Diagnostic Approaches to CTE Evaluation

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Motivation for a Diagnostic Approach to CTE evaluation

- Reports suggest that CTE pathology will often originate years to decades prior to death
- Currently CTE remains a post-mortem diagnosis
- The ability to determine CTE diagnosis is incredibly invasive and not translatable in its present form for in-vivo evaluation
- Non-invasive/minimally-invasive medical diagnostics have the appeal of allowing for indirect examination of the brain and have been identified as a potential candidate biomarker for in life screening
- Question remains – Are there imaging approaches that are sensitive and specific to CTE?
  - Challenge: Lots of pathological overlap with AD, PD, ALS, Lewy Body Dementia, Progressive Supranuclear Palsy, Pick's disease, Corticobasal degeneration, Frontotemporal dementia, etc
  - Recent efforts suggest there are anatomical specificities to these disease that can aid in differentiating one from another but some are also found co-morbid with CTE (eg CTE-MND)

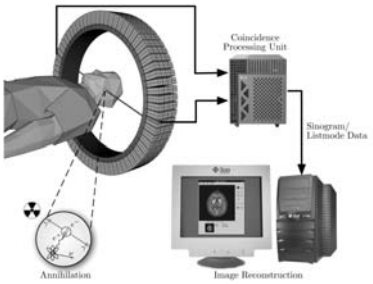
Current Imaging Approaches for CTE Evaluation

- The two most prevalent technologies currently under development for potential evaluation of CTE are PET and MRI
- To date, there is NO validated imaging method for CTE evaluation
  - Only current FDA approved tool for brain injury clinical trials is Computed Tomography
  - MRI is 'still' under review for as a detection method for 'conventional imaging' of pathoanatomical lesions…..
- BUT incredible progress has been made in advancing this application of medical diagnostics with promising candidates on the horizon

Introduction to PET Imaging

Positron Emission Tomography (PET)

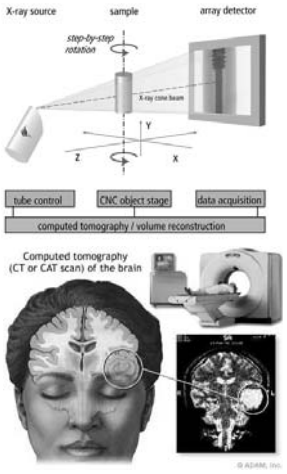
- PET is a nuclear medicine technique that produces 3D maps of functional processes in the human body
- System detects gamma ray pairs emitted by a tracer (positron-emitting radionuclide)
- Tracers are given prior to scan via injection
  - These are biologically active molecules
- Images of tracer concentration in different regions a in 3D space are then reconstructed by a computer analysis algorithm.
- This reconstruction is often done with the aid of a CT scan (now some w/ MRI) set done prior to the PET scan for registration.



Computed Tomography (AKA: Cat Scan)

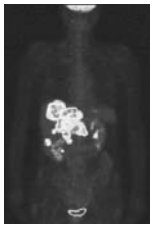
Computed Tomography

- CT is similar to X-Ray
- Like X-Ray, it's a form of radiation directed at the body
- Different body parts and tissue absorb x-rays at varying degrees
- X-Ray: Small burst of radiation passes through the body & signal is recorded on film
- CT: Many bursts of x-ray beams rotate around the body & signal is measured by a computer
  - Special program reconstructs information to make 3D image which is displayed on a monitor
- PRO: CT is very fast (large body sections can be scanned in a few seconds)
  - Important for children, elderly and critically ill
- CON: Very low resolution when it comes to brain.
  - Only basic information can be gained (i.e. blood, tumor, etc)

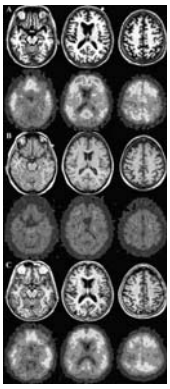


PET Applications

- Applications:
  - Cancer Detection, Progression & Treatment
  - Blood flow to heart muscle
  - Myocardial Infarction & assess cardiac tissue damage
  - Brain abnormalities: tumors, memory disorders, seizures, CNS disorders and Neurodegenerative Disease
  - Map brain & heart function
- PRO: Specificity to molecular binding unmatched by other methods, Functional information about biological systems
- CON: Very expensive, Time Consuming, False Positives, Timing is everything due to decay rate of radio-active molecules, Pt must be on time and in fairly stable condition

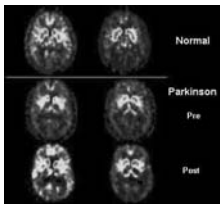


Neurodegenerative Disease

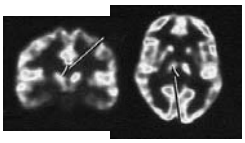


Carbon 11-PIB binding to Aβ plaques in patients with Alzheimer's Disease.

Fagan et al: In Vivo Amyloid and CSF A42



18-flurodopa binding images of Parkinson's Patient compared to Control assessing the functional state of the nigrostriatal dopaminergic pathway



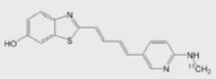
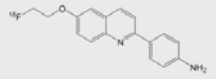
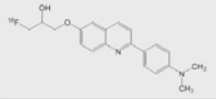
FDG binding images of Patient with Traumatic Brain Injury for neurometabolism

21-year-old male riding as an unrestrained passenger in a vehicle struck by a 10-wheel coal truck. FDG imaging revealed hypometabolic activity in the right thalamus.

PET Ligands Specifically for CTE (Current Status)

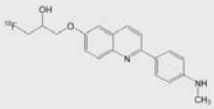
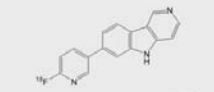
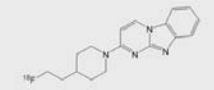
- Current Molecular Challenge: There are multiple Tau Isoforms and its an intracellular protein so any ligand must cross cell membrane, but both Aβ and tau have beta sheet structure so the challenge is to design a selective tau agent that does NOT bind to Aβ or any of its isoforms.
- Current Disease Challenge: Multiple tauopathies (Progressive Supranuclear Palsy, AD, etc) – ligands don't care 'where' the molecule is, just that it is present
- Strategy for Resolution: Use tau ligand with Aβ ligand and others for comparison/subtraction and knowledge of regional anatomical propensity of CTE vs. other tau disease states to increase specificity of findings specially for 'tau pathology of the CTE-like type'

Potential Candidates

Ligand	Structure	Affinity for Tau [nM]	Specificity for Tau relative to Aß	Mouse brain uptake at 2 min [%ID/g]	Mouse brain washout (2min/ 30 min)
^{11}C-PBB3[16]		K_{i1}=2.5* K_{i2}=100	40-to-50-fold	NA	NA
^{18}F-THK523[13, 15]		K_{i1}=1.99† K_{i2}=50.7	15-fold	2.72	1.9
^{18}F-THK5105[17]		K_{i1}=1.45† K_{i2}=7.40	25-fold	9.2	2.6

*K_d determined by ligand-binding to Tau-positive human brain sections
†K_d determined by ligand-binding to Tau-fibrils
‡K_i determined by competitive inhibition of ^{18}F-THK5105 to Tau-fibrils
§ 2.5 min; ‖ washout 2.5 min/20 min
NA= Not available; N.B. The affinity values for various ligands are generated from different types of experiments and may not always be directly comparable.

Shah M, **Catafau** AM J Nucl Med. 2014 Jun;55(6):871-4.

Ligand	Structure	Affinity for Tau [nM]	Specificity for Tau relative to Aß	Mouse brain uptake at 2 min [%ID/g]	Mouse brain washout (2min/ 30 min)
^{18}F-THK5117[15]		(K_i=10.5)‡	(NA)	6.06	10.3
^{18}F-T807[18]		K_d=14.6*	>25-fold	4.16	6.7
^{18}F-T808[17]		K_d≈22*	27-fold	6.7§	2.9‖

*K_d determined by ligand-binding to Tau-positive human brain sections
†K_d determined by ligand-binding to Tau-fibrils
‡K_i determined by competitive inhibition of ^{18}F-THK5105 to Tau-fibrils
§ 2.5 min; ‖ washout 2.5 min/20 min
NA= Not available; N.B. The affinity values for various ligands are generated from different types of experiments and may not always be directly comparable.

Shah M, **Catafau** AM J Nucl Med. 2014 Jun;55(6):871-4.

And the Tau Ligand List is Growing…

- None to date have been clinically validated and/or approved by the FDA
- Recently 'bad press' for FDDNP, an early potential candidate developed for Aβ that showed preliminary promise for tau
- Current focus is on Validation:
  - Reliable
  - Repeatable
  - Sensitive
  - Specific
  - Standardized

SUNDAY, APRIL 26, 2015

FDA says no to marketing FDDNP for CTE

The U.S. Food and Drug Administration recently admonished TauMark™, a brain diagnostics company, for advertising brain scans that can diagnose chronic traumatic encephalopathy (CTE), Alzheimer's disease, and other types of dementia. The Los Angeles Times reported that the FDA ordered UCLA researcher Dr. Gary Small and his colleague/business partner Dr. Jorge Barrio to remove misleading information from their company website (example shown below).

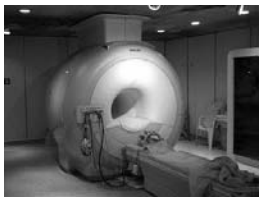
http://neurocritic.blogspot.com/2015/04/fda-says-no-to-marketing-fddnp-for-cte.html

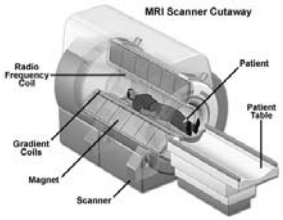
Introduction to Magnetic Resonance Imaging (MRI)

Strategies for 'CTE' ~ TBI Pathology

Magnetic Resonance Imaging

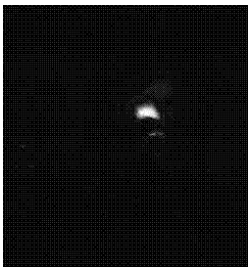
- Based on Nuclear Magnetic Resonance or NMR (name change due to cold war & atomic bombs)
- Discovered by Felix Bloch and Edward Purcell independently in 1946
  - Awarded Nobel Prize in Physics in 1952
- Raymond Damadian showed normal tissue signal different from tumor signal in 1971
- Richard Ernst demonstrated Fourier Transformed Phase & Frequency encoding of MR signal
  - Awarded the Nobel Price in Chemistry 1991
  - Foundation of how MRI is performed today

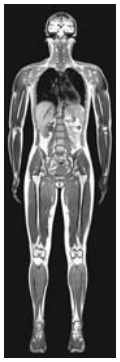




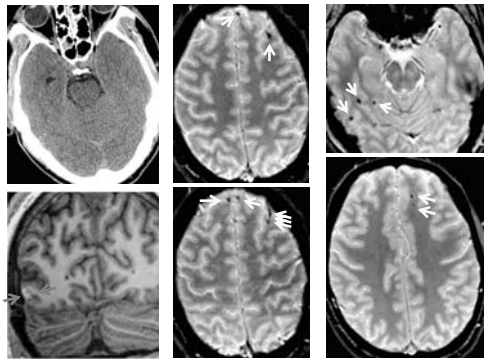
MRI : Basics

- MRI uses magnets NOT radiation like x-ray or CT
- This technique utilizes the water molecules in the human body

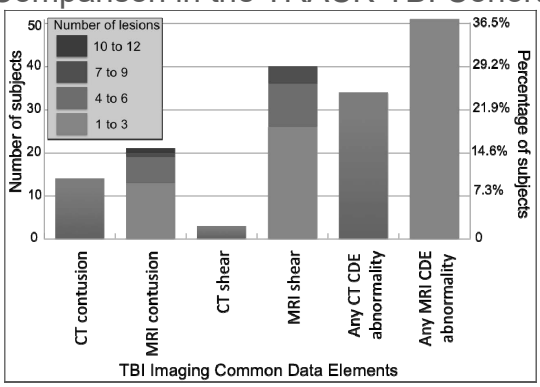




Sensitivity to Brain Injury Pathology (CT vs MRI)



Comparison in the TRACK-TBI Cohort



MRI consistently identified greater lesion load than CT
In addition 1/4 with negative CT have positive MRI

Courtesy of Dr. G Manley, TRACK-TBI Study

Table 3. Multivariate ordinal logistic regression of 3-month GOS-E upon clinical, demographic, socioeconomic, CT, and MRI predictors

Model	Covariates	Multivariate odds ratio of covariate	Overall model significance	Cox and Snell pseudo-R^2	Nagelkerke pseudo-R^2
Model 1. Clinical and demographic/ socioeconomic predictors only	Prior TBI resulting in acute medical evaluation	1.8 (p=0.10)	p=0.005**	9.5%**	10.2%**
	Adults ≥19 y.o. with less than diploma/G.E.D.	2.6 (p=0.09)			
	Unemployed	2.4* (p=0.04)			
Model 2. Clinical, demographic/ socioeconomic, and CT predictors	Prior TBI resulting in acute medical evaluation	2.0 (p=0.07)	p = 0.0006***	14.4%***	15.3%***
	Adults ≥19 y.o. with less than diploma/G.E.D.	2.7 (p=0.08)			
	Unemployed	2.6* (p=0.03)			
	CT: Subarachnoid hemorrhage	3.5* (p=0.01)			
Model 3. Clinical, demographic/ socioeconomic, CT, and MRI predictors	Prior TBI resulting in acute medical evaluation	2.0 (p=0.06)	p = 0.00005****	20.6%%****	21.9%****
	Adults ≥19 y.o. with less than diploma/G.E.D.	3.2* (p=0.05)			
	Unemployed	2.9* (p=0.02)			
	CT: Subarachnoid hemorrhage	1.3 (p=0.70)			
	MRI: ≥1 contusion	4.5** (p=0.01)			
	MRI: ≥4 foci shear	3.2* (p=0.03)			

Yuh, et al, Ann Neurol, 2013

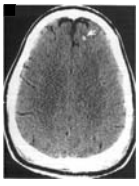
Motivation for Advanced MR Methods for CTE

- 'Best Guess' – At present – Repeated head injury is a potential instigator of CTE like pathology
- Strategy: Could we 'work backwards' and seek to identify early, subtle changes in the brain that ultimately lead to this tau pathology?
- Axonal damage is a major pathophysiological process following brain injury
  - Possibly a primary cause of adverse neurological outcome
- Current clinical imaging modalities have been optimized for the visualization of hemorrhage and ischemia but are inadequate for direct assessment of axonal injury and neuroinflammation
- Most commonly acquired method – CT – provides very limited information
- More advanced methods like Diffusion Tensor Imaging may be more sensitive to changes following brain injury and provide us new insight into underlying progression towards CTE.

Example: Axonal Injury

(Comparison of imaging methods)

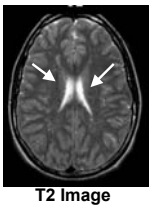
Imaging and Injury



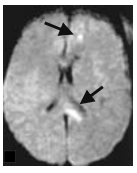
CT Image

- CT recognizes punctate hemorrhage *associated* with axonal injury due to shearing of blood vessels
- T2-weighted MRI recognizes edema again *associated* with axonal injury due to energy failure or breakdown of blood brain barrier
- T2* MRI recognizes small areas of hemorrhage again due to the shearing of blood vessels with much higher sensitivity than CT
- Diffusion weighted MR imaging (DWI) recognizes global movement of water in areas of ischemia *associated* with axonal injury

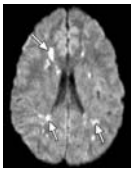
NONE OF THESE TECHNIQUES DIRECTLY ASSESS INJURED AXONS



T2 Image



Inverted T2* Image



DWI Image

Diffusion Tensor Imaging (DTI)

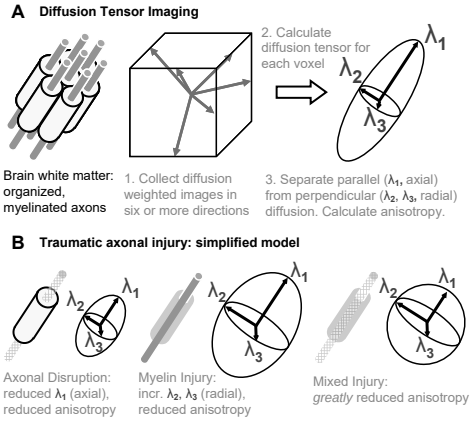


Figure adapted from M. Budde

Injury vs. Imaging Parameter

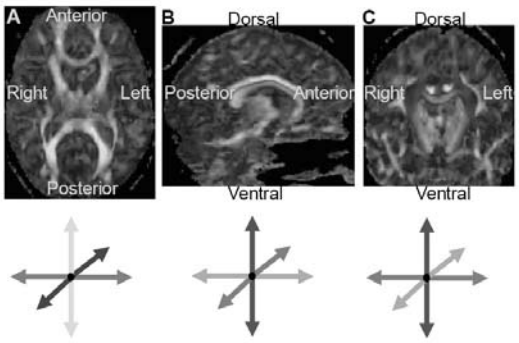
Injury Type	RA/FA	MD <D>
Axonal Injury	↓	↓
Myelin Injury	↓	↑
Mixed Injury	↓↓	↓↑

$$FA = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_1-\lambda_3)^2+(\lambda_2-\lambda_3)^2}}{\sqrt{(\lambda_1^2+\lambda_2^2+\lambda_3^2)}}$$

$$\langle D\rangle = \frac{(\lambda_1+\lambda_2+\lambda_3)}{3}$$

$$RA = \sqrt{\frac{(\lambda_1-\langle D\rangle)^2+(\lambda_2-\langle D\rangle)^2+(\lambda_3-\langle D\rangle)^2}{\sqrt{3}\langle D\rangle}}$$

DTI Color Orientation ➡ Information



Inclusion of Advanced Neuroimaging

LINEAR REGRESSION OF RIVERMEAD POSTCONCUSSIVE QUESTIONNAIRE (RPQ-13) ON PREDICTORS

Predictor	Categories (number of patients)	Linear regression B (95% CI, p-value)	Adjusted R^2	
Any MRI T2* hemorrhagic axonal injury	Yes (9) No (21)	7.3 (1.01-13.5, p=0.02)	13.8%	
DTI axonal injury present	Yes (7) No (23)	8.2 (1.4-14.9, p=0.02)	15.2%	
Any conventional MRI traumatic brain lesion	Yes (12) No (18)	9.7*** (4.5-14.9 p = 0.0007)	31.7%	31%
Any conventional MRI and/or DTI traumatic brain lesion	Yes (13) No (17)	10.1*** (2.4-8.9, p = 0.0003)	36.1%	36%

<u>Take Home</u>:

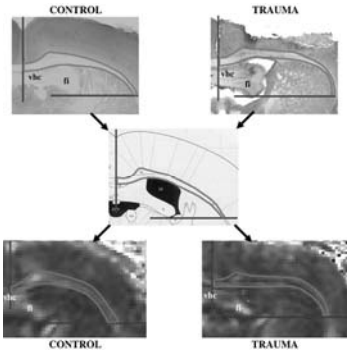
Multivariate Approach Will Yield Best Result

Yuh, et al, J Neurotrauma, 2014

DTI Assessment of an Experimental Model of TBI

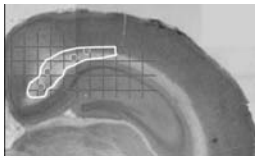
(Supportive Evidence for Validation)

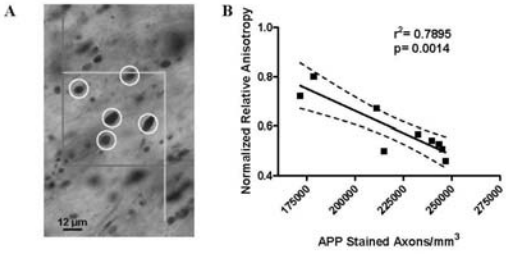
DTI Validation in a Mouse Model of Brain Injury



Mac Donald et al, Exper. Neurol 2007

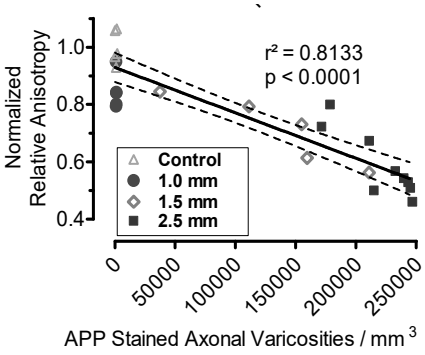
Stereological Quantification of Axonal Injury





Mac Donald et al, Exper. Neurol 2007

Correlation with Axonal Injury Severity



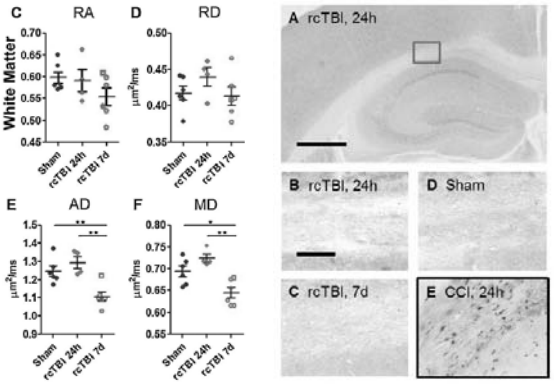
Change in Relative Anisotropy accurately reflects injury severity.

For the least severe injuries, (1.0 mm) DTI may be more sensitive than APP immunohistochemistry.

Further investigation of these least severe injuries is warranted.

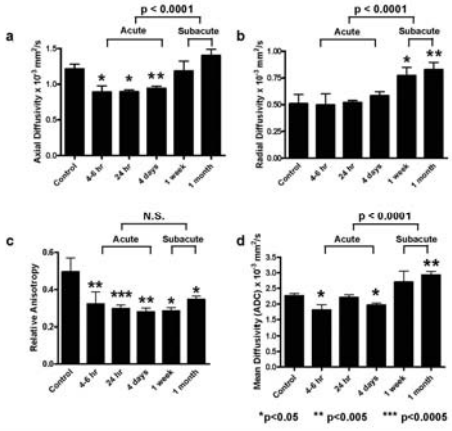
Brody, Mac Donald & Shimony, Handbook of Clinical Neurology, 2015

Results Replicated in a Repetitive Concussive TBI model



Bennett, Mac Donald, Brody, Neurosci Let, 2012

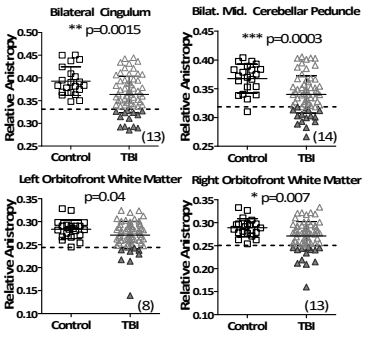
DTI Sensitivity Over Time



Mac Donald et al, J Neuroscience 2007

Human Brain Imaging Translating what we have learned from 'Mouse to Man'

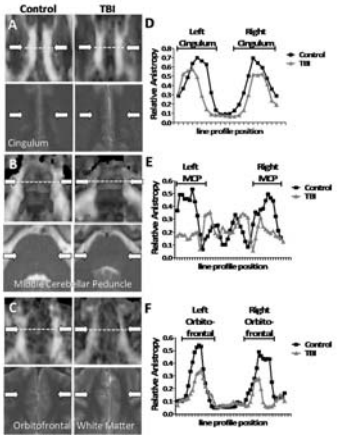
DTI Abnormalities following Concussive TBI (When CT and Conventional MRI were Normal)



Dashed lines indicated 2 SD below mean control

Mac Donald et al, NEJM 2011

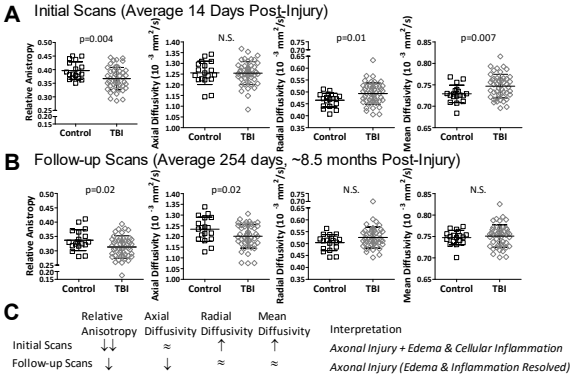
Comparison of DTI to Conventional MRI



Results are useful even on a single subject level.

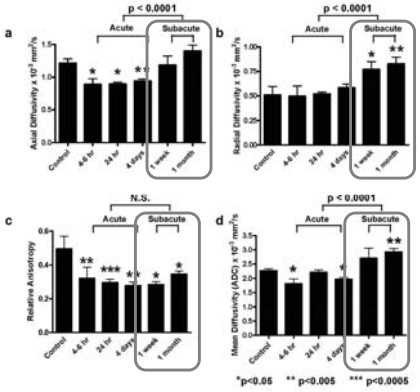
Mac Donald et al, NEJM 2011

Follow-up Scans 6-12 Months Later: Evolution, not Resolution of DTI Abnormalities



Mac Donald et al, NEJM 2011

Similar Findings in Preclinical Models of TBI – Cautious Success in Translation of Imaging Method



Human Study
1 week – 1 month:

≈ Axial Diffusivity

⇧ Radial Diffusivity

⇩ Relative Anisotropy

⇧ Mean Diffusivity

Mac Donald et al, J Neuroscience 2007

Post-Mortem DTI of Human Brain Tissue

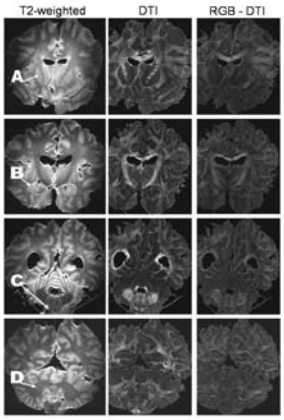
Coming Full Circle with One of the Original Motivations of Experimental Brain Injury Models

Direct Comparison with Injury Pathology

High Resolution DTI of Excised Human Brain

Image Voxel Size: 0.75 x 0.75 x 0.85 mm

Standard 3T Clinical Voxel Size for Reference: 2 x 2 x 2 mm



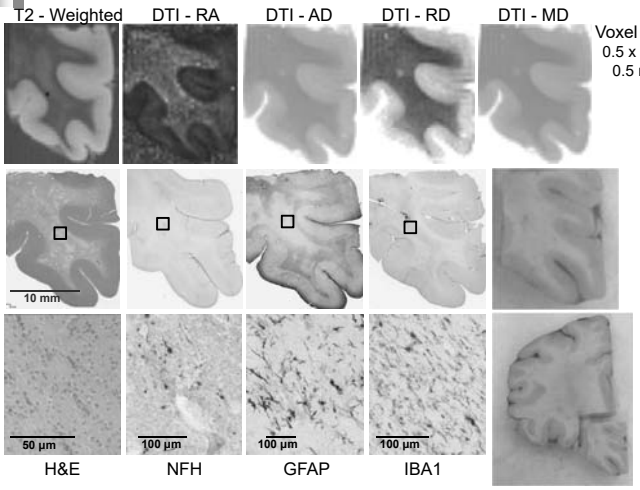
A – Interdigitated white and grey matter anterior limb of internal capsule

B- Hippocampal Substructures

C-Subdivision of brain stem white matter tracts

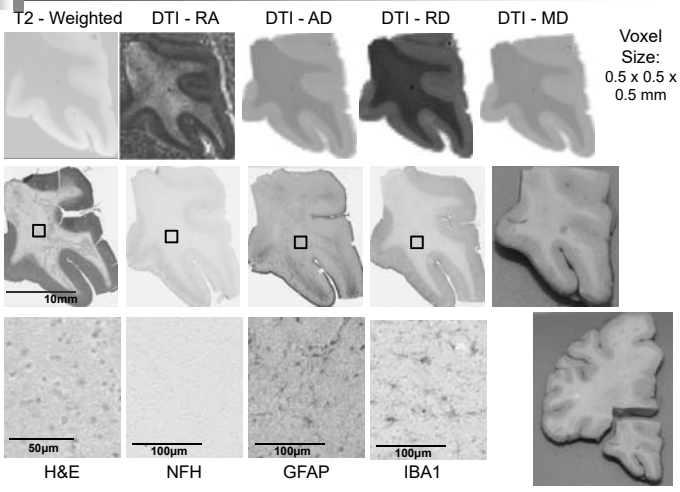
D- Substructures of dentate nucleus

Orbitofrontal White Matter – Chronic Blast -TBI



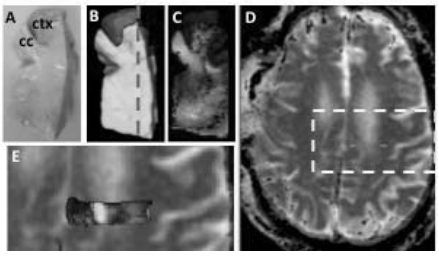
Voxel Size: 0.5 x 0.5 x 0.5 mm

Orbitofrontal White Matter – Control



Voxel Size: 0.5 x 0.5 x 0.5 mm

Registration of ante-mortem and post-mortem DTI imaging



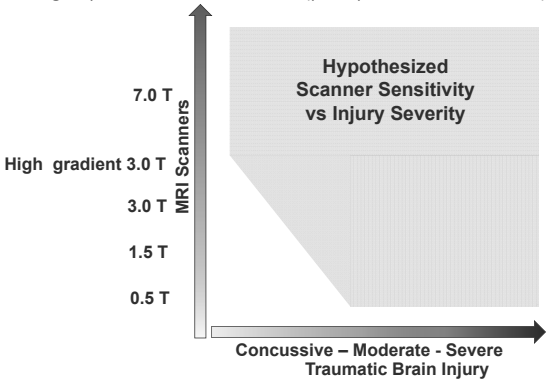
Panel A is a picture of the WM tissue block, with location of corpus collosum (cc) and cerebral cortex (ctx) indicated. Post-mortem MRI data are used to segment gray and white matter; a surface model of segmentation result is shown in Panel B. Panel C shows a color-orientation diffusion anisotropy map in the coronal plane of the block faces shown in A and B. Panel D shows a mean diffusivity map acquired from our participant's clinically ordered standard stroke protocol. We registered the postmortem diffusion MRI to the ante-mortem images, and show an overlay of the postmortem color orientation map in Panel E, corresponding to the dashed yellow box in D. The approximate coronal intersection of the image shown in Panel C is shown with the dashed red line in Panel D, and the axial intersection of the tissue block from E is shown with the dashed red line in Panel B.

From Mac Donald, Crane, Larson Proposal 2015 in collaboration with CD Keene, C Kroenke

Moving Forward

Future directions

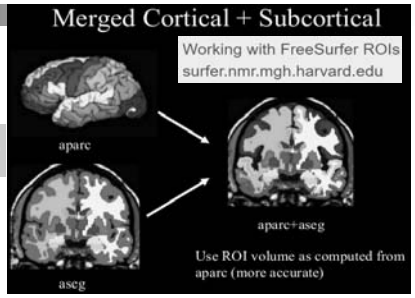
Advanced PET-MR & MR methods using modern 3T, high gradient strength scanners are now feasible, and may substantially improve sensitivity to brain injury pathology following, in particular, mild-concussive (perhaps even sub-concussive) TBI.



Quantitative Volumetrics

FreeSurfer

http://freesurfer.net/



CORTICAL THICKNESS POST-TBI IN VETERANS 1755

FIG. 2. Cortical thickness comparison between healthy controls (HC) and blast-induced participants with traumatic brain injury (TBI). Display of the resulting threshold corrected clusters to the familywise error rate of $p<0.05$ the using null-Z method. The group comparisons are HC versus mild TBI (**A**), HC versus moderate TBI (**B**), and HC versus mild + moderate TBI (**C**). Color image is available online at www.liebertpub.com/neu

Michael et al, J Neurotrauma. 2015 Nov 15;32(22):1751-8

On the Horizon

- Preliminary findings are encouraging
- 'Diagnostics are Duplicative' – A Strength!
  - Can serial image for intra-subject comparison and monitoring over time vs. 'permanent nature' of tissue sampling
- Hopefully advanced neuroimaging techniques will provide greater sensitivity to earlier detection of the underlying pathology to this progressive neurodegenerative disease
- This will aide in:
  - Stratification for therapeutic intervention
    - Giving the right patients the right drugs
  - Identification of more targeted rehabilitation
    - Customize approach for each patient (precision medicine in an often imprecise and heterogeneous brain injury population)
  - Better informed decision making for providers, patients and families
    - 'Should my child continue to play sports?'
    - 'Should I return to deployment or deploy again to combat?'
  - Potential support for resolution with disability claims/medicolegal disputes

http://www.myphotodump.com/seattle-washington-and-mt-rainier-oc-3680x2453/