Longitudinal Analysis of Brain Recovery after Mild Traumatic Brain Injury Based on Groupwise Consistent Brain Network Clusters

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Abstract. Traumatic brain injury (TBI) affects over 1.5 million Americans each year, and more than 75% of TBI cases are classified as mild (mTBI). Several functional network alternations have been reported after mTBI; however, the network alterations on a large scale, particularly on connectome scale, are still unknown. To analyze brain network, in a previous work, 358 landmarks named dense individualized common connectivity based cortical landmarks (DICCCOL) were identified on cortical surface. These landmarks preserve structural connection consistency and maintain functional correspondence across subjects. Hence DICCCOLs have been shown powerful in identifying connectivity signatures in affected brains. However, on such fine scales, the longitudinal changes in brain network of mTBI patients were complicated by the noise embedded in the systems as well as the normal variability of individuals at different times. Faced with such problems, we proposed a novel framework to analyze longitudinal changes from the perspective of network clusters. Specifically, multiview spectral clustering algorithm was applied to cluster brain networks based on DICCCOLs. And both structural and functional networks were analyzed. Our results showed that significant longitudinal changes were identified from mTBI patients that can be related to the neurocognitive recovery and the brain's effort to compensate the effect of injury.

Keywords: traumatic brain injury, brain network clustering, DTI, fMRI, longitudinal analysis, t-test.

1 Introduction

Mild traumatic brain injury (mTBI) accounts for over one million emergency visits each year in the United States [1]. Most mTBI patients have normal findings in clinical neuroimaging. Advanced magnetic resonance imaging (MRI) has detected microstructural damage in major white matter tracts by diffusion tensor imaging (DTI), and

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functional network alternations by functional MRI (fMRI) [2, 3]. However, the field is still short of investigations on the overall extent of structural and functional network disruptions after mTBI and its recovery process. Moreover, there is lack of investigation in the alteration of connectivity on large-scale brain networks after mTBI and their recovery process. We hypothesize that mTBI results in network connectivity changes, and brain structural and functional recovery occurs over time.

In a literature work, Zhu et al. identified 358 landmarks on cortical surface that preserve structural connection consistency across subjects named dense individualized common connectivity-based cortical landmarks (DICCCOL). The previous studies have shown that DICCCOLs are highly reproducible across individuals [4, 5] and they also preserves structural and functional correspondence across individuals [6]. Moreover, in recent studies, Zhu et al. have shown that, by taking these DICCCOLs as network nodes, the connections between them could be taken as connectome signature of mental diseases such as mild cognitive impairment [7] or prenatal cocaine exposure [8]. With DICCCOL framework, the brain network alternations after injury and its recovery process of mTBI patients could be analyzed.

Intuitively, the changes in network connections during brain recovery can be derived by comparing the MRI scans of healthy subjects and the mTBI patients using t-test. Yet a considerable amount of changes in brain network connections were also seen in the two scans of the same group of healthy control (HC) subjects (E.g. the functional connection changes shown in Fig. 1). This result suggested that pairwise network connections comparison is sensitive to individual variability as well as system noise on a fine scale and thus cannot serve our purpose.

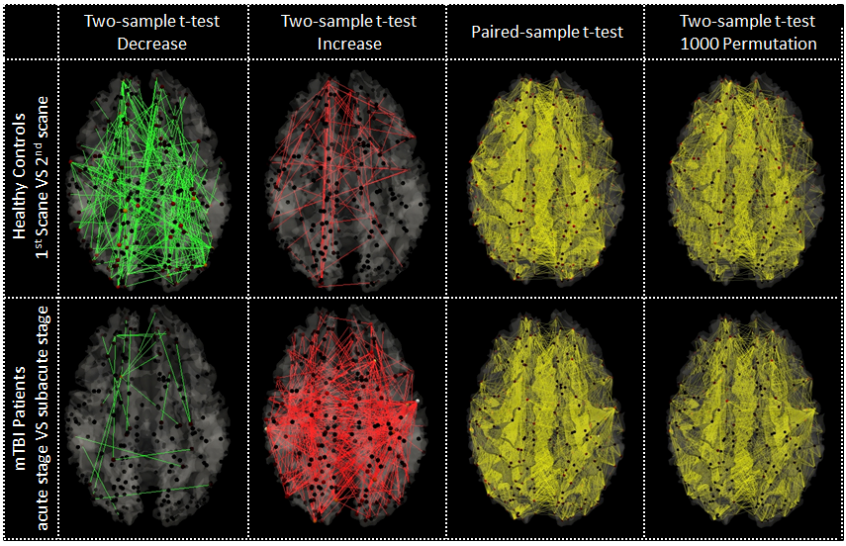

Fig. 1. Significantly different (P<0.05) pairwise functional connections among DICCCOLs between two scans of each population identified by different types of t-test.

Faced with such problem, we addressed the issue from the level of connectivity changes of brain network clusters. Whole brain networks were clustered into group-wisely common sub-networks based on the multiview spectral clustering algorithm. Each network cluster is a subset of nodes that are more densely connected within the cluster than between clusters. By comparing the connection changes within and between the clusters, the noises due to individual variability were greatly diminished and we have observed consistent pattern of disruption in structural and functional networks after mTBI. Interestingly, over time the decrease in structural connectivity is accompanied by the increase in functional connectivity. This finding is in agreement with the temporally evolving and deteriorating nature of brain injury. On the other hand, the increase in functional connectivity suggested that brain is highly plastic as it tries to recruit more regions and remodel the functional connectivity to compensate the alteration in structural connectivity. Together, these results may shed light to the network alteration mechanism of brain recovery and plasticity.

2 Data Acquisition

This study was approved by the local Human Investigation Committee. Written informed consent was obtained from each subject before enrollment. In this study, the DTI and rsfMRI data were acquired from 24 healthy subjects twice in two independent scans and from 16 mTBI patients at both acute and subacute stages after injure. In acute stage, patients were scanned 82.64/17 (average/median) hours after injury. For subacute stage, patients returned 4-6 weeks after injury to take the second scan.

Data were collected on a 3-Tesla Siemens Verio scanner with a 32-channel radiofrequency head-only coil. Diffusion imaging was acquired using a gradient echo EPI sequence in 30 diffusion gradients directions with the following parameters: b = 1000, TR = 13300 ms, TE = 124 ms, slice thickness = 2 mm, pixel resolution =1.333 x 1.333 mm, matrix size = 192 x 192, flip angle = 90°, and number of averages (NEX) =2. Resting state functional imaging was performed by a gradient echo EPI sequence with the following imaging parameters: TR/TE = 2000/30 ms, slice thickness = 3.5 mm, slice gap = 0.595 mm, pixel spacing size = 3.125 x 3.125 mm, matrix size = 64 x 64, flip angle = 90°, 240 volumes for whole-brain coverage, NEX = 1. During resting state scans, subjects were instructed to keep their eyes closed.

3 Method

Each DICCCOL node is a region of interest (ROI) [4]. The connectivity between DICCCOLs was obtained based on DTI/rsfMRI data to construct structural/functional networks. The group-wise common clusters were calculated based on multi-view spectral clustering algorithm [5] for structural or functional networks separately by taking the brain network of each subject as a ‘view’. Based on those clusters, we further analyzed the connection changes of mTBI patients over the recovery period.

3.1 Preprocessing

Preprocessing of DTI data was performed using FSL toolbox [9] which includes eddy current correction, skull and background removal, fractional anisotropic (FA) estimation. The white matter (WM)/grey matter (GM) was segmented based on FA image and WM surface was then reconstructed [10, 11]. DTI tractography was performed based on MedINRIA [12] to reconstruct fiber streamlines. For rsfMRI data, the first 5 volumes were removed before preprocessing. Then, brain extraction, motion correction, slice-time correction, spatially smoothing (FWHM=5mm), temporal prewhitening, grand mean removal, and temporally high-pass filter were applied on rsfMRI data accordingly in FSL [9].

3.2 Predict DICCCOLs and Construct Brain Networks

DICCCOLs were predicted based on the DTI derived fiber streamlines and the reconstructed cortical surface by using the tool downloaded from http://dicccol.cs.uga.edu/. In brief, DICCCOL is composed by 358 cortical landmarks obtained based on group-wise training process described in [4]. These landmarks were defined as a patch on cortical surface and the DTI derived fiber connection profile of each patch is consistent across individuals. To predict DICCCOLs on a new subject, the subject's brain will be aligned to the template space. Then for each ROI, the closest point to the template center will be identified on the subject's reconstructed cortical surface as initial location. By searching around the neighborhood of this initial location, the patch with similar structural connection profile to the template will be identified as the location of this ROI on the new subject.

Based on obtained 358 ROIs, brain networks were reconstructed by similar approaches in [5, 7]. The average fractional anisotrophy (FA) value along the fiber streamlines connecting each pair of DICCCOLs was taken as the structural connection strength. And if there is no fiber streamline connecting two DICCCOLs, the connection strength between them will be set 0. The functional connection strength between each pair of DICCCOLs was defined by the Pearson correlation between preprocessed rsfMRI signals derived from GM area of DICCCOLs. The obtained structural and functional connection matrices were represented by symmetric affinity matrices.

3.3 Multi-view Spectral Clustering

To analyze brain network alternations of mTBI patients as well as the network longitudinal changes during recovery, common network clusters were needed for comparison between different populations and different stages. Thus, we applied multi-view spectral clustering which has been shown to be reliable in obtaining group-wisely consistent brain network clusters [5]. Specifically, the brain network of each subjects were taken as a view. Its affinity matrix W will be projected to the eigenspace of the graph Laplacian of other views and then projected back such that:

$$proj(W,U) = (UU^T W + (UU^T W)^T)/2 \quad (1)$$

where $U = \Re^{n \times k}$ is the first k eigenvectors corresponding to the top k smallest eigenvalues of graph Laplacian of other affinity matrices and $n = 358$. The idea is similar to principal component analysis. Since the space represented by the top eigenvectors of graph Laplacian of affinity matrices can be viewed as the principal direction of corresponding graphs in which the graph expands most, by projecting other graphs to this space, the common part (the connections within clusters) will be retained and the disagreed part (the connections between clusters) will be eliminated. Then by doing so iteratively, the networks will converge to common connections and the common clusters across individuals will be retained. For the detailed mathematical derivation, algorithm description, and experimental validations, one can refer to [5].

4 Results

By performing multi-view spectral clustering on all the 80 affinity matrices derived from the data obtained from the two scans of 24 healthy controls and 16 mTBI patients, the clustering algorithm has converged to 13 common structural network clusters and 8 common functional network clusters (Fig. 2). The network clusters largely agree with the ones obtained from young healthy subjects in previous works [5]. The average within and between clusters connectivity are shown in Fig. 3(a) for structural networks and Fig. 3(c) for functional networks, respectively. It is obvious that within cluster connections is stronger than between cluster connections.

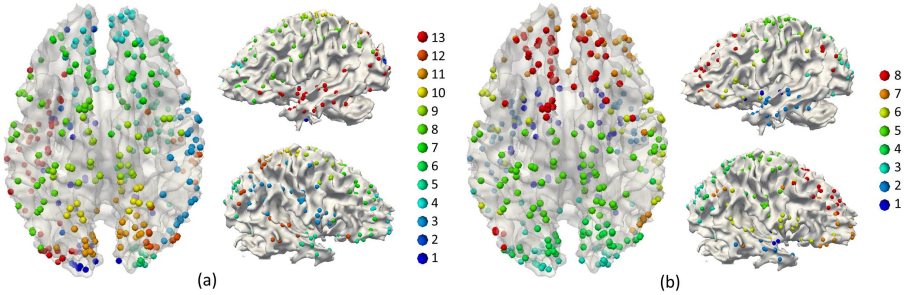

Fig. 2. Visualization of brain network clusters. Each DICCCOL is represented by a bubble color-coded by clusters (color legend on right). (a) 13 group-wise consistent structural network clusters. (b) 8 group-wise consistent functional network clusters.

For structural connections, the connectivity pattern is relatively similar between patient and control populations. Comparing the differences between the two scans of the same group (Fig. 3(b)), the brain network of normal controls is relatively consistent between two scans while those of mTBI patients from the acute stage to the subacute stage presented significant changes in brain networks. However, it is intriguing that the majority of the changes are the decreased connection strength during recovery such as those highlighted by green and red arrows in Fig. 3(b). Another intriguing observation is that, some of these changes were not detected by paired-sample t-test (as highlighted by red arrows in Fig. 3(b)). Meanwhile, with paired-sample t-test, the connections that do not change significantly could be selected (magenta arrows in Fig. 3(b)). This is

partially because though the connections strength is extremely small, the t-test will still pick up the connections when there is relative significant difference between groups (E.g. average connection is 0.01 for one set of data and 0.005 for another set). However, we are not interested in such connection in our analysis. And we would like to call attention on the usage of t-test in such applications.

Similar observation has also been obtained in functional connection between clusters. The network connection between and within clusters remained similar between two scans of healthy subjects while significant changes in cluster connections were observed between two stages of mTBI patients Fig. 3(d)).

In our analysis, we noticed that the connection within and between structural cluster 5 and cluster 12 both decreased in subacute stage. By comparing the structural network of mTBI patients and healthy controls, the connections related to these two clusters is also weaker than normal controls for patients (Fig. 4). These two clusters locate at the occipital lobe and temporal lobe of right hemisphere Fig. 5(a). Since the major fiber pathway in this area is inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UF), it may suggest longitudinal degradation of these tracts over time. Interestingly, the functional connection between cluster 2 (temporal lobe, Fig. 5(b)) and other clusters increased significantly during brain recovery, which is in consistency with the observation based on structural networks.

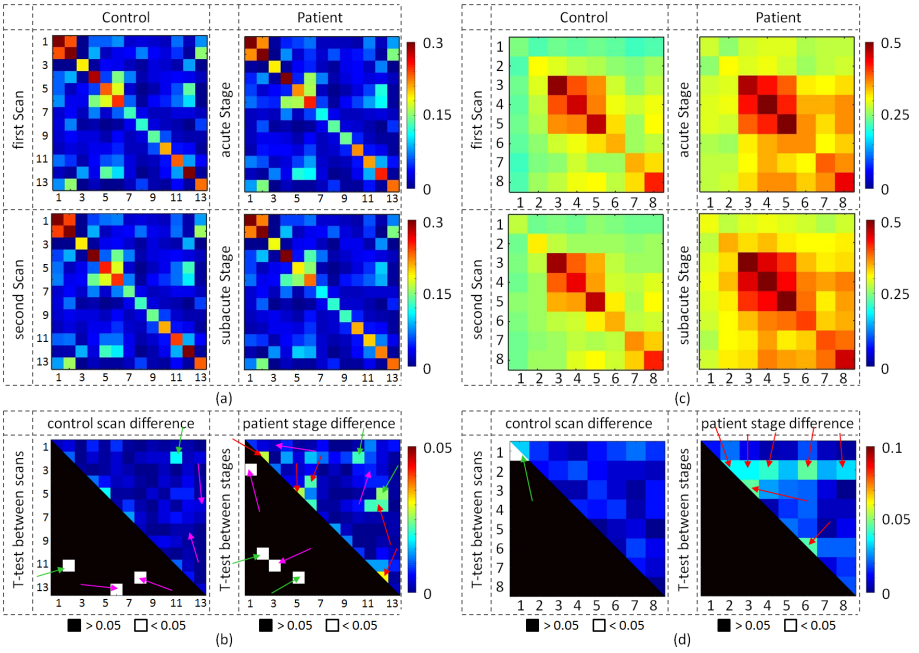

Fig. 3. Average (a) structural connection density or (c) functional connection strength within and between clusters for each group of scans. Comparison between two scans for each population for (b) structural or (d) functional connection were shown on the bottom accordingly. In the matrix shown in (b) and (d), top right part is the absolute difference between the average connection densities of two scans/stages; and bottom left part is the significantly changed connections ($P<0.05$) tested by paired-sample t-test.

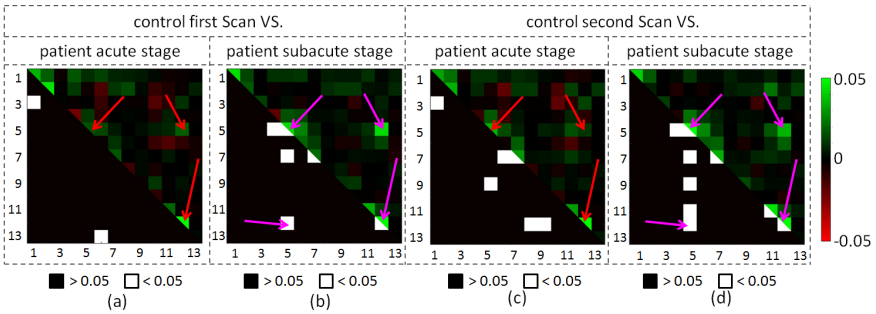

Fig. 4. Comparison of average structural connection densities between healthy controls and mTBI patients. In each subfigure, top right part of the matrix is the difference (control minus patient) and bottom left part is the significant different connections tested by two-sample t-test with 1000 permutations.

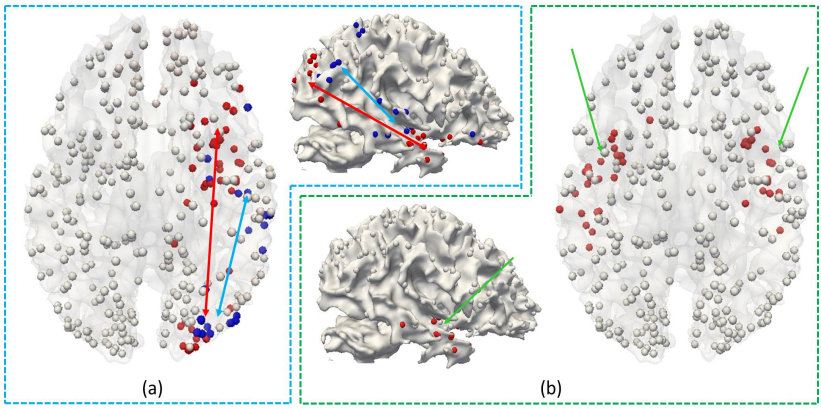

Fig. 5. (a) Visualization of structural network cluster 5 (red) and 12 (blue). (b) Visualization of functional network cluster 2 (red). Each cluster is highlighted by arrows of different colors.

5 Discussion and Conclusion

Mounting evidence in histopathology demonstrates that TBI has a progressive nature. After initial traumatic insult, the axons will undergo a temporal progression of degradation to final disruption. Recent evidence demonstrates that a prior history of brain injury, even a concussion, will make the patient more vulnerable to poor outcome after the second insult. Our structural network finding also demonstrates the progressive degradation nature in large-scale networks in mTBI. Furthermore, despite brain concussion, most mTBI patients enjoy a full recovery within several months from neurocognitive assessment perspective. This leads to the hypothesis that brain is highly plastic. Our data further support this hypothesis. In spite of structurally reduced connectivity in temporal white matter, this area tends to increase functional connectivity with other regions of the brain to compensate. Putting together, our work represents the first finding on progressive pathology of brain injury and functional com-

pensation after mTBI from large scale network perspective. Particularly the identification of brain networks undergoing structural degradation and functional plasticity would help clinicians to make proper neurorehabilitation plan to proactively treat the patient for a speedy recovery.

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