Journal of Integrative Neuroscience

J. Integr. Neurosci. **2022**; 21(3): 93
https://doi.org/10.31083/j.jin2103093

Original Research

Relationship between short-term memory impairment and the dorsolateral prefrontal cortex injury in patients with mild traumatic brain injury

Min Jye Cho[1], Han Do Lee[2], Jae Woon Kim[3], Sung Ho Jang[1,*]

[1]Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, 42415 Taegu, Republic of Korea
[2]Department of Physical Therapy, College of Natural Science, Ulsan College University, 44022 Ulsan, Republic of Korea
[3]Department of Radiology, College of Medicine, Yeungnam University, 42415 Taegu, Republic of Korea
*Correspondence: strokerehab@hanmail.net (Sung Ho Jang)
Academic Editor: Mauro Ursino
Submitted: 27 September 2021 Revised: 20 December 2021 Accepted: 29 December 2021 Published: 12 May 2022

Abstract

Background: The prefrontal cortex (PFC) has been reported to be related to memory function. Especially, the dorsolateral PFC (DLPFC) is a substantial neural structure in short-term memory. In this study, using diffusion tensor tractography (DTT), we investigated the relationship between short-term memory impairment and the DLPFC injury in patients with mild traumatic brain injury (TBI). **Methods**: We recruited 46 consecutive chronic patients with mild TBI and 42 normal control subjects. Fractional anisotropy (FA) and fiber number (FN) of the prefronto-thalamic tracts were determined for both hemispheres. **Results**: Significant differences were detected in the FA value of the DLPFC and FN value of the prefronto-thalamic tracts in the patient and control groups ($p < 0.05$). However, no significant differences were detected in the ventrolateral PFC (VLPFC) and orbitofrontal cortex (OFC) between the patient and control groups ($p > 0.05$). In addition, the FN value of the DLPFC showed moderate positive correlation with short-term memory ($r = 0.510$, $p < 0.05$). However, no significant correlations were detected between the short-term memory and the FA value of the DLPFC, and the FA and FN values of the VLPFC and OFC in the patient group ($p > 0.05$). **Conclusions**: We found that the short-term memory impairment was closely associated with the DLPFC injury in patients with mild TBI. Our results suggest that the estimation of the DLPFC using DTT would be useful for patients with severity of short-term memory impairment following mild TBI.

Keywords: Prefronto-thalamic tracts; Short-term memory; Dorsolateral prefrontal cortex; Mild traumatic brain injury; Diffusion tensor tractography

1. Introduction

Traumatic brain injury (TBI) is one of the most common causes of disability in adults, and is categorized as mild, moderate, and severe, depending on the severity [1,2]; 70–90% patients with TBI is categorized as mild TBI [3,4]. Memory impairment is an important sequelae of mild TBI, with previously reported incidence up to 25% of patients with postconcussional syndrome among patients with mild TBI [5–7]. Memory is related to accumulate and preserve individual experiences and plays a key role in the mental activities and whole brain [8]. Among the variety of memory function, the short-term memory means keeping information in mind for a short period of time and temporary storage, organization, and processing of information to guide reasoning and goal-directed behavior [9,10]. It takes charge of transient information processing and direction of complex cognitive activity related to frontal and posterior cortical areas and subcortical structures [11]. The prefrontal cortex (PFC) has been reported to be involved in memory function [12–14]. specially, the dorsolateral prefrontal cortex (DLPFC) among the PFC is an important neural structure in short-term memory [11,15]. Therefore, elucidating the relationship between short-term memory impairment and the DLPFC injury following TBI would be important in terms of rehabilitation; especially, for neuromodulation such as repetitive transcranial magnetic stimulation and transcranial direct-current electrical stimulation [16,17]. However, it has not been clearly elucidated so far.

Previous studies have employed functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and electroencephalographic (EEG) to evaluate the DLPFC [6,18–21]. However, these methods are not sufficient to detect DLPFC injury, because the DLPFC is not clearly distinguished from near neural structures. By contrast, the introduction of diffusion tensor tractography (DTT), which is developed from diffusion tensor imaging (DTI) results, has enabled three-dimensional reconstruction and assessment of the DLPFC. Therefore, DTT has advantage to determine the degree of detect injury of the DLPFC more accurately than the above evaluation methods [22]. However, no study on the relationship between short-term memory impairment and the DLPFC injury in patients with mild TBI has been reported.

In this study, using DTT, we investigated the relationship between short-term memory impairment and the DLPFC injury in patients with mild TBI.

2. Methods

2.1 Subjects

Forty-six consecutive patients (male: 19, female: 27, mean age 32.84 ± 6.49 years) with TBI and 42 normal control subjects (male: 16, female: 26, mean age 35.17 ± 8.33 years) with no previous history of neurological, physical, or psychiatric diseases were enrolled. Inclusion criteria for the patients were as follow: (1) post-traumatic amnesia for ≤ 24 hours, an initial Glasgow Coma Scale score of 13–15, and loss of consciousness for <30 min [23,24]. (2) no specific lesion identified on T1-weighted, T2-weighted, and Fluid attenuated inversion recovery MRI images, (3) more than one month since TBI, (4) age range 20–49 years, (5) no previous history of head trauma, neurologic or psychiatric disease. Table 1 summarizes the demographic and clinical data of the patient and control groups. This retrospective study protocol was admitted by the institutional review board of Yeungnam University Hospital (ethical number: YUMC 2021-03-014).

Table 1. Demographic and clinical data of the patient and control groups.

	Patients group	Control group
Age (years)	32.84 ± 6.49	35.17 ± 8.33
Number (n)	46	42
Male:Female	19:27	16:26
Mean duration to DTI (months)	5.86 ± 3.36	-
Short-term memory subscale score	84.77 ± 15.47	-

DTI, diffusion tensor imaging; Values presented are means ± standard deviations.

2.2 Clinical evaluation

The short-term memory subscale of the Memory Assessment Scale (MAS) was used to estimate the short-term memory performance of all patients at a similar time (within a week) with DTI scanning. The short-term memory subscale is one of the four subsets (verbal memory, visual memory, short-term memory, and global memory) of the MAS [25]. The standard score of the short-term memory scale has a mean of 100 with a standard deviation of 15, and a standard score below 86 indicates memory difficulties [25]. The reliability and validity of MAS is well-established [26].

2.3 Diffusion tensor imaging

DTI data were acquired an average of 5.86 ± 3.36 months after the onset of TBI using Synergy-L Sensitivity Encoding (SENSE) head coil on a 1.5 T Philips Gyroscan Intera system (Philips Ltd, Best, Netherlands) with a single-shot, spin-echo planar imaging pulse sequence. 60 contiguous slices were obtained parallel to the anterior commissure-posterior commissure line for each of the 32 non-collinear diffusion sensitizing gradients according to the following condition: acquisition matrix = 96 × 96, reconstructed to matrix = 192 × 192, field of view = 240 mm × 240 mm, TR = 10.398 ms, TE = 72 ms, parallel imaging reduction factor (SENSE factor) = 2, EPI factor = 59 and b = 1000 s/mm^2, number of excitations (NEX) = 1, thickness = 2.5 mm. Using probabilistic tractography in the default tractography option, fiber tracking was performed in the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Diffusion Software (FSL version 5.0, Analysis group, FMRIB, Oxford, UK) (5000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2). Including the diffusion in each voxel of both dominant and non-dominant orientation, 5000 streamline samples from seed regions of interest (ROI) were calculated. For tracking of the prefronto-thalamic tracts [22,27], a seed ROI was assigned on the mediodorsal nucleus of the thalamus on the coronal plane of the b0 map and each target ROI was placed on the b0 map as follow: DLPFC of 8, 9, and 46 Brodmann areas (BAs) on the coronal plane, ventrolateral PFC (VLPFC) of 44, 45, and 47 BAs on the coronal plane, and orbitofrontal cortex (OFC) of 47/12, 10, 11, and 13 BAs on the axial plane [27,28]. With the threshold of 2 streamlines, the prefronto-thalamic tracts were implemented by choosing fibers passing through seed and each target ROI (Fig. 1).

2.4 Statistical analysis

Through the SPSS software (v. 5.0; SPSS Inc., Chicago, IL, USA), the independent t test was conducted for evaluation of differences between DTT parameters [fractional anisotropy (FA) and fiber number (FN) values] of the prefronto-thalamic tracts (DLPFC, VLPFC, and OFC) in the patient and control groups. The Pearson correlation test was used to identify the Relationships between short-term memory and DTT parameters of the prefronto-thalamic tracts. The correlation coefficient (r-value) indicates the relative strength and direction of the linear relationship (none or very weak: <0.3, weak: 0.3–0.5, moderate: 0.5–0.7, strong: >0.7) between two values [29]. The significance level of the p value was set at <0.05.

3. Results

The results for DTT parameters of the patient and control groups, and correlation of the short-term memory with the three prefronto-thalamic tracts in the patient group are listed in Table 2. Regarding of the FA value, significant difference was observed in the DLPFC between the patient and control groups [t(71) = –4.24, p = 0.00]. However, no significant differences were detected in the VLPFC and OFC between the patient and control groups [FA value of VLPFC: t(69) = –1.40, p = 0.17; FA value of OFC: t(66) = –0.42, p = 0.68]. In addition, regarding of the FN value, significant differences were shown in the three prefronto-thalamic tracts between the patient and control groups [FN value of DLPFC: t(65) = –2.26, p = 0.03; FN value of

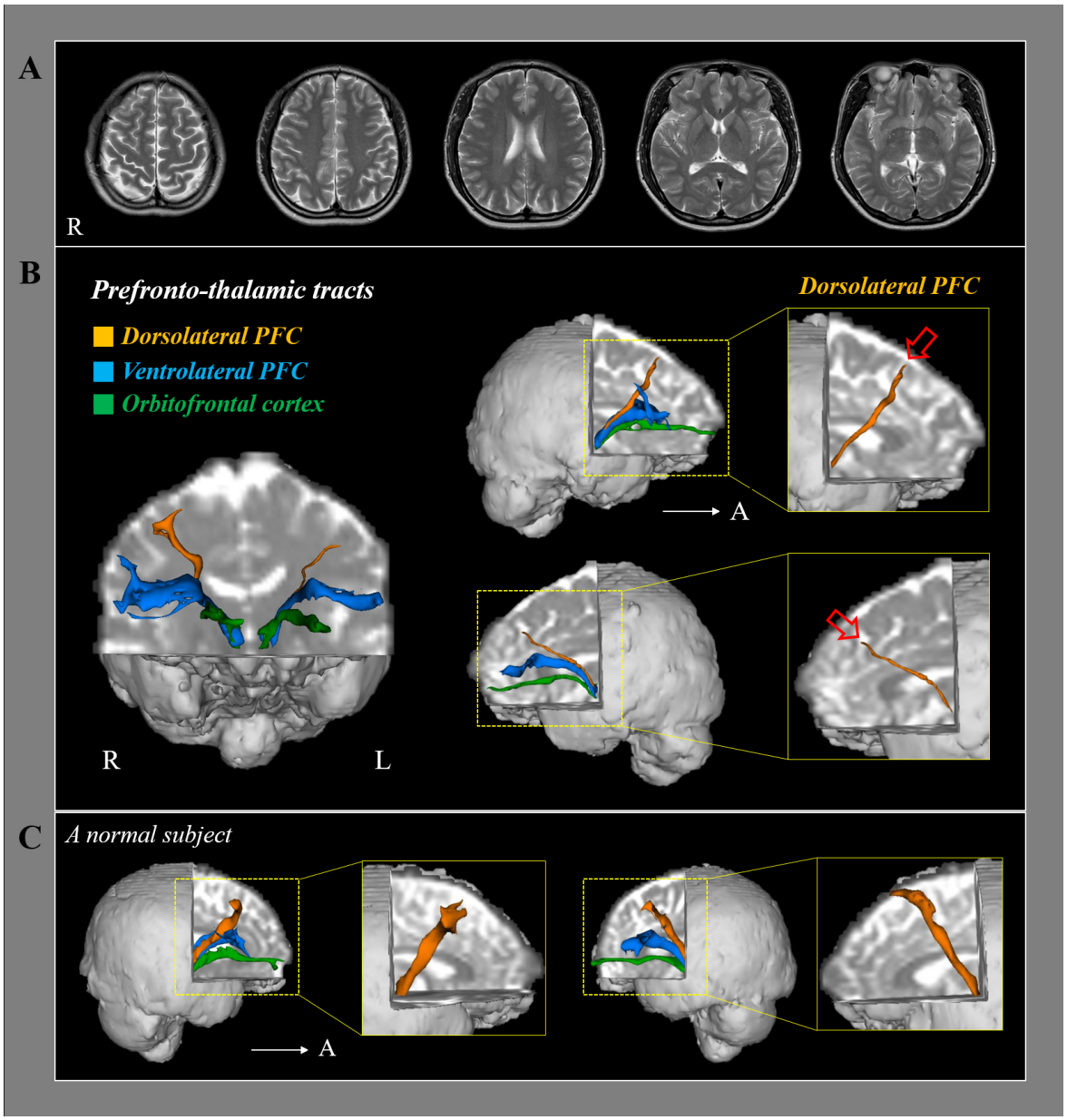

Fig. 1. Results of diffusion tensor tractography (DTT) of the prefronto-thalamic tracts. (A) T2-weighted brain magnetic resonance images show no abnormality in a representative patient (35-year-old female). (B) Results of DTT of the prefronto-thalamic tracts, the dorsolateral prefrontal cortex (DLPFC) show narrowing (red arrow) on the both side compared with a normal subject. (C) DTT results of the prefronto-thalamic tracts in a representative normal subjects (33-year-old female).

VLPFC: t(58) = –3.65, p = 0.00; FN value of OFC: t(54) = –6.29, p = 0.00].

In the correlation analysis between the DTT parameters of the prefronto-thalamic tracts and short-term memory in the patient group, moderate positive correlation was detected between the FN value of the DLPFC and the short-term memory (r = 0.510, p = 0.00). However, there were no significant correlations between the short-term memory and the FA value of the DLPFC, and the values of FA and FN of the VLPFC and OFC in the patient group (FA value of DLPFC: r = 0.150, p = 0.35; FA value of VLPFC: r = 0.226, p = 0.19; FN value of VLPFC: r = 0.120, p = 0.48; FA value of OFC: r = 0.280, p = 0.11; FN value of OFC: r = 0.100, p = 0.56).

4. Discussion

In this study, using DTT, we identified the relation between the short-term memory and the status of the three prefronto-thalamic tracts in the patients with mild TBI. The results can be summarized in the following; (1) The FA value of the DLPFC and the FN values of the three prefronto-thalamic tracts in the patient group were lower than those of the control group. (2) Only the FN value of the DLPFC shown moderate positive correlation with

Table 2. Diffusion tensor tractography parameters of the prefronto-thalamic tracts in the patient and control groups.

DTT parameters		
Group	Fractional anisotropy	Fiber number
DLPFC		
Patient	0.35 (0.02)**	396.77 (172.30)*
Control	0.37 (0.02)	514.10 (264.40)
p-value	0.00	0.03
VLPFC		
Patient	0.36 (0.01)	400.30 (171.02)**
Control	0.37 (0.02)	728.94 (322.90)
p-value	0.17	0.00
OFC		
Patient	0.37 (0.02)	316.79 (147.28)**
Control	0.38 (0.02)	529.47 (296.32)
p-value	0.68	0.00
Correlation between short-term memory and DTT parameters		
	Fractional anisotropy	Fiber number
DLPFC		
Correlation	0.15	0.51**
p-value	0.35	0.00
VLPFC		
Correlation	0.226	0.12
p-value	0.19	0.48
OFC		
Correlation	0.28	0.10
p-value	0.11	0.56

Values represent mean (±standard deviation); DTT, diffusion tensor tractography; *Significant differences between patient and control group, $p < 0.05$; ** Significant differences between working memory and in the patient group. $p < 0.01$.

the short-term memory. The FA value reflects the state of white matter microstructure by representing axonal density, myelination, and the degree of directionality, and the FN value indicates the total number of voxels [30,31]. Therefore, a decrease in the values of FA or FN means an injury of the neural structure [30,31]. Our results reveal that the FA and FN values in the all of prefronto-thalamic tracts in the patient group were lower than those of the control group, suggesting injuries of the three prefronto-thalamic tracts in the patient group. According to the correlation between the short-term memory and three prefronto-thalamic tracts, the short-term memory showed a moderate positive correlation with the FN value of the DLPFC in the patient group. These results suggest that severity of the short-term memory impairment correlated to the decreased FN value of the DLPFC. As a result, the severity of the short-term memory impairment was closely associated with the degree of DLPFC injury.

A few studies have demonstrated on abnormality of the DLPFC in patients with short-term memory impairment using brain imaging techniques including fMRI, magnetoencephalography (MEG), and electroencephalographic (EEG) following mild TBI [6,20,21]. In 2012, Chen *et al.* [6], reported that decreased activation in the around of the DLPFC including bilateral frontal and parietal areas during memory test using fMRI in 20 patients with memory impairment following mild TBI. In 2018, Arakaki *et al.* [20], demonstrated decreased activation on the fronto-parietal areas among the 10–20 system during memory test on EEG in 20 patients with short-term memory impairment following mild TBI. In 2019, Lawton *et al.* [21], reported on the low-level visual timing deficits and high-level cognitive functioning including the short-term memory during memory test in four patients with mild TBI who remarkable lower activating in the DLPFC including frontal pole on MEG. As a result, to the best of our knowledge, the present study is the first to demonstrate a relationship between the short-term memory impairment and the DLPFC injury in patients with mild TBI using DTT. However, the limitations of this study should be considered. First, although short-term memory impairment might be associated with various neural tracts including the fornix, cingulum, prefronto-limbic circuit and Papez circuit, these tracts were not investigated due to the main purpose of this study describing DLPFC injury in mild TBI. Second, because this study was conducted retrospectively, we could not able to evaluate additional clinical data about the short-term memory for the DLPFC injury. Furthermore, we could not provide clinical data for memory of normal control subjects. In addition, the education period of each group could not be considered. Lastly, DTI data should be corrected when examining the frontal area that is vulnerable artifacts because of geometric distortion and signal drop [32]. Therefore, further studies to control the above limitations should be recommended.

5. Conclusions

In conclusion, using DTT, we found that the short-term memory impairment was closely associated with the DLPFC injury in patients with mild TBI. The results suggest that the investigation of the DLPFC using DTT would be useful for neuro-rehabilitation in patients with short-term memory impairment following mild TBI; particularly, neuromodulation. For example, recently developed non-invasive brain stimulation therapies such as repetitive transcranial magnetic stimulation or transcranial direct current stimulation can be applied to the DLPFC to facilitate the recovery of short-term memory impairment in patients with mild TBI [16,17]. However, further studies on this topic should be warranted.

Abbreviations

TBI, traumatic brain injury; PFC, prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; DTT, diffusion tensor tractography; DTI, diffusion tensor imaging; MAS, memory assessment scale; ROI, regions of interest; VLPFC, ventrolateral prefrontal cortex; OFC, orbitofrontal cortex; FA, fractional anisotropy; FN, fiber number.

Author contributions

MJC, HDL, and SHJ designed the research study. MJC and HDL performed the research. SHJ provided help and advice on the study. JWK analyzed the data. HDL and SHJ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All participants signed a written informed consent beforehand, which complies with the Helsinki Declaration, and all research activities were admitted by the institutional review board of Yeungnam University Hospital (YUMC 2021-03-014).

Acknowledgment

Not applicable.

Funding

This work was supported by the Medical Research Center Program (2015R1A5A2009124) through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT, and Future Planning.

Conflict of interest

The authors declare no conflict of interest.

References

[1] De Kruijk JR, Twijnstra A, Leffers P. Diagnostic criteria and differential diagnosis of mild traumatic brain injury. Brain Injury. 2001; 15: 99–106.

[2] DeCuypere M, Klimo P. Spectrum of Traumatic Brain Injury from Mild to Severe. Surgical Clinics of North America. 2012; 92: 939–957.

[3] Jennett B, MacMillan R. Epidemiology of head injury. BMJ. 1981; 282: 101–104.

[4] Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. Acta Neurochirurgica. 2006; 148: 255–268.

[5] Brown SJ, Fann JR, Grant I. Postconcussional disorder: time to acknowledge a common source of neurobehavioral morbidity. The Journal of Neuropsychiatry and Clinical Neurosciences. 1994; 6: 15–22.

[6] Chen C, Wu C, Liao Y, Hsu H, Tseng Y, Liu H, *et al*. Working Memory in Patients with Mild Traumatic Brain Injury: Functional MR Imaging Analysis. Radiology. 2012; 264: 844–851.

[7] Jang SH, Kim SH, Do Lee H. Relation between Memory Impairment and the Fornix Injury in Patients with Mild Traumatic Brain Injury. American Journal of Physical Medicine & Rehabilitation. 2018; 97: 892–896.

[8] Chen X, He X, Tao L, Li J, Wu J, Zhu C, *et al*. The Working Memory and Dorsolateral Prefrontal-Hippocampal Functional Connectivity Changes in Long-Term Survival Breast Cancer Patients Treated with Tamoxifen. International Journal of Neuropsychopharmacology. 2017; 20: 374–382.

[9] Goldman-Rakic PS. Cellular basis of working memory. Neuron. 1995; 14: 477–485.

[10] Arnsten AT, Wang M, Paspalas C. Neuromodulation of Thought: Flexibilities and Vulnerabilities in Prefrontal Cortical Network Synapses. Neuron. 2012; 76: 223–239.

[11] Eriksson J, Vogel E, Lansner A, Bergström F, Nyberg L. Neurocognitive Architecture of Working Memory. Neuron. 2015; 88: 33–46.

[12] Curtis CE, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. Trends in Cognitive Sciences. 2003; 7: 415–423.

[13] Feredoes E, Heinen K, Weiskopf N, Ruff C, Driver J. Causal evidence for frontal involvement in memory target maintenance by posterior brain areas during distracter interference of visual working memory. Proceedings of the National Academy of Sciences. 2011; 108: 17510–17515.

[14] Brunoni AR, Vanderhasselt M. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain and Cognition. 2014; 86: 1–9.

[15] Kaplan JT, Gimbel SI, Harris S. Neural correlates of maintaining one's political beliefs in the face of counterevidence. Scientific Reports. 2016; 6: 39589.

[16] Phipps CJ, Murman DL, Warren DE. Stimulating memory: reviewing interventions using repetitive transcranial magnetic stimulation to enhance or restore memory abilities. Brain Sciences. 2021; 11: 1283.

[17] Hara T, Shanmugalingam A, McIntyre A, Burhan AM. The effect of Non-Invasive Brain Stimulation (NIBS) on executive functioning, attention and memory in rehabilitation patients with traumatic brain injury: a systematic review. Diagnostics. 2021; 11: 627.

[18] van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. European Neuropsychopharmacology. 2010; 20: 519–534.

[19] Rosazza C, Minati L. Resting-state brain networks: literature review and clinical applications. Neurological Sciences. 2011; 32: 773–785.

[20] Arakaki X, Shoga M, Li L, Zouridakis G, Tran T, Fonteh AN, *et al.* Alpha desynchronization/synchronization during working memory testing is compromised in acute mild traumatic brain injury (mTBI). PLos ONE. 2018; 13: e0188101.

[21] Lawton T, Huang M. Dynamic cognitive remediation for a Traumatic Brain Injury (TBI) significantly improves attention, working memory, processing speed, and reading fluency. Restorative Neurology and Neuroscience. 2019; 37: 71–86.

[22] Jang SH, Yeo SS. Thalamocortical Connections between the Mediodorsal Nucleus of the Thalamus and Prefrontal Cortex in the Human Brain: a Diffusion Tensor Tractographic Study. Yonsei Medical Journal. 2014; 55: 709.

[23] Anderson SD. Postconcussional disorder and loss of consciousness. Bulletin of the American Academy of Psychiatry and the Law. 1996; 24: 493–504.

[24] Wilde EA, Li X, Hunter JV, Narayana PA, Hasan K, Biekman B, *et al*. Loss of Consciousness is Related to White Matter Injury in Mild Traumatic Brain Injury. Journal of Neurotrauma. 2016; 33: 2000–2010.

[25] Williams JM. MAS: memory assessment scales: professional manual. Psychological Assessment Resources: Odessa, FL. 1991.

[26] Williams D. Manual wechsler adult intelligence scale revised. Psychological Corporation: New York. 1981.

[27] Klein JC, Rushworth MFS, Behrens TEJ, Mackay CE, de Crespigny AJ, D'Arceuil H, *et al*. Topography of connections between human prefrontal cortex and mediodorsal thalamus studied with diffusion tractography. NeuroImage. 2010; 51: 555–564.

[28] Johansen-Berg H, Behrens TEJ, Sillery E, Ciccarelli O, Thompson AJ, Smith SM, *et al*. Functional–Anatomical Validation and Individual Variation of Diffusion Tractography-based Segmen-

tation of the Human Thalamus. Cerebral Cortex. 2005; 15: 31–39.
[29] Mindrila D, Balentyne P. Scatterplots and correlation. Retrieved From. 2017. Available at: https://www.westga.edu/academics/research/vrc/assets/docs/scatterplots_and_correlation_notes.pdf (Accessed: 12 November 2012)
[30] Assaf Y, Pasternak O. Diffusion Tensor Imaging (DTI)-based White Matter Mapping in Brain Research: a Review. Journal of Molecular Neuroscience. 2008; 34: 51–61.
[31] Mori S, Crain BJ, Chacko VP, Van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Annals of Neurology. 1999; 45: 265–269.
[32] Taylor PA, Alhamud A, van der Kouwe A, Saleh MG, Laughton B, Meintjes E. Assessing the performance of different DTI motion correction strategies in the presence of EPI distortion correction. Human Brain Mapping. 2016; 37: 4405–4424.