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Small World Properties Changes in Mild Traumatic Brain Injury

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Abstract

Purpose—To investigate local and global efficiency changes characterized by small-world properties based on resting-state functional MRI, such as centrality and clustering coefficient, in mild traumatic brain injury (MTBI) patients; and to associate these findings with axonal injury as measured by diffusion tensor imaging (DTI) as well as with post-concussive symptom (PCS).

Materials and Methods—Thirty patients (mean age 35 ± 13 years) with clinically defined MTBI and 45 age-matched healthy controls (mean age 37 ± 10 years) participated in the experiments. Resting-state functional MRI was performed using gradient echo planar imaging sequence with 3 Tesla MRI scanner to obtain functional small-world networks. Out of all participants, 20 MTBI patients and 20 controls had available DTI data with three b-values (0, 500, 1000) s/mm² and 30 directions for diffuse axonal injury analyses.

Results—Compared with controls, MTBI patients showed lower relative betweenness centrality ($P = 0.01$), but significantly higher clustering coefficient ($P = 0.04$), and these two metrics correlated negatively in patients ($r = -0.77$; $P < 0.001$). Regions with lower betweenness centrality (e.g., frontal and occipital) corresponded with the regions of reduced FA in patients, while global FA reduction correlated with betweenness centrality ($r = 0.48$; $P = 0.03$) and clustering coefficient ($r = -0.46$; $P = 0.04$) in MTBI patients. In addition, there was significantly higher thalamocortical connectivity that correlated with clustering coefficient ($r = 0.39$; $P = 0.03$) in patients. Also, patients with higher clustering coefficient tended to have less PCS score with negative correlation ($r = -0.4$; $P = 0.04$).

Conclusion—Our results demonstrated significant functional small-world properties changes in patients with MTBI, and suggest decreased global efficiency, possibly due to diffuse axonal injury and local network upregulation including increased thalamo-cortical connectivity.

The brain displays small-world properties, in such a way that the neighboring neurons are densely connected but also have long-distance connections for optimal neural activity synchronization (by means of 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 damage when insults are applied.² The functional connected brain network can be represented as a graph, consisting of nodes (i.e., regions of interest, ROIs), and edges (i.e., connections), between regions that are functionally linked.³ Quantitative

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large-scale results generated from the graph theory-based analysis has been confirmed by using different imaging metrics including functional MRI (fMRI), electroencephalography (EEG), and diffusion tensor imaging (DTI).^{4,5} Small-worldness computed from functional connectivity had shown to be scalable and reproducible in that large-scale brain functional networks had robust small-world architecture at different spatial scales using different brain atlases⁶; stationary with a relative short (2 min) window acquisition⁷; and reliable as graph metrics are sufficient to be considered for further longitudinal studies of functional brain network changes.⁸ Graph theory based small-worldness analysis have been applied to such neurologic diseases including Alzheimer's disease^{9–11} and multiple sclerosis.¹²

In traumatic brain injury (TBI), diffuse axonal injury (DAI) resulting in disruption of functional networks in the brain is thought to be a major contributor to cognitive dysfunction.^{13,14} Studies of moderate and severe TBI patients have reported longitudinal white matter (WM) volume decline in several areas, possibly due to Wallerian degeneration after DAI.¹⁵ Multifocal white matter ultra-structural abnormalities had been reported in mild traumatic brain injury (MTBI) with cognitive disability using voxel-wise analysis of DTI.¹⁴ DTI had also indicated WM diffusion changes at the subacute stage in MTBI with persistent neurobehavioral impairment.¹³ Longitudinal follow-up data from MTBI patients further found measurable atrophy a year after a single concussive episode affecting the anterior cingulum WM and was associated with anxiety and post-concussive symptoms (PCSs).¹⁶ These findings of WM abnormalities in MTBI and TBI patients seem to support the notion of axonal damage, edema, axonal swelling, axoplasmic transport, and disconnection in the intermediate and long-term following injury.^{17,18}

The disruption of default mode network (DMN) functional connectivity, hypothalamic and thalamic functional network and activity based on resting-state fMRI (RS-fMRI) has been reported in MTBI.^{19–21} Furthermore, neurocognitive assessments with six cognitive domains had found to be correlated with functional connectivity MRI (fcMRI) data of MTBI in our previous reports, for the participants recruited with the same cohort.^{19,20} Functional connectivity abnormalities of other brain networks and systematic-level analysis needs to be further quantified. The alteration of small-world properties such as increase of clustering coefficient in TBI and shortest paths during recovery had been reported.²² To date, however, few studies have been published regarding the systematic network changes using small-worldness analysis in MTBI patients compared with controls and link such systematic whole-brain changes to other brain dysfunction including axonal injury.

The unique advantage of using graph-theory based small-worldness lies in the characterization capabilities of the systematic efficiencies of brain neuronal resources, independent of the atlas (e.g., different networks or consisting of different number of edges) and imaging metrics (fMRI or DTI) used.⁷ Compared with traditional decomposition method, small-world network analysis can provide globally large-scale and locally cluster-wise interregional modulation information of real-time brain anatomical and functional organizations.¹² The brain dynamic equilibrium or mesastability has largely been accepted to explain the divergent functional connectivity alterations observed in different brain regions in MTBI patients.^{20,23} Whether the network-level disruption is resulted from local injury and possible diffuse cellular-level axonal injury, as proposed as the common

pathology in MTBI, and, furthermore, is there any spatial correspondence between functional and structural disconnectivity, remains an open question.

A recent study based on connectome-level large scale structural and functional connectivity had found disrupted structural conductivity and reduced intra-network connectivity within the emotion network and among emotion-cognition interactions.²⁴ The interactions between functional and structural imaging findings, and associations between imaging findings and clinical data have not been examined extensively.

The purposes of this study were to: (1) investigate the absolute local and global efficiency changes characterized by small-world properties based on RS-fMRI fcMRI such as centrality and clustering coefficient in MTBI patients; (2) quantify the correlations between the small-world properties and axonal injury measured by DTI spatially and globally, as well as the correlation between the imaging findings and clinical PCS score (PCSS) in patients.

Materials and Methods

Subjects

This institutional review board–approved prospective study was in compliance with the Health Insurance Portability and Accountability Act. Patients with MTBI were recruited from a university-affiliated level 1 trauma center and a university hospital, and healthy control subjects were identified and recruited from a database of ongoing neuroimaging projects. Patients with MTBI were identified based on those defined by the American Congress of Rehabilitation Medicine and are as follows: closed head injury with either posttraumatic amnesia of less than 24 h or loss of consciousness of approximately 30 min or less, with a Glasgow Coma Scale score of between 13 and 15.^{19–21} All participants had signed the informed consent form after the nature of this study was explained.

Thirty patients (mean age 35 ± 13 years; 6 women, 24 men) 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; 20 women, 25 men) were also recruited. All the patients had varied posttraumatic symptoms such as fatigue, sleep disturbance, emotional stress, memory trouble, and headache. Exclusion criteria included a history of alcohol or drug abuse; a preexisting psychiatric disorder; a prior brain injury other than the current episode; and a history of other neurologic disease, including stroke, epilepsy, and somatic disorders. Control subjects were also confirmed to have no history of psychiatric, neurologic, or central nervous system diseases and had normal conventional MR imaging findings.²⁵

Neuropsychological tests and PCSs including anxiety, depression, and fatigue were performed within 12 h of MRI scan for patients with MTBI. The PCSSs were assessed by using self-report questionnaires and were reported in Z-scores, for which higher scores indicated greater symptom.²⁶

MRI Imaging

MR imaging data were obtained with a 3 Tesla (T) whole-body MR scanner (Siemens Tim Trio; Siemens Medical Systems, Erlangen, Germany) by using a 12-channel head coil. Standard gradient-echo echo-planar resting-state functional MR imaging (repetition time/echo time [TR/TE] = 2 s/30 ms, number of volumes = 153, flip angle = 75 °, field of view [FOV] = 220 × 220 mm², matrix = 128 × 128, 153 volumes) was performed in the axial plane, parallel to a line through the anterior and posterior commissures (section thickness, 5 mm; section gap, 1 mm) and positioned to cover the entire cerebrum (spatial resolution, 1.72 × 1.72 × 6.00 mm³) with an acquisition time of 5 min 6 s. Individuals were instructed to close their eyes for better relaxation but to stay awake during the imaging protocol.

For coregistration and normalization of resting-state functional MR imaging data, three-dimensional T1-weighted magnetization-prepared rapid gradient-echo imaging (TR/TE/inversion time [TI] = 2300/2.98/900 ms, flip angle = 9 °, resolution = 1 × 1 × 1 mm³) was performed. Of the total participants, 20 MTBI patients and 20 controls had also performed whole-brain DTI sequence based on the similar coverage space as the fMRI with 3 b-values (0, 500, 1000) s/mm² and 30 directions (TR/TE = 6800/85 msec, resolution of 2.3 × 2.3 × 2.3 mm³, 55 axial slices). In addition, T2-weighted fast double spin-echo and high-spatial-resolution susceptibility-weighted imaging sequences (TR/TE/TI = 45/20/900 ms; flip angle = 15 °; resolution = 0.5 × 0.5 × 2.0 mm³; 52 axial sections) were also implemented to help detect hemorrhagic or other lesions. The conventional T1- and T2-weighted images were reviewed by two radiologists with 15 years of experience in diagnostic MRI imaging, and lesions, if present, were reported.

For correction of motion artifacts, head movement–constraint headphones and a cushion were used to prevent movement during imaging, and all individuals were instructed to keep still during the imaging protocol. AFNI motion-correction algorithms were used to perform more realignment steps with three angular rotations (roll, pitch, and yaw in units of degrees) and three directional displacement (in millimeters) adjustments to further minimize motion artifacts. After these correction steps, no statistical differences were observed in the previous six motion parameters and frame displacement along all temporal frames between MTBI and control groups ($P > 0.05$).²⁴

Data Analysis

SMALL-WORLDDNESS ANALYSES—A few key terminologies commonly used in graph theory^{27–30} and this work include: (1) degree (D): equal to the number of connections (edges) attached to each node (ROI). (2) Clustering coefficients (C_p): measure number of connections of a node with its nearest nodes (neighbors), namely the fraction of the number of a node's neighbors that are also neighbors of each other; reflecting how efficiently the network exchanges information at the cluster level. (3) Betweenness centrality (BC): measure number of shortest paths between pairs of other nodes that pass through the node; reflecting how efficiently the network exchanges the information at the global level. Path lengths (L_p) record the length of the shortest path between a pair of nodes. BC is high for nodes that are located on many short paths in the network and low for nodes that do not participate in many short paths and are, therefore, more peripheral. For group comparisons,

the measures of global (BC) and local (CC) efficiency were primarily considered for further quantification in this work.

RS-fMRI data (preprocessed and normalized to standard Montreal Neurologic Institute-MNI 2-mm template space)²⁰ were used to obtain functional small-world networks. In the preprocessing step of fMRI data, regression model was used to remove nuisance signal results from possible motion and nongray matter signals, including six motion parameters, signals derived from cerebrospinal fluid (CSF), and white matter masks after segmentation as well as global signal. For structural MPAGE data used for fMRI data normalization, preprocessing included reorientation to the right–posterior–inferior convention and skull stripping, and segmentation into three tissue types: gray matter,²⁸ white matter (WM), and CSF. The segmental tissue masks were used to derive the nuisance fMRI signals in WM and CSF.

Finally, the MPAGE image was co-registered with the fMRI data and normalized to the Montreal Neurologic Institute (MNI) 152-brain template (2 mm isotropic voxels). The first four volumes of the RS-fMRI data of each subject were discarded for scanner and image stability. Preprocessing steps for RS-fMRI data included rigid alignment of the time frames using AFNI motion correction algorithms, spatial smoothing using a Gaussian kernel with 6 mm full-width-at-half-maximum (FWHM), and band-pass temporal filtering of 0.005–0.1 Hz to improve signal-to-noise ratio. Removal of nuisance signals was then performed using a Gaussian regression model after co-registration to MPAGE data. Namely, motion parameters, global signal, and signals derived from CSF and WM based on the tissue masks were modeled in the Gaussian linear mixed model, and residual signal at each voxel was maintained for further analyses. Finally, the residual 4D fMRI data after regression were transformed to MNI standard space.²⁰

The Pearson correlation between fMRI time courses after preprocessing of two Brodmann areas (BA) ROIs of each subject with 44 BAs from MRICro (www.cabiatl.com/mricro) standardized landmarks was computed to derive the correlation matrix, which is used to generate small-world graphic topology with a threshold of $P < 0.001$ (corresponding $r > 0.265$, approximate sparsity = 50%) to maintain sparseness (based on sparse graph definition, tree-like graph, see correlation matrix in Fig. 1A). Small-world properties such as betweenness centrality (i.e., shortest path length) and clustering coefficient were then computed and analyzed with in-house Matlab scripts and adapted programs from matlab_bgl (http://www.stanford.edu/~dgleich/programs/matlab_bgl) in all subjects.⁹

For evaluation of underlying axonal injury in patients, voxelwise tract-based spatial statistics (TBSS) from the FMRIB Software Library (FSL, <http://fsl.fmrib.ox.ac.uk/fsl>) toolbox was used to analyze DTI fractional anisotropy (FA) data on white matter skeleton. A standard linear regression fitting was used to estimate the FA with multiple b-values and gradient diffusion files using FSL dtifit tool. Namely, FA data from all participants were registered and transformed to the FSL FA template to create a WM skeleton to reduce number of statistical comparisons between MTBI and control groups (with morphological thinning and thresholding algorithms). To improve spatial normalization, the FA data (with a threshold of $FA > 0.2$ to confine to WM) were transformed to the FSL MNI (1-mm isotropic resolution)

common space by using the nonlinear registration tool FNIRT based on a b-spline representation of the registration warp field. Statistical nonparametric permutation analysis was used to compare the difference of FA between two groups. The average FA from global whole brain white matter (FA-whole brain) and average FA from DAI regions (FA-DAI) were obtained in patients as the global DTI metrics.

VALIDATION—To confirm the small-world characteristics of the fcMRI used in the analysis, a threshold of correlational r value from 0.2 to 0.95 was applied to the correlation matrix to investigate the small-worldness measures at different sparsity levels (range of 0.1–0.8). A random network with the same number of degrees as the real network was generated and used as a scaling factor to compute the relative local efficiency ($\gamma = C_p/C_p\text{-random}$, supposed to be $\gg 1$ for a small-world property graph) and global efficiency ($\lambda = L_p/L_p\text{-random}$, supposed to ≈ 1 for a small-world property graph).⁹

To further validate with the small-worldness characterized by functional connectivity, whole-brain tractography based on DTI FA was performed to characterize the small-worldness properties based on structural connectivity with fiber bundles with the Diffusion Toolkit toolbox (<http://tractvis.org>). The WM parcellation was done based on Freesurfer (surfer.nmr.mgh.harvard.edu/fswiki, V5.3) with a total of 70 WM regions delineated in the whole brain first. Then the correlation matrix was derived directly based on the fiber bundle numbers connected between two white matter regions with in-house Matlab scripts. The DTI fiber bundle number was chosen to reflect structural connectivity strength between two white matter regions to parallel the functional connectivity measure, and had been reported to be an effective metric for graph theory-based analyses.¹² Small-worldness properties including local and global efficiencies were quantified with the method described previously.

CONVENTIONAL FUNCTIONAL CONNECTIVITY (FCMRI)—To elucidate the underlying mechanism of alterations of small-worldness network properties, functional connectivity seeding from thalamus, a previously found abnormal region, and another control seed region (i.e., striatal caudate) were computed^{19,20} and correlated with the small-worldness metrics. These two seeds were obtained from the FSL sub-cortical thalamus and caudate template, respectively. Functional connectivity maps from the two seeds for each subject were computed based on the methods described previously.^{19,20} The voxel number (N) and average correlational z value (Z) were computed from each seed after a correlational threshold with $P < 0.01$ for further global quantification.

Statistical Analysis

Two-sample t -test was applied to test the median differences of the estimated small-world parameter between MTBI patients and controls. Statistical correlations between these metrics and FA (FA-whole brain or FA-DAI in patients compared with controls), functional connectivity metrics (V and Z), as well as PCSS (PCSSs with higher score indicates worse symptom) were computed in patients.

Results

Compared with control group (Fig. 1A), the average correlation matrix in MTBI patients computed from 44 BA interregional correlation demonstrated more regionally within-module connectivity clubs with lack of a few key hubs (Fig. 1D). The distribution patterns of scaled BC over the whole brain average from control subjects identified central hub regions with the criteria (Mean + 2 standard deviation, SD) in the frontal and temporal regions (Fig. 1B). In MTBI patients, there was reduced averaged scaled BC, with the most prominent reduction in the medial orbital frontal region (Fig. 1E), followed by regions in occipital and parietal cortices. The whole-brain average Cp from controls identified higher Cp in the medial frontal regions as well compared with other brain regions (Fig. 1C), and there was increased Cp in the dorsal frontal and posterior parietal regions in MTBI patients compared with controls (Fig. 1F).

Globally, compared with controls, MTBI patients showed significant lower scaled BC ($P = 0.01$) and higher Cp ($P = 0.04$) (Fig. 2A). Furthermore, in MTBI patients, the scaled BC (reduced in MTBI patients) was highly correlated with the Cp (increased in patients) ($r = -0.77$; $P < 0.001$; Fig. 2B).

Figure 3A–C demonstrated a consistent pattern of voxel-wise FA reductions in MTBI patients compared with controls based on TBSS analysis ($P < 0.05$); the regions with reduced FA (diffuse axonal injury) mainly involved frontal and occipital regions, as well as corpus callosum. MTBI patients showed reduced globally FA-DAI ($P = 0.038$) and FA-whole brain ($P = 0.035$) compared with controls (Fig. 3D). Moreover in patients, the reduced FA in DAI regions revealed on TBSS in MTBI correlated with scaled BC ($r = 0.48$; $P = 0.03$; Fig. 4A). The FA-DAI also correlated negatively with the Cp in MTBI patients ($r = -0.46$; $P = 0.04$). And spatially, the regions with reduced scaled BC (e.g., frontal and occipital) corresponded with the regions of reduced FA in patients (Fig. 4B) (e.g., reduced medial orbitofrontal fMRI-based BC and reduced FA in the corresponding anterior cingulum bundle).

In terms of seed-based functional connectivity analysis, no significant changes of caudate-cortical connectivity were found between MTBI patients and controls. However, there was significantly increased thalamo-cortical connectivity in MTBI patients compared with controls (corrected $P < 0.05$). The thalamic connected voxel number was significantly higher in patients ($P < 0.001$) (Fig. 5A). And this thalamo-cortical connectivity correlated significantly with Cp in MTBI ($r = 0.39$; $P = 0.03$; Fig. 5B). Furthermore, patients with higher Cp tend to have a lower PCSS with a negative Spearman correlation between Cp and PCSS ($r = -0.4$; $P = 0.04$; Fig. 6). Some other correlations between neuropsychological tests and fMRI were: significant correlation ($r = 0.60$; $P = 0.02$; Bonferroni corrected) between decreased DMN fMRI in the posterior regions with the Trail Making Test B, a measure of executive functioning to assess mental flexibility.²⁰ The increased medial frontal connectivity in patients correlated negatively with posttraumatic symptoms including depression, anxiety, fatigue, and postconcussion syndrome. Furthermore, there was a positive correlation between low-frequency thalamo-cortical coherence averaged across all

cortical BA regions over the low-frequency band and PCS in MTBI patients (Spearman rank $r = 0.4$; $P = 0.029$).¹⁹

For confirmation of the small-worldness graph presented with fcMRI data, a representative control participant's fcMRI data analyzed at different sparsity levels are shown in Figure 7. The fcMRI data demonstrated the small-world characteristics with reduction of relative local efficiency ($\gamma \gg 1$) in Figure 7a and reduction of relative global efficiency ($\lambda \approx 1$) in Figure 7b when the sparsity level drops. The absolute local efficiency in Figure 7c and absolute global efficiency in Figure 7d also indicated the sparsity level of 50% quantification used in our data is a good representative median number.

To validate the small-worldness properties characterized by fcMRI, whole-brain tractography based on DTI FA (color indicates fiber orientation) of the same representative participant is shown in Figure 8A. A total of 70 WM regions were delineated in the whole brain with Freesurfer (Fig. 8B). The correlation matrix was derived directly based on the fiber track numbers connected between two white matter regions (Fig. 8C). The betweenness centrality measured from the DTI data of this subject is very close to the betweenness centrality measured from fMRI with less than 1% error between the two numbers derived based on two imaging modality for an individual subject. This further validates that our small-worldness techniques based on fMRI are robust tools to quantify brain efficiency that reflects neuronal resource distribution.

Discussion

In this study, there were significant functional small-world properties changes in patients with MTBI, including lower global efficiency (BC) with higher local efficiency (Cp). The reduced global efficiency is likely due to the disrupted diffuse white matter (axonal) integrity as indicated by significant negative correlation with the decreased FA in DAI regions. Specifically, the spatial correspondence between the diffuse axonal injury sites (i.e., frontal and occipital) and decreased global efficiency in these regions might suggest the underlying pathological mechanism of functional network integration changes directly caused by the axonal injury in patients. Both spatial and global correlations between reduced global efficiency and reduced FA in diffuse axonal injury sites indicated a distributed and global-level functional network disruption in patients, probably secondary to the structural disconnectivity.

On the other hand, the highly significant correlation between increased local efficiency and higher thalami-cortical connectivity in patients compared with controls indicated a possible cascade of abrupt functional thalami-cortical connectivity that could lead to the decreased neuronal usage efficiency in patients. The increased local clustering coefficient (Cp) in MTBI may also reflect a compensatory mechanism from local network upregulation based on the negative correlation with PCS, as well as a significant negative correlation with the global efficiency (BC). The significant negative correlation between local and global efficiencies in MTBI patients confirmed the dynamic equilibrium status of brain networks (i.e., both changes in different directions, but highly correlated). The small-worldness properties of fcMRI data had been confirmed with comparison to a random network at the

same sparsity level. Finally, the quantification of the local and global efficiencies using fcMRI had been validated with the small-worldness properties computed based on the DTI data.

There has been tremendous progress made of the connectivity studies in MTBI for the past several years, including more heterogeneous patients population, different disease stages including acute and recovery, multiple imaging metrics including DTI, EEG, blood flow, metabolism (MR spectroscopy), and large-scale network studies.^{31–36} It has been generally accepted that small-worldness nature of brain networks is dynamically appealing and robust. It is not surprising that higher small-worldness (i.e., higher local efficiency but lower global efficiency) was found in MTBI patients in comparison to controls, possibly to maintain dynamic equilibrium efficiency after injury. This result is also in line with a recent study using EEG and fMRI data in participants with MTBI.³⁷ Similar changes in efficiencies had also been reported in patients with TBI based on either RS-fMRI or task-related fMRI data.^{22,38}

The normalized characteristic path length to random network was higher in spinal cord injury patients than in controls, suggested reduced normalized global efficiency as well.³⁹ The disruption of the global efficiency (and, therefore, disturbance of the global integration of networks) agreed with a recent study which reported that MTBI patients with chronic PCSs revealed an imbalance in the ratio of cerebral blood flow between the default mode nodes and task positive nodes across multiple stages of recovery.⁴⁰ Consistent abnormal thalamocortical connectivity and decreased activity had been found from recent studies in our group,^{19,41} partially due to the center relay station role of the thalamus in contrast to other sub-cortical regions such as caudate, which was found not to be functionally disrupted in patients in our data.

Aberrant thalamo-cortical connectivity in the epileptic hemisphere was mirrored in a loss of behavioral in association with spatio-temporal memory performance specifically in patients with hippocampal atrophy.⁴² Although direct micro-structural thalamic injury is difficult to detect, the functional disruption of thalamus, reduced functional thalamic activity,²⁰ and even hypothalamic connectivity disruption²¹ observed in our data might provide a clue to the underlying pathology in addition to diffuse axonal injury that could lead to the functional small-world properties disruption and brain functional state change in patients.⁴³ Further recruitments of more patients and demographic-matched controls, relating the MRI results to injury causes and injury sites, are warranted in the near future.

Although graph-theory based small-worldness provided a large-scale whole-brain network quantification, it remains a challenge to elucidate the full spectrum of static and dynamic functional connectivity patterns and to achieve a superior high accuracy to differentiate between patients and controls.⁴⁴ The all time-lag correlation (e.g., frequency-domain coherence) based small-world analysis to remove time dependence of functional connectivity computation or using partial correlation method warrants further investigation. Applying other metric-based small-worldness analyses including structural DTI and cortical thickness, and correlating with more neuropathological data are needed to validate current findings. Even small-worldness properties had been reported to be not influenced much by

the spatial resolution of the raw fMRI data,⁷ improvement with higher spatial resolution fMRI data acquisition is expected.

In conclusion, results found from this study demonstrated significant functional small-worldness changes in patients with MTBI, suggesting decreased global and increased local efficiencies of neuronal source usage. The reduced betweenness centrality is likely due to disrupted global white matter (axonal) integrity. The increase of local efficiency indicated by higher clustering coefficient in MTBI may reflect a compensatory mechanism, with the negative correlations with PCS and global efficiency, but positive correlation with the local network upregulation indicated by increased thalamo-cortical connectivity.

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FIGURE 1.

Compared with control group (A), the average correlation matrix in MTBI patients computed from 44 Brodmann area (BA) interregional correlation showed more regionally local connectivity clubs and with lack of a few key hubs (e.g., crossing node) (D). B: The distribution patterns of scaled BC over the whole brain average from control subjects showed central hub regions with the criteria ($\text{mean} + 2 \text{SD}$) in the frontal and temporal regions, in red and green colors. E: In MTBI patients, there was reduced averaged scaled BC with the most prominent reduction in the medial orbital frontal region (marked in white arrows). The whole brain average Cp from controls showed higher Cp in the medial frontal regions as well compared with other brain regions (red and yellow colors) (C), and there was increased Cp in the dorsal frontal and posterior parietal regions in MTBI patients compared with controls (marked in white arrows) (F).

FIGURE 2.

A: Compared with controls, MTBI patients showed significant lower scaled BC ($P=0.01$) and higher Cp ($P=0.04$). **B:** The scaled BC (reduced in MTBI patients) correlated with the Cp (increased in patients) ($r=-0.77$; $P<0.001$) in patients.

FIGURE 3.

Whole-brain FA reductions, or diffuse axonal injury (DAI) in MTBI patients compared with controls based on TBSS analysis ($P < 0.05$), mainly in the frontal, occipital and corpus callosum areas. **A:** Coronal view. **B:** Sagittal view. **C:** Axial views. **D:** Globally, MTBI patients showed reduced FA-DAI ($P = 0.038$) and FA-whole brain ($P = 0.035$) compared with controls.

FIGURE 4.

Global and spatial correlations between DTI FA and functional global efficiency (betweenness centrality) in MTBI patients. **A:** The reduced FA in DAI regions revealed on TBSS in MTBI correlated with scaled BC ($r = 0.48$; $P = 0.03$). **B:** Regions with reduced scaled betweenness centrality (e.g., frontal and occipital areas marked in white arrows) corresponded with the regions of reduced FA in patients (color showed significant reduced FA with $P < 0.05$). **C:** FA reductions, or diffuse axonal injury (DAI) in MTBI patients compared with controls in sagittal view.

FIGURE 5. Correlation between functional connectivity with seed-based analysis and local efficiency (clustering coefficient) in MTBI patients. **A:** The thalamic connected voxel number was significantly higher in patients ($P < 0.001$). **B:** The thalamic-cortical connectivity (connected voxel numbers) correlated significantly with clustering coefficient in MTBI ($r = 0.39$, $P = 0.03$).

FIGURE 6.

In MTBI patients, there was a significant negative correlation between clustering coefficient and PCS Z-score (Spearman rank $r = -0.4$; $P = 0.04$); indicating patients with higher clustering coefficient tend to compensate for the post concussive syndrome.

FIGURE 7.

Small-worldness properties of a representative control participant's fcMRI data analyzed at different sparsity levels. The fcMRI data demonstrated a small-world characteristics with reduction of relative local efficiency ($\gamma \gg 1$) in (a) and reduction of relative global efficiency ($\lambda \approx 1$) in (b) when the sparsity level drops. The absolute local efficiency at different sparsity levels was demonstrated in (c) and absolute global efficiency shown in (d).

FIGURE 8.

A: Whole-brain fiber tractography based on FA (color indicates fiber orientation). **B:** White matter (WM) parcellation based on Freesurfer (color indicates whole brain ROI delineation) in individual subject space. A total of 70 WM regions were delineated in the whole brain. **C:** Correlation matrix derived directly based on the fiber track numbers connected between two white matter regions (pink and yellow color as examples).