Safety and efficacy of simple training protocol in patients after mild traumatic brain injury

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Aims. Mild Traumatic Brain Injury (mTBI) is the most common type of craniocerebral injury. Proper management appears to be a key factor in preventing post-concussion syndrome. The aim of this prospective study was to evaluate the effect and safety of selected training protocol in patients after mTBI.
Methods. This was a prospective study that included 25 patients with mTBI and 25 matched healthy controls. Assessments were performed in two sessions and included a post-concussion symptoms questionnaire, battery of neurocognitive tests, and magnetic resonance with tractography. Participants were divided into two groups: a passive subgroup with no specific recommendations and an active subgroup with simple physical and cognitive training.
Results. The training program with slightly higher initial physical and cognitive loads was well tolerated and was harmless according to the noninferiority test. The tractography showed overall temporal posttraumatic changes in the brain. The predictive model was able to distinguish between patients and controls in the first (AUC=0.807) and second (AUC=0.652) sessions. In general, tractography had an overall predictive dominance of measures.
Conclusion. The results from our study objectively point to the safety of our chosen training protocol, simultaneously with the signs of slight benefits in specific cognitive domains. The study also showed the capability of machine learning and predictive models in mTBI patient recognition.

Key words: mild traumatic brain injury, training, tractography, predictive model, machine learning

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INTRODUCTION

Mild traumatic brain injury (mTBI) and its aspects remain the subject of debate. Although mTBI generally has a relatively good prognosis compared with other neurological disorders, the underestimation of the importance of appropriate management can lead to needless medical and socioeconomic burden. Proper management of patients with mTBI is a crucial factor in preventing post-concussion syndrome (PCS). In general, physical and mental rest is recommended during an acute postinjury period (approximately the first 24–48 h after the injury). Subsequently, the patient can return to daily activities with a gradually increasing load. Unfortunately, the exact length of the ideal resting phase and the intensity of progressive load are still unknown and appear to be individual-specific[1,2].

The aim of this prospective study was to evaluate the effect and safety of selected training protocol with slightly higher initial physical and cognitive loads in patients after mTBI.

MATERIALS AND METHODS

This prospective study included 25 patients with mTBI and 25 healthy controls. The study was approved by the ethics committee of Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Slovak Republic (approval number: EK 76/2020). All participants signed informed consent forms.

Inclusion criteria and recruitment

The inclusion criteria for patients and controls included age ranging from 18 to 55 years, the ability to participate in the study and to provide informed consent, and the absence of preinjury neurological disorders and other medical conditions associated with brain damage. All listed patients presented at the Emergency Department of the University Hospital Martin (Martin, Slovak Republic) or University Hospital F. D. Roosevelt (Banska Bystrica, Slovakia) between 2019 and 2021, underwent an initial brain CT scan, and met the criteria for mTBI according to the WHO Collaborating Task Force on Mild Traumatic Brain Injury[3]. For each case, a control matched for sex, age (±5 years), and the highest level of education attained was enrolled.

Exclusion criteria

The exclusion criteria for participants according to anamnestic data and CT/MRI brain imaging findings were as follows: demyelinating and neurodegenerative diseases, brain tumors (in addition to tiny extra-axial brain tumors, such as meningiomas), previous severe brain injuries, cerebral palsy, epilepsy, cerebrovascular diseases (including asymptomatic brain lesions), arterial hypertension and cardiovascular diseases, diabetes mellitus and a spectrum of metabolic diseases, connective tissue disorders, common genetic disorders, and psychiatric disorders.

Procedures

All study assessments were performed in two identical sessions. In the patient group, the first session occurred 24–72 h after the injury. For all groups, the second session was conducted 24–48 days after the first session. The average interval between the injury and the first session was 50.1 h (SD=16.9; Me=48). Between the first and second sessions, the mean intervals were 36.7 days in the patient group (SD=15.7; Me=31) and 36.4 days in the control group (SD=17.5; Me=33).

A modified post-concussion symptoms questionnaire was used for the study. A set of 35 items was created from available literature, each with a scale ranging from 0 to 6 points. The resulting summary scores were used for the analysis as well as partial scores for different symptom categories: somatic symptoms, emotional symptoms, cognitive impairments, and sleep disorders.

Neuropsychological tests were performed to evaluate cognitive domains commonly impacted by mTBI, including learning, working memory, recognition, attention, processing speed, divided attention, and inhibitory control. Specific tests included the Digit Span and Word List I and II (Slovak language version for NeuroNorm) (ref.[4]); subtests from the Wechsler Memory Scale, 3rd edition (WMS-III) (ref.[5]); Trail Making Test (TMT) (ref.[6]); Symbol Digits Modalities Test (SDMT) (ref.[7]); and Stroop Color and Word Test (Slovak language version for NeuroNorm) (ref.[4]).

A brain MRI scan was performed on all patients with no contraindication to undergo this examination. Magnetic resonance images were obtained using a Siemens Magnetom Symphony 1.5T scanner with an eight-channel head coil (Erlangen, Germany) at the University Hospital Martin (Martin, Slovak Republic). For the anatomical reference, T1-weighted images were acquired using a 3D magnetization-prepared rapid gradient echo (MP-RAGE) pulse sequence as follows: 192 contiguous sagittal slices with TE (echo time) = 3.93 ms, repetition time (TR) = 2080 ms, inversion time (TI) = 1100 ms, flip angle = 15°, FOV = 250 mm, slice thickness = 1 mm, and acquisition matrix = 256 × 256 mm. Diffusion MRI images were acquired using an echo planar imaging (EPI) pulse sequence as follows: TE (echo time) = 91 ms, TR (repetition time) = 5200 ms, field of view (FOV) = 280 mm, voxel size = 2.9 × 2.9 × 2.8 mm, slice thickness = 2.8 mm, and bandwidth = 1184 Hz/Px. Diffusion gradients were applied in 12 directions with b = 0 and 1000 s/mm^2. The automated global probabilistic tractography tool TRACULA (TRActs Constrained by UnderLying Anatomy) was used to reconstruct the set of predetermined major white matter pathways from each participant's diffusion-weighted images[8]. Preliminary anatomical information derived from the cortical parcellation and subcortical segmentation was obtained from the FreeSurfer version 7.1.0 software package (Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, Massachusetts, USA), and the TRACULA processing workflow was achieved by tools available in FSL (FMRIB Software Library; FMRIB Analysis Group, University of Oxford, Oxford, UK). All data were visually inspected before and after processing. Eighteen major pathways were reconstructed, including forceps major and forceps minor of the corpus callosum, anterior thalamic radiation, cingulum-angular bundle, cingulum-cingulate gyrus bundle, corticospinal tract, parietal and temporal bundle of superior longitudinal fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus. For each listed pathway, average fractional anisotropy (FA) and mean diffusivity (MD) values were selected for further analysis as the primary diffusivity metrics for axonal integrity and severity of brain injury[9].

Groups and training protocol

Each patient and their corresponding control were assigned to the active or passive subgroup. Participation in the active subgroup with a special training protocol was offered to all patients with mTBI. If the patients did not agree to be included in the active subgroup, they were assigned to the passive subgroup. We assumed that individual preference and inclination to follow or not to follow the training protocol properly would lead to a better division of subgroups with overall higher and lower activity than in the case of randomization. Participants in the passive subgroups received no recommendations or restrictions (in addition to standard medical advice from the emergency department). Participants in the active subgroup started with a 14-day at-home training program on the second day after the first assessment session. The daily program included 30 min of physical training and 30 min of cognitive training. The goal attributes of the selected training program were mainly its simplicity and minimal burden on the health sector. Physical training consisted of moderate-intensity aerobic activity in the form of speed walking (in addition to normal daily activities). The training load was chosen in accordance with the general recommendations of the American Heart Association (AHA), which recommends 150–300 minutes per week of moderate-intensity aerobic activity (with a heart rate of approximately 130–140 beats per minute and a respiratory rate that still allows normal verbal communication) (ref.[10]). A special workbook was created for cognitive training. The participant's task was to solve three puzzles daily: a maze, a word search, and a Sudoku puzzle. The individual puzzles were obtained from freely available internet sources and processed into the workbook, whereas the task complexity gradually increased during the training. Even though our cognitive training program does not meet the criteria for standard cognitive rehabilitation, there is demonstrable benefit even in unconventional cognitive training approaches[11]. During the training, the success of the procedures was monitored by a short phone call every other day. In the case of sudden complications (such as exacerbating posttraumatic symptoms), participants were instructed to initiate a phone call immediately.

Statistical analysis

Statistical analyses were performed with R software version 4.0.5 (The R Foundation for Statistical Computing, Vienna University of Economics and Business, Vienna, Austria), including data from the post-concussion symptoms questionnaire, neuropsychological tests, and MD and FA values from the tractography. The median (Me) and interquartile range (IQR) were calculated for the continuous variables. In the case of factors, a contingency table was created instead. The nonparametric Wilcoxon rank-sum test and chi-square test were used. Due to the large amount of analyzed data, the false discovery rate (FDR) correction of all P values was performed in the final step to achieve Q values using the standard Benjamin-Hochberg procedure[12]. All data from the post-concussion symptoms questionnaire, neuropsychological tests, and tractography were used as predictive factors for the machine learning algorithm using the random forest method[13,14]. Prediction ability was graphically displayed using a receiver operating characteristics (ROC) curve and quantified by the area under the curve (AUC) value.

RESULTS

Sample characteristics

Out of a total of 28 patients enrolled in the study, 25 attended both sessions. Data from patients who did not participate in both sessions (three patients) were not further analyzed. The active subgroup consisted of 14 patients, whereas the passive subgroup included 11 patients. All control groups were the same size as patient groups and consisted of volunteers matched for sex, age (±5 years), and the highest level of education. Sample demographic characteristics are given in Table 1.

The post-concussion symptoms questionnaire was completed by 23 patients (14 from the active subgroup and nine from the passive subgroup). The neuropsychological tests were performed on all 25 patients (14 from the active subgroup and 11 from the passive subgroup). MRI and tractography were performed on 17 patients (11 from the active subgroup and six from the passive subgroup).

Subjective training evaluation

All patients in the active group subjectively rated the training as beneficial. There were no significant complications during the training program. In one case, a headache appeared after the patient exceeded the recommended load threshold (the patient started running instead of fast walking). After a telephone consultation, the patient decreased their load to the recommended level, and the headache promptly disappeared.

Post-concussion symptoms results

Patients had an overall decrease in symptom scores (compared to controls) at the time of the second session for all examined modalities, as presented in Table 2. There was a significant decrease in the total score (P<0.001; Q=0.009), somatic symptoms score (P<0.001; Q=0.009),

Table 1. Sample demographic characteristics.

	Total Sample				Active Subgroup				Passive Subgroup			
	Patients		Controls		Patients		Controls		Patients		Controls	
Variable	(n = 25)		(n = 25)		(n = 14)		(n = 14)		(n = 11)		(n = 11)	
Age												
Mean	33		32.7		32.8		32.7		33.4		32.6	
SD	(10.7)		(10.1)		(11.5)		(11.6)		(10.1)		(8.3)	
	n	%	n	%	n	%	n	%	n	%	n	%
Sex												
Male	13	52	13	52	7	50	7	50	6	54.5	6	54.5
Female	12	48	12	48	7	50	7	50	5	45.5	5	45.5
Education												
Higher	13	52	13	52	7	50	7	50	6	54.5	6	54.5
Lower	12	48	12	48	7	50	7	50	5	45.5	5	45.5

SD, Standard Deviation; n, number.

emotional symptoms score (*P*<0.001; *Q*=0.015), and sleep disorders score (*P*=0.004). Comparison within the patient group showed insignificant trends of a slightly larger decrease in most symptoms (especially cognitive impairment scores) at the time of the second session in the active subgroup. The results are presented in Table 3. There were no significant changes or trends within the active and passive subgroups in the controls.

Neuropsychological test results

A few analyzed variables exceeded the significance threshold, as presented in Table 4, but none of them were significant after FDR correction. There was a significant improvement in distraction score from the Word List Test (*P*=0.026) and Stroop Test, Part 2 (*P*=0.042) at the time of the second session in the patient group (which corresponds to the speed of color labelling). A significantly larger improvement in the Stroop test, Part 3 (*P*=0.049) and difference 3–2 (*P*=0.04), was also found at the time of the second session in the active patient subgroup (which corresponds to the ability of inhibitory control and interference). Other analyzed parameters and tests (including the digit span test, Trail Making Test, and Symbol Digits Modalities Test) did not yield any significant results.

The noninferiority test showed no evidence of the negative effect of the selected training program on the cognitive functions within the patient group, as no p value of the hypothesis reached the level of significance.

Table 2. Postconcussion symptoms questionnaire – patients vs. controls.

	Patients (S1–S2) (n = 23)		Controls (S1–S2) (n = 23)		*P* (*)	*Q* (†)
Score	Me	IQR	Me	IQR		
Somatic symptoms	6	1.5; 7.5	0	-1.5; 1	< 0.001	0.009
Emotional symptoms	2	0; 4.0	-1	-1.5; 0	< 0.001	0.015
Cognitive impairments	2	0; 5	0	-2; 2	0.083	0.4
Sleep disorders	2	0; 5.5	-1	-1; 0	0.004	0.061
Total	11	4; 20	-1	-7; 3	< 0.001	0.009

*According to Wilcoxon rank-sum test. †After FDR correction.
S1-S2, session 1 value minus session 2 value; n, number; Me, median; IQR, interquartile range.

Table 3. Postconcussion symptoms questionnaire – active patient vs. passive patient subgroup.

	Active (S1–S2) (n = 14)		Passive (S1–S2) (n = 9)		*P* (*)	*Q* (†)
Score	Me	IQR	Me	IQR		
Somatic symptoms	6	2.2; 9.2	3	0; 6.0	0.2	> 0.9
Emotional symptoms	0.5	-0.75; 3.75	3	1; 4	0.3	> 0.9
Cognitive impairments	4	1; 9	0	0; 1	0.057	0.7
Sleep disorders	2.5	0.2; 5.8	1	0; 5	0.8	> 0.9
Total	12	5; 22	8	5; 11	0.3	> 0.9

*According to Wilcoxon rank-sum test. †After FDR correction.
S1-S2, session 1 value minus session 2 value; n, number; Me, median; IQR, interquartile range.

Table 4. Neuropsychological tests – patients vs. controls and active patient vs. passive patient subgroup (only *P*<0.05 results).

	Patients (S1–S2) (n = 25)		Controls (S1–S2) (n = 25)		*P* (*)	*Q* (†)
Score	Me	IQR	Me	IQR		
Word List – distraction	1	0; 3	0	-2; 1	0.026	0.2
	Patients (S1–S2) (n = 24)		Controls (S1–S2) (n = 24)		*P* (*)	*Q* (†)
Score	Me	IQR	Me	IQR		
Stroop test – pt. 2	6	2; 11.2	3	1; 4.2	0.042	0.3
	Active (S1–S2) (n = 14)		Passive (S1–S2) (n = 10)		*P* (*)	*Q* (†)
Score	Me	IQR	Me	IQR		
Stroop test – pt. 3	11	3.5; 13	4	0.5; 6.5	0.049	0.7
Stroop test – diff. 3-2	10	2; 12	2	-1; 3	0.04	0.7

*According to Wilcoxon rank-sum test. †After FDR correction.
S1–S2, session 1 value minus session 2 value; n, number; Me, median; IQR, interquartile range; pt., part; diff., difference.

Tractography results

Within the tractography analysis, several significant results were found, as presented in Table 5. However, similar to neuropsychological tests, no results from the tractography reached the level of significance after FDR correction.

There was a uniform tendency of relative mean diffusivity increase in the patient group at the time of the second session within multiple tracts: forceps minor (*P*=0.045), left anterior thalamic radiation (*P*=0.045), right cingulum-cingulate gyrus bundle (*P*=0.045), and right corticospinal tract (*P*=0.022). At the same time, there was a relative decrease in fractional anisotropy within the right corticospinal tract (*P*=0.022) in this group. Comparison within the patient group showed a similar relative increase in mean diffusivity in the passive subgroup, which was found within the right cingulum-angular bundle (*P*=0.02) and left uncinate fasciculus (*P*=0.048).

The results in the comparison of control subgroups were inconclusive. In the passive subgroup, there was a relative increase in mean diffusivity within the right cingulum-angular bundle (*P*=0.027), a relative decrease in mean diffusivity within the left anterior thalamic radiation (*P*=0.048), and a rather high relative decrease in fractional anisotropy within the left inferior longitudinal fasciculus (*P*=0.01).

Predictive model

The predictive model was able to distinguish between patients and controls in the first (AUC=0.807) and the second (AUC=0.652) sessions. However, machine learn-

Table 5. Tractography – patients vs. controls, active patient vs. passive patient subgroup, and active control vs. passive control subgroup (only *P*<0.05 results).

	Patients (S1–S2) (n = 17)		Controls (S1–S2) (n = 17)		*P* (*)	*Q* (†)
Measures	Me*	IQR*	Me*	IQR*		
MD FMinor	-0.0027	-0.0116; 0.0021	0.0061	0.0007; 0.0146	0.045	0.3
MD ATR (left)	0.0013	-0.0151; 0.0095	0.009	0.0027; 0.013	0.045	0.3
MD CCG (right)	-0.0052	-0.0122; 0.0065	0.0101	-0.0007; 0.0238	0.045	0.3
MD CST (right)	-0.0024	-0.009; 0.0018	0.0025	-0.0012; 0.0073	0.022	0.2
FA CST (right)	6.492	1.934; 11.194	-4.614	-17.092; 3.578	0.022	0.2
	Active p. (S1–S2) (n = 11)		Passive p. (S1–S2) (n = 6)		*P* (*)	*Q* (†)
Measures	Me*	IQR*	Me*	IQR*		
MD CAB (right)	0.0086	-0.002; 0.0322	-0.0194	-0.0245; -0.0121	0.02	0.7
MD UNC (left)	0.0063	0.0015; 0.0203	-0.0064	-0.0098; 0.0025	0.048	0.7
	Active c. (S1–S2) (n = 11)		Passive c. (S1–S2) (n = 6)		*P* (*)	*Q* (†)
Measures	Me*	IQR*	Me*	IQR*		
MD CAB (right)	0.0145	-0.002; 0.0293	-0.0172	-0.0267; -0.0081	0.027	0.6
MD ATR (left)	0.006	-0.0033; 0.0107	0.0135	0.0099; 0.0177	0.048	0.6
FA ILF (left)	-1.153	-3.41; 7.9685	13.5125	11.1085; 18.0015	0.01	0.6

Values divided by 0.001 to simplify presentation of data (e.g., 0.0000013/0.001 = 0.0013).
*According to Wilcoxon rank-sum test. †After FDR correction.
S1–S2, session 1 value minus session 2 value; n, number; Me, median; IQR, interquartile range; MD, average mean diffusivity; FA, average actional anisotropy; FMinor, forceps minor; ATR, anterior thalamic radiation; CCG, cingulum-cingulate gyrus bundle; CST, corticospinal tract; CAB, cingulum-angular bundle; UNC, uncinate fasciculus; ILF, inferior longitudinal fasciculus; p., patient; c., control.

Table 6. Predictors selected by machine learning (ranked in descending order).

Patients vs. controls, first session	Patients vs. controls, second session	Patient active vs. patient passive subgroup, second session
Stroop test (part 2)	FA SLFT (left)	MD CCG (right)
Somatic symptoms score	Stroop test (part 2)	FA CST (left)
MD CCG (right)	FA UNC (left)	MD ATR (right)
FA UNC (left)	FA ILF (right)	FA CCG (left)
FA FMajor	MD ATR (left)	MD SLFP (left)
MD FMinor	MD CAB (left)	
FA ILF (right)		

MD, average mean diffusivity; FA, average actional anisotropy; CCG, cingulum-cingulate gyrus bundle; UNC, uncinate fasciculus; Fmajor, forceps major; Fminor, forceps minor, ILF, inferior longitudinal fasciculus; SLFT, temporal bundle of superior longitudinal fasciculus; ATR, anterior thalamic radiation; CAB, cingulum-angular bundle; CST, corticospinal tract; SLFP, parietal bundle of superior longitudinal fasciculus; vs., versus.

ing was unable to distinguish between the active patient and passive patient subgroups in the second session (AUC=0.494). ROC curves are presented in Fig. 1–3. In general, there was the overall predictive dominance of measures from tractography. Similarly, the result from the Stroop test (Part 2) also had notable predictive potential. The most important predictors (selected by machine learning) are presented in Table 6.

DISCUSSION

In our study, simple posttraumatic training techniques were chosen in the active group. The training started approximately 24–72 h after the injury, and a 24–48-hour rest phase preceded it immediately after the injury. The chosen time periods followed the principles of the Concussion in Sport international conference[1].

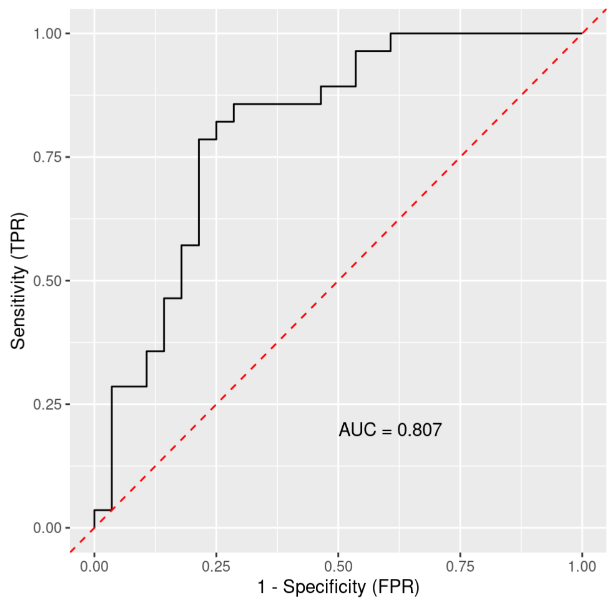

Fig. 1. ROC curve – patients vs. controls, first session.

Several studies point to the possible harmfulness of the prolonged resting phase. The first mentions of this issue can even be found in articles from the early 1950s (ref.[15,16]). According to a randomized controlled trial by Thomas et al., five-day strict bedrest showed no benefits in a group of adolescents and young adults with mTBI within symptom scores and neurocognitive tests. Compared to the 24–48 h rest phase group (followed by a standard stepwise return to activity), patients with prolonged bedrest reported more daily post-concussive symptoms and an average of three days longer symptom resolution[17]. Similarly, Silverberg and Otamendi observed a delayed return to pretraumatic activities in patients with recommended rest for more than two days[18]. Relander et al. examined the impact of strict bedrest and proactive posttraumatic management with concomitant physiotherapy. Patients in the active group could return to work 14 days earlier[19].

As reported in our study protocol, we used fast walking with no load alterations during the training period, representing a slightly higher initial load when compared with individual programs usually used in athletes[1]. The advantage of a uniform training program is its apparent simplicity for the average (nonathlete) patient (as a trainer is not needed). On the other hand, an excessive load can also be counterproductive. A retrospective study by Majerske et al. compared groups of young athletes with mTBI and subsequently different load levels in the postinjury period. The group with the highest load shortly after the injury had the worst results in cognitive tests, whereas a light load seemed to be the most beneficial[20]. De Kruijk et al. found no significant differences between patients with immediate return to previous activities and patients with prolonged six-day bedrest[21].

In our active patient subgroup, no exacerbation of

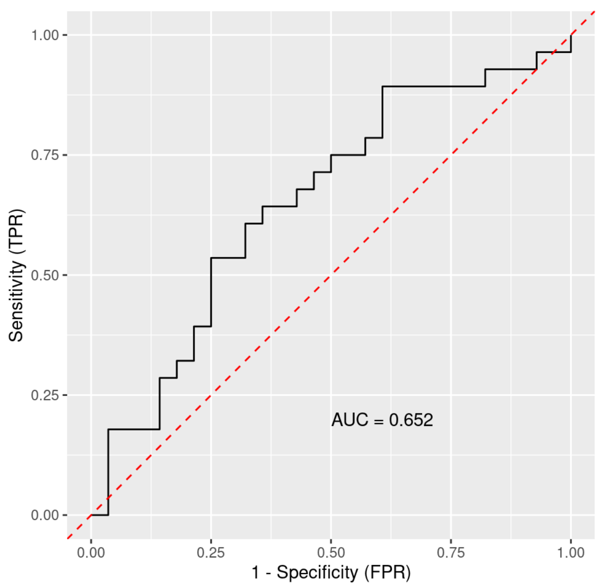

Fig. 2. ROC curve – patients vs. controls, second session.

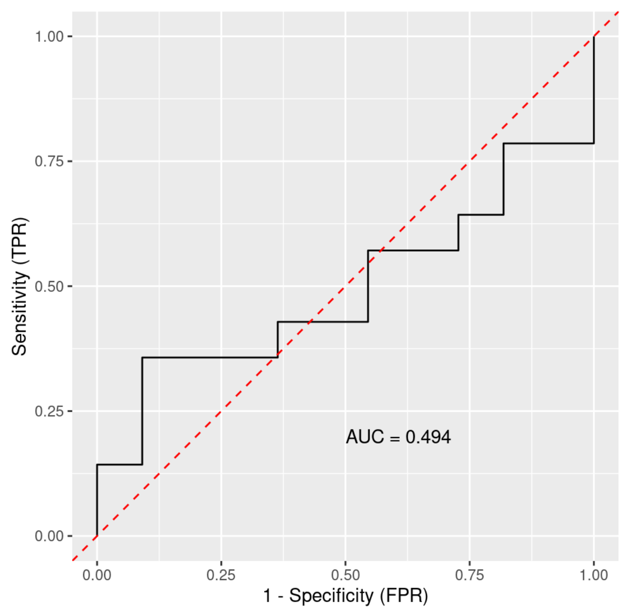

Fig. 3. ROC curve – active patient vs. passive patient subgroup, second session.

symptoms was reported during the training program. In one case, a headache appeared after the patient exceeded the recommended threshold. After returning to the recommended load level, the patient's condition improved immediately. Based on the trends for a more pronounced decrease in post-concussion symptoms in the active patient subgroup (compared to the passive patient subgroup) and the overall positive rating of the training program by patients, we consider the chosen training intensity to be appropriate from the subjective perspective.

Our modified post-concussion symptoms questionnaire revealed a highly significant (P<0.001; Q=0.009) decrease in symptoms over time in the patient group (compared to controls). A similar improvement in the patient group was observed in distraction score from the Word List Test (P=0.026) and speed of color labelling from the Stroop Test (P=0.042). The Stroop test is the most commonly used method to evaluate attention distribution problems and inhibitory control in patients with mTBI (ref.[22]). In our study, there was an improvement (P=0.042 and 0.04) in the ability of inhibitory control and interference in the active patient subgroup (compared to controls). Moreover, the noninferiority test indicated no significant decline or delayed recovery of cognitive functions in this group. The above results objectively point to the safety of our chosen individual training, simultaneously with the signs of slight benefits in specific cognitive domains.

The interpretation of results obtained from tractography is quite complicated. Several studies have yielded inconsistent results, and human studies usually lack the preinjury values of diffusive parameters. In the acute phase of mTBI (demonstrably within two weeks after injury), there are predominant trends towards an increase in FA with a concomitant decrease in MD (ref.[9,23,24]). These diffusion changes are primarily attributed to axonal oedema[25,26]. In the late posttraumatic phase (typically several months after the injury), the opposite phenomenon can be observed, with a decrease in FA and an increase in MD. The presumed causes are the gradual development of parenchymal damage after the oedema phase, axonal degeneration, and the disruption of nerve fibers[27,28]. A meta-analysis by Eierud et al. (comparing different MRI modalities in patients with mTBI across 122 publications) also reported similar diffusion parameter change trends[29]. However, the fundamentals of the subacute period within three months after the injury remain unclear. In this postinjury phase, a meta-analysis by Dodd et al. reported approximately the same number of studies with increased FA values and reduced FA values[30].

In our study, there were notable changes in diffusive parameters within five tracts in the patient group (compared to controls) at the time of the second session. There was an increase in MD in four tracts (FMinor, left ATR, right CCG, and right CST) and a decrease in FA in one tract (right CST). These changes resemble the typical picture of the chronic posttraumatic phase. However, the significance of these results was undoubtedly influenced by changes in diffusion parameters in the control group, where there is no logical reason to assume significant changes (i.e., we could not find a relevant basis for the development of brain structural changes in healthy controls in our study). One of the most common problems in evaluating tractography and diffusion measurements (especially in studies based on correlation analysis) is the ease with which the significance threshold is exceeded, resulting in conclusions with minimal interpretative value[31]. Therefore, we consider the presented results from tractography (none of which reached the significance level after FDR correction) to be trends, rather than truly significant results. Nevertheless, all results showed the same trends in the development of typical chronic posttraumatic brain changes over time in the patient group. A similar phenomenon also occurred when comparing the active and passive subgroups of patients. In the passive subgroup, there was an increase in MD in two tracts (left UNC and right CAB) compared to the active subgroup. These results seem to point to worse outcomes in the passive subgroup, but the evidence is insufficient to draw firm conclusions. On the other hand, it also does not indicate a deterioration in the active subgroup of patients (rather the opposite), which further proves our training program's safety. When comparing the active and passive subgroups of controls, the results were even less clear-cut (a notable decrease in MD in the left ATR and in FA in the left ILF in the passive subgroup and a decrease in MD in the right CAB in the active subgroup). These results are most likely to result from the wide range of parameters evaluated in this study.

Even though the tractography tool TRACULA has been used in many studies focused on a wide range of neurological and neuropsychiatric diseases, only a few of them have dealt with brain injuries. Goodrich-Hunsaker et al. compared FA, MD, RD, and AD parameters in children with mTBI and orthopedic injury. The resulting diffusion parameters were obtained using three different methods in processing diffusion-weighted images: the tract-based spatial statistics (TBSS) method, the automating fiber-tract quantification (AFQ) method, and probabilistic tractography using TRACULA. None of the methods was superior to the others. However, tractography is more sensitive for detecting changes related to physiological brain development in specific brain areas[32]. Similarly, Yeh et al. evaluated various techniques of diffusion data processing in soldiers with persistent post-concussion syndrome. Whereas simple DTI analysis did not show significant brain changes, TRACULA was able to verify white matter damage (especially in the frontal area). Lower FA values also correlated with the intensity of post-concussion symptoms and cognitive deficits[33]. These findings point to the satisfactory ability of TRACULA to assess structural connectivity in patients with mTBI. TRACULA is also easy-to-use software and can quickly process large amounts of data.

In addition, few studies have been published to identify patients with mTBI using machine learning based on different MRI modalities. The results are usually limited by a small patient group size. Minaee et al. used diffusion-weighted images obtained within one month after the injury. Through machine learning, nine diffusion parameters (including FA and MD) from predefined brain areas (mostly the thalamus and splenium of the corpus callosum) were used to identify key injury regions. However, the resulting predictors varied considerably depending on the technique used[34]. Mitra et al. applied a prediction algorithm to a structural connectome from probabilistic tractography. The identified areas with significant changes in connectivity were in line with the general consensus[35]. Finally, diffusion-weighted images and measurements from resting-state fMRI were used by Vergar et al. The resulting AUC value for detecting mTBI when using both modalities was 0.745. However, using data from fMRI alone, the AUC value increased to 0.841, although for diffusion measurements, it was only 0.755 (ref.[36]). Our study showed the overall predictive potential of tractography measures compared to the symptom scores and results from neurocognitive tests. The large amount of data resulting from tractography seems to be more useful when machine learning is used compared to conventional statistical approaches. In this case, artificial intelligence has the potential for pattern recognition and complex analysis of these waste datasets.

The main limitation of this pilot study is the small sample size. Recruitment was significantly affected by the outbreak of the COVID-19 pandemic, which also complicated planned cooperation with other hospitals. In a larger final study sample size, stronger statistical power could be expected (especially in the case of tractography). In addition, the lack of randomization when dividing patients into active and passive groups might be biased. Division based on individual preference was chosen to reduce dropouts from the study and will be eliminated in the final study. The study on a larger sample would also make it possible to divide patients into specific subgroups (according to mechanism of the injury, type of the impact on the head, length of unconsciousness, etc.), since some variables can affect pattern of tractography findings.

CONCLUSION

In this prospective pilot study, we evaluated the effect and safety of defined training protocol with slightly higher initial physical and cognitive loads in patients after mTBI. Our results objectively point to the safety of our chosen training protocol, simultaneously with the signs of slight benefits in specific cognitive domains. The study also showed the capability of machine learning and predictive models in mTBI patient recognition.

ABBREVIATIONS

mTBI, mild traumatic brain injury; PCS, post-concussion syndrome; CT, computed tomography; WHO, World Health Organization; MRI, magnetic resonance imaging; WMS, Wechsler memory scale; TMT, trail making test; SDMT, symbol digits modalities test; MP-RAGE, magnetization-prepared rapid gradient echo; FOV, field of view; EPI, echo planar imaging; TRACULA, tracts constrained by underlying anatomy; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity; AHA, American Heart Association; IQR, interquartile range; FDR, false discovery rate; ROC, receiver operating characteristics; AUC, area under the curve; FMinor, forceps minor; ATR, anterior thalamic radiation; CCG, cingulate gyrus; CST, corticospinal tract; UNC, uncinate fasciculus; CAB, cingulum angular bundle; TBSS, tract-based spatial statistics; AFQ, automating fiber-tract quantification; DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging.

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REFERENCES

1. McCrory P, Meeuwisse W, Dvořák J, Aubry M, Bailes J, Broglio S, Cantu RC, Cassidy D, Echemendia RJ, Castellani RJ, Davis GA, Ellenbogen R, Emery C, Engebretsen L, Feddermann-Demont N, Giza CC, Guskiewicz KM, Herring S, Iverson GL, Johnston KM, Kissick J, Kutcher J, Leddy JJ, Maddocks D, Makdissi M, Manley GT, McCrea M, Meehan WP, Nagahiro S, Patricios J, Putukian M, Schneider KJ, Sills A, Tator CH, Turner M, Vos PE. Consensus statement on concussion in sport-the 5th international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med 2017;51(11):838-47.
2. Schneider KJ, Leddy JJ, Guskiewicz KM, Seifert T, McCrea M, Silverberg ND, Feddermann-Demont N, Iverson GL, Hayden A, Makdissi M. Rest and treatment/rehabilitation following sport-related concussion: a systematic review. Br J Sports Med 2017;51(12):930-4.
3. Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004;(43 Suppl):113-25.
4. Hajdúk, M, Brandoburová, P, Pribišová, K, Abrahámová, M, Cviková, V, Dančík, D, Gergely, S, Kralovská, S, Málišová, E, Svingerová, A, Heretik, A, Heretik, A. NEUROPSY: Štandardizácia neuropsychologickej testovej batérie na dospelej slovenskej populácii. 1st ed. Bratislava (SK): Univerzita Komenského v Bratislave; 2020.
5. Wechsler D. Wechsler Memory Scale – Third Edition manual. San Antonio (TX): Psychological Corporation; 1997.
6. Reitan RM, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. 2nd ed. Tucson (AZ): Neuropsychology Press; 1993.
7. Smith A. Symbol Digits Modalities Test: Manual. Los Angeles (CA): Western Psychological Services; 2007.
8. Yendiki A, Panneck P, Srinivasan P, Stevens A, Zöllei L, Augustinack J, Wang R, Salat D, Ehrlich S, Behrens T, Jbabdi S, Gollub R, Fischl B. Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy. Front Neuroinform 2011;5:23.

9. Hulkower MB, Poliak DB, Rosenbaum SB, Zimmerman ME, Lipton ML. A decade of DTI in traumatic brain injury: 10 years and 100 articles later. AJNR Am J Neuroradiol 2013;34(11):2064-74.
10. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD. The Physical Activity Guidelines for Americans. JAMA 2018;320(19):2020-8.
11. Cicerone KD, Dahlberg C, Malec JF, Langenbahn DM, Felicetti T, Kneipp S, Ellmo W, Kalmar K, Giacino JT, Harley JP, Laatsch L, Morse PA, Catanese J. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. Arch Phys Med Rehabil 2005;86(8):1681-92.
12. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J R Stat Soc Ser B Methodol 1995;57(1):289-300.
13. Boulesteix A, Janitza S, Kruppa J, König IR. Overview of random forest methodology and practical guidance with emphasis on computational biology and bioinformatics. Wiley Interdiscip Rev Data Min Knowl Discov 2012;2(6):493-507.
14. Breiman L. Random Forests. Machine Learning 2001;45(1):5-32.
15. Meerloo AM. Cerebral concussion; a psychosomatic survey. J Nerv Ment Dis 1949;110(4):347-53.
16. Voris HC. Mild head injury (concussion). Am J Surg 1950;80(6):707-13.
17. Thomas DG, Apps JN, Hoffmann RG, McCrea M, Hammeke T. Benefits of strict rest after acute concussion: a randomized controlled trial. Pediatrics 2015;135(2):213-23.
18. Silverberg ND, Otamendi T. Advice to Rest for More Than 2 Days After Mild Traumatic Brain Injury Is Associated With Delayed Return to Productivity: A Case-Control Study. Front Neurol 2019;10:362.
19. Relander M, Troupp H, Af Björkesten G. Controlled trial of treatment for cerebral concussion. Br Med J 1972;4(5843):777-9.
20. Majerske CW, Mihalik JP, Ren D, Collins MW, Reddy CC, Lovell MR, Wagner AK. Concussion in sports: postconcussive activity levels, symptoms, and neurocognitive performance. J Athl Train 2008;43(3):265-74.
21. de Kruijk JR, Leffers P, Meerhoff S, Rutten J, Twijnstra A. Effectiveness of bed rest after mild traumatic brain injury: a randomised trial of no versus six days of bed rest. J Neurol Neurosurg Psychiatry 2002;73(2):167-72.
22. Ben-David BM, Nguyen LL, van Lieshout PH. Stroop effects in persons with traumatic brain injury: selective attention, speed of processing, or color-naming? A meta-analysis. J Int Neuropsychol Soc 2011;17(2):354-63.
23. Asken BM, DeKosky ST, Clugston JR, Jaffee MS, Bauer RM. Diffusion tensor imaging (DTI) findings in adult civilian, military, and sport-related mild traumatic brain injury (mTBI): a systematic critical review. Brain Imaging Behav 2018;12(2):585-612.
24. Wallace EJ, Mathias JL, Ward L. Diffusion tensor imaging changes following mild, moderate and severe adult traumatic brain injury: a meta-analysis. Brain Imaging Behav 2018;12(6):1607-21.
25. Bazarian JJ, Zhu T, Blyth B, Borrino A, Zhong J. Subject-specific changes in brain white matter on diffusion tensor imaging after sports-related concussion. Magn Reson Imaging 2012;30(2):171-80.
26. Mayer AR, Ling J, Mannell MV, Gasparovic C, Phillips JP, Doezema D, Reichard R, Yeo RA. A prospective diffusion tensor imaging study in mild traumatic brain injury. Neurology 2010;74(8):643-50.
27. Niogi SN, Mukherjee P, Ghajar J, Johnson C, Kolster RA, Sarkar R, Lee H, Meeker M, Zimmerman RD, Manley GT, McCandliss BD. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. AJNR Am J Neuroradiol 2008;29(5):967-73.
28. Rutgers DR, Toulgoat F, Cazejust J, Fillard P, Lasjaunias P, Ducreux D. White matter abnormalities in mild traumatic brain injury: a diffusion tensor imaging study. AJNR Am J Neuroradiol 2008;29(3):514-9.
29. Eierud C, Craddock RC, Fletcher S, Aulakh M, King-Casas B, Kuehl D, LaConte SM. Neuroimaging after mild traumatic brain injury: review and meta-analysis. Neuroimage Clin 2014;4:283-94.
30. Dodd AB, Epstein K, Ling JM, Mayer AR. Diffusion tensor imaging findings in semi-acute mild traumatic brain injury. J Neurotrauma 2014;31(14):1235-48.
31. Lange RT, Yeh PH, Brickell TA, Lippa SM, French LM. Postconcussion symptom reporting is not associated with diffusion tensor imaging findings in the subacute to chronic phase of recovery in military service members following mild traumatic brain injury. J Clin Exp Neuropsychol 2019;41(5):497-511.
32. Goodrich-Hunsaker NJ, Abildskov TJ, Black G, Bigler ED, Cohen DM, Mihalov LK, Bangert BA, Taylor HG, Yeates KO. Age- and sex-related effects in children with mild traumatic brain injury on diffusion magnetic resonance imaging properties: A comparison of voxelwise and tractography methods. J Neurosci Res 2018;96(4):626-41.
33. Yeh PH, Guan Koay C, Wang B, Morissette J, Sham E, Senseney J, Joy D, Kubli A, Yeh CH, Eskay V, Liu W, French LM, Oakes TR, Riedy G, Ollinger J. Compromised Neurocircuitry in Chronic Blast-Related Mild Traumatic Brain Injury. Hum Brain Mapp 2017;38(1):352-69.
34. Minaee S, Wang Y, Aygar A, Chung S, Wang X, Lui YW, Fieremans E, Flanagan S, Rath J. MTBI Identification From Diffusion MR Images Using Bag of Adversarial Visual Features. IEEE Trans Med Imaging 2019;38(11):2545-455.
35. Mitra J, Shen KK, Ghose S, Bourgeat P, Fripp J, Salvado O, Pannek K, Taylor DJ, Mathias JL, Rose S. Statistical machine learning to identify traumatic brain injury (TBI) from structural disconnections of white matter networks. Neuroimage 2016;129:247-59.
36. Vergara VM, Mayer AR, Damaraju E, Kiehl KA, Calhoun V. Detection of Mild Traumatic Brain Injury by Machine Learning Classification Using Resting State Functional Network Connectivity and Fractional Anisotropy. J Neurotrauma 2017;34(5):1045-53.