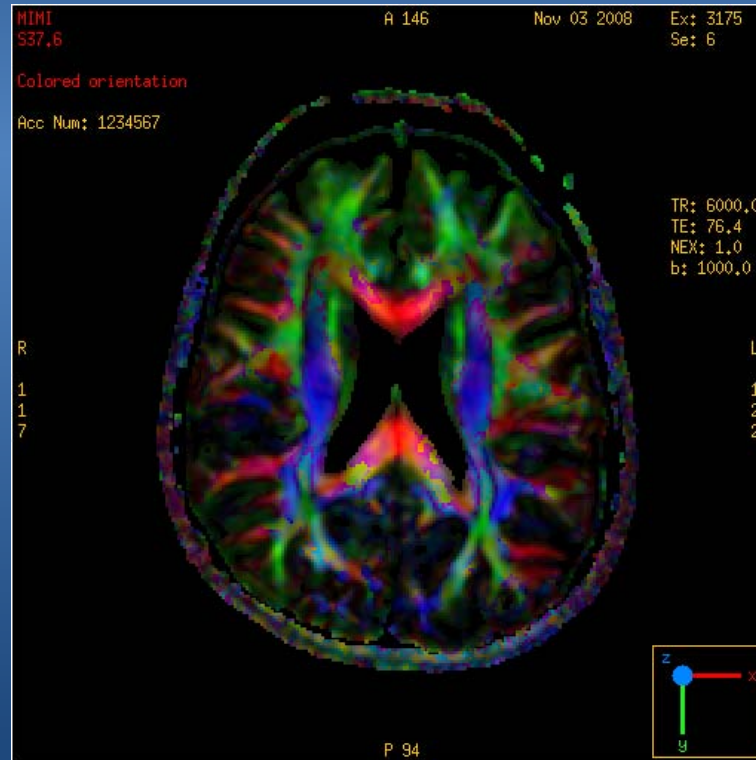


# Diffusion Tensor Imaging in Mild Traumatic Brain Injury Litigation



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# Goals/Objectives...

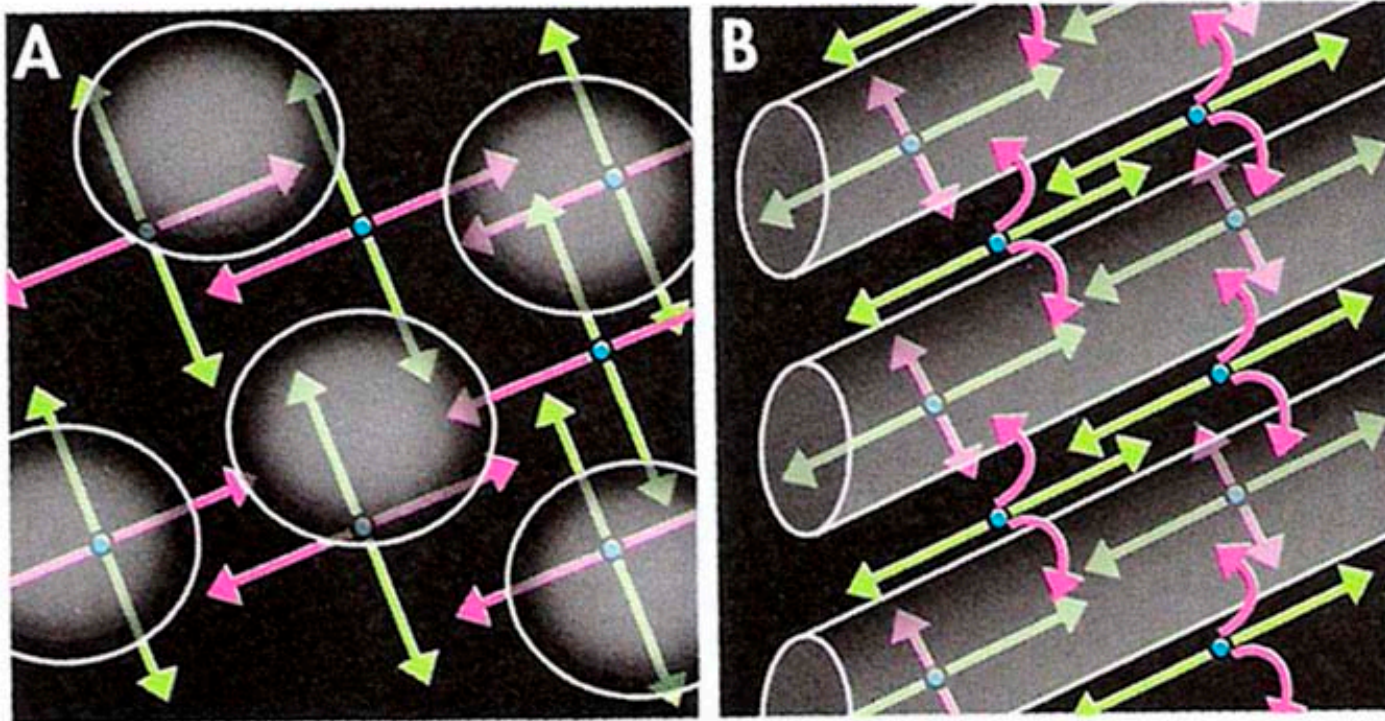
- A growing body of literature addresses application of DTI to TBI
- Most TBIs are of mild severity; diagnosis and prognostication is often challenging, and exacerbated in medicolegal contexts
- Plaintiffs seek objective evidence supporting diagnosis of mTBI
- DTI permits quantification of white matter integrity, TBI frequently involves white matter injury, thus DTI is conceptually appealing method to demonstrate white matter pathology
- Guided by rules of evidence shaped by *Daubert*, review and analyze literature describing DTI in mTBI and related neuropsychiatric disorders.

# Not a New Problem...

- Previously addressed same issue with SPECT and continue to see troubling medicolegal applications
- Not just forensic contexts, but “commercialization” for clinical purposes
- Adinoff and Devous (2010) argue early misapplications of neuroimaging, if left unchallenged, may poison the waters...
  - *“Unfortunately, if previously led astray by unsupported claims, patients and their doctors may be less inclined to utilize scientifically proven approaches once these are shown in the peer-reviewed literature to be effective. It is therefore incumbent upon all of us to monitor and regulate our field. We encourage physicians to remain vigilant of unproven approaches practiced by our peers and to immediately report these trespasses to their state medical boards.”*
- Litigation, with adversarial environment and compensation issues, can lead to early transgressions... charge issued to preserve the scientific merit of emerging technologies must fall to forensic psychiatrist too

# Diffusion Tensor Imaging

- Powerful and new tool for evaluating brain structure, especially white matter
- Exploits water's differential diffusion along versus across axons
- Provides information on axonal direction and integrity
- Images modified for sensitivity to water movement in different directions

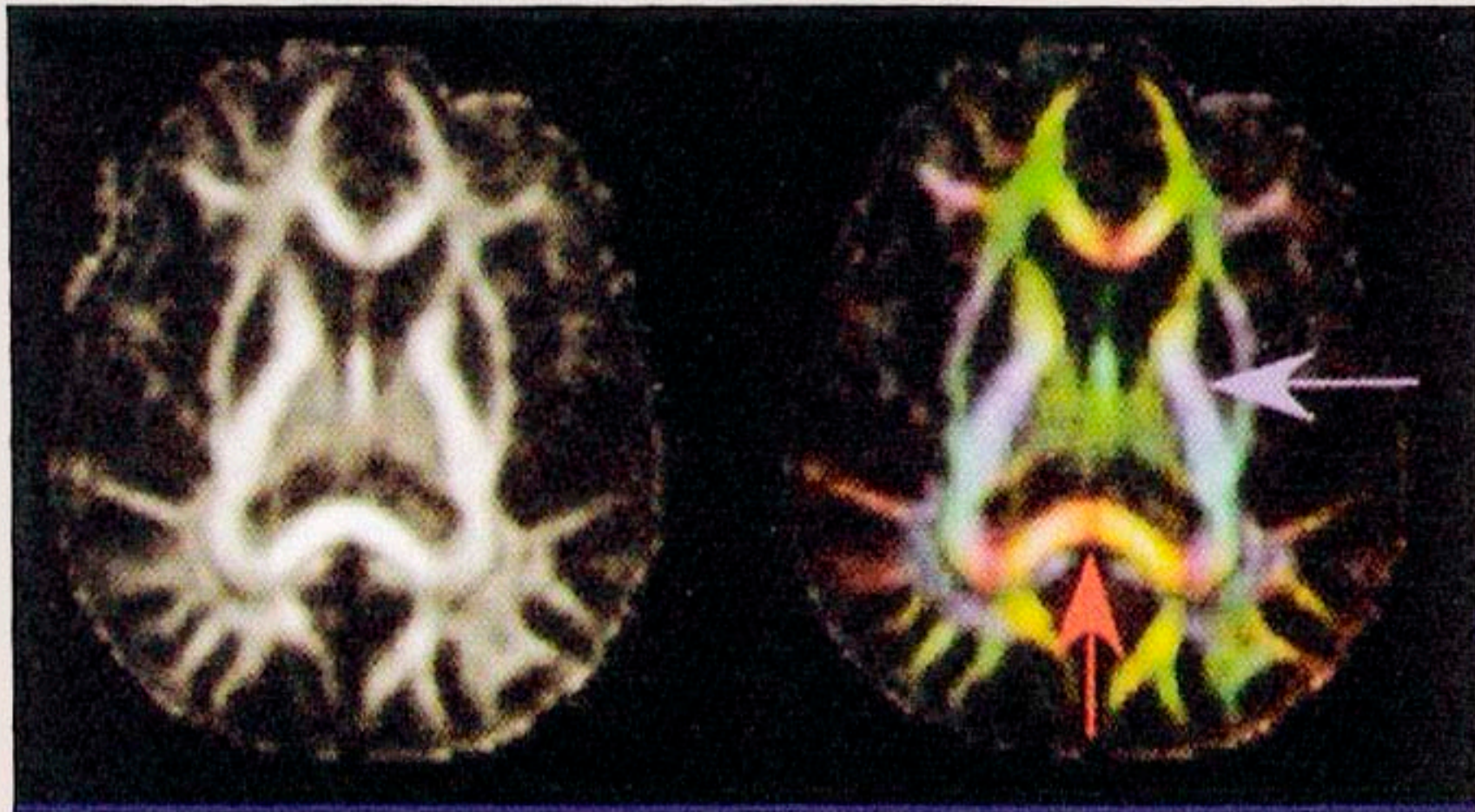


**FIGURE 7-12.** Gray matter contains cell bodies and processes and is quite heterogeneous. Water diffusion is the same in all directions (isotropic), as indicated by (A) the similar length of the green and pink arrows. White matter contains tightly packed axons. Water diffusion is faster (B, green arrows) along the length of (parallel to) axons than it is (B, pink arrows) across axons.



# Diffusion Tensor Imaging

- Acquires several MR images modified to increase sensitivity to water movement in multiple directions
- Data combined and matrixed to provide information about shape of the diffusion tensor (mathematical term referring to the abstract object created by this matrix) at each voxel
- Fractional anisotropy (FA) is derived from these data; FA value (ranges from 0-1) reflects degree to which diffusion tensor at each voxel is isotropic (assigned a value of '0') or anisotropic (assigned a value of '1')
- Some other measures: ADC, AD, RD



**Figure 2-19.** Diffusion tensor imaging (DTI). Anisotropy map (*left*) and color-coded DTI (*right*) of a healthy control subject.

Image from Hurley (2008)

# DTI Findings in Neurological and Neuropsychiatric Disorders

- *White et al. (2008)* reviewed DTI in psychiatric disorders (schizophrenia, depression, anxiety, OCD, ADD, PD, etc.)
  - nearly 100 publications identified
  - “Tremendous” heterogeneity and substantial overlap between these conditions.
  - Positive findings predominate in the cingulum bundle (CB), corpus callosum (CC), and frontal and temporal white matter – regions common mTBI literature
  - Authors note differences in methodologies, scanner sequences, imaging processing algorithms, all complicate interpretation of results
  - Lack of studies comparing/contrasting different clinical populations precludes knowledge of specificity



# DTI Findings in Neurological and Neuropsychiatric Disorders

- Cigarette smokers - Paul *et al.* (2007)
- Obstructive sleep apnea - Macey *et al.* (2008)
- Drug of abuse – MJ: Ashtari (2009), CA: Lim (2002), EtOH: Yeh (2009)
- Early life stress - Paul (2008)
- Parental Verbal Abuse - Choi (2009)
- Nonspecific alterations of white matter integrity are the rule and locations of alterations are common to multiple conditions

# DTI in the Mild TBI Literature

- Pubmed/MEDLINE search anchored to terms “diffusion tensor imaging,” “mild traumatic brain injury,” and variations on this theme (e.g. “mTBI and DTI”)
- Search yielded 30 results
- Only those studies reporting findings specifically relating to mTBI included for further analysis.
- 24 remaining studies

# Generalized Issues from Existing Literature

- Definition of mTBI employed in these studies is highly variable
  - Some define mTBI according to the American Congress of Rehabilitation Medicine (ACRM) definition
  - others limit mTBI to the mildest of mTBI based on a Glasgow Coma Scale score of 15
  - whereas other permit the entire range of mTBI based on this scale (GCS of 13-15)
  - others employ criteria that depart from these standard definitions of mTBI

# Variability in the Imaging Timing

- Ranging from day of injury to many years later
- But traumatic axonal injury is a progressive event that evolves first several days to weeks after TBI
- DTI studies are thus evaluating white matter change at different stages of a dynamic neuropathological process
- The heterogeneity of reported findings between studies is therefore not unexpected



# Analytic Approaches to DTI Data

- Some studies calculate apparent diffusion coefficient (ADC) as a measure of white matter integrity
- Other use FA for this purpose
- Others use additional measures such as radial diffusivity (RD, reflecting myelin integrity) and axial diffusivity (AD, reflecting axonal integrity)
- Some employ hypothesis-free analyses of whole brain and apply methods of correction for multiple unplanned comparisons
- Some use a region of interest (ROI) method in order to test specific anatomic or anatomic-clinical hypotheses
  - even within these there are methodological differences: which ROI(s) are targeted, how ROI is defined, whether a manual (i.e., hand-traced) versus semi-automated versus automated technique is employed

# mTBI and DTI literature available presently suffers from:

- Differences in the definition of mTBI employed and the heterogeneity of injury captured under the term “mild TBI”
- Heterogeneity in the time post-injury at which persons with mTBI have been studied using DTI
- Lack of a standard, widely used and generally accepted method for acquiring, analyzing, and interpreting DTI data

# Consideration of *Daubert* Criteria to DTI in Mild TBI

- Criteria established in *Daubert*, *Joiner*, and *Kuomo* intended for flexible application
- Flexible approach will be crucial for courts given potential for variability in equipment, technique, experience level, clinical circumstances, and reporting of results is enormous.
- *Daubert* analysis is a judicial exercise to be applied on a case-by-case basis. But, *Daubert* criteria may usefully guide review and analysis of the medical literature.
- Analysis offered is merely anchored to *Daubert* criteria and not intended to supplant need for the judicial exercise and obviously does not dictate the admissibility of DTI evidence in any given instance

Has the theory behind the technique been tested?

- DTI's remarkable ability to assess white matter integrity makes it a compelling choice for the study of TBI and the known white matter damage associated with such injuries.
- DTI's ability to identify mTBI has already been the subject of considerable scientific inquiry at multiple institutions worldwide



# Has it been subjected to peer review/publication?

- This issue more complicated than it appears at surface
- As discussed, major problems with literature as a whole: definitions, timing, and techniques
- Problem render many findings difficult translate clinically or medicolegally
- There exist no studies demonstrating the ability of DTI to serve as a valid and reliable diagnostic assessment of mTBI at the single-subject (patient) level
- Different missions and applications of peer-reviewed scientific publications and the court's
- Inability to translate between group findings to single-litigant applications

# Known rate of error and established standards?

- Lack of “gold standard” for diagnosing mTBI makes determining rates impossible
- Multiple confounding factors – comorbidities, environmental influences, medications, substances of abuse – operative in individual patient and may generate patterns indistinguishable from mTBI
- Sensitivity, specificity, positive and negative predictive value remains unknown

# Known rate of error and established standards?

- DTI, and its application to mTBI, is lacking widely accepted and commonly applied quality assurance standards
- Research and clinical facilities differ substantially in terms of equipment, techniques
- No clear front-runner has established itself as the preferred method

# Generally accepted?

- Must pose the proper inquiry when considering this criterion
- DTI's ability to characterize white matter integrity may meet this bar
- But more pertinent set of questions is:
  - Can DTI identify changes in white matter integrity caused by mTBI
  - distinguish changes by mTBI from those produced by other conditions
  - Determine relative contributions of mTBI and other conditions to a given DTI data set
  - Offer information that informs on neurological or neuropsychiatric impairments and functional disability experienced by an individual subject, patient, or litigant.
- The most accurate answer to this set of is “no.”



# Potential for Misuse

- Society for Nuclear Medicine's Brain Imaging Council: use of "nonreplicated, unpublished or anecdotal" data is "inappropriate and has ominous implications. This can lead to unsupportable conclusions if introduced as 'objective evidence'"
- Particularly relevant to DTI and its presently unregulated state of affairs:
  - Technological aspects and limits of DTI remain inaccessible to many experts and lay-persons
  - Needed expertise is generally lacking
  - Because the DTI in TBI is predicated on compelling theory, and because the images produced are so visually spectacular, the seductive power of DTI may be exceptional
- DTI far too promising to allow early misapplications interfere with eventual realization of its full potential

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Hi!