DTI-Tractography to Detect and Quantify Brain Pathways Affected in Traumatic Brain Injury

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Introduction

Accurate diagnosis of traumatic brain injury (TBI) and prediction of outcome following treatment is a key factor in head-trauma management. One of the serious consequences of TBI is diffuse axonal injury (DAI). Though the exact model of axonal damage leading to changes in diffusivity and diffusion anisotropy measures such as fractional anisotropy (FA) is not well-understood, there is converging opinion that DAI represents a progressive injury, beginning with local swelling of axons, followed by cytoskeletal perturbations including misalignment of fibers and eventual disconnection [Arfanakis et al. AJNR 23:794(2002); Bazarian et al. J Neurotrauma 24:1447(2007)]. It has been hypothesized that the consequences of TBI on DTI would be a *decrease* in FA resulting mainly from a decrease in diffusivity along the principal direction. However, an *increase* in FA and a *decrease* in the trace or mean diffusivity have been reported very recently [Bazarian et al. 2007] in a 6-subject study of acute mild TBI. In addition to FA changes, which could be used to locate the injured regions, a thorough evaluation of DAI requires knowledge of specific brain connections that may be disrupted by the injury. The objective of this work was to use DTI to first locate injured regions in individual subjects via changes in the FA compared to a normal group, and then use normalized tractography to quantify disruption along specific brain pathways likely to be affected by the injury.

Method

Whole-brain single shot EPI DTI data were acquired from four TBI subjects (traffic accidents) and 10 age-matched healthy normal control (NC) human volunteers on a 1.5 T GE EXCITE scanner at TR=10.3s, field-of-view 26cm, 128x128 matrix, 28 contiguous 4mm thick slices using 25 isotropic gradient directions with b=1000s/mm^2, one b=0 acquisition, and number of excitations (NEX)=2 for a total acquisition time of 7min 50s. A customized FA template was created by normalizing individual FA maps of the 10 NC subjects through a two-step procedure relying on normalization of segmented white matter voxels (co-registered to the b_0 images) to the MNI white-matter template using a 12 parameter affine/non-linear transformation, followed by refinement in a second step through whole-brain EPI to EPI normalization. FA-template based normalization was then used to map the center points of all voxels in MNI space to each subject's native space by inverse normalization. These inverse mapped coordinates were used as seeds for whole-brain tractography in individual subjects. This procedure ensured that not only were the number of seeds equal in all subjects but also that seeds were distributed at anatomically equivalent locations in the native space of each subject. All tracts from each subject (streamline tractography, 0.2mm step size, FA>0.2, deflection<45°) were then individually transferred back to the MNI space using forward mapping of every 0.2mm spaced point on each tract. Thus the number of tracts remains unchanged from normal to standard space. Also this procedure maintains the continuity of individual tracts, does not introduce any additional smoothing, and normalizes for different head sizes, shapes and individual white-matter variations by distributing an equal number of seeds at anatomical equivalent locations in each subject. Moreover, as tracts from all subjects reside in one common space after normalization, it now becomes possible to isolate actual pathways intersecting any region-of-interest (ROI) in normalized space. Also, as the number of tracts between regions reflects the density of axonal connections between regions, the connectivity between or among specified ROIs for an individual can be quantified by counting tracts between targeted regions. If injured regions contain more voxels whose FA is below the threshold than normals (which is likely in TBI), the number of tracts through the injured regions will also be less than normals. Thus by using the injured regions as ROIs to sort tracts, one can identify specific brain pathways along which connectivity is disrupted by the injury and quantify the loss of connectivity by counting and comparing tracts between individual TBI subjects and normals at a specified FA threshold.

Results and Discussion

An example of a T-score based voxel-based-analysis to detect statistical significant FA changes between a TBI subject and the control group, followed by demarcation of specific brain pathways affected by the top 3 (ranked according to their T-scores) injured regions, is presented in **Fig. 1.**

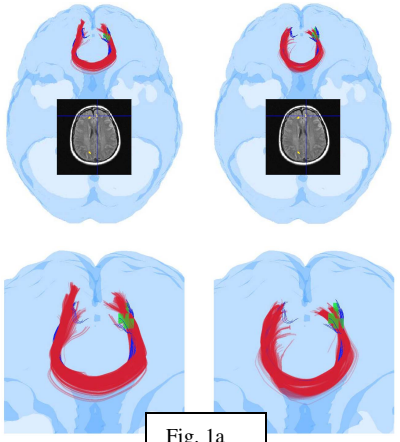

Fig. 1a

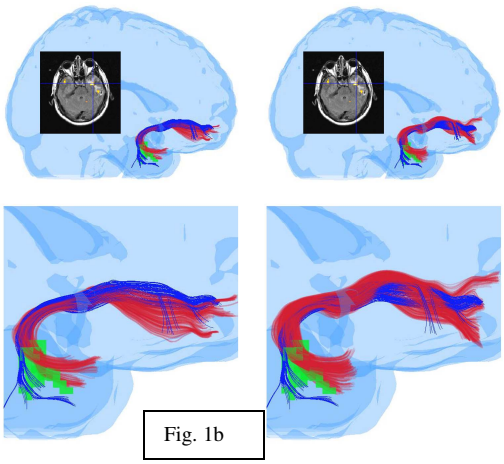

Fig. 1b

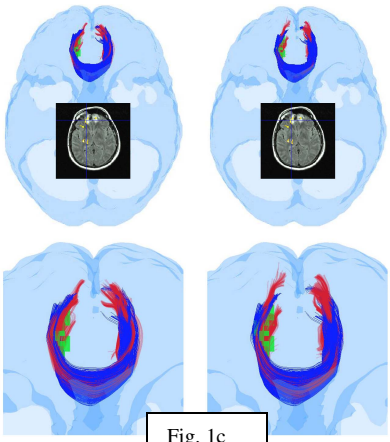

Fig. 1c

The inset images show regions (yellow-orange spots) where FA was significantly reduced in a TBI subject ($p<0.001$), superimposed on the subject's FLAIR images. No significant spots were detected where FA would have increased in any of the four TBI subjects. Pathways (FA>0.2) affected by the highest T-score FA-difference region are shown in **Fig. 1a**. The blue tracts are from the TBI subject whereas the red tracts are from two normal subjects (shown at the left and right respectively). The bottom row is a magnified version of the affected pathways. Tracts in the anterior portion of the corpus callosum (genu) are reduced, thus compromising the frontal right-left communications due to this specific injury. **Fig. 1b** similarly shows tracts identified by the second highest FA-difference region (blue for TBI) superposed on the corresponding tracts from two normal subjects (red). This injury is in the temporal lobe (see inset) and the connectivity disruption is along the temporal-frontal pathways. **Fig. 1c** shows sorted tracts from the third highest ROI. This injury is also to the genu and shows further disruption of the right-left connectivity but the specific pathways here are different from those identified by the first ROI.

Results of the tract count along specific pathways are presented in **Fig. 2**. Though there is variability in the connectivity among normal subjects, which is expected, the connectivity along the three specific pathways identified in Fig. 1 is significantly reduced in this example. Similar results were obtained from the other 3 TBI subjects. Interestingly, all had injury to their anterior corpus callosum in addition to several other regions. These results suggest that it is possible to detect and quantify disruptions along specific brain pathways affected by TBI.

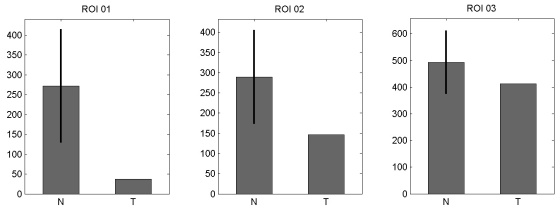

Fig. 2: Comparison of the tract count between normals (N) and the TBI subject (T) along pathways shown in Fig. 1 at FA>0.2. The effect sizes for the connectivity reduction are: 1.66, 1.24 and 0.68 respectively, which are significant large effects.