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Diffusion Tensor Imaging (DTI) in Traumatic Brain Injury

Todd Arthur, MD
Assistant Professor of Pediatrics and Neurology
3/27/15

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Disclosures

- No Financial

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Outline

- DTI basics
- DTI in clinical research and practice
- DTI future directions

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Course objectives

By the end of this presentation, the participant will:

1) Understand the basic principles of Diffusion Tensor Imaging (DTI) regarding
   a) The physics of how images are captured and results obtained
   b) Limitations of this imaging modality
   c) Strengths of this imaging modality

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Course objectives, continued

2) How DTI is being applied to clinical research and clinical practice

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MRI- Magnetic Resonance Imaging

- All tissues contain hydrogen (which has protons). Protons have a charge that spins
  - A spinning charge creates a magnetic field
  - Therefore each proton acts as a magnet

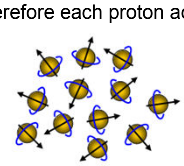

Figure 1

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MRI- Magnetic Resonance Imaging

- The MRI scanner puts patient into a large magnetic field
  - This causes the small "magnets"/protons to line up.

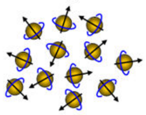

Figure 1

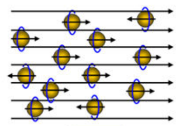

Figure 2

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MRI- Magnetic Resonance Imaging

- The scanner magnet is always on, so the protons stay lined up but spin in random directions.

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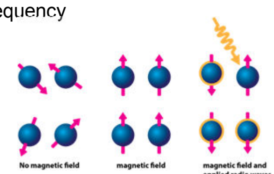
MRI- Magnetic Resonance Imaging

- The scanner then sends a pulse of energy that causes the protons to spin together
  - This energy is sent at the RESONANCE Frequency



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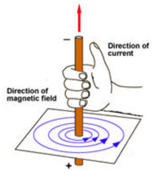
MRI- Magnetic Resonance Imaging

The MRI then has a receiver (coil) that picks up the electrical current caused by the spinning protons (right hand rule)



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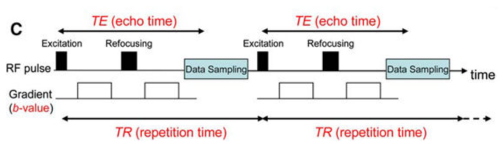

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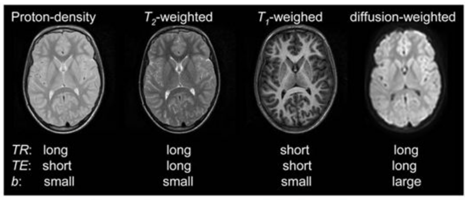
MRI signal (S)

- S=PD(1- $e^{-TR/T1}$) $e^{-TE/T2}$ e^{-bD}
  - PD is the density of water molecules in that region
  - D is the inherent movement of all small particles (Brownian motion), in this case water.
  - TR is the repetition time (Time between “Bell rings” or excitations)
  - TE is the echo time (time between excitation and data collection)
  - T1 and T2 are relaxation times (time for the protons to return to their original orientation)

Susumu M and Jiangyang Z. Neuron 2006: 51, 527–539.

MRI signal (S)

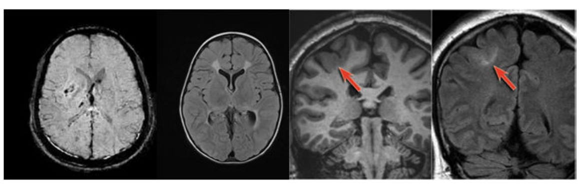
- Depending on what you want to highlight, the MRI can be manipulated to change the TR or TE



Susumu M and Jiangyang Z. Neuron 2006: 51, 527–539.

MRI

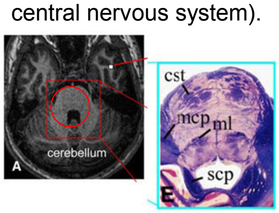
- The “usual” MRI images obtained are useful to evaluate for blood, tumors, gliosis (scars), acute injury, and brain malformations.



http://www.radiologyassistant.nl/en/p4f53597deae16/role-of-mri-in-epilepsy.html

MRI

- However, these modalities are poor at finely defining white matter tracts (the wiring of the central nervous system).



Susumu M and Jiangyang Z. Neuron 2006: 51, 527–539.

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MRI

Can we do better?

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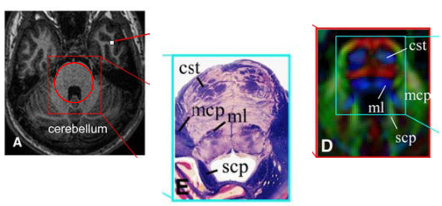
MRI

- Yes



Diffusion Tensor Imaging (DTI

Susumu M and Jiangyang Z. Neuron 2006: 51, 527–539.

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Diffusion Tensor Imaging (DTI)-Apparent Diffusion Coefficient

- $S=PD(1- e^{-TR/T1})\ e^{-TE/T2}\ e^{-bD}$
    - Acquire data repeatedly, varying only the little b with each picture. Compare the difference in the signal then solve for D (Computer does some crazy math and gives you a value)
    - D will be different in each spot tested based on what surrounds that area of measurement.

Susumu M and Jiangyang Z. Neuron 2006: 51, 527–539.

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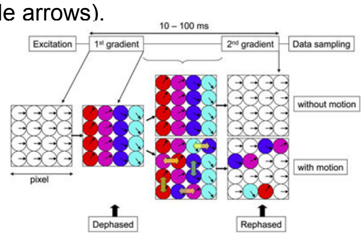
DTI- How is this possible?

D represents random motion in water (the double arrows).



Susumu M and Jiangyang Z. Neuron 2006: 51, 527–539.

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D- How is This Possible- Real Life Example

- Imagine a line of 3-5 year olds in the aisle of a store. They are perfectly lined up (Protons are lined up in the magnetic field)
- Now we tweak the line (chaperone for each child pushes child to his/her right)- first gradient. Then wait for it….
- The random motion of the 3-5 year old….
- Now opposite force applied (chaperone goes to pull child back to original position)- Second Gradient

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D- Real life example of ADC

- Data Sample= What?? Less children are back in line (some got out of arms reach)- That is the value of D, that loss of signal (shorter line). The higher D, the more kids that got away (the higher the random motion)

D- Real life example ADC

- Now what can affect this D (random motion)?
  - Surroundings
    - Kids run through water faster than molasses (viscosity)
    - Kids will run up and down an aisle easier than climbing the shelf.
      - If you find kids restricted along an aisle (axis) this is anisotropic diffusion (vs no aisles, kids are distributed in a circle (isotropic))
      - This concept of anisotropic diffusion (anisotropy) can be expressed as a number from 0 to 1 (fractional anisotropy, 0 is isotropic and 1 is complete anisotropic)

D- Real life example of ADC

- Now it gets cool.
  - Imagine looking at this line of kids from 3 angles
    - Left/right, Up/down, Forward/backward
  - You push the kids in each direction and measure how many got away. If they are restricted by a floor, ceiling, or wall, less get away (D is smaller). If you are pushing parallel to the aisle, more disperse.
    - This tells you which way a structure (axon/aisle) is oriented.

"Tensor" of Diffusion Tensor Imaging

- Tensor is an application of math equations to the ADC (apparent diffusion coefficient or left/right, up/down, forward/backward) values to find the "sweet spot" of highest diffusion
  - Difference in "north to south" versus "Northwest, mostly north, with 1 degree of elevation"

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Diffusion Tensor Imaging (DTI)

- Tractography takes a point, calculates the DTI signal and decides if enough anisotropic diffusion exists to continue to the next point.

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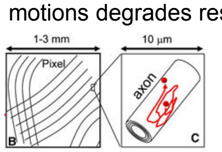
DTI limitations

- The signal is an average of about 1000 axons, so orientation is still imperfect
- The direction of travel along the axon is unknown
- The scan times are longer, so physiologic motions degrades resolution.



Susumu M and Jiangyang Z. Neuron 2006: 51, 527–539.

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What can DTI tell us about the typical brain?

- Important to understand the norms before trying to define the abnormal condition

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White Matter on DTI over the Life Span

- White matter (WM) FA increases from newborn to mid-adolescence, slowly increases until middle age then declines
- WM tracts develop central toward the periphery (i.e. internal capsule then corona radiata)
- Inter-hemispheric tracts mature by adolescence- reaction time and regulation of behaviors emerge

Yap QJ et al. J Neural Transmission (2013) 120:1369–1395

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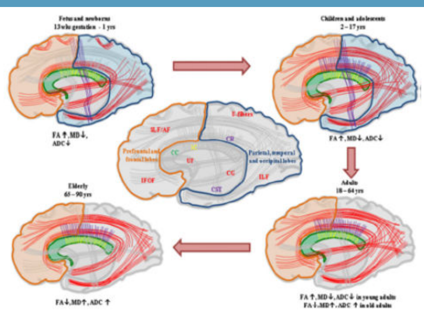

WM Changes on DTI over the Life Span

Yap QJ et al. J Neural Transmission (2013) 120:1369–1395

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White Matter on DTI over the Life Span

- Gender differences have been noted in different regions of the brain
  - Genu of Corpus Callosum and the Superior Longitudinal Fasciculus

Brouwer RM et al. NeuroImage (2010) 53:1085–1092

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White Matter on DTI over the Life Span

- Left and right regions can differ particularly in the arcuate fasciculus (language), suggesting specialization may influence structure.
- This phenomenon of specialization affecting structure (FA) has also been reported in musicians.

Schmithorst VJ et al. Radiology (2002) 222(1):212–218
Schmithorst VJ and Wilke M. Neuroscience Letters (2002) 321:57–60

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Genetics play a role DTI findings

- 185 nine-year old children
  - Monozygotic and dizygotic twin pairs

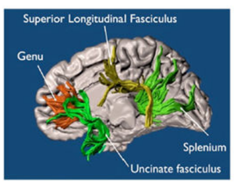

Fig. 1. Fiber tracking results for a typical subject (first-born monozygotic female). Visible are the fiber bundles in the left hemisphere.

Brouwer RM et al. NeuroImage (2010) 53:1085–1092

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Genetics play a role DTI findings

Table 4
Relative contributions of genetic (A), common environmental (C) and unique environmental (E) factors to variation in radial diffusivity.

	A (%)	C (%)	E (%)
Genu of corpus callosum	**32** [2–66]	18 [0–43]	50 [35–75]
Splenium of corpus callosum	**33** [5–60]	14 [0–37]	53 [34–76]
Left uncinate fasciculus	**29** [2–53]	1 [0–24]	70 [47–93]
Right uncinate fasciculus	17 [0–55]	20 [0–42]	63 [41–87]
Left SLF	**64** [30–81]	0 [0–14]	36 [19–68]
Right SLF	**27** [5–52]	8 [0–27]	65 [43–91]

Columns 2–4 present estimated contributions of A, C and E and 95% confidence intervals.
SLF = superior longitudinal fasciculus. Significant contributions of genetic factors (A) or common environmental factors (C) are printed in bold.

Brouwer RM et al. NeuroImage (2010) 53:1085–1092

Correlation of WM density to Cognition

- 23 pairs of monozygotic twins
- 23 pairs of dizygotic twins
- Age = 25.1±1.5 years
- DTI imaging selected for major tracts after acquisition to increase signal:noise ratio
- Multidimensional Aptitude Battery (MAB)
  - Verbal (information, arithmetic, vocabulary)
  - Performance (spatial and object assembly)

Ming-Chang Chiang et al. *J Neurosci*. (2009) 29(7): 2212–2224

Connection of WM density to Cognition

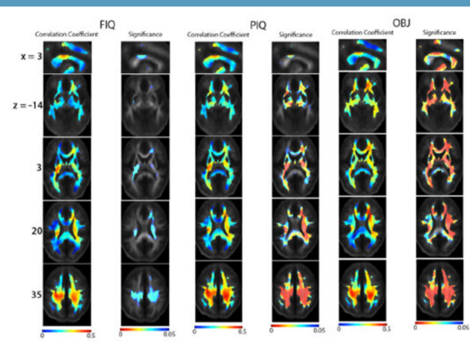
Table 4

Overall significance of correlations between FA and IQ scores.

	FDR values*
Verbal IQ	1.00
Information	0.67
Arithmetic	1.00
Vocabulary	1.00
Performance IQ	**0.01**
Spatial	0.13
Object assembly	**0.007**
Full-scale IQ	**0.04**

*FDR (false discovery rate) was computed only in regions where the individual IQ score correlated positively with FA. FDR < 0.05 (presented in bold font) indicated that 5% of the voxels where FA were found to be associated with the IQ score are in fact false positive findings. In other words 95% of the associations labeled are true. The maps of negative correlations between each of these measures and FA were not significant.

Ming-Chang Chiang et al. *J Neurosci*. (2009) 29(7): 2212–2224



Ming-Chang Chiang et al. *J Neurosci*. (2009) 29(7): 2212–2224

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Summary of "Norms"

- Age, sex, specialization, and genetics all play a role in the formation and maintenance of white matter tracts of the brain.

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DTI in clinical research

- Focus on the idea of exploring networks of the brain and the effects of TBI on these networks
- Focus on the integrity of pathways and the effects of TBI on the pathways
- Use of DTI to predict outcomes in TBI

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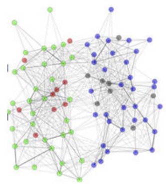
DTI in Clinical Research- Severe TBI

- Kim et al. – Moderate/severe TBI >2 months post-injury



Kim, J et al. J. of the International Neuropsychological Society (2014) 20: 887–896.

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DTI in Clinical Research-Severe

- In patients with moderate to severe TBI and Diffuse Axonal Injury vs Controls
  - Network efficiency, as defined by the shortest route between 2 points of the brain
    - Correlated to performance in executive function and verbal learning
    - Correlated to family reports of executive behavioral problems
  - Subcortical structures exhibited lower connectivity vs controls

Kim, J et al. J. of the International Neuropsychological Society (2014) 20: 887–896.

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DTI in Clinical Research- Mild TBI

- Measuring tract size/ integrity in 76 mTBI vs 50 control patients (Fractional Anisotropy) at 8-14 days post-injury
- Outcomes at 3 and 6 months
  - Verbal Learning
  - Processing Speed and working memory
  - Visual Attention, task switching, executive function
  - Global Outcome (GOS-E)

Yuh, EL et al J of Neurotrauma (2014) 31:1457-1477

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DTI in Clinical Research- Mild TBI

- In patients with mTBI and abnormal CT/ MRI, reduction in FA (integrity) of tracts noted in:
  - Right internal and external capsule
  - Genu of Corpus Callosum (connects the prefrontal cortices (executive function))
  - Bilateral uncinate fasciculi (postulated to play a role where memory is used to alter behavior—approaching or avoiding stimuli based on reward and punishment history)
  - Bilateral anterior corona radiata- network of anterior cingulate cortex- executive function

Yuh, EL et al J of Neurotrauma (2014) 31:1457-1477
Von der Heide RJ et al. Brain (2013) 136: 1692–1707

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DTI in Clinical Research- Mild TBI

- In patients with mTBI and normal CT/ MRI, these reductions in FA were not noted statistically more often than controls or less often than patients with abnormal MRI
- Outcomes between imaging positive and negative mTBI patients were similar across all tests.

Yuh, EL et al J of Neurotrauma (2014) 31:1457-1477

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DTI in Clinical Research- Mild TBI

- However, relative to controls, if you had reduction in FA (integrity) of tracts, this showed a predictive effect for worse outcome on the Glasgow Outcome Scale-Extended (GOS-E) (for imaging positive or negative patients).

Yuh, EL et al J of Neurotrauma (2014) 31:1457-1477

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DTI in Clinical Research- Mild TBI

- They also went back and separated out mTBI patients without prior psychiatric or substance abuse history and stratified them by normal or abnormal imaging.
  - This showed that prior psychiatric or substance abuse history masked the difference in the proportion of patients with FA reductions
    - Implies psychiatric or substance abuse history may affect the structure of tracts
  - The effect of abnormal tracts on outcome held up in this analysis

Yuh, EL et al J of Neurotrauma (2014) 31:1457-1477

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Pediatric meta-analysis

- Early (within 4 weeks) imaging
  - Mild TBI only
  - Increased FA and decreased ADC- suggesting acute swelling and cytotoxic edema
  - No data for more severe injuries at this early stage (n=4 studies)

Roberts RM, Mathias JL & Rose SE Developmental Neuropsychology (2014) 39:600-637.

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Pediatric meta-analysis

- Medium to long term imaging (3 to 45 months post-injury)
  - Mild to severe injuries
  - More regions appear to be affected following pediatric TBI than adults
    - Increased susceptibility to TBI effects??

Roberts RM, Mathias JL & Rose SE Developmental Neuropsychology (2014) 39:600-637.

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Pediatric meta-analysis

- Medium to long term imaging
  - Decreased FA and increased ADC noted
    - Internal capsule (all regions)
    - Corpus callosum (genu and total region)
    - Frontal lobes
    - Left inferior longitudinal fasciculus
    - Left dorsolateral region,
    - Temporal lobe (left and right)
    - Right inferior longitudinal fasciculus
    - Uncinate fasciculus (left and right)

Roberts RM, Mathias JL & Rose SE Developmental Neuropsychology (2014) 39:600-637.

Overall

- Although showing promise, DTI studies still show variability in results
  - Time from injury
  - Severity of injury
  - Age of patients/developmental trajectory
  - Area of impact
  - Variations in algorithms or data acquisition (models used)
  - Anisotropy is affected by other conditions (psychiatric and drug use, neurologic)

So….

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Overall

- American College of Radiology Head Injury Institute at this time finds
  - "…there remains insufficient evidence at the time of writing to suggest that these methods are valid, sensitive, and specific for routine clinical evaluation of TBI at the individual patient level."
  - "…there is insufficient evidence at the time of writing this article that DTI can be used for routine clinical diagnosis and/or prognostication at the individual patient level."

Wintermark et al. AJNR Am J Neuroradiol (2015) 36:E1–E11

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Future

- Combining different imaging modalities
  - MR spectroscopy (MRS)
  - DTI
  - Functional MRI (fMRI)
  - SPECT
  - PET
- With Outcomes/Neuropsychology results

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Thank You

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DTI, fMRI, MRS, Neuropsychological

- 8 with PCS after mTBI (>1 year postinjury)
- 8 without PCS
- 9 Non-head injured controls
- Performance of working memory and attention/processing speed tasks.
- Correlation analyses were performed
  - Relationship between the functional data (fMRI) and structural (DTI) and metabolic alterations (MRS) in the same participants.

Dean PJA et al. Brain and Behavior (2015) 5(1):1-17

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DTI, fMRI, MRS, Neuropsychological

- n-Back
  - The subject is presented with a sequence of stimuli, and the task consists of indicating when the current stimulus matches the one from *n* steps earlier in the sequence.
  - Activates lateral premotor cortex; dorsal cingulate and medial premotor cortex; dorsolateral and ventrolateral prefrontal cortex; frontal poles; and medial and lateral posterior parietal cortex

Dean PJA et al. Brain and Behavior (2015) 5(1):1-17

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DTI, fMRI, MRS, Neuropsychological

- Paced Visual Serial Addition Task (PVSAT)
- Sustained attention and concentration

Dean PJA et al. Brain and Behavior (2015) 5(1):1-17

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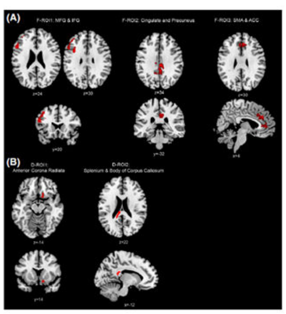

Figure 2. Regions of Interest for fMRI (F-ROI, A) and DTI (D-ROI, B).

Dean PJA et al. Brain and Behavior (2015) 5(1):1-17

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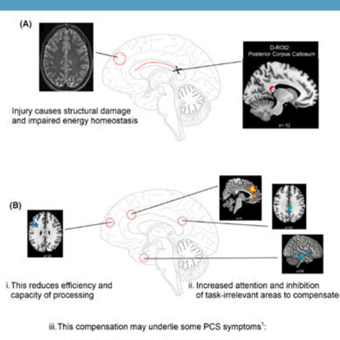

Dean PJA et al. Brain and Behavior (2015) 5(1):1-17