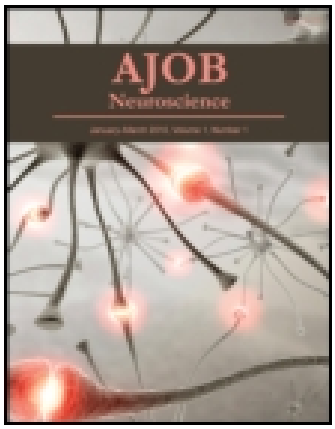

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Clarifying the Robust Foundation for and Appropriate Use of DTI in mTBI Patients

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issues that concerned Wortzel and colleagues, such research can be a valuable aid in dealing with the basic inverse inference problem pertaining to DTI interpretation in medicolegal settings.

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Clarifying the Robust Foundation for and Appropriate Use of DTI in mTBI Patients

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As clinicians and scientists, we believe scientific evidence and prudent clinical practice form the proper basis for determining the utility of diagnostic measures, which should subsequently inform forensic use. The misleading and often entirely unsubstantiated opinions and positions of Wortzel, Tsiouris, and Filippi (2014), in opposition to diffusion tensor imaging (DTI) as a useful measure in mTBI, are at odds with the clear consensus of the scientific literature regarding mild traumatic brain injury (mTBI), its clinical assessment, and its natural history. The authors' critique contains numerous errors. We focus on four areas: (1) the clinical reality of mTBI, (2) the true substance of the scientific evidence supporting use of DTI in mTBI, (3) the authors' erroneous and off-target opinions regarding DTI analysis, and (4) critical appraisal and integration of clinical information for diagnosis of mTBI.

First, an underlying theme of the authors' arguments claims that lasting sequelae from mTBI is not a clinical reality. For example, "best available evidence does not support notions that mTBI results in long-term cognitive impairments" (12). mTBI is a reality that results in lasting sequelae in a substantial minority (Bigler et al. 2013; McMahon et al. 2014). mTBI is modeled in animals, yielding reproducible microstructural neuropathological and behavioral findings, as well as with finite biomechanical models of human mTBI. The impact of mTBI cannot be argued away by focusing on the majority who recover. Clinical, scientific, and even forensic focus must be on the affected minority. Moreover, traditional neuropsychological approaches are problematic in assessing the cognitive effects of mTBI; they were never designed to assess subtle but important deficits.

Second, the authors' critique of DTI challenges the "believability" of quantitative DTI findings, juxtaposing visual detection of spinal disk herniation and detection of microscopic mTBI pathology. They imply that because the microstructural abnormality cannot be "seen" without quantification its existence is in question. This "straw man" argument would also imply that other neuroimaging findings that cannot be seen without quantification, such as spectroscopic and perfusion-based detection of tumor infiltration into normal-appearing white matter, are not real or reliable. The substance and implications of the American Society for Functional Neuroradiology (ASFNR) guideline are mischaracterized to support the authors' position: "the guidelines . . . detailing the limitations in using DTI clinically, especially at the individual level and when analyzed by voxel-based techniques" (11). The guideline deals exclusively with clinical use in patients and does not isolate single patient

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assessment for scrutiny. Important cautions are listed, but the message is: When DTI is used in accordance with the guideline, reliable clinical use can be achieved. Assessment of DTI parameters is not singled out as most of concern; greater attention is paid to limitations of tractography and its misuse.

Third, the authors argue that method variance renders DTI research studies and clinical assessments inconclusive. Statements similar to "Numerous factors can influence results without current consensus as to the best parameters" (10) recur throughout the article, often without supporting citations, and imply that method variance across published studies undermines reliability and leads to (even willful) type 1 errors (i.e., false positives). The authors claim differences in acquisition, analysis, and so on preclude salient conclusions. This approach completely misses the point of a very large literature, which speaks with essentially one voice: Low fractional anisotropy (FA) is characteristic of TBI patients, *despite significant variability across studies* (e.g., Aoki et al. 2012; Hulkower et al. 2013; Niogi and Mukherjee 2010; Shenton et al. 2012). Even if we assume that DTI metrics, such as FA, vary across scanners and institutions, we will not encounter bias in the identification of abnormalities in any individual; this issue is simply not germane to a properly conducted analysis. What does matter is that patient and control data are acquired, processed, and analyzed in the same manner and that temporal variation be substantially less than the magnitude of the effect sought. This latter requirement, of course, is out of concern for type 2 errors (i.e., false negatives). It is even more illogical to expect that method variance would yield regionally localized "abnormalities" that in fact represent type 1 errors. Bias due to acquisition and processing variation across subjects, if it were in fact a problem, would lead to a uniform bias at all brain locations. This would be the result, not the manufacture of lesions, if it were true that "technological parameters can be manipulated in ways that impact results" (10). Digging deeper into the authors' case for fatal variability of DTI metrics, we again note a void of supporting evidence. The authors conclude that "unlike traditional MR sequences . . . the very existence of a lesion . . . in any given single patient identified via DTI is fundamentally questionable" (10). The only relevant citation (Vollmar et al. 2010), however, is completely misconstrued by the authors; it in fact documents the high degree of intra- and interinstitutional fidelity of FA measurements, also reported by others (Fox et al. 2012). Such misunderstanding of the science suffuses the discussion of technical issues. Glib citations such as "Not too surprisingly, when the same DTI data set was provided for analysis to nine different research groups . . ., nine different results were obtained" (11) entirely misrepresent the substance of an unpublished abstract to suit the authors' bias. The authors of the cited abstract actually conclude: "This serves as a reminder of what is being tested under the null hypothesis, i.e. just because one method finds a particular difference, it does NOT mean that there were NO other differences—a fact that can be easily overlooked" (Jones et al. 2007, 74). The concern is not that any of the findings are not "real", but that additional real findings may be missed in any analysis.

Another methods-specific argument is that abnormalities could occur simply by chance: "Statistical science also portends problems for the analysis of DTI" (11). After exaggerating the typical number of simultaneous comparisons by at least 50% and invoking a "typical 5% chance of error," the authors conclude that "statistical realities represent yet another potential avenue for abuse" (11). This rudimentary analysis does not acknowledge that 5% is not a typical threshold and that corrections should be and are made for multiple testing (not just that they "fortunately exist"). Most glaring is the authors' omission of spatial clustering, which dramatically reduces type 1 errors. DTI analyses do not seek individual voxel abnormalities, but ask, "What is the likelihood that hundreds of voxels comprising a contiguous tissue volume several milliliters in size will all appear abnormal by mere chance alone?" Along these lines, the authors state, "Given that even carefully selected healthy controls will feature areas of 'abnormality' . . ., it should be anticipated that most unselected patients/litigants will feature areas of abnormality when compared to such normative databases" (11). This is a gross misrepresentation of Kraus and colleagues (2007), in the same way that Wortzel misused it previously (Wortzel et al. 2011). The criterion for "abnormality" in the Kraus article (1SD) is well within all concepts of normal. That some controls had some regions of interest outside of 1SD is expected and does not bear on the finding that patients had significantly more regions of interest outside of 1SD (Kraus et al. 2007, Figure 5). This citation provides no basis whatsoever for inferring that normals will have "abnormalities" when reasonable thresholds for abnormality are employed. This sentence and especially its italicized emphasis have no basis in the cited paper or any scientific communication.

Fourth, diagnosis of mTBI, or any other disorder, is based on integration of clinical information, not the result of one diagnostic test. The authors offer another "straw man" argument that insinuates DTI should not be used as a standalone definitive diagnostic test, a use for which it has not been proposed. The realities of DTI use in the clinic entail weighing the strength of all clinical evidence. The authors argue that "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" (11). Placing these two sentences back to back is blatantly misleading. The authors cite White and colleagues (White et al. 2008), who reviewed studies of psychiatric patients, not of healthy people who unknowingly harbor as-yet-undiagnosed psychopathology. No literature exists to support that such individuals can be identified with DTI. Moreover, the authors do not consider that the literature on psychiatric diagnosis is comprised of studies detecting modest group differences, whereas TBI studies have specifically shown that individuals, though not all individuals, can differ from population norms to a degree that normals do not (see Hulkower et al. 2013). It is not at all clear that DTI abnormalities in

individuals with as-yet-undiagnosed psychiatric disease can be detected in the way that such abnormalities may be detected in TBI patients. Moreover, statements, such as "early life stress and/or parental verbal abuse may result in differences in white matter integrity as measured by DTI" (11) give equal weight to single reports of small samples and fail to assess subject/control overlap and whether any inference at the individual level might even be supported. In stark contrast, the overwhelming consensus of a substantial body of scientific inquiry supports DTI for detecting pathology in mTBI patients.

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Functional Magnetic Resonance Imaging in Court

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It was more than 30 years ago that neuroimaging evidence was first presented in criminal court in the United States. The charges included two counts of murder and one count of attempted murder, and the defendant asserted the insanity defense. Defense experts testified that the defendant suffered from schizophrenia with prominent psychotic features and was thus legally insane at the time of the crimes. Prosecution experts testified that the defendant did not have psychosis and was legally sane at the time of the crimes. The defense presented a computer-assisted tomography (CAT) scan that revealed the defendant had widened sulci and enlarged ventricles. These structural characteristics are

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