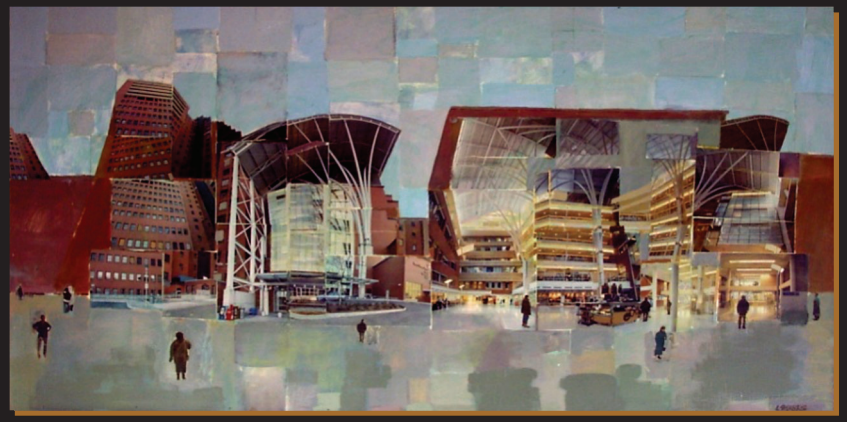
Recent Research into the Imaging of Concussion and Persisting Symptoms of Concussion



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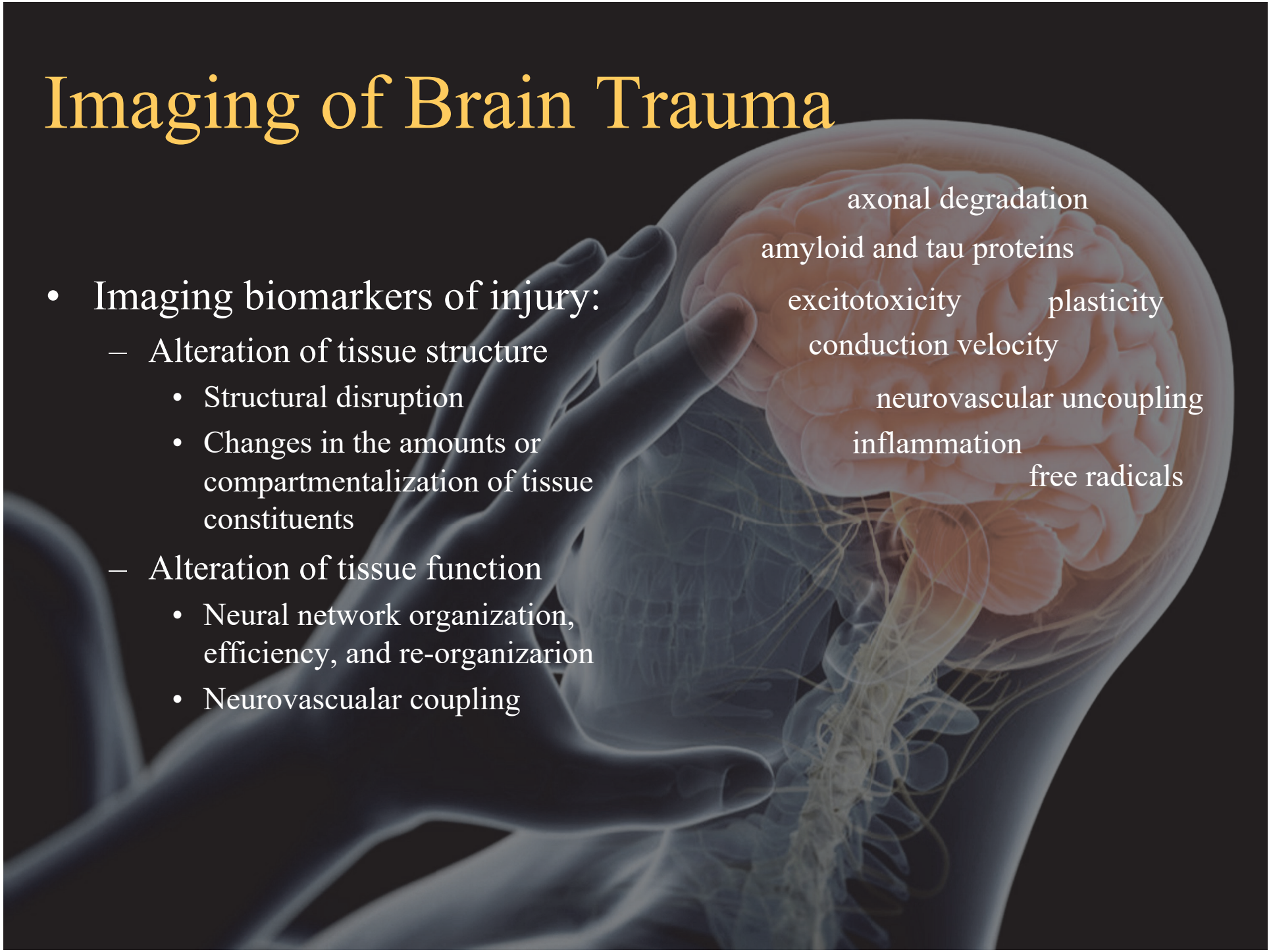
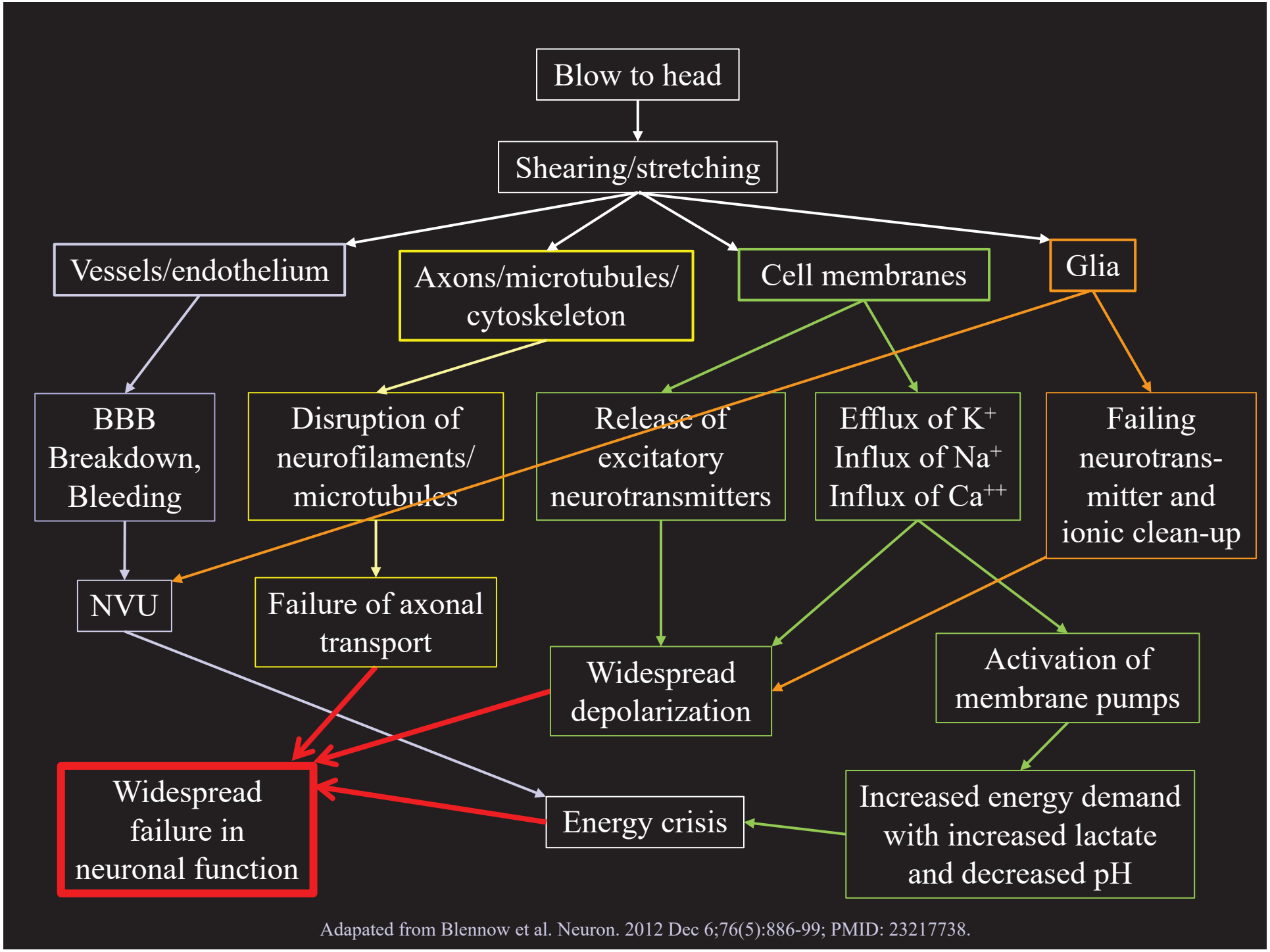
Disclosures

- Investigational device
  - RespirAct™ (Thornhill Research, Inc.)
  - Minor equity in Thornhill Research, Inc.

Imaging of Brain Trauma



- Imaging biomarkers of injury:
  - Alteration of tissue structure
    - Structural disruption
    - Changes in the amounts or compartmentalization of tissue constituents
  - Alteration of tissue function
    - Neural network organization, efficiency, and re-organizarion
    - Neurovascualar coupling



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

. . . and what is seen on the most sensitive clinical imaging tool - MRI?

The brain is normal

Why are we struggling to diagnose concussion with imaging?

- Concussion falls within the category of brain abnormalities that have normal MRI scans

Role of advanced neuroimaging, fluid biomarkers and genetic testing in the assessment of sport-related concussion: a systematic review

Michael McCrea,[1] Timothy Meier,[1,2] Daniel Huber,[1] Alain Ptito,[3,4] Erin Bigler,[5] Chantel T Debert,[6] Geoff Manley,[7] David Menon,[8] Jen-Kai Chen,[9] Rachel Wall,[10] Kathryn J Schneider,[11] Thomas McAllister[10]

McCrea M, *et al*. *Br J Sports Med* 2017;**51**:919–929. doi:10.1136/bjsports-2016-097447

- Ranked published research as:
  - High, moderate, low, or very low level of confidence in the strength of the existing findings demonstrating reliability, validity and clinical utility of the tool(s) for use in the assessment of SRC

Role of advanced neuroimaging, fluid biomarkers and genetic testing in the assessment of sport-related concussion: a systematic review

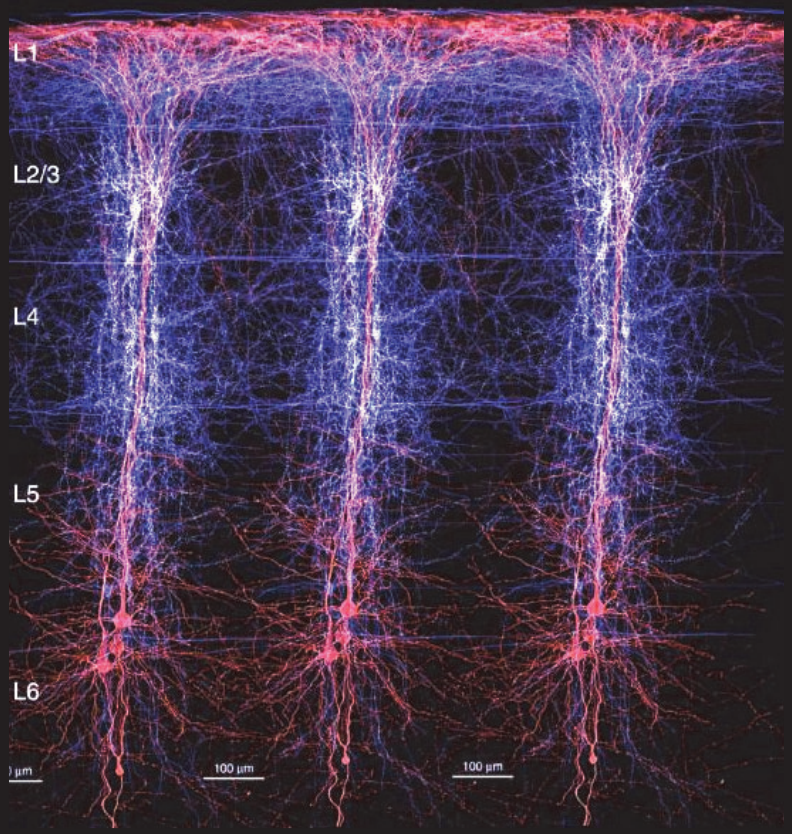
Michael McCrea,[1] Timothy Meier,[1,2] Daniel Huber,[1] Alain Ptito,[3,4] Erin Bigler,[5] Chantel T Debert,[6] Geoff Manley,[7] David Menon,[8] Jen-Kai Chen,[9] Rachel Wall,[10] Kathryn J Schneider,[11] Thomas McAllister[10]

McCrea M, *et al*. *Br J Sports Med* 2017;**51**:919–929. doi:10.1136/bjsports-2016-097447

- "In terms of their current readiness for *clinical application*, our systematic review rated the level of evidence as low for advanced neuroimaging, low for fluid biomarkers and low for genetic testing."
- "At the same time, however, our systematic review generally supports the utility of advanced neuroimaging, fluid and genetic biomarkers in studies aimed at identifying the neurobiological effects of concussion and the natural history of neurobiological recovery after injury."

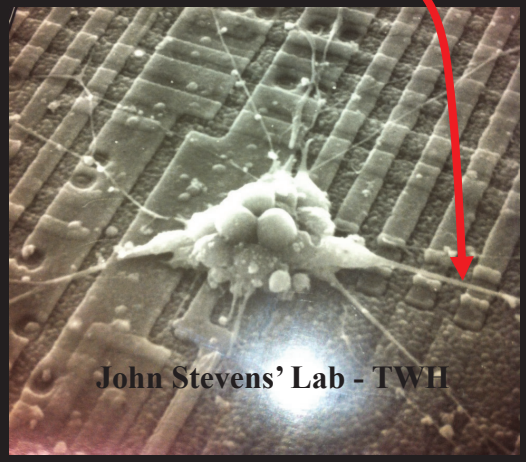
Why is it so difficult to see this injury?

Brain Structure

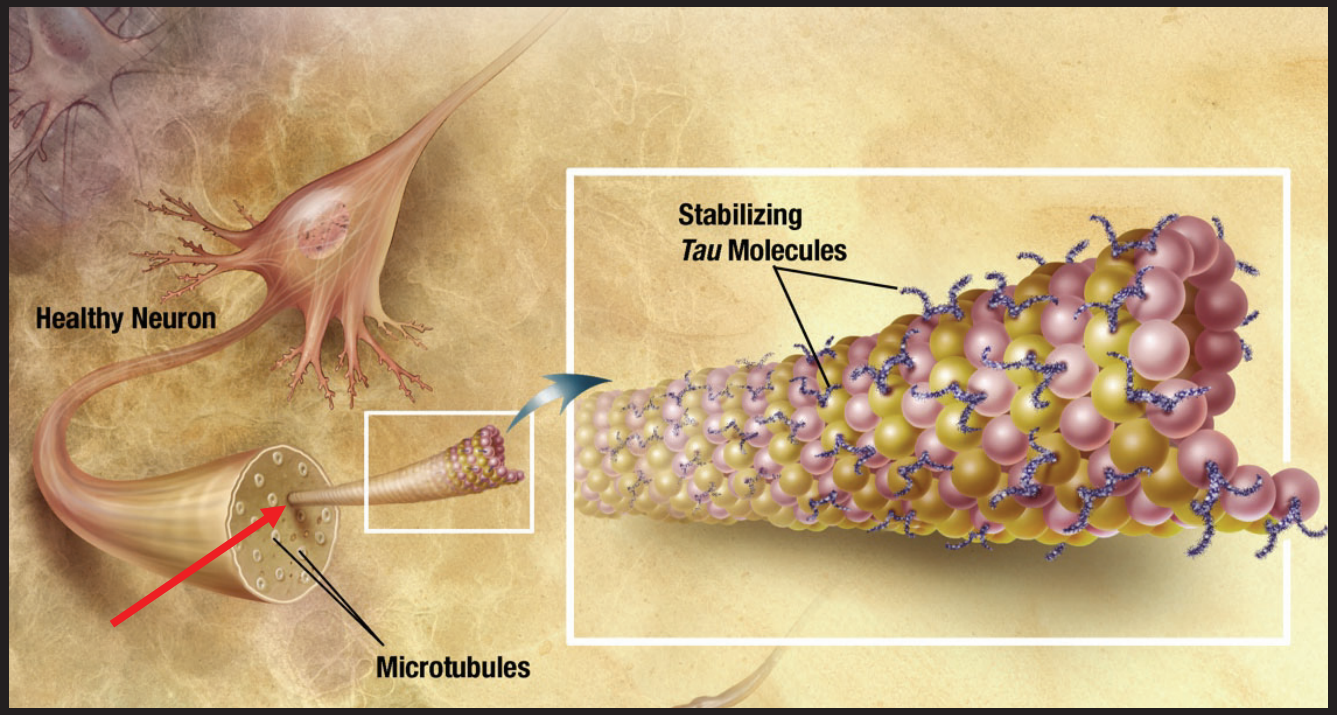


http://biomedicalcomputationreview.org

Primary site of injury



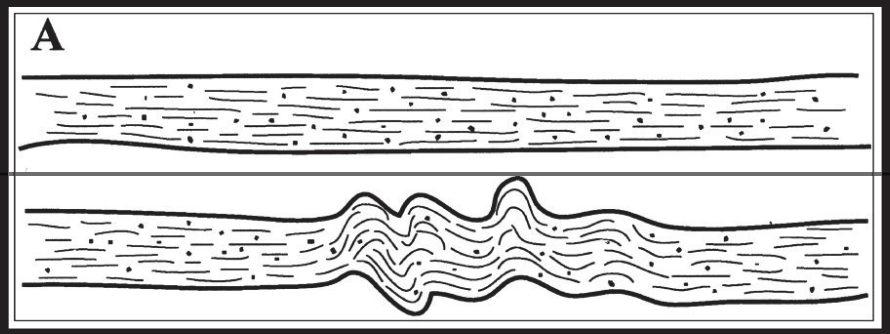
- 100 billion neurons
- 100 trillion synapses
- 1 million axons/mm^3
- MRI resolution ~ $1mm^3$

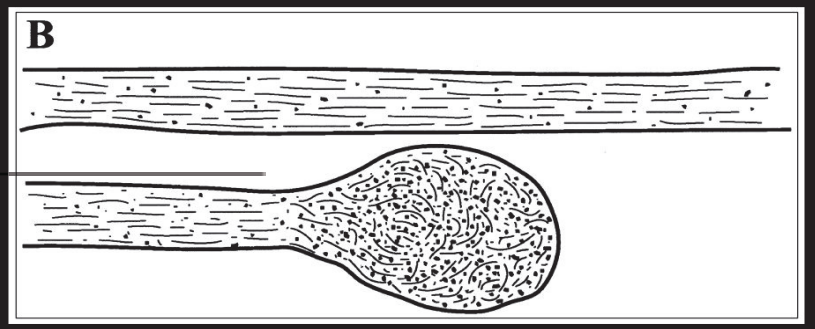


Concussion typically causes “diffuse axonal injury”

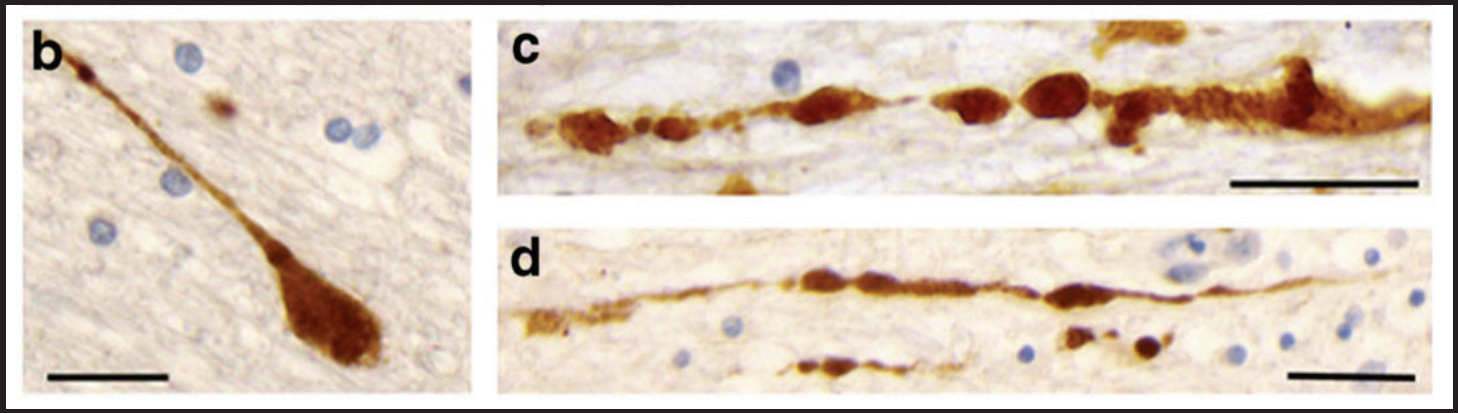
- Microtubules can break at the moment of injury (8,9)
- Axonal bending ruptures microtubules interrupting axoplasmic transport
- Accumulation of transported proteins causes regional swelling of the axons forming varicosities and bulbs

Diffuse Axonal Injury



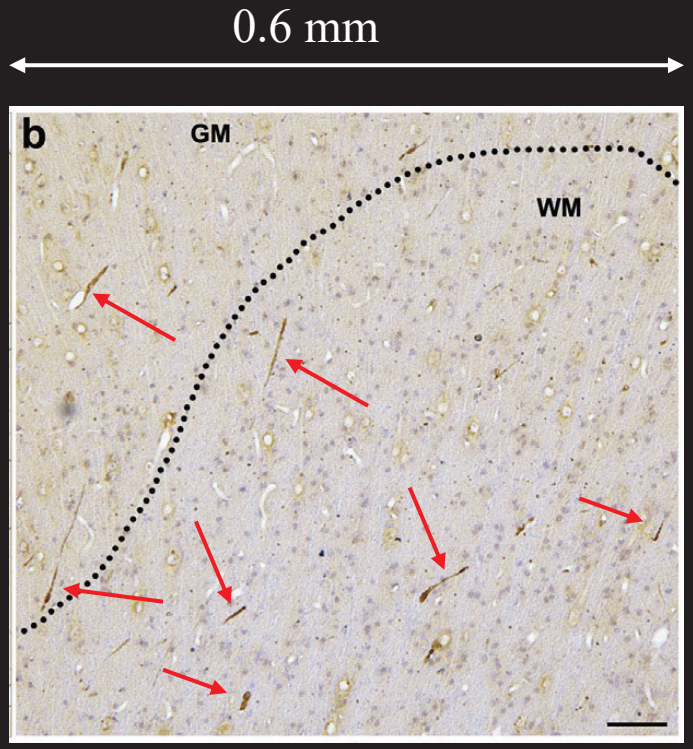


- Axonal bending ruptures microtubules interrupting axoplasmic transport forming varicosities
- Axon breaks with accumulation of transported proteins causing retraction bulbs

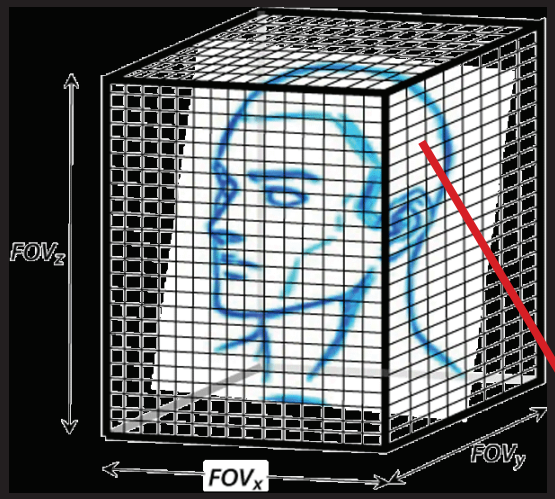


Shin SS, et al. Structural imaging of mild traumatic brain injury may not be enough: overview of functional and metabolic imaging of mild traumatic brain injury. Brain Imaging Behav. 2017 Apr;11(2):591-610. doi: 10.1007/s11682-017-9684-0. PMID: 28194558.

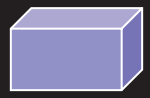
Can we image this injury?



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



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



Are there enough of theses abnormal neurons to alter the structural or functional MRI signal?

Brain Imaging and Behavior (2017) 11:591–610
DOI 10.1007/s11682-017-9684-0

REVIEW ARTICLE

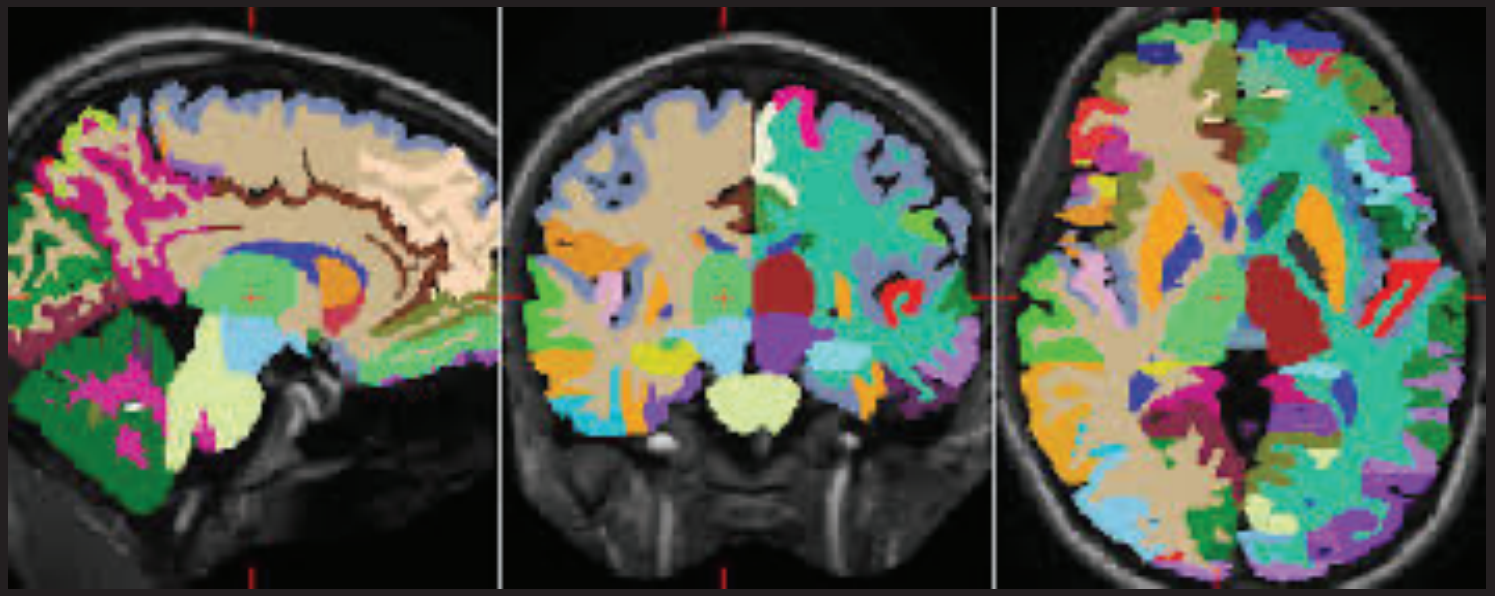
Structural imaging of mild traumatic brain injury may not be enough: overview of functional and metabolic imaging of mild traumatic brain injury

Samuel S. Shin[1] · James W. Bales[2] · C. Edward Dixon[3] · Misun Hwang[4]

- "Moreover, structural damage may be present at a microscopic and molecular level that is not detectable by a structural imaging modality. The use of functional and metabolic imaging modalities can provide information on pathological changes in mild TBI patients that may not be detected by structural imaging."

Volumetric Imaging

- Use high reolution 3D MRI images
- Divide gray matter and white matter into regions for measuring volumes



Volumetric Imaging

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

Advanced MRI Methods

- Cortical thickness
- DTI
- Resting State

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.

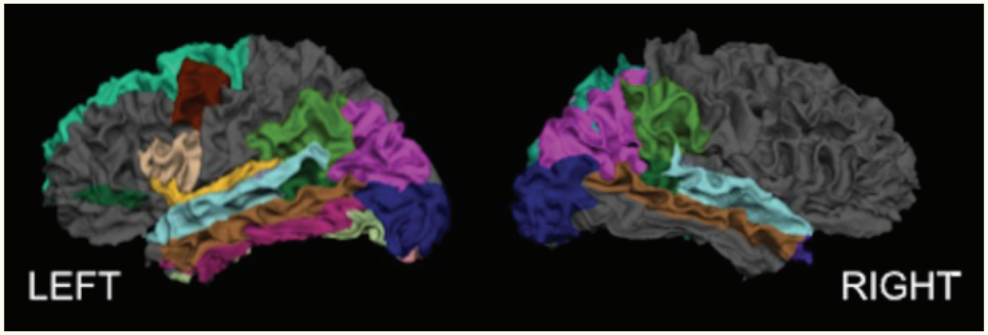


Figure 1

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

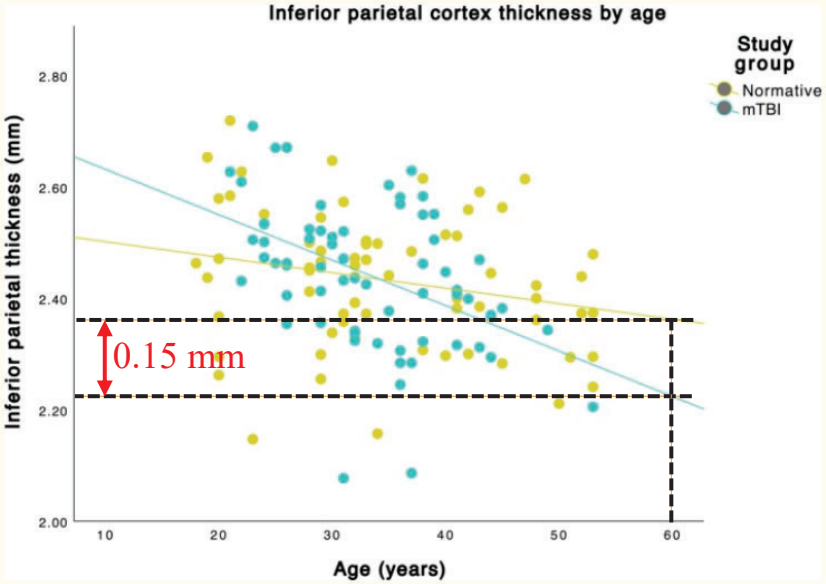


Figure 2

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

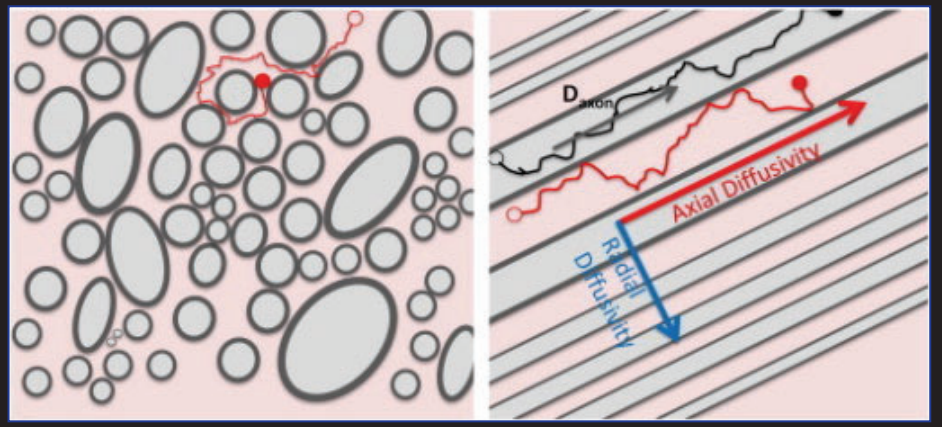
Conventioanl imaging

Courtesy Tim Roberts

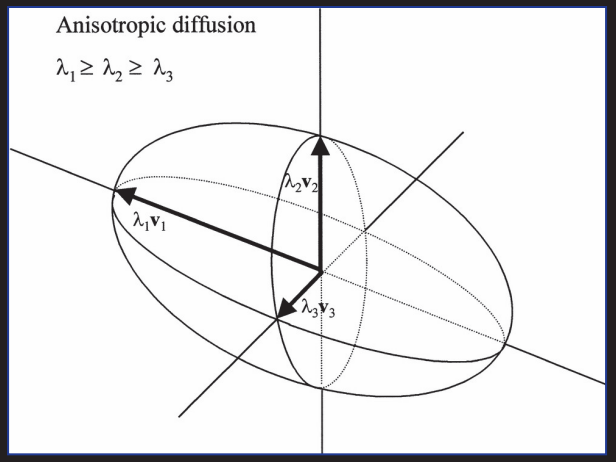
Add diffusion gradients

Courtesy Tim Roberts

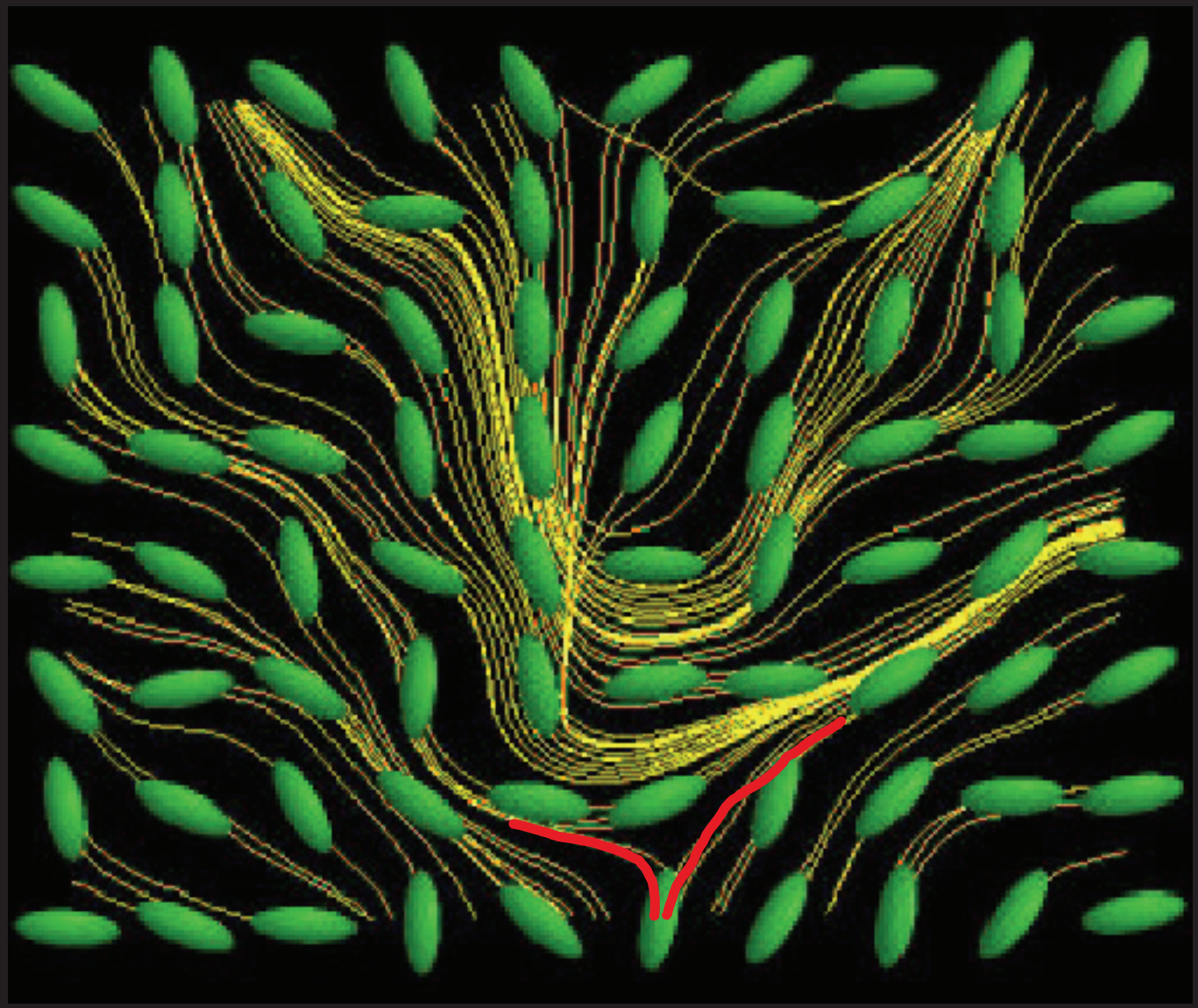
White Matter Diffusion



The diffusion tensor

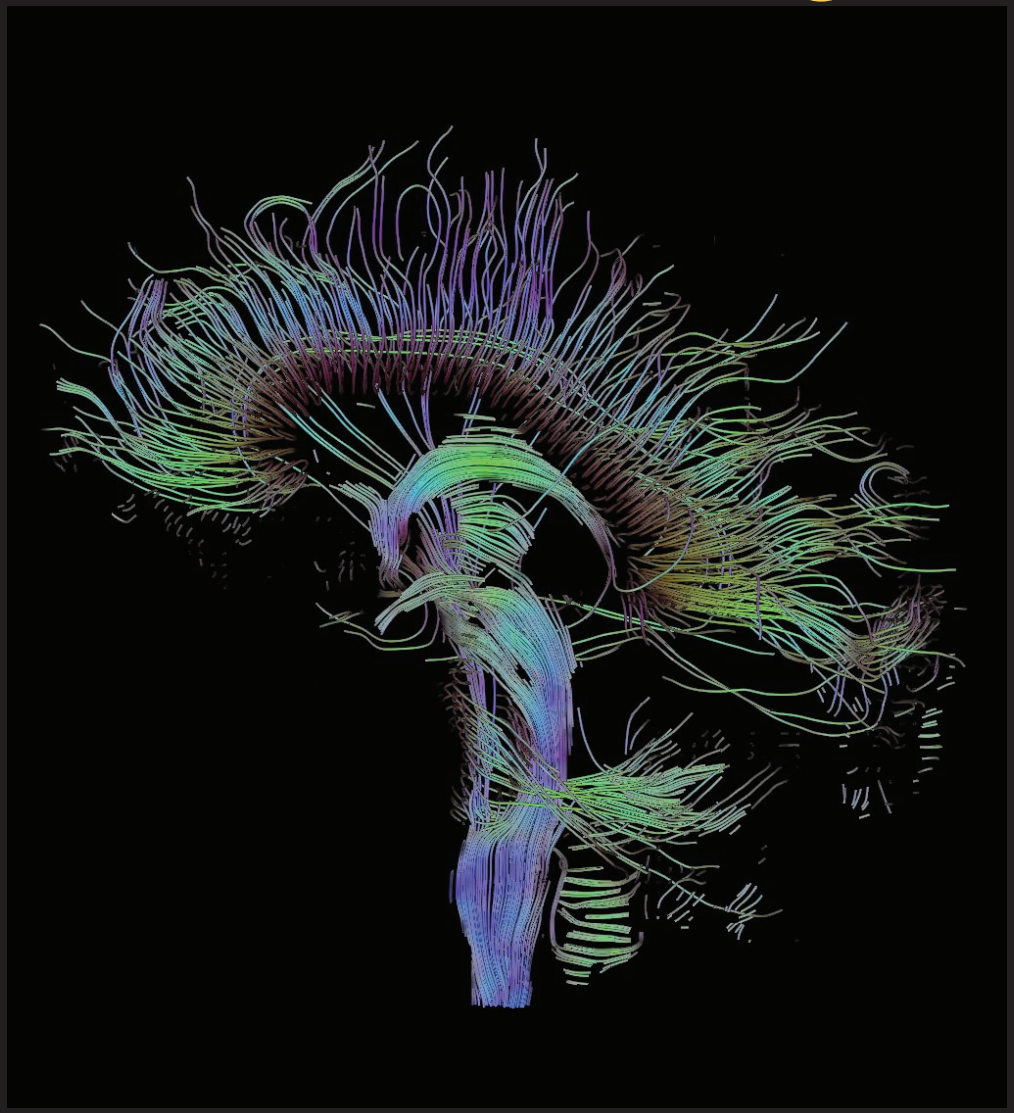


Wiegell M R et al. Radiology 2000;217:897-903

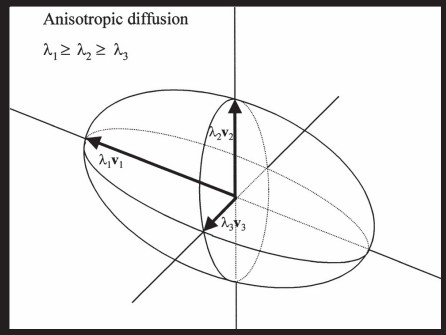


Deriche and Tschumperle (http://www.inria.fr)

Fiber Tracking



DTI Metrics

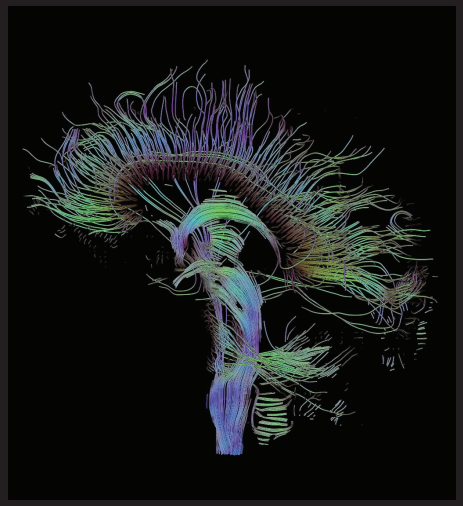


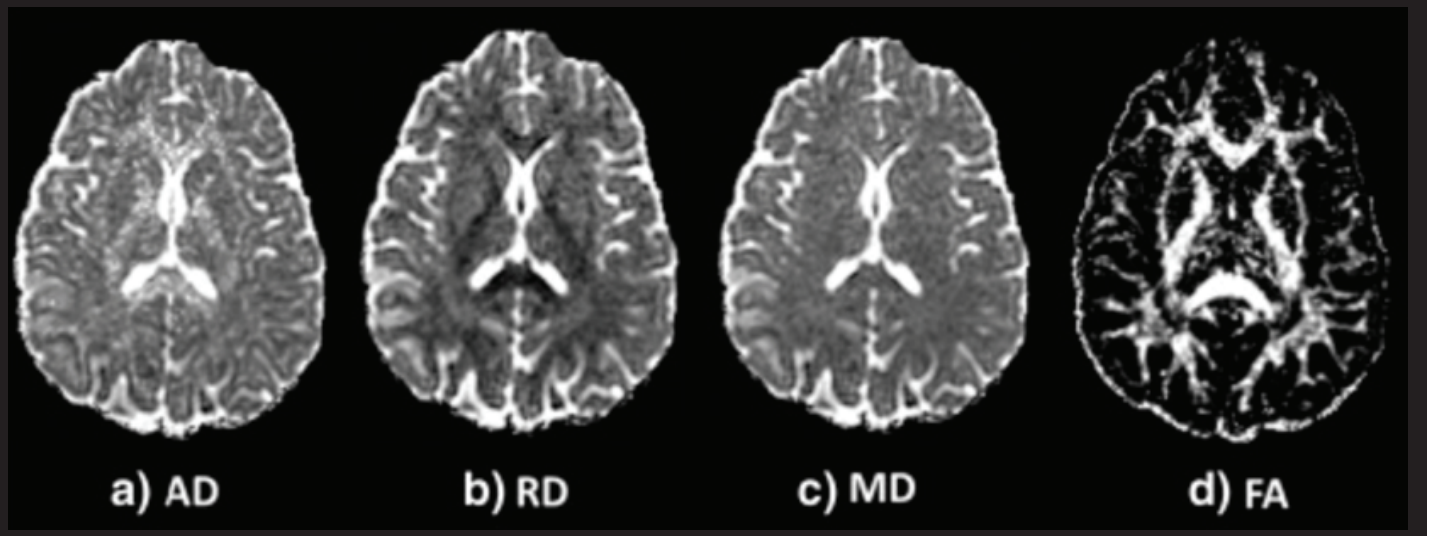
- Mean diffusivity (mD) = $(\lambda_1 + \lambda_2 + \lambda_3)/3$
  - Gliosis
- Radial diffusivity (rD) = $(\lambda_2 + \lambda_3)/2$
  - Demyelination
- Axial diffusivity (aD) = λ_1
  - Axonal disruption
- Fractional anisotropy
  - Sensitive to any axonal pathology
  - Describes the percent of the tensor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

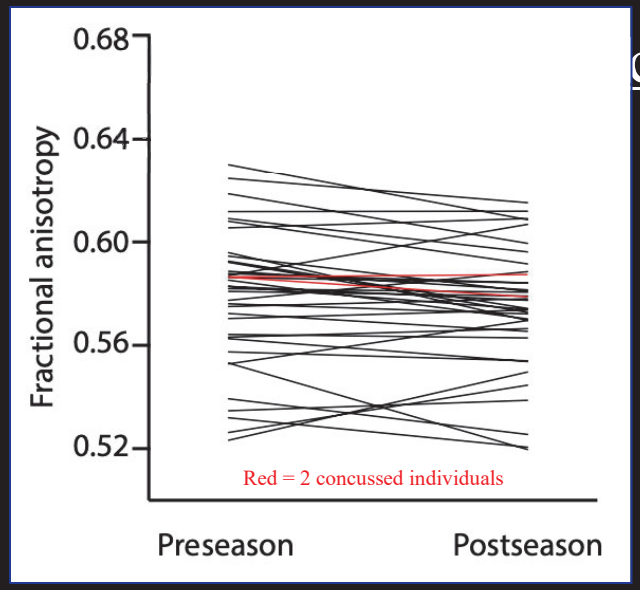
Metrics of Water Diffusion





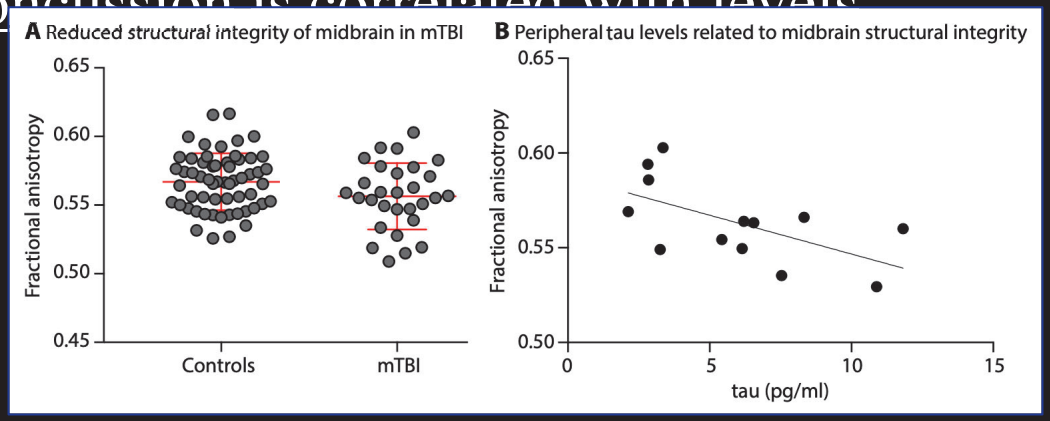
DTI: Sports Concussion

- Repetitive <u>sub-concussive</u> head impacts measured with helmet accelerometers
  - Decreased FA in midbrain CST over a single season of collegiate football
  - Decreased FA related to the amount of rotational force



Sub-concussion

concussion is correlated with levels



Concussion

Concussion and FA: Other studies

- Decreased FA:
  - Increased reaction time[1]
  - Reduced cognitive performance[2]
    - Executive planning and organization
- Increased axial and radial diffusivity but not FA

Niogi et al. *AJNR* 29, 967–973 (2008)
Miles et al. *Brain Inj.* **22**, 115–122 (2008)
Koerte et al. JAMA 308(18):1859–61 (2012)

Biphasic FA

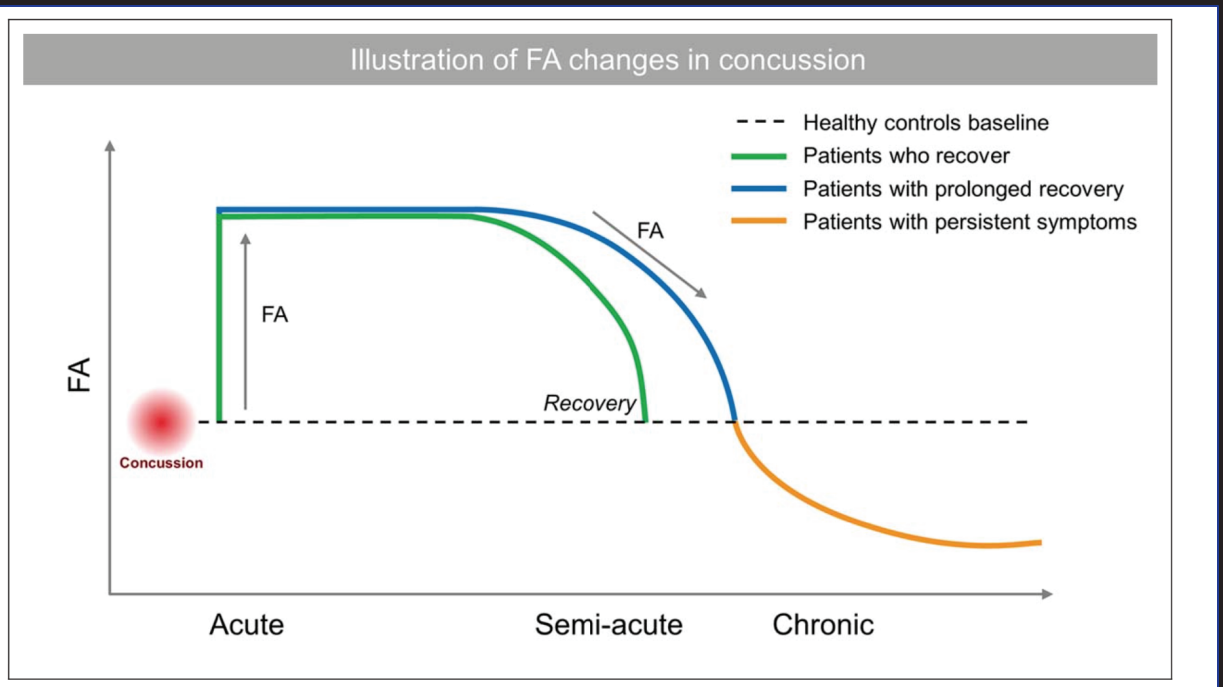
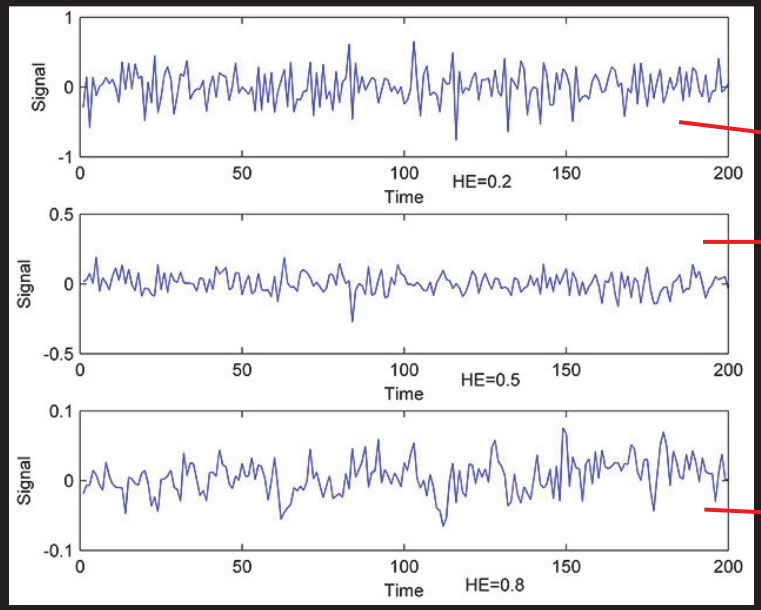
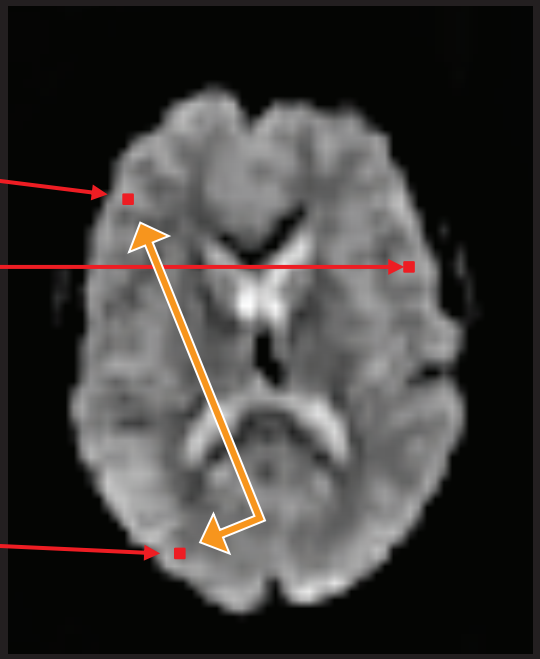


Fig.—Schematic illustration of potential changes in fractional anisotropy (FA) in patients with concussion. The black dotted line shows baseline FA in healthy controls. The green curve illustrates diffusion changes in patients who recover. It is presumed that after an initial increase in FA (during the acute phase of the concussion) FA begins to fall during recovery. In patients who have prolonged symptoms, the acute phase of increased FA might be prolonged (gray line). The orange line illustrates reduced FA during the chronic phase of concussion in patients with persistent post-traumatic symptoms.

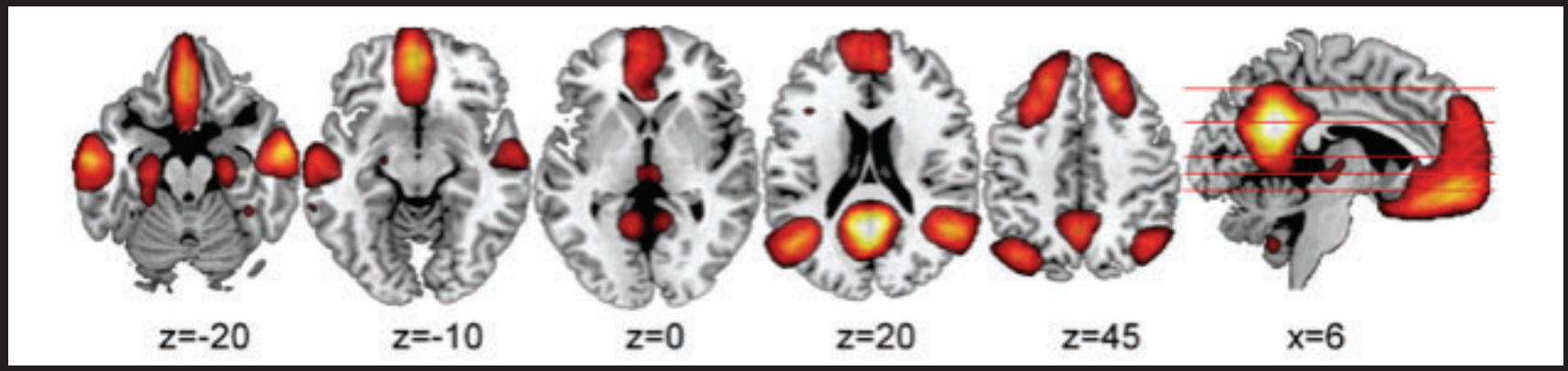
Chong CD, Schwedt TJ. Research Imaging of Brain Structure and Function After Concussion. Headache. 2018 Jun;58(6):827-835. doi: 10.1111/head.13269. Epub 2018 Feb 24. PMID: 29476532.

Resting State fMRI





- Measurement based on neurovascular coupling
- How well correlated voxels are to each other

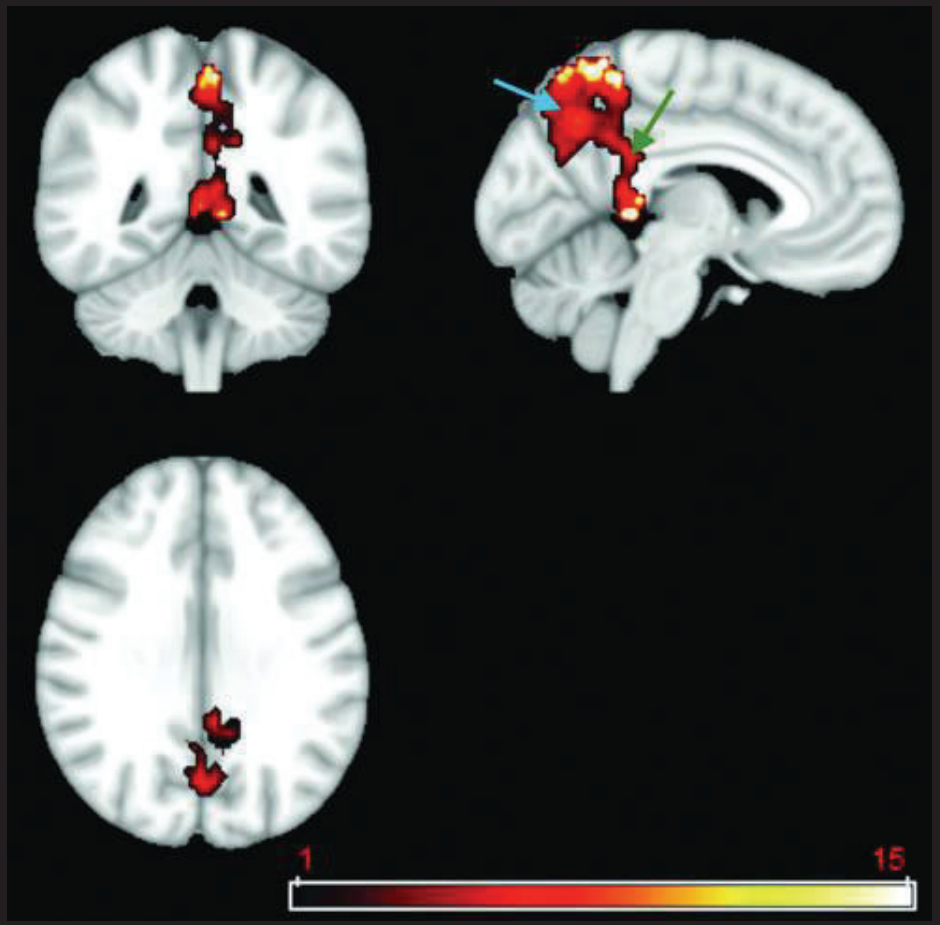

z=-20
z=-10
z=0
z=20
z=45
x=6

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

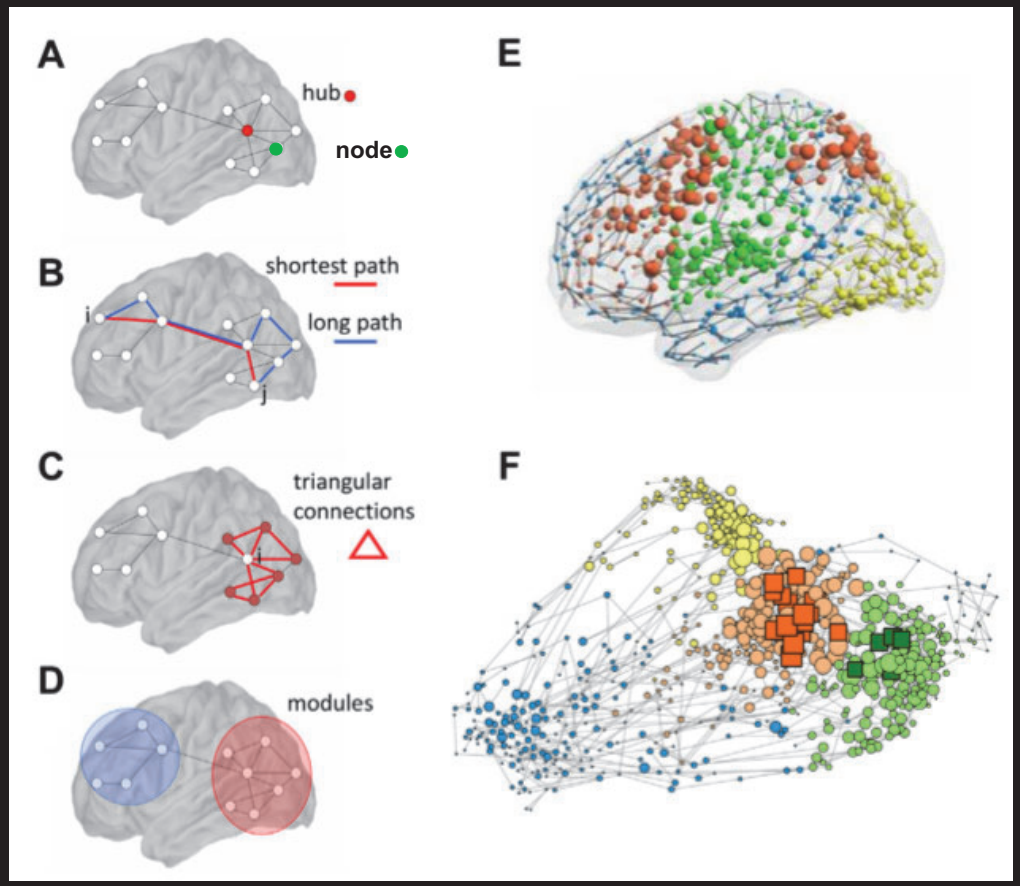
Resting State Functional Connectivity in Mild Traumatic Brain Injury at the Acute Stage: Independent Component and Seed-Based Analyses

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
- Group-level differences in the DMN showing reduced connectivity



Resting State - Graph theory



Functional “connectome” from resting state data

Clustering coefficient is a measure of the degree to which nodes in a graph tend to cluster together.

Morgan SE et al. PubMed PMID: 29703679.

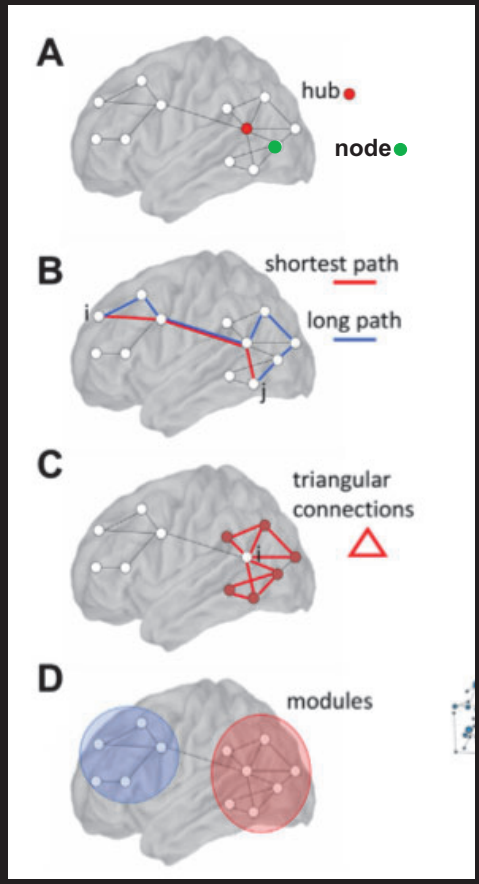
Concussion Connectome Meta-Analysis

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*

- 10 studies included in a random-effects meta-analysis of global graph metrics examining the confounding effects of severity and time since injury
- Higher values of a normalised clustering coefficient and a longer characteristic path length in TBI patients compared with healthy controls.
- Graph metrics may be useful markers of neurocognitive dysfunction in TBI



"We conclude that the pattern of change revealed by our analysis should be used to guide hypothesis-driven research into the role of graph metrics as diagnostic and prognostic biomarkers."

From imaging water to other molecules

- Molecular imaging
  - SPECT or PET imaging
    - Radiopharmaceuticals applied to detect emitted radiation for assessing tissue structure and function
    - Radioactive tracers target specific molecules and biological pathways
  - Advantage of SPECT/PET:
    - Can detect very low levels of a target

https://essay.biz/article/molecular-imaging

european journal of neurology
the official journal of the european academy of neurology

Original Article | Full Access

Volume 26, Issue 12
December 2019
Pages 1426-1432

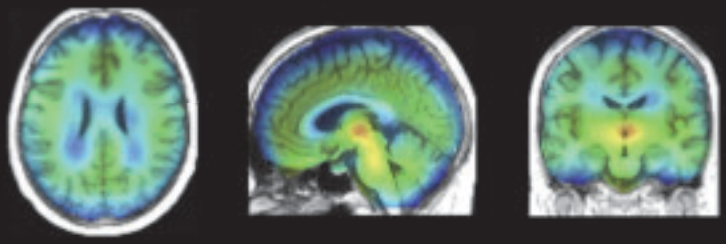
Molecular imaging of neuroinflammation in patients after mild traumatic brain injury: a longitudinal ^{123}I-CLINDE single photon emission computed tomography study

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

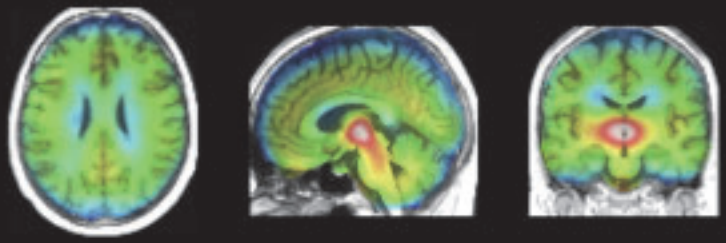
First published: 19 April 2019 | https://doi-org.myaccess.library.utoronto.ca/10.1111/ene.13971 |

- In general imaging with radioactive tracers has higher sensitivity to tissue abnormalities than MRI
- SPECT imaging using ^{123}I-CLINDE tracer
  - Binds translocator protein that is upregulated in active microglia.
- Patients with and without post concussion syndrome (PCS) at 3-4 months also had increased uptake but to a lesser degree

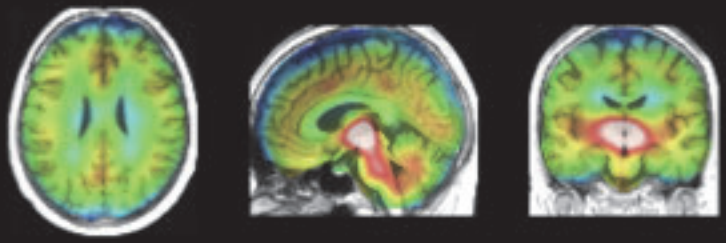
12 controls



7 patients 1-2 weeks post injury

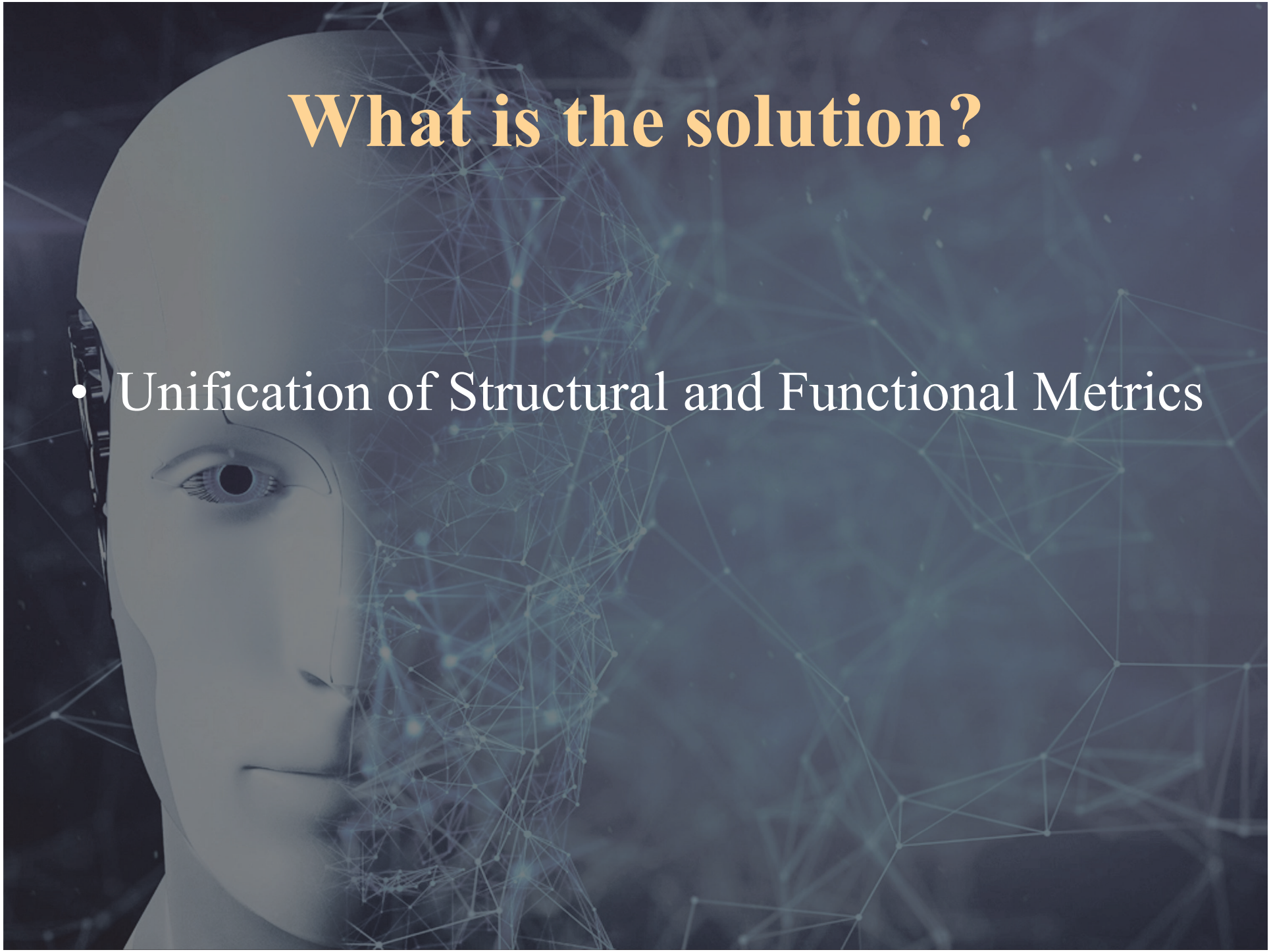


6 patients with PCS 3-4 months post injury



Functional imaging common theme:

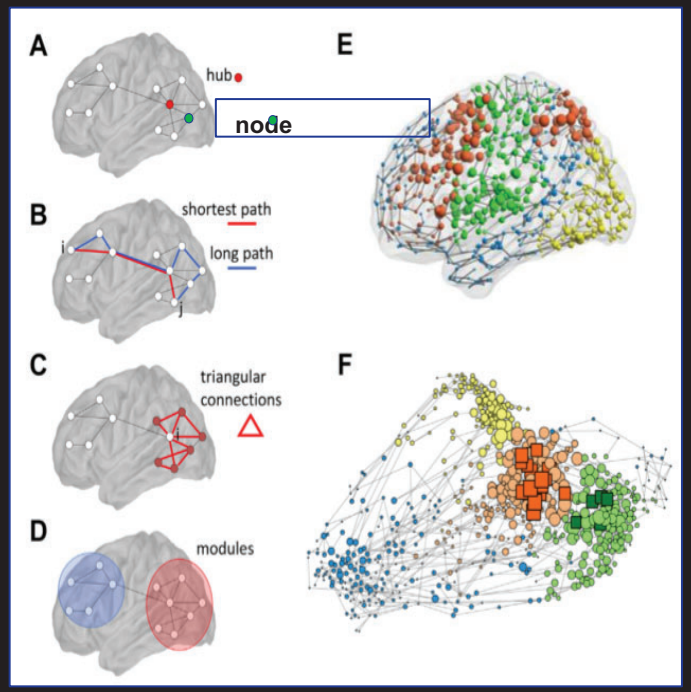
- Despite highly advanced imaging and sophisticated image analysis:
  - Group level diagnosis possible
  - Single subject diagnosis remains elusive



What is the solution?

- Unification of Structural and Functional Metrics

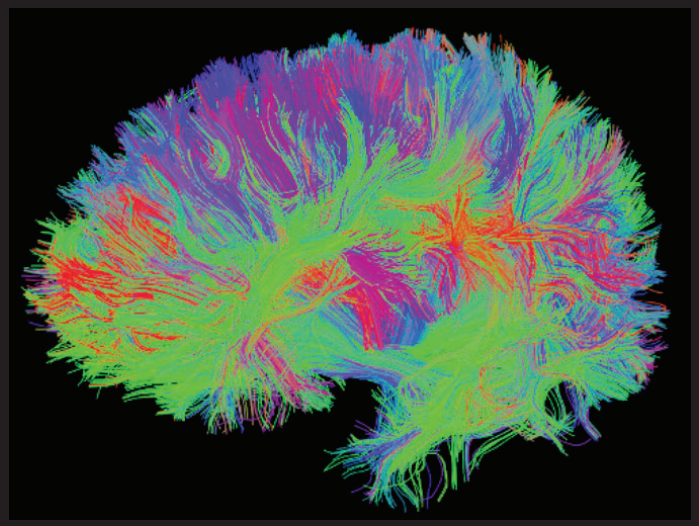
Unification of Structure with Function: Fingerprints of Invisible Disease



Functional connectome from resting state data

Morgan SE et al. PubMed PMID: 29703679.

Connecting the connectomes!

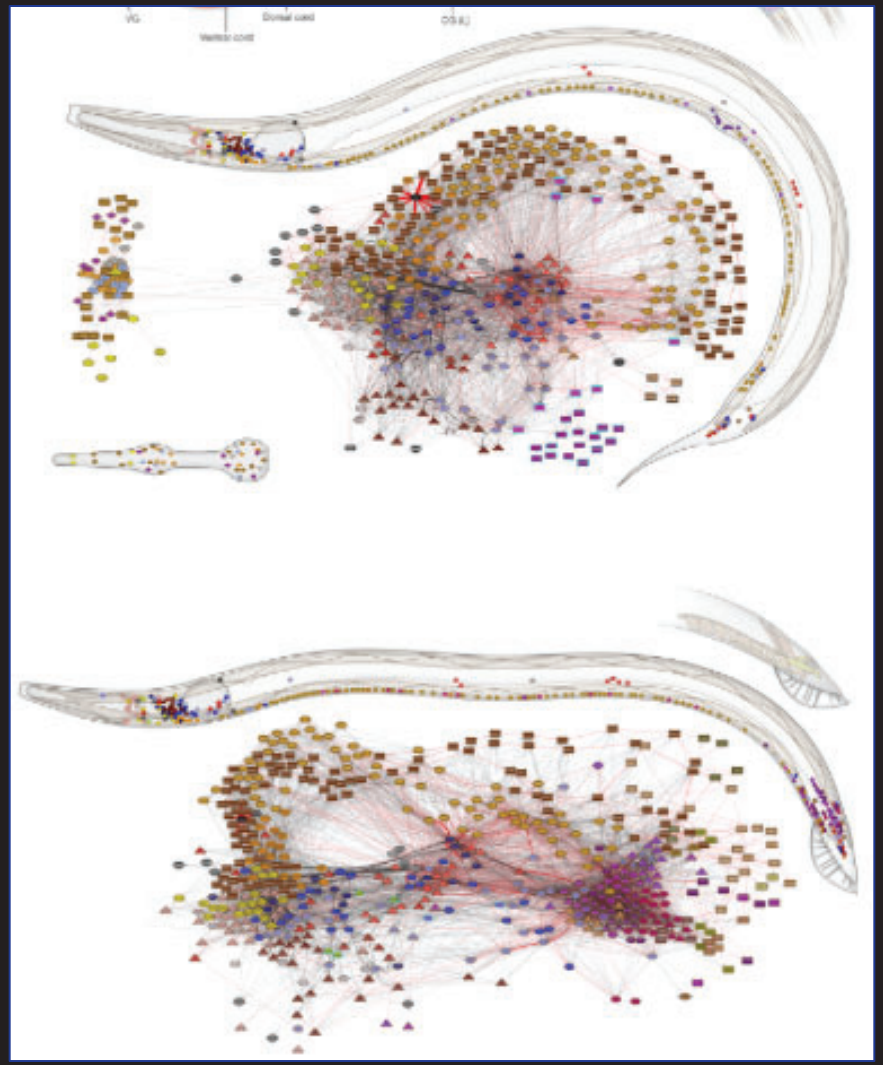


Structural connectome from diffusion data

Human Connectome Project– Harvard/Wash U/USC

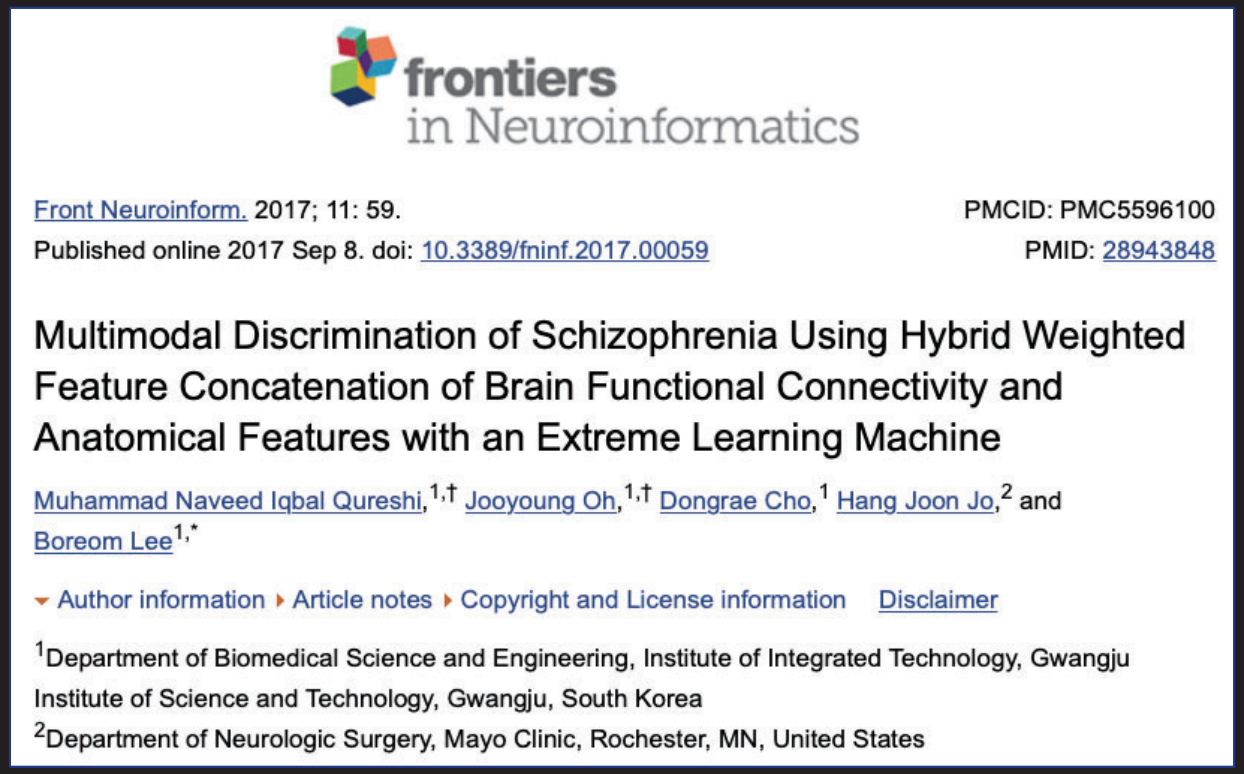
We have succeed in …..

Nematode C. Elegans Connectome



Role of Artifical Intelligence

Glimpse of the Future: Imaging ***Diagnosis*** of Invisible Disease



frontiers in Neuroinformatics

Front Neuroinform. 2017; 11: 59.
Published online 2017 Sep 8. doi: 10.3389/fninf.2017.00059
PMCID: PMC5596100
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,*]

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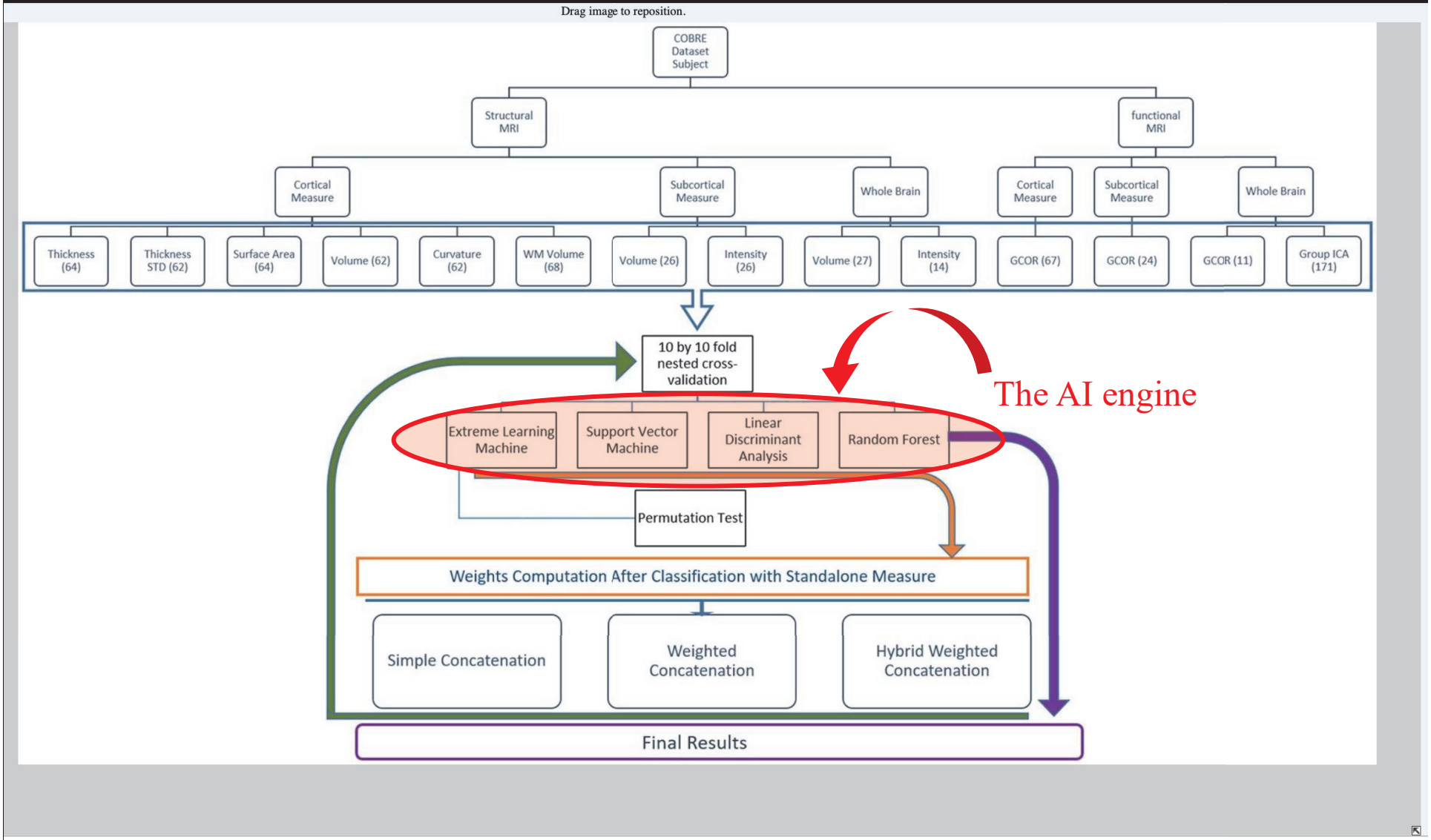
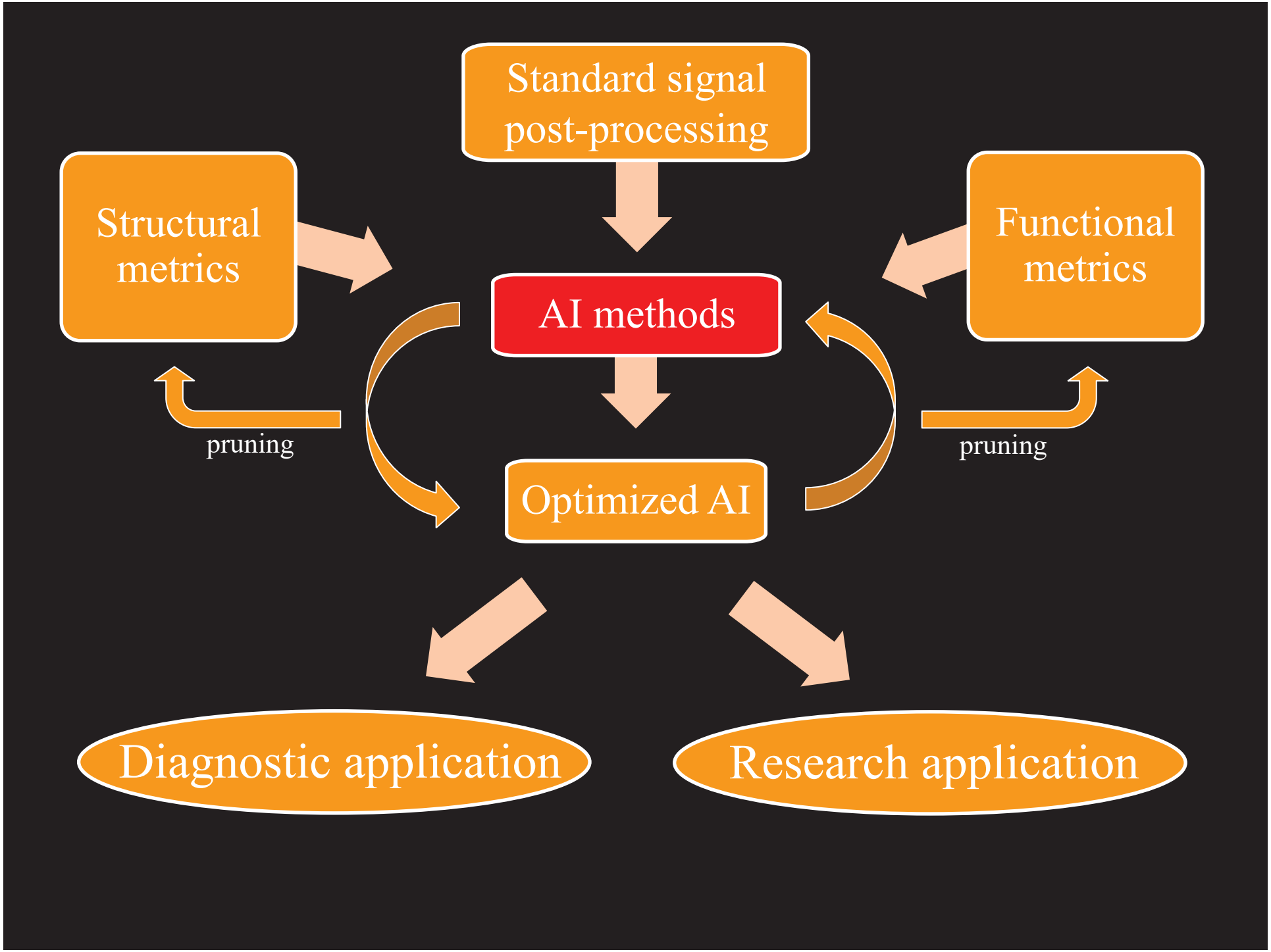


Qureshi MNI et al. Front Neuroinform. 2017 Sep 8;11:59. doi: 10.3389/fninf.2017.00059. PMID: 28943848; PMCID: PMC5596100.

Glimpse of the Future: 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.


Standard signal post-processing
Structural metrics
Functional metrics
AI methods
pruning
pruning
Optimized AI
Diagnostic application
Research application

› 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

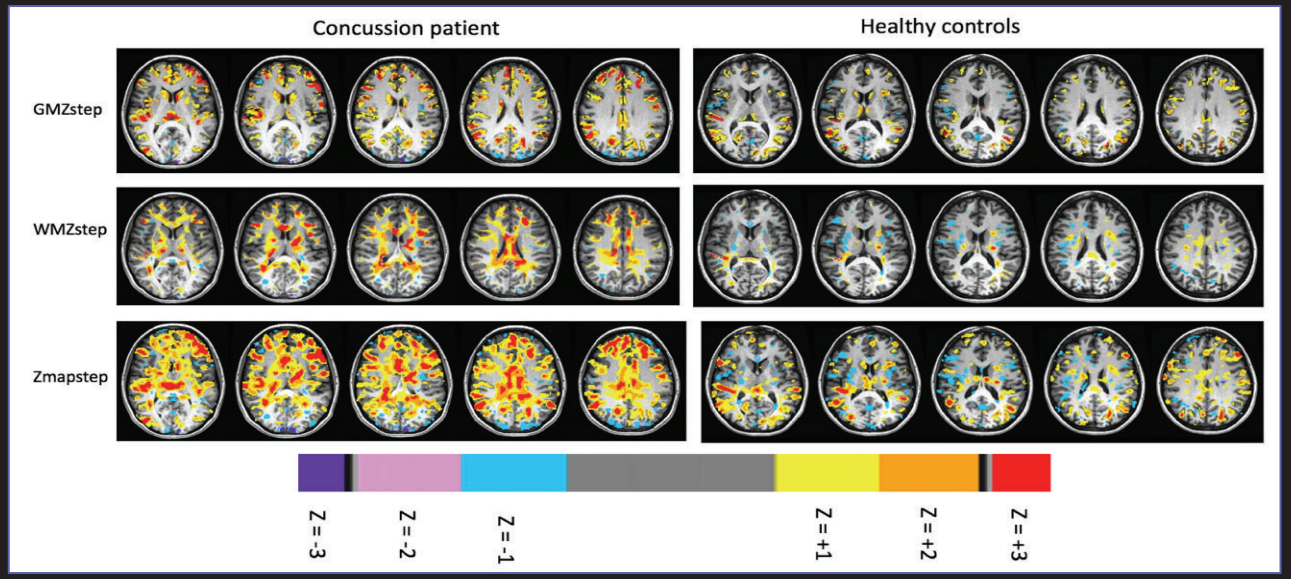
Reema Shafi [1], Julien Poublanc [1], Lashmi Venkatraghavan [2], Adrian P Crawley [1], Olivia Sobczyk [1], Larissa McKetton [1], Mark Bayley [3], Tharshini Chandra [3], Evan Foster [3], Lesley Ruttan [4 3 5], Paul Comper [6 3], Maria Carmela Tartaglia [7 8 9 5], Charles H Tator [10 5], James Duffin [2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

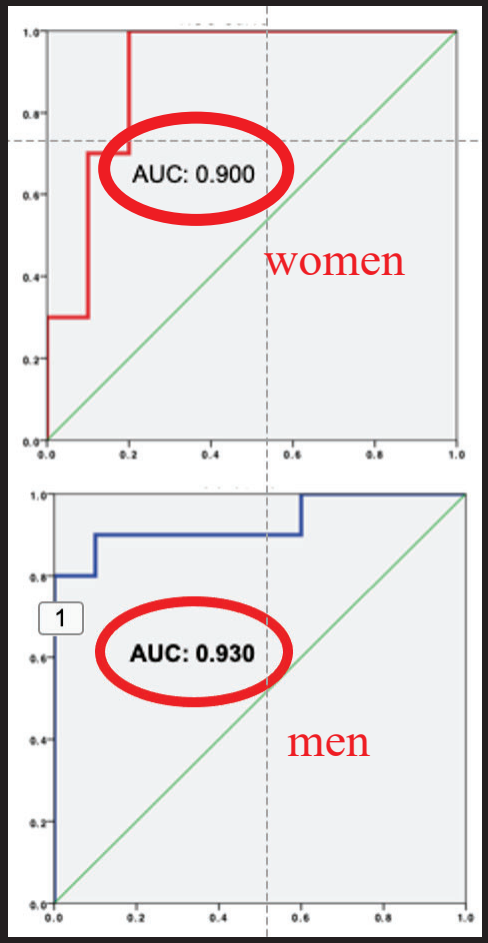
Affiliations + expand

PMID: 33096952 DOI: 10.1089/neu.2020.7272

Vascular Performance Metrics

- Response to a vasodilatory stimulus:
  - Speed
  - Magnitude
- Subjects within 1 week of concussion
- Individuals compared to a control atlas





Persistence of Symptoms

- Link between injury metrics and certain symptoms is reasonably established e.g. reaction time and cognitive function with axonal injury.
- The cause of other other persistent symptoms such as headache are unknown
- “Further longitudinal studies are critically needed if we are to elucidate the neurobiological underpinnings of the long-term pathophysiology of sports concussion*

* Henry et al. Neuroscientist. 2017 Oct;23(5):567-57. Epub 2016 May 17. PMID: 27188455


Thank you!