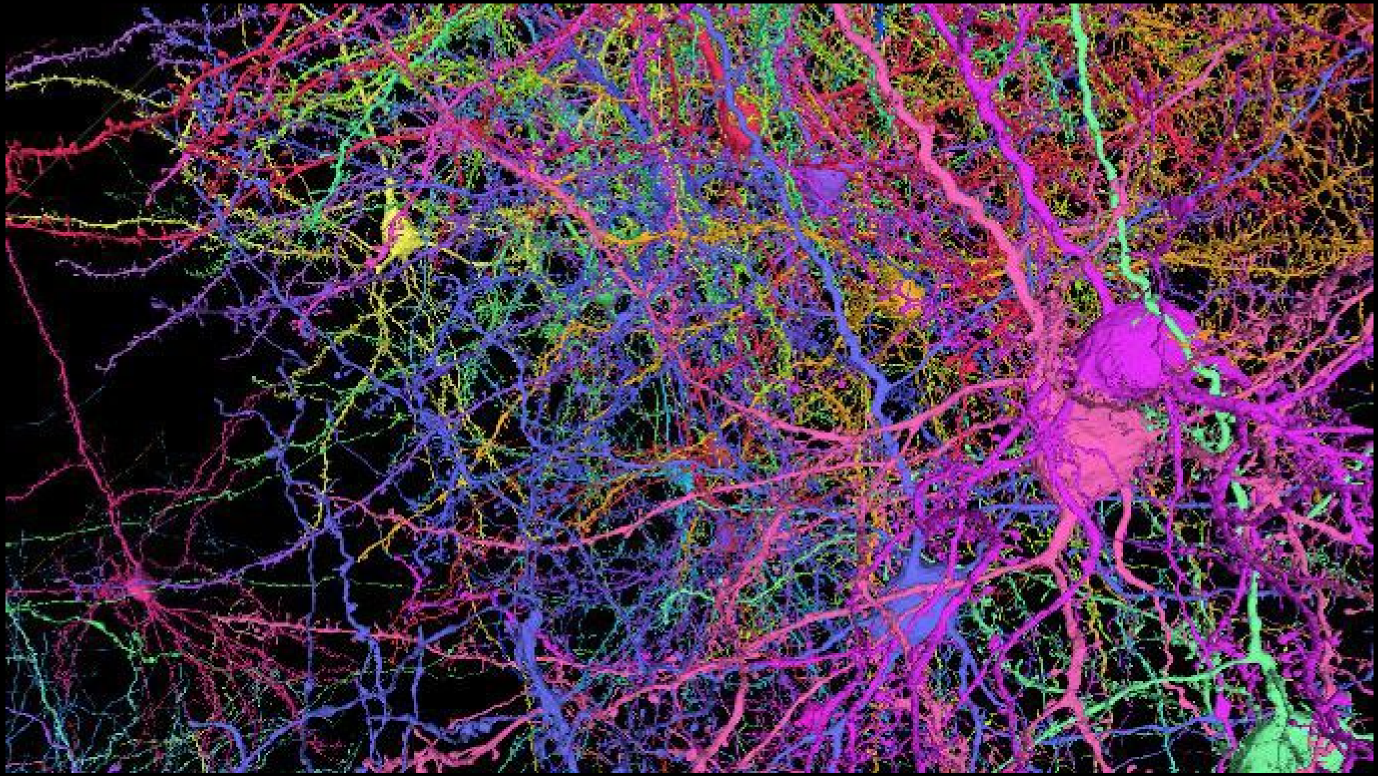
Outline

- Brain structure
- Concussion injury
- Imaging tools
- Limitations

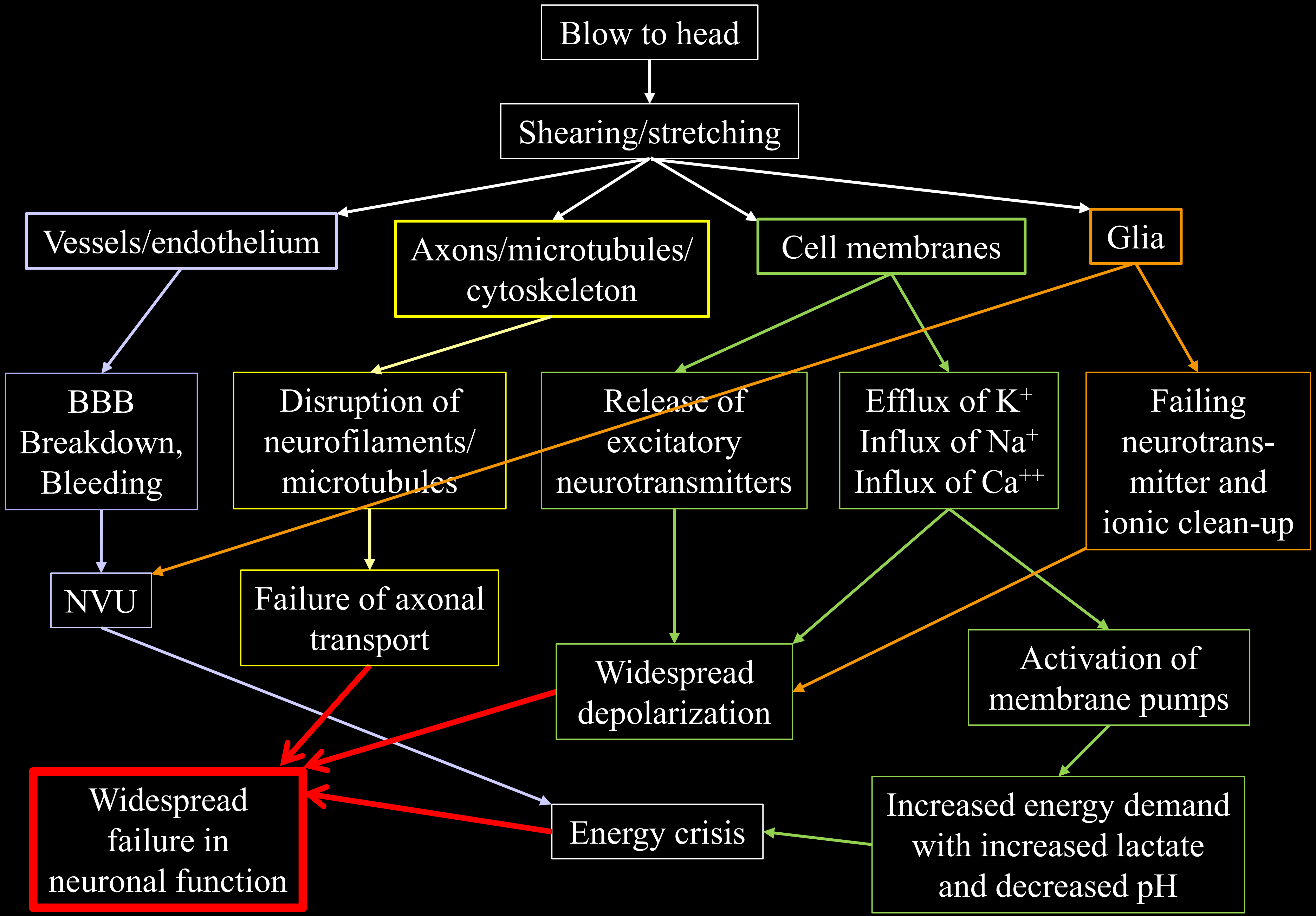
Introduction

The brain is a very complex structure with multiple interconnected components:

- Neurons
- Glial cells, microglia, oligodendroglia
- Blood vessels



Allen Institute fMICrONS Explorer:
A virtual observatory of the cortex,
Princeton University and
Baylor College of Medicine



Blow to head

Shearing/stretching

Vessels/endothelium

Axons/microtubules/ cytoskeleton

Cell membranes

Glia

BBB Breakdown, Bleeding

Disruption of neurofilaments/ microtubules

Release of excitatory neurotransmitters

Efflux of K^+
Influx of Na^+
Influx of Ca^{++}

Failing neurotrans-mitter and ionic clean-up

NVU

Failure of axonal transport

Widespread depolarization

Activation of membrane pumps

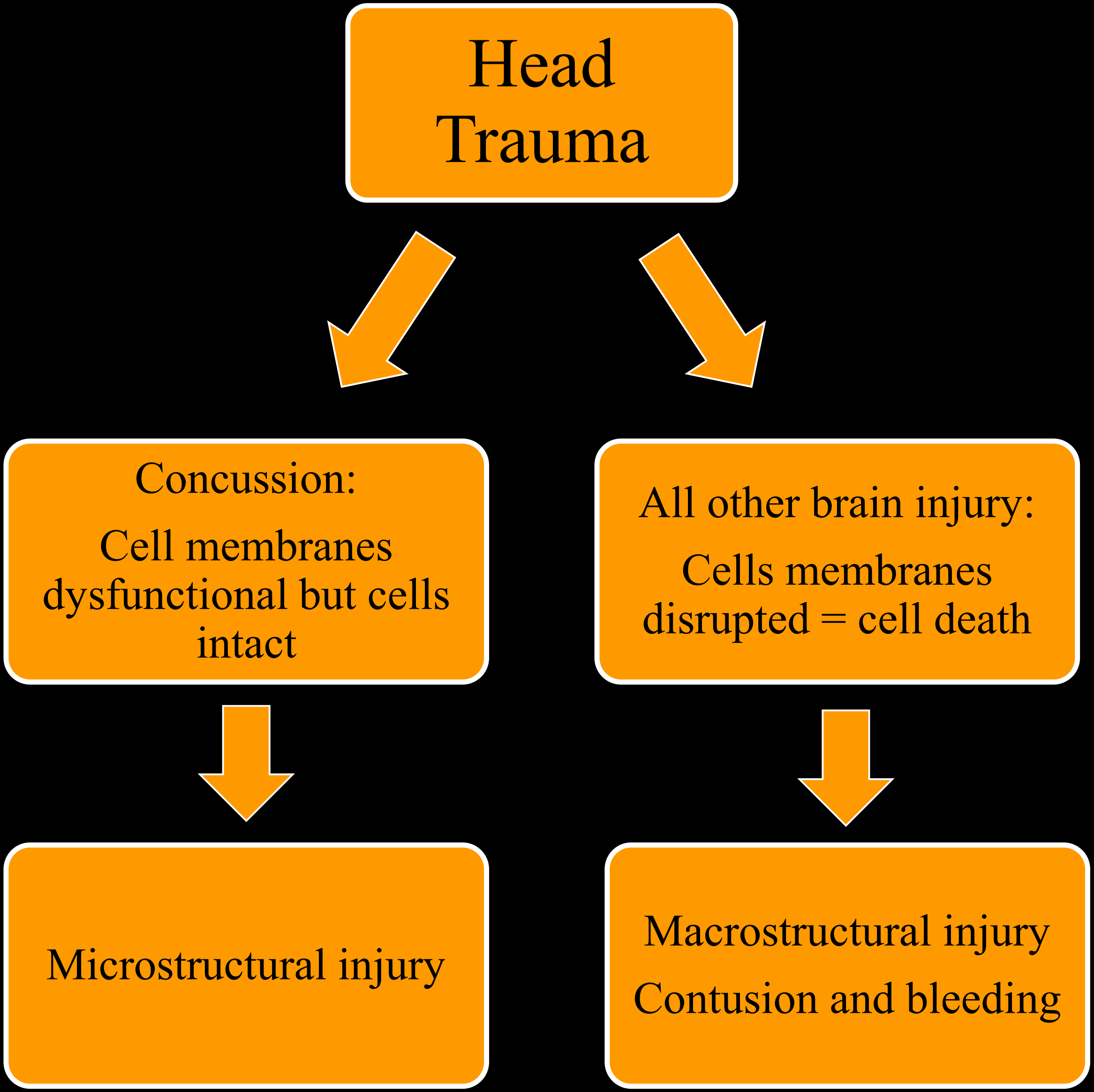
Widespread failure in neuronal function

Energy crisis

Increased energy demand with increased lactate and decreased pH

Adapated from Blennow et al. Neuron. 2012 Dec 6;76(5):886-99; PMID: 23217738.

Immediate Events After Head Injury



Head Trauma

Concussion:

Cell membranes dysfunctional but cells intact

Microstructural injury

All other brain injury:

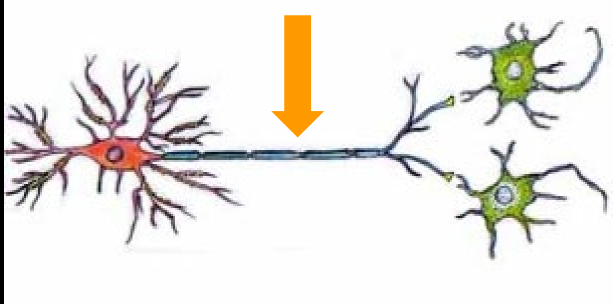
Cells membranes disrupted = cell death

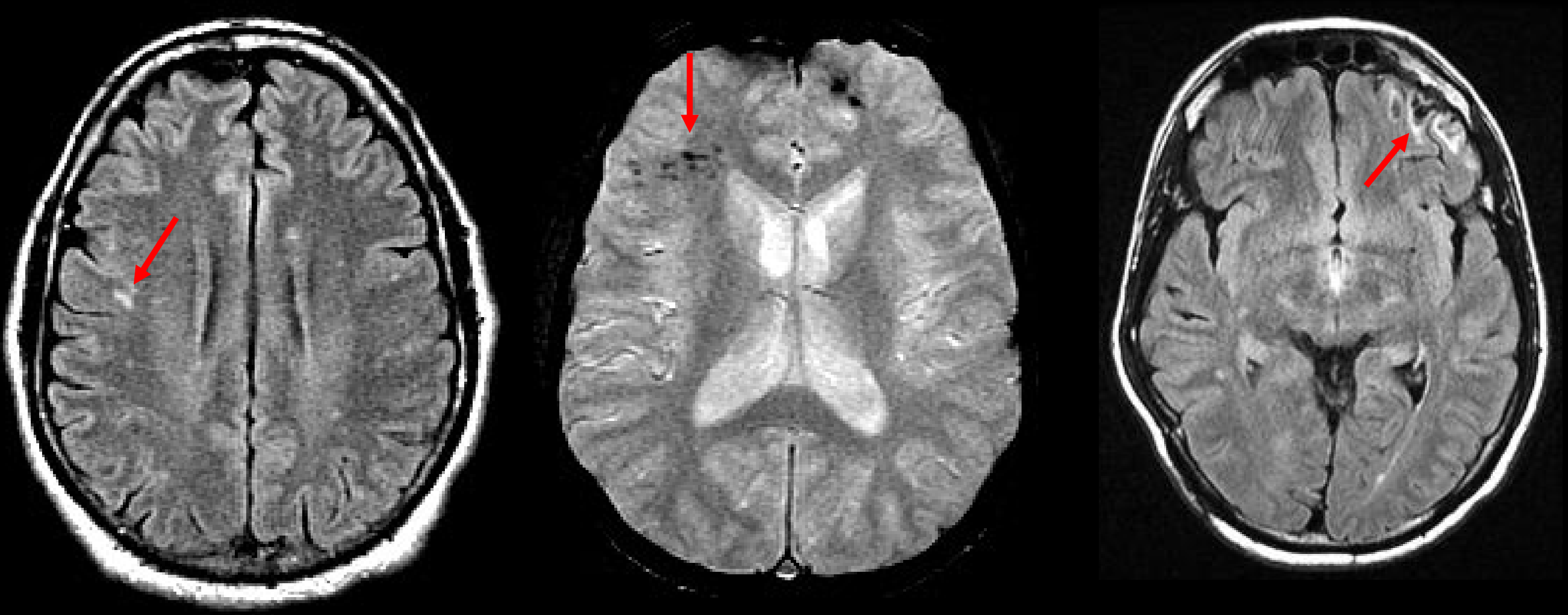
Macrostructural injury

Contusion and bleeding

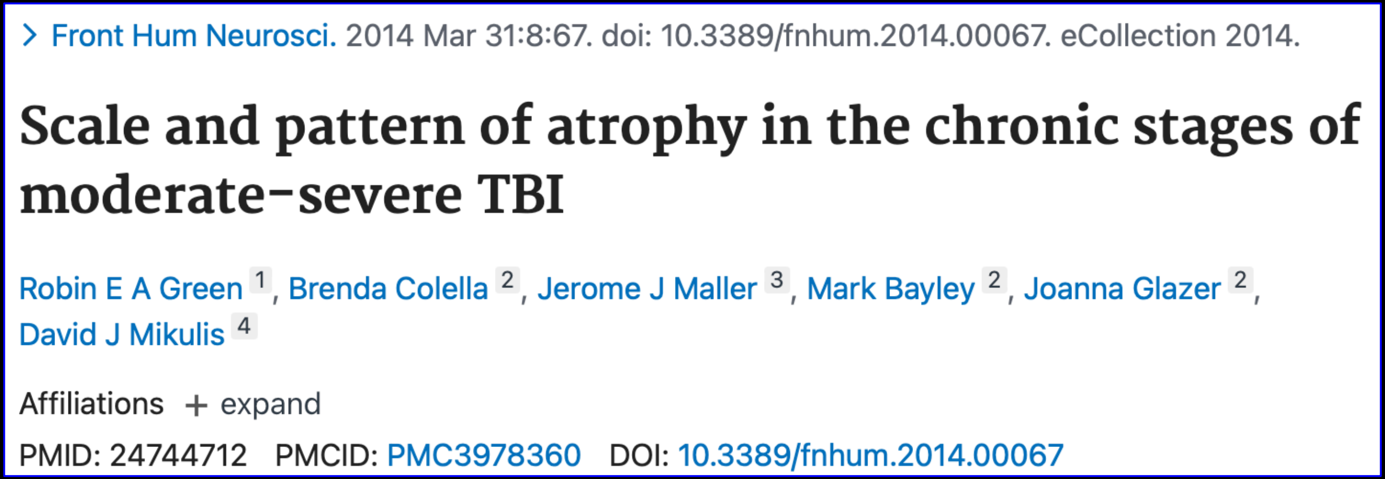
Imaging of Traumatic Brain Injury

- Shear and pressure forces
  - Diffuse axonal injury (DAI)
  - Microbleeds
  - Contusions





Surprising finding in "recovered" patients with moderate to severe TBI



> Front Hum Neurosci. 2014 Mar 31:8:67. doi: 10.3389/fnhum.2014.00067. eCollection 2014.

Scale and pattern of atrophy in the chronic stages of moderate–severe TBI

Robin E A Green [1], Brenda Colella [2], Jerome J Maller [3], Mark Bayley [2], Joanna Glazer [2], David J Mikulis [4]

Affiliations + expand

PMID: 24744712 PMCID: PMC3978360 DOI: 10.3389/fnhum.2014.00067

- 96% of patients showed significantly greater brain atrophy compared to healthy controls in at least one brain region (whole brain, bilateral hippocampi, or corpus callosum) between 5 and 20 months post-injury

Imaging of Concussion

- Extent of the structural injury and its functional consequences are not fully understood
- Current imaging techniques focus mostly on structural neuronal injury, and to a lesser extent blood vessels (blood flow impairment)
- The temporal evolution of these changes is gathering significant research interest

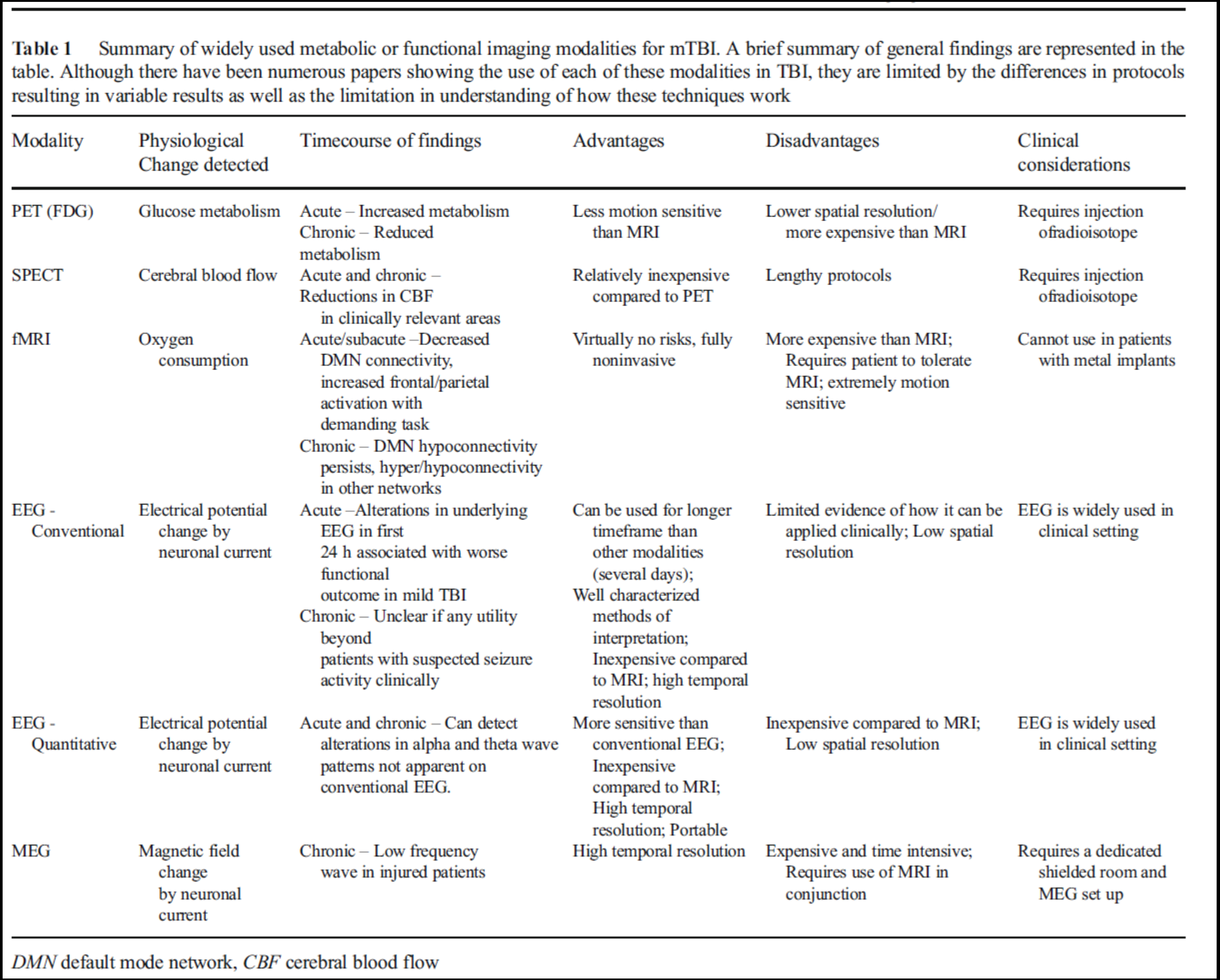


Table 1 Summary of widely used metabolic or functional imaging modalities for mTBI. A brief summary of general findings are represented in the table. Although there have been numerous papers showing the use of each of these modalities in TBI, they are limited by the differences in protocols resulting in variable results as well as the limitation in understanding of how these techniques work

Modality	Physiological Change detected	Timecourse of findings	Advantages	Disadvantages	Clinical considerations
PET (FDG)	Glucose metabolism	Acute – Increased metabolism Chronic – Reduced metabolism	Less motion sensitive than MRI	Lower spatial resolution/ more expensive than MRI	Requires injection ofradioisotope
SPECT	Cerebral blood flow	Acute and chronic – Reductions in CBF in clinically relevant areas	Relatively inexpensive compared to PET	Lengthy protocols	Requires injection ofradioisotope
fMRI	Oxygen consumption	Acute/subacute –Decreased DMN connectivity, increased frontal/parietal activation with demanding task Chronic – DMN hypoconnectivity persists, hyper/hypoconnectivity in other networks	Virtually no risks, fully noninvasive	More expensive than MRI; Requires patient to tolerate MRI; extremely motion sensitive	Cannot use in patients with metal implants
EEG - Conventional	Electrical potential change by neuronal current	Acute –Alterations in underlying EEG in first 24 h associated with worse functional outcome in mild TBI Chronic – Unclear if any utility beyond patients with suspected seizure activity clinically	Can be used for longer timeframe than other modalities (several days); Well characterized methods of interpretation; Inexpensive compared to MRI; high temporal resolution	Limited evidence of how it can be applied clinically; Low spatial resolution	EEG is widely used in clinical setting
EEG - Quantitative	Electrical potential change by neuronal current	Acute and chronic – Can detect alterations in alpha and theta wave patterns not apparent on conventional EEG.	More sensitive than conventional EEG; Inexpensive compared to MRI; High temporal resolution; Portable	Inexpensive compared to MRI; Low spatial resolution	EEG is widely used in clinical setting
MEG	Magnetic field change by neuronal current	Chronic – Low frequency wave in injured patients	High temporal resolution	Expensive and time intensive; Requires use of MRI in conjunction	Requires a dedicated shielded room and MEG set up

DMN default mode network, *CBF* cerebral blood flow

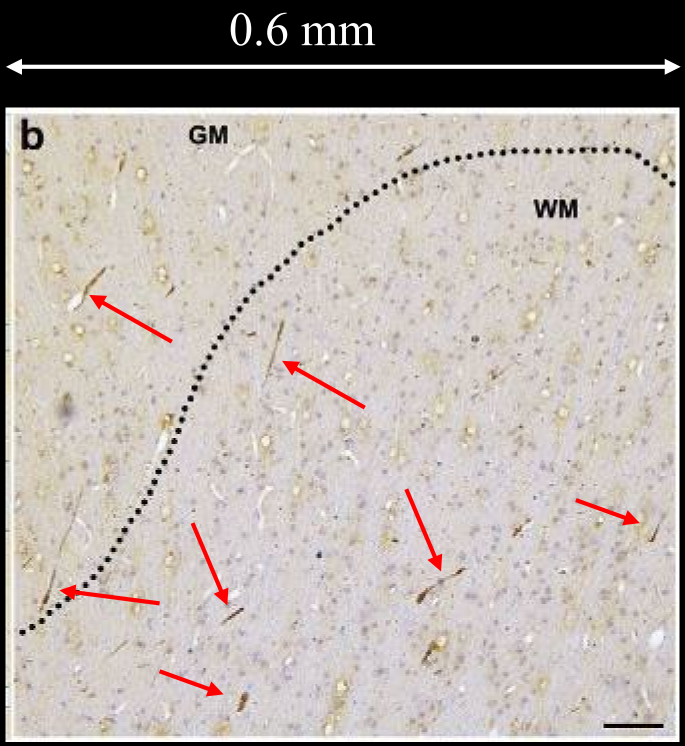
Shin SS, et al. Structural imaging of mild traumatic brain injury may not be enough: overview of functional and metabolic imaging of mild traumatic brain injury. Brain Imaging Behav. 2017 Apr;11(2):591-610. doi: 10.1007/s11682-017-9684-0. PMID: 28194558.

Concussion Imaging Problem

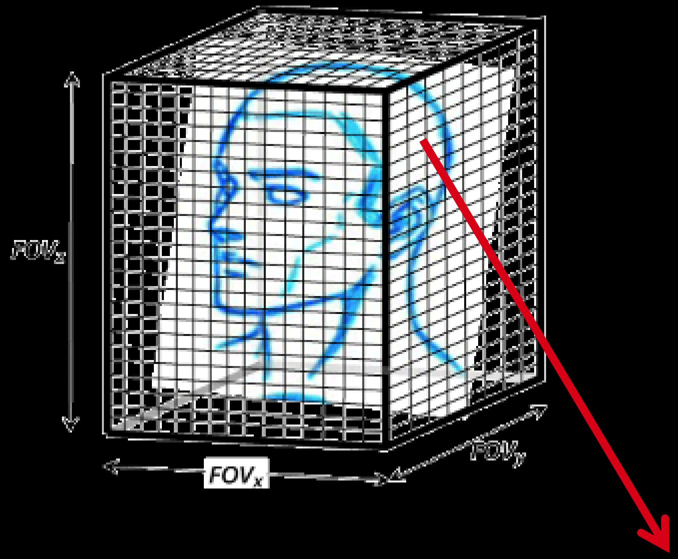
- Structural concussive injury is microscopic and sparse

- Better “pictures” and super-computing are making this task possible

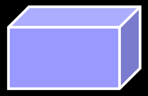
Concussive Brain Injury



Alisafaei et al. Biophysical Journal 119,1290–1300, October 6, 2020



Voxel - Typical size:
1-3 mm on a side



Conventional MRI averages all the different signals coming from everything in a voxel

What do we see on imaging?

- Conventional imaging
- Advanced imaging
- The road to a diagnostic biomarker

CT

- CT scans should be normal in concussed individuals
- Performed to rule out more severe injury, particularly in the acute setting (ER)

MRI

- Concussion falls within the category of neurological conditions that have *normal* clinical MRI scans
- ~ 30% of patients with a normal CT scan and GCS 15 have positive MRI → traumatic brain injury (TBI)

Yuh, E.L et al. Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. Ann. Neurol. 2013, 73, 224–235.

MRI

- 127 prospectively enrolled post-concussion syndrome (PCS) patients and 29 controls underwent MRI brain at 3T
- Images reviewed for
  - Areas of abnormal tissue signal (white matter hyperintensities =WMH)
  - Brain scars (encephalomalacia)
  - Loss of brain volume (atrophy)
  - Previous bleeding in or on the surface of the brain (microhemorrhages, pial siderosis)
- 97% of patients had scans indistinguishable from healthy population
- The presence of blood or tissue loss atrophy indicates more severe form of injury
- In patients with a clinical diagnosis of concussion, a normal MRI is expected

Panwar J et al. Magnetic Resonance Imaging Criteria for Post-Concussion Syndrome: A Study of 127 Post-Concussion Syndrome Patients.
J Neurotrauma. 2020 May 15;37(10):1190-1196. doi: 10.1089/neu.2019.6809. Epub 2020 Jan 31. PMID: 31822164.

Other imaging modalities

SPECT

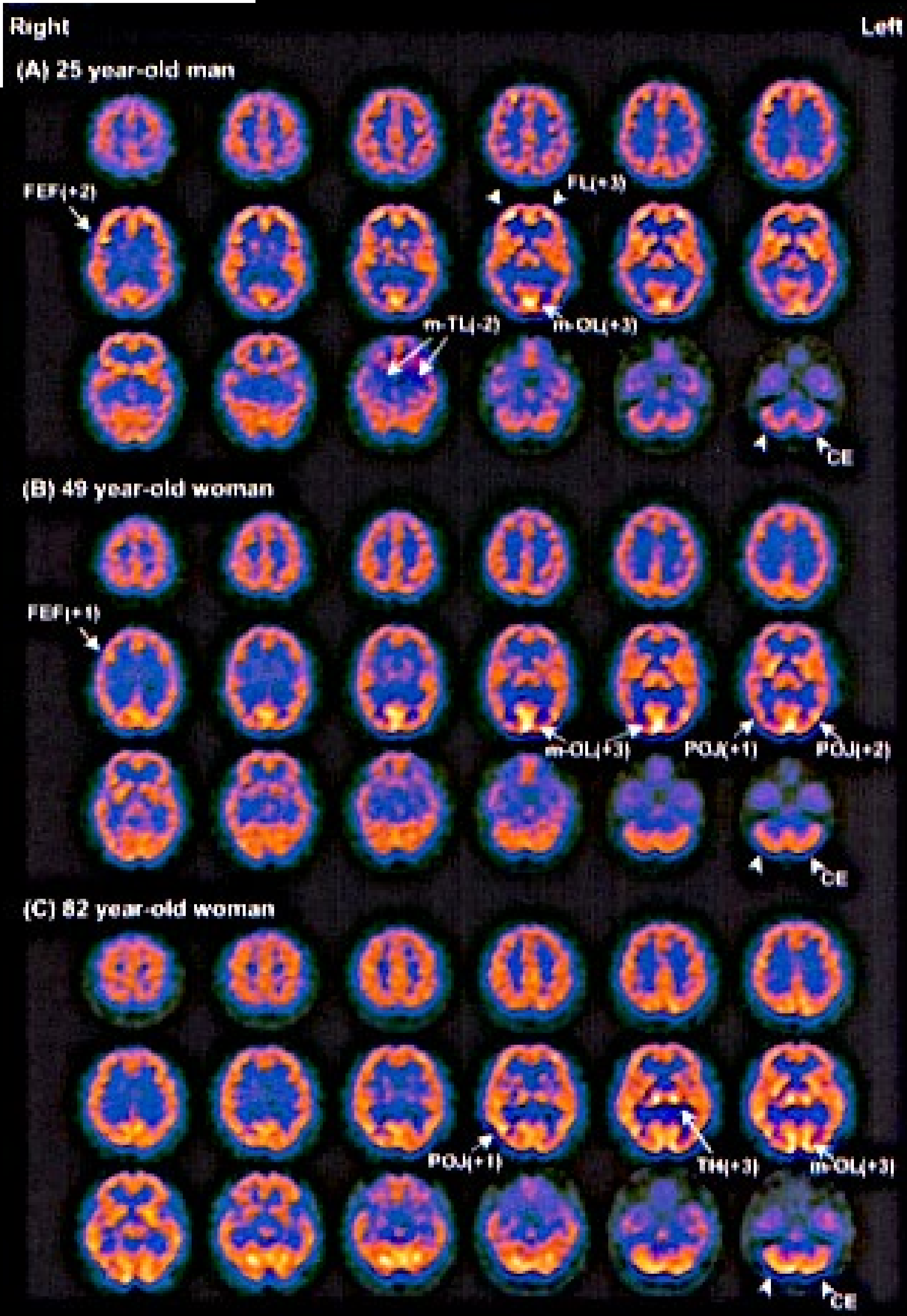
(Single photon emission computed tomography)

- Injection of a radioactive tracer usually to measure *blood flow*
- Used in epilepsy and dementia

https://www.gehealthcare.com/products/molecular-imaging/nuclear-medicine/nm-ct-870-czt?utm_medium=cpc&utm

Normal Patterns on ^{99m}Tc-ECD Brain SPECT Scans in Adults

Fumiko Tanaka, Douglass Vines, Tatsuro Tsuchida, Morris Freedman and Masanori Ichise
Journal of Nuclear Medicine September 2000, 41 (9) 1456-1464;



- SPECT studies in healthy adults show small but significant regional variation in tracer uptake.
- Difficulty distinguishing normal variation from variations caused by pathology

SPECT

- In a study of 43 mTBI patients, imaging showed abnormal results in:
  - SPECT 53%
  - MRI 9%
  - CT 4.6%
- Changes in blood flow (hypoperfusion) have been identified using SPECT imaging at as early as 24 h after injury up to 3 years after injury
- Comorbidities associated with TBI can make interpretation of SPECT difficult, eg migraine, depression or post traumatic stress disorders, may result in alteration in SPECT imaging

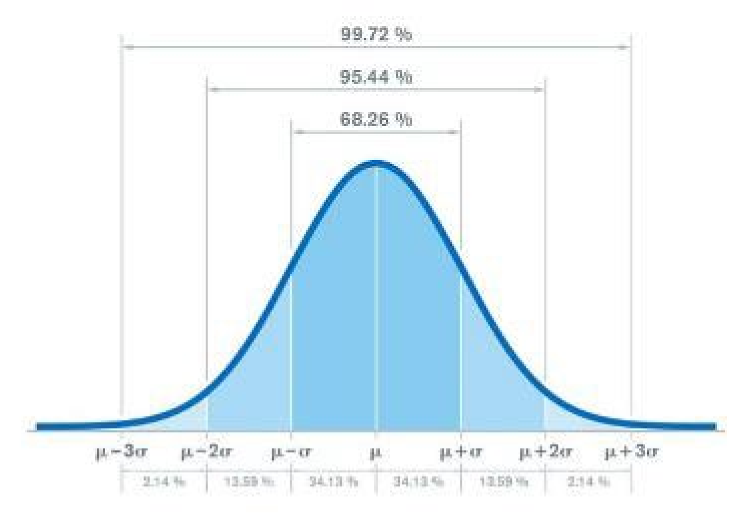
Shin et al. Structural imaging of mild traumatic brain injury may not be enough: overview of functional and metabolic imaging of mild traumatic brain injury. Brain Imaging Behav. 2017 Apr;11(2):591-610. PMID: 28194558 DOI: 10.1007/s11682-017-9684-0

SPECT Issues

- SPECT imaging
  - Subjective assessment
- Standardization:
  - Data acquisition
  - Quantitative analysis
    - Enables objective assessment

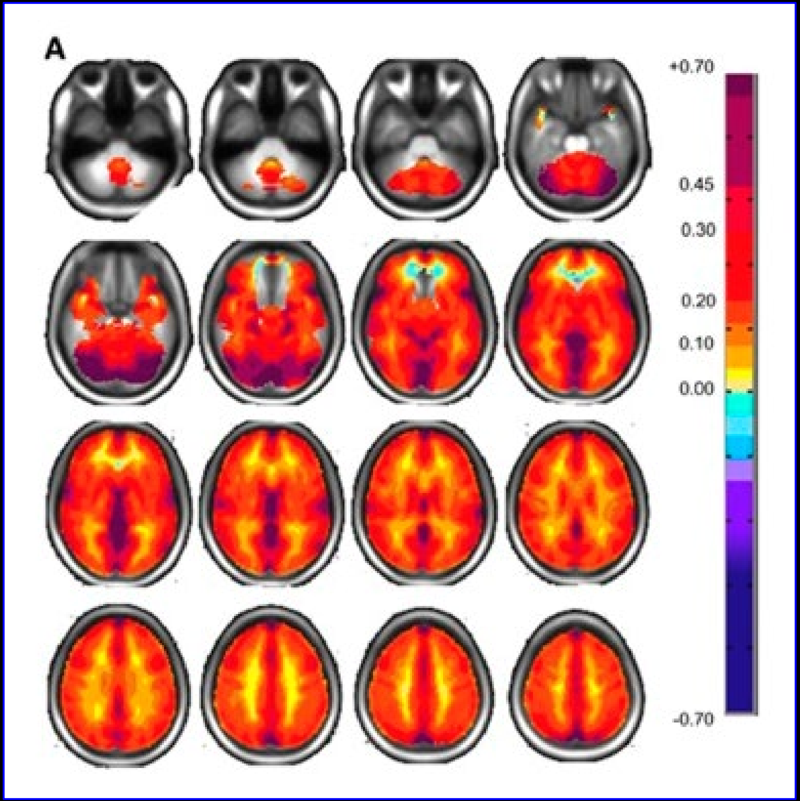
SPECT scan Z-scoring

- Build an atlas of controls consisting of a map showing mean tracer uptake and standard deviation
- Consider *<u>two standard deviations</u>* as threshold for abnormal findings

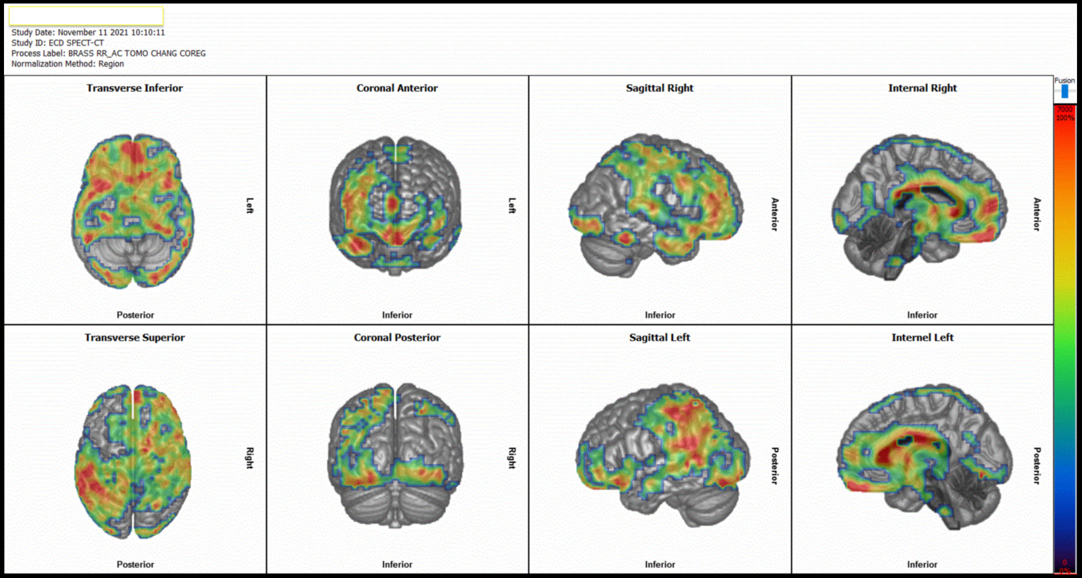


Building a Healthy Brain Atlas

- Acquire brain scans from healthy volunteers
- “Warp” each brain scan so it fits on the same template
- Once all the subjects’ scans are in the template, record the mean and standard deviation for each voxel in the brain



GE SPECT scan post processing software



[redacted]
Study Date: November 11 2021 10:10:11
Study ID: ECD SPECT-CT
Process Label: BRASS RR_AC TOMO CHANG COREG
Normalization Method: Region

BRASS Report - Z-Score Plot
[redacted]
Study Date: November 11 2021 10:10:11
Study ID: ECD SPECT-CT
Process Label: BRASS RR_AC TOMO CHANG COREG
Normalization Method: Region

Counts Per Voxel

Region Name	Mean	Z-Score
L cerebellar ctx	686.30	-2.70
R cerebellar ctx	689.48	-1.42
L cerebellar white matter	855.84	4.09
R cerebellar white matter	831.13	3.00
L nucleus lentiformis	816.15	1.35
R nucleus lentiformis	766.99	0.21
L nucleus caudatus	296.11	-5.12
R nucleus caudatus	290.45	-6.38
L thalamus	485.58	-3.21
R thalamus	504.06	-2.89
L sensorimotor ctx	598.24	-0.92
R sensorimotor ctx	565.74	-1.54
L occipital ctx	574.12	-2.60
R occipital ctx	590.68	-2.67
L sup parietal lobule	599.09	-0.77
R sup parietal lobule	646.04	-0.18
L ant dorsal frontal ctx	549.68	-1.32
R ant dorsal frontal ctx	466.72	-2.72
L post dorsal frontal ctx	601.26	-0.77
R post dorsal frontal ctx	536.10	-2.02
L ant orbital frontal ctx	455.54	-4.30
R ant orbital frontal ctx	421.54	-3.99
L post orbital ctx	531.94	-3.11
R post orbital ctx	468.65	-4.31
L parieto-temporal ctx	492.65	-3.90
R parieto-temporal ctx	547.50	-2.35
L medial temporal lobe	441.46	-3.54
R medial temporal lobe	488.68	-2.04
L lateral temporal lobe	540.35	-3.51
R lateral temporal lobe	565.37	-3.11
L post temporal lobe	516.95	-5.94
R post temporal lobe	567.00	-3.60
L temporal pole	497.55	-2.08
R temporal pole	372.68	-8.34
L insular ctx	594.86	-3.02
R insular ctx	578.43	-3.57
L ant gyrus cinguli	460.20	-3.37
R ant gyrus cinguli	475.39	-3.87
L post gyrus cinguli	541.15	-2.38
R post gyrus cinguli	400.95	-3.78
Pons and midbrain	462.52	-2.38
L ant subcortical	398.61	-4.14
R ant subcortical	387.92	-4.53
L post subcortical	464.89	-4.50
R post subcortical	426.51	-5.03
Other subcortical	463.69	-3.84

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Original Article | Full Access

Molecular imaging of neuroinflammation in patients after mild traumatic brain injury: a longitudinal ^{123}I-CLINDE single photon emission computed tomography study

S. E. Ebert, P. Jensen, B. Ozenne, S. Armand, C. Svarer, D. S. Stenbaek, K. Moeller, A. Dyssegaard, G. Thomsen, J. Steinmetz, B. H. Forchhammer, G. M. Knudsen, L. H. Pinborg ✉ ... See fewer authors

First published: 19 April 2019 | https://doi-org.myaccess.library.utoronto.ca/10.1111/ene.13971 |

Volume 26, Issue 12
December 2019
Pages 1426-1432

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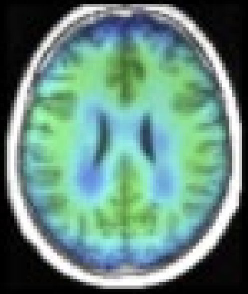
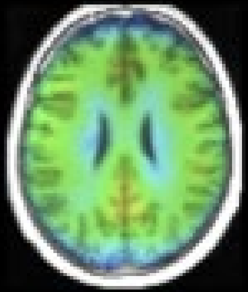
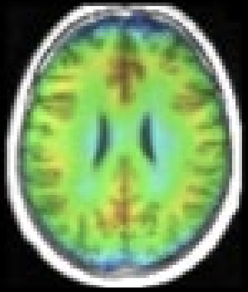


12 controls

- Radioactive tracers can have very high sensitivity to tissue abnormalities
- SPECT imaging using ^{123}I-CLINDE identifies *increased microglial activity* after mild TBI:
  - Binds translocator protein that is upregulated in active microglia (neuroinflammation)
  - Neuroinflammation was present in mTBI at 1–2 weeks post-in- jury and persisted at 3–4 months post-injury with a tendency to be most pronounced in patients with PCS.



7 patients 1-2 weeks post injury

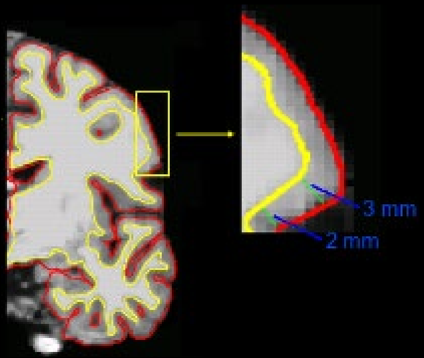


6 patients with PCS 3-4 months post injury

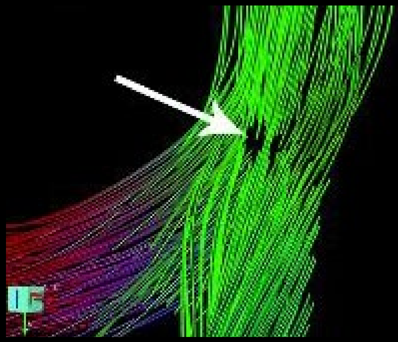
Can advanced neuroimaging do better?

Advanced MRI Methods

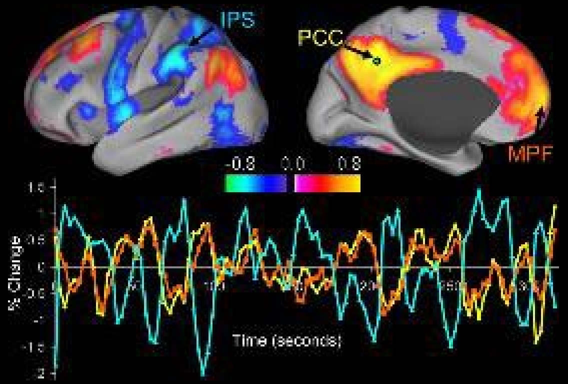
Cortical thickness



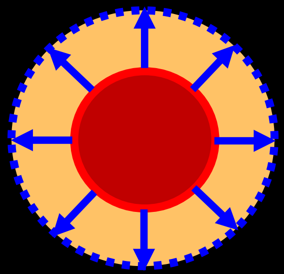
Diffusion tensor imaging



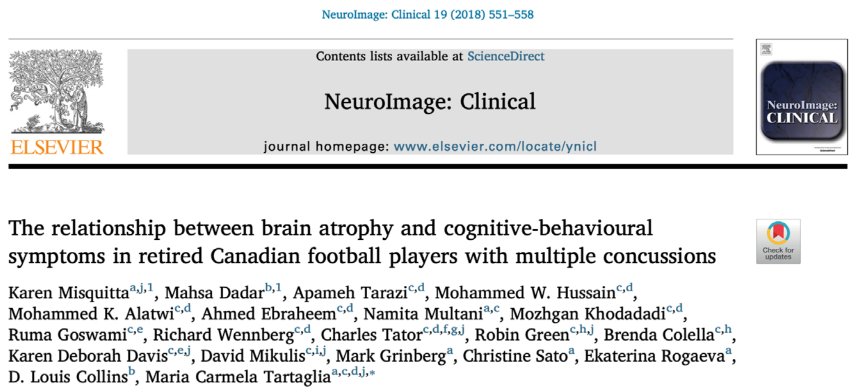
Resting state connectivity



Vascular reactivity



Volumetric Imaging



NeuroImage: Clinical 19 (2018) 551–558

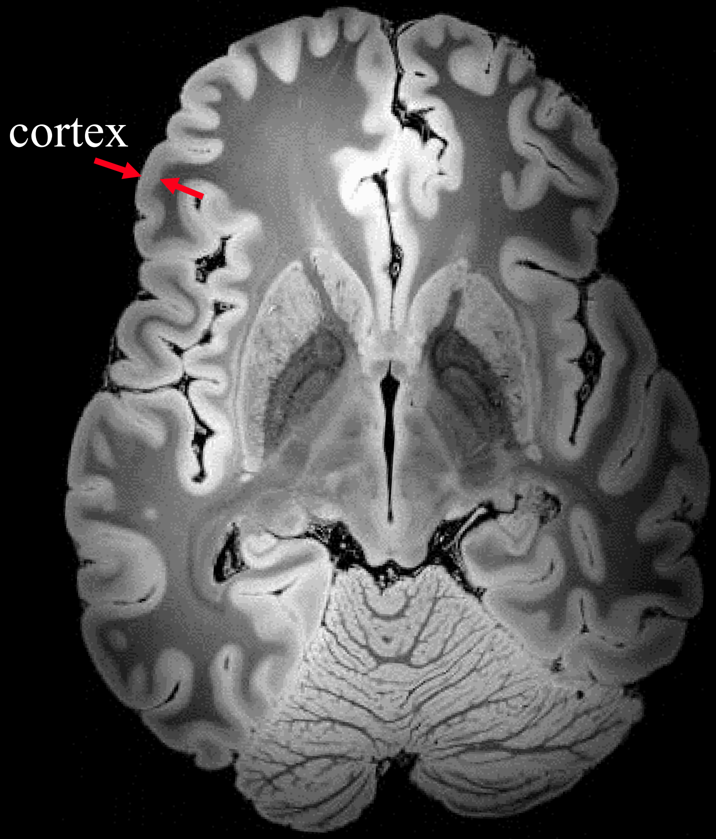
Contents lists available at ScienceDirect

NeuroImage: Clinical

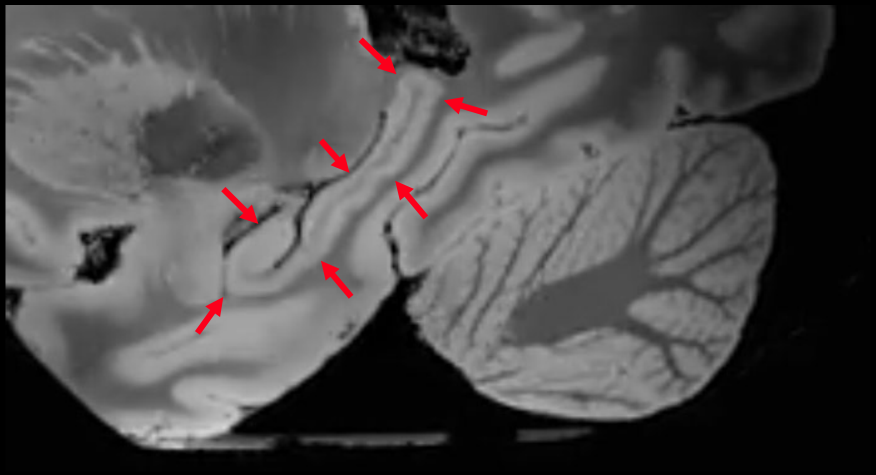
journal homepage: www.elsevier.com/locate/ynicl

The relationship between brain atrophy and cognitive-behavioural symptoms in retired Canadian football players with multiple concussions

Karen Misquitta[a,j,1], Mahsa Dadar[b,1], Apameh Tarazi[c,d], Mohammed W. Hussain[c,d], Mohammed K. Alatwi[c,d], Ahmed Ebraheem[c,d], Namita Multani[a,c], Mozhgan Khodadadi[c,d], Ruma Goswami[c,e], Richard Wennberg[c,d], Charles Tator[c,d,f,g,j], Robin Green[c,h,j], Brenda Colella[c,h], Karen Deborah Davis[c,e,j], David Mikulis[c,i,j], Mark Grinberg[a], Christine Sato[a], Ekaterina Rogaeva[a], D. Louis Collins[b], Maria Carmela Tartaglia[a,c,d,j,*]



Post-mortem 7T MRI - Brian L. Edlow, M.D. of Massachusetts General Hospital



Little evidence of volume changes in the brain after concussion except for possible decrease in hippocampal size

Brain Behav. 2019 Jan; 9(1): e01161.
Published online 2018 Nov 28. doi: 10.1002/brb3.1161
PMCID: PMC6346670
PMID: 30488646

Accelerated age-related cortical thinning in mild traumatic brain injury

Priya Santhanam,[1] Steffanie H. Wilson,[2] Terrence R. Oakes,[3] and Lindell K. Weaver[4,5]

- Inclusion criteria:
  - Active US service and veterans with blast or non-penetrating concussive injury with persistent symptoms
- Conclusion:
  - The presence of mTBI appeared to accelerate age-related cortical thinning across the cortex in our study population
  - Difficult to apply to individuals

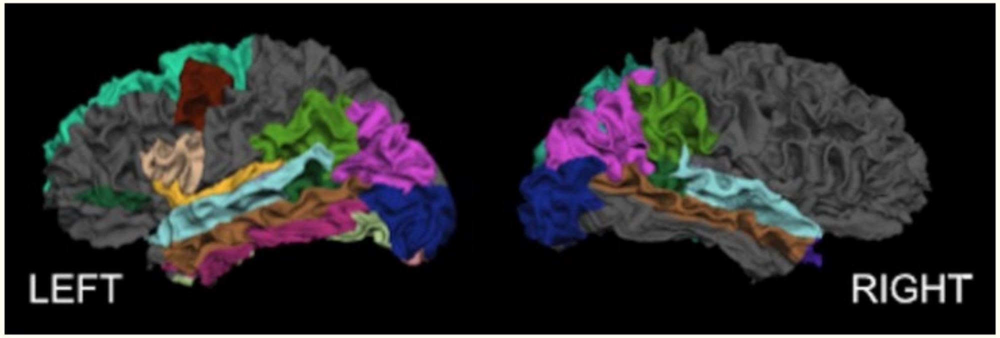
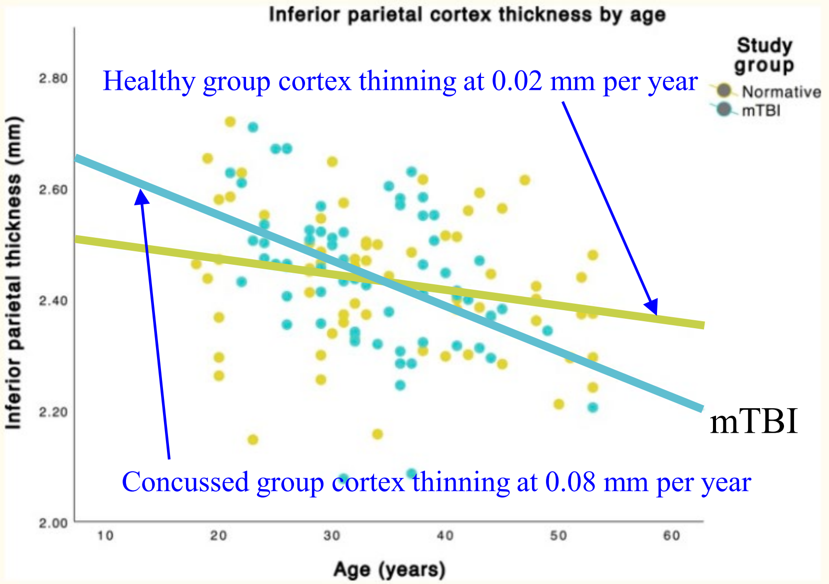


Figure 1

Cortical surface rendering highlighting regions with significantly increased age-related cortical thinning with mTBI



Healthy group cortex thinning at 0.02 mm per year

mTBI

Concussed group cortex thinning at 0.08 mm per year

Figure 2

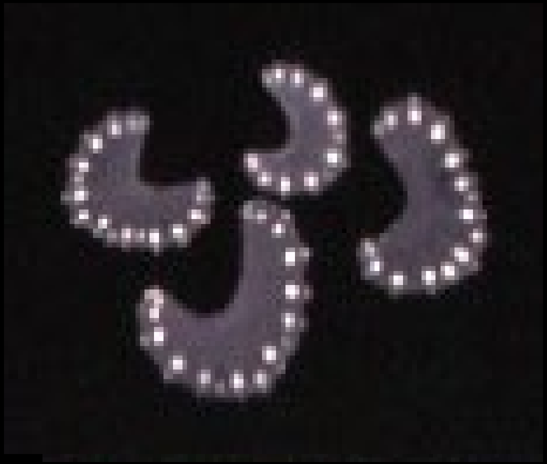
Plot of left hemisphere inferior parietal cortex thickness by age. The steeper slope of the mTBI group indicates a greater thinning with age in this group

MRI Diffusion Tensor Imaging

- Measures structural changes in the tissue based on how water movement is altered by the way a disease disrupts normal biological barriers

Conventional MRI

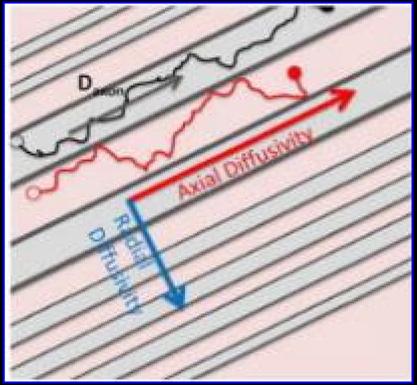
Courtesy Tim Roberts



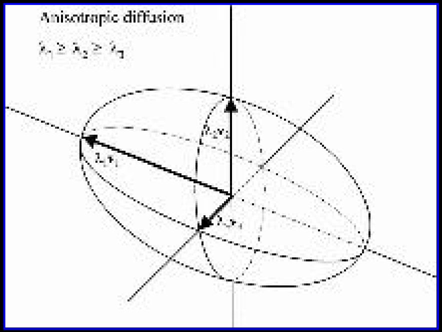
Add diffusion gradients

Courtesy Tim Roberts

Fiber Tracking



DTI Metrics



- Mean diffusivity (mD) = $(\lambda_1 + \lambda_2 + \lambda_3)/3$
  - Gliosis
- Radial diffusivity (rD) = $(\lambda_2 + \lambda_3)/2$
  - Demyelination
- Axial diffusivity (aD) = λ_1
  - Axonal disruption
- Fractional anisotropy
  - Sensitive to any axonal pathology
  - Describes the percent of the tensor that is anisotropic

$$FA = \sqrt{\frac{3}{2}\left(\frac{\left(\lambda_1 - \bar{\lambda}\right)^2 + \left(\lambda_2 - \bar{\lambda}\right)^2 + \left(\lambda_3 - \bar{\lambda}\right)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}\right)}$$

(water diffusivity ~10^{-3} mm^2/sec in brain)

DTI: Sports Concussion

- Repetitive sub-concussive head impacts measured with helmet accelerometers
  - Decreased FA in midbrain cortico-spinal tract over a single season of collegiate football
  - Decreased FA related to the amount of rotational force
- Decreased FA after concussion is correlated with levels serum tau protein

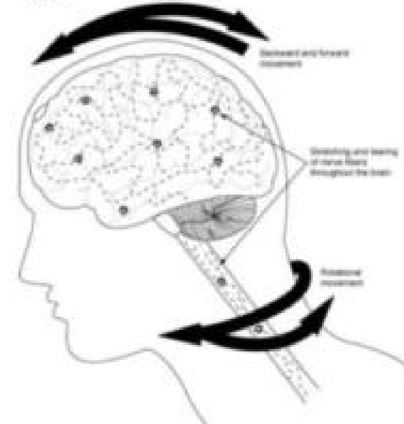
SCIENCE ADVANCES | RESEARCH ARTICLE

NEUROSCIENCE

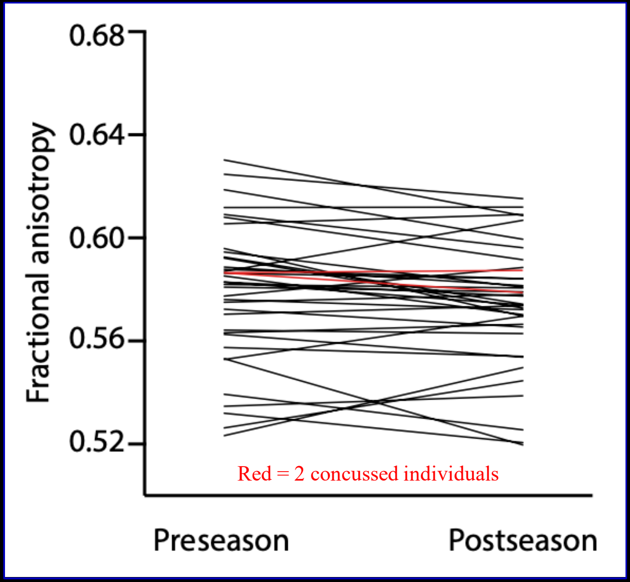
A common neural signature of brain injury in concussion and subconcussion

Adnan A. Hirad[1,2]*, Jeffrey J. Bazarian[1], Kian Merchant-Borna[1], Frank E. Garcea[3,4], Sarah Heilbronner[5,6], David Paul[7], Eric B. Hintz[8], Edwin van Wijngaarden[9], Giovanni Schifitto[10], David W. Wright[11], Tamara R. Espinoza[11], Bradford Z. Mahon[3,7,10,12,13,14]*

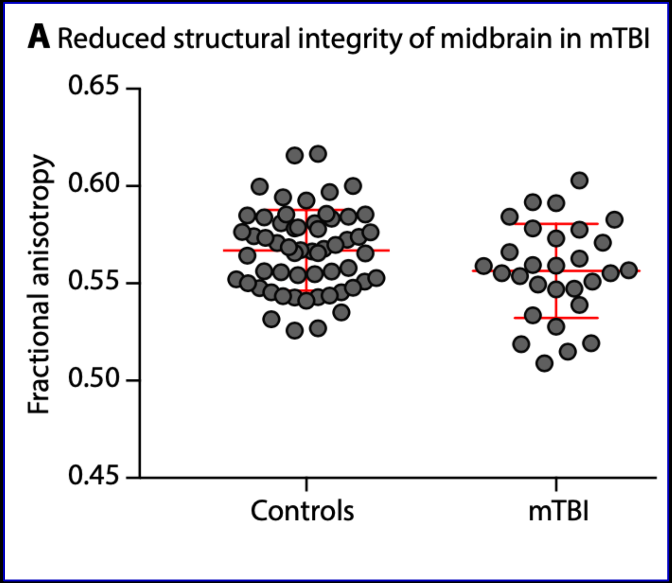
Hirad *et al*., *Sci. Adv.* 2019; **5** : eaau3460 7 August 2019



DTI: Sports Concussion

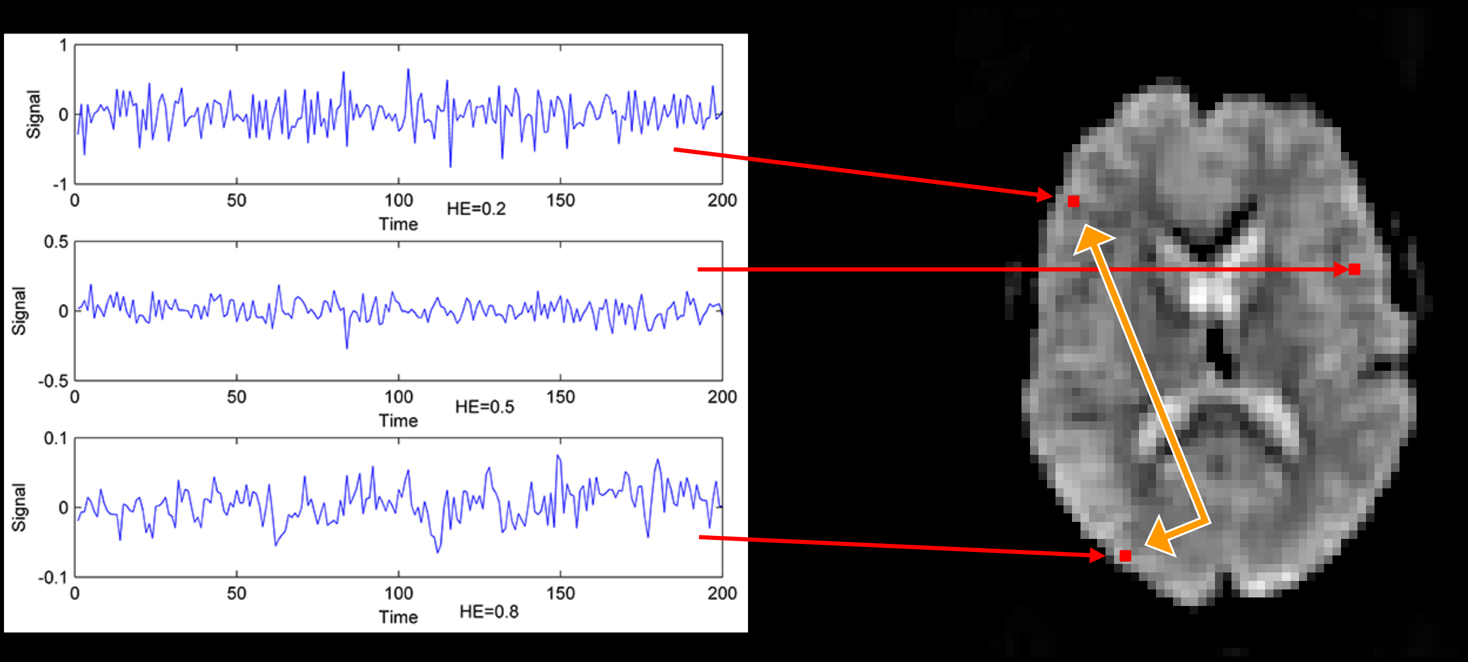


Sub-concussion



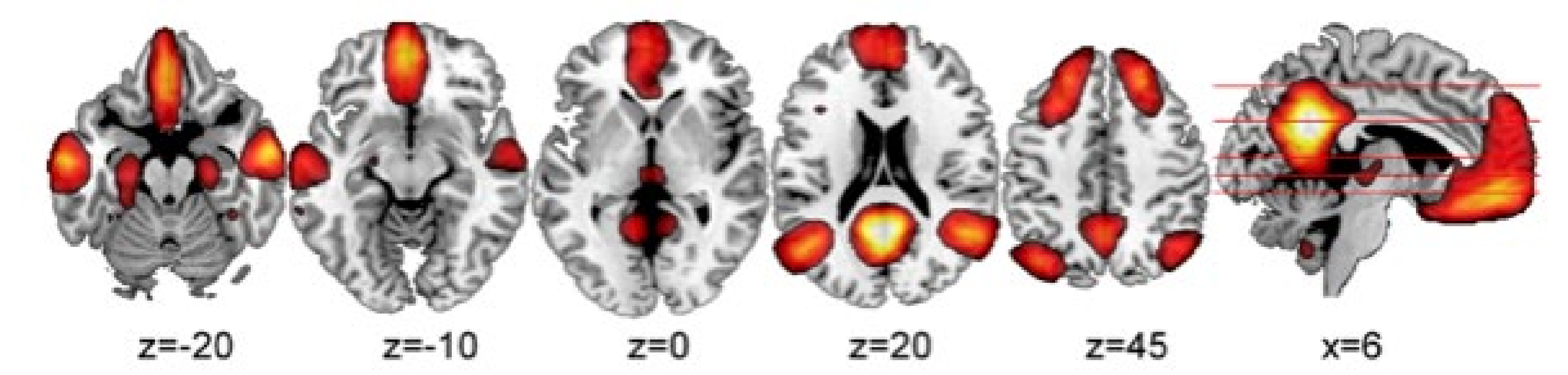
Concussion

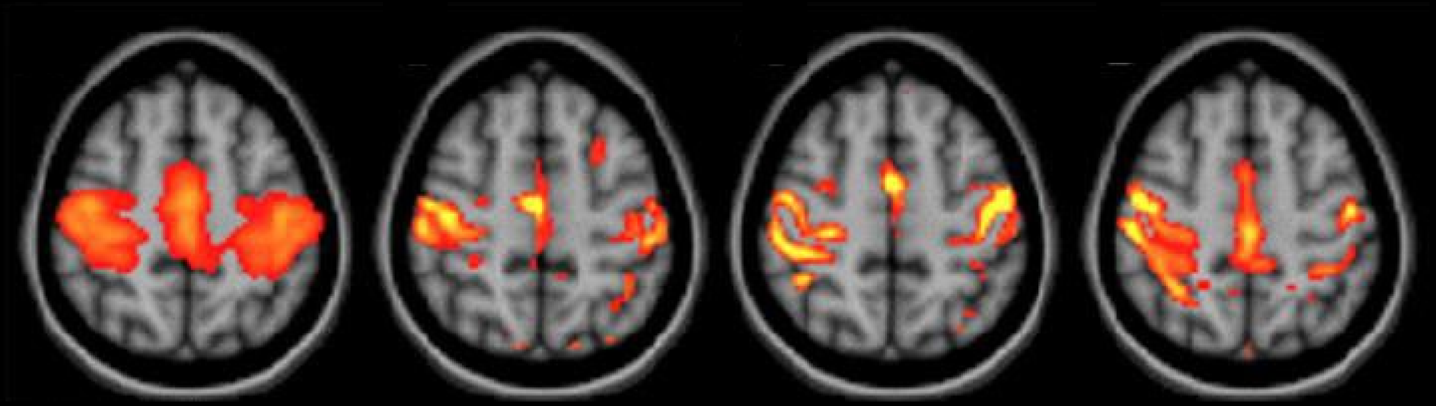
Resting State fMRI



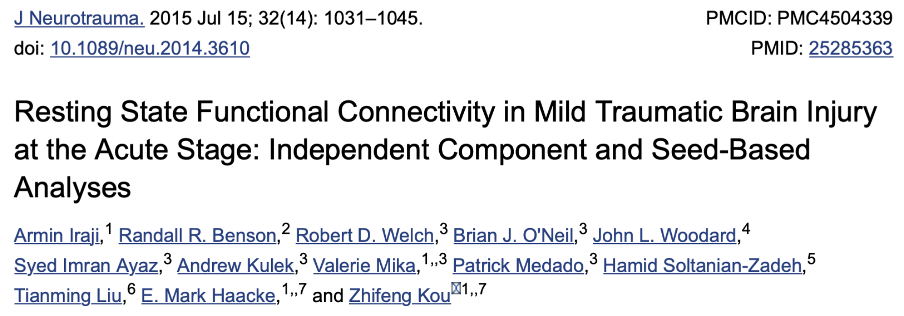
- Measurement based on neurovascular coupling (active tissue signals the blood vessels to open more)
- How well correlated small parts of the brain are to each other

Default Mode Network (DMN): “Vigilance” network





Motor network

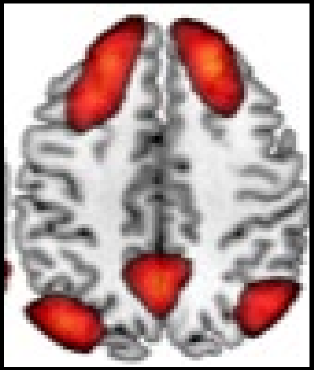


J Neurotrauma. 2015 Jul 15; 32(14): 1031–1045.
doi: 10.1089/neu.2014.3610
PMCID: PMC4504339
PMID: 25285363

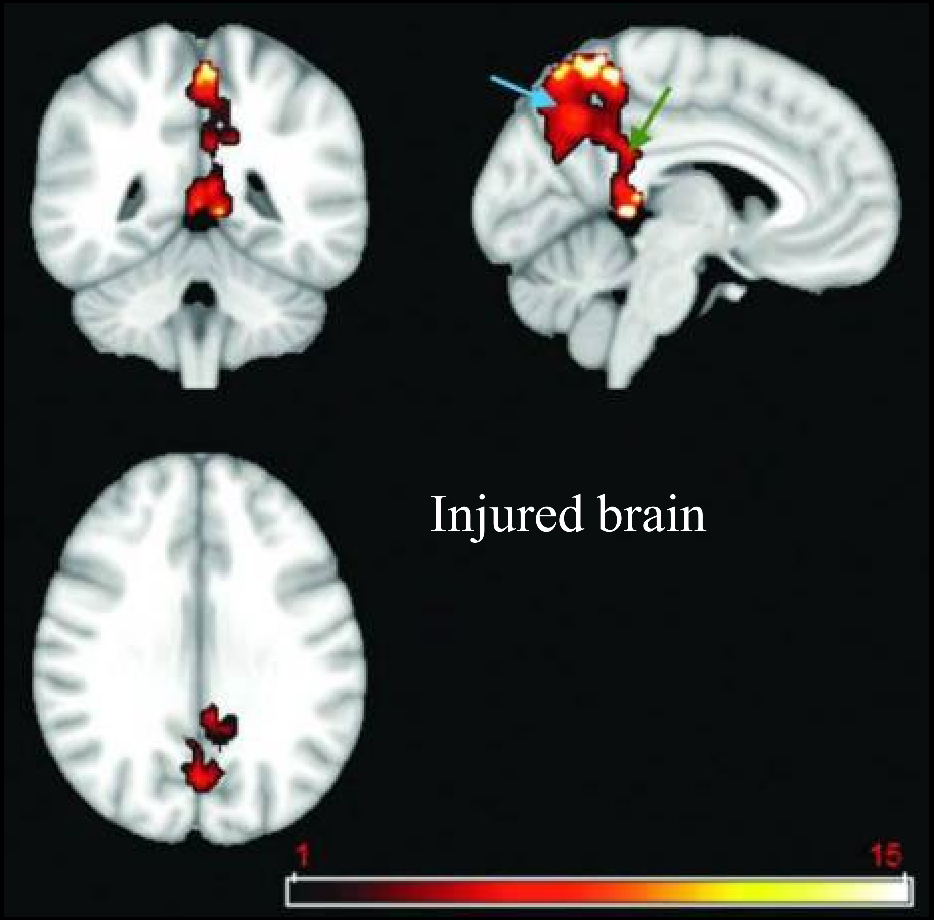
Resting State Functional Connectivity in Mild Traumatic Brain Injury at the Acute Stage: Independent Component and Seed-Based Analyses

Armin Iraji,[1] Randall R. Benson,[2] Robert D. Welch,[3] Brian J. O'Neil,[3] John L. Woodard,[4] Syed Imran Ayaz,[3] Andrew Kulek,[3] Valerie Mika,[1,,3] Patrick Medado,[3] Hamid Soltanian-Zadeh,[5] Tianming Liu,[6] E. Mark Haacke,[1,,7] and Zhifeng Kou[1,,7]

- Civilian head trauma with GCS 13-15 (mild decreased level of consciousness)
- Group-level differences in the DMN showing reduced connectivity

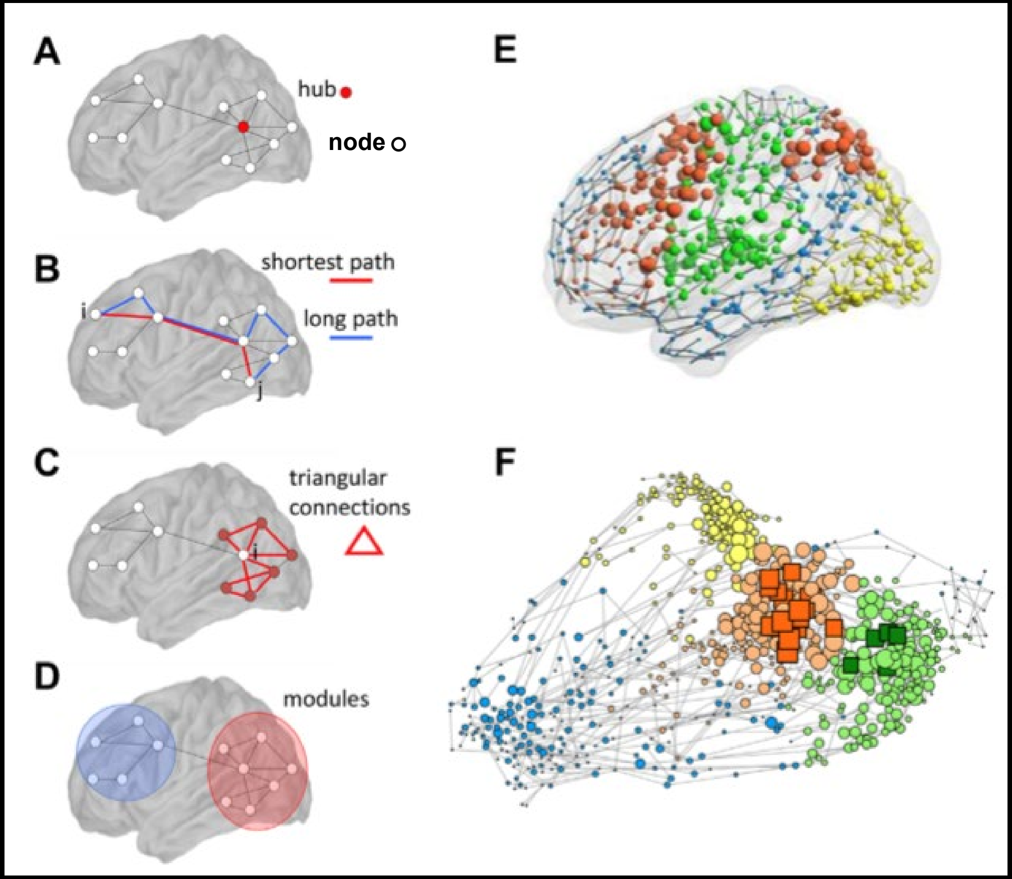


Healthy brain



Injured brain

Resting State - Graph Theory

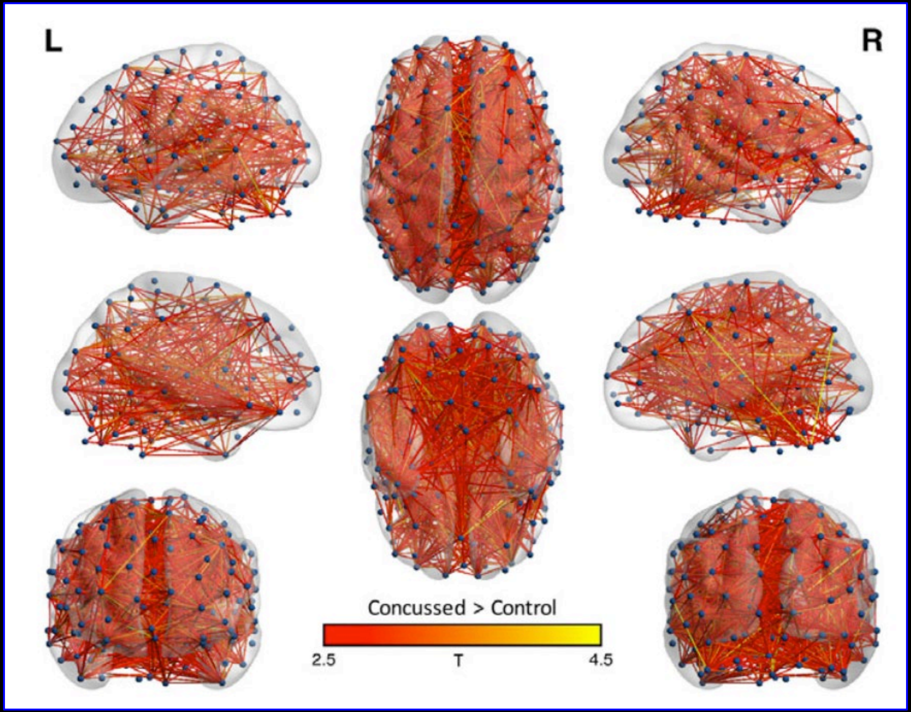


Functional "connectome" from resting state data

Clustering coefficient is a measure of the degree to which hubs tend to cluster together.

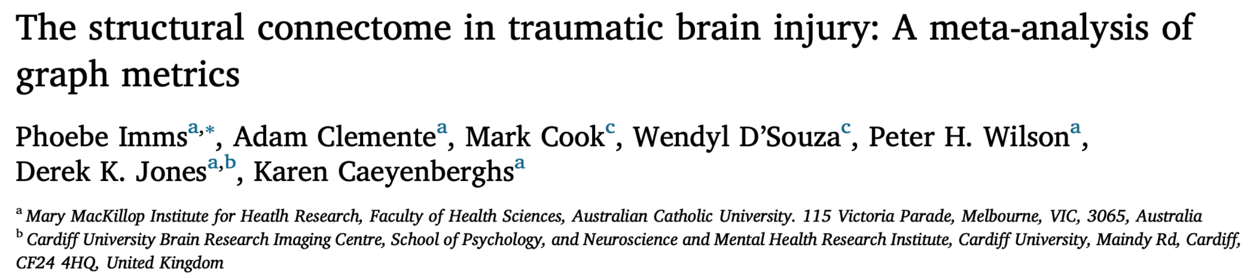
Morgan SE et al. PubMed PMID: 29703679.

Resting State fMRI and Acute Concussion



- Global increase in connectivity at 8 days post-concussion relative to controls
- Recruitment of additional neural resources to enable communication following disruption of functional networks.

Kaushal M, et al. Resting-state functional connectivity after concussion is associated with clinical recovery. Hum Brain Mapp. 2019 Mar;40(4):1211-1220. doi: 10.1002/hbm.24440. PMID: 30451340

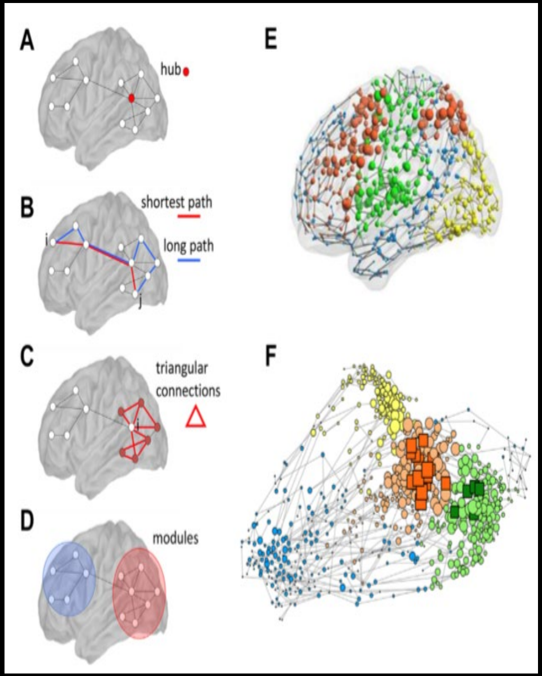


The structural connectome in traumatic brain injury: A meta-analysis of graph metrics

Phoebe Imms[a,*], Adam Clemente[a], Mark Cook[c], Wendyl D'Souza[c], Peter H. Wilson[a],
Derek K. Jones[a,b], Karen Caeyenberghs[a]

[a] *Mary MacKillop Institute for Heatlh Research, Faculty of Health Sciences, Australian Catholic University. 115 Victoria Parade, Melbourne, VIC, 3065, Australia*
[b] *Cardiff University Brain Research Imaging Centre, School of Psychology, and Neuroscience and Mental Health Research Institute, Cardiff University, Maindy Rd, Cardiff, CF24 4HQ, United Kingdom*
[c] *Department of Medicine, St. Vincent's Hospital, University of Melbourne. 41 Victoria Parade, Melbourne, VIC, 3065, Australia*

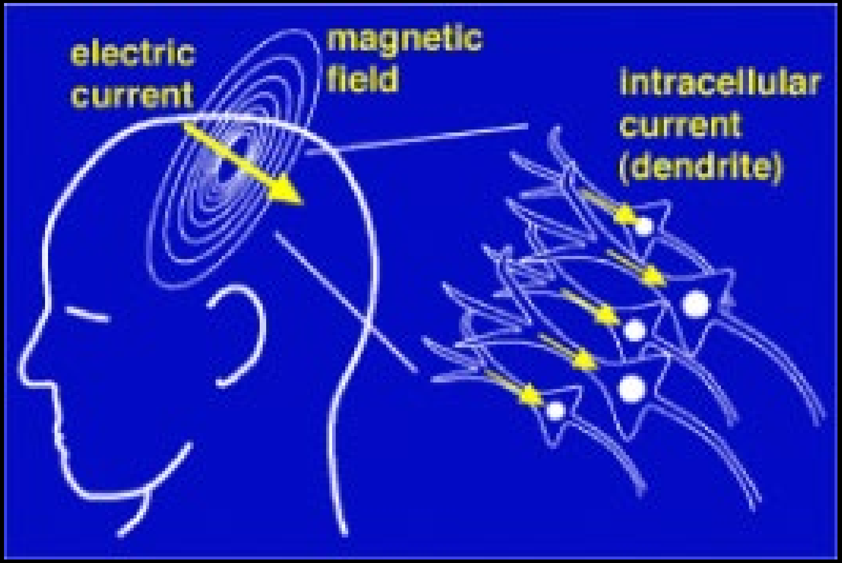
- Findings: Higher values of a normalised clustering coefficient and a longer characteristic path-length in a group of TBI patients compared a group of healthy individuals.
- Brain is more connected to itself locally and the path between distant connections is longer



Clustering coefficient is the degree to which nodes tend to cluster together.

- Provides insight into how concussion alters connections in the brain
- Is this network re-arrangement evidence of network compensation (adaptive plasticity)?

Magnetoencephalography (MEG)



Functional neuroimaging technique for mapping brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain, using very sensitive magnetometers.

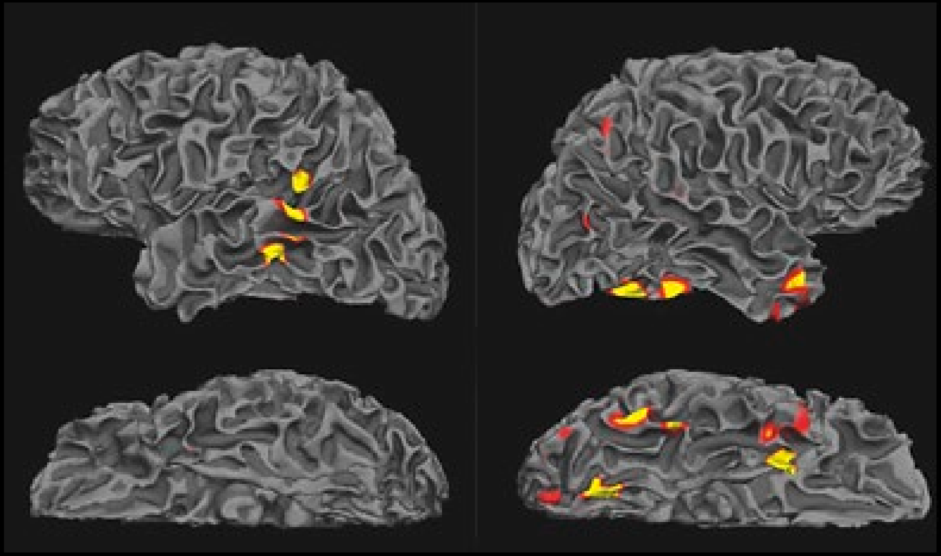
http://commons.wikimedia.org/wiki/File:NIMH
MEG.jpg#mediaviewer/File:NIMH_MEG.jpg

MEG and Mild TBI

Injured brain tissues in mTBI patients generate abnormal slow-waves (1–4 Hz) that can be measured and localized by resting-state.

Slow-wave generation in prefrontal areas positively correlated with personality change, trouble concentrating, affective lability, and depression symptoms.

Slow waves thought to be due to cortical deafferentation after axonal injury.



Huang MX. J Neurotrauma 2009;26:1213-1226

MEG and Mild TBI

- “This review has identified that while MEG has demonstrated clear promise as a functional neuroimaging modality, it is not yet a diagnostic or prognostic clinical tool in mTBI of sufficient sensitivity and specificity.”

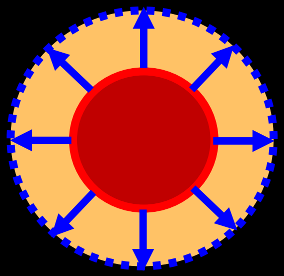
Neuroimage Clin. 2021; 31: 102697. PMCID: PMC8141472
Published online 2021 May 8. doi: 10.1016/j.nicl.2021.102697 PMID: 34010785

Magnetoencephalography abnormalities in adult mild traumatic brain injury: A systematic review

Christopher M. Allen,[a,*] Lloyd Halsey,[a] Gogem Topcu,[b] Lukas Rier,[c] Lauren E. Gascoyne,[c] John W Scadding,[d] Paul L. Furlong,[e] Benjamin T. Dunkley,[f] Roshan das Nair,[b] Matthew J. Brookes,[c] and Nikos Evangelou[a]

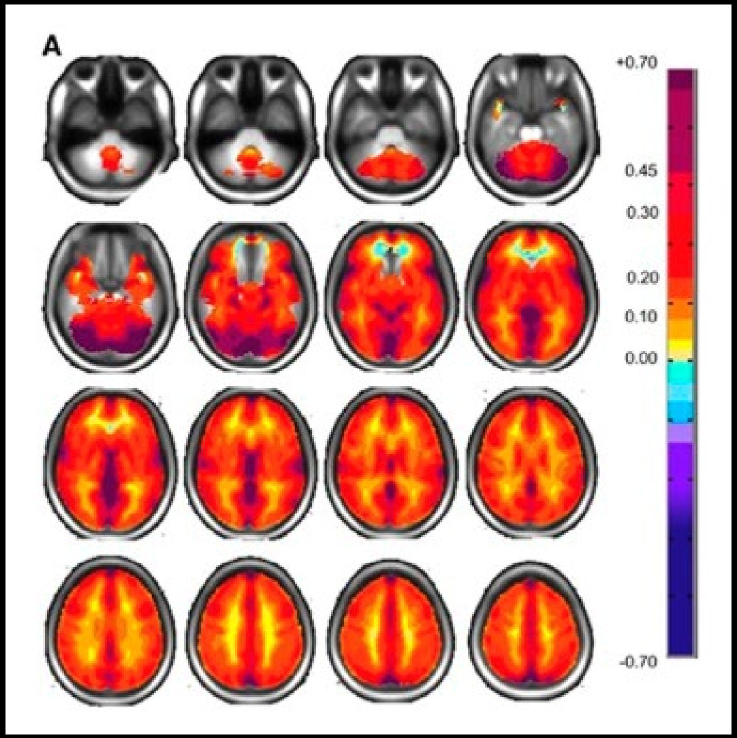
Measuring Blood Vessel “Performance”

Mapping Cerebrovascular
Reactivity (CVR)

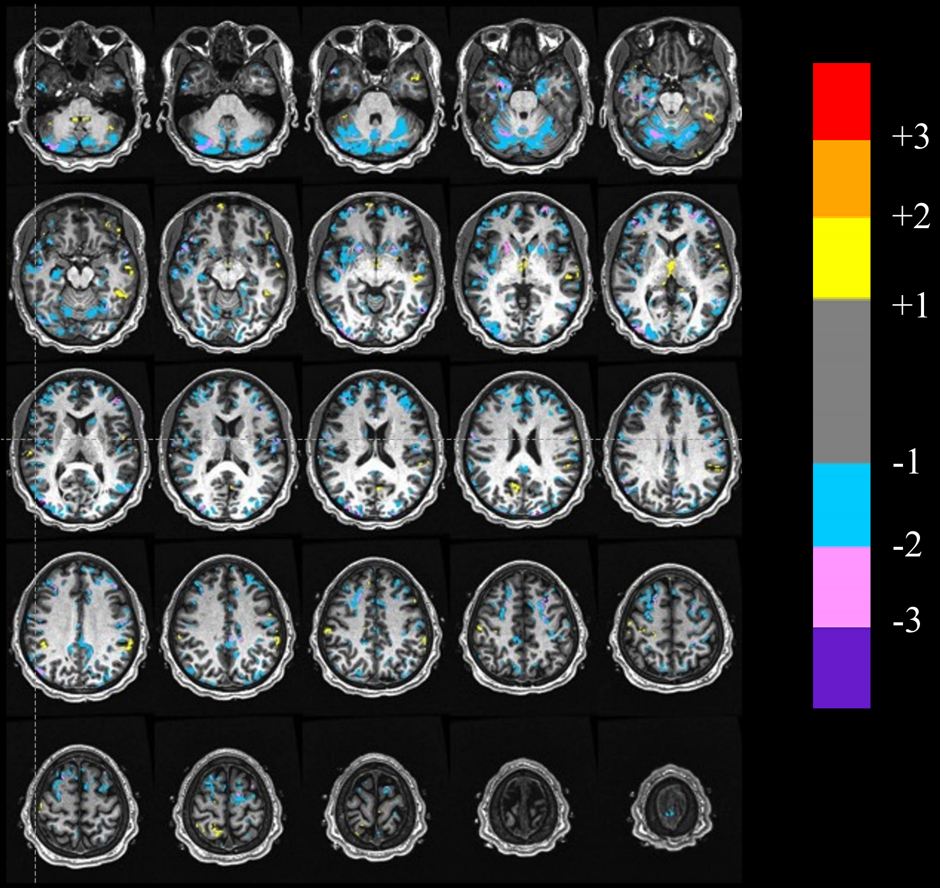


$$\mathrm{CVR} = \frac{\overbrace{\Delta\ \text{blood flow}}}{\underbrace{\Delta\ \text{stimulus}}} \rightarrow \frac{\text{BOLD MRI}}{\text{Quantitative CO2}}$$

- MRI mapping of blood flow changes (vascular reactivity) to a vasodilatory stimulus (CO2)
- Can measure how much and how fast vessels open



- Group atlas of healthy individuals showing speed of vessel opening
- Note gray matter vessels open faster than white mater vessels



Colors indicate number of standard deviations slower or faster than normal

> J Neurotrauma. 2020 Dec 14. doi: 10.1089/neu.2020.7272. Online ahead of print.

A Promising Subject-Level Classification Model for Acute Concussion Based on Cerebrovascular Reactivity Metrics

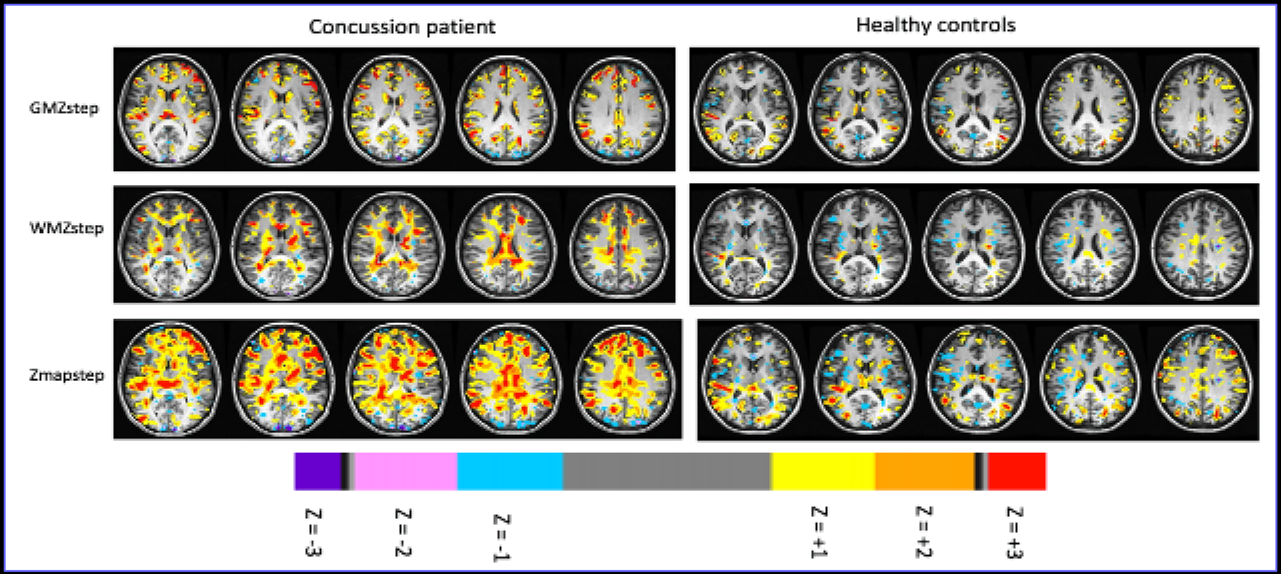
Reema Shafi[1], Julien Poublanc[1], Lashmi Venkatraghavan[2], Adrian P Crawley[1], Olivia Sobczyk[1], Larissa McKetton[1], Mark Bayley[3], Tharshini Chandra[3], Evan Foster[3], Lesley Ruttan[4] [3] [5], Paul Comper[6] [3], Maria Carmela Tartaglia[7] [8] [9] [5], Charles H Tator[10] [5], James Duffin[2] [11], W Alan Mutch[12], Joseph Fisher[2] [11], David J Mikulis[1] [5]

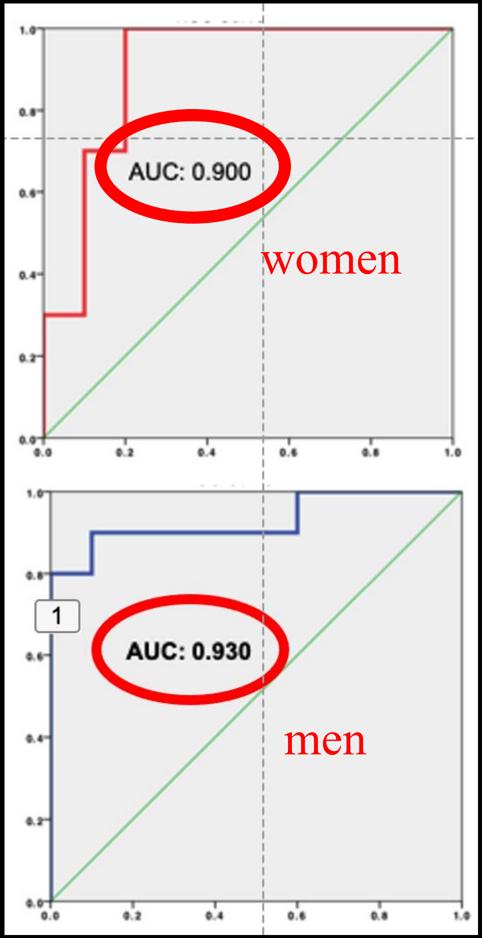
Affiliations + expand

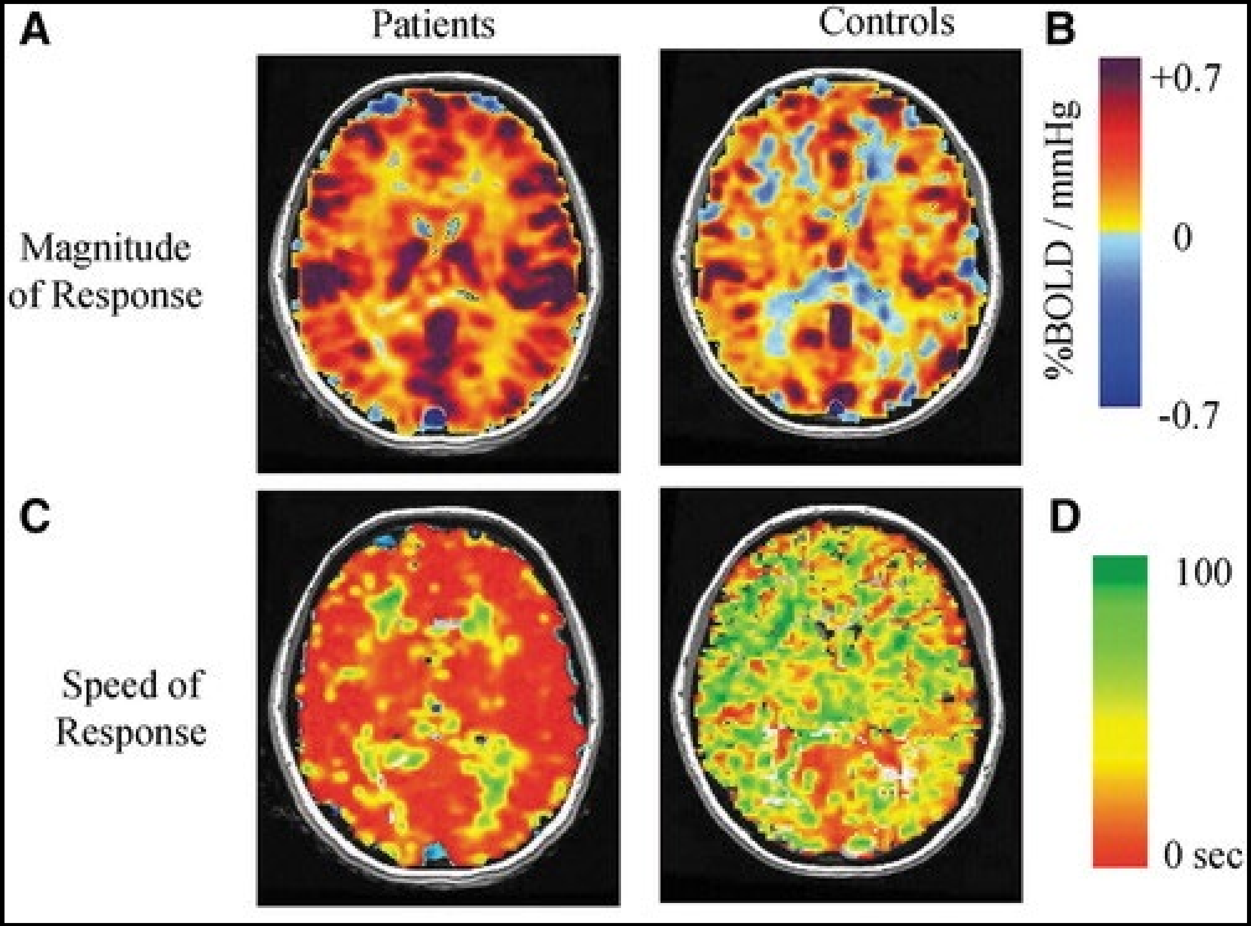
PMID: 33096952 DOI: 10.1089/neu.2020.7272

Vascular Performance Metrics

- Subjects within 1 week of concussion
- Individuals compared to a control atlas





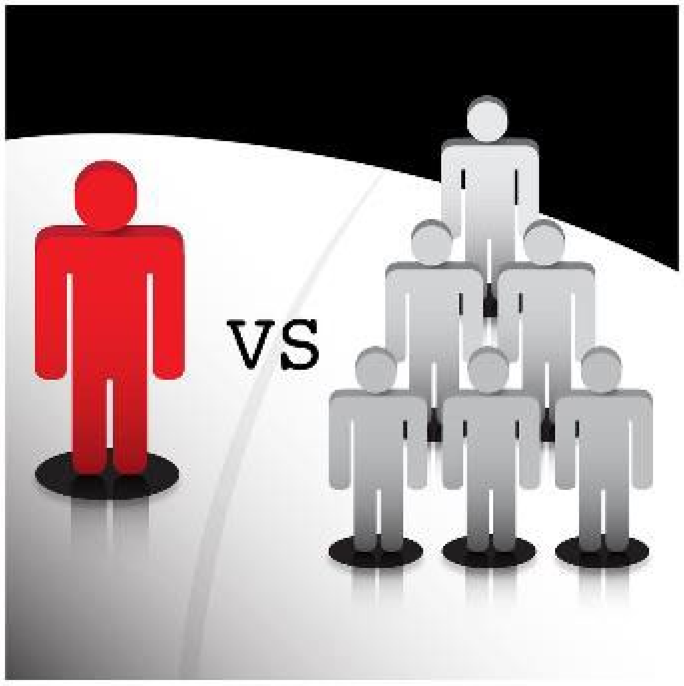


- Magnitude of CVR response is increased
- Speed of CVR response is increased

Advantage of CVR

- Blood vessels react *faster and stronger* than normal
- All other brain disorders we have studied show slower and weaker responses
- Sensitive and specific for concussion only
- Issue of comorbidities:
  - Is the test able to still make a Dx in in concussed individuals who happen to have other diseases conditions?

Advanced Neuroimaging Status:

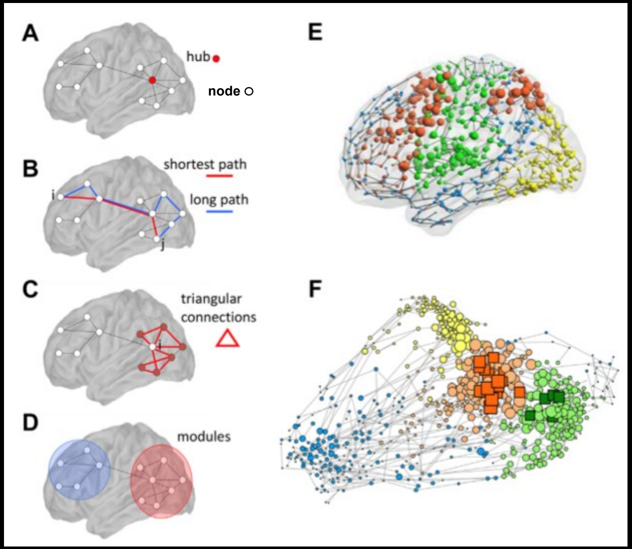


- Despite highly advanced imaging and sophisticated image analysis:
  - Group level diagnosis possible
  - Single individual diagnosis not possible

Toward a Diagnostic Biomarker of Concussion

- Can we do better than detecting group level differences?

Unification of Structure with Function: Fingerprints of Invisible Disease



Connecting
the connectomes!

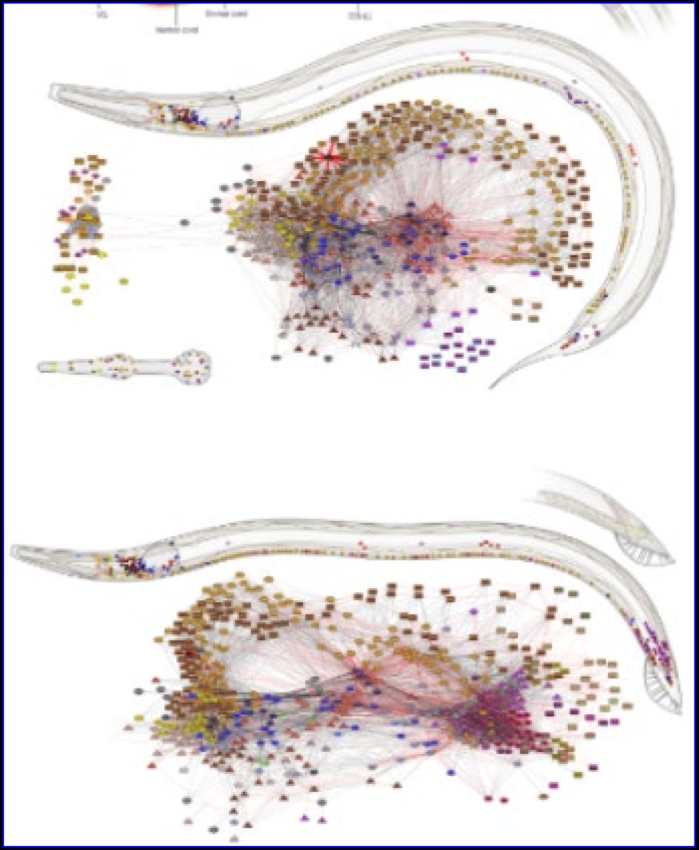
Functional connectome
from resting state data

Morgan SE et al. PubMed PMID: 29703679.

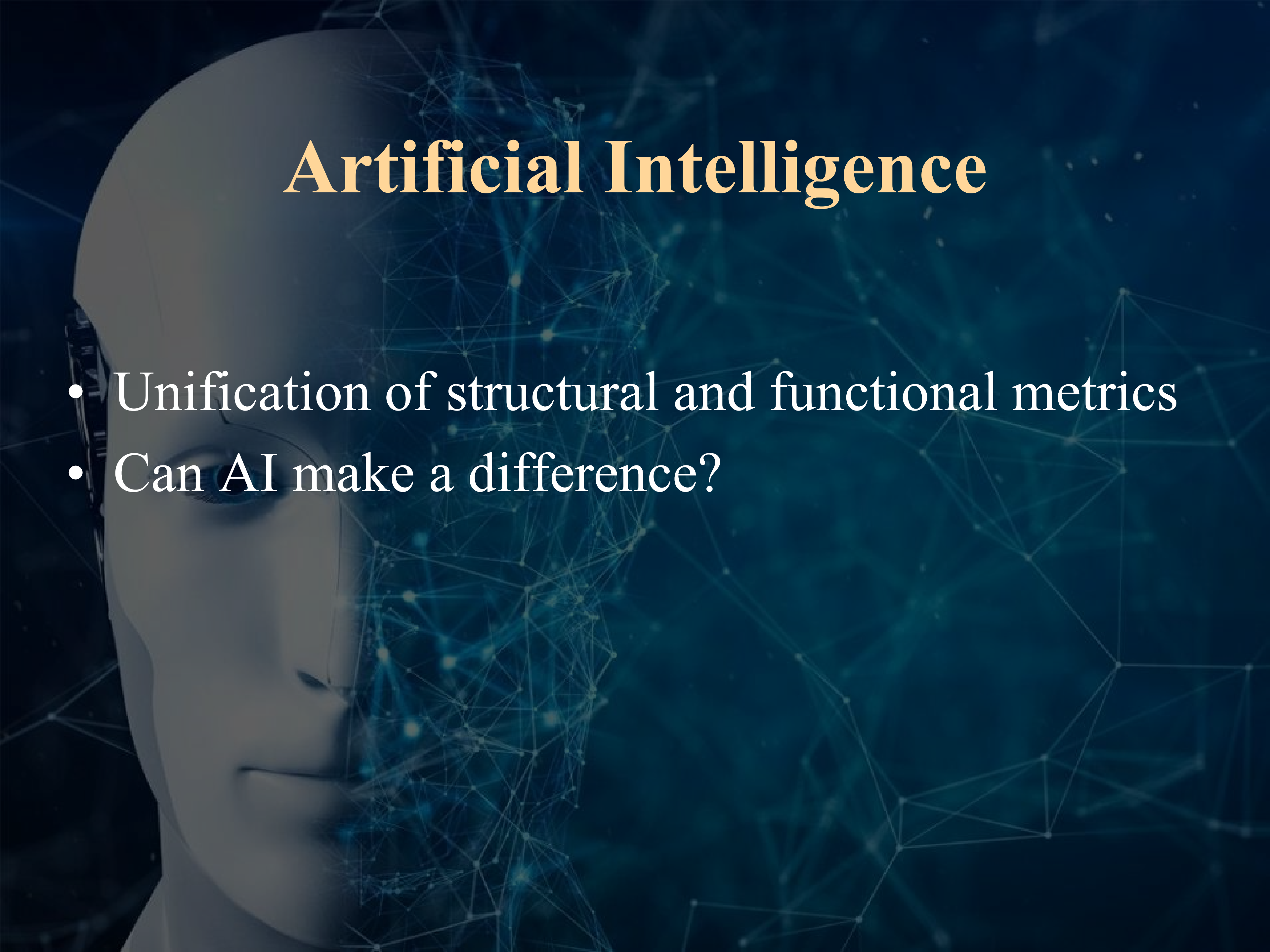
Structural connectome
from diffusion data

Human Connectome Project– Harvard/Wash U/USC

Successful in nematode brain …..



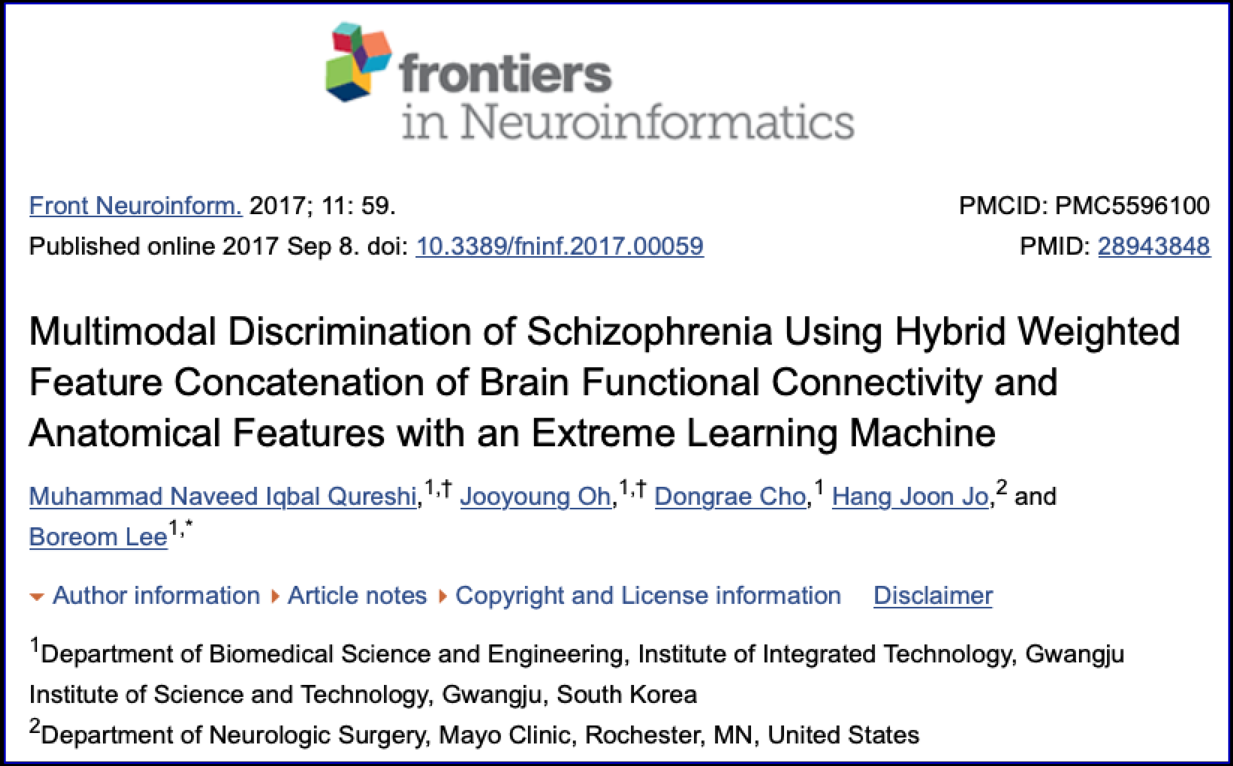
- Nematode brain 300 neurons
- Human brain 85 billion neurons



Artificial Intelligence

- Unification of structural and functional metrics
- Can AI make a difference?

Lessons from other CNS Disorders
Imaging ***Diagnosis*** of “Invisible” Disease



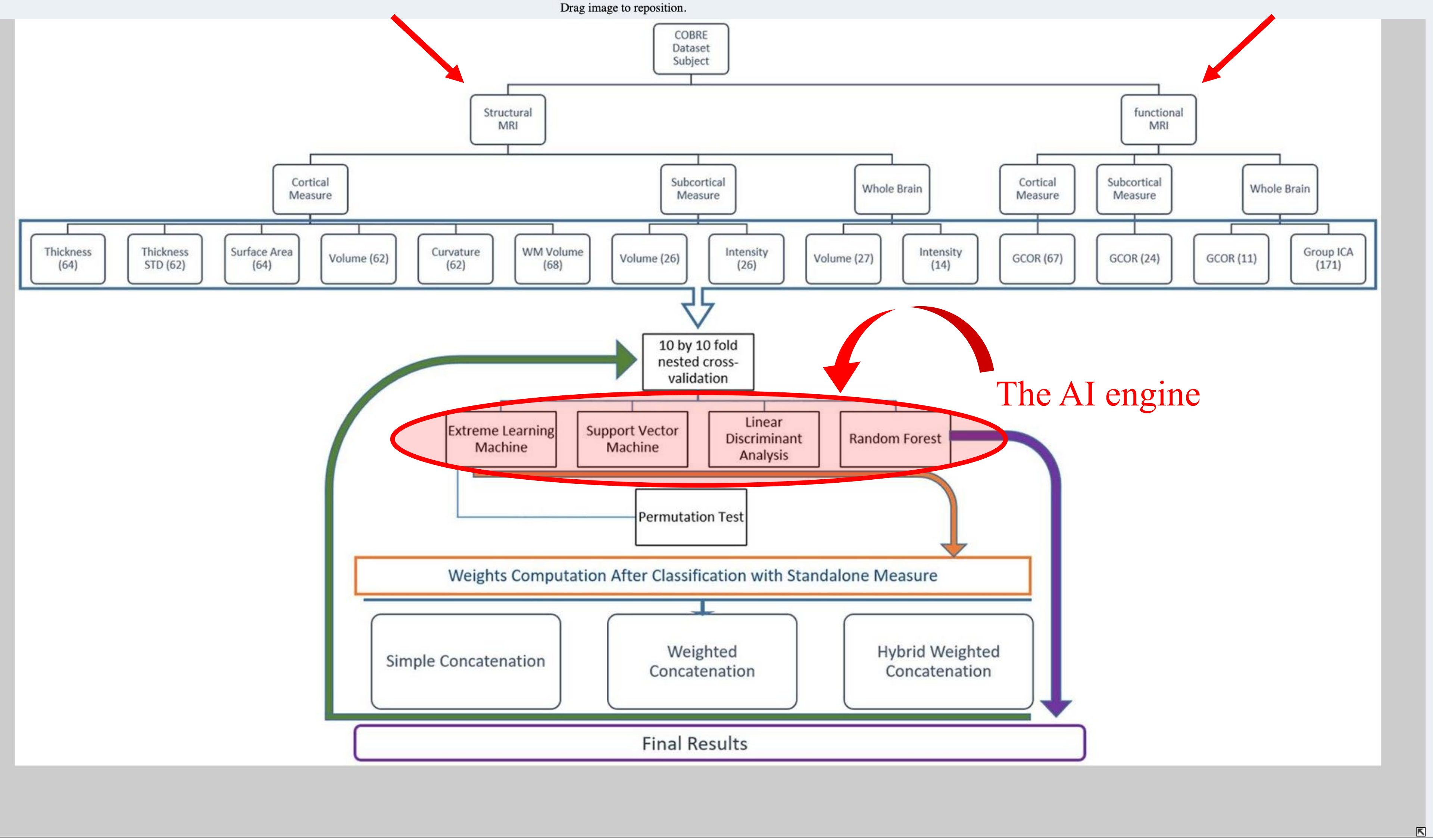
frontiers
in Neuroinformatics

Front Neuroinform. 2017; 11: 59. PMCID: PMC5596100
Published online 2017 Sep 8. doi: 10.3389/fninf.2017.00059 PMID: 28943848

Multimodal Discrimination of Schizophrenia Using Hybrid Weighted Feature Concatenation of Brain Functional Connectivity and Anatomical Features with an Extreme Learning Machine

Muhammad Naveed Iqbal Qureshi,[1,†] Jooyoung Oh,[1,†] Dongrae Cho,[1] Hang Joon Jo,[2] and Boreom Lee[1,*]

[1]Department of Biomedical Science and Engineering, Institute of Integrated Technology, Gwangju Institute of Science and Technology, Gwangju, South Korea
[2]Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, United States



The AI engine

Qureshi MNI et al. Front Neuroinform. 2017 Sep 8;11:59. doi: 10.3389/fninf.2017.00059. PMID: 28943848; PMCID: PMC5596100.

Imaging ***Diagnosis*** of Invisible Disease

- Tour de force implementation using AI and multiple imaging metrics
  - Resting-state functional MRI (ICA)
  - GM WM (volumetrics, morphology, functional connectivity, signal intensity variation, curvature, surface area)
- AI implementation
  - Extreme learning machine classifier (MatLab)
  - Combined multiple imaging metrics using a hybrid weighted feature concatenation method
- Accuracy in determining presence of schizophrenia in a single subject
  - ***99.3%***
  - ***Black box – What was AI detecting?***
- Functional connectivity information showed slightly greater value than structural information

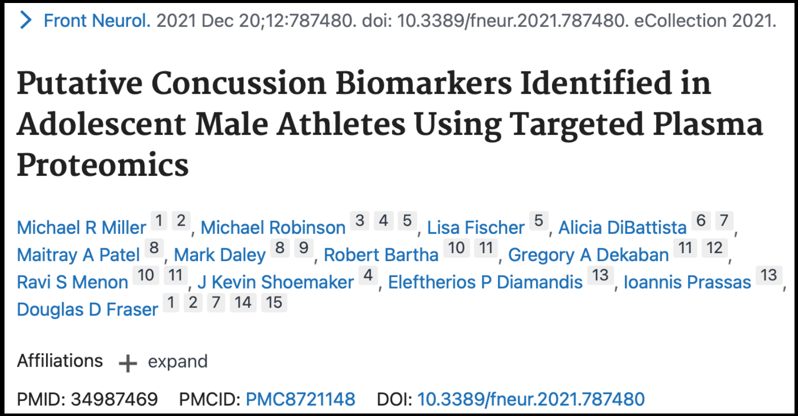
Qureshi MNI et al. Multimodal Discrimination of Schizophrenia Using Hybrid Weighted Feature Concatenation of Brain Functional Connectivity and Anatomical Features with an Extreme Learning Machine. Front Neuroinform. 2017 Sep 8;11:59. doi: 10.3389/fninf.2017.00059. PMID: 28943848; PMCID: PMC5596100.

Can we add "biomarkers" to imaging?

Serum Markers of TBI

- Neuronal injury
  - Serum UCH-L1 (ubiquitin carboxyl-terminal hydrolase L)
  - S100B (S100 calcium-binding protein B)
  - Tau protein
  - NF-L (neurofilament-light)
  - Alpha-synuclein
  - AMPAR (Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor peptide)
- Glial injury
  - Serum GFAP (glial fibrillary acid protein)
- Oligodendrocyte injury
  - Myelin basic protein
- Vascular injury
  - Maybe

- Differences on group level, not individual
- Technically not biomarkers as can be seen in other CNS conditions too



> Front Neurol. 2021 Dec 20;12:787480. doi: 10.3389/fneur.2021.787480. eCollection 2021.

Putative Concussion Biomarkers Identified in Adolescent Male Athletes Using Targeted Plasma Proteomics

Michael R Miller[1,2], Michael Robinson[3,4,5], Lisa Fischer[5], Alicia DiBattista[6,7], Maitray A Patel[8], Mark Daley[8,9], Robert Bartha[10,11], Gregory A Dekaban[11,12], Ravi S Menon[10,11], J Kevin Shoemaker[4], Eleftherios P Diamandis[13], Ioannis Prassas[13], Douglas D Fraser[1,2,7,14,15]

Affiliations + expand

PMID: 34987469 PMCID: PMC8721148 DOI: 10.3389/fneur.2021.787480

Proteomics

- 1,472 plasma proteins screened in adolescent hockey players, 11 concussed, 24 non-concussed

- ATOX1
  - Cytosolic protein essential role in copper homeostasis
- SPARC (best performer)
  - Basement membrane protein expressed in endothelium, fibroblasts, and macrophages.
  - Induced in mature blood vessels close to an injury site and angiogenesis develop following injury
- NT5C3A
  - Enzyme that dephosphorylates nucleoside 5'-monophosphates
- Combination of the three = AUC of 0.98 for concussion diagnoses (*P* < 0.001; 95% CI: 0.95, 1.00)

- AI will have a major impact on imaging and proteomics:
  - Single subject diagnosis will become feasible
  - Assist in linking the biology of concussion with the physiology of recovery vs. persistence of symptoms
- Can the tools have diagnostic success in individuals with co-morbidities?

Imaging and Concussion Summary

1. The brain is complex and delicate.

2. In concussion, conventional imaging with CT and MRI should be normal in these patients who despite the absence of findings can have severe and persistent symptoms.

3. Advanced neuroimaging can “see” findings but only when comparing a group of concussed against a group of controls. It is not yet diagnostic in individual patients.

4. AI could change this.

Routine clinical imaging diagnosis of concussion is not there yet!
The future is bright -Thank you!