Leveraging abnormal structural integrity to enhance detection of disease-specific alterations in functional connectivity.

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Purpose. It is implicit that changes in structural connectivity or integrity of white matter tracts — the infrastructure for functional networks of cortical gray matter — impact functional brain connectivity. This has led to many investigations of relationship of (1) diffusion measures of structural white matter integrity and (2) BOLD fMRI measures of functional connectivity to disease status and/or behavioral outcomes. Commonly[1,2], diffusion metrics are averaged over predefined regions of interest (ROI) or fiber tracts and functional connectivity is characterized by the degree of temporal coherence in the resting state fMRI signals from two ROIs or a seed ROI and the rest of the brain in a voxel-wise manner. Structural and functional measures are then contrasted against each other and/or clinical metrics of the disease state. This approach has revealed important observations regarding the role of connectivity in brain disorders. However, this approach is inherently limited by the essentially separate and parallel nature of its structural and functional methodologies. We propose a method of leveraging abnormal structural integrity to enhance detection of disease-specific alterations in functional connectivity rather than using predefined ROIs or tracts. We illustrate its utility in a cohort of patients with mild traumatic brain injury (mTBI).

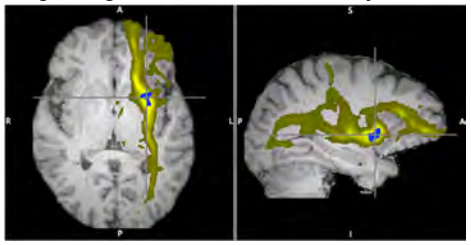

Fig.1. Cluster (blue) of abnormally low FA in mTBI group compared to controls and fiber tract (shades of yellow) seeded by it.

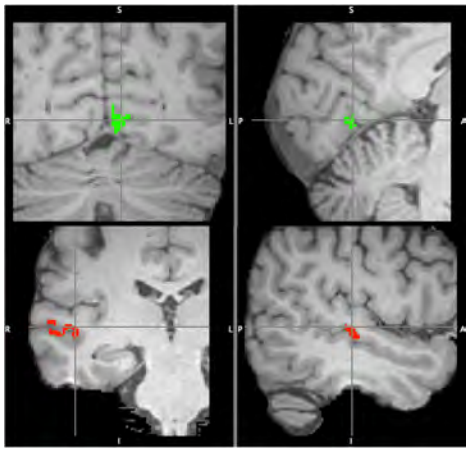

Fig.2. Clusters 1 (green) and 2 (red) of increased functional connectivity in mTBI associated with fiber damage in Fig.1.

Methods. Traumatic brain injury is known to lead to axonal injury manifesting as deficits in fractional anisotropy (FA) in diffusion images in patients compared to controls. Such clusters are identified with a voxel-based analysis between the groups after morphing individual FA maps onto a template brain of a healthy volunteer. Projecting the cluster of FA deficit onto gray matter by using it as a seed for fiber tracking on the template's DTI defines the gray matter regions communication with which might be directly affected by the damaged fibers. Functional connectivity between the defined gray matter regions and the rest of the brain is contrasted in patients and healthy controls to identify the differences attributable to the damaged fibers.

Twenty-three mTBI patients assessed by emergency room physicians having Glasgow Coma Scale not less than 13 were scanned within 48 hours of mild TBI injury. Forty-three normal controls were recruited from a general population. All participants were briefed on the procedure and gave written IRB approved consent. The imaging was performed using a 3T Philips Achieva TX scanner and its 8-channel head coil. Protocol: T1-weighted image TR/TE=9.9/4.6msec, flip angle 8°, 1mm^3 isotropic resolution, 240x240x176 matrix; DTI with 32 diffusion encoding directions, b-value=800s/mm^2, TR=11.2sec, TE=51msec, 2mm^3 isotropic resolution, 120x120 matrix, 70 slices; resting fMRI TR/TE=2762/40msec, 2x2mm^2 in-plane resolution, 115x115matrix, 3mm thick slices, 38 slices, 180 time points; and an auxiliary T2W TSE image to correct EPI distortions in DTI and fMRI[6]: TR/TE=4000/100msec, TSE factor=15, 0.6x0.9mm^2 in-plane resolution, 384x270matrix, 2mm thick slices, 70 slices. Brain extraction, rigid body registration, eddy current correction, tensor fitting, probabilistic fiber tracking, slice timing correction were performed using FSL[3]. EPI distortion correction and non-linear registration to the template (T1W image of one of the controls) were done using Automated Registration Toolbox (ART)[4,5]. Temporal correlation and high-pass filtering (0.05Hz cut off) were done using AFNI[6]. Clusters of abnormally low FA voxels were identified using voxel-wise t-test over white matter mask regressing out age, gender and years of education with threshold of $p < 0.01$, accepting clusters of at least 100 mm^3. The same cluster identification was applied to Fisher-transformed correlation map over the gray matter mask.

Results. Several clusters of low FA were identified; one — in the external capsule region shown in Fig.1, on the white matter tract to dorsolateral prefrontal cortex (DLPFC) — was selected as a seed for fiber tracking because loss of integrity of white matter subjacent to the DLPFC was found to be significantly correlated with worse executive function performance in mTBI patients[7]. Frontal areas of the cortex where the tract terminates were used as seed in the resting fMRI correlation analysis. Voxel-wise comparison of the correlation maps between the groups identified two gray matter regions where connectivity in mTBI was higher than in controls (Fig.2) and none where it was lower. Volumes of clusters 1 and 2 are 116 and 315 mm^3; Fisher correlations averaged over these clusters are -0.26 and -0.20 for controls and 0.70 and 0.99 for mTBI respectively.

Discussion. Linking evidence of structural damage to functional consequences in brain disorders such as mTBI remains essential for advancing the diagnostic utility of DTI and its capability to help select and monitor patients for response to therapy[7]. The proposed method enhances ability to establish such links by eliminating the need for predefined ROIs and by directly coupling functional to structural arms of the analysis. We illustrated this method in a cohort of mTBI patients during the acute post-injury phase, and found altered connectivity between cortical regions affected by structural defects detected by DTI FA analysis. Ongoing evolution of acute structural injuries from TBI, and their progression or recovery following treatment can be followed with greater sensitivity using proposed approaches.

Conclusion. Effectively incorporating knowledge of acute structural pathology observed after TBI into functional assessments of brain communication during recovery using the demonstrated methods may improve understanding of cognitive impairment and provide valuable insight into brain mechanisms leading to improved prognosis and the need for treatment intervention.

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