Identification of Mild Traumatic Brain Injuries by Comparison of Free-Water Corrected z-Distributions

Ofer Pasternak[1], Sylvain Bouix[1], Yogesh Rathi[1], Craig A Branch[2], Carl-Fredrik Westin[1], Martha E Shenton[1,3], and Michael L Lipton[2]

[1]*Harvard Medical School, Boston, Massachusetts, United States,* [2]*The Gruss Magnetic Resonance Research Center, Albert Einstein College of Medicine, Bronx, NY, United States,* [3]*VA Boston Healthcare System, Brockton, MA, United States*

PUPRPOSE Mild traumatic brain injury (mTBI) is difficult to diagnose because often the brain appears normal on clinical computed tomography (CT) and magnetic resonance imaging (MRI) scans [1]. In addition, brain trauma is a very heterogeneous disorder, and group analyses are not well suited for accurate detection because they obscure the individual differences that characterize brain injuries. One approach to circumvent the problem of heterogeneity is to compare individual subjects with normative atlases [2], which requires robust statistics to detect "out-of-the-normal" features. The most common feature used is the z-score. Here we study the distribution of z-scores (z-distribution) in conjunction with free-water elimination (FWE) diffusion MRI [3] to establish the sensitivity and specificity of z-distributions to mTBI. Our results suggest that comparison of z-distributions may prove as an effective way to construct a diagnostic mTBI tool, and that the application of FWE provides better insight towards the possible pathologies that drive the abnormal distributions, when comparing with conventional diffusion tensor imaging (DTI).

METHODS Twenty-five patients within the first 14 days following a mild injury, and 31 matched controls were scanned on a 3T MRI (Philips). The protocol included high-resolution (2x2x2 mm^3) diffusion scan with 32 gradient directions at b=1000 s/mm^2. FA maps were calculated using 3D-Slicer. Free-water and FWE FA maps (FAt) were calculated following the methods in [3]. The maps were co-registered to MNI template and projected onto the white matter skeleton using the TBSS software (FSL). The z-score maps were created for each subject by comparing the individual measure (FA, FAt and free-water) with the mean and standard deviation of the measure over the 31 controls, along the white matter skeleton. Age and gender were regressed out. Z-score maps were created for each control using the leave-one-out estimation by comparing a subject with the remaining 30 controls. All the z-scores were collected to create a z-distribution per subject. These z-distributions were then group-compared using the maximum mean discrepancy (MMD) framework [4]. A post-hoc t-test ($p<0.05$) was applied to locate the ranges within the distribution that are different between groups. The specificity of each range was determined by counting the number of subjects that had extreme (>1.96 std) values within the range when comparing to the control population.

RESULTS The estimated z-distribution over the mTBI population for the three diffusion measures (FA, FAt and Free-water) were statistically significant different (MMD; $p<0.05$) than that of controls, suggesting that the diffusion measures are sensitive to the injury. This is in contrast with TBSS based voxel-wise comparison that did not yield any significant difference between the groups. **Figure 1** plots the specificity and sensitivity of the z-distribution comparison. The sensitive range (noted by green stars) of the FA z-distribution was in the negative-z range (lower FA in mTBI), whereas the sensitive range of the FAt and Free-water z-distributions was both in the negative and positive domains. The blue (controls) and red (mTBI) plots show the specificity of the different z-distribution ranges, i.e., the number of subjects that were identified as "abnormal" within each range. The range around z=0 was also significantly different, since there were less "normal" voxels in the mTBI distribution. When summing over the tested ranges (not including the z=0 range), we find that the negative-z range of the free-water z-distribution is the most specific to mTBI, with 12/25 mTBI subjects identified as abnormal comparing with 1/31 of the controls. The FAt distribution identifies 20/25 mTBI subjects as abnormal (22/25 when combined with free-water) but also 12/31 of the controls. This is comparing with the FA distribution that identifies 16/25 abnormal mTBI subjects and 7/31 controls.

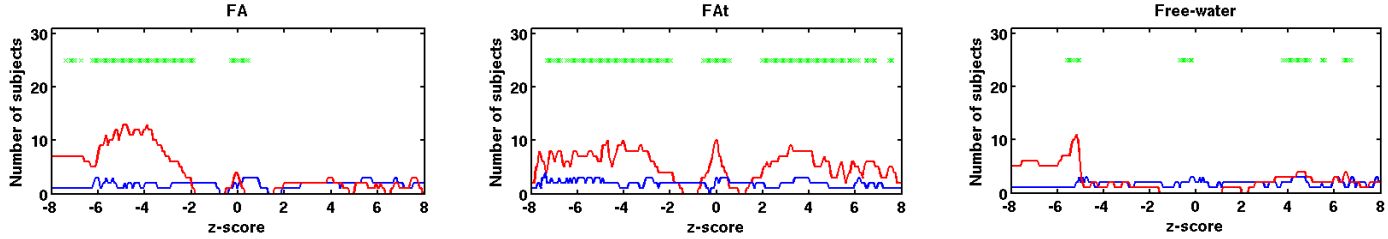

Fig.1: Sensitivity and specificity of z-distributions over 25 mTBI subjects (red) and 31 controls (blue). The plot shows the number of subjects that appear abnormal in each z-score range. High number of mTBI patients comparing with low number of controls indicates ranges with high specificity to the injury. Green stars indicate the sensitivity range in which there is a significant difference between the average controls z-distribution and the mTBI z-distribution.

DISCUSSION The z-distribution provides a mean for comparing groups that is not affected by the heterogeneity in the location of the expected abnormalities. Moreover, by comparing the z-distributions between the two groups we are able to profile the expected abnormalities. As such we see that mTBI patients tend to have lower FA in the white matter. When applying the FWE method we further learn that there are a number of abnormality types (increased and decreased FAt or free-water) suggesting that there are a number of different pathologies that may occur in mTBI. The z-distribution also predicts that using thresholded z-scores as basis for a diagnostic tool may yield false positive decisions (See Fig. 2), since the z-distribution of the healthy control is non-zero for extreme z-scores (albeit significantly lower than mTBI). Our findings suggest that the specificity of the measures can be further optimized, since in each single range the number of controls that show abnormal values is low (<4 for all the measures), however in the current application that sums over ranges of z-scores, the number of controls that seem abnormal is higher. In future work the z-distribution may be further utilized for robust identification of the location of abnormalities, by evaluating the expected number of false-positives and screening those that do not form spatial patterns such as continuity or clustering. In addition it is likely that the positive and negative z-ranges of the FWE measures will allow differentiation between types of pathologies, such as axonal degeneration, inflammation and gliosis.

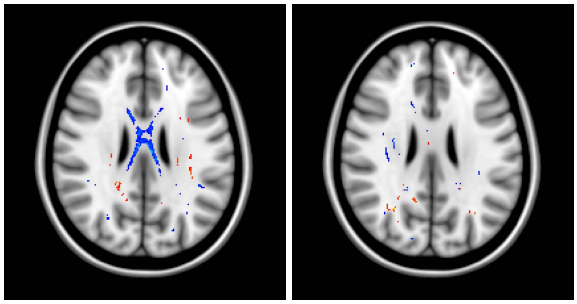

Fig.2: A mTBI patient (left) and Control (right) FAt z-maps. Both extreme positive (red) and negative (blue) values are found for the control and the patient. However, there are many more voxels with extreme values for the patient, and these voxels form patterns, such as the corpus callosum seen here.

REFERENCES [1] Shenton et al., Brain imaging and behavior 2012; [2] Lipton et al., Brain imaging and behavior 2012; [3] Pasternak et al., Magnetic Resonance in Medicine 2009. [4] Gretton et al., Journal of Machine Learning Research 2012. **Grant support:** Department of Defense X81XWH-07-CC-CSDoD; NIH P41RR013218, P41EB015902; VA Merit Award.