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Target Article

The Potential for Medicolegal Abuse: Diffusion Tensor Imaging in Traumatic Brain Injury

Hal S. Wortzel, University of Colorado
A. John Tsiouris, Weill Cornell Medical College
Christopher G. Filippi, Columbia University Medical Center

This article discusses the nature and value of diffusion tensor imaging (DTI) in medicolegal settings. Although the technology and theory that supports DTI is provocative and exciting, we argue that expert testimony that confidently relies on DTI is highly problematic. In this article, we discuss the current limitations inherent in acquiring and analyzing DTI data; list problems especially with specificity that limit DTI's appropriateness in single-subject instances; and provide a brief history of the misuse and abuse of neuroimaging in mental illness and brain injury. We conclude with a plea for healthy skepticism regarding the value of these latest modalities in medicolegal settings, especially given the nature of their frequently visually spectacular impact on judges and jurors.

Keywords: law, neuroimaging

Dense controversy surrounds the use of advanced neuroimaging in the medicolegal setting. While many aspects of these persisting debates were discussed in the multidisciplinary consensus conference regarding the ethical use of neuroimaging in medical testimony held on December 7 and 8, 2012, at Emory University (Meltzer et al. 2013), opinions regarding the use, and potential for abuse, of diffusion tensor imaging (DTI) in traumatic brain injury (TBI) litigation were particularly polarized. The identification of DTI in TBI litigation for exposition in the consensus report reflects the degree of controversy and common concern surrounding this particular practice, and collective awareness of the fact that transgressions are actually occurring. Importantly, the report's statement about the lack of consensus regarding DTI's utility in cases of mild TBI suggests that general acceptance has yet to be achieved, a statement that is not without precedent or importance for considering the evidentiary appropriateness of DTI for mild TBI litigation (Wortzel et al. 2011).

Notably, the report expounds upon a few illustrative subjects "that were exemplary of use and abuse of neuroradiological data in the courtroom," with brain trauma included among them. In particular, the controversy and potential pitfalls of DTI in the medicolegal context are highlighted:

> This technique promises to offer unique insights into the natural history of brain injury and potentially inform therapeutic approaches. Yet the manner in which DTI data are acquired produces findings that not only lack specificity, but also continue to be highly variable across institutions and among researchers. The American Society for Functional Neuroradiology (ASFNR) has developed general guidelines for the acquisition and post-processing of DTI data. But the rapidity of evolution of this technique has contributed to the challenge of achieving true standardization. At present, the ASFNR guidelines include a suggested disclaimer in clinical reports of DTI and notes that "it is critical that physicians basing clinical decisions on DTI be familiar with the limitations and potential pitfalls inherent to the technique". Furthermore, the neuroradiology community has not arrived at a consensus view of the value of DTI in (particularly mild) head trauma. Non-specific patterns or findings obtained with DTI prohibit the confirmation or diagnosis of mild TBI with reliability. If DTI or other non-specific imaging findings are introduced into legal evidence, the expert should offer alternative explanations for the findings, including technical factors and normal variation. (Meltzer et al. 2013, XX)

The report reflects a tremendous respect and regard for the technology and compelling theory behind DTI, which represents a powerful research tool yielding exciting results for the investigation of white matter integrity in vivo. But the report also features considerable humility regarding diagnostic ability and clinical utility at the single subject (or litigant) level. Unfortunately, expert testimony relying on DTI imaging data is often lacking in such humility, with a tendency among witnesses to overstate the

Address correspondence to Christopher G. Filippi, Columbia University Medical Center, New York, NY, USA. E-mail: cf2529@columbia.edu

strengths of the technology while neglecting very real and salient limitations.

TECHNICAL LIMITATIONS: NORMAL VERSUS ABNORMAL

The fact that standardized, best practices are not yet established for acquiring and analyzing DTI data frequently goes unmentioned. Different methodologies across institutions for the acquisition and postprocessing of DTI data yield substantial heterogeneity in results for any given individual, such that normal interindividual variability may be erroneously labeled as an "abnormal" finding and proffered as "proof" of a remote TBI. Various technological parameters can be manipulated in ways that impact results. It is important to reflect upon the fundamental difference in the way data from advanced neuroimaging, including DTI, are typically analyzed relative to the interpretation of conventional imaging acquired for most clinical purposes. Standard anatomic magnetic resonance imaging (MRI) pulse sequences can be acquired with similar imaging parameters on different scanners, with different magnetic field strengths and hardware capabilities, and produce objectively similar anatomical images. A trained neuroradiologist can determine, via visual inspection, the quality and resolution of these images, and there is typically excellent interobserver correlation regarding anatomic MRI findings. Although such interpretation has a subjective component, experts will generally agree on the presence of abnormal findings, even if they disagree over their clinical significance or underlying etiology (e.g., acute vs. chronic disc herniation on a lumbar spine MRI).

The acquisition and interpretation of DTI are markedly more complex, with many technical determinations that influence results, such that agreement regarding even the existence of abnormal findings is often lacking. A full discussion of the physics behind the acquisition of a diffusion tensor is beyond the scope of this article; however, there are numerous factors that influence DTI data acquisition and can introduce bias. The magnetic field strength, choice of receiver coil, degree of diffusion weighting (b-value), field of view, acquisition matrix, number of diffusion directions, number of excitations, slice thickness, and the use of parallel imaging are all user-dependent variables that are known to alter DTI data (Alexander et al. 2006; Huisman et al. 2006; Jones and Basser 2004; Papinutto, Maule, and Jovicich 2013). It is well known that fractional anisotropy (FA) values, the most widely used postprocessed derivative of DTI data for the assessment of axonal integrity, vary widely based on differences in the DTI acquisition parameters just described. For example, FA values increase significantly with higher magnetic field strengths and number of diffusion directions.

Numerous well-described artifacts such as subject motion, magnetic field inhomogeneities (eddy currents and magnetic susceptibility effects), image and radiofrequency (RF) noise, and improper magnetic field shimming must all be taken into consideration when acquiring and interpreting DTI data. Such artifacts generally decrease the FA of the white matter, currently the primary DTI metric used to quantify white matter integrity in the setting of TBI, and lead to falsely decreased values that may be interpreted as "proof" of injury.

It has also been shown that magnetic resonance (MR) scanners with different field strengths and from different manufacturers will produce different DTI metrics on the same subject (Ref.). Different results have also been demonstrated on the same subject scanned on the same MR scanner in a different location because of slight variations in the system hardware (Vollmar et al. 2010). Moreover, a single subject scanned on the same MR scanner later in the same day may produce different results. Although some studies have demonstrated improved reproducibility and accuracy of the DTI data by using greater than 30 diffusion directions (Jones and Basser 2004; Mukherjee, Berman, et al. 2008; Mukherjee, Chung, et al. 2008), imaging at higher field strengths (Alexander et al. 2006), and decreasing slice thickness (Papinutto et al. 2013), currently there is no consensus as to the best or optimal DTI sequence parameters within the medical and scientific communities. Hence, unlike traditional MR sequences where qualitative visual inspection suffices and agreement regarding the existence of an abnormality is typically not at issue, the very existence of a lesion (let alone its clinical significance and/or etiology) in any given single patient identified via DTI is fundamentally questionable in many instances. This is especially problematic in cases involving mild TBI.

Furthermore, once DTI data are successfully acquired, it must be preprocessed, representing yet another technically complicated task featuring decision points with the potential for impacting results; the diffusion tensor must be estimated, quantitative parameters (fractional anisotropy, mean diffusivity, etc.) must be extracted, and a statistical analysis must be performed. Currently, there is no consensus as to the optimal DTI analysis technique to obtain quantitative parameters. Region of interest (ROI) methods are generally considered the "gold standard" for image analysis. ROI analysis involves creating a region around the desired white-matter tract to be analyzed. But this method is prone to artifact-minimizing group differences when ROIs are placed within the maximal FA regions on postprocessed FA maps. It may also underestimate FA values if the ROI is placed adjacent to a low-FA structure—in the junctional white matter adjacent to the cerebral cortex or in the periventricular or callosal white matter adjacent to the ventricles—where partial volume averaging occurs.

Voxel-based analysis, an alternative analytic technique, involves co-registering an experimental group's DTI data and a control group's DTI data to a common template and then comparing each pixel in the brain between the two groups. Numerous factors can influence results without current consensus as to the best parameters. All voxel-based methods (including tract-based specific statistics) require normalization of the DTI data to a common space. In other words, anatomical variability across individual brains (i.e., size and shape) needs to be corrected for when comparing white-matter tracts and their integrity. There are

multiple registration algorithms that produce different results, with some known to produce more white-matter registration errors than others. These local areas of misalignment between images can be interpreted erroneously as abnormalities (Ashburner and Friston 2000; Davatzikos 2004). To counter minor errors in normalization, some research groups use smoothing algorithms. The amount of smoothing has been reliably shown to alter the data to such an extent that the same data analyzed using different amounts of smoothing can result in two completely different areas of abnormality (Jones et al. 2005). Additionally, smoothing algorithms can introduce a systematic bias in the anatomic localization of group differences (Bookstein 2001).

Yet another major challenge with all DTI analysis algorithms is partial volume effects, defined as averaging different tissues into one voxel. Partial volume effects between two adjacent differing tissue types will contaminate results; this is more problematic with voxel-based analysis and becomes paramount when slice thickness is increased to greater than 2–3 mm or certain smoothing algorithms are utilized.

The guidelines put forth by the American Society of Functional Neuroradiology DTI Standards and Practice Subcommittee contain multiple statements detailing the limitations in using DTI clinically, especially at the individual level and when analyzed by voxel-based techniques:

> In performing tractography, many choices must be made (algorithm, seed number/locations, step size, stopping criteria, etc.) that can profoundly influence the end results, limiting reproducibility. No widely accepted guidelines for making these choices currently exist. The same caveat applies to statistical image analysis methods (especially voxel-based analyses, including tract-based spatial statistics), some of which are designed for group analysis and may yield erroneous results in the assessment of individual patients. (American Society of Functional Neuroradiology 2012)

Statistical science also portends problems for the analysis of DTI data, and the potential for abuse. One of the strengths of voxel-based analysis is that it analyzes every pixel in the image, with approximately 2 million pixels in the average case. In statistics, the likelihood that one of these pixels is abnormal by chance increases with the number of comparisons made. Assuming a typical 5% chance of error, about 100,000 pixels would be abnormal just by chance alone. Fortunately, there are multiple comparison correction algorithms available, although some comparison corrections are stricter than others. This statistical reality was well illustrated in a study by Craig Bennett involving functional MRI (fMRI) and a dead fish (Magrigal 2009). The deceased fish was placed into the scanner and shown pictures of humans engaged in social situations, and fMRI results demonstrated brain activity in response to the stimuli. The experiment was of course a tongue-in-cheek one, intended to illustrate statistical realities and the potential for erroneous interpretations. Nevertheless, these statistical realities represent yet another potential avenue for abuse, wherein "abnormal" voxels due to chance alone are misrepresented as proof of injury.

In summary, there are many steps and factors involved in DTI acquisition and analysis that will profoundly influence the outcome. The large number of studies published on the use of DTI for mild TBI have been performed on a wide range of MRI scanners and have utilized many different combinations of acquisition, pre- and postprocessing, and analytic techniques. Therefore, DTI metrics such as FA in uninjured and injured brains have significantly varied from study to study. Currently there is no consensus as to which parameters should be used. Not too surprisingly, when the same DTI data set was provided for analysis to nine different research groups using voxel-based analysis techniques, nine different results were obtained (Jones et al. 2007).

CLINICAL LIMITATIONS: SPECIFICITY AND FUNCTIONAL IMPLICATIONS

Even if the numerous technical and statistical issues are resolved, problems with specificity severely limit the appropriateness of DTI analysis in many single-subject instances. Patient and/or litigant is not synonymous with "healthy control," such that comparison of many individuals' brains to normative databases is complicated by relevant neuropsychiatric comorbidity. Healthy controls are screened to rule out a wide variety of neuropsychiatric conditions that might influence both brain structure and function. Such neuropsychiatric conditions are common in the general population, and are often present in individual litigants. The potential impact of common psychiatric conditions on DTI findings is well illustrated in a report by White and colleagues (White, Nelson, and Lim 2008). These authors reviewed the literature on DTI across many psychiatric disorders, including schizophrenia, depressive disorder, anxiety disorders, obsessive–compulsive disorder, attention deficit disorder, autism, and personality disorders. Results revealed extensive heterogeneity and substantial overlap among these various conditions. Furthermore, positive findings tended to predominate in the cingulum bundle (CB), corpus callosum (CC), and frontal and temporal white matter, regions that are also identified by DTI in mild TBI (mTBI). Extraordinarily common factors such as cigarette smoking (Paul, Grieve, et al. 2008), early life stress (Paul, Henry, et al. 2008), and/or parental verbal abuse (Choi et al. 2009) may result in differences in white-matter integrity as measured by DTI. Given that even carefully selected healthy controls will feature areas of "abnormality" when compared to the normative database they helped to create (Kraus et al. 2007), it should be anticipated that most unselected patients/litigants will feature areas of abnormality when compared to such normative databases. Plaintiffs/litigants come as they are, with common neuropsychiatric conditions occurring commonly. One would fully expect a single individual with, for example, history of migraine, prior substance abuse, and depression to feature areas of low FA when measured against a normative database, irrespective of the issue of TBI. But this fundamentally flawed process is precisely what routinely occurs when DTI imaging is applied to mild TBI litigation.

Rather than acknowledgment of the poor specificity and nearly ubiquitous associations between neuropsychiatric illness and DTI findings, experts offering DTI-based testimony suggest that the overall pattern of the lesions identified is specific to mild TBI, and claim a unique ability to identify these patterns. Such arguments contradict both the state of the DTI literature and the realities surrounding TBI, not to mention various other neuropsychiatric illnesses. Every human brain is unique, and to some extent, every TBI (regardless of injury severity) may be unique. In other words, any given TBI will involve a distinct combination of forces acting upon a unique brain, with the potential to yield any number of possible injury patterns. While there are some generalities regarding areas of the brain most susceptible to damage from TBI-inducing forces, these soft rules do not facilitate accurate predictions regarding where damage from any given TBI will manifest in any given individual's brain. Much as TBI can clinically mimic numerous other neuropsychiatric illnesses in terms of signs and symptoms, the underlying neuropathology may similarly approximate neuroanatomical and/or neurochemical changes associated with other neuropsychiatric conditions, and will thus yield nonspecific patterns on advanced neuroimaging studies. Experts claiming signature patterns for mild TBI, whether identified on DTI, PET, SPECT, volumetric analysis, or even neuropsychological testing, should be greeted with skepticism.

An illustrative example of DTI abuse that seems to appear with some regularity surrounds claims of DTI-proved mild TBI in the setting of chronic ischemic white-matter disease. Findings of long-standing white-matter change on routine structural neuroimaging, with clinical scenarios (i.e., long-standing diabetes and hypertension in a middle-aged male) and classic imaging patterns (i.e., cuffing of the ventricles and periventricular white-matter lesions), may go neglected and entirely unmentioned, while satellite lesions of that chronic ischemic process are cherry-picked and labeled as "junctional." Predictably, DTI identifies areas of decreased FA in corresponding voxels. Convergent validity is then claimed, with the suggestion that the combination of a junctional white-matter lesion and concomitant reductions in FA must be referable to TBI. However, although the subcortical U-fibers have a richer blood supply in the brain than the deep and periventricular white matter and are therefore classically less affected by end-vessel ischemia (Pantoni and Garcia 1997), due to the high prevalence of small-vessel ischemia in the general population that clearly increases with age, subcortical or "junctional" T2 hyperintensities are far more likely to be the result of chronic microvascular ischemia than of TBI (Longstreth et al. 2000; Vermeer et al. 2003).

Even if a unique ability to identify signatures of remote mild TBI via DTI is granted, there still remain serious limitations regarding the functional implications of such findings. Uncomplicated mTBI, defined as an injury that meets the American Congress of Rehabilitation Medicine definition of mTBI (Kay et al. 1993) and does not entail abnormal day-of-injury intracranial routine neuroimaging findings (not advanced neuroimaging findings, such as DTI, single photon emission computed tomography [SPECT], positron emission tomography [PET], or functional MRI [fMRI]) (Williams, Levin, and Eisenberg 1990), carries a very favorable long-term prognosis for the vast majority of individuals sustaining such injuries (Belanger et al. 2005; Carroll et al. 2004; Dikmen, McLean, and Temkin 1986; Dikmen et al. 1995; Larrabee 1997; Rohling et al. 2011). A systematic review conducted by the WHO Collaborating Center Task Force on Mild TBI (Carroll et al. 2004) revealed that complete recovery following mild TBI is the norm, and that recovery typically occurs within weeks or months of injury. Similarly, systematic reviews performed by the Institute of Medicine (Dikmen et al. 2009) and two meta-analyses (Belanger et al. 2005; Rohling et al. 2011) yielded results consistent with those of the Collaborating Center Task Force on Mild TBI (Carroll et al. 2004). In prospective, unselected samples of persons with mTBI, early deficits in neuropsychological function usually resolve within about 3 months time, and the best available evidence does not support notions that mTBI results in long-term cognitive impairments.

A more recent systematic review (O'Neil et al. 2012) extends such findings to the veteran population, including veterans with blast-related mild TBI. The strength of the literature, as revealed through the systematic reviews and meta-analyses described earlier, demonstrates that mTBI carries a good prognosis for the vast majority of persons who experience such injuries. Whether or not there exists an identifiable signature of mild TBI on DTI, the natural history of such injuries remains unchanged, and the presence of such a signature would not portend, or even explain, an atypical outcome involving persisting impairment in any given individual. In other words, if DTI is presumed to be a uniquely sensitive test for historical mild TBI, the identification of a mild TBI signature would only prove the occurrence of the historic injury event, and would still not be able to explain, or prove, the persistence of symptoms or impairment. Of course, exceptional sensitivity typically comes at the expense of specificity. Thus, while it is possible, and atypical, for a mild TBI to engender adverse long-term outcomes, the differential diagnosis for poor outcomes is extensive and involves comorbid conditions that might better account for both persisting neuropsychiatric symptoms in the late period following mTBI (Hoge, Goldberg, and Castro 2009; Hoge et al. 2008; McCrea et al. 2009; O'Neil et al. 2012) and any "abnormal" DTI imaging results (White et al. 2008).

A HISTORY OF MISUSE/ABUSE

The current state of the science features serious limitations surrounding single-subject uses of DTI, and tremendous potential for medicolegal abuses. In considering this potential for abuse, and how likely it is that such potential will result in actual transgressions, it is prudent to reflect upon the history surrounding single-subject and medicolegal applications of various neuroimaging/neurodiagnostic modalities (Wortzel 2013). While it sometimes seems that Q4

the controversies surrounding neuroimaging in courts of law are new, such problems have existed for more than a half a century. In fact, history provides us with some rather illustrative and dramatic examples of neuroimaging and neurodiagnostic techniques being utilized in ways that have failed the test of time. Many Americans know that Jack Ruby shot John F. Kennedy's assassin, but few are aware that that he claimed to have done so during a seizure. Controversy surrounding the interpretation of a "rhythmic temporal theta burst" pattern on electroencephalography (EEG) featured prominently at Ruby's trial (Gutmann 2007). An expert for the defense cited EEG evidence, and seemingly neglected more compelling clinical and historical factors, in offering testimony that Ruby was unable to distinguish right from wrong at the time of his offense. Notably, the psychomotor variant of epilepsy claimed at Ruby's trial is now referred to as rhythmic temporal theta bursts of drowsiness and "as a type of epilepsy, has become a historical footnote" (Gutmann 2007). Another powerful historical example involves the case of John Hinckley, who was adjudicated as legally insane when he attempted to assassinate President Ronald Reagan. Expert dispute surrounded the significance of Hinkley's computed tomography (CT) scan results, with some arguing that it evidenced a diagnosis of schizophrenia. The case and its outcome were very controversial. Consternation surrounding the verdict is often cited as resulting in pervasive changes in legal definitions around the nation, including the elimination of volitional prongs to legal criteria for insanity in many jurisdictions. While the extent to which CT imaging and related testimony influenced the jury's verdict remains uncertain, one thing is perfectly clear: Claims/testimony that Hinckley's CT scan of the brain evidenced his diagnosis of schizophrenia have not withstood the test of time, and 30 years later we remain without a diagnostic imaging study for that psychiatric condition.

More recent controversy has surrounded the clinical and medicolegal commercialization of quantitative electroencephalography (qEEG) (Arciniegas 2011; Coburn et al. 2006) and SPECT (Adinoff and Devous 2010; Wortzel et al. 2008). Arciniegas offers a detailed review of the literature directly addressing the issue of EEG and qEEG as applied to persons with mild traumatic brain injury (mTBI), and with specific reference to medicolegal applications:

> qEEG discriminant functions are of debatable value in the clinical or forensic diagnostic evaluation of persons with mTBI. Having said this, it is important for clinicians and forensic practitioners to remain mindful that this is a matter of controversy. Clinicians involved in the care and medicolegal evaluation of individuals with mild TBI are advised to consider all arguments regarding this technology before deciding on the advisability and value of using qEEG. (Arciniegas 2011, XX)

Similar controversy surrounds SPECT imaging as applied to neuropsychiatric disorders (Adinoff and Devous 2010). That controversy is demonstrated in an exchange of letters (Adinoff and Devous 2010; Amen 2010) published in the *American Journal of Psychiatry*. Adinoff and Devous offer the compelling argument that unchallenged early misapplications of neuroimaging may create an atmosphere of cynicism in both clinical and medicolegal venues that persists even when legitimate clinical applications are finally realized. The subject of SPECT as specifically applied to mild TBI litigation was reviewed by the Neurobehavioral Disorders Program at the University of Colorado (Wortzel et al. 2008). Preceding encounters with SPECT in the context of litigation prompted that analysis, and ongoing exposures reveal that this technology continues to be offered as "proof" of brain injury. Such evidence often comes in isolation from or in contrast to clinical presentations and history, and is frequently accompanied by interpretive reports that fail to abide by existing ethical reporting requirements (Society for Nuclear Medicine 2002; Society for Nuclear Medicine Brain Imaging Council 1996).

CONCLUSION

We are now faced with the latest wave of advanced neuroimaging techniques, of which DTI is but one. As we consider these latest contenders, it is worth keeping in mind that both novelty and youth are fleeting conditions. CT and EEG were once fantastic new technologies, much as fMRI, PET, and DTI are today. But despite advances in the science, significant limitations persist, especially when it comes to single-subject applications of these technologies. The reality of such limitations is reflected in the fact that these techniques chiefly serve research roles in the world of neuropsychiatry, and have realized very modest clinical applications. Like preceding emerging technologies, the impressive science, generally inaccessible technical aspects, and spectacular images create the potential for medicolegal abuse. In light of this potential for misuse, and history lessons suggesting that such potential tends to be realized, healthy skepticism regarding the ability of these latest modalities to differentiate between various neuropsychiatric conditions, or even to discern pathology from normal variability, remains necessary (Mayberg 1996; Reeves et al. 2003; Silver 2012; Wortzel et al. 2008; Wortzel et al. 2011). It is also prudent to recognize that new neuroimaging techniques, like DTI, carry the potential for misapplication in medicolegal settings with perhaps previously unrealized influential power predicated upon visually spectacular images. Our collective experience reveals that the medicolegal abuse of DTI imaging is not merely a theoretical possibility, but an actual commonplace occurrence, particularly in mild TBI litigation. The preceding discussion should help alert medical and legal professionals to circumstances portending potential abuse of DTI technology, and some of the tactics that frequently accompany such misapplications.

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