Improving the Reliability of between group analyses in DTI-FA analyses by detecting and removing anatomical anomalies

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Introduction: Traumatic brain injury (TBI) is a leading cause of death and disability as well as over a million emergency visits in the United States. Diffuse axonal injury (DAI) is a significant pathology of TBI and accounts for a significant portion of mortality and prolonged functional deficits in patients sustaining TBI. Conventional clinical neuroimaging is notoriously insensitive to milder traumatic brain injury (TBI). Advanced magnetic resonance imaging (MRI) techniques can detect diffuse vascular and axonal injury, using susceptibility weighted imaging (SWI) and diffusion tensor imaging (DTI), respectively. While hemorrhages on SWI are quite evident by visual inspection, detection of axonal injury using diffusion MRI which looks at microstructural alterations in water flow within and around axons requires comparison with healthy, uninjured subjects' images. Two general methods are used to compare injured and healthy images, largely differing in their approach to spatially matching images between subjects. Voxel-based analysis (VBA) employs a linear and nonlinear warping of image to template utilizing all brain elements while tract-based methods (e.g., TBSS, Smith et al., 2006) match only white matter tracts between subjects and analyze only the central "skeleton" of white matter tracts. Both methods give similar, reliable results when TBI images have normal anatomy and both methods are less reliable when there are anatomical anomalies, either congenital or acquired. These anomalies may be evident on inspection but may be subtle and difficult for spatial normalization algorithms to remove. Failure to exclude these images or the anomalies from analysis can introduce false positive artifacts in results, particularly with small sample sizes. We describe herein a method to analytically identify and exclude these deviations from analysis using a group of mild TBI patients with a high rate of anomalous anatomy.

Materials and Methods:

Image Acquisition: Thirteen mild (GCS= 13-15) TBI patients (age range = 19-56 yrs) were recruited from the emergency department at Detroit Receiving Hospital. Eighteen (18) healthy controls (age range = 21-65 yrs; 35 ± 14 M±SD) were also recruited for comparison. All patients were scanned within 24 hours of injury on a Siemens 3T-Verio system; 32-channel head coil; 30 directions; voxel dim = 1.3x1.3x2mm; 60 axial slices; TR/TE = 13300/124 ms and b values 0 and 1000 sec/mm^2). Eight of 13 patients were scanned again in the chronic stage at 1-2 years.

Image Processing: DTI studio [(1)] was used to create FA maps from diffusion images. A nonlinear warping algorithm within TBSS is used to register all the subjects' FA images to the FMRIB-FA template[(2)]. After nonlinear normalization of FA images, a variance map (s1) is calculated from the 18 controls using Matlab script. For a given patient, a second variance map (s2) is created which includes the patient's image (18+1). A difference (s2-s1) or ratio (s2-s1/s1) map is calculated using Matlab to highlight regions of anatomical deviance. The resulting difference or ratio image is smoothed (FWHM =4mm) given the spatial scale of anatomical anomalies. A lower threshold is applied on the smoothed difference or ratio image which effectively distinguishes normal from anomalous anatomy on the patient's images, relying on empirically determined normal variance from the 18 controls to identify abnormal variance from 18 controls + patient. The threshold is used to mask out the anomalies ("anomaly mask"). Since DAI is a white matter pathology we also mask out voxels which are not located in white matter on the patient's image and on the control mean image. This "white matter mask" step involves using segmentation in SPM8. Statistical comparison of patient vs. controls is performed using VBA followed by application of both masks.

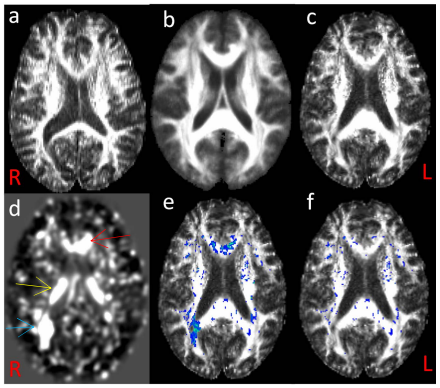

Figure1: *Effect of Removing Anomalies on VBA Results*
a) Native FA image of a mTBI patient with anomalies anatomy;
b) FMRIB FA template;
c) FA image after nonlinear registration; d) Smoothed difference map (see Results)
e) Z-score statistical map overlaid image from c;
f) image from e after applying anomaly and white matter masks.

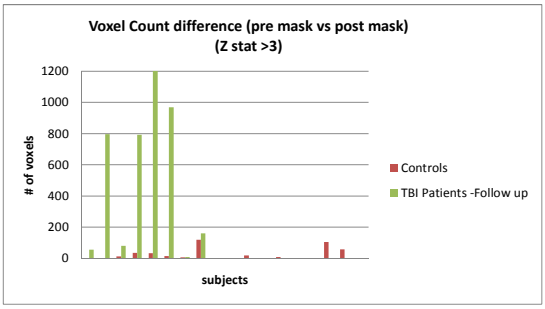

Figure 2: Difference in total voxels exceeding Z > 3 for each subject (N=18) and mTBI patient (N=8) with and without anatomical anomaly mask. Note the greater differences for the mTBI patients which is caused by more anomalies in the patients compared with controls.

Results: Figure 1 demonstrates the ability to remove false positive artifact from voxel based analysis of FA images between subjects. Figure 1a shows ventricular enlargement on the right with thinning of the temporooccipital (TO) white matter. High variance difference is also observed in thalamus and genu of the corpus callosum; Figure 1c shows the same slice after nonlinear registration in FSL. Figure 1d is the difference between variance images with and without the patient's image. High variance difference is seen in right TO white matter (blue arrow), thalamus (yellow arrow) and genu of the corpus callosum (red arrow); Figure 1e shows VBA results before masking; Figure 1f shows same VBA results after applying the thresholded (m >0.004)difference image (Fig. 1d) as a mask to remove outlier anatomy. Note that only anomalies affecting white matter (e.g., blue and red arrows) will affect the final result (Fig. 1f). A t-test of difference in suprathreshold voxels before and after anatomical masking was done on the two groups to determine whether there was a group difference in the effect of anomalous anatomy on FA statistical analysis. Results (t =1.82, p <0.03) indicated the method detected the visually apparent anatomical anomalies which were more prevalent in the mTBI group and also detected other anatomical deviations less apparent by visual inspection.

Discussion and Conclusion: Anomalous white matter anatomy can lead to false positive errors in DTI analysis. Even nonlinear registration methods may not be adequate or may lead to partial voluming of anomaly with normal tissue. Masking aberrant anatomy is one way to salvage imaging data depending on the degree and spatial extent of anomalous anatomy. We present a method which uses sampled variance in normal FA images to remove anomalies defined as outlier FA values at larger spatial scales. This and similar methods should be employed to maximize the specificity of DTI results.

References:: 1) http://www.mri.kennedykrieger.org 2) http://www.fmrib.ox.ac.uk/fsl/tbss/index.html.