Diffusion Tensor Imaging in Mild Traumatic Brain Injury Litigation

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A growing body of literature addresses the application of diffusion tensor imaging (DTI) to traumatic brain injury (TBI). Most TBIs are of mild severity, and their diagnosis and prognosis are often challenging. These challenges may be exacerbated in medicolegal contexts, where plaintiffs seek to present objective evidence that supports a clinical diagnosis of mild (m)TBI. Because DTI permits quantification of white matter integrity and because TBI frequently involves white matter injury, DTI represents a conceptually appealing method of demonstrating white matter pathology attributable to mTBI. However, alterations in white matter integrity are not specific to TBI, and their presence does not necessarily confirm a diagnosis of mTBI. Guided by rules of evidence shaped by *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, we reviewed and analyzed the literature describing DTI findings in mTBI and related neuropsychiatric disorders. Based on this review, we suggest that expert testimony regarding DTI findings will seldom be appropriate in legal proceedings focused on mTBI.

J Am Acad Psychiatry Law 39:511–23, 2011

Demonstrating structural and functional brain abnormalities among persistently symptomatic survivors of mild traumatic brain injury (mTBI) remains a challenge in clinical medicine. Physicians, patients, plaintiffs, and attorneys are interested in identifying methods, including technology-based diagnostic tests, that offer unequivocal evidence of mTBI. In this context, neuroimaging modalities such as cerebral single-photon emission computed tomography (SPECT) have been and continue to be entered as objective evidence of mTBI in civil litigation. In a relatively recent publication,[1] the Behavioral Neurology and Neuropsychiatry faculty of the University of Colorado School of Medicine performed a *Daubert* criteria-guided analysis of the literature pertaining to the application of cerebral SPECT to mTBI. Based on that analysis, we discuss the challenges and potential pitfalls surrounding the introduction of this specific form of neuroscientific evidence into mTBI litigation. Our ongoing experience with medicolegal applications of cerebral SPECT imaging as evidence of mTBI reveals that such practices frequently fail to comport with the *Daubert* analysis and recommendations offered.

Equally concerning is the continued application and commercialization of cerebral SPECT imaging for clinical purposes for which it lacks a sufficient evidence basis. The potential perils of such inappropriate deployment are well articulated in a recent exchange of letters[2,3] featured in the *American Journal of Psychiatry*. Adinoff and Devous[2] make the compelling argument that early misapplications of neuroimaging, if left unchallenged, may poison the waters such that when the technology becomes appropriate for meaningful clinical application its history of misapplication creates an untenable barrier to its acceptance in clinical and medicolegal settings:

> Unfortunately, if previously led astray by unsupported claims, patients and their doctors may be less inclined to

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Support for this work was provided by the VISN-19 MIRECC (HSW) and in part by National Institutes of Health Grant K23 MH068787 from the National Institute of Mental Health (MFK). The opinions offered in this article do not necessarily reflect those of the Veterans Administration or the VISN 19 MIRECC.
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Disclosures of financial or other potential conflicts of interest: None.

> utilize scientifically proven approaches once these are shown in the peer-reviewed literature to be effective. It is therefore incumbent on 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 [Ref. 2, p 598].

Litigation, which entails an adversarial environment and is driven largely by the question of compensation can lead to transgressions that involve the misinterpretation and misuse of imaging studies. The charge issued by Adinoff and Devous[2] to preserve the scientific merit of emerging technologies thus appropriately falls to the forensic psychiatrist as well.

Subsequent to our analysis of the forensic applications of SPECT in mTBI litigation, newer neuroimaging techniques have been applied in the search for more objective evidence of neuropathology in mTBI. Among the most often discussed of these currently is diffusion tensor imaging (DTI). The application of DTI to mTBI litigation is proceeding despite a paucity of critical analyses of the available data on which its use in this context is predicated. For instance, a publication by Lipton *et al.*[4] is misrepresented in a report indicating that DTI "showed the presence of major areas of structural damage" (Ref. 5) and arguing that DTI can help "identify those patients who should receive rehabilitation earlier when it is more useful to the patient."[5] The incorrect implication of such a statement is that group-level DTI findings are presently useful at the single-patient level. Statements of this kind, as well as personal in-court experience by some of the present authors, indicate that attorneys are aware of this neuroimaging technique and are prepared to use it in mTBI-related civil litigation in a manner lacking scientific precision.

At the time of this writing, a rigorous analysis of the peer-reviewed literature surrounding DTI as applied to mTBI or its application to single patients for clinical or forensic purposes has not been published. The challenges surrounding the diagnosis of mTBI, particularly in the context of litigation, and the need for such a review are articulated in an analysis of SPECT previously offered.[1] In the service of providing forensic psychiatrists, a review of the points relevant to the forensic application of DTI to mTBI and related litigation, the current paper aims to provide a brief overview of DTI and its application to various neuropsychiatric conditions; a review and summary of the literature describing DTI findings in mTBI; an analysis of that literature guided by criteria established by *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579[6]; and preliminary recommendations regarding the contexts and manner in which DTI might be incorporated appropriately into legal proceedings related to mTBI.

The overall goal of the following analysis is to evaluate the science of DTI as applied to mTBI and to determine what kinds of evidence are reasonably offered based on that science. As clinician-scientists, our approach is necessarily critical of the methods and interpretations of this literature and cautious about the implications of findings reported therein. We attempt to defend the science of DTI and its application to the study of mTBI against premature medicolegal application or frank misapplication and thereby preserve the scientific integrity and promise of this neuroimaging technique. DTI represents an ever-evolving research technology with powerful research potential that will hopefully lead ultimately to practical clinical applications.

Overview of Diffusion Tensor Imaging

DTI is a relatively new magnetic resonance imaging (MRI)-based data-analysis technique based on the somewhat older and clinically well established technique of diffusion-weighted imaging (DWI). Diffusion of water molecules along a magnetic field gradient reduces the magnetic resonance signal associated with those water molecules. When there is relatively little water diffusion (referred to as 'restricted' diffusion), there is little signal loss from these water molecules along the magnetic field gradient. The resulting display of this signal is intense (i.e., bright), thereby allowing DWI to serve as a marker of disrupted water diffusion in the brain, whether that disruption is due to biomechanical trauma, ischemia, hypoxia-ischemia, or some other cause. DTI is a more refined adaptation of this data analytic technique that allows for the determination of the directionality as well as the magnitude of water diffusion in the brain and more specifically within and between different brain tissue types.[7] The degree of restriction of diffusion (or, conversely, the freedom of water movement) is different along (i.e., parallel to) axons from the way it is across axons.[8] Water molecules will distribute themselves randomly and in all directions when movement is unimpeded, a phenomenon known as isotropic diffusion. However, in constrained environments, diffusion will predomi-

nate in directions of least resistance. Thus, in highly organized (i.e., normal) white matter tissue, the direction of water diffusion is predominantly parallel to axons; this is termed anisotropic diffusion. DTI capitalizes on these properties of water diffusion within the brain, specifically along white matter tracts, and is thereby sensitive to many processes that alter axonal or myelin integrity and hence the diffusion of water along those tracts.[8,9]

DTI acquires several MR images that are modified in a manner that increases sensitivity to water movement in multiple directions. The data acquired in this manner are combined and matrixed to provide information about the shape of the diffusion tensor (a mathematical term referring to the abstract object created by this matrix) at each voxel (a box-shaped element of the three dimensional space within the image of the brain), giving DTI its name.[8] One commonly used measure, the fractional anisotropy (FA) value, is derived from these data. The FA value (which ranges from 0 to 1) reflects the degree to which the diffusion tensor at each voxel is isotropic (assigned a value of 0) or anisotropic (assigned a value of 1). For a more detailed but accessible overview of the fundamentals of DTI, readers may benefit from reviewing Taber *et al.*[8]

Traumatic Axonal Injury and Diffusion Tensor Imaging

White matter, which connects various cortical areas with one another as well as to the subcortical structures, brainstem and cerebellum, and the spinal cord, is vulnerable to damage when mechanical force is applied to the brain and particularly to the shearing and straining forces resulting from rotational force and angular acceleration or deceleration.[10–12] Traumatic axonal injury, more commonly referred to in the clinical literature as diffuse axonal injury (DAI) or, perhaps more accurately, as multifocal axonal injury,[13] is a common feature across the spectrum of TBI severity (see Povlishock and Christman[11] for a review). Traumatic axonal injury has been described as the consequence of mechanically induced tearing of axons, with subsequent retraction and expulsion of a portion of the axoplasm that forms an axonal retraction ball. Recent evidence, reviewed in detail by Büki and Povlishock,[14] suggests that while this classic model may apply to a subpopulation of axons in very severe injuries, traumatic axonal injury is more accurately understood in most cases as a progressive but relatively short-duration event (i.e., one that is measured in days) in which mechanically induced focal axonal alterations evolve through a complex cytochemical cascade to delayed axonal disconnection. White matter injury of this sort occurs diffusely, but predominates in the brainstem, cerebral parasagittal white matter, corpus callosum, and gray-white junctions of the cerebral cortex, especially at the ventral and anterior frontal and temporal lobes.[13]

Given the frequency of white matter damage in TBI and the ability of DTI to identify alterations of white matter integrity, there is a reasonable theoretical foundation for the application of DTI to the study of TBI and, perhaps, the clinical evaluation of persons with TBI. However, although traumatic axonal injury is a common feature of TBI, it is not an invariable one.[15] Additionally, the precise contribution of traumatic axonal injury to the morbidity associated with TBI (in experimental injury models) is difficult to assess, even at the severe end of the injury spectrum.[14,16] The functional relevance of traumatic axonal injury (i.e., the effect of this specific type of neuropathology not only on cognitive, psychiatric, and elementary neurologic impairments but also occupational, interpersonal, and other daily activities), as well as the relationship between DTI findings (e.g., alterations in cerebral white matter integrity) in mTBI and functional status are largely still matters of speculation. In addition, alterations of white matter integrity are present in many other neurologic and neuropsychiatric conditions and also appear to be relevant to the spectrum of normal functioning across cognitive, emotional, and behavioral dimensions.[17] Accordingly, any account of the relationship between DTI findings in mTBI and functional outcome needs to account as well for the relative contributions of these other common conditions to those findings and their clinical correlates.

A review of all applications of DTI to various neuropsychiatric conditions is beyond the scope of this article. However, brief consideration of this literature will be necessary to address the specificity and limitations of DTI as a marker of traumatic axonal injury in mTBI, as well as the ability of DTI findings to differentiate between traumatic axonal injury, other neurologic and neuropsychiatric conditions, and normal healthy individuals.

DTI Findings in Neurologic and Neuropsychiatric Disorders

White *et al.*[18] performed a review of the literature on DTI used to study psychiatric disorders, including schizophrenia, depressive disorder, anxiety disorders, obsessive-compulsive disorder, attention deficit disorder, autism, and personality disorders. Nearly 100 publications were identified. Results indicated extensive heterogeneity and substantial overlap among these conditions. Positive findings tend to predominate in the cingulum bundle (CB), corpus callosum (CC), and frontal and temporal white matter, regions in which abnormalities are also identified by DTI among groups of subjects with mTBI (review to follow). The authors noted that differences in methodologies, including scanner sequences and imaging processing algorithms, complicate the interpretation of results and that the lack of studies comparing different clinical populations precludes knowledge regarding the specificity of such findings.[18] A growing body of literature reflects the breadth of conditions that might exert an impact on white matter integrity and highlights persisting uncertainty regarding the meaning and specificity of DTI findings in these and other conditions.

Paul *et al.*[19] used DTI to compare healthy cigarette smokers with nonsmokers, and reported significantly increased FA within the CC of smokers, results generally at odds with findings of reduced FA with other substances of abuse.[19–22] Macey *et al.*[23] compared subjects with obstructive sleep apnea with healthy controls and reported multiple regions of reduced FA, including the CC, CB, and internal capsule (IC), among others. There are even studies indicating that early life stress[24] and/or parental verbal abuse[25] may result in differences in white matter integrity as measured by DTI. In short, investigation of white matter across a broad spectrum of neuropsychiatric conditions using DTI suggests that nonspecific alterations of white matter integrity are the rule and that the locations of these alterations are common to multiple conditions. This observation portends problems for the use of DTI findings for diagnostic purposes, since any such findings will entail a broad differential diagnosis of common neuropsychiatric conditions and especially for diagnostic purposes at the single-subject level.

DTI in the Mild TBI Literature: Review and Commentary

Challenges to the Interpretation and Generalization of Findings From Existing Studies

A PubMed/MEDLINE search, anchored to the terms diffusion tensor imaging, mild traumatic brain injury, and variations on this theme (e.g., mTBI and DTI), was performed. The search yielded 30 results; only those studies reporting findings specifically relating to mTBI were included for further analysis. An overview of the remaining 24 studies is offered in Table 1. As the table indicates, the methodological variation among these studies is extensive, making comparisons between them challenging, at best. With respect to the population under study, the definition of mTBI employed in these studies is highly variable: some studies define mTBI according to the American Congress of Rehabilitation Medicine (ACRM) definition[48]; others limit mTBI to the mildest form based on a Glasgow Coma Scale[49] score of 15, whereas others permit the entire range of mTBI based on this scale (GCS, 13–15); and others employ criteria that depart from these standard definitions of mTBI. Even where standard definitions of mTBI are employed, it is not entirely clear that mTBI as defined by the ACRM is equivalent to that captured by GCS 15, and there are differences in initial injury severity and outcome between mTBI subjects whose GCS scores are 13 to 14 and those with GCS scores of 15.[50,51] Between-subject and -group differences within and across these studies necessitate caution when describing findings from any of them as characteristic of persons with mTBI.

As highlighted in Table 1, there also is substantial variability in the times after injury at which these studies were performed, ranging from the day of injury to many years later. As noted earlier, traumatic axonal injury, the neuropathologic consequence of TBI that DTI purportedly indexes, is a progressive event that evolves over the first several days to weeks after TBI.[14] Since the DTI studies performed in this population are evaluating white matter changes at different stages of a dynamic neuropathologic process, the heterogeneity of findings between studies is not unexpected. That heterogeneity, driven in part by discrepancies in the time postinjury at which studies are conducted, precludes generalization of findings from any one of them to the entire population of persons with mTBI as a whole.

Table 1 DTI and mTBI

Study	Participants	mTBI Criteria and/or Characteristics	DTI Timing Average (Range)	Brain Regions	Analytic Approach
2010					
Little *et al.*[26]	12 mTBI, 12 controls	ACRM mTBI criteria	>12 months	VA thalamic nucleus	ROI analysis: FA
Geary *et al.*[27]	40 mTBI, 35 controls	ACRM mTBI criteria	5.29 years	SLF, SS, UF	ROI analysis: FA
Levin *et al.*[28]	32 mTBI, 15 controls (8 healthy, 7 extracranial injury)	OEF/OIF veterans with blast injury, 32 mild plus 5 moderate TBIs, essentially ACRM criteria	871.5 days	No group differences in FA or ADC	Tractography, ROI, and voxel-based analysis: FA, ADC
Mayer *et al.*[29]	22 mTBI, 21 controls	ACRM mTBI criteria	12.5 days (2–20)	CC, CR, UF	ROI analysis: FA, AD, RD
2009					
Chu *et al.*[30]	10 mTBI, 10 controls	Initial GCS 15, negative CT, otherwise not reported	2.7 days (1–6)	Left thalamus, scattered white matter	Whole-brain voxel-wise analysis: ADC,FA, AD
Wu *et al.*[31]	12 mTBI, 11 controls	GCS of 15 in ED and +LOC (<10 min)	2.92 days (1–6)	CB	ROI analysis: FA, ADC
Lipton *et al.*[4]	20 mTBI, 20 controls	GCS ≤ 13, LOC < 20 min, PTA < 24 hr	(2–14 days)	Frontal white matter (DLPFC)	Whole-brain voxel-wise analysis: FA, MD
Kumar *et al.*[32]	26 mTBI, 33 controls	GCS 13–15, all + LOC (<20 min), all + CT	8.9 days (5–14)	CC	ROI analysis: FA, MD, AD, RD
Huang *et al.*[33]	10 mTBI, 14 controls	LOC < 15 min, GCS 13–15, PTA < 24 hr, persistent PCS	(1–46 months)	ILF, SLF, temporal, parietal, occipital, frontal	Whole-brain voxel-wise analysis: FA
Lo *et al.*[34]	10 mTBI, 10 controls	GCS ≥ 13, persistent cognitive impairment	(>2 yrs)	CC, IC	ROI analysis: FA, ADC
2008					
Lipton *et al.*[35]	17 mTBI, 10 controls	GCS ≥ 13, LOC < 20 min, PTA < 24 hr, persistent cognitive impairment	(8 months to 3 years)	CC, subcortical white matter, IC	Whole-brain voxel-wise analysis: FA, MD
Niogi *et al.*[36]	43 mTBI, 23 controls	GCS ≥ 13, +PTA	16.9 months (1–53 months)	Corona radiata, UF	ROI analysis: FA
Rutgers *et al.*[37]	24 mild TBI, 10 controls	GCS ≥13	2.8 months (0.4–26.2)	CC	ROI analysis: FA, ADC
Wilde *et al.*[38]	10 mTBI, 10 controls	GCS of 15 in ED and +LOC (<10 min)	2.7 days (1–6)	CC	Whole CC analysis: FA, ADC, RD
Niogi *et al.*[39]	34 mTBI, 26 controls	GCS 13–15, +LOC,+PTA, ≥1 post concussive symptom	(1–65 months)	Anterior corona radiate, UF, CC, ILF, CB	ROI analysis: FA
Miles *et al.*[40]	17 mTBI, 29 controls	GCS 13–15, LOC < 20 min, PTS < 24 hr	4 days (1–10)	CS, CC, posterior limb IC	ROI analysis: MD, FA
Rutgers *et al.*[41]	21 mTBI, 11 controls	GCS ≥13	5.5 months (0.1–109.3 months)	Cerebral lobar white matter, cingulum, CC	Whole-brain voxel-wise analysis: FA, ADC
2007					
Bazarian *et al.*[42]	6 mTBI, 6 orthopedic controls	GCS 13–15, +LOC or amnesia	≤72 hours	Left anterior IC, posterior CC	ROI and whole-brain analysis: trace, FA
Kraus[7]	20 mTBI, 18 controls	ACRM mTBI criteria	107 months	CST, SS	White matter load and ROI analysis: FA, AD, RD
Hashimoto *et al.*[43]	1 mTBI (case report)	GCS 13 at 30 min	3 years	CC, cingulate, prefrontal area	MR tractography
Wozniak *et al.*[44]	6 mTBI, 14 controls	LOC, PTA, altered MS, recurrent emesis or persistent headache, or transient focal neurological deficits + GCS 13–15	8.2 months	Supracallosal	ROI analysis: FA
Benson *et al.*[45]	6 mTBI, 14 controls	LOC or PTA + GCS 13–15, 4/6 with +CT findings	35.3 months (3 days–15 years)	Global white matter	Global white matter histogram analysis: FA
2002–2005					
Inglese *et al.*[46]	46 mTBI, 29 controls	ACRM mTBI criteria	4.05 days for 20 subjects, 5.7 years for 26	CC, IC, CS,	Whole brain histogram and ROI analysis: FA, MD
Arfanakis et al.[47]	5 mTBI, 10 controls	Amnesia, disorientation, or confusion + GCS 13–15	<24 hours	CC, IC, EC	ROI analysis: FA, LI

VA, ventral anterior; CB, cingulum bundle; DLPFC, dorsolateral prefrontal cortex; CC, corpus callosum; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; IC, internal capsule; UF, uncinate fasciculus; CS, centra semiovale; CST, corticospinal tract; SS, sagittal stratum; EC, external capsule.

The approaches to the analyses of DTI data in these studies are also heterogeneous and preclude the development of a common frame of reference for the comparison of findings between studies. For example, some studies calculate apparent diffusion coefficient (ADC) as a measure of white matter integrity, while others use FA for this purpose, and still others use additional measures such as radial diffusivity (RD, reflecting myelin integrity) and axial diffusivity (AD, reflecting axonal integrity) to help determine the contribution of various types of pathology to the FA value. In addition, some studies employ hypothesis-free analyses of the whole brain and apply one of several methods of correction for multiple unplanned comparisons to identify significant findings. Other studies use a region of interest (ROI) method to test specific anatomic or anatomic-clinical hypotheses and to limit the need to perform corrections for multiple unplanned comparisons. However, even within these studies there are methodologic differences with respect to which ROI(s) are targeted, how the ROI is defined, and whether a manual (i.e., hand-traced) versus semiautomated versus automated technique is used.

A related technical problem is the lack of a large normative database, including at least age and gender as foundations for its construction, for each make and model of MRI scanner and for each software version employed on those MRI scanners used to collect DTI data. Normative databases, much as are used to guide the interpretation of serum, urine, cerebrospinal fluid, and other quantitative laboratory assessments, are needed to interpret individual (i.e., single subject or single patient) FA, ADC, or other values for clinical purposes. In the absence of population-based normative databases of these sorts, each institution at which DTI is performed is left to develop and employ their own normative data when attempting to interpret group or single-subject DTI data. The size and normality of subjects included in these databases is highly variable between institutions, rendering the interpretation of any individual DTI result as normal or abnormal based on comparison to local normative data preliminary at best.

In summary, the mTBI and DTI literature available presently is adversely affected by the differences in the definition of mTBI employed and the heterogeneity of injury captured under the term mild TBI; heterogeneity in the time after injury at which persons with mTBI have been studied with DTI; and the lack of a standard, widely used, and generally accepted method for acquiring, analyzing, and interpreting DTI data. In light of these limitations, the diverse and sometimes contradictory results produced by the studies performed to date are not surprising, and they present substantive challenges to their use in nonresearch contexts.

Examples of Specific Problems Translating Studies Into the Medicolegal Setting

Despite the limitations and challenges noted in the preceding section, DTI is a potentially powerful research tool for investigating white matter pathology across a broad spectrum of neuropsychiatric disorders, including mTBI. The work summarized in Table 1 provides foundational research with which to expand our collective knowledge of the strengths and limitations of DTI in this context. In this section, we review and critique select publications with respect to their implications on DTI for single-subject use, particularly in the context of litigation. It is important to note that this review is not intended as a critique of these studies *per se* but instead on the problems with translating findings from these studies from the group-level research context to that of the individual litigant.

Inglese *et al.*[46] performed DTI histogram analysis and failed to detect any statistically significant differences between early and/or late mTBI participants and controls. However, ROI analysis did reveal significantly increased mean diffusivity (MD) and reduced FA in the CC, centra semiovale (CS), and IC of mTBI participants. This frequently cited study supports the contention that DTI may detect between group differences when comparing mTBI patients with healthy controls, and suggests that DTI is sensitive to white matter damage following such injuries. It does not, however, address the specificity of such findings to mTBI, nor does it suggest that DTI is sensitive to white matter damage at the single-subject level. As for the statistically significant between-group results, the means and standard deviations reveal the potential for substantial overlap in white matter findings between mTBI patients and healthy controls. For instance, MD at the CC splenium for late mTBI participants was .56 ± .07 and .49 ± .04 for controls; all other statistically significant results in this study demonstrate similar overlap between the mTBI and control groups. While the mean ± standard deviation differences between

groups may be sufficient to permit statistical discrimination between groups at the α level of .05 or lower, any individual subject with MD values in the range of overlap between these groups cannot be reliably determined to be in one or the other group on the basis of MD value alone.

Kraus *et al.*[7] conducted ROI DTI analysis to characterize white matter integrity across the spectrum of TBI and to examine the relationship between white matter integrity and neuropsychological performance. Although the moderate/severe TBI group demonstrated reduced FA in all ROI, the mTBI group demonstrated significantly reduced FA in the corticospinal tract (CST), the sagittal stratum (SS), and the superior longitudinal fasciculus (SLF). The mTBI group had increased axial diffusivity (AD) in the SS and SLF relative to controls, but not in the whole brain, and no significant differences were found in RD. Kraus *et al.*[7] also examined white matter load, determining the total number or regions with FA values 1 standard deviation below the control mean. Although the mTBI group had an average load of 6 regions in which FA values were reduced, each control subject had an average of 3.6 regions of reduced FA. These observations suggest that DTI is probably very sensitive to white matter pathology following TBI, but they reveal substantial interindividual differences in white matter integrity even among healthy controls. These findings suggest that the specificity of such DTI abnormalities to mTBI, even when as well characterized as in this study, is limited. These observations illustrate well the problem of applying this technique to the examination of individual subject, patients, or litigants. In their article, Kraus *et al.*[7] present scatterplots demonstrating the relationship between neuropsychological domain scores (executive, attention, and memory) versus white matter load for individual study participants. These scatterplots make clear the substantial overlap between the mTBI and control groups and the difficulty of distinguishing control from mTBI. Notably, results from neuropsychological testing in these groups demonstrated similar overlap. Although a trend toward greater impairment in executive function and attention for the mTBI group is reported, no significant differences were found for any neuropsychological domain score.[7]

Miles *et al.*[40] conducted an investigation to determine if baseline DTI results were predictive of cognitive functioning six months after mTBI. DTI consisted of ROI analysis to determine MD and FA in the CS, the CC (genu and splenium), and the posterior limb of the IC. Patients with mTBI were found to have statistically significant higher average MD and lower average FA when compared with controls. However, baseline DTI failed to reveal any statistically significant correlations with baseline neuropsychological testing, even though 41 percent of the mTBI group was cognitively impaired on baseline testing. For follow-up neuropsychological testing, a single statistically significant correlation was found between baseline FA values and performance on prioritization form B. Notably, of the five mTBI subjects who failed to return for follow-up testing, four were not impaired at baseline testing. In addition, as the authors themselves acknowledged, psychological status and other possible confounds were not assessed.

Rutgers *et al.*[37] performed ROI DTI analysis of the genu, body, and splenium of the CC. Patients with mTBI showed no significant difference in FA, ADC, and number of fibers for the genu, body, and splenium. However, when only those mTBI participants scanned less than three months after injury were compared with the controls, DTI abnormalities were associated with a history of mTBI. The authors suggested that DTI abnormalities in mTBI may be reversible,[37] a finding that would comport with an extensive body of literature on the natural history of such injuries.[52]

Niogi *et al.*[36] conducted an interesting ROI DTI analysis examining the correlation between FA in the anterior corona radiata (CR) and the uncinate fasciculus (UF) with attention and memory function in both healthy controls and mTBI patients. Although the mTBI group demonstrated a wider range of scores for attention, memory, and FA, there was considerable overlap between groups, and both featured correlations between attentional control and FA in the CR, and between memory and FA in the UF. These results suggest that tract-specific variations in white matter integrity for both healthy individuals and mTBI patients can account for variation in performance across specific cognitive domains. The fact that DTI can apparently capture anatomic differences in white matter anatomy that correlate with normal variation in cognitive performance indicates the likelihood of substantial problems regarding the specificity of abnormal findings derived from DTI, particularly at the individual patient level.

Lipton *et al.*[35] performed a retrospective study using whole-brain, voxel-wise DTI analysis to compare participants with cognitive impairment due to mTBI with healthy controls. This group reported an overall shift toward lower FA in mTBI patients, with significantly decreased FA noted in the CC, subcortical white matter, and bilateral IC. A similar study by Lo *et al.*[34] also compared patients with persistent cognitive impairment following mTBI with healthy controls using ROI DTI analysis. They reported decreased FA and increased ADC at the left genu of the CC in mTBI patients and increased FA in the posterior limb of the IC. Both of these studies involve retrospective designs wherein patients were identified based on persisting cognitive impairment, with the presumption that such cognitive deficits were the result of biomechanical trauma induced by mTBI. Relationships between the nature and/or severity of persisting symptoms and DTI findings were not explored. Although Lipton *et al.*[35] and Lo *et al.*[34] demonstrate white matter differences in their respective patient populations compared with healthy controls, given the nonspecific nature of postconcussive symptoms and the small number of subjects included in these studies, the specificity of their findings to TBI, rather than to other causes of postconcussive symptoms (e.g., depression, anxiety, and sleep disorders), remains uncertain and the translation of their findings to diagnosis of mTBI by DTI at the single-subject untenable.

Kumar *et al.*[32] used DTI to examine the CC in the acute period following mild and moderate TBI and correlated neuroimaging findings with neuropsychological testing at six months after injury. All TBI participants experienced a loss of consciousness, and all had demonstrable computed tomographic (CT) findings at the time of injury. A significant decrease in FA in the genu of the CC was observed in the mild and moderate TBI groups; the study authors also observed an increase in RD at the genu and splenium among the mild and moderate TBI groups when compared with the healthy control group. Changes in FA, RD, AD, and MD at various locations within the CC were associated with impaired performance on various elements of neuropsychological testing. The authors concluded that CC abnormalities were more common in the moderate TBI group than in the mTBI group, with a trend toward worse cognitive outcome at six months. They also suggested that RD may prove to be a better marker of axonopathy and myelin breakdown in the early postinjury period. For the purposes of the present discussion, it is crucial to note the atypical nature of the mTBI group in this investigation, all of whom had both loss of consciousness and positive CT imaging; results based on such a study group are not likely to be generalizable to most mTBI patients or litigants. It is hardly surprising that this group of injured subjects separated from healthy controls, and such findings do little to establish the specificity of the DTI results reported. DTI data from this study were acquired during the acute injury period; it remains unclear if such findings persist into the chronic stages of injury. In addition, the authors' proposal of RD as a better marker for acute axonal injury reflects the yet-to-be-determined optimal method for DTI imaging and best metrics as applied to the injured brain.

Lipton *et al.*[4] compared patients with mTBI and matched controls using whole-brain, voxel-wise DTI analysis and neuropsychological assessment, both within two weeks of injury, to determine whether frontal white matter diffusion abnormalities can predict acute impairments in executive function. The mTBI group performed significantly worse on neuropsychological testing, and voxel-wise analysis of FA revealed 15 clusters of significantly reduced white matter FA, 5 of which occurred in the frontal lobes. A significant relationship between three of the frontal FA measurements and neuropsychological tasks was identified, with the most robust relationship for white matter subjacent to the left dorsolateral prefrontal cortex. Although the mTBI group exhibited higher levels of depression, stress, and anxiety, correlation analyses suggested that the association between DTI findings and neuropsychological test performance was independent of such emotional factors.[4] This study offers evidence that the frontal lobes and its cognitive functions are indeed vulnerable to acute biomechanical trauma as sustained in mTBI, a finding consistent with a large body of literature describing the well-established natural history of mTBI. However, these results do not facilitate prognosis at the individual subject level, including determinations of who will fail to follow the typical course of complete recovery or why they do so. These authors also discuss the relative advantages and disadvantages of voxel-wise versus ROI DTI analysis, reflecting the persisting controversies surrounding how best to apply this new technology to the injured brain.

Mayer *et al.*[29] performed ROI DTI analysis comparing a group of mTBI subjects in the subacute period with a healthy comparison group. Clinical assessment of attention, working memory, processing speed, executive function, memory, and emotional status was also performed and compared with DTI metrics in terms of accuracy for distinguishing patients from controls. FA in the mTBI group was increased in the CC, left CR, and left UF, and RD was lower in the CC genu, left UF, and left CR. Neuropsychological testing using premorbid intelligence as a covariate did not reveal significant between-group differences. Using binary logistic regression modeling, the authors sought to determine which of their objective measures of deficits, FA or neuropsychological battery, more accurately classified subjects as mTBI versus healthy control. Both models discriminated between controls (65% accuracy) and mTBI patients (66.7%) at slightly above chance levels. The addition of traditional neuropsychological measures of attention, memory, and executive function reportedly helped little, raising accuracy to 60 percent and 71.4 percent, respectively. The addition of right and left FA indices to the model did improve accuracy, but only to 70 and 81 percent, respectively. Notably, even the best model in this recent study suggested substantial error rates when sorting healthy controls from subacute mTBI patients using the combination of DTI and neuropsychological assessment. Levin *et al.*[28] used DTI tractography, ROI, and voxel-based DTI analysis, as well as measures of postconcussion symptoms, posttraumatic stress disorder (PTSD), global distress and depression, and cognition to compare Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans with mild and moderate blast-related TBI to 15 control OEF/OIF veterans, eight uninjured subjects, and 7 with extracranial injury. Given the veteran cases and controls and the mechanism of injury investigated, results from this study may not be generalizable to civilian populations. Nevertheless, it is striking that, despite the application of several DTI analytic techniques and a patient group including several cases of moderate TBI, no group differences in either FA of ADC could be detected. Correlations between DTI findings and symptoms measures failed to achieve statistical significance, and were inconsistent. In this study, DTI failed to identify white matter injury despite persisting symptoms, including difficulties with verbal memory.[28] There are several possible ways to interpret these results. Perhaps the long interval between injury and scanning allowed for natural recovery. Alternatively, the sensitivity of DTI to white matter injury following mTBI may be largely dependent on the techniques employed and parameters measured, or may simply not be as robust as previous investigations have suggested. Finally, this study may reveal problems surrounding our present gold standard for detecting mTBI, a clinical history derived from patient self-report. Exposure to biomechanical trauma frequently coincides with psychological trauma, and either may yield subjective experiences akin to feeling dazed, confused, or even unconsciousness.

In a very recent study published by the lab of one of our authors (MFK), Geary *et al.*[27] offered perhaps the most compelling evidence to date of DTI's ability to identify lesions in postacute mTBI yielding measurable neuropsychological impairment. These authors reported a combination of statistically significant differences in FA between mTBI participants and controls, and significant relationships between FA in various ROI and neuropsychological test performance. Although the mTBI group performance on the California Verbal Learning Test-II (CVLT-II) Trial 1 was the only statistically significant between-group difference on neuropsychological testing, FA values in the UF and left SLF accounted for a significant amount of the variance.[27] These data provide persuasive evidence that mTBI can produce lasting alterations in white matter integrity with neuropsychiatric implications, supporting the theory behind DTI's application to mTBI and the associated enthusiasm for this application. At the same time, these results are derived from between-group comparisons and reveal the potential for overlap between mTBI patients and healthy individuals on the applicable measures (both DTI metrics and neuropsychological test performance). Readiness for single-subject use, particularly in real-world instances involving a host of potential influences on white matter integrity, has yet to be demonstrated.

Consideration of *Daubert* Criteria to DTI in Mild TBI

The criteria established in the *Daubert*,[6] *General Electric v. Joiner*,[53] and *Kumho Tire Co., v. Carmichael*[54] cases are intended for flexible application; such an approach will be crucial for courts considering evidence involving DTI, where the 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. However, in reviewing the state of the science of DTI as applied to mTBI and its appropriateness for single-subject or forensic application, *Daubert* criteria may usefully guide review and analysis of the medical literature. The analysis that follows is merely anchored to *Daubert* criteria and is not intended to supplant the need for the judicial exercise and obviously does not dictate the admissibility of DTI evidence in any given instance.

The first *Daubert* inquiry asks whether the theory behind and the techniques related to the performance of DTI can be, or have been, tested. On this point, DTI as applied to mTBI fares well. As previously discussed, 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. Indeed, DTI's ability to identify mTBI has already been the subject of considerable scientific inquiry at multiple institutions worldwide.

The second *Daubert* factor asks whether those theories and techniques have been subjected to peer review and publication. As the above literature review and Table 1 demonstrate, DTI's application to mTBI has been the subject of many peer-reviewed publications to date. However, this second *Daubert* criterion is arguably far more complicated than it appears and warrants deeper consideration if it is to guide determinations of evidentiary appropriateness. Although each of these studies has been subjected to peer review and publication, the lack of uniform, including some idiosyncratic, definitions of mTBI remains a major problem in the current DTI literature. This problem renders many findings from this literature difficult to compare with one another and hard to translate clinically or medicolegally. Further complicating the interpretation and translation of findings from these studies is the variability in the time after injury at which subjects were enrolled, ranging from hours to years after TBI. In terms of adherence to guidelines, no such guidelines yet exist for DTI and its application to mTBI, a problem in interpreting this body of literature for its quality.

An additional general comment regarding this second *Daubert* criterion warrants consideration: although DTI findings in mTBI at the group level have been subjected to peer review and publication, there are no studies that demonstrate the ability of DTI to serve as a valid and reliable diagnostic assessment of mTBI at the single-subject (patient) level. Absent any such publication, the forensic expert's need to testify with reasonable medical certainty that an individual litigant's DTI findings are attributable to mTBI is challenged. Thoughtful attention to the different missions and applications of peer-reviewed scientific publications and the court's evaluation of findings presented in those publications as legal evidence is appropriate. Peer reviewers are apt to accept manuscripts that advance the science, even if its application at the individual subject or patient level is not yet achievable; conversely, the court, in the context of mTBI litigation, is generally concerned only with application of that science to the case of the litigant. This review of the DTI and mTBI literature suggests that the research findings published thus far do not translate well from the group to the individual litigant level, and they do not appear to have been intended (by either authors or reviewers) for such translation.

The third *Daubert* criterion asks whether there is a known or potential error rate for the technique in question. As noted by Hoge *et al.*,[55] attributing cognitive, emotional, behavioral, and physical symptoms to mTBI, rather than posttraumatic stress disorder, depression, or other conditions, in the late postinjury period is challenging, and may not be possible in many cases. Nonetheless, clinical interview and self-reported history remain the gold standard for clinical and research diagnosis of mTBI. In the absence of a biomarker specific for mTBI with which to confirm the history-based diagnosis, definitive determination of error rates (i.e., sensitivity, specificity, positive and negative predictive values) for DTI as a diagnostic assessment for mTBI is not possible presently. Although error rates remain unknown, the preliminary data available from the existing literature portend substantial problems in this regard: The published findings demonstrate substantial overlap in DTI findings (and their correlation with neuropsychological performance) between mTBI and control groups.[7,28,29,36,46] Unaddressed in the literature is the extent to which other common neuropsychiatric conditions and environmental factors contribute to the mTBI versus control group DTI differences reported thus far. Also unaddressed is the more difficult and more typical task encountered in real-world patients: attributing DTI abnormalities to

mTBI at the single-litigant level, in which mTBI frequently co-occurs with other neuropsychiatric comorbidities and environmental stressor that can affect white matter integrity. In the absence of such studies addressing the interpretation of DTI findings in this very complex real-world setting, the potential error rate of DTI as a diagnostic assessment for mTBI is simply not knowable.

The third *Daubert* criterion also asks whether standards exist to support quality assurance in the performance of the technology at issue. DTI, and its application to mTBI, is lacking widely accepted and commonly applied quality assurance standards. DTI research and clinical facilities differ substantially in terms of equipment and techniques, and no clear front-runner has established itself as the preferred method for such investigations. In terms of current clinical applications, variability is even more pronounced between institutions that offer DTI and the methods they employ when interpreting clinical data.

The remaining *Daubert* inquiry asks whether general acceptance of the theory and technique has been achieved in the relevant scientific community. Those performing *Daubert* analyses must pose the proper inquiry when considering this criterion. While DTI's ability to characterize white matter integrity may meet this bar, the more pertinent set of questions for evidentiary usefulness is whether DTI can identify changes in white matter integrity caused by mTBI; distinguish changes produced by mTBI from those produced by other conditions; absent distinct differences in DTI findings between conditions, parse out the relative contributions of mTBI and other conditions to a given DTI data set; and produce information that informs usefully on any neurologic or neuropsychiatric impairments and functional disability experienced by an individual subject, patient, or litigant. The most accurate answer to this set of questions, based on the present literature in this field, is no. As stated by Bigler and Bazarian, "the newness of the DTI approach indicates the need for more research" (Ref. 56, p 643).

The state of the science suggests that in most instances DTI's evidentiary appropriateness for mTBI litigation will be poor. Well-designed investigations yielding peer-reviewed publications in support of DTI's single subject use for the diagnosis of mTBI do not exist. Error rates remain unknown, but the specificity of alternations in white matter integrity is evidently problematic. Moreover, no standards exist surrounding the technical performance of DTI, or the reporting of its findings. The likelihood that an individual lab providing DTI data to a court in a given case could, at present, rise above the general state of DTI's evidentiary usefulness seems low. Also unlikely is the availability of the expertise needed to critically assess such data on a case-by-case basis to ensure that only appropriate evidence is being entered, or that the entered evidence is delivered in a manner that comports with scientific and ethical requirements.

Given the present state of the literature for DTI as applied to mTBI, the potential for this technology to be misapplied and granted far more evidentiary weight than scientifically justified seemingly exceeds the marginal value of its valid evidentiary applications. While few forensic experts have commented directly on DTI at this point, the potential for misuse of neuroimaging data in courts of law is a well-established concern.[1,57,58] The example of functional neuroimaging proves illustrative in this context. The Society for Nuclear Medicine's Brain Imaging Council,[59,60] in addressing the use of functional neuroimaging evidence, cautioned that the use of "nonreplicated, unpublished or anecdotal" data are "inappropriate and has ominous implications. This can lead to unsupportable conclusions if introduced as 'objective evidence'" (Ref. 57, p 1257). This observation seems particularly relevant to DTI and its presently unregulated state of affairs: The technological aspects and limits of DTI remain inaccessible to many experts and laypersons alike and therefore makes it likely to serve as a vehicle for medicolegal misguidance rather than clinical truth. When used this way in courts, neuroimaging may offer more in the way of jury seduction than clinical science. Because the use of DTI in TBI is predicated on a reasonably compelling and accessible theory, and because the images produced by this technology are so visually spectacular, the seductive power of DTI may be exceptional.

Conclusions

Careful analysis of the DTI in mTBI literature, guided by *Daubert* criteria, suggests that, presently, the admission of DTI evidence in mTBI litigation is seldom appropriate. Under the best of circumstances, with DTI data generated by highly experienced labs and from patients with clinically unam-

biguous mTBI, the imaging data may add a quantifiable measure of white matter integrity to the body of evidence describing such patients. However, in these cases DTI would serve as superfluous evidence in support of an otherwise well-established mTBI. More alarming though is the potential use of DTI to prove mTBI in cases wherein other forms of more reliable and accepted clinical evidence fail to uphold, or directly refute, such conclusions. The compelling visual images and promises of objectivity that frequently accompany such presentations of neuroimaging data may serve to seduce rather than educate triers of fact. Until DTI acquisition, analysis, and interpretation techniques are standardized, and the error rates of these techniques with respect to the diagnosis of mTBI by DTI at the single-patient level are established, published in peer-reviewed scientific journals, and generally accepted by the medical field, the authors suggest that case-by-case *Daubert* analysis should seldom prove favorable to the admission of DTI evidence to establish mTBI.

Admission policies in many courts are relatively liberal, however, and not all jurisdictions apply the same standards; it therefore seems likely that DTI will continue to play a role in mTBI litigation despite the current state of the science. Accordingly, medical experts, courts, and attorneys must prepare themselves for this reality and become familiar with the requirements for ethical reporting derived from other neuroimaging technologies.[1,59,60] Offering an exhaustive differential diagnosis for any abnormal DTI finding regarding white matter integrity is an ethically mandated element of expert testimony when such findings are introduced as evidence. Officers of the court should be wary of any expert offering testimony involving definitive relationships between a DTI image and an illness or symptom, or refusing to identify limitations or confounding factors surrounding the study. Experts must be discouraged from claiming too much for this technology, using it to form opinions in isolation of or in conflict with other diagnostic data, or making bold cause-and-effect claims between mild TBI and white matter integrity findings.

If misused and left unchallenged, DTI imaging findings in mild TBI can be misleading. The ethical expert witness will acknowledge this fact, and the court should be prepared to exercise gate-keeping authority when the expert fails to present opinions regarding DTI data in a manner that comports with ethical requirements and scientific realities. DTI is a far too promising emerging neuroimaging technique to allow early misapplications to interfere with the eventual realization of its full potential as a research, clinical, and medicolegal tool.

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