Microstructural changes in memory and reticular formation neural pathway after simple concussion☆

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Abstract
Patients with concussion often present with temporary disturbance of consciousness. The microstructural and functional changes in the brain associated with concussion, as well as the relationship with transient cognitive disorders, are currently unclear. In the present study, a rabbit model of simple concussion was established. Magnetic resonance-diffusion tensor imaging results revealed that the corona radiata and midbrain exhibited significantly decreased fractional anisotropy values in the neural pathways associated with memory and the reticular formation. In addition, the apparent diffusion coefficient values were significantly increased following injury compared with those before injury. Following a 1-hour period of quiet rest, the fractional anisotropy values significantly increased, and apparent diffusion coefficient values significantly decreased, returning to normal pre-injury levels. In contrast, the fractional anisotropy values and apparent diffusion coefficient values in the corpus callosum, thalamus and hippocampus showed no statistical significant alterations following injury. These findings indicate that the neural pathways associated with memory and the reticular formation pathway exhibit reversible microstructural white matter changes when concussion occurs, and these changes are exhibited to a different extent in different regions.

Key Words
brain; microstructural white matter; MRI; diffusion tensor imaging; simple concussion; consciousness disturbance; brain injury; reversibility; regeneration; neural regeneration

Research Highlights
(1) Simple concussion may result in changes in microstructural white matter in the memory-related reticular formation neural pathway.
(2) Microstructural changes were reversible, and were exhibited to a different extent in different regions. The brainstem reticular formation and corona radiata (corticospinal tract pathway) were more susceptible to concussive impact than deeper brain structures such as the corpus callosum, thalamus and hippocampus.

Abbreviation
MR-DTI, magnetic resonance diffusion tensor imaging
INTRODUCTION

Patients with concussion often present with rapid onset temporary disturbance of consciousness, including cognitive and perceptual deficits. However, the neuropathophysiological mechanisms of concussion-related dysfunction are currently unclear, because of the poor correlation between routine imaging examination results and abnormal clinical findings\(^1\). With the development of modern advanced imaging methods, understanding of brain structure and function has been improved. It is widely accepted that the organic origin of the symptoms of post-concussion syndrome is related to microstructural white matter damage. This damage is thought to result from straining, stretching, deforming or even shearing force in the brain, causing nerve conduction abnormalities and dysfunction\(^2\) that are not detectable with conventional neuroimaging\(^3\). Previous studies found no macroscopic neuropathological abnormalities following simple concussion, but reported reversible changes in brain function\(^4\). However, advanced imaging modalities such as magnetic resonance diffusion tensor imaging (MR-DTI) have the ability to detect white matter microstructural alterations\(^5\). Evaluating the effects of simple concussion on white matter microstructural and neurobehavioral outcomes is important for the prevention and cure of post-concussion syndrome. In recent years, DTI has provided new dimensions for the characterization of white matter anatomy, clarified the status of intra-white matter structures, and deepened our understanding of white matter structures and their abnormalities under pathological conditions. These research questions could not be examined with previous noninvasive imaging techniques, and DTI is the only current technology that can noninvasively provide orientation information about axonal tracts\(^6\). Recent studies have successfully witnessed MR-DTI detecting microstructure alteration in brain in some diseases, such as Alzheimer’s disease\(^7\), dementia\(^8\), schizophrenia\(^9\), sleep behavior disorder\(^10\), acute multiple sclerosis\(^11\), cerebral small vessel disease\(^12\), and epilepsy\(^13\). Previous MR-DTI studies have primarily focused on microstructural white matter changes following complicated mild or moderate-to-severe traumatic brain injury with no spot MR-DTI examination. The present study used MR-DTI to analyze microstructural white matter changes at different parts of the memory loop and the neural pathways of the reticular formation in a simple rabbit model of concussion, to understand the neuropathophysiological mechanisms underlying consciousness disturbance in simple concussion.

RESULTS

Quantitative analysis of experimental animals

A total of 14 adult rabbits were used to establish a simple concussion model. One rabbit model failed to finish the whole detection procedure, and died from excessive anesthetic administration and long-term anesthesia. Thus, a total of 13 rabbits were included in the final analysis after successfully completing the examination procedure, including routine MRI and DTI.

Verification of simple concussion models

The subjects presented with an unconsciousness state, exhibiting the corneal reflex, pain response to acupuncture, and external auditory meatus response to stimulation disappearance. Routine MRI revealed no intracranial hemorrhage or brain contusion (Figures 1A–C).

Pathological changes of brain tissue in simple concussion models

General observation and profile observation revealed no edema or hemorrhage. Optical microscopic observation revealed no abnormalities or mild swelling in neurons (Figures 1D, E).
Brain DTI fractional anisotropy of memory and reticular formation neural pathway in simple concussion rabbit models

The fractional anisotropy values in the corona radiata and midbrain significantly decreased following injury ($P < 0.05$), and significantly increased following a period of quiet rest for 60 minutes ($P < 0.05$), returning to normal pre-concussion levels ($P > 0.05$). In contrast, fractional anisotropy values in the corpus callosum, thalamus and hippocampus exhibited no significant effect of injury ($P > 0.05$; Figure 2, Table 1).

Brain DTI apparent diffusion coefficient in the neural pathways associated with memory and apperception in simple concussion rabbit models

The apparent diffusion coefficient values in the corona radiata and midbrain were significantly increased following injury ($P < 0.05$), and significantly decreased following a 60-minute quiet rest period ($P < 0.05$), returning to normal pre-injury levels ($P > 0.05$). However, the apparent diffusion coefficient values in the corpus callosum, thalamus and hippocampus exhibited no significant changes following concussion, or after quiet rest, compared with before concussion ($P > 0.05$; Figure 2, Table 2).

DISCUSSION

A few recent MR-DTI studies of complicated mild or moderate-to-severe traumatic brain injury reported significantly lower fractional anisotropy and a higher apparent diffusion coefficient compared with healthy controls[14-15]. The current results revealed that, in the corona radiata and midbrain regions of interest, fractional anisotropy values significantly decreased and apparent diffusion coefficient values significantly increased following injury. After a 60-minute quiet rest period, fractional anisotropy values in these regions significantly increased and the apparent diffusion coefficient values significantly decreased, returning to normal pre-injury levels. In contrast, the fractional anisotropy values and apparent diffusion coefficient values in the corpus callosum, thalamus and hippocampus regions of interest exhibited no significant changes following concussion and a quiet rest period. These different effects of simple concussion brain suggest that different regions exhibit different levels of microstructural sensitivity to external injury.

Our findings suggest that the corona radiata may have been the most easily injured because it is the closest region to the external force. In contrast, the corpus callosum, thalamus and hippocampus are located more deeply, potentially lessening the extent of trauma. The midbrain is prone to be injured in simple concussion because of external force being dispersed through the cranium to the brain, then centralizing at the brainstem. Several studies have reported similar findings, indicating that the midbrain, corona radiata, corpus callosum and other memory-related neural pathways are important predilection regions for traumatic axonal injury, but may be unevenly affected in head trauma[15-18].
The severity of post-concussive symptoms after mild traumatic brain injury was reported to be significantly correlated with a reduction of white matter integrity, indicating that microstructural brain injury may be involved in the neuropathological substrate of the syndrome\cite{19}. Immediately following mild traumatic brain injury, several metabolic, hemodynamic, structural, and electrophysiological changes alter normal cerebral function, via pathophysiological processes involving glucose and biochemistry metabolic changes, mitochondrial dysfunction, axonal injury, electrophysiological changes and microstructural biomechanical strain, which may be related to changes in white matter detected by MR-DTI\cite{17,23-24}. Human consciousness involves perceptive function and perceptual ability, which are regulated by the brainstem reticular formation, and cerebral hemisphere function, respectively\cite{16}. As such, we predicted that, in simple concussion, reversible microstructural changes in the brainstem reticular formation may be the main neuropathological substrate of transient consciousness disturbance. Increased understanding of the pathophysiology of this disorder is important for managing acute and chronic post-concussion syndrome. The current findings indicated that microstructural white matter in neural pathways related to memory and the reticular formation exhibited reversible changes following simple concussion. These changes occurred to a different extent at different regions, and the brainstem reticular formation and corona radiata were more susceptible to concussive impact than deeper brain structures. To our knowledge, these findings have not

Table 1  Brain diffusion tensor imaging fractional anisotropy of memory and reticular formation neural pathway in simple concussion rabbits

| Region                  | BI     | FI     | FR     | Univariate tests | Pairwise comparisons*  |
|-------------------------|--------|--------|--------|------------------|------------------------|
|                         |        |        |        |                  | F  | P    | P_{BI-FI} | P_{FI-FR} | P_{BI-FR} |
| Corona radiate (left)   | 324.2±66.7 | 220.8±63.8 | 320.9±57.7 | 5.83  | 0.00 | 0.03     | 0.05      | 1.00      |
| Corona radiate (right)  | 321.6±113.2 | 208.6±66.4 | 321.7±66.2 | 5.83  | 0.00 | 0.01     | 0.01      | 1.00      |
| Corpus callosum         | 301.9±97.6 | 283.1±73.9 | 282.8±72.1 | 0.18  | 0.83 | 1.00     | 1.00      | 1.00      |
| Thalamus (left)         | 384.5±87.6 | 338.4±96.6 | 357.8±84.6 | 2.30  | 0.06 | 1.00     | 1.00      | 1.00      |
| Thalamus (right)        | 303.7±104.5 | 276.4±82.0 | 282.1±93.4 | 2.30  | 0.06 | 1.00     | 1.00      | 1.00      |
| Hippocampus (left)      | 317.2±105.0 | 296.7±93.9 | 301.4±83.2 | 0.28  | 0.93 | 1.00     | 1.00      | 1.00      |
| Hippocampus (right)     | 314.5±135.4 | 283.6±101.8 | 280.7±75.1 | 0.28  | 0.93 | 1.00     | 1.00      | 1.00      |
| Midbrain                | 559.7±187.1 | 384.0±121.0 | 555.7±182.7 | 4.73  | 0.02 | 0.03     | 0.04      | 1.00      |

*: The mean difference is significant at the 0.05 level. Superscript "a": Adjustment for multiple comparisons: Bonferroni. BI: Before injury; FI: following injury; FR: following rest.

Table 2  Brain diffusion tensor imaging apparent diffusion coefficient of memory and reticular formation nervous pathway in simple concussion rabbits

| Region                  | BI     | FI     | FR     | Univariate tests | Pairwise comparisons*  |
|-------------------------|--------|--------|--------|------------------|------------------------|
|                         |        |        |        |                  | F  | P    | P_{BI-FI} | P_{FI-FR} | P_{BI-FR} |
| Corona radiate (left)   | 730.4±102.7 | 898.4±126.3 | 728.6±121.2 | 5.83  | 0.00 | 0.03     | 0.05      | 1.00      |
| Corona radiate (right)  | 744.7±103.1 | 892.2±130.8 | 747.2±124.6 | 5.83  | 0.00 | 0.01     | 1.00      | 1.00      |
| Corpus callosum         | 855.7±138.1 | 888.3±155.4 | 867.0±133.2 | 0.18  | 0.83 | 1.00     | 1.00      | 1.00      |
| Thalamus (left)         | 737.1±97.0 | 769.6±104.5 | 767.2±126.2 | 2.30  | 0.06 | 1.00     | 1.00      | 1.00      |
| Thalamus (right)        | 742.7±85.2 | 752.8±85.2 | 741.8±127.3 | 2.30  | 0.06 | 1.00     | 1.00      | 1.00      |
| Hippocampus (left)      | 849.0±160.7 | 879.4±124.4 | 835.1±175.4 | 0.28  | 0.93 | 1.00     | 1.00      | 1.00      |
| Hippocampus (right)     | 770.9±148.5 | 772.9±133.4 | 775.3±182.2 | 0.28  | 0.93 | 1.00     | 1.00      | 1.00      |
| Midbrain                | 728.8±95.01 | 849.0±136.3 | 716.4±112.3 | 4.73  | 0.02 | 0.03     | 0.04      | 1.00      |

*: The mean difference is significant at the 0.05 level. Superscript "a": Adjustment for multiple comparisons: Bonferroni. BI: Before injury; FI: following injury; FR: following rest.
been reported in prior studies using an animal model of simple concussion. In conclusion, MR-DTI analysis appears to be sensitive enough to detect microstructural white matter changes in simple concussion.

**MATERIALS AND METHODS**

**Design**
A randomized block design, animal model experiment.

**Time and setting**
Experiments were performed in the Center Laboratory, Southeast Hospital Affiliated to Xiamen University, China from August 2010 to May 2011.

**Materials**
A total of thirteen 6-month-old, healthy, Japanese big ear white rabbits (specific pathogen free level, breeding conditions: temperature 20–25°C, humidity 60–65%, illumination intensity 100–200 lx), of either sex and weighing 2.5 kg, were provided by Qingdao Kangda Biology Technology Limited Company, Qingdao, China (license No. SCXK (Lu) 2011-0001). Experimental procedures were in strict accordance with the Guidance Suggestions for the Care and Use of Laboratory Animals, issued by the Ministry of Science and Technology of China\(^{[25]}\).

**Methods**

**Establishment of simple concussion models**
Rabbits were anesthetized via a 0.1–0.2 mL/kg gluteal muscle injection of veterinary Sumianxin II (Jilin Huamu Animal Health Product, Jilin Province, China). A simple rabbit model of concussion was produced using a technique based on the impact/compression trauma model method reported by Marmarou and Foda et al\(^{[26,27]}\). This method involved striking the cranium using a calibration balance weight to induce traumatic brain injury (supplementary Figure 1 online). Because of the small size and flat distribution of the cranial cavity of rabbit brains, the area below the roofing bone represented the maximum area of the brain. The skull region between the ears was placed opposite to the balance weight to ensure that a maximal area of rabbit roofing bone would be struck by the balance weight. The balance weight was 300 g. A preliminary experiment indicated that setting the panning angle of the balance weight at 30° would result in a suitable model of simple concussion. Anesthetized rabbits were examined by routine MRI and DTI-MRI before injury to exclude primary brain lesions, and to provide a control comparison. When each animal woke from the anesthetized state, the calva was struck with a calibration balance. The successful models were returned to an unconscious state, judged by the disappearance of corneal reflex, pain response to acupuncture and external auditory meatus response to stimulation. Routine MR (Magnetom Trio; Siemens, Berlin, German) (T1WI, T2*WI, SWI) scans were performed to rule out the presence of intracranial hemorrhage or brain contusion. Scan program: rabbits were fixed and scanned with wrist-defined phased-array coil in supine position. T1WI axial scan: repetition time (TR)/echo time (TE) = 250 ms/2.90 ms, T2*WI axial and sagittal scan: flip angle 30°–45°, TR/TE = 20–50 ms/15–25 ms, SWI axial scan: TR/TE = 28 ms/20 ms. The other parameters were the same: slice group 1, slice 15–25, distance factor 10%, field of view (FOV) read 130 mm (transversal imaging) and 150 mm (sagittal imaging), FOV phase 68.8%, slice thickness 2.0 mm, average 2, filter prescan normalize, matrix = 320 × 320.

**Pathological examination**
Rabbits were sacrificed under anesthesia immediately following the completion of the experiment. The brains were harvested and fixed in 5% formalin. Prior to pathological examination, general observation was conducted to detect edema and/or hemorrhage. The maximal oblique coronal plane of the entire brain was then incised immediately after general observation along the MR-DTI scanning localizer line, via bilateral corona radiata, corpus callosum, upper third ventricle, bilateral thalamus, bilateral hippocampus, midbrain (brainstem)\(^{[28]}\), and brain tissues were cut into 2-mm thick slices parallel to the maximal oblique coronal plane, followed by profile observation, then followed by dehydration, transparency, de-waxing, embedding, and hematoxylin-eosin staining. Brain parenchyma was observed under an optical microscope (× 200; BX50, Olympus, Pangu, Japan).

**Quiet rest after simple concussion (acute stage)**
Immediately after simple concussion (acute stage), the rabbits were housed in separate cages in a dark, well-ventilated room with no sound or light stimulation for 60 minutes.

**MR-DTI examination**
MR-DTI was performed before injury, immediately following injury, and following a 60-minute quiet rest period. DTI acquisition was processed using a 3.0 T magnetic resonance scanner (Siemens, Trio, German), and the collected data were used to automatically generate the DTI map. Fractional anisotropy and
apparent diffusion coefficients are reported to be closely related to brain trauma. As such, we used these two measures as evaluation indices. The fractional anisotropy and apparent diffusion coefficient values were automatically calculated by manually drawing regions of interest at the areas under observation. The fractional anisotropy and apparent diffusion coefficient values were compared as follows: before injury and following injury; following a quiet rest period and following injury; following a quiet rest period and before injury. According to previous reports, the memory circuit loop consists of the hippocampus-fornix-anterior nuclei of thalamus-corpus callosum-white matter nerve fiber radiata-frontal lobe-white matter nerve fiber radiata-corpus callosum-anterior nuclei of thalamus-fornix-hippocampus, and the ascending reticular activating system consists of the spinal cord and brain nerve nuclei-brainstem reticular formation-dorsal thalamus-white matter nerve fiber radiata-pallium. DTI was performed using standard single-slice region-of-interest measurement. In the DTI analysis, 12 diffusion directions were isotropically distributed on a sphere (b value = 1 000) and one had no diffusion weighting (b value = 0). The acquisition parameters were as follows: matrix 192 × 192 × 192, voxel size 1.0 × 1.0 × 1.0 mm³, echo time 120 ms, repetition time 5 500 ms, four averages. On 3-dimensional T1 magnetization-prepared rapid acquisition with gradient echo, the acquisition parameters were as follows: sagittal acquisition, 176 slices, matrix 256 × 256 × 256, isotropic voxel size 0.5 × 0.5 × 0.5 mm³, echo time 2.52 ms, repetition time 1 900 ms, one average. We assessed white matter lesions in T2-weighted sequences. DTI acquisition data was analyzed with a SIEMENS 3.0T Verio MR graphics work station (Copyright © SIEMENS AG 2009. Series No. 40265. Software: NUMARIS/4. Version: syngo MRB17. Product ID: 097). Data was processed by offline tensor calculation, which automatically generated fractional anisotropy and apparent diffusion coefficient maps. The regions of interest for acquiring fractional anisotropy and apparent diffusion coefficient values included the bilateral corona radiata, corpus callosum, bilateral thalamus, hippocampus and midbrain. The sizes of the regions of interest were manually drawn for each individual, and were approximately 2/3 of the area of each anatomical region. It is important to ensure that the regions of interest for each participant are identical for pre-injury, after injury and after quiet rest.

**Statistical analysis**

Data were analyzed using SPSS 17.0 statistical software (SPSS, Chicago, IL, USA) and measurement data were expressed as mean ± SD. MR-DTI measurements of fractional anisotropy and apparent diffusion coefficients before injury, following injury, and following quiet rest were compared using univariate analysis in the general linear model. Adjustment for multiple comparisons was performed with the Bonferroni correction. A threshold of P < 0.05 was considered statistically significant.

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**Author contributions:** Lin Ouyang was responsible for study concept and design, data analysis, manuscript writing and validation, statistical analysis, and funding. Rongyue Shi was responsible for anesthesia and fixation, simple concussion injury and treatment after injury, and animal sacrifice. Yuhui Xiao was responsible for routine CT, MRI and MR-DTI technical operations and data acquisition. Yihe Guo was responsible for craniotomy and brain harvesting. Jiarong Meng was responsible for staining, sectioning, and pathological diagnosis of injured rabbit brains. Guangming Lu was involved in data integration, provided MR-DTI support, and instructed the study.

**Conflicts of interest:** None declared.

**Ethical approval:** The experiment was approved by Animal Ethics Committee, Xiamen University School of Medicine, China.

**Supplementary information:** Supplementary data associated with this article can be found in the online version by visiting www.nrronline.org.

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