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Comparison of Functional Network Integrity in TBI and Orthopedic ControlPatientsUsing Graph-Theoretical Analysis*

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***Abstract*—The integrity of functional brain networks inpatients (n=12) diagnosed with traumatic brain injury (TBI) was compared to age-matched subjects (n=12) with orthopedic injury (OI) during a working memory task. A graph-theoretical analysis algorithm was developed and integrated into the AFNI software. Functional networks with correlations between time courses as edge-weights were automatically created and their integrity was quantified by determining the statistical significance of the following network parameters: diameter, density, clustering coefficient, average path length, two largest eigenvalues, spectral density, and minimum eccentricity. Network graphs using a spring-embedded layout (Cytoscape) and a 3D layout integrated into the anatomical space (Paraview) were created. Functional images were composed by color-coding the degree of each voxel (network node) and transformed into Talairach space. Using the AFNI Talairach atlas, degrees of distinct brain regions were quantified. Reduced averaged BOLD responses were found for the TBI group with a higher network integrity potentially as a compensatory mechanism. Regions of high functional connectivity varied in between groups with largest differences in the cerebellum, the temporal lobes and deep brain structures including the lentiform nucleus, caudate and thalamus.**

I. Introduction

Recently, correlation analysis of resting state functional magnetic resonance imaging (fMRI) data has attracted considerable interest for the investigation of functional brain subnetworks while the subject is in the so-called Default Mode State of the brain[1-3]. Here, we present the application of correlation analysis for a tasked-related paradigm in connection with graph-theoretical methods to evaluate functional networks when performing this specific task in a group of subjects diagnosed with traumatic brain injury (TBI) compared to a control group consisting of subjects diagnosed with orthopedic injuries (OI). We present the integration of these methods within the Analysis of Functional NeuroImages (AFNI) software and describe an interface for creating functional maps of network parameters (i.e. node degree) in analogy of functional maps for the blood-oxygen-level-dependent (BOLD) effect. With these tools, differences in the integrity of the functional networks in the TBI and the OI group were visualized and quantified.

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II. Materials and Methods

A. Human Subjects and fMRI Memory Task

University of KentuckyIRB approval was obtained for this study. Twelve TBI subjects (> 6 months post-injury) and twelve OI controls participated in this study. All participants studied and memorized 80 line-drawings until they reached 90% accuracy in immediate recognition before being trained on the fMRI task. Inside the 3T MRI scanner, participants performed a modified delayed match-to-sample task. For each memory trial, each subject was presented with a target sample object, and then judged whether each of the 10 test objects (new or studied)was a match or nonmatch to the target in rapid succession. Participants were instructed to forget the previous target object when a new target appeared in the next trial. fMRI image data was analyzed using the General Linear Model (GLM) with AFNI and functional activation maps were created. Average fMRI activation maps were created for the TBI group and the OI group.

B Image Preprocesing

High-resolution whole brain structural MRI were obtained

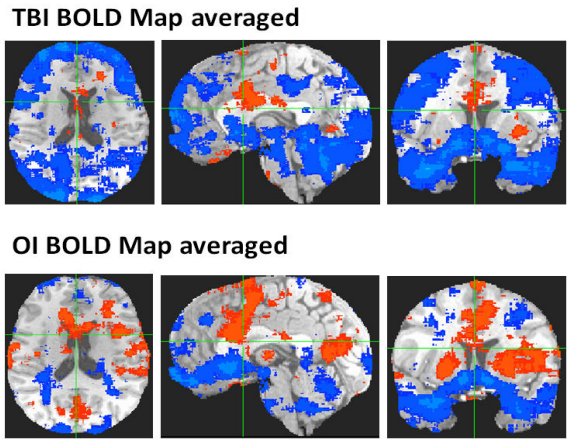

Figure 1: Top: average fMRI (BOLD) activation maps for the TBI group, below, averaged fMRI (BOLD) activation maps for the OI group. Details of the observed activation patterns are given in the text, in general a similarity can be appreciated with larger areas of activation for the OI group. Orange-red: positive signal change (activation), blue: negative signal change (deactivation)

for each subject. Twenty-two slices whole brain T2* weighted functional images were obtained every 2.0 seconds for each of the four series (T2*-weighted EPI: 64 x 64

matrix, 2.0 sec TR, whole brain, 3.6 mm cubic voxel size). Images were realigned for head motion correction using AFNI. The fMRI image volumes were reconstructed. Motion was corrected, the slice timing differences adjusted, and intensity normalized to allow for the calculation of activation as percentage signal change. General linear models were applied for the multiple regression analysis. The multiple regression models contain orthogonal contrasts of interest and additional regressors of no interest to obtain changes in mean fMRI signals.

C *Graph-Network Analysis Algorithms*

From the original fMRI images, signal time curves were extracted using the AFNI program '3dmaskdump' for voxel exceeding an activation threshold so that for each subjects, 2000 voxels were included in the creation of the graph networks. Due to the variation in activation strength statistical thresholds varied amongst subjects (table 1). From these signal time courses, a correlation matrix was calculated which then served as the adjacency matrix for the network graph with an internal implementation of the 'cor' function

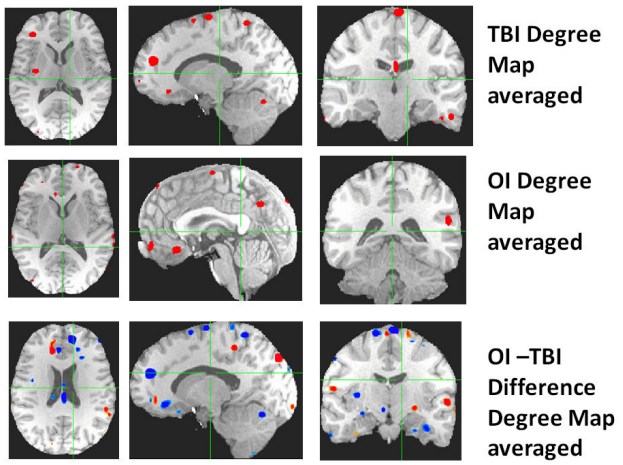

Figure 2: Average Degree maps (top TBI, below OI). Focal regions of high degree (connectivity) are visible which vary in between groups. In both group, high frontal connectivity is appreciated**.** Last row shows difference maps of datasets shown in first two rows (red positive, blue negative).

from the R statistical language. With the 'igraph' package (R statistical language), a network graph was stored in the 'gml' format. Parallel to that, the coordinates of each voxel was stored in the same order as the signal time courses in a separate file again using the '3dmaskdump' AFNI program, this time with the -xyz option. The tracking of voxel (or node) coordinates allows the recovery of anatomical position of node properties (such as degree). With functionality implemented in the 'igraph' package, the following global network parameters were then calculated: network diameter, graph density, clustering coefficient, average path length, first and second-largest Eigenvalue, mean degree value. In addition, the degree value for each node was calculated and stored. Using the AFNI program '3dUnDump', a functional map of the stored degree values (using the previously stored voxel or node coordinates) was then created and displayed in the original anatomical space for each subject. Graph networks were visualized using the 2D spring-embedded layout using of Cytoscope[4] and custom-made 3D layouts within the original anatomical space were constructed with the Paraview software (Kitware, Inc.).

D *Statistical Analysis*

The Student t-test was employed to identify statistical inter-group significance (TBI versus OI subjects) of the global network parameters. Functional maps of node degrees were transferred into Talairach space ('@auto_tlrc') and averaged for each group. Using these averaged maps, mean degree values were calculated for the 114 brain regions of the AFNI-built in Talairach atlas and regions with highest differences were determined.

III. RESULTS

A. *fMRI Activation Maps*

In general, larger regions of activations were found in the averaged fMRI activation maps for the OI group than for the TBI group. Common areas of activation for both groups included:

- rightprecentralgyrus,
- the left and right medial frontal gyrus,
- the anterior and posterior cingulate gyrus (bilateral),
- the insula (bilateral),
- thelentiform nucleus (bilateral),
- the left superior temporal gyrus,
- the left middle occipital gyrus, and
- theinferior temporal gyrus (bilateral).

TBI subjects showed additional activation in

- the left parahippocampalgyrus,
- and the culmen of vermis.

OI subjects showed additional activation in the

- theleft superior frontal gyrus,
- the left precuneus,
- the left paracental lobe,
- the middle frontal gyrus (bilateral),
- the caudate (bilateral),
- the right anterior thalamic nucleus,
- the transverse temporal gyrus (bilateral), and
- the middle temporal gyrus (bilateral).

In addition to these areas of activation, large regions of deactivation in the frontal, parietal and temporal lobes were present in both averaged activation maps (figure 1). In the consequent graph analysis, these areas of deactivation were not further considered.

B. Global Graph Network Analysis

The global network parameters showing a statistical difference, i.e. network density, clustering coefficient, largest and second-largest Eigenvalues as well as mean degree were all found larger for the TBI group than for the OI group indicating a stronger integrity of the functional network for the TBI group than the OI group.

TABLE I. GLOBAL NETWORK PARAMETERS

Network Parameters	*TBI*	*OI*
Diameter	9.97	9.73
Density (0.0003)	0.03	0.01
Clustering Coefficient (0.002)	0.64	0.58
Average Path Length	3.85	4.16
Largest Eigenvalue (2e-5)*	244	122
Second-largest Eigenvalue (0.004)*	116	82
Mean Degree (0.0003)*	60.1	27.7

(p-values in parenthesis if difference between TBI group and OI group was found significant *).

C. Functional Degree maps

In the averaged functional degree maps, regions of high degree for the TBI group included:

- pre andpostcentralgyrus,
- theanterior and posterior cingulate gyrus (bilateral),
- the left insula,
- the right lentiform nucleus,
- the right middle occipital gyrus,
- the right substantianigra, and
- thecerebellar tonsil (bilateral),

as well as several regions in the frontal and temporal lobes (figure 2). In the OI group, regions of high degree included the

- theprecuneus (bilateral),
- the left paracentral lobule,
- thecuneus,
- the right anterior cingulate,
- the left inferior parietal lobule,
- the left lentiform nucleus,
- the right uvula and
- theleft declive,

as well as several regions in the frontal and temporal lobes (figure 2).

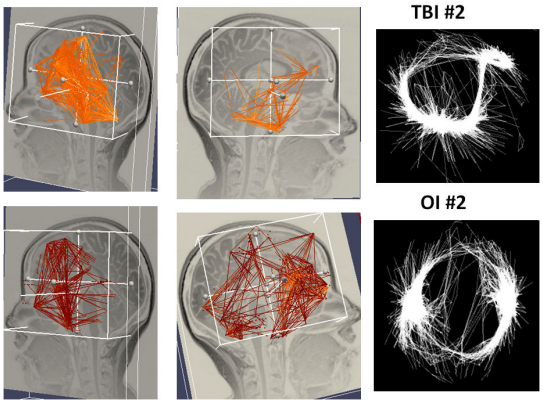

Figure 3: 3D layouts (orange, left right views on the left side of the image superimposed on a central sagittal slice) and spring-embedded layouts of the same networks on the right side of the image. Both layouts demonstrate a small-world character of the networks. In addition, the 3D layout allows the identification of brain regions with highest connectivity (predominantly frontal).

D. Functional Degree maps

Both the 2D spring-embedded layout as well as the 3D layout showed a small-world structure of the functional network, i.e. localized hubs interconnected by long-range edges. The 3D layout demonstrated predominantly frontal lobe involvement for both groups (figure 3), however, variations existed between subject (figure 2).

E. Region-based Analysis

Brain regions showing a higher connectivity for the TBI group than the OI group were located in the cerebellum (vermis and declive, bilateral), in the rectal gyrus (bilateral), the inferior temporal gyrus (left) the superior parietal lobule (left) and the substantianigra (bilateral). Regions with higher connectivity for the OI group included the left caudate (bilateral), the left precuneus, the left lentiform nucleus, the right thalamus (anterior nucleus, ventral anterior nucleus) the left superior temporal gyrus and the right transverse temporal gyrus (figure 4a). No functional relationship between BOLD activation and node degree was discernable (figure 4b), indicating at the node degree (as a measure of functional connectivity) as an independent parameters.

IV. DISCUSSION

The focus of the here presented study is the quantification of network integrity as measured by global network parameters and by node degree as a surrogate for functional connectivity. From the global measures, a higher integrity for the TBI group can be extrapolated. Considering the smaller extent of BOLD activation, it might be concluded that while similar brain regions are involved in executing the memory task for TBI subjects, this is done in with a higher degree of connectivity, potentially as a compensation mechanism. The functional maps for the node degrees and the consequent difference analysis also indicate that while similar brain regions are involved, connectivity between them varies. The 3D network layout appears more informative than the traditional 2D spring-embedded network layouts as highly connected functional brain regions can be readily identified. For the here investigated memory task, less involvement of parietal regions but stronger connectivity of frontal, temporal and cerebellar regions was visible, however, variations between subjects is noted. The here presented algorithm has been interfaced with AFNI to utilize its strong technical abilities for image and data manipulations and in-depth programming requirements (such creating the network graph) was solved

by incorporating elements from the R language. All software is freely available and our methodologies can be easily reproduced for similar kind of analysis.

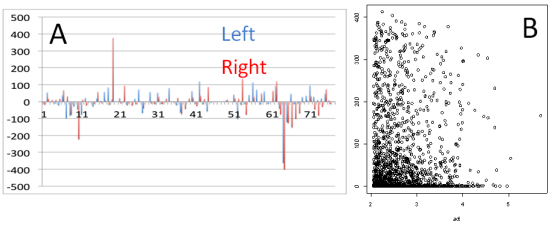

Figure 4:A: Difference of degrees in brain regions extracted with the Talairach atlas available in AFNI. **B:** BOLD activation (T-score) versus degree of the network nodes. No functional relationship is discernable.

V. Conclusion

Higher integrity of functional networks for the execution of a memory task was found in TBI subjects compared to an OI control group. Differences in functional connectivity werevisualized with node degrees as metric and visualized by functional maps using the AFNI software. The current exploratory analysis has great potential for future individualized medicine for indexing cognitive ability in patients with TBIs.

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