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Commentary

Correlation between standardized assessment of concussion scores and small-world brain network in mild traumatic brain injury

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ABSTRACT

This study investigated the characteristics of the small-world brain network architecture of patients with mild traumatic brain injury (MTBI), and a correlation between brain functional connectivity network properties in the resting-state fMRI and Standardized Assessment of Concussion (SAC) parameters. The neurological conditions of 22 MTBI patients and 17 normal control individuals were evaluated according to the SAC. Resting-state fMRI was performed in all subjects 3 and 7 days after injury respectively. After preprocessing the fMRI data, cortex functional regions were marked using AAL90 and Dosenbach160 templates. The small-world network parameters and areas under the integral curves were computed in the range of sparsity from 0.01 to 0.5. Independent-sample *t*-tests were used to compare these parameters between the MTBI and control group. Significantly different parameters were investigated for correlations with SAC scores; those that correlated were chosen for further curve fitting. The clustering coefficient, the communication efficiency across in local networks, and the strength of connectivity were all higher in MTBI patients relative to control individuals. Parameters in 160 brain regions of the MTBI group significantly correlated with total SAC score and score for attention; the network parameters may be a quadratic function of attention scores of SAC and a cubic function of SAC scores. MTBI patients were characterized by elevated communication efficiency across global brain regions, and in local networks, and strength of mean connectivity. These features may be associated with brain function compensation. The network parameters significantly correlated with SAC total and attention scores.

1. Introduction

Mild traumatic brain injury (MTBI), also referred to as brain injury with a Glasgow Coma Scale score of 13–15, is the most common subtype of brain injury. Annually, about 42 million people worldwide suffer a MTBI [1,2] However, MTBI is difficult to diagnose because the brain often appears quite normal on conventional computed tomography (CT) and magnetic resonance imaging (MRI) scans. Furthermore, the clinical severity of MTBI is usually overlooked, since patients often present with slight symptoms that appear transient and resolve within days to weeks [2–4] Yet, in recent years studies have found that 15–30% of MTBI patients can develop cognitive, physiological, and clinical symptoms that do not resolve by 3 months post-injury. Such symptoms have been termed post-concussive syndrome (PCS) and include headache, dizziness, attention deficiency, and even depression [5–8]. These symptoms may persist and in some cases lead to permanent disability that has been referred to as chronic traumatic encephalopathy [9]. There are studies indicating that athletes can develop fatal brain swelling during a second concussion [10,11]. Thus, the assessment of MTBI and the study of injury mechanisms are of great importance.

There have been multiple scales to evaluate MTBI. These include the King-Devick test, the Balance Error Scoring System, the Sport Concussion Assessment Tool-3, and the Standardized Assessment of Concussion (SAC) [12–15]. The SAC comprises evaluations of orientation, attention, and transient memory and delayed memory. It is an outstanding assessment scale with high reliability and validity [16–18].

Some studies indicate that the brain functional network may be disrupted in patients with traumatic brain injury. Previous evidence indicated that severe traumatic brain injury can lengthen the shortest path and lower the efficiency of communication [19]. In addition, some scholars have proposed that some cortex nodes with high efficiency and connectivity are changed in coma

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patients after brain injury [20]. There are also reports that the local efficiency and connectivity in MTBI patients may be higher [21]. Thus, we speculate that the brain small-world functional network may be a sensitive index for the assessment of brain functional activity.

This study investigated the characteristics of the small-world brain network architecture of patients with MTBI, and a correlation between brain functional connectivity network properties in the resting-state functional MRI (fMRI) and SAC parameters.

2. Methods

2.1. Subjects

The Ethic Committee of Wuhan General Hospital of PLA approved this study. Twenty-two MTBI patients (17 men and 5 women) were enrolled; the ages of the patients ranged from 18 to 60 y (median, 23.5 y).

The diagnostic criteria for MTBI were: definite history of trauma; Glasgow Coma Scale score 13–15; coma duration <30 min; admitted within 12 h of injury; closed brain injury; treated with the standardized strategy. Criteria for inclusion in the study were: aged 18–60 y; right handed; native language is Chinese; school education $\geq$5 y; normal neurological functions (consciousness, vision, hearing, language ability); normal interpersonal communication skills; normal viscera functions; no metal implants; no lacunar infarct lesion on MRI; and no history of previous trauma, stroke, brain tumor, psychiatric care, or craniocerebral surgery or general anesthesia or relevant family history of the same. Patients with the following were excluded: unstable condition; needing decompressive craniectomy or intracranial pressure probe implantation; newly occurring complications, such as organ failure or severe infection; or a subjective decision to withdraw from the study.

The conditions of the patients were assessed by 2 neurosurgeons independently. Routine MRI scan was performed from the 3rd to the 7th day after injury. Seventeen healthy adults (13 men and 4 women) were recruited as the normal control group; their ages ranged from 20 to 59 y (median, 30 y). All subjects or their relatives provided signed informed consent.

2.2. Neurological assessments

Physical examinations and radiological evaluations were performed by 2 neurosurgeons and one radiologist, respectively. SAC assessments were performed upon admission and ±12 h the time of MRI examination by the same neurosurgeon. The words used in instantaneous memory tests were selected randomly from the modern Chinese vocabulary. SAC assessment was performed twice for each subject, and the mean was calculated for further analyses.

2.3. Functional MRI examinations

All the subjects underwent fMRI examinations in the Department of Radiology at Wuhan General Hospital of PLA. During functional runs, subjects were required to keep alert with their eyes closed, and instructed to avoid to think anything. The resting-state fMRI measurements were performed using a 1.5-T scanner (GE Signa HDxt scanner, GE, USA).

Whole-brain T2-weighted images were acquired using an echo planar imaging (EPI) sequence, and the following parameters were used: repetition time (TR), 2000 ms; echo time (TE), 40 ms; field of view (FOV), 240 mm × 240 mm; matrix, 64 × 64; slice thickness, 5 mm; interslice gap, 1 mm; flip angle, 90°; number of excitations, 1; scanning, 186 times (2 s time; total scanning time, 6 min 12 s). Anatomical images of the whole head were acquired with a T1-weighted 3-dimensional fast fluid-attenuated inversion recovery (FLAIR) sequence (TR, 11.5 ms; TE, 5.1 ms; FOV, 240 mm × 240 mm; slice thickness, 1.2 mm; inter slice gap, 0 mm; 232 slices covering the whole brain).

2.4. Resting-State fMRI preprocessing

The preprocessing of resting-state fMRI data was performed using MATLAB-based GRETNA_1.1.1 software (National Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, http://www.nitrc.org/projects/gretna). Data preprocessing included: image format conversion from DICOM to NIFTI; removal of the initial 10 timepoints; time correction between the layers; head motion correction; 3-dimensional data standardization; imaging smoothing; removal of drift and filtering; and removal of covariates. The last included removal of the following signals: whole brain, white matter, cerebrospinal fluid, and head moving. During processing, data associated with head moving >2 mm or flip angle >2° were excluded.

2.5. Brain network construction

Two templates were used to mark the regions of interest (ROIs). First, the cerebrum was considered to have 90 ROIs, based on the Automated Anatomical Labeling brain atlas. Second, with reference to Dosenbach's 160 functional ROIs [22], the network threshold value was set at 0.3, and the differences between lengths of connection were defined as 75. Node time courses of fMRI signals for each epoch were extracted from the preprocessed EPI images by averaging the voxel time courses within the ROIs for each participant.

To estimate functional connectivity, Pearson's correlation coefficients between all node pairs were calculated, resulting in 90 × 90 or 160 × 160 correlation matrices. The matrices were weighted, and both positive and negative connections were used to construct the whole brain weighted connectivity networks. We set thresholds with reference to the connection density K (the ratio of the number of edges to all possible node pairs). We applied a range of thresholds ($0.01 \leq K \leq 0.50$, in 0.01 increments) to calculate the network parameters.

2.6. Small-world organization

Two parameters were used to quantify the small-world organization of the brain functional network: the characteristic path length (L) and clustering coefficient (C). L is the average of the shortest path length between all pairs of nodes, which was calculated according to the following formula ($d_{i,j}$ is the shortest path length between nodes i and j):

$$L = [0.5\,N \times (N-1)]^{-1} \sum_{i,j,i<j} d_{i,j}$$

The clustering coefficient C is the strength of interconnectedness in local networks, consisting of direct neighbors of each node. C_i was set as the clustering coefficient of the node i:$C_i = E_i/[0.5K_i \times (K_i - 1)]$, where E_i is the number of edges between the neighbors of node i, and K_i is the number of edges connected to node i.

The average shortest path length Lp and the average clustering coefficient Cp were calculated. According to the definition for small-world network, when

$\gamma = Cp/Crand > 1$, then $\lambda = Lp/Lrand \approx 1$, and $\sigma = \gamma/\lambda > 1$, where under similar connection density Cp is the clustering coefficient of the studied network, Crand is the clustering coefficient of the random network, Lp is the average shortest path length of the