

Robust detection of white matter injury in individual patients after mild traumatic brain injury

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BACKGROUND

Numerous prior studies, including our own (Lipton 2008, 2009), have used DTI to demonstrate white matter abnormalities in mild traumatic brain injury (mTBI), which are associated with important clinical outcomes. The group-wise analyses employed in these studies implicitly assume that the location of injury will be the same across subjects. This is a highly questionable assumption, given the wide variation in mechanism of injury among mTBI patients. An approach to identifying loci of brain injury in individual subjects is needed to fully understand the nature and extent of mTBI pathology *in vivo*. Furthermore, any translation of DTI to clinical use in mTBI requires the ability to reliably identify injury in individuals. Nonetheless, single subject assessment requires unique statistical approaches and specific validation. We have implemented a voxelwise Z-score approach to assessment of FA, optimized for use in single subjects, which accounts for the variance in inference for an individual patient due to potentially high dependence on the composition of the control group. Because the approach accounts for violation of some assumptions of classical Z-score analysis, we have termed this a “Pseudo Z-score Analysis”. Our results demonstrate the robustness of the technique and its utility in consistently identifying white matter pathology in mTBI.

STUDY DESIGN & ANALYSIS METHODS

20 mTBI patients within 2 weeks of injury and with normal structural imaging and 40 control subjects were imaged at 3.0T. DTI was acquired with 32 directions, $b=1000$ and $8 \mu\text{l}$ resolution. DTI data were corrected for eddy current affects and EPI distortions and registered to MNI space using a multistep procedure. FA images transformed to the standard space and masked to white matter only were analyzed.

The null hypothesis for this study is that FA in a patient does not differ from that of the control group. Because mTBI is a multifocal disease that will affect only a small portion of voxels, we expect NOT to reject the null hypothesis at the vast majority of voxels. In fact, whole brain FA histograms from patient and control groups ($n=20$ each) are similar (Figure 1), supporting this expectation. Our pseudo Z-score (PZ) method thus calculates the Z-score at each voxel for a single patient, using the mean and SD derived from the control group. An assumption of the Z-score method is that the distribution of FA at each voxel within the control population follows a Gaussian distribution. However, due to its limited size, the control group may not accurately represent the population from which it was selected. As a result, we might underestimate variance and make in erroneous inference. To account for this issue, we estimated this additional variance in the PZ by a bootstrap procedure. Significance of difference in FA from a patient compared to a group of control subjects at each voxel (i) was then determined by a threshold $\hat{\sigma}_i^B z_{\alpha/2}$, where $\hat{\sigma}_i^B$ is the bootstrap estimate of SD of voxel i. This threshold was then employed to determine patient voxels significantly different from the control group.

We evaluated the method on two criteria: (1) detection rate (γ) and (2) robustness (δ). (1) Since the distributions of FA from the patient and control groups are similar (Figure 1), we tested the discriminatory ability of the PZ by comparing the detection rates for both mTBI patients and control subjects. Either a single patient or a single control was compared to the control group and detection rates at various levels of α (0.5 to 1 at 0.005 increments) were recorded. (2) Robustness measures heterogeneity in two resultant statistical maps, when the same patient is compared to each of two different control groups. High robustness indicates that we will detect similar abnormalities when comparing a single individual to each of two unique control groups.

Detection Rate (γ) = $\frac{\text{number of significant voxels}}{\text{total number of voxels}}$, and **Robustness** (δ) = Correlation(S_n^1, S_n^2), where

S is a vector holding statistical significance measures of voxels for each testing procedure, and $n = 20$.

RESULTS

At FDR=5% abnormalities were detected in all patients. However, when we compared individual control subjects to the control group, significantly smaller “abnormalities” were detected (Figure 2; $P<0.001$). Similar results were detected for each subject with the use of either of two groups of 20 control subjects (example in Figure 3).

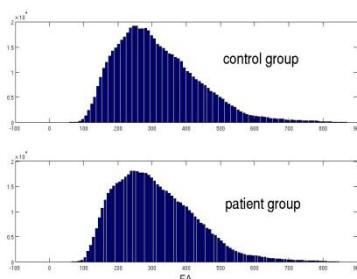


Figure 1

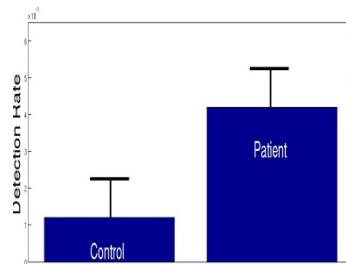


Figure 2

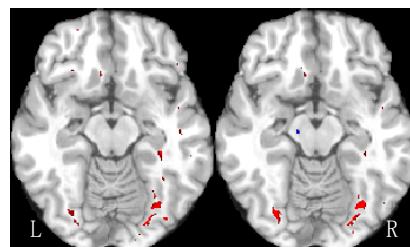


Figure 3

Figure 1. Distribution of FA across 20 control subjects (top) and 20 patients (bottom), adjusted for age and gender by multiple regression. Patients showed overall minimally lower whole brain mean FA compared to controls. **Figure 2.** Proportion of abnormal voxels detected. Detection rate for patients is significantly greater ($P<0.001$) than for controls. **Figure 3.** 2 PZ images for one patient compared to each of two different control groups ($n=20$; $P<0.005$). Similar abnormalities are detected by each analysis; robustness (δ) = 0.88.

CONCLUSIONS

The Pseudo Z-score method robustly detects abnormal FA in mTBI patients, providing an approach for single subject assessment of DTI in research and clinical applications.

REFERENCES

1. Lipton, et al., J Neurotrauma 2008., 2. Lipton, et al., Radiology 2009.