Longitudinal changes in brain morphology 12 months after mild traumatic brain injury: associations with cognitive functions and clinical variables

Authors: T. Hellstrom[a,b], L.T. Westlye[c,d], S. Sigurdardottir[e,f], C. Brunborg[g], H. L. Soberg[a], Ø. Holthe[a], A. Server[h], M. J. Lund[c], O. A. Andreasse [b,c], N. Andelic[a,f]

Affiliations:

[a]Department of Physical Medicine and Rehabilitation, Oslo University Hospital, Oslo, Norway

[b]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

[c]KG Jebsen Centre for Psychosis Research / Norwegian Centre for Mental Disorder Research (NORMENT), Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway& Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[d]Department of Psychology, University of Oslo, Oslo, Norway

[e] Sunnaas Rehabilitation Hospital, Dept. of Research, Nesoddtangen, Norway

[f] Institute of Health and Society, CHARM Resarch Centre for Habilitation and Rehabilitation Models & Services, Faculty of Medicine, University of Oslo, Oslo, Norway

[g] Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Oslo, Norway[h] Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway

ABSTRACT

Objective: To investigate longitudinal changes in cortical and subcortical volumes in patients with mild traumatic brain injury (MTBI) and to evaluate whether such changes were associated with self-reported post-concussive symptoms, global functional outcomes and neuropsychological functioning.

Methods: This was a prospective, longitudinal cohort study of patients with complicated (i.e., presence of intracranial abnormalities on the day-of-injury CT) and uncomplicated MTBI (i.e., absence of intracranial abnormalities). MRI was performed at approximately 4 weeks and 12 months after injury. We utilized a 3T MRI-system (Signa HDxt, GE Medical Systems, Milwaukee, WI, USA), cortical reconstruction and volumetric segmentation by FreeSurfer software. We included 33 patients with uncomplicated and 29 with complicated MTBI, aged 16-65 years.

Results: 12 months after MTBI, significant within-group volume reductions were detected in the left accumbens area and right caudate nucleus for both patients groups, but no significant differences between groups were revealed. No associations between volumetric variables and post-concussive symptoms or global functioning were found. The left temporal thickness was significantly associated with executive functioning.

Conclusion: Structural subcortical alterations occur after complicated and uncomplicated MTBIs but these findings were not associated with symptoms burden or functional outcomes. Nonetheless, worse executive functioning was found in patients with shrinkage of the left temporal lobe.

Keywords: Mild brain injury; Longitudinal; Radiology; Neuroimaging; Intracranial injury; Cortical thickness.

INTRODUCTION

A considerable number of patients with mild traumatic brain injury (MTBI) experience cognitive, psychological and somatic symptoms during the acute phase after injury [1, 2]. These symptoms may be present in both patients with minor trauma-related intracranial changes or depressed skull fractures (complicated MTBI) and patients who lack evidence of intracranial injury (uncomplicated MTBI) according to computer tomography (CT) or magnetic resonance imaging (MRI) scans.

The majority of these patients generally fully recover within 3 to 6 months post-injury [3-6]. Yet, a subgroup of patients with MTBI present with persistent cognitive complaints [7]. Investigations including patients with mixed TBI severities have demonstrated brain atrophy in areas directly related to the injury [8-10]. For example, contusions to the brain tissue are most likely to occur in the frontal and temporal regions adjacent to the bony protuberances of the interior base of the skull [11]. Studies of patients with MTBI using diffusion tensor imaging (DTI) corroborate findings from patients with more severe injuries, demonstrating that frontal and temporal pathways are most vulnerable to traumatic damage [12-15].

Narayana reported no cross-sectional or longitudinal changes in global or regional volumes in a cohort of patients with MTBI [16] in a multi-model MRI study with scans performed at approximately 24 hours and 3 months post-injury. In a review of studies of MRI brain volumetry in patients with TBI, Ross found that the longitudinal design was more powerful than the cross-sectional approach [17] for understanding the progression of brain atrophy after injury. In this study, the amount of atrophy also correlated significantly with important clinical variables, such as loss of consciousness, duration of coma, and duration of post-traumatic amnesia, and the rate of atrophy was associated with worse long-term functional

outcomes after injury [17]. Most of these studies, however, were based on relatively small samples with variable post-injury scanning times, differences in diagnoses and staging severity of TBI, little-to-no information regarding the specificity of brain atrophy to TBI and differences in volumetric techniques that may affect volume measurements.

Recent advances in neuroimaging methodology have resulted in a number of sensitive techniques for in-vivo and non-invasive detection of subtle brain pathologies associated with MTBI [18-20]. Neuroimaging findings may serve a biomarker role for the investigation of cognitive outcomes [19]. Monitoring persistent symptoms combined with neuroimaging biomarkers may be the next line of research examining the effects of MTBI, including emotional outcomes and the occurrence of non-specific symptoms [13].

However, few MTBI studies have investigated atrophy [21-28] and even fewer have investigated the associations between amount of atrophy and post-concussive symptoms, functional outcome and neuropsychological functioning. A recent study demonstrated significant volume decreases one year after a single concussive episode in the bilateral anterior cingulate white matter, left cingulate gyrus isthmus white matter and right precuneal gray matter [25]. Volume loss in the left and right rostral anterior cingulum white matter correlated with changes in neurocognitive measures of memory and attention, and white matter volume loss in the left cingulate gyrus isthmus correlated with clinical scores of anxiety and post-concussive symptoms [25].

Building on previous research, we performed a prospective longitudinal cohort study. The initial MRI scans were obtained 4 weeks after injury, and the follow-up scans were obtained 12 months post-injury. Cortical reconstruction and volumetric segmentation were performed

to explore neuroanatomical characteristics. Patients were categorized as having uncomplicated or complicated MTBIs according to intracranial structural changes observed via conventional brain scans. We usually do clinical follow-ups on patients who exhibit visible intracranial injuries because this evaluation is considered necessary for the development and planning of appropriate rehabilitation strategies.

In the first aim of this study, we investigated longitudinal changes in global and regional brain volumetric and morphometric properties in patients with MTBI from 4 weeks to 12 months after injury. We hypothesized that there would be evidence of atrophy in patients with both complicated and uncomplicated MTBIs. We expected the volumetric change to be greater in the complicated group compared to the uncomplicated group. In the second aim, we evaluated whether the structural changes were associated with self-reported symptoms, global functional outcomes and neuropsychological functioning at 12 months post-injury. Based on earlier research [17, 24, 25], we expected that a larger amount of brain atrophy would be associated with higher levels of post-traumatic symptoms, global functional outcomes and executive functioning.

MATERIALS AND METHODS

Design

This was a prospective, longitudinal cohort study of patients with MTBI. MRI data were obtained at 4 weeks and 12 months post-injury. We assessed the potential associations of the initial MRI data with the follow-up data at 12 months.

Subjects

Patients with MTBI were admitted to the university-affiliated, trauma-referral center (Oslo University Hospital) between September 2011 and September 2013. MTBI was defined using the criteria from the American Congress of Rehabilitation Medicine [29]. The inclusion criteria were patients aged 16-65 years with injury occurring within the preceding 24 hours, hospitalization with ICD-10 (International Classification of Diseases) diagnosis S06.0-S06.9 and a Glasgow Coma Scale (GCS) score between 13 and 15, loss of consciousness (LOC) lasting less than 30 minutes and post-traumatic amnesia (PTA) of less than 24 hours. The lowest GCS score within the first 24 hours is reported.

Patients were excluded if they had previous ICD-10 diagnosis of substance dependence, psychiatric disease (e.g., major depression, psychotic or bipolar disorder diagnosed by a psychiatrist or psychologist), progressive neurological disease, contraindications for MRI (including pregnancy and claustrophobia) or lacked Norwegian language skills.

Of the 153 patients investigated via MRI at baseline and 12 months, 88 patients were scanned with different head coils at the two time points and were therefore excluded from this longitudinal analysis (see Figure 1 for a flowchart of the recruitment process). Of the final sample, 33 patients had uncomplicated MTBI, and 29 had complicated MTBI.

Insert Figure 1 here

Procedures

The study was approved by the Norwegian Regional Committee for Medical Research Ethics 2010/1899. All subjects provided written informed consent.

Demographic variables (age, gender, education, marital status, and pre-injury employment status) and injury-related characteristics (cause of injury, GCS, CT scan, PTA, LOC, associated injuries, and length of hospital stay (LOS)) were obtained from medical records and self-administered questionnaires. Baseline data included clinical information based on medical records and brain imaging (CT) in the acute phase. Both symptomatic and asymptomatic individuals were followed-up at 4 weeks (MRI), 8 weeks (clinical examinations and self-reported questionnaires) and 12 months (clinical evaluation, neuropsychological testing and MRI).

MRI data acquisition and image analysis

MRI scans were performed using a 3T whole-body MRI system (Signa HDxt, GE Medical Systems, Milwaukee, WI, USA). Eighty-eight patients were scanned using different head coils at baseline and 12 months (n=88, Head/Neck/Spine (HNS) coil at baseline and 8HRNBRAIN at 12 months). The use of multi-element coils makes the receiving (B1-) field inhomogeneous, which is dependent on coil element size and location and the number of elements in the coils. Different coils yield different B1-field maps, which can result in altered image quality. Thus, the best way to correct for the acquired images is by collecting coil sensitivity maps [30] for each individual patient. The method of choice is to include this calibration scan in the sequence itself, with an automatic correction for the field inhomogeneity before the images are produced. However, this method was not available when the study was performed. Because we were not able to acquire individual coil sensitivity maps in this study, we preferred to exclude the patients scanned with different head coils. The protocol included a 3D Fast Spoiled Gradient Echo (FSPGR) T1-weighted sequence used for morphometric assessments (repetition time msec/echo time msec/inversion time msec,

7,8/2.96/450; flip angle, 12°; and spatial resolution, 1×1×1.2 mm). Acquisition parameters were optimized for increased gray/white matter contrast. In addition, a T2-weighted sequence and a T2 Susceptibility-Weighted Angiography (SWAN) sequence were performed to depict hemorrhagic or other lesions. No major scanner upgrade occurred during the study period. All MRI data were evaluated for extra-axial hemorrhages and injuries to the brain parenchyma (e.g., cortical contusions or diffuse axonal injury) by a neuroradiologist (AS).

Cortical reconstruction and volumetric segmentation was performed with FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). This processing includes removal of non-brain tissue [31], automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures [32], intensity normalization, tessellation of the gray/white matter boundary, topology correction and surface deformation [33, 34] to produce representations of cortical thickness, which are calculated as the closest distance from the gray/white boundary to the gray/CSF (Cerebrospinal Fluid) boundary at each vertex on the surface. The maps are not restricted to the voxel resolution of the original data and are capable of detecting submillimeter differences between groups. For each dataset, the mean cortical thickness and volume were calculated within surface and volume-based regions of interest (ROIs) [35] and then submitted to statistical analyses.

Measures of post-injury functioning

Self-reported symptoms

The Rivermead Postconcussion Symptoms Questionnaire (RPQ) consists of 16 items, which represent the most frequently reported symptoms after MTBI. This instrument covers cognitive, emotional and physical domains and has been shown to be valid for diagnosing Post-Concussion Syndrome (PCS) [36]. The patients are asked to rate the degree for which

each item has become more of a problem during the previous 24 hours compared to before the TBI. The responses are then rated on a 5-point Likert scale as follows: 0 = not experienced at all; 1 = no more of a problem; 2 = a mild problem; 3 = a moderate problem; and 4 = a severe problem. The RPQ items are then summed to a total score, excluding ratings of 1 as recommended by King et al. [36].

Global functioning

The Glasgow Outcome Scale Extended (GOSE) is a global assessment of functioning tool for the areas of independence, work, social and leisure activities and participation in social life. The GOSE is rated on an 8-point ordinal scale [37], and the categories are divided into upper and lower levels of good recovery (7, 8), moderate disability (5,6), severe disability (3,4), vegetative state (2) and dead (1). GOSE ratings are based on a structured interview.

Malingering

The Rey Fifteen-Item Test (FIT) is a test used to assess symptom validity. Subjects are shown 15 items for 10 seconds and are then requested to draw what they recall. Anyone who is not significantly impaired should be able to recall at least 9 of the 15 items [38]. In this study, a lack of motivation or malingering was defined as a score of ≤ 9.

Executive functioning

Letter-Number Sequencing from the Wechsler Adult Intelligence Scale Third Edition (WAIS-III) [39], the Color Word Interference Test (CWIT) and the Letter Fluency Task (FAS) from the Delis-Kaplan Executive Function System [40] were used as measures of executive functioning.

We incorporated six z-scores to create an executive functioning composite score (Composite EF), which consisted of Letter-Number Sequencing (working memory), CWIT 3 minus CWIT 1 (inhibition), CWIT 4 minus CWIT 1 (switching), error scores on CWIT 3 (response inhibition), error scores on CWIT 4 (response inhibition), and Letter Fluency Task (productivity). All CWIT scores were reversed before the measures were summed and divided by six. Thus, low Composite EF scores were indicative of worse executive functioning.

Statistical analyses

Cortical and subcortical ROIs included the left and right frontal and temporal lobes, accumbens area, caudate nucleus, hippocampus, putamen, amygdala, corpus callosum, pallidum, left and right lateral ventricle, thalamus and brainstem. To test and adjust for global measures in the volumetric statistical analyses, we also included intracranial volume, total gray matter volume, or total cortical volume in the additional statistical models.

Statistical comparisons were performed using IBM SPSS statistics for Windows, version 22 (International Business Machines Statistical Package for the Social SciencesInc., Chicago, IL, USA). Sample characteristics are presented as means and standard deviations (SD), medians with 25^{th} and 75^{th} percentiles, interquartile range (IQR), 95% Confidence Interval (CI) or proportions. Differences in demographic and injury related data and in volumetric changes between patients with uncomplicated and complicated MTBI for continuous variables were tested using independent sample t-tests for normally distributed data. Mann – Whitney U tests were utilized for skewed data at baseline and follow-up. The chi-square test for contingency tables was performed to detect group differences in categorical variables. All brain volumetric and morphometric differences between the two follow-ups were normally distributed and tested with paired sample t-tests within the group.

Independent sample t-tests were conducted to test whether the mean change in any MRI measures from baseline to follow-up differed between patients with uncomplicated and complicated MTBI. To adjust for possible confounders, multiple linear regression analyses were performed to test for differences in the mean change in MRI measures between the two patient groups, while co-varying for age, sex, education, handedness, time between first and second MRI scan and, for the volumetric measures, total intracranial volume. Associations between regional volume measures (volume change between two visits) and symptoms (RPQ), global functioning (GOSE) and executive function (Composite EF) at the 12 months follow-up were further examined with a multiple linear regression model while retaining age and sex as covariates. The regression results are presented as β coefficients, standard error of β (SE(β)), p-values and explained variance (R^2). A two tailed p value <.01 was considered significant to adjust for the number of tests performed.

RESULTS

Comparison groups, demographics and injury related variables

Based on the presence of intracranial findings via CT or MRI scans at baseline, the patients (n=62) were classified as either uncomplicated (no CT/MRI findings, n=33) or complicated MTBI (positive CT/MRI findings, n=29). The CT scan upon admission was negative in 37 patients. Four of these patients (11%) displayed injury-related findings on MRI at approximately 4 weeks after injury (3 diffuse axonal injuries, 3 cerebral contusions and 1 subdural hemorrhage) and were thus reclassified as complicated MTBI.

Demographic and injury related data for the included patients are summarized in Table 1. The mean age was 39.9 years (SD12,8) in the uncomplicated group and 40.1 years (SD13.6) in

the complicated group. Briefly, there were no significant differences regarding the demographic or injury-related variables between the two groups, except the complicated TBI group had a significantly longer LOS (p=.001), (mean (SD): 1.70 (1.59)) for the uncomplicated group and (mean (SD): 3.86 (4.03))for the complicated group. The majority of the injuries occurred as traffic injuries (42%) following by falls (40%).

The majority of the patients had a GCS score of 15 (76%) and an isolated MTBI without any associated injuries (63%). The number of days between when the first and second MRI were performed was a median of 505 (IQR 126) days for the uncomplicated group and a median of 463 (IQR 243) days for the complicated group.

Insert Table 1 here

Self-reported and neuropsychological variables

Self-reported and neuropsychological variables are summarized in Table 2. Three patients were excluded from the analyses of the association with Composite EF due to malingering on neuropsychological testing. There were no significant differences regarding RPQ, GOSE or Composite EF between the uncomplicated and complicated MTBI group at 12 months post-injury.

Insert Table 2 here

Regional volumetry and morphometry

Tables 3 and 4 summarize the mean (SD) volume and thickness measurements per ROI at baseline and 12 months and the mean univariable within-group change and between-group change (95% Confidence Interval).

Insert Tables 3 and 4 here

Significant within-group reductions in the univariable analyses were detected between the 4 weeks and 12-months scans in the left accumbens area and right caudate for both the uncomplicated and complicated groups. In addition, in the uncomplicated MTBI group, significant volume reductions occurred in the total gray area, cortex, left caudate and left putamen. The uncomplicated MTBI group also exhibited a significant volume increase in the left pallidum. No significant within-group volume changes were detected over time in other investigated structures, including cortical thickness. Total brain volume did not decrease. There were no significant differences in volume change over time between the uncomplicated and complicated MTBI groups in the univariable analyses.

Tables 5 and 6 summarize the results from the multiple regression analyses for effects of group on neuroanatomical volumes and cortical thickness, respectively, while co-varying for age, gender, handedness, education, time between MRI at baseline and at 12 months and total intracranial volume. The multiple regressions revealed no significant differences between the mild uncomplicated and complicated groups in the assessed ROIs.

No associations between volumetric variables, symptom burden (RPQ) or global functioning (GOSE) were observed in the regression analysis adjusted for age and sex. There was a significant association between left temporal thickness and executive functioning (Composite EF; R^2=.179, β=.034, SE=.011, p≤.004) indicating lower executive functioning in patients with reduced left temporal thickness.

Insert Tables 5 and 6 here

Global measures

The multiple linear regression analyses revealed no significant differences between the two patient subgroups for total intracranial volume, left or right hemisphere thickness (adjusted for age, sex, education, time between MRI scans and handedness) or total cortical volume (adjusted for intracranial volume, age, sex, education, time between the two MRI scans and handedness).

DISCUSSION

Previous findings regarding alterations in subcortical volume and cortical thickness after MTBI are limited and inconsistent. In the present study, we used automated techniques to objectively measure longitudinal volume changes over a 12 months period in a well-defined cohort of patients with MTBI. The uncomplicated and complicated groups largely exhibited similar structural changes with regards to reductions or increases in subcortical volume or cortical thickness during the course of the first 12 months after injury.

Significant volume reduction from 4 weeks to 12 months was observed in the left accumbens area and right caudate nucleus in both groups. In addition, for the mild uncomplicated group, total cortical volume, total gray volume and the volume of the left putamen significantly decreased, while the volume of the left pallidum significantly increased. In contrast to our hypothesis, we did not reveal any significant differences between the mild uncomplicated and mild complicated groups in the univariate analysis or when accounting for confounding factors. Cortical volumetric decrease is a normal part of aging [41], but we observed more atrophy than would be expected as a result of aging in the univariate analyses in both groups. This result is in contrast to the study by Ling et al. [21] who did not find any evidence of

cortical atrophy in a group of MTBI patients between 14 days and 4 months post-injury. In a pilot study, Wang et al. [27] observed alterations in cortical thickness at an early stage after MTBI. Thus, the frontal cortical structures may change dynamically over the initial 3 months after injury.

In this study, the volume of the right caudate decreased significantly in both groups. This is in line with Zagorchev who observed reductions in subcortical structures, including the caudate nucleus [26]. Mounting evidence indicates that the caudate nucleus plays an important role in processing information and relays this information back to distinct cortical regions. The caudate nucleus has also been implicated in learning, memory, sleep and social behaviors, which are all reportedly affected by TBI.

The volume of the left pallidum increased in the uncomplicated MTBI group, which may reflect atrophy of the anatomically adjacent putamen. No significant changes were observed in cortical thickness. The univariate analysis does not account for covariates, and the cause of the observed changes may lie in factors other than the head injury. The functional relevance of these structural changes is unclear.

The relationship between the pathology revealed via MRI scans and clinical measures is still poorly understood. Previous studies on MTBI demonstrating brain atrophy or other pathology according to MRI observed no correlations with cognitive functions [42]. Other studies found a correlation with both cognitive function and clinical symptoms, including post-concussive symptoms [25]. In our study sample, we did not identify any obvious correlations between change in subcortical brain volume or cortical thickness and symptoms or global function measured with RPQ and GOSE, respectively. Atrophy in temporal thickness was associated

with worse executive functioning and agrees with previous findings demonstrating that executive dysfunction is correlated with alterations in frontal areas and temporal regions [43].

One mechanism that may contribute to the observed findings is normalization of initial brain edema after injury rather than brain atrophy over time. The time increments chosen for the early and late MRI scans were carefully considered and took into account the results of previous studies. Edema is normally resolved by the first time point, which was on average one month after injury. None of our patients underwent the initial MRI scan within a week of their injury. We also observed no significant differences in volume change between patients who were imaged within the first two weeks of injury and patients who were imaged later. The late time-point, at one year post-injury, would allow for atrophy to develop.

Findings of volume loss were observed bilaterally in the putamen and caudate nucleus; however, other areas, including the left accumbens area and left pallidum, showed unilateral volume loss. The patients had variable laterality in terms of the site of intracranial injury; therefore, this is most likely not related to the side of impact. Frontal regions are at risk for contusions after moderate and severe head trauma [44]. Our findings of atrophy in the accumbens suggest that such frontal regions may also be at risk for injury after mild head trauma.

According to a literature review, a longitudinal study design is more powerful than a cross-sectional design for understanding the progression of brain atrophy after injury and understanding its association with clinical variables [17]. Some longitudinal studies have described the development of atrophy after MTBI [23-28]. In contrast, two other studies observed no atrophy in patients diagnosed with MTBI [16, 21]. Most of these studies,

however, were based on relatively small sample sizes with variable post-injury scanning times, differences in methods for diagnosis and staging severity of MTBI, little-to-no information regarding the specificity of progressive brain atrophy to TBI and a variety of volumetric techniques. Thus, the interpretation of these data are difficult [17]. Our use of a prospective design may have provided a more sensitive (within-subject) test of atrophy relative to previous cross-sectional studies. We excluded patients with other brain disorders associated with brain atrophy and patients with neuropsychiatric disorders, including depression and post-traumatic stress disorder. We also excluded patients scanned with different head coils at baseline and 12 months. Although there appears to be no final verdict about the likely cause of the discrepant findings between studies, the differences may be due to the imaging methods that have been previously used for measuring volume and thickness from MR images. One possible strategy for better understanding these differences and identifying the causes of the divergent results is promoting data sharing and encouraging independent groups to work on the same datasets.

In our study, post-traumatic volume loss can be minute in both uncomplicated and complicated MTBI, and advanced methods were needed to detect them. We were also reminded of the inherent limitations of brain imaging methods for revealing underlying pathophysiology. In a recent review, Byrnes et al. have demonstrated sustained hypometabolismus using fluorodeoxyglucose- positron emission tomography (FDG PET) imaging in frontotemporal regions of the brain that may last for months after MTBI and correlation with both cellular and functional alterations post-TBI [45]. Combined genetic, biomarker and MRI studies are required to better establish the relationships between available imaging-derived measures and the underlying pathophysiology. Further, it is unknown whether the atrophy is due to direct effects of the TBI, common co-morbid conditions, such as

chronic pain, insomnia or psychosocial stress, or an interaction between TBI and co-morbid conditions. The time point at which the brain stops atrophying after TBI and whether there are different longitudinal changes for different brain structures also remain unknown. Further research will be needed to address these issues.

This study has several limitations that should be considered. One limitation was the potential selection bias towards studying relatively more symptomatic individuals at follow-up. Some of the eligible patients declined to participate, and some patients dropped out before structural MRI follow-up, possibly leading to a somewhat biased patient sample.

The use of a control group would possibly have ensured that the changes measured were greater than observed with normal development. Furthermore, our sample size was modest, and larger samples might reveal more group differences. Because we did not obtain volumetric measures before the brain injury, we cannot ascertain whether the volumetric differences between scan times 1 and 2 were attributable to the injury itself. There are factors other than trauma that can contribute to the observed changes. Nevertheless, our findings indicate that there are measurable brain volume changes 12 months after injury.

The population of patients with MTBI is by definition a heterogeneous population, as is reflected in the different injury mechanisms and various brain injury sites; however, we adhered strictly to the American Congress of Rehabilitation Medicine criteria. We also divided the patient groups into uncomplicated and complicated MTBI to make the groups as homogeneous as possible. This longitudinal study used two time points for quantitative MRI scans and only assessed atrophy that occurred between the subacute and chronic periods. To more fully understand the time course and regional distribution of post-traumatic atrophy, it

will be necessary to obtain additional serial MRI scans at shorter intervals including acute and over a longer study period. Thus, our results should be validated in larger patient and control samples with longer follow-up times.

In the present study, there were variations in the time between the injury and follow-up MRI scans. Although this interval was included as a covariate in the statistical analyses, this may have impacted the MRI findings. Finally, we did not collect data to assess pre-injury exposure to adverse life events (subjective chronic stress and cumulative life events) that may influence the volume in the orbitofrontal cortex, insula, and anterior and subgenual cingulate regions [46].

CONCLUSIONS

Subcortical volume changes in the current study suggest that structural subcortical alterations may occur after complicated as well as uncomplicated MTBI. The magnitude of brain changes did not differ between groups. We did not find these changes to be linked to functional outcome or symptoms in MTBI patients, but volume reduction in left temporal thickness was associated with lower executive functioning. Understanding the neuropathological underpinnings of brain alterations after TBI is critical for both diagnostic considerations and clinical decisions regarding return to normal activity levels and the development of novel treatment strategies. Additional studies with larger samples are needed to further investigate cortical and subcortical alterations and their contribution to symptomatology and functional outcomes after MTBI.

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Declaration of interest

The authors alone are responsible for the content and writing of this paper.

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