Small World Properties Changes in Mild Traumatic Brain Injury (MTBI)

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Introduction: The brain displays small world properties in that the neighboring neurons are densely connected but also has long-distance connections for optimal neural activity synchronization (via central hubs) between different brain regions [1]. These highly resilient small world properties are believed to play a role in protecting the brain from random or deliberate damages under disease conditions. The aims of this study were to investigate the local and global efficiency changes characterized by small world properties based on resting-state functional MRI (RS-fMRI) such as centrality and clustering coefficient in patients with mild traumatic brain injury (MTBI), and to correlate with axonal injury measured by diffusion tensor imaging (DTI) and post concussive syndrome (PCS).

Methods: Thirty-three patients (mean age 35±13 years) with clinically-defined MTBI participated in the experiments with a mean interval between MRI and trauma of 22 days (3~53 days), and various cognitive symptoms. For comparison, 45 age-matched healthy controls (mean age 37±10 years) were also recruited. 3D high resolution T1-MPRAGE (TR/TE/TI=2300/2.98/900ms, flip angle=9^o, resolution=1x1x1mm^3) were obtained at 3T Siemens Tim Trio MR scanner. Resting state (RS)-fMRI was performed using a gradient echo EPI sequence (TR/TE=2000/30msec, flip angle=70^o, resolution=3x3x3mm^3, 0.6mm slice gap,153 volumes) with 33 slices collected parallel to a line passing through the anterior-posterior commissure (AC-PC line) and positioned to cover the entire cerebrum. In addition, out of all patients and controls, 20 MTBI patients and 20 controls had whole-brain DTI data with 3 b-values (0, 500, 1000) s/mm^2 and 30 directions (TR/TE = 6800/85msec, resolution of 2.3x2.3x2.3mm^3, 55 axial slices).
We used RS-fMRI data (preprocessed and normalized to standard MNI 2mm template space) to obtain functional small world networks. The Pearson correlation between time courses of two Brodmann areas (BA) ROIs of each subject (44 BAs from MRIcro standardized landmarks) was computed to derive the correlation matrix, which is used to generate small world graphic topology with a threshold of P<0.001 to maintain sparseness. Small world properties such as betweenness centrality (i.e. short path length), clustering coefficient and core numbers [2] were then computed and analyzed with in-house Matlab scripts and programs from [3] in all subjects. For evaluation of underlying axonal injury in patients, voxel-wised tract-based spatial statistics (TBSS)[4] was used to analyze DTI fractional anisotropy (FA) data on white matter skeleton. Statistical correlation between small world properties and FA of diffuse axonal injury (DAI) region, PCS score (higher score indicates worse symptom), RS-fMRI whole brain connectivities seeding from thalamus and striatal caudate regions are also computed to elucidate the underlying disease mechanism.

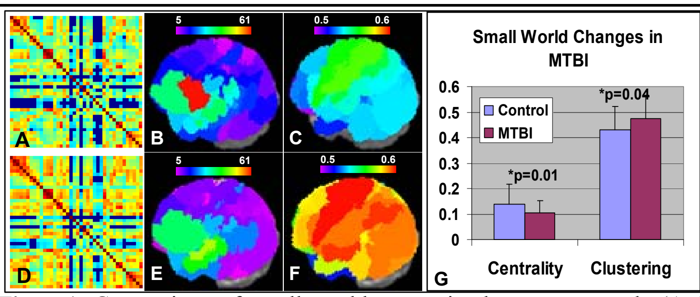

Figure1. Comparison of small world properties between controls (A-C) and MTBI patients (D-F) measured with correlation matrix (A, D), surface betweenness centrality (B, E) and clustering coefficient (C, F). Patients showed reduced scaled betweenness centrality (most prominently in the medial orbital frontal region) and increased clustering coefficient (G); indicating a redistribution of local and global efficiency after injury.

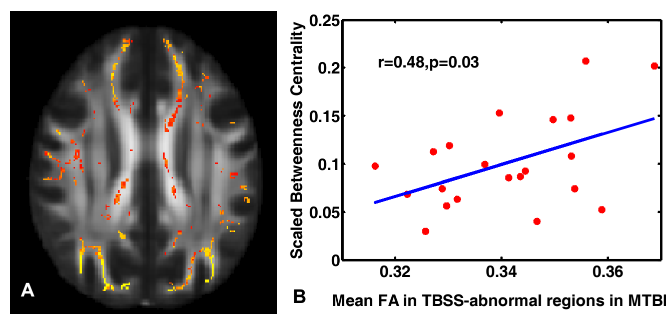

Figure2. Axonal injury revealed by DTI TBSS in brain regions (i.e. corpus callosum, temporal, occipital and frontal lobes) in patients with MTBI (P<0.05) (A) and its positive correlation with scaled betweenness centrality (B).

Results: As demonstrated in *Figure 1*, comparing with controls, MTBI patients showed lower relative betweenness centrality (average of 0.14 in controls vs. 0.10 in patients, P=0.01); indicating increase of path lengths for information flow (reduction of global efficiency) in MTBI patients. We also found significantly increase of clustering coefficient in MTBI patients as compared to controls (P=0.04), which may reflect compensatory increase of local efficiency after injury, as suggested by a prior study [5]. The decrease of global betweenness centrality correlated with the increase of clustering coefficient in patients (r= -0.77, P<0.001). In addition, we found significantly increased thalamocortical (not caudate-whole brain) connectivities, which had a positive correlation with clustering coefficient (r=0.39, P=0.03, N=33) in MTBI patients. *Figure 2A* showed reduced FA regions revealed on TBSS correlated with changes of betweenness centrality (r=0.48, P=0.03, N=20) *(Figure 2B)* and clustering coefficient (r=-0.46, P=0.04, N=20) in MTBI patients. Furthermore, patients with higher clustering coefficient tend to have less PCS with a negative Spearman correlation (r=-0.4, P=0.04, N=27).

Conclusion: Our preliminary data demonstrated there were significant functional small world properties changes in patients with MTBI, suggesting decreased global and increased local efficiencies of neuronal source utilization. The reduced betweenness centrality is likely due to disrupted global white matter (axonal) integrity. The increase of local efficiency indicated by increased clustering coefficient in MTBI may reflect a compensatory mechanism as indicated by the negative correlation with PCS and the local network upregulation such as increased thalamic connectivity found in this and the previous study [6].

References:

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