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Longitudinal investigation of optic chiasm in patients with traumatic brain injury

Hyun-ho Kim[1,2,3], Wonpil Jang[1], Cheol-Woon Kim[1] and Joon Yul Choi[1*]

Abstract

Background Traumatic brain injury (TBI) often precipitates a cascade of neurophysiological alterations, impacting structures such as the optic nerve and ocular motor system. However, the literature lacks expansive investigations into the longitudinal changes in the optic chiasm and its relationship with the clinical recovery of visual processing. This study aimed to scrutinize longitudinal changes in optic chiasm volume (OCV) and establish the relationship of OCV with process speed index at 12 months post-injury. Process speed index is derived from Wechsler Adult Intelligence Scale IV.

Methods Thorough cross-sectional and longitudinal analyses were executed, involving 42 patients with moderate to severe TBI and 35 healthy controls. OCV was acquired at 3, 6, and 12 months post-injury using T1-weighted images. OCV of healthy controls and that of patients with TBI at 3, 6, and 12 months post-injury were compared using a Mann-Whitney U test. A multiple linear regression model was constructed to assess the association between OCV and PSI and to predict PSI at 12 months post-injury using OCV at 3 months post-injury.

Results OCV of patients with TBI was significantly larger compared to healthy controls, persisting from 3 to 12 months post-injury ($p < 0.05$). This increased OCV negatively correlated with PSI at 12 months post-injury, indicating that larger OCV sizes were associated with decreased PSI ($p = 0.031$). Furthermore, the multiple linear regression model was significant in predicting PSI at 12 months post-injury utilizing OCV at 3 months post-injury ($p = 0.024$).

Conclusion For the first time, this study elucidates the increased OCV and the significant association between OCV in sub-chronic stage and PSI at 12 months post-injury, potentially providing clinicians with a tool for anticipatory cognitive rehabilitation strategies following TBI.

Keywords Traumatic brain injury, Optic chiasm volume, Processing speed index, Neuro-ophthalmology, Neuroplasticity, Neurodegeneration

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Introduction

Traumatic brain injury (TBI) is the leading cause of disability worldwide, affecting approximately 50 million people each year [1]. Despite remarkable medical advances, survivors of TBI still suffer from long-term cognitive impairment and neurological problems.

After TBI, patients undergo a series of processes such as inflammation [2–4], oxidative stress [5, 6], and excitotoxicity [7, 8] as well as the primary physical injury to the brain. These lead to secondary injury resulting in the loss of myelin in white matter [9]. While primary injury may appear to recover, secondary injury can contribute to the development of neurodegenerative diseases such as Alzheimer's disease [10, 11] and Parkinson's disease [12]. TBI has gained significant attention to better understand the mechanisms of neurodegeneration due to its substantial impact on the quality of life for patients [7, 13, 14].

In the early stages of moderate to severe TBI, patients often present with clinical symptoms that indicate disturbances of the optic nerve and the ocular motor system (e.g. diplopia, accommodative dysfunction, visual field defects, and nystagmus) [15]. While some of these symptoms may initially be caused by transient events, such as optic nerve compression due to increased intracranial pressure from hemorrhage or edema, persistent and/or potentially worsening symptoms may result from the interaction of various aspects of the pathophysiological mechanism [16, 17]. In addition to direct trauma to the optic nerve, secondary injury from vascular injury [18], damage to the cerebral cortex [19], and neurotransmitter imbalances [20] might result in medium- to long-term functional losses of the optic tract and optic chiasm in cases of moderate to severe TBI [21].

Despite the important clinical manifestations of optic nerve and oculomotor disturbances in patients with moderate to severe TBI, the literature remains devoid of any comprehensive cross-sectional and longitudinal studies exploring the change of optic tract and optic chiasm. The optic nerves intersect and connect to the brain through optic chiasm and the optic chiasm plays a crucial role in the transmission of visual information to both hemispheres of the brain. Damage to this structure can impact the transfer and processing of visual information, potentially affecting the speed at which visual information is processed. The Processing Speed Index is one of the metrics used to evaluate how quickly an individual can process and respond to visual information [22]. It measures the ability to rapidly recognize and process visual information, which is a key aspect of cognitive function [23]. The study hypothesized that changes to the optic chiasm resulting from moderate to severe traumatic brain injury could affect the pathways for transmitting and processing visual information, potentially impacting the processing speed index. In this study, we endeavor to scrutinize the changes in optic chiasm volume (OCV) at intervals of 3, 6, and 12 months post-moderate to severe TBI. By developing a linear regression model to estimate the index of visual processing at 12 months post-injury based on OCV at 3 months post-injury, we aim to elucidate the relationship between OCV and clinical recovery of process speed index.

Materials and methods

Subject information

This secondary analysis study utilized a de-identified data set previously acquired as part of a longitudinal neuroimaging project supported by the National Institutes of Health (NIH R01NS065980; PI: Junghoon J. Kim, PhD, CUNY School of Medicine, New York, NY, USA). Results from neuropsychological [24] and other imaging modalities [25–28] from this data set have previously been reported.

Patients with moderate to severe TBI were recruited from a specialized inpatient rehabilitation unit for the purpose of correlating structural changes and functional recovery in a longitudinal cohort.

Inclusion criteria were (1) age between 18 and 64 years old, (2) a diagnosis of non-penetrating moderate to severe TBI as defined by at least one of the following (Glasgow Coma Scale (GCS) score < 13 in the emergency department (not due to sedation, paralysis, or intoxi- cation), (3) loss of consciousness documented loss of consciousness ≥ 12 h, and (4) prospectively documented post traumatic amnesia (PTA) ≥ 24 h [24], (5) high velocity, high impact closed head injury resulting from vehicular accidents or falls [28].

Exclusion criteria were as follows: (1) presence of prior TBI history, central nervous system diseases, seizure disorder, schizophrenia, or bipolar disorder, (2) history of serious alcohol or psychostimulant (e.g., cocaine) abuse, (3) pregnancy, (4) inability to undergo MRI scanning due to ferromagnetic implants, claustrophobia, or restlessness, and (5) a level of impairment that precluded the subject's ability to complete testing and scanning at 3 months post-injury.

Healthy controls without any medical history of TBI (i.e. alteration or loss of consciousness) were also recruited to match with patients in terms of age, gender, and race. Exclusion criteria for healthy controls were the same as above.

The study was approved by the Institutional Review Board of the home institution. All participants, either directly or through their legally authorized representatives, provided written informed consent prior to the participation. All methods were performed in accordance with the Declaration of Helsinki guideline. Finally, MRI data were collected from 42 patients with TBI and 35

Table 1 Demographic and clinical characteristics of the patients and controls

	TBI ($N=42$)	Control ($N=35$)	*P*-value
Age (years)	35.0 ± 14.6	35.0 ± 10.2	0.986
Sex (M: F)	29: 13	26: 9	0.800
Race	1 A : 3 H : 21 W : 17 AA	1 A : 1 H : 12 W : 21 AA	0.352
Process Speed Index[+]	38.7 ± 12.7 (83.0 ± 19.0)	47.9 ± 11.2 (96.9 ± 16.8)	0.002
Post-Traumatic Amnesia (days)	28.1 ± 21.5	-	-
Glasgow Coma Scale[++]	9.8 ± 4.1[++]	-	-
Brain volume (mm^3)	1,123,016 ± 103,294	1,146,414 ± 99,138	0.3230

M = Male; F = Female; A = Asian; H = Hispanic; W = White; AA = African American

[+]This score is T transformed scores of original scores. The scores in the parenthesis are the original scores

[++]This number is the mean score of 28 subjects; intubated (6) and sedated (8) were excluded

healthy controls. Demographic and clinical information for retained subjects are described in Table 1.

Data acquisition and processing

For a neuropsychological test, participants were assessed at the time of scanning using processing speed index. The Processing speed index is a scoring index derived from Wechsler Adult Intelligence Scale IV [22, 23] and it assesses a specific aspect of cognitive function. This index evaluates how quickly an individual responds to and processes visual, motor, or cognitive stimuli. It is used to understand the individual's reaction speed within tasks and their ability to process tasks along with attention and concentration [29].

A 3D T1 weighted magnetization prepared rapid gradient echo (T1w MPRAGE) sequence was acquired from 35 healthy controls and 42 patients with TBI with the following parameters (repetition time (TR) = 1620 ms, echo time (TE) = 3.0 ms, inversion time (TI) = 950 ms, in-plane resolution = 1 × 1 × 1 mm^3, flip angle = 15°, the number of slices = 160, the scan time = 5 min 11 s). To investigate longitudinal changes, we scanned the same patients at the following designated time points: 3 months (104 ± 19 days), 6 months (184 ± 16 days), and 12 months (363 ± 23 days). The number of patients with TBI was 45, 34, and 35 at 3 months post-injury, 6 months post-injury, and 12 months post-injury, respectively.

Acquired T1 weighted images were utilized to derive volumetric data of the optic chiasm through 'recon-all' in Freesurfer [30]. The recon-all process is divided into two main steps: Autorecon1 and Autorecon2 as shown in Fig. 1. A simple description of each step is as follows: Autorecon1 primarily focuses on motion correction, intensity normalization, and skull stripping; Autorecon2 involves a series of advanced preprocessing and analysis steps including linear and non-linear registration to standard template, segmentation of gray and white matters, and generation of volumetric label map (aseg.mgz) that segments the brain into subcortical structures. The recon-all process automatically computes OCV in the aseg.stats file. For the comparison with OCV, the volumes of pericalcarine, cuneus, and lingual gyri (i.e. visual cortex) were extracted.

Statistical analysis

All statistical analyses were performed using the Statistics and Machine Learning Toolbox in MATLAB 2021a (MathWorks, Natick, Massachusetts, USA). For the demographics and clinical characteristics, a Student t test was conducted to compare the difference in age and PSI between healthy controls and TBI. Gender and race are categorical variable. A chi-square test was performed to confirm that there is no significant difference between healthy controls and TBI.

After obtaining OCV from healthy controls and TBI at 3, 6, 12 months post-injury, we compared the difference between healthy controls and each time point of TBI using a Mann-Whitney U test. To investigate differences between time points in TBI, a Wilcoxon signed rank test was performed for 3 and 6 months post-injury, 3 and 12 months post-injury, and 6 and 12 months post-injury after matching the number of subjects.

Since individual differences in the inherent brain volume could affect the analysis results [31], OCV was normalized by the whole brain volume of each individual. Another Mann-Whitney U test was conducted with the normalized OCV.

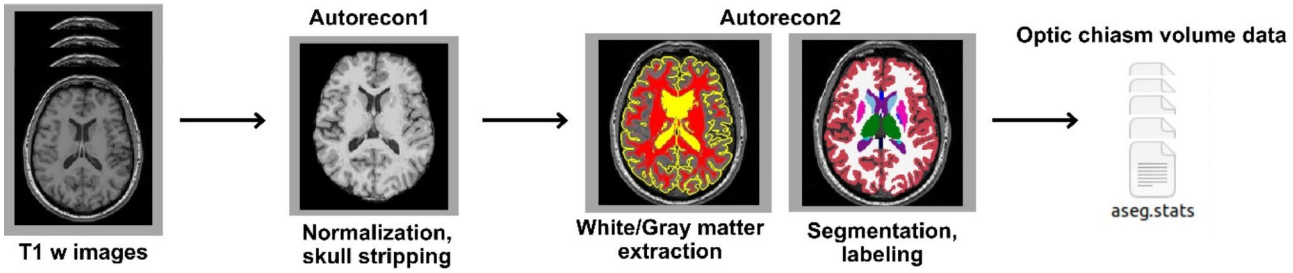

Fig. 1 Post-processing of acquired T1 weighted images from one representative subject to obtain OCV. OCV: optic chiasm volume

Predicting future cognitive function in TBI is clinically important because it can maximize patient recovery by improving neuroplasticity and cognitive recovery [32]. The multiple linear regression model was constructed to assess the association between OCV and PSI, and to predict PSI at 12 months post-injury using fitlm in MATLAB. As demonstrated in Eq. 1, the independent variables were OCV, age, and gender at 3 months post-injury because age and gender are readily obtainable data in clinical settings and are factors that could influence brain volume [33]. The dependent variable was PSI at 12 months post-injury.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 \quad (1)$$

where, $\beta_{1,2,3}$: Coefficients of independent variables ($X_1, X_2,$ and X_3, respectively), β_0: intercept, and Y: dependent variable.

We additionally analyzed the pericalcarine, cuneus, and lingual gyri to determine whether OCV is a more sensitive indicator of TBI than the visual cortex. For this analysis, we observed the volume differences in the visual area between HC and TBI patients using a Mann-Whitney U test and examined the association between PSI and visual area volumes using GLM as performed for OCV.

Results

Demographic and clinical characteristics of the patients were summarized in Table 1. It was found that age, gender, and race were not significantly different between healthy controls and TBI (p=0.986, p=0.800, and p=0.352 for age, gender, and race, respectively). In the analysis to assess neurological profiles, brain volume did not show a statistically significantly difference between groups (p=0.323). PSI of healthy controls was significantly higher than that of TBI (p=0.002).

OCV of TBI at 3 months post-injury (mean OCV=188±46 mm^3, median OCV=188 mm^3, interquartile range (IQR)=65.9) was significantly larger than those of healthy controls (mean OCV=157±44 mm^3, median OCV=165 mm^3, IQR=65.5, p=0.017, 16.6% larger in Fig. 2 (left)). The elevated OCV persists even until 12 months post-injury (mean OCV=181±49 mm^3, median OCV=196 mm^3, IQR=52.6) and significantly different from OCV of healthy controls (p=0.008, 14.8% larger). When comparing between 3 and 6 months, 6 and 12 months, and 3 and 12 months in TBI, all times points showed a significant difference (p<0.001).

When comparing OCV normalized by the whole brain volume of TBI with that of healthy controls, patients with TBI consistently exhibit larger OCV than healthy controls (mean OCV=0.0138±0.0038, median OCV=0.0143, IQR=0.0047), with the difference remaining significant at 12 months post-injury (p=0.007 at 3 months post-injury (mean OCV=0.0164±0.0041, median OCV=0.0165, IQR=0.0047), p=0.013 at 6 months post-injury (mean OCV=0.0165±0.0041, median OCV=0.0167, IQR=0.0065), and p=0.002 at 12 months post-injury (mean OCV=0.0164±0.0044, median OCV=0.0181, IQR=0.0056)). The mean differences are 18.8%, 19.6%, and 18.8% at 3 months post-injury, 6 months post-injury and 12 months post-injury, respectively. At 12 months post-injury, there is a tendency for the normalized OCV to increase compared to 3 months post-injury due to brain atrophy [25].

The estimated β value for each variable signifies how it influences the dependent variable. As shown in Table 2, OCV had a significantly negative β value (β = -0.139 and p=0.031), demonstrating that PSI tends to decrease as the size of OCV increases. The multiple linear regression model itself was significant to predict PSI at 12 months post-injury using OCV at 3 months post-injury (p=0.024).

As shown in Supplementary Table 1, there were no significant differences in visual area volumes (pericalcarine, cuneus, and lingual gyri) between HC and TBI at 3, 6 or 12 MPI (p>0.3). The GLM analysis revealed no significant associations between visual area volumes at 3 MPI and PSI at 12 MPI (p>0.3, Supplementary Table 2), suggesting that OCV is a more sensitivity indicator of PSI compared to the volume of the visual cortex.

Discussion

This study demonstrated a significant increase in OCV 3 months after moderate to severe patients with TBI compared to healthy controls, and this increase remained over the course of 1 year. The multiple linear regression model showed a significant association between the increased OCV in patients with TBI and a decrease in PSI. Additionally, the model, incorporating OCV at 3 months post-injury as a predictor, demonstrated statistical significance in predicting PSI at 12 months post-injury. To the best of our knowledge, this is the first study to investigate the longitudinal OCV and its relationship with PSI.

Increase in OCV after moderate to severe TBI

The finding of increased OCV in post-moderate to severe patients with TBI carries important clinical implications. Based on the previous literature, we propose several possible mechanisms for the cause of increased OCV in post-moderate to severe patients with TBI. The first mechanism involves inflammation-induced swelling. TBI triggers a cascade of secondary injuries that often manifest over hours, days, or even months following the initial trauma [9, 34] At the molecular level, TBI upregulates inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1),

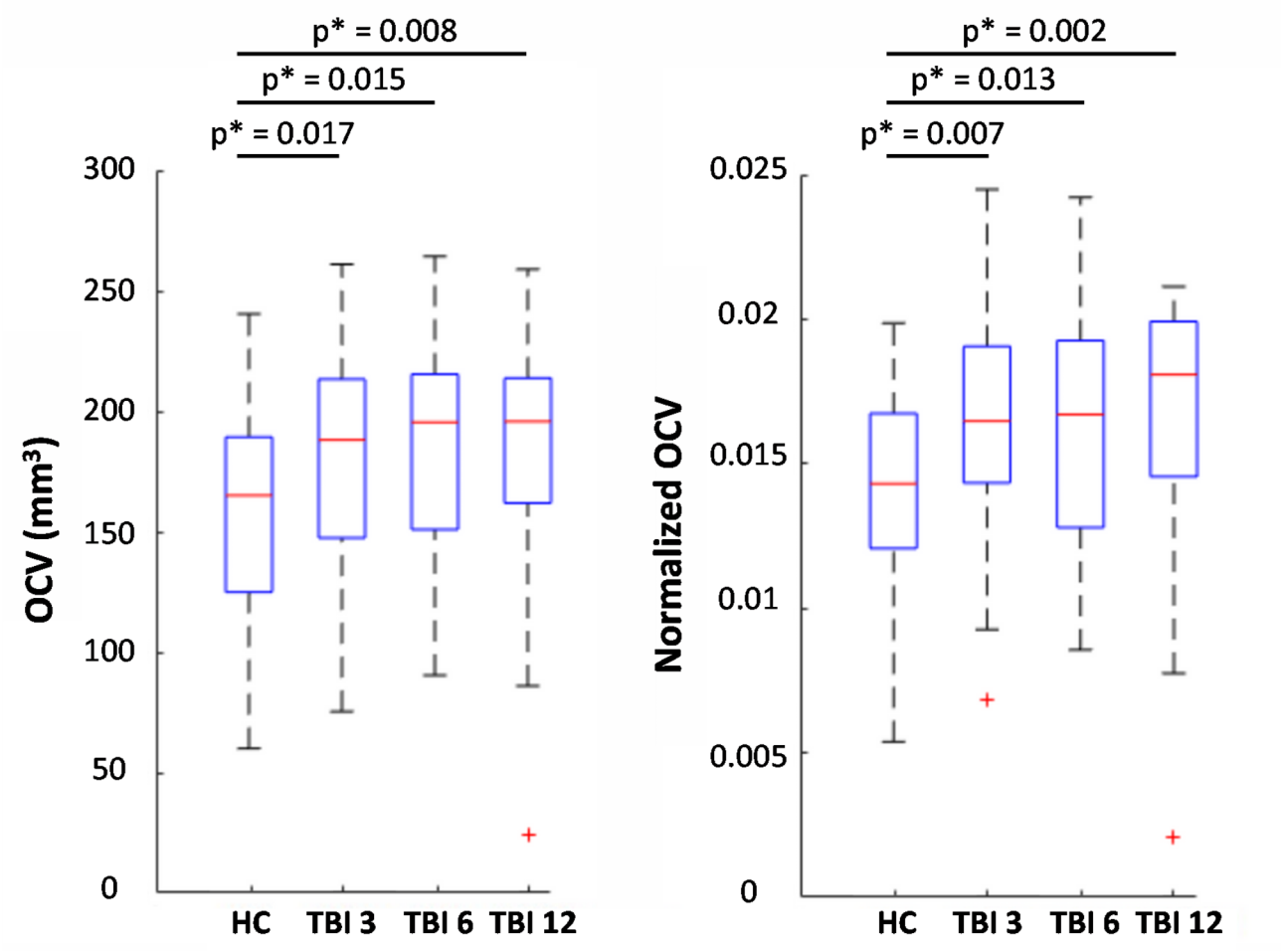

Fig. 2 The results of statistical tests for the differences in OCV (left) and normalized OCV by the whole brain volume (right) between healthy controls and patients with TBI at 3, 6 and 12 months post-injury. Red lines in boxes: medians of groups. Rectangular boxes: interquartile range from the first quartile (Q1) to the third quartile (Q3). Dotted lines: whiskers. Red crosses: outliers. OCV: optic chiasm volume, TBI: traumatic brain injury

Table 2 The estimated β and *p* values of the multiple linear regression model to predict PSI at 12 months post-injury using OCV at 3 months post-injury

	OCV	Age	Gender	Intercept
Estimated β	-0.139	-0.153	6.641	71.838
P-value	0.031*	0.419	0.199	< 0.001*
Confidence interval (95%)	(-0.262, -0.017)	(-0.515, 0.208)	(-3.316, 16.599)	(51.254, 92.422)
Effect size	-2.257	-0.820	1.312	-

The multiple linear regression model was constructed to assess the association between OCV and PSI and to predict PSI at 12 months post-injury. Age and gender were used as covariates in the model. * indicates significance at a level less than 0.05. OCV: optic chiasm volume, PSI: processing speed index

and interleukin-6 (IL-6), leading to brain parenchymal swelling and edema. In this process, OCV may increase as a secondary effect. The second mechanism involves changes in neurons and glial cells due to post-traumatic neurodegeneration. The result, that elevated OCV persists even after 3 months of injury (i.e., 6 and 12 months), is not just due to swelling but also to parenchymal changes in the glial cells. Post-traumatic neuroplasticity could result in adaptive or compensatory alterations in the optic chiasm and its associated neural structures. Growth factors such as brain-derived neurotrophic factor and nerve growth factor can trigger cell proliferation by improving neuronal survival and neural plasticity [35]. These signal substances cause hypertrophy and hyperplasia of astrocytes and microglia. Consequently, this process can trigger reactive gliosis, characterized by glial cell proliferation [36]. These changes may result in the increase in the volume of the affected area, including the optic chiasm, or may represent an attempt to restore visual and related cognitive functions in the sub-chronic stage.

Negative association between PSI and OCV

The optic chiasm plays a pivotal role in the transmission of visual signals for visual processing. Structural changes in the optic chiasm directly affect the speed of transmission and processing of visual information, which in turn

can impact tasks that rely on fast visual processing [37]. The significant negative association between OCV and PSI demonstrated in this study suggests that increased OCV at 3 months post-injury has a broad impact on the brain regions responsible for cognitive processing speed as a part of the post-TBI process. Cognitive processing speed impairment is related to a consequence of diffuse axonal injury in TBI [38]. This suggests that changes in OCV may serve as an indirect outcome of diffusion axonal injury and a complementary information of its severity.

Multiple linear prediction model and its clinical implications

This study constructed a linear regression model to predict PSI at 12 months post-injury using OCV at 3 months post-injury and demonstrated the significance of the model. It potentially holds several important clinical implications. Clinicians could utilize the prediction model to stratify the cognitive processing speed impairment of patients with TBI and develop customized management strategies for each individual. Based on OCV, it is possible to proactively anticipate the extent of potential cognitive deficits, especially those related to processing speed. Early cognitive and visual rehabilitation interventions could be initiated in a timely manner. Furthermore, clinicians could integrate MRI evaluations of OCV as part of the early diagnostic and monitoring process for patients with moderate to severe TBI. Periodic evaluations of OCV at 3 months, 6 months, and 12 months post-injury could aid in assessing the recovery of neurological status. Finally, in a multidisciplinary care setting, alterations in OCV could serve as a quantitative measure to track neurological health of TBI patients.

Limitations

This study has several limitations. While OCV was measured through precise processes, extracting OCV remains challenging due to the structure's location. It would be advantageous to conduct further research with a larger sample size to strengthen the findings of this study. In this study, a multiple linear regression model was employed to examine the significant association between OCV at 3 months post-injury and PSI at 12 months post-injury. Linear regression is the most commonly used statistical methodology for medical studies, especially for analyzing relationships between variables [39]. Introducing advanced artificial intelligence models is also a potential direction for predictive modeling. This study did not perform paired t-tests between 3, 6, and 12 months post-injury as not all the same patients underwent MRI scans at these time points which is a challenge in longitudinal studies. However, when compared to healthy controls, significant differences were observed at all three time points, indicating that the increase in OCV persists over time. This study investigated the increase in OCV using MRI. To support the findings of this study, more comprehensive research on biological mechanisms, including inflammation, gliosis, and cellular or molecular alterations, is warranted. It would provide insight into a deeper understanding of changes in OCV related to functional outcomes and recovery trajectories.

The mean age of this study was 35.0±10.2 years, indicating a relatively young study population. For further studies, investigating the relationship between OCV changes and age and gender with a larger sample size is warranted after dividing subjects into younger and older age groups, as well as male and female categories. While our study provides evidence for a significant association between OCV and PSI, further research is needed to distinguish whether this relationship is a direct relationship or if OCV changes are a secondary indicator of broader brain injury severity. Finally, PSI derived from the Wechsler Adult Intelligence Scale IV is a general measure of cognitive processing speed. Future studies could consider more direct measures of visual processing, such as reaction time to visual stimuli, visual search tasks, motion perception tests, or standard visual acuity tests. These measures would provide additional information on how changes in OCV affect visual processing abilities following TBI.

Conclusion

For the first time, the study demonstrated that OCV increases after moderate to severe TBI compared to healthy controls, and this increase persists for one year. The increase in OCV was significantly associated with a decrease in PSI. The linear prediction model generated in this study could potentially facilitate the use of OCV as complementary information. We believe that this pilot study supports that OCV could serve as a potential biomarker for predicting the extent of visual cognitive deficits in patients with post-TBI, allowing for timely interventions by clinicians.

Abbreviations

GCS	Glasgow Coma Scale
OCV	Optic chiasm volume
PTA	Post traumatic amnesia
PSI	Processing speed index
TBI	Traumatic brain injury
T1w MPRAGE	T1 weighted magnetization prepared rapid gradient echo
TR	Repetition time
TE	Echo time
TI	Inversion time
IQR	Interquartile range

Supplementary Information

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Supplementary Material 1

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Author contributions
HK analyzed data, interpreted the results and drafted the manuscript. WJ and CK suggested the original study idea, interpreted the results, contributed to writing. JYC analyzed data and contributed to data interpretation and manuscript editing.

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Data availability
This secondary analysis study utilized a de-identified data set previously acquired as part of a longitudinal neuroimaging project supported by the National Institutes of Health (NIH R01NS065980; PI: Junghoon J. Kim, PhD, CUNY School of Medicine, New York, NY, USA).

Declarations

Ethics approval and consent to participate
This study was approved by the Yonsei University Mirae Institutional Review Board (Approval No. 1041849-202310-SB-202-01) for the secondary data analysis of an existing de-identified data set.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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