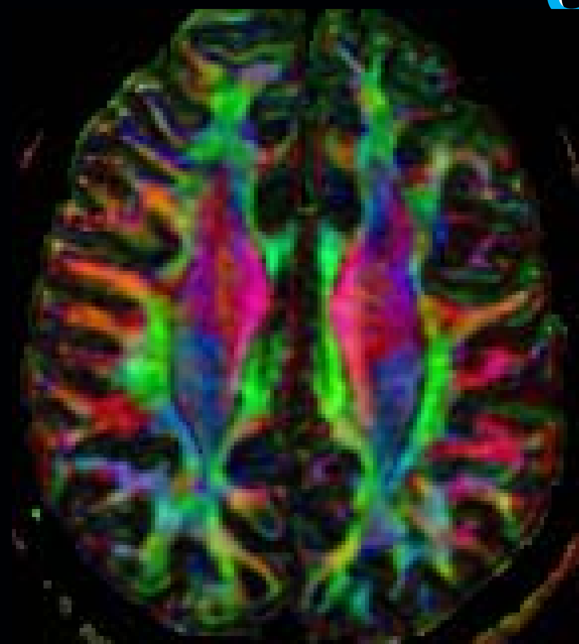
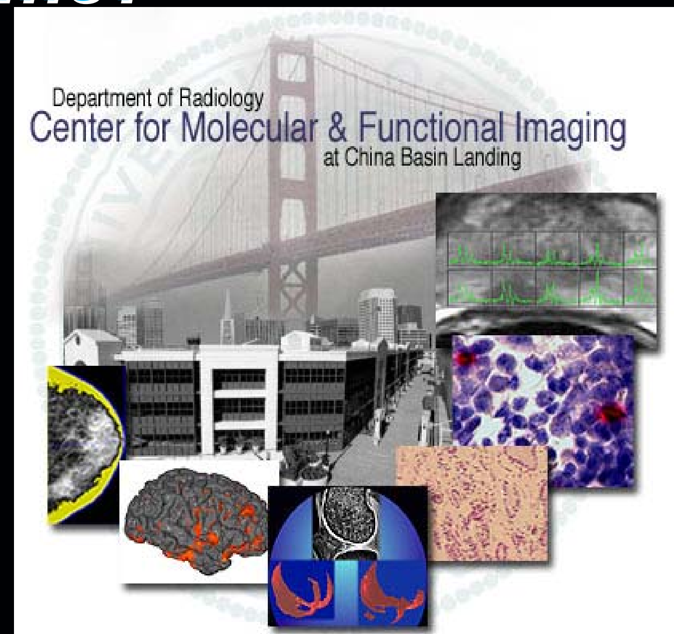
Diffusion Tensor Imaging of Mild TBI:

A Potential Biomarker of Neurocognitive Outcome?





CNRC
TBI

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Synopsis

- **Conventional Clinical Neuroimaging:** ***current limitations for TBI***
  - ***CT is still the mainstay of head trauma imaging, but is grossly insensitive to parenchymal brain injury in mild TBI***
  - ***3T and now 7T MR imaging are growing increasingly sensitive to focal lesions in mild TBI, yet these lesions do not correlate with patient outcome***

- **Diffusion Tensor Imaging (DTI):** ***a potential biomarker of TBI?***
  - ***Provides quantitative pathophysiological parameters (e.g. FA) that correlate with neurocognitive outcome in mild TBI***
  - ***In chronic symptomatic mild TBI, provides structure-function correlation that can relate injury in particular***

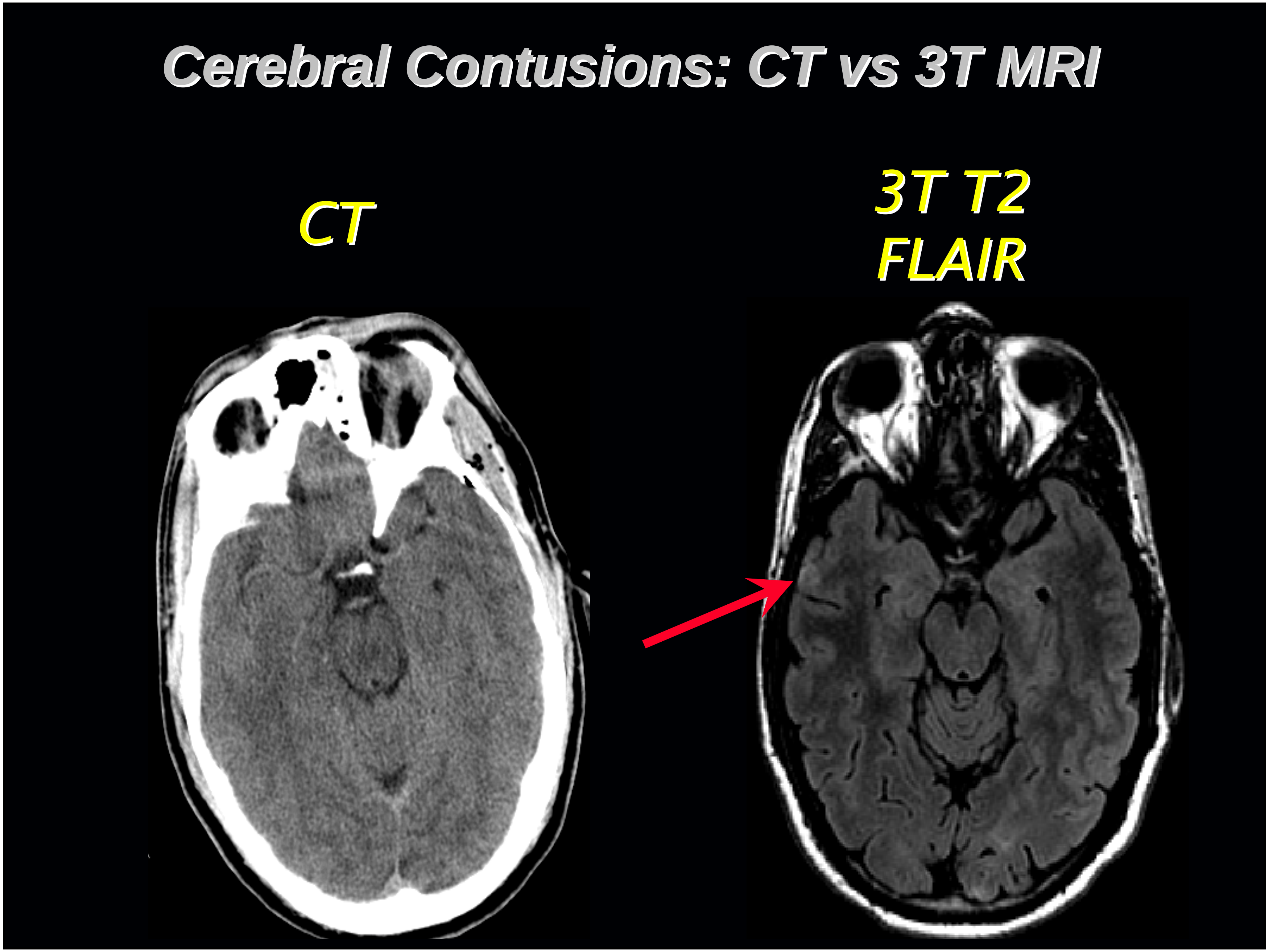
Mild TBI is Not Necessarily "Mild"

- *Mild TBI*
  - The great majority of TBI is "mild TBI", also called "concussion" or "minor TBI"
  - Mild TBI is commonly defined as Glasgow Coma Scale (GCS) 13-15, with loss of consciousness no greater than 30 minutes and post-traumatic amnesia not greater than 24 hrs
  - Although most mild TBI victims recover quickly, ~15% suffer persistent *post-concussive syndrome* (PCS)
  - Somatic and emotional complaints in PCS include headache, fatigue, dizziness, insomnia, anxiety, depression, and even seizures
  - Impairments in memory and executive attention are the two most common neurocognitive manifestations

Conventional Neuroimaging of Mild TBI

- ***X-ray Computed Tomography (CT)***
  - *Detects surgical emergencies (hematoma, mass effect, etc.)*
  - *Detects cortical surface contusions*
  - *Depicts the small focal hemorrhages sometimes associated with axonal shearing injury ("DAI", "TAI")*

- ***Magnetic Resonance Imaging (MRI)***
  - *Gradient echo T2*-weighted images are more sensitive than CT for the microhemorrhages of DAI*
  - *Fast spin echo T2-weighted and FLAIR images are more sensitive than CT to contusions and to non-hemorrhagic axonal shearing injuries*


Cerebral Contusions: CT vs 3T MRI
CT
3T T2
FLAIR

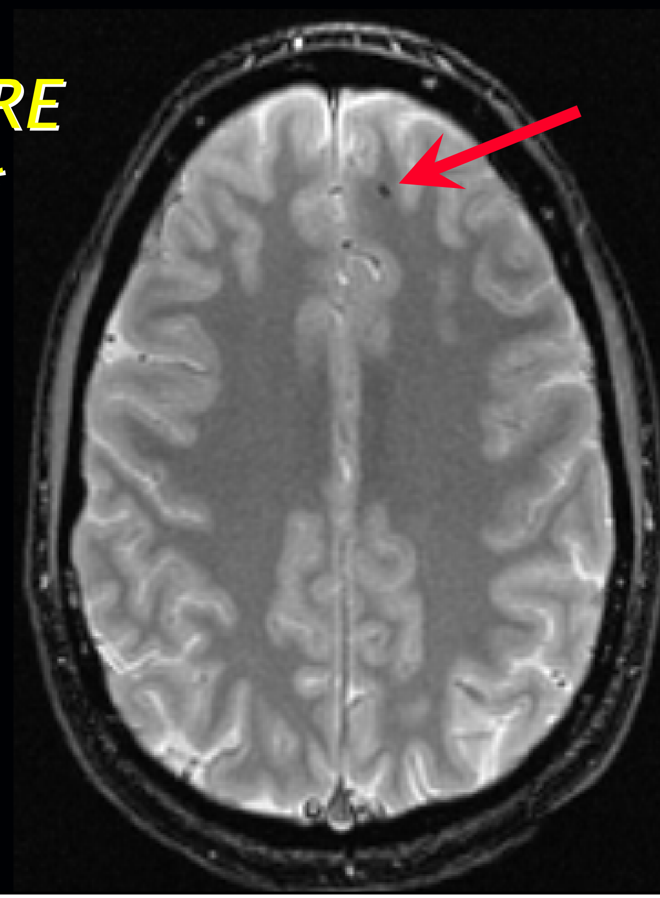
Microhemorrhages: CT vs 3T MRI

3T detects twice as many microhemorrhages as 1.5T on gradient-echo T2*-weighted images

Scheid et al., *J Neurotrauma* (2007)

CT

*3T GRE T2**

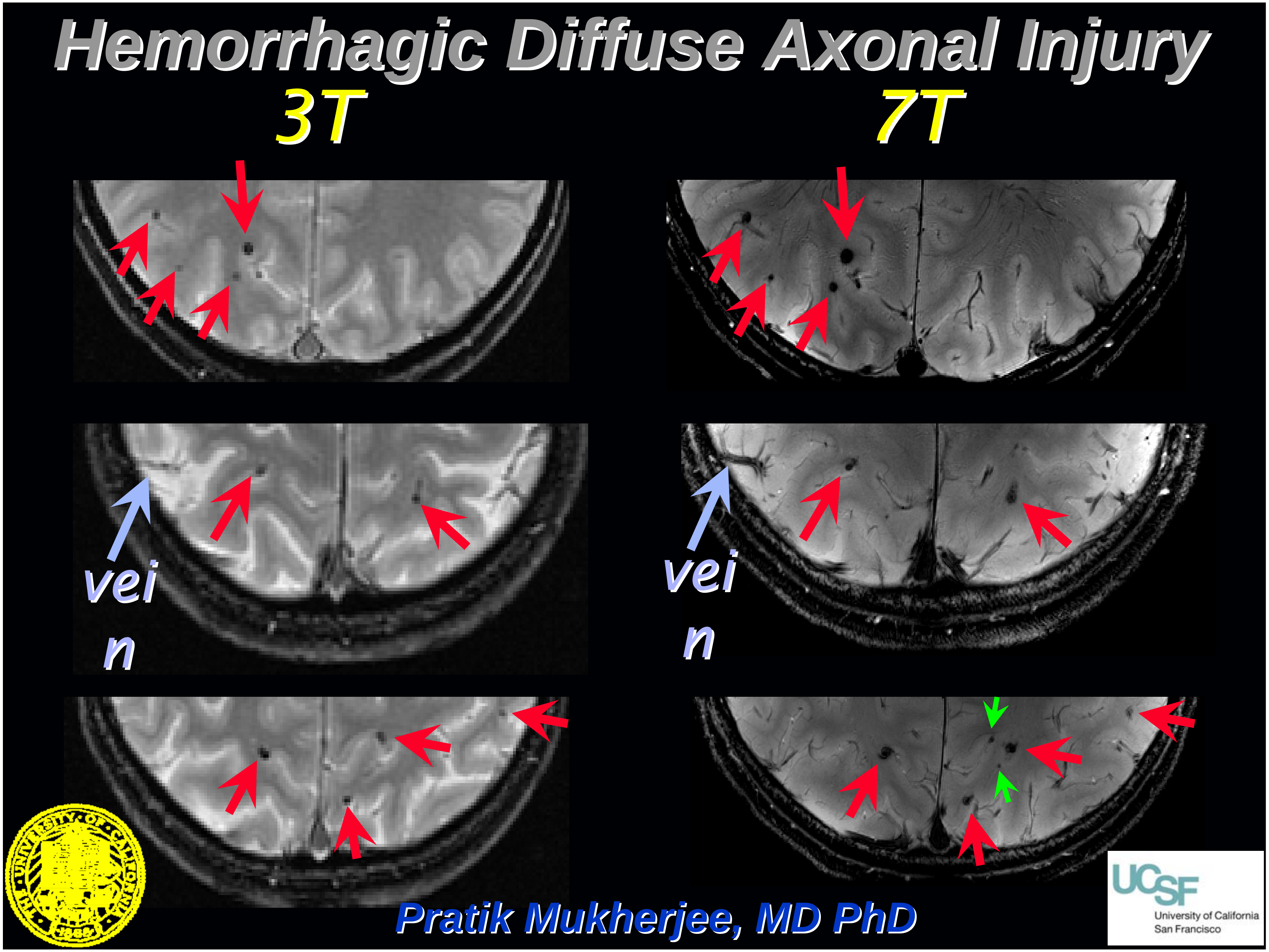


Mild Traumatic Brain Injury: CT vs 3T MRI

- ***38 mildTBI patients (blunt head trauma) prospectively enrolled***
  - ***All with GCS 13-15 in the Emergency Dept.; no prior history of head trauma***
  - ***All with loss of consciousness; none for more than 30 min.***
  - ***All with post-traumatic amnesia***
    - » ***Positive for brain injury***
      - ***15/38 (39%) CT scans versus 29/38 (76%) 3T MRI scans***
    - » ***Positive for hemorrhagic axonal shearing injury***
      - ***3/38 (8%) CT scans versus 15/38 (39%) 3T MRI scans***
    - » ***Positive for non-hemorrhagic axonal shearing injury***
      - ***1/38 (3%) CT scans versus 4/38 (11%) 3T MRI scans***
    - » ***Positive for cerebral contusions***
      - ***11/38 (29%) CT scans versus 21/38 (55%) 3T MRI scans***

- **The difference between CT and 3T MRI in *per lesion* detection rates even greater than in *per patient* detection rates**

Lee H, Wintermark M, Gean A, Ghajar J, Manley G, Mukherjee P. *J Neurotrauma* 2008; 25:1049-56


Hemorrhagic Diffuse Axonal Injury
3T
7T
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University of California
San Francisco

Mild Traumatic Brain Injury: Do CT and 3T MR Findings Affect Outcome?

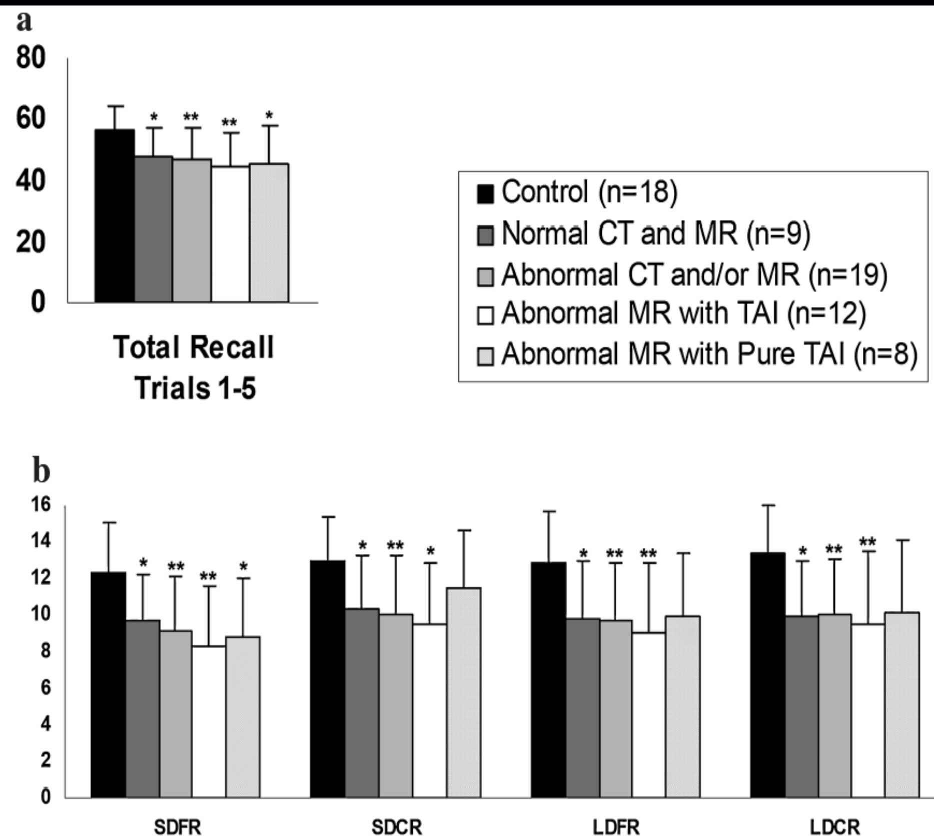


FIG. 3. California Verbal Learning Test (CVLT) comparison by imaging findings in mild traumatic brain injury (mTBI) subjects and healthy controls at the acute time point. (**a**) Total Recall Trial 1—5. (**b**) SDFR, SDCR, LDFR, LDCR. *p-value $<$ 0.05; **p-value $<$ 0.01 for significant difference between controls and mTBI groups.

Lee H, Wintermark M, Gean A, Ghajar J, Manley G, Mukherjee P.
J Neurotrauma 2008; 25:1049-56

Lack of Utility of Conventional MRI in Mild TBI

- **Acute Mild TBI:**
  - *Lack of correlation between 1.0T MR imaging findings and long-term outcome as determined by neurocognitive tests & functional recovery*

    Hughes et al. *Neuroradiology* (2004)

- **Chronic TBI (Mild to Severe):**
  - *Lack of correlation between microhemorrhages on 3T MR imaging and long-term outcome as determined by the Glasgow Outcome Scale*

    Scheid et al. *AJNR* (2003)

Rationale for DTI in TBI

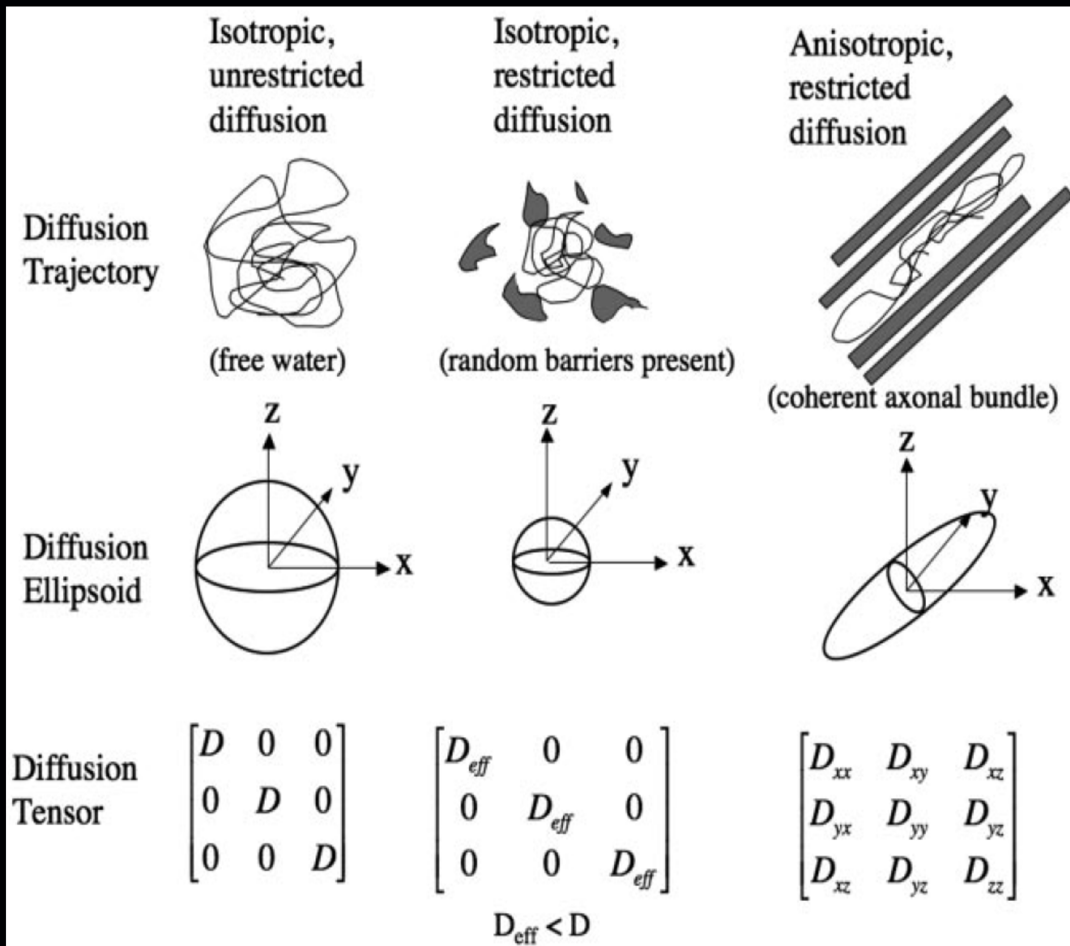
- **Diffusion Tensor Imaging (Basser et al., 1994)**
  - *Is sensitive to microstructural changes within white matter tracts, which may* ***improve the detection of axonal injury***

    Arfanakis et al. *AJNR* (2002) and many other studies
  - *can localize axonal shearing injury to specific white matter tracts, for* ***structure - function correlation***

    Le et al. *Neurosurgery* (2005) and other studies
  - *can provide* ***quantitative pathophysiological information*** *that might be useful for determining prognosis and monitoring therapeutic interventions in TBI*

    Huisman et al. *AJNR* (2004) and other studies
  - ***3T MRI with parallel imaging*** *vastly improves the ability to perform high-resolution, high quality DTI in a clinically feasible scan time*

Diffusion Tensor Imaging



in the range
b = 0 - 1000 sec/mm² …

Pure water at 37°C:
ADC ~ 3.0 x 10^{-3} mm^2/sec

Normal adult brain: (GM & WM)
ADC ~ 0.7 x 10^{-3} mm^2/sec

Normal term newborn brain:
***GM:* ADC ~ 1.1 x 10^{-3} mm^2/sec**
***WM:* ADC ~ 1.5 x 10^{-3} mm^2/sec**

Fractional Anisotropy (FA):
0 (spherical) to 1 (linear)

Mukherjee P, et al., *AJNR* 2008; 29:632-41

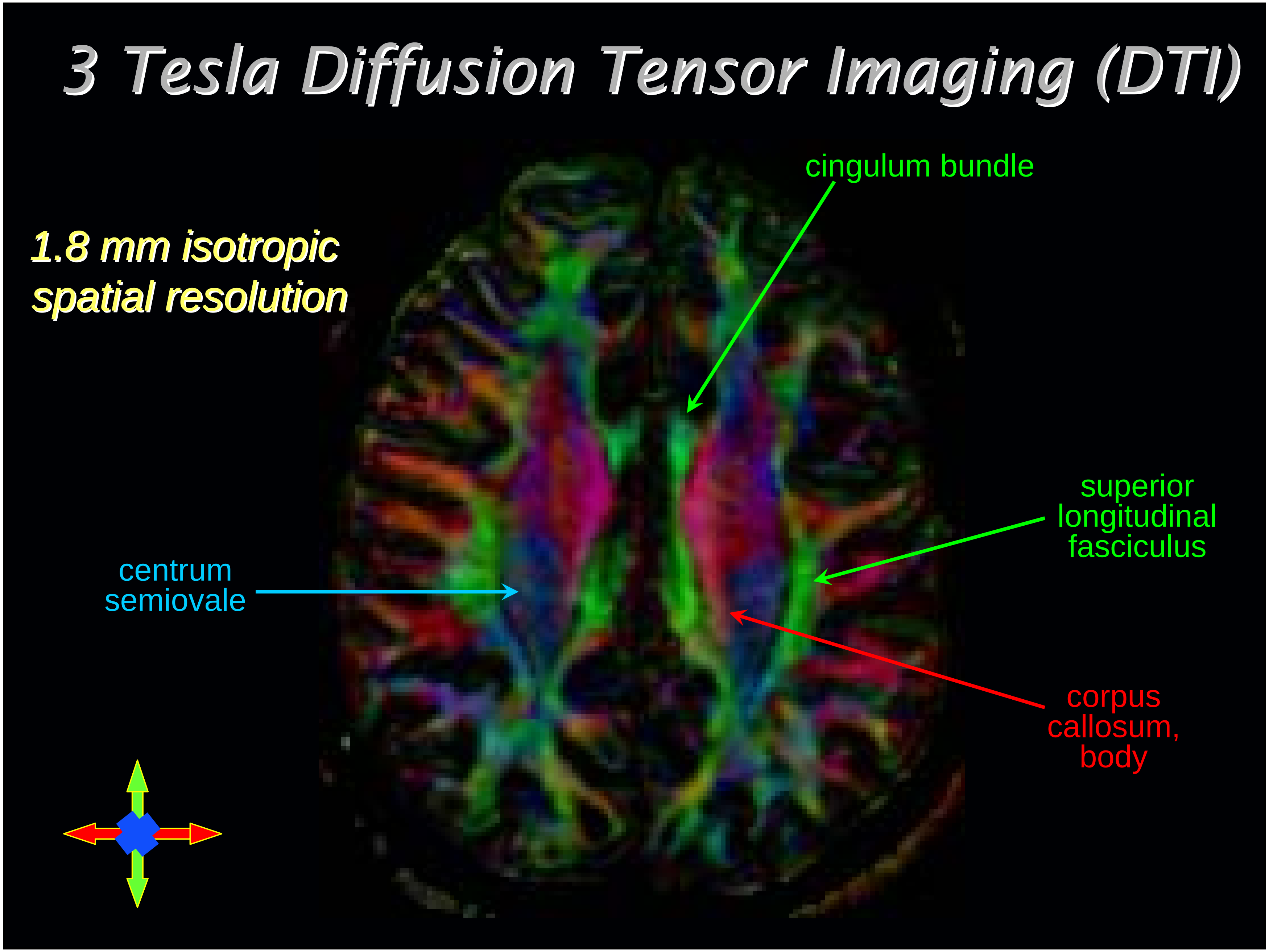
3T MRI-DTI of Mild TBI

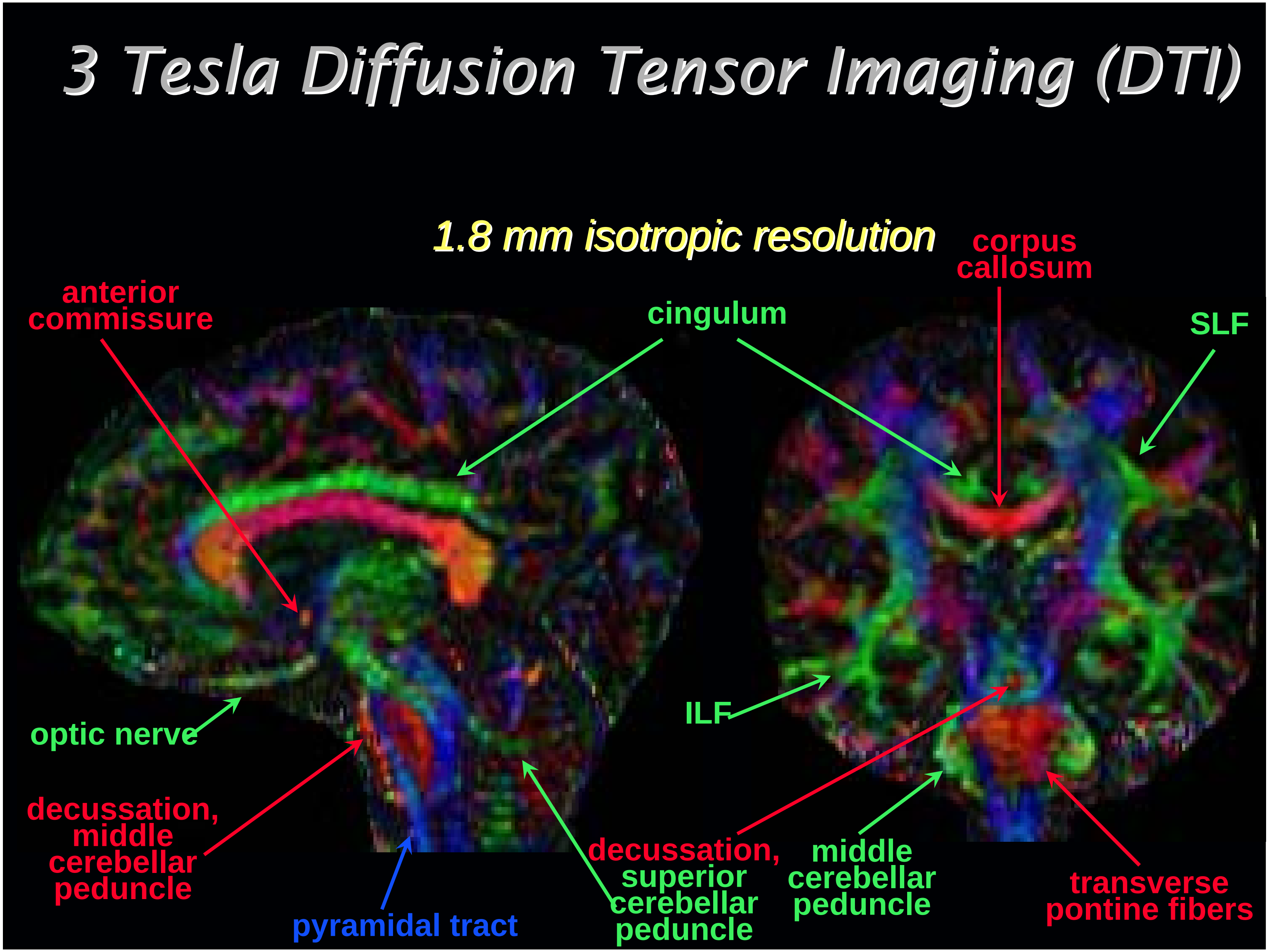
- **Conventional 3T MRI sequences**
  - ***FLAIR T2-weighted:*** **whole-brain axials @ 3 mm slices (4 min)**
  - ***MPGR T2*-weighted:*** **whole-brain axials @ 3 mm slices (4 min)**
  - ***3D IR-FSPGR T1-weighted:*** **whole-brain, 1 mm isotropic (5 min)**

- **Experimental 3T MRI sequences**
  - ***DTI:*** **128x128 with FOV 23x23 cm, *72 interleaved slices @ 1.8-mm***

    TE=64 ms, TR=14 s, *55 diffusion-encoding directions*, b=1000 s/mm^2

    ASSET parallel imaging with acceleration factor of 2 (13 min)


3 Tesla Diffusion Tensor Imaging (DTI)
1.8 mm isotropic
spatial resolution
cingulum bundle
superior
longitudinal
fasciculus
centrum
semiovale
corpus
callosum,
body


3 Tesla Diffusion Tensor Imaging (DTI)
1.8 mm isotropic resolution
corpus callosum
anterior commissure
cingulum
SLF
ILF
optic nerve
decussation, middle cerebellar peduncle
pyramidal tract
decussation, superior cerebellar peduncle
middle cerebellar peduncle
transverse pontine fibers

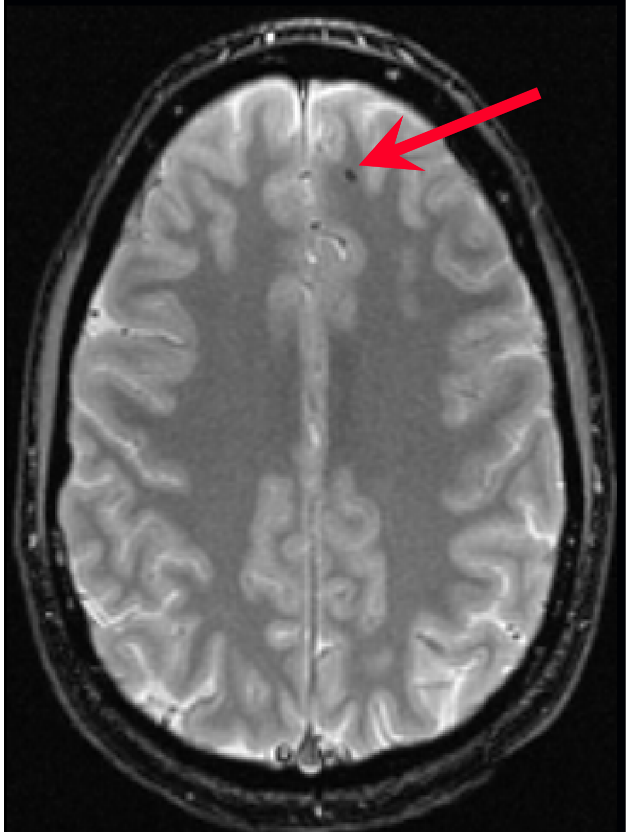
Cornell - UCSF Study: 3T MRI-DTI of Mild TBI

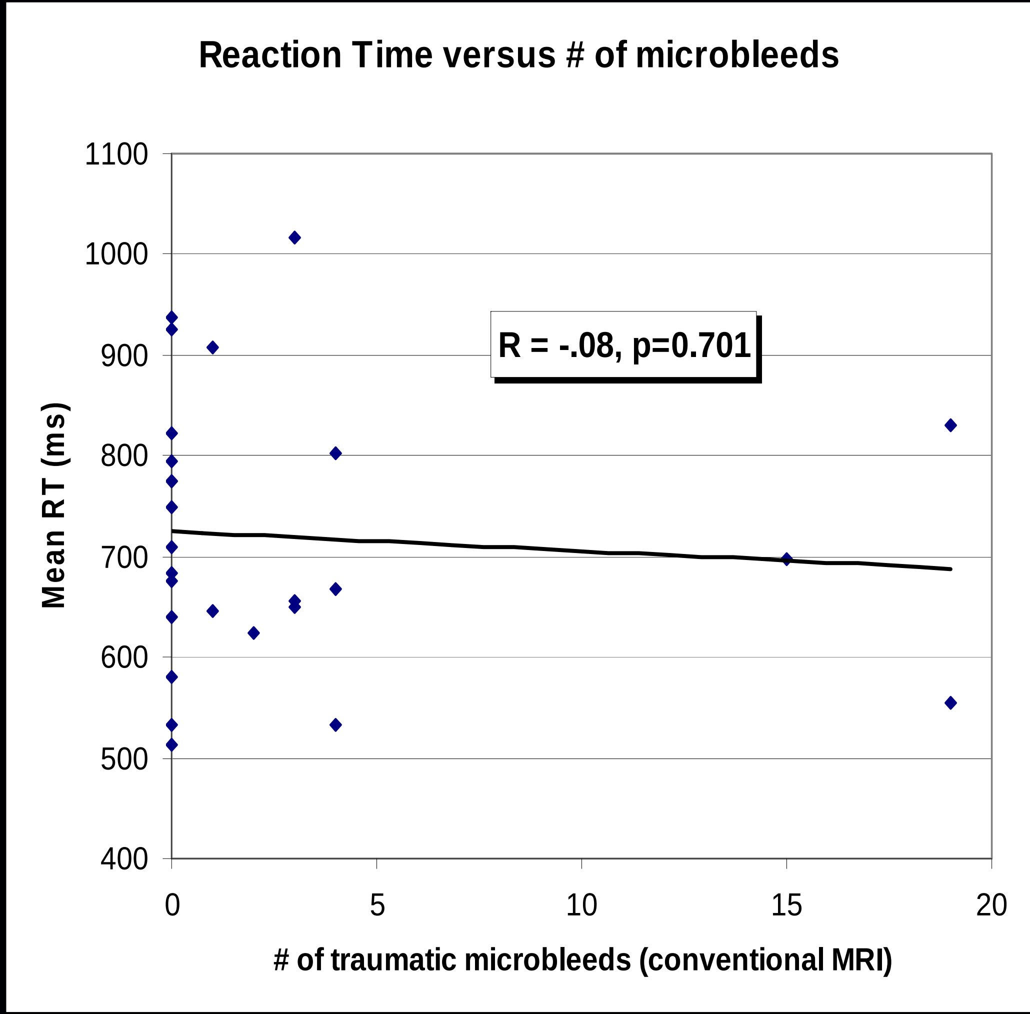
Is Extent of Microstructural White Matter Injury Related to Global Cognitive Processing Speed?

- ***34 chronic symptomatic mild TBI patients prospectively enrolled 1-65 months after injury, both in NY & SF***
  - ***All with only a single episode of head trauma (predominantly MVAs, assaults, & falls)***
  - ***All with no history of chronic medical or neuropsychiatric illness (including drug or EtOH abuse)***
  - ***All presented with GCS 13-15 in the Emergency Dept.***
  - ***All presented with post-traumatic amnesia***
  - ***All with persistent post-concussive symptoms***
- ***26 normal volunteers from NY & SF matched for:***
  - ***age***
  - ***gender***
  - ***handedness***
  - ***years of education***

Niogi S, Mukherjee P, Ghajar J et al., *AJNR* 2008; 29:967-73.

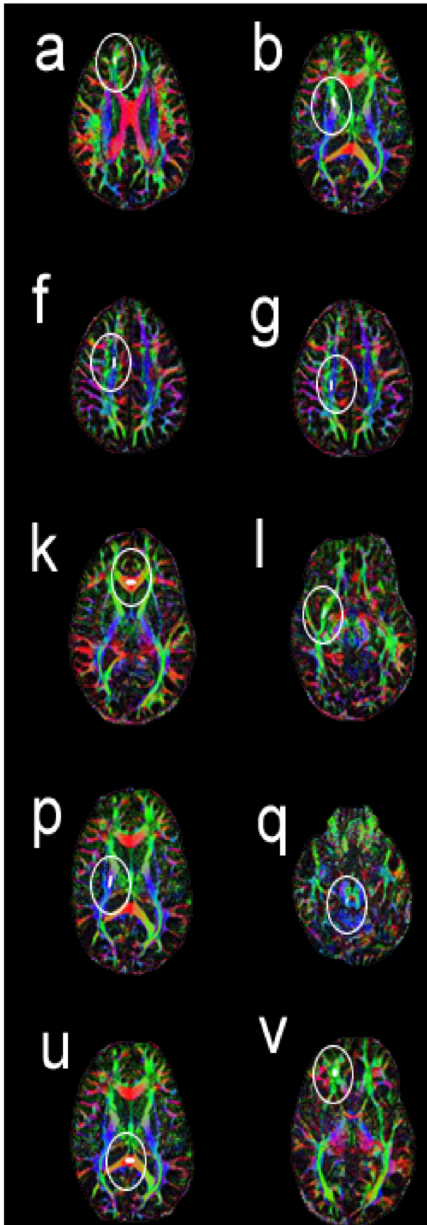
3T T2*-GRE MRI of Mild TBI: No Correlation with Cognitive Processing Speed





Niogi S, Mukherjee P, Ghajar J et al., *AJNR* 2008; 29:967-73.

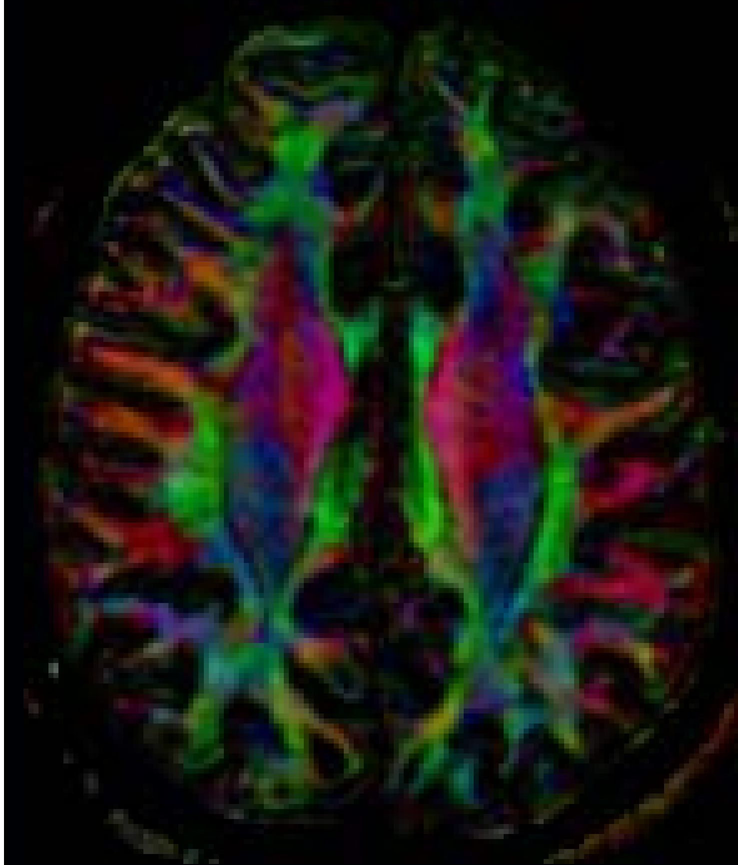
3T DTI of Mild TBI

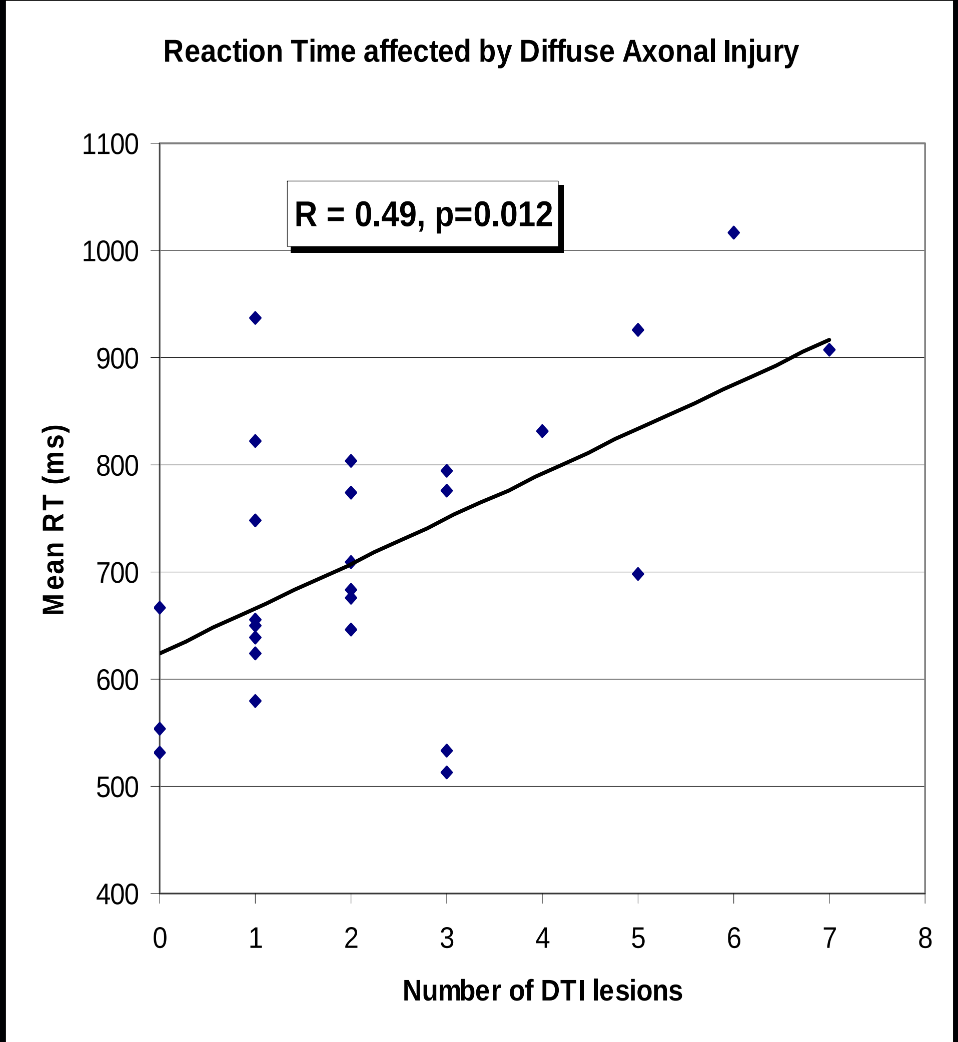


Patient	ACR	UNC	Genu	Cing	ILF	SCR	pct	plic	CP	alic	mcp	scp	Fmaj	BCC	SLF	dscp	arcF	Fmin	CS	Splen	total
1				X	X	X	X		X				X	X							7
2		X	X	X				X	X		X										6
3	X	X	X		X	X															5
4	X	X	X	X				X													5
5	X	X			X		X														4
6	X	X	X							X											4
7		X			X		X														3
8		X			X			X													3
9	X		X	X																	3
10	X		X									X									3
11		X	X	X																	3
12						X										X					2
13	X					X															2
14	X				X																2
15				X											X						2
16	X								X												2
17	X			X																	2
18							X														1
19										X											1
20	X																				1
21	X																				1
22		X																			1
23											X										1
24	X																				1
25		X																			1
26												X									1
27						X															1
28	X																				1
29							X														1
30																					0
31																					0
32																					0
33																					0
34																					0
	14	10	7	7	6	5	5	3	3	2	2	2	1	1	1	1	0	0	0	0	

Niogi S, Mukherjee P, Ghajar J et al., *AJNR* 2008; 29:967-73.

Spatial Extent of White Matter Injury on DTI Correlates with Cognitive Processing Speed in Mild TBI





Niogi S, Mukherjee P, Ghajar J et al., *AJNR* 2008; 29:967-73.

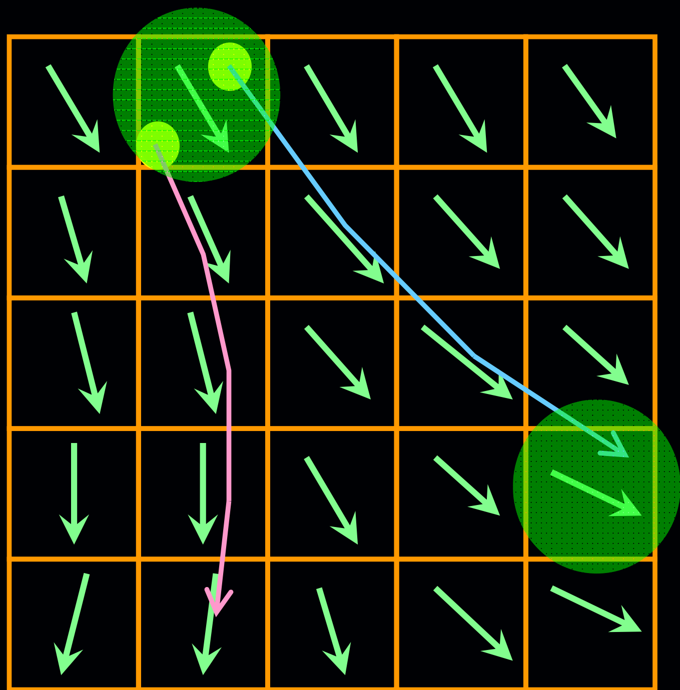
DTI of Mild TBI

- ***Microstructural White Matter Injury in Mild TBI***
  - ***10 of 11 patients with normal findings on conventional 3T MR imaging had evidence of reduced FA in one or more WM tracts***
  - ***The most frequently injured tracts are large longitudinal fiber bundles anteriorly located in the brain (ACR, UF, genu of CC), farthest from the axis of rotation in rotational TAI***

Niogi S, Mukherjee P, Ghajar J et al., *AJNR* 2008; 29:967-73.

3D Diffusion Tensor Fiber Tractography

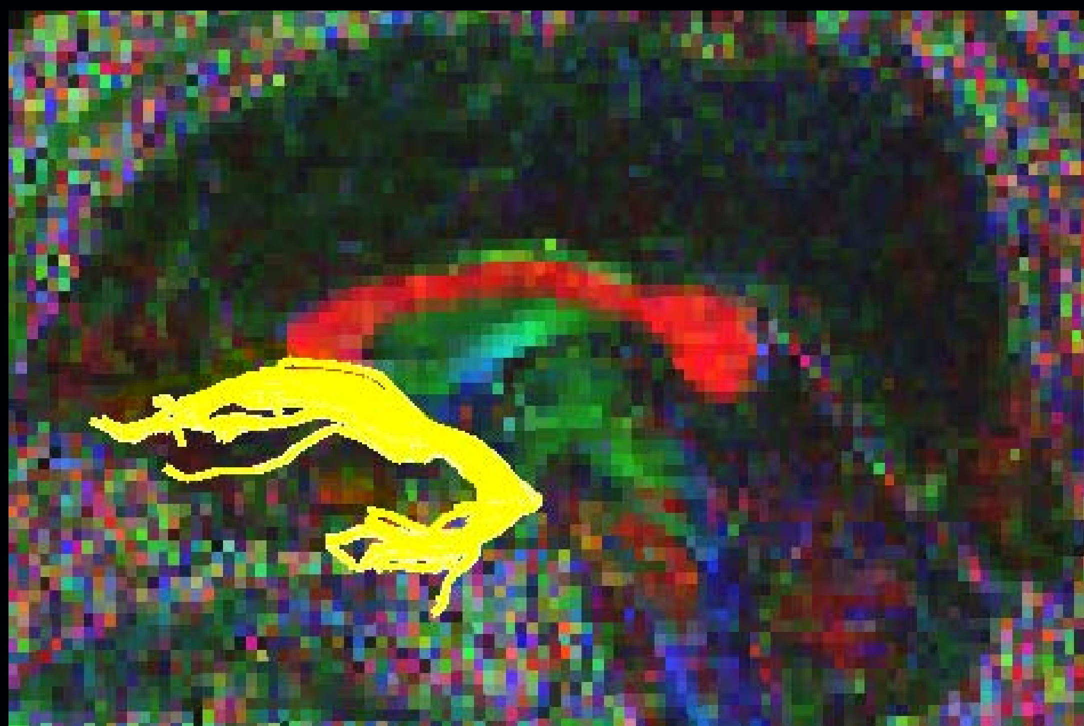
"Streamline Tractography"



- **FACT** – **f**iber **a**ssignment by **c**ontinuous **t**racking in 3D along the primary eigenvector *(Mori et al. 1999)*
- **dense seeding** – multiple seed points within a voxel *(Conturo et al. 1999; Mori et al. 1999)*
- **interpolation** – step sizes smaller than a voxel *(Conturo et al. 1999)*
- **multi-ROI filtering** – retain only those tracts passing through start and end ROIs, and other intermediary ROIs *(Conturo et al. 1999)*

3T DTI Tractography of the Uncinate Fasciculus

Important for memory
Correlate with performance on the
California Verbal Learning Test (CVLT)



3T DTI Tractography of the Cingulum Bundle and Anterior Corona Radiata

Important for attentional control
(focusing on task in the presence of distracters)
Correlate with conflict on the Attention Network Task (ANT)

"congruent"

→ → → → →

"incongruent"

← ← → ← ←

Cornell - UCSF Study: 3T MRI-DTI of Mild TBI

Are Attentional and Memory Impairment Related to Damage in Specific White Matter Tracts?

- ***43 chronic symptomatic mild TBI patients prospectively enrolled 1-65 months after injury, both in NY & SF***
  - ***All with only a single episode of head trauma (predominantly MVAs, assaults, & falls)***
  - ***All with no history of chronic medical or neuropsychiatric illness (including drug or EtOH abuse)***
  - ***All presented with GCS 13-15 in the Emergency Dept.***
  - ***All presented with post-traumatic amnesia***
  - ***All with persistent post-concussive symptoms***
- ***23 normal volunteers from NY & SF matched for:***
  - ***age***
  - ***gender***
  - ***handedness***
  - ***years of education***

Niogi S, Mukherjee P, Ghajar J et al., *Brain* 2008; in press.

doi:10.1093/brain/awn247 Brain (2008) Page 1 of 13

Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury

Sumit N. Niogi*, Pratik Mukherjee*, Jamshid Ghajar, Rachel Kolster, Hana Lee, Minah Suh, Geoffrey Manley and Bruce D. McCandliss

*These authors contributed equally to this work.

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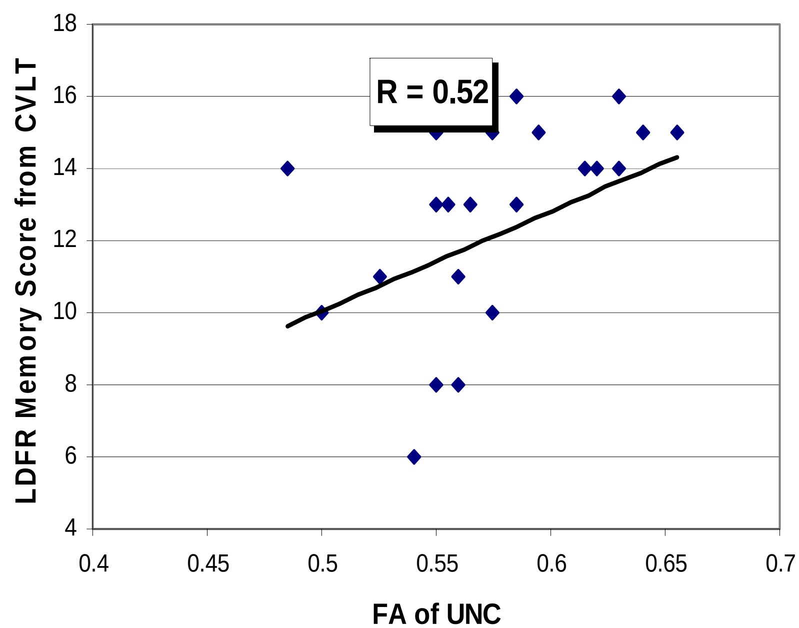
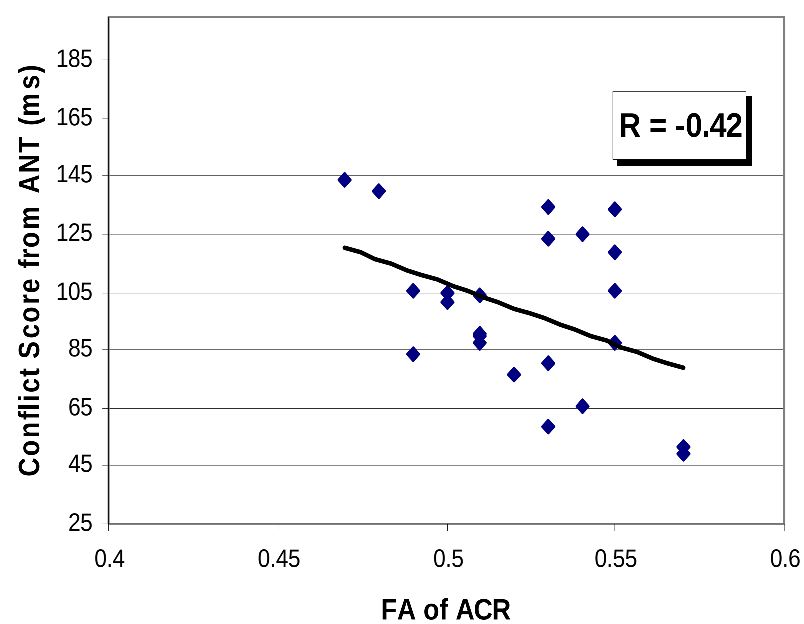
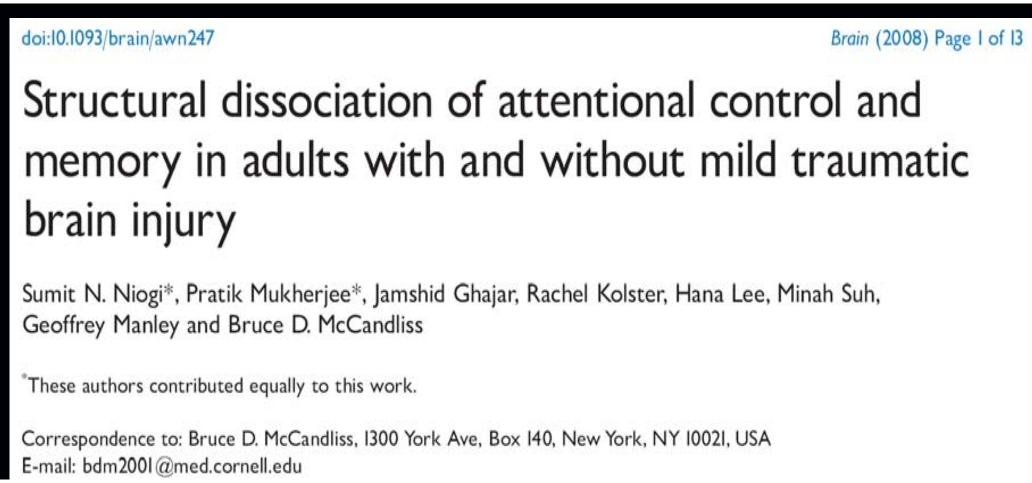
E-mail: bdm2001@med.cornell.edu

Bilateral UNC correlates with Memory in Normal Adults



Left hemisphere ACR correlates with Conflict in Normal Adults





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Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury

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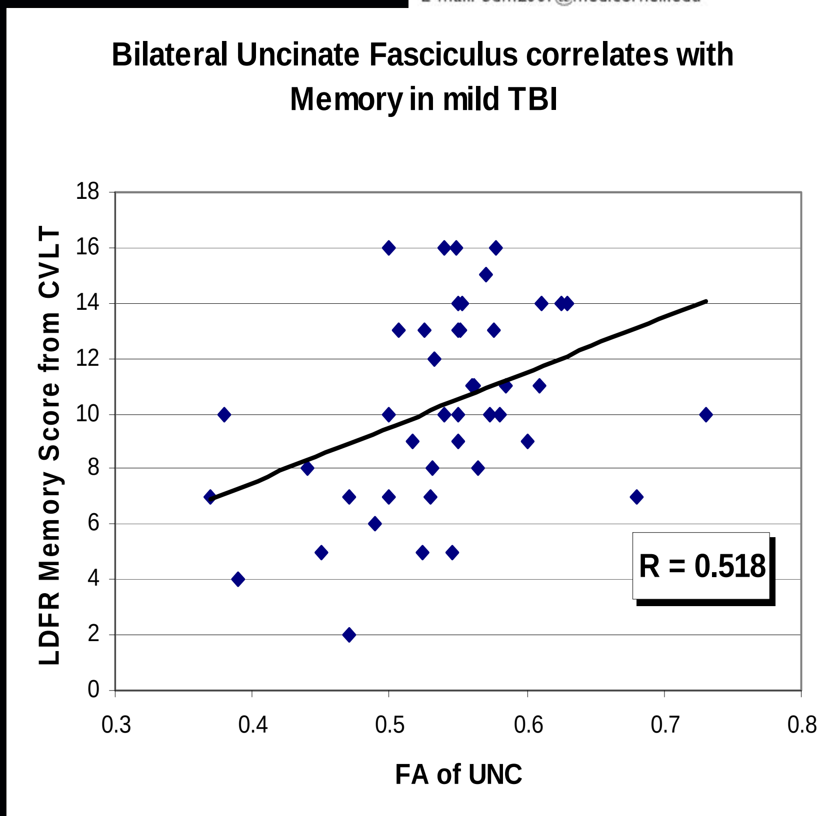
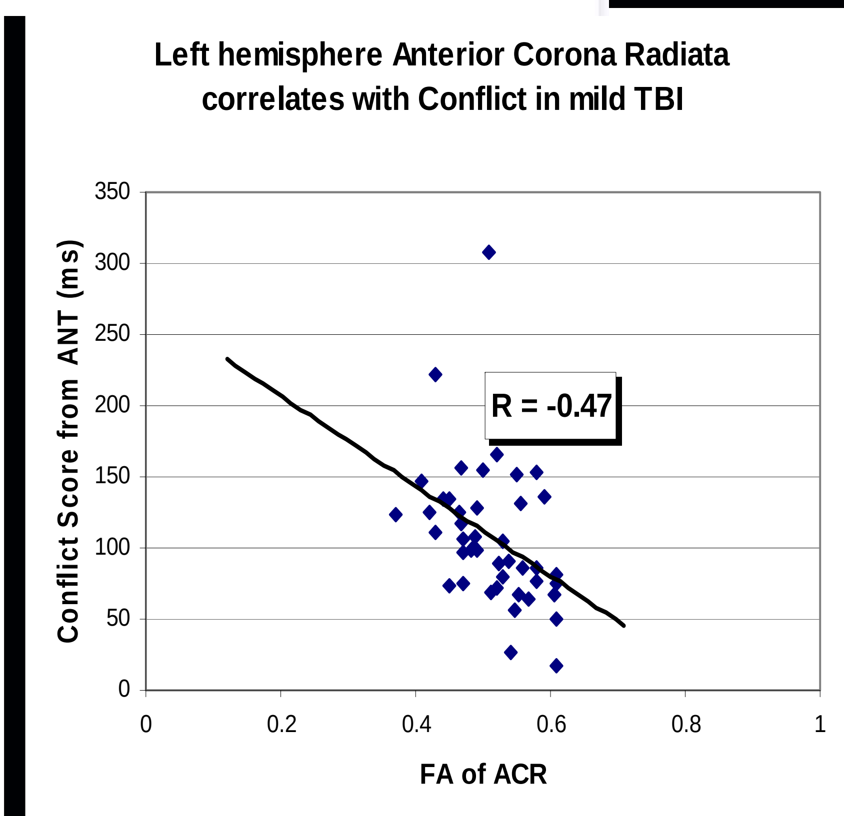
E-mail: bdm2001@med.cornell.edu





UCSF Prospective Longitudinal Study of Mild TBI with 3T MRI-DTI

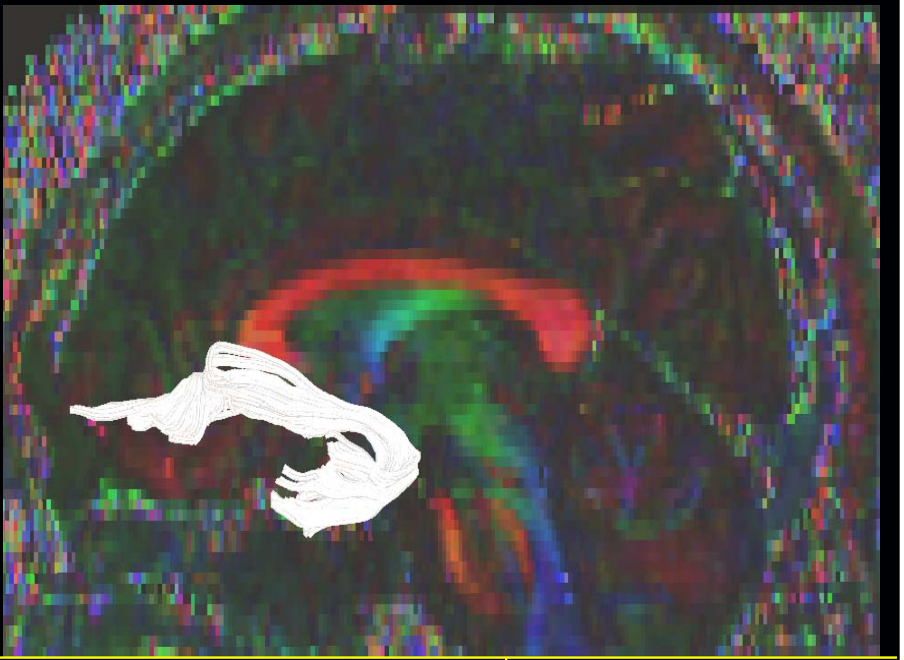
- ***31 mild TBI patients prospectively enrolled in Emergency Dept.***
  - ***All with only a single episode of head trauma (predominantly MVAs, assaults, & falls)***
  - ***All with no history of chronic medical or neuropsychiatric illness (including drug or EtOH abuse)***
  - ***All presented with GCS 13-15 in the Emergency Dept.***
  - ***All presented with witnessed loss of consciousness (LOC)***
  - ***All presented with post-traumatic amnesia***

  - ***Patients scanned serially with 3T MRI and DTI at acute (< 2 wks), 1-month, and 1-year time points after injury***
- ***19 age-, gender-, & education-matched normal volunteers***

3T DTI Tractography of the Uncinate Fasciculus

Important for memory;

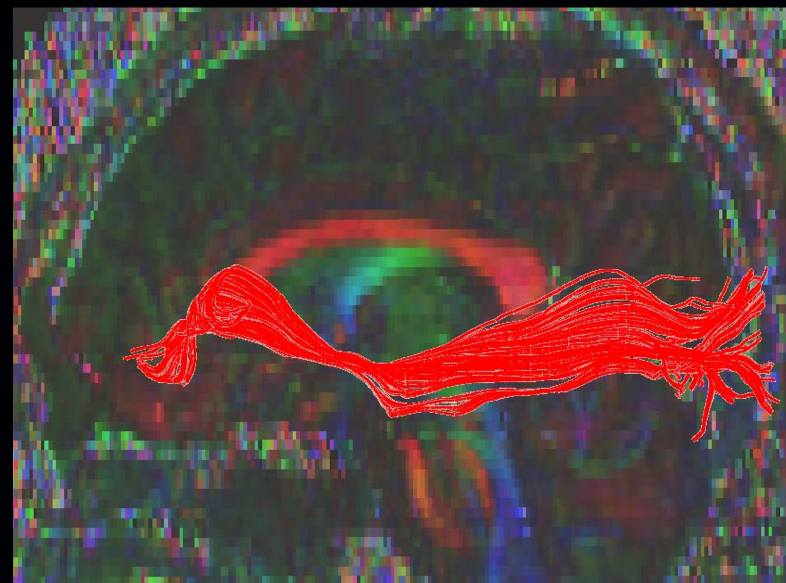
Correlates with performance on the California Verbal Learning Test



FA	Control	< 2 wks	1-month	1-year	Control vs TBI (p)		
Left	0.492±0.022	0.474±0.21	0.475±0.020	0.472±0.021	0.009	0.015	0.006
Right	0.470±0.022	0.455±0.24	0.459±0.020	0.457±0.024	0.033	0.080	0.065
Average	0.481±0.020	0.465±0.020	0.467±0.018	0.464±0.018	0.008	0.019	0.009

3T DTI Tractography of the Inferior Fronto-Occipital Fasciculus (IFO)

The major tract connecting the frontal and occipital lobes

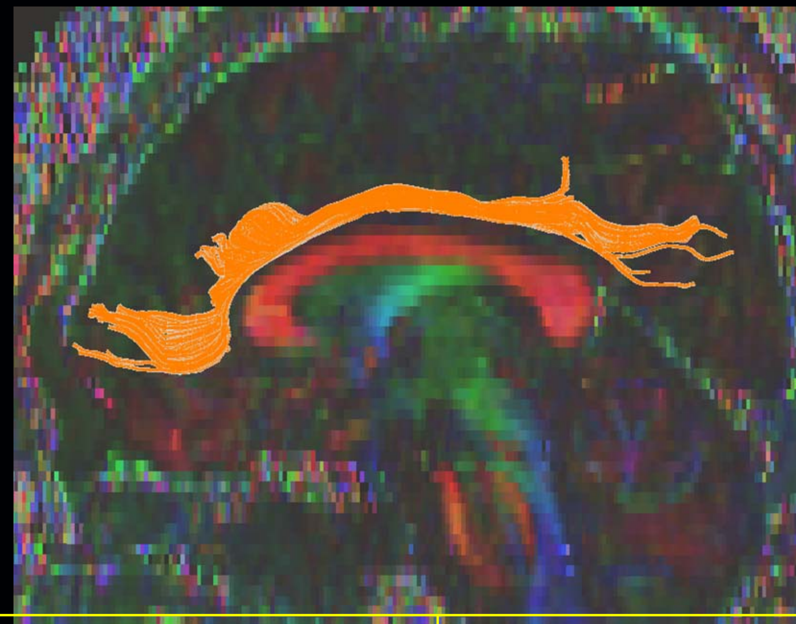


FA	Control	< 2 wks	1-month	1-year	Control vs TBI (p)		
Left	0.550±0.024	0.539±0.023	0.543±0.024	0.535±0.021	0.111	0.342	0.045
Right	0.533±0.022	0.524±0.023	0.521±0.023	0.518±0.023	0.158	0.063	0.036
Average	0.542±0.022	0.531±0.020	0.532±0.021	0.527±0.019	0.106	0.135	0.026

3T DTI Tractography of the Cingulum Bundle

Important for executive attention;

Injury leads to poor conflict monitoring



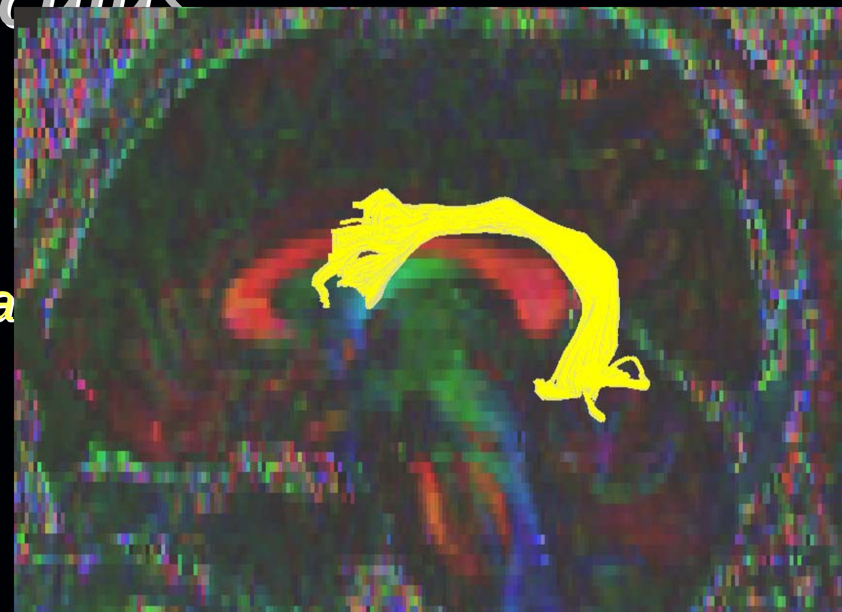
FA	Control	< 2 wks	1-month	1-year	Control vs TBI (p)		
Left	0.562±0.033	0.549±0.028	0.553±0.036	0.542±0.031	0.186	0.368	0.059
Right	0.520±0.022	0.512±0.025	0.515±0.029	0.510±0.023	0.263	0.463	0.143
Average	0.541±0.026	0.531±0.025	0.534±0.031	0.526±0.023	0.180	0.379	0.060

3T DTI Tractography of the Arcuate Fasciculus

Important for speech and language;

Connects Broca's and Wernicke's area

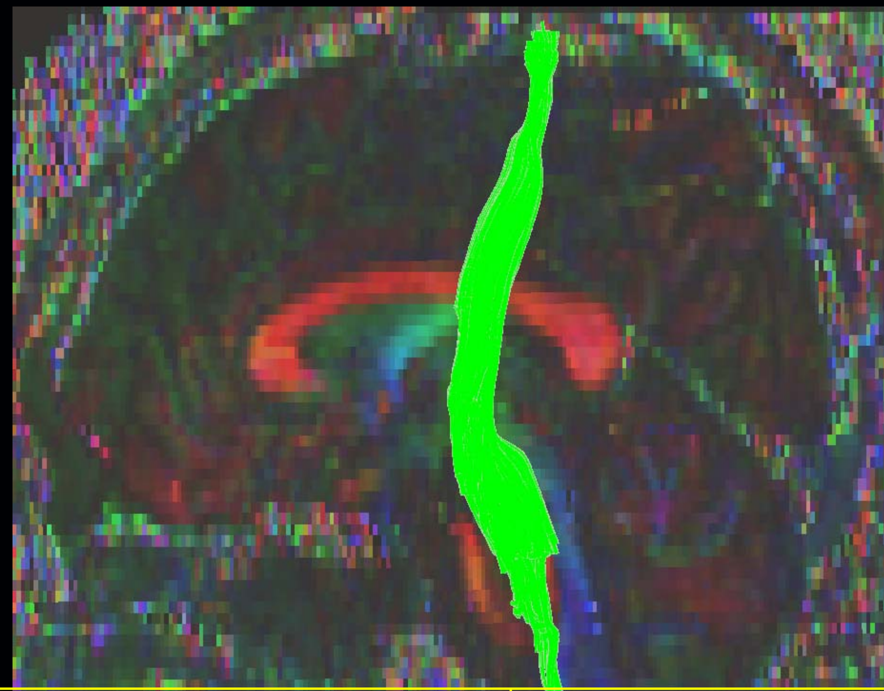
Injury leads to conduction aphasia



FA	Control	< 2 wks	1-month	1-year	Control vs TBI (p)		
Left	0.516±0.022	0.517±0.019	0.513±0.023	0.516±0.018	0.927	0.643	0.978
Right	0.491±0.022	0.484±0.027	0.480±0.026	0.482±0.025	0.635	0.131	0.233
Average	0.504±0.018	0.505±0.021	0.500±0.021	0.503±0.019	0.838	0.131	0.872

3T DTI Tractography of the Corticospinal Tract

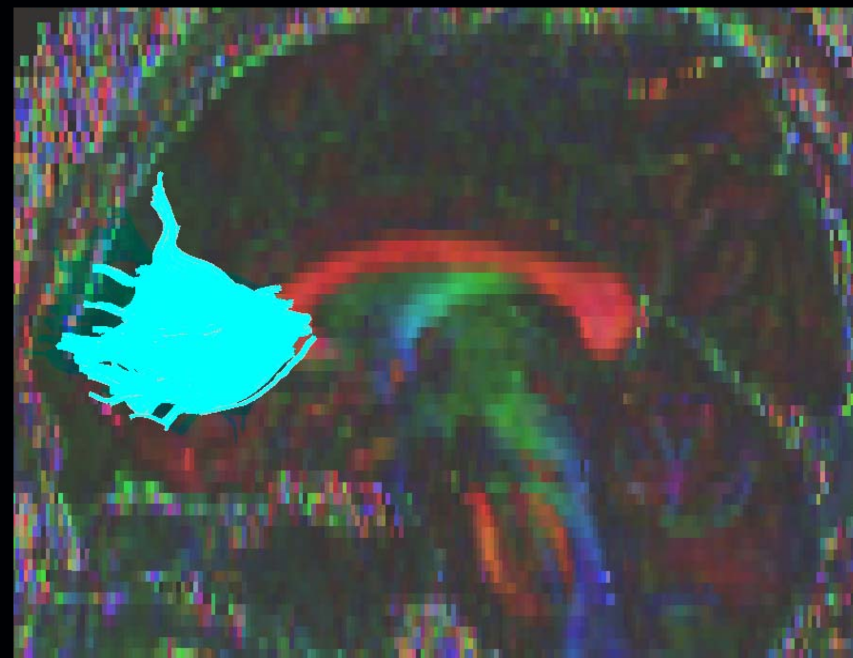
The major tract responsible for motor function



FA	Control	< 2 wks	1-month	1-year	Control vs TBI (p)		
Left	0.587±0.028	0.589±0.022	0.586±0.021	0.581±0.024	0.762	0.945	0.479
Right	0.573±0.023	0.571±0.027	0.570±0.021	0.561±0.022	0.748	0.725	0.119
Average	0.580±0.024	0.580±0.022	0.578±0.023	0.571±0.022	1.000	0.829	0.239

3T DTI Tractography of the Genu of the Corpus Callosum

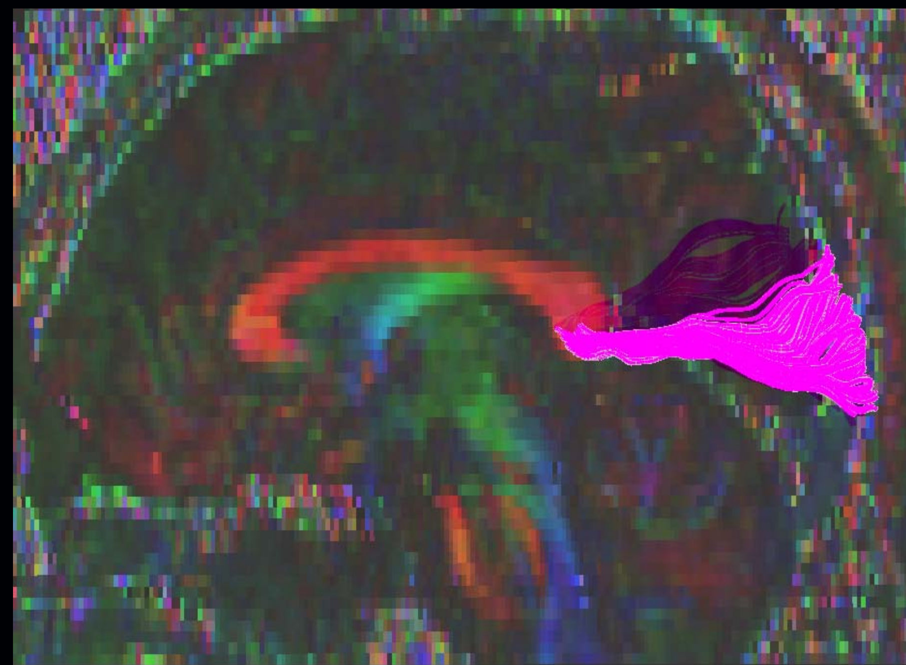
The major tract connecting the left and right frontal lobes



	Control	< 2 wks	1-month	1-year	Control vs TBI (p)		
FA	0.556±0.022	0.542±0.022	0.544±0.025	0.542±0.019	0.038	0.084	0.032

3T DTI Tractography of the Splenium of the Corpus Callosum

The major tract connecting the left and right occipital lobes



	Control	< 2 wks	1-month	1-year	Control vs TBI (p)		
FA	0.669±0.025	0.658±0.027	0.656±0.030	0.653±0.027	0.144	0.094	0.044

Neuroimaging of Mild TBI: Conclusions

- Conventional MR Imaging Techniques
  - Growing increasingly sensitive to the focal lesions of mild TBI, especially microbleeds of TAI on T2* GRE or SWI
  - However, no evidence that focal lesions are relevant to long-term neurocognitive status or functional recovery in mild TBI
- Diffusion Tensor Imaging of Mild TBI
  - DTI measures such as FA are correlated with cognitive processing speed, memory, & attention
  - Specific (micro)structure-function relationships can be found between particular white matter tracts and their associated neurocognitive domain (UF-memory, ACR-attention)
  - Reduced microstructural integrity of specific WM tracts can be detected within 2 wks after mild TBI – prognostic biomarker?
  - However, overlap with normal variation may limit utility for clinical diagnosis in individual cases of mild TBI

DTI – Application to Blast-Related TBI?

- *Diffusion Tensor Imaging (DTI) – structural connectivity*
  - *DTI is sensitive in blunt trauma, so might also be sensitive in blast*
  - *Does the distribution of microstructural WM injury differ in blast?*
    - » *Blunt TBI: anterior WM tracts (prefrontal connectivity) appear most affected*
    - » *Blast TBI: are posterior cerebral and posterior fossa tracts most affected?*
  - *What is the relationship between white matter FA and biomechanical susceptibility to blast injury?*
    - » *Current limitation of DTI: it is largely unknown what are the biological determinants of DTI parameters such as FA, and what are the pathophysiological changes that cause reduced FA after trauma*
  - *Can DTI be used to help model strain and deformation in the brain due to blast exposure?*

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