TO THE EDITOR: Mac Donald et al. (June 2 issue) executed a unique and logistically difficult study in which they used quantitative diffusion tensor imaging (DTI) metrics to evaluate blast-injured military personnel with and without a clinical diagnosis of mild traumatic brain injury (mTBI). Although nominally identical magnetic resonance imaging (MRI) scanners were used at the two locations, the measurements of relative anisotropy in the cingulum bundles obtained in Landstuhl, Germany, for the two cohorts (about 0.39 for the control group and about 0.37 for the TBI group [Fig. 4A of the article]) differed from those noted on the follow-up scans obtained in St. Louis in the United States (about 0.33 and about 0.31, respectively [Fig. 4B of the article]). Systematic differences between the scanners (about 0.06 in each case) far exceed the differences between the two cohorts (about 0.02 in each case). Apparently this scanner-related bias precluded performing a pairwise statistical analysis to characterize and convincingly probe the evolution of DTI abnormalities. Hence, the interpretation of longitudinal changes becomes problematic. Furthermore, although the abnormalities identified on DTI may be consistent with axonal injury, they are not diagnostic and do not exclude other interpretations (e.g., evolving extracellular edema or mild gliosis). Until DTI metrics can be calibrated reproducibly within and across MRI scanners, it is premature for the authors to suggest that quantitative DTI metrics be routinely used to assess individual patients with mTBI for the purpose of “diagnosis, triage, and treatment planning in clinical practice.”

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The views expressed in this letter are those of the authors and do not reflect the official position of the Department of Defense or any of the institutions with which the authors are affiliated.

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THIS WEEK’S LETTERS

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TO THE EDITOR: The report by Mac Donald et al. highlights the need for further refinement in the definition of TBI. Mild, combat-related TBI is strongly associated with post-traumatic stress disorder, cognitive deficits, depression, and physical health problems. Therefore, diagnostic accuracy, availability, and awareness are essential. Although it is not feasible or suggested that serial DTI be performed on all patients with mild TBI — after exposure to combat or otherwise — this study provides insight into the pathophysiology of a poorly understood process. The findings contribute to a growing body of evidence that neuroanatomic changes exist but evade our commonly used tools of detection. Such changes constitute a spectrum of disorders that relate to the severity of the injury and correlate with substantial cognitive deficits. With advanced neuroimaging techniques, screening, clinical definitions, and stratification of these injuries can be improved for both soldiers and civilians. We must overcome the fundamental barrier of the heterogeneity of disorders associated with brain injury that hampers our treatment of patients and confounds clinical trials.

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No potential conflict of interest relevant to this letter was reported.


TO THE EDITOR: The journey by Mac Donald et al. into the statistical intricacies of DTI raises important questions with respect to scientific and clinical clarity. How did the investigators select the 122 service members for the initial screening from approximately 7000 who were medically evacuated to Landstuhl during the study year? If 63 subjects all had “uncomplicated” concussions, why were they evacuated in the first place, and in what way are they representative of the tens of thousands of service members who have deploy-

ment-related concussions who remain in theater? Were there clinical differences between those with concussion and the control subjects in terms of the severity of their injuries (e.g., hemorrhagic shock) or among the subjects with concussion (e.g., loss of consciousness) that might explain the presence of DTI abnormalities that exceeded those “expected by chance”? Most importantly, without the inclusion of a comparison group of service members who had deployment-related concussions due to non–blast-related injuries (e.g., falls or accidents), and notwithstanding speculation concerning susceptible brain regions, this study does not appear to be about the effects of blast. Since the 21 control subjects also had blast exposure, the only difference between those with concussion and the controls was the presence of clinical signs that define any concussion. Therefore, apparent differences on DTI can be attributed only to the concussion injury, not to the blast mechanism. This design is analogous to comparing persons with blast concussions to normal (noninjured) controls and then misattributing neuroimaging abnormalities to the mechanism instead of to the injury.

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No potential conflict of interest relevant to this letter was reported.


THE AUTHORS REPLY: Ystad and colleagues correctly note substantial differences in the DTI parameters between the initial scans (obtained
in Landstuhl) and the follow-up scans (obtained in St. Louis) for the control subjects. Because of these differences, none of our initial inferences involved direct comparisons between scans. We have reanalyzed the data presented in Figure 4 (Panels A and B) of our article by assessing the pairwise differences in DTI parameters between the initial and follow-up scans for each of the subjects who returned for follow-up scans. The results indicate a significantly greater drop in axial diffusivity (P = 0.03) and a reduced rise in mean diffusivity (P = 0.05) in the 47 subjects with TBI, as compared with the results for the 18 control subjects (Table 1). Overall, this analysis supports our assertion that the imaging changes are most consistent with the evolution of DTI abnormalities over time. Larger sample sizes and improved standardization across scanners will be required to definitively resolve longitudinal changes.

We concur that our interpretation of the DTI abnormalities (Fig. 4C of our article) is but one of many possibilities. Direct radiologic–pathologic correlations in the human brain and biophysical modeling will be required to resolve this matter definitively. This is an area of active investigation. We do not suggest that DTI is at present ready for routine clinical use in TBI; our statements in the discussion were meant to indicate the potential usefulness of this approach in the future. Improved calibration and standardization will be required before this potential can be realized. An approach similar to that of the Alzheimer’s Disease Neuroimaging Initiative could be considered if appropriately anisotropic, nonliving phantoms can be generated and validated.

We recognize the concerns raised by Hoge and Castro regarding the interpretation of our results. The 122 subjects in our study represent a convenience sample identified by the TBI screening team at the Landstuhl Regional Medical Center (LRMC). Injury severities and reasons for evacuation were not reported because of operational security. Since we studied only patients who were evacuated to the LRMC, we have no information regarding U.S. military personnel with TBI remaining in theater. An important new direction for research along these lines will open up when MRI scanners in Afghanistan become operational. Ongoing studies include direct, DTI-based comparisons of U.S. military personnel with blast-related TBI, non–blast-related TBI, and other injuries that are blast-related and non–blast-related. In the interim, we wish to reiterate that “the contribution of primary blast exposure as compared with that of other types of injury could not be determined directly” from our data.

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Since publication of their article, the authors report no further potential conflict of interest.


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### Table 1. Differences in the DTI Data for the Cingulum Bundles between the Initial and Follow-up Scans on Reanalysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Group (N = 18)</th>
<th>TBI Group (N = 47)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative anisotropy</td>
<td>-0.059±0.019</td>
<td>-0.054±0.034</td>
<td>0.52</td>
</tr>
<tr>
<td>Axial diffusivity</td>
<td>-0.022±0.052</td>
<td>-0.053±0.051</td>
<td>0.03‡</td>
</tr>
<tr>
<td>Radial diffusivity</td>
<td>0.039±0.017</td>
<td>0.033±0.026</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean diffusivity</td>
<td>0.019±0.022</td>
<td>0.004±0.028</td>
<td>0.05§</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD and represent the difference between the initial and follow-up scans for each parameter. DTI denotes diffusion tensor imaging, and TBI traumatic brain injury.
† P values were obtained with the use of two-sided t-tests.
‡ There was a significantly greater drop in axial diffusivity between the initial and follow-up scans in the subjects with TBI, as compared with the results for the control subjects.
§ There was a significantly reduced rise in mean diffusivity between the initial and follow-up scans in the subjects with TBI, as compared with the results for the control subjects.