Journal of Alzheimer's Disease 72 (2019) 293–300
DOI 10.3233/JAD-190708
IOS Press

MRI Volumetric Quantification in Persons with a History of Traumatic Brain Injury and Cognitive Impairment

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Accepted 23 August 2019

Abstract.
Background: While traumatic brain injury (TBI) is recognized as a risk factor for dementia, there is lack of clinical tools to identify brain changes that may confer such vulnerability. Brain MRI volumetric quantification can sensitively identify brain atrophy.
Objective: To characterize regional brain volume loss in persons with TBI presenting with cognitive impairment.
Methods: IRB approved review of medical records in patients with cognitive decline focused on those who had documented TBI histories and brain MRI scans after TBI ($n = 40$, 67.7 ± 14.5 years) with volumetric quantification by applying an FDA cleared software program. TBI documentation included head trauma mechanism. Brain volumes were compared to a normative database to determine the extent of atrophy. Correlations between these regions and global tests of cognition (MMSE in $n = 17$, MoCA in $n = 27$, $n = 14$ in both) were performed.
Results: Multiple regions demonstrated volume loss in TBI, particularly ventral diencephalon, putamen, and pallidum with smaller magnitude of atrophy in temporal lobes and brainstem. Lobar structures showed strongest correlations between atrophy and lower scores on MMSE and MoCA. The hippocampus, while correlated to tests of cognitive function, was the least atrophic region as a function of TBI history.
Conclusion: Persons with TBI history exhibit show regional brain atrophy. Several of these areas, such as thalamus and temporal lobes, also correlate with cognitive function. Alzheimer's disease atrophy was less likely given relative sparing of the hippocampi. Volumetric quantification of brain MRI in TBI warrants further investigation to further determine its clinical potential in TBI and differentiating causes of cognitive impairment.

Keywords: Magnetic resonance imaging, traumatic brain injury, volumetric quantification

INTRODUCTION

Traumatic brain injury (TBI) affects about 2.5 million persons per year in the U.S., resulting in an estimated annual cost of 76.5 billion dollars [1]. TBI of all severities, including mild TBI, are

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related to increased cognitive impairment as well as a higher risk for dementia [2]. Additionally, TBI may potentially reduce the age of onset and expedite the emergence of Alzheimer's disease (AD) [3]. Repetitive, mild TBIs are also associated with chronic traumatic encephalopathy (CTE), a neurodegenerative disorder which is neuropathologically distinct from AD [4, 5].

Imaging of TBI is utilized mostly in the acute clinical care setting with non-contrast computerized tomography (CT) brain scans used to identify critical findings such as hemorrhage, hydrocephalus, herniation, and vascular injury [6]. Some patients with a remote history of TBI may have overt brain atrophy, ventricular enlargement, a cavum septum pellucidum, white matter changes, or other residual findings from TBI; however, many of these patients have visually interpreted "normal" neuroimaging [7]. Consequently, individuals with the late cognitive consequences of TBI may not have identifiable measures of brain changes on conventional imaging. Clinicians need an objective neuroimaging measure to assess whether remote TBIs are associated with cognitive complaints in later life.

Quantitative volumetric MR brain imaging, which has been utilized for AD and cognitive disorders [8, 9], may be a potential tool for assessing the chronic, delayed effects of TBI. Given that TBI is thought to increase risk for cognitive decline such as AD and CTE, our purpose was to apply readily available quantitative volumetric MRI, with normative data, to persons presenting for cognitive complaints and having a history of TBI sometime in the past. We hypothesized that these patients would have a distinct neuroimaging profile, different from age-related changes and distinct from the usual patterns seen in common dementias such AD.

METHODS

Participants

As part of an IRB approved study at UCLA (IRB# 16-001491), we retrospectively evaluated 40 MRI scans from patients who were referred for cognitive complaints and had a documented history of a traumatic brain injury by hospital records. All subjects received referral to and/or evaluation by either internal medicine, neurosurgery, geriatricians, subspecialty cognitive and behavioral neurologist (VRP or MFM), or a geriatric psychiatrist (DAM). We did not include persons with a TBI history who lacked corresponding documentation of trauma mechanism. As the data and mechanism of trauma were extracted by history, severity of classification for mild, moderate, and severe TBI were not invoked for this study.

As part of their medical evaluation, subjects were screened for history of known dementia or other disorders that would influence cognition including metastatic cancer to the brain, primary brain malignancy, or large territorial ischemic infarcts. We also used the medical records to identify history of vascular disease such as hypertension and type 2 diabetes mellitus. For all subjects, time of MRI scan from injury was extracted from their medical records and ranged from as recent as 1 month to years. We defined four categories of time of MRI scan from injury: 1) less than 6 months, 2) 6 months but less than 1 year, 3) 1 year or longer but less than 5 years, and 4) 5 years or longer. Cognitive evaluations at intake included either the Mini-Mental State Examination (MMSE) [10] ($n = 17$), the Montreal Cognitive Assessment (MoCA) [11] ($n = 27$), or both ($n = 14$). The 10 subjects who did not receive MMSE or MoCA received heterogeneous neuropsychological tests that included both commercial vendors (CNS Vital Signs, $n = 2$, and Web Neuro, $n = 1$), a conventional neuropsychological test battery at UCLA ($n = 5$) and mental status examinations that documented cognitive decline or impairment ($n = 2$). They were not included for analysis with the brain regions due to the heterogeneity of these methods. Subject demographics, including mechanism of TBI are detailed in Table 1 (average age in Men: 59.5 ± 16.5; Women 68 ± 11.9; $p = 0.05$).

MRI methods

Each subject had an MRI of the brain including a 3D volumetric MPRAGE sequence on a 3.0 Tesla Siemens Scanner. All subjects were then analyzed with an FDA cleared volumetric program (Neuroreader) as detailed in prior work [10]. For each scan, 45 brain structures were quantified including the hippocampus, lobar structures, subcortical regions (thalamus, caudate, putamen, etc.), ventral diencephalon, midbrain, ventricular, and white matter volumes with an atlas-based segmentation. Total gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes were also computed. Total intracranial volume (TIV) was calculated by summing GM, WM, and CSF volumes, and separate computations were done correcting individual brain structural volumes for this total head size metric. For

Table 1
Subject information

Variable ($n = 40$)	Mean $\pm \sigma$ or Percentage
Age	67.7 ± 14.5 (Range: 25–85 y)
Gender	Women (57%), Men (43%)
Mechanism of TBI	Fall (48%), MVC (30%), Contact Sports (10%), Direct Blow (7%), Blast Injury (5%)
Time from Injury	Less than 6 months (10%), 6 months to less than 1 year (17.5%), 1 year or longer but less than 5 years (35%), 5 or more years (37.5%)
Vascular disease(HTN, T2DM, CAD)*	70%
MMSE	24.1 ± 5.9 (Median: 27, Range: 12–30)
MoCA	21.5 ± 5.9 (Median: 23, Range: 6–29)

TBI, traumatic brain injury, HTN, hypertension; T2DM, type 2 diabetes mellitus; CA, coronary artery disease; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MVC, motor vehicle collision.

each brain region, the following metrics were calculated: 1) region of interest volume in ml; 2) the ratio of a region of interest volume to TIV; 3) the number of standard deviations from the normative database (NR index); 4) the number for standard deviations from the mean scaled between –2 and +2 (Z-score); and 5) percentile of comparison to the normative database. The normative database was drawn from control subjects from the Alzheimer's Disease Neuroimaging Initiative ($n = 231$) with an age range of 60–90 and 53% women, 47% men. All normative database comparisons for computing Z-scores and percentiles were adjusted for age, gender, and TIV in a multiple regression model. A typical example of a Neuroreader segmented brain is noted in Fig. 1.

A full list of structures obtained is detailed in Fig. 2.

Data analysis

All statistical analyses were conducted using SPSS (Version 25, IBM, Armonk NY). For the purposes of this evaluation, regions of two or more unscaled standard deviations below the control mean (NR index of ≥ -2) were considered abnormal. These standard deviations were averaged across all subjects. Because these averages consisted of single subject comparisons to the normative database, multiple comparison corrections were not invoked for this analysis. Interaction terms were calculated between TBI and vascular disease status and TBI and age to determine if the volume loss in relation to TBI varied as a function of age or vascular disease in multiple regression models. Separate correlations between TBI mechanism and abnormally low volume regions were also applied. Additionally, correlations were modeled between MoCA and MMSE scores and computed volumes as a proportion of TIV. Finally, we correlated time from injury to brain volumes, adjusting for age, gender, mechanism of injury, and vascular disease.

RESULTS

Table 2 displays a ranked table of the average negative NR indices. Other metrics, including the percentile, are also included. Regions with positive NR regions are not included in the table but included the parietal and occipital lobes as well as cerebellum.

Figure 3 highlights the disparity between the most severe regional volume loss in the ventral diencephalon in contrast with the relatively preserved volume in the hippocampus. The black bars show the lower ventral diencephalon NR indices compared to the hippocampus. The gray bars show the highlight the lower percentile compared to normative database in the ventral diencephalon compared to the higher percentile in the hippocampus.

There were no statistically significant interactions between TBI status and vascular disease. There were statistically significant interactions between age and TBI related atrophy such as the level of volume loss increased in older persons for total gray matter volume ($t = –3.7$, $p = 001$), ventral diencephalon ($t = –7.2$, $p < 0.001$), and putamen ($t = –5.7$, $p < 0.001$). There was a statistically significant interaction between gender and TBI status in total gray matter ($t = –2.1$, $p = 0.04$), ventral diencephalon ($t = –2.1$, $p = 0.04$), putamen ($t = –2.9$, $p = 0.006$), and left thalamus ($t = –3.1$, $p = 0.003$). These findings suggest that in these regions the findings vary as a function of gender with men with TBI having a higher degree of volume loss than women with TBI. It was noted that women experienced TBI more often than men in falls and motor vehicle collisions ($\chi = 9.56$, $p = 0.05$), but men accounted for all of the blast injuries and direct blows. There were no statistically significant differences between brain volumes and mechanism of TBI nor was there an interaction effect.

Table 3 shows statistically significant correlations between the MMSE and MoCA scores and Neuroreader quantified regions. We did not correct for TIV as it reduced the variance. Overall, the average

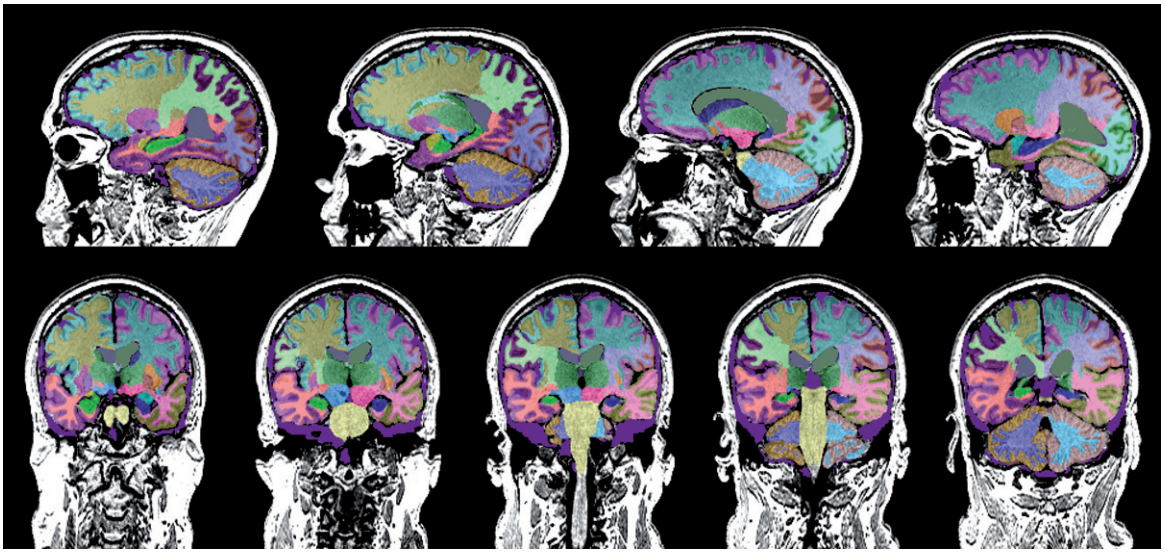

Fig. 1. Sagittal and coronal MRI images segmented by Neuroreader for one of the subjects in this study are displayed. Different colors correspond to different regions on different sides of the brain.

Whole Brain Matter	Ventral Diencephalon	Left Parietal Lobe
Gray Matter	Right Ventral Diencephalon	Occipital Lobe
White Matter	Left Ventral Diencephalon	Right Occipital Lobe
Hippocampus	Pallidum	Left Occipital Lobe
Right Hippocampus	Right Pallidum	Temporal Lobe
Left Hippocampus	Left Pallidum	Right Temporal Lobe
Amygdala	Caudate	Left Temporal Lobe
Right Amygdala	Right Caudate	Cerebellum
Left Amygdala	Left Caudate	Right Cerebellum
Putamen	Brain Stem	Left Cerebellum
Right Putamen	Frontal Lobe	CSF (+ dura)
Left Putamen	Right Frontal Lobe	Lateral Ventricle
Thalamus	Left Frontal Lobe	Right Lateral Ventricle
Right Thalamus	Parietal Lobe	Left Lateral Ventricle
Left Thalamus	Right Parietal Lobe	measured Total Intracranial Volume (mTIV)

Fig. 2. List of structures volumetrically measured by Neuroreader.

MMSE and MoCA scores met diagnostic criteria for cognitive impairment (average MMSE = 24.1 ± 5.9, average MoCA = 21.5 ± 5.9). The MMSE and MoCA scores were highly correlated ($r = –0.79$, $p < 0.001$). There were no statistically significant correlations between trauma mechanism and MMSE or MoCA scores nor was there an interaction effect. There were no statistically significantly correlations between time from injury and brain volumes.

DISCUSSION

TBI may be related to brain atrophy and subsequent cognitive decline [14]. Affected regions shown in prior studies include total gray matter volume [15], putamen [16], and ventral diencephalon [13, 17]. Prior work has suggested that the presence of TBI can accelerate age-related volume loss [18]. Other investigators have found a gender-based interaction

Table 2
Abnormally low regional brain volumes in TBI group

Structure	NR Index	Volume (mL)	Volume/TIV (%)	Z-score	Percentile
Total Gray Matter	–12.9	492.3	26.7	–0.9	27.6
Ventral Diencephalon	–4.6	9.8	0.5	–0.3	38.4
Right Ventral Diencephalon	–4.7	4.9	0.2	–0.3	37.9
Left Ventral Diencephalon	–4.2	4.9	0.2	–0.3	39.2
Putamen	–4.3	8.3	0.4	–0.3	39.2
Right Putamen	–3.8	4.1	0.2	–0.3	40.5
Left Putamen	–4.6	4.2	0.2	–0.3	38.6
Pallidum	–3.7	3	0.1	–0.2	40.5
Left Thalamus	–2.6	8.9	0.5	–0.1	43.3
Temporal Lobes	–1.7	253.9	11.1	–0.1	45.9
Right Caudate	–1.4	3.6	0.2	–0.1	46
Brainstem	–0.7	19.5	1.1	0.8	48
Frontal Lobe	–0.7	493	20.2	0.1	48.8
Amygdala	–0.5	3.93	0.2	–0.03	49
Hippocampus	–0.4	9.6	0.4	–0.02	49.2

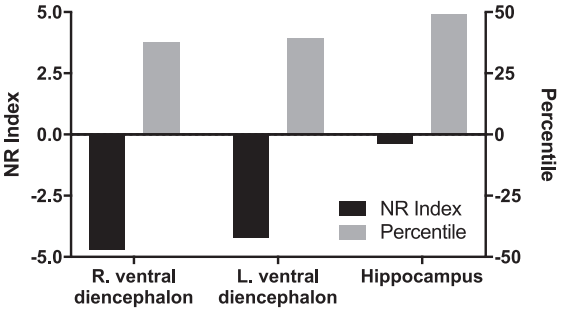

Fig. 3. Neuroreader (NR) index and percentiles of notable regions. See Table 2 for full list of regions.

with brain volumes after TBI with greater decreases in women as compared to men [19]. In this finding, our results differ as we found higher atrophy in men than in women despite the greater number and older age of the women. While women have been shown to have worse outcomes after TBI than men [20], it has also been suggested that men may have an intrinsically higher vulnerability to TBI than women [21]. In this study, we noted a trend toward statistical significance for women experiencing TBI from falls and motor vehicle collisions more often than men. By contrast, men accounted for all of the blast injuries and direct blows. These differences in mechanism of TBI may thus explain why men experienced more volume loss. Critically, the lack of interaction between vascular disease and TBI volume loss suggests that the influence of TBI on brain volumes does not vary as a function of co-morbid vascular disease.

We also found statistically significant correlations between MMSE and MoCA scores and Neuroreader-computed brain regional volumes important for cognition including the frontal, temporal, and parietal lobes and weaker correlations in the hippocampus. Previous studies have suggested that brain volumes can correlate with tests of even global cognitive function [22, 23], but evidence of this in persons with TBI is lacking. Thus, our study adds to previously understood relationships in a patient group that experiences impaired cognition. The fact that the most abnormal regions were those not correlated with MMSE or MoCA, such as the ventral diencephalon, suggests that domain specific neuropsychological tests may be needed to detect abnormalities already apparent on quantified volumetric MR imaging. Thus, both quantified volumetric MRI and neuropsychological tests are best used in conjunction in evaluating TBI as both types of data are complementary.

The major implication of this study is the ability of volumetric quantification to detect brain atrophy following TBI among older patients who present with cognitive complaints [25, 26]. Additionally non-atrophy related findings of TBI such as microbleeds or significant white matter sheer injury are seen only 34% of the time on conventional MR sequences [27]. Furthermore, the fact that we did not find predominant hippocampal or temporal-parietal atrophy in this group compared to other regions suggests that TBI related brain damage is distinct, and that the mechanisms of TBI-related cognitive decline are potentially distinguishable from those for AD and other dementias. The abnormally low ventral diencephalon volumes, for example, do correspond to prior work suggesting that CTE neuropathology deposits in this area [17]. Thus, while volumetric quantification is not currently recommended in standard clinical practice guidelines for even mild TBI

Table 3
Correlations between MMSE, MoCA, and quantified regions

Structure	Correlation with MMSE p ($n = 17$)	Correlation with MoCA p ($n = 27$)
Whole Brain Matter	0.585, 0.014	0.459, 0.016
Grey Matter	0.266, 0.302	0.306, 0.121
White Matter	0.441, 0.077	0.237, 0.234
Hippocampus	0.481, 0.051	0.365, 0.061
Right Hippocampus	0.433, 0.083	0.351, 0.073
Left Hippocampus	0.495, 0.043	0.369, 0.058
Amygdala	0.515, 0.035	0.453, 0.018
Right Amygdala	0.424, 0.089	0.392, 0.043
Left Amygdala	0.559, 0.020	0.485, 0.010
Putamen	0.547, 0.023	0.341, 0.082
Right Putamen	0.559, 0.020	0.361, 0.064
Left Putamen	0.515, 0.034	0.307, 0.119
Thalamus	0.733, 0.001	0.614, 0.001
Right Thalamus	0.728, 0.001	0.624, 0.001
Left Thalamus	0.715, 0.001	0.584, 0.001
Ventral Diencephalon	0.603, 0.010	0.332, 0.090
Right Ventral Diencephalon	0.598, 0.011	0.359, 0.066
Left Ventral Diencephalon	0.592, 0.012	0.299, 0.129
Pallidum	0.413, 0.099	0.231, 0.245
Right Pallidum	0.401, 0.111	0.209, 0.296
Left Pallidum	0.415, 0.098	0.240, 0.229
Caudate	0.206, 0.428	0.038, 0.851
Right Caudate	0.277, 0.282	0.073, 0.717
Left Caudate	0.127, 0.628	0.002, 0.991
Brainstem	0.553, 0.021	0.185, 0.356
Frontal Lobe	0.518, 0.033	0.334, 0.089
Right Frontal Lobe	0.526, 0.030	0.358, 0.067
Left Frontal Lobe	0.506, 0.038	0.307, 0.119
Parietal Lobe	0.584, 0.014	0.512, 0.006
Right Parietal Lobe	0.583, 0.014	0.519, 0.006
Left Parietal Lobe	0.573, 0.016	0.496, 0.009
Occipital Lobe	0.364, 0.150	0.465, 0.014
Right Occipital Lobe	0.359, 0.157	0.506, 0.007
Left Occipital Lobe	0.357, 0.159	0.405, 0.036
Temporal Lobe	0.658, 0.004	0.547, 0.003
Right Temporal Lobe	0.653, 0.005	0.578, 0.002
Left Temporal Lobe	0.628, 0.007	0.489, 0.010
Cerebellum	0.483, 0.050	0.229, 0.250
Right Cerebellum	0.489, 0.046	0.213, 0.286
Left Cerebellum	0.470, 0.057	0.242, 0.224
Cerebrospinal fluid	–0.046, 0.861	–0.361, 0.064
Lateral Ventricle	–0.211, 0.416	–0.278, 0.161
Right Lateral Ventricle	–0.177, 0.496	–0.282, 0.154
Left Lateral Ventricle	–0.237, 0.360	–0.269, 0.175

[28], it does hold potential future applications for this population.

There are several potential limitations of this study. First, we do not establish causation between the low brain volumes and cognitive impairment or the mechanism of TBI of these patients. Second, the assessment of TBI was retrospective and, consequently, fraught with problems with the recall of specific details of TBIs, as is usual for this type of study. Third, our study is additionally limited in its generalization to the overall population by the relatively small sample size. Larger samples sizes for various mechanisms may demonstrate specific differences as suggested in prior work [29]. The lack of TBI severity grading is another limitation. It is possible that the study findings may only apply to moderate or severe TBI; however, atrophy can be seen even in mild TBI with one study showing increasing atrophy with loss of consciousness [30]. Additionally, post-traumatic impairment of memory function also predicts increased atrophy [31]. Different 3T magnets were also used in this study. While this could be a potential limitation, Neuroreader has produced reproducible high quality regional brain segmentation regardless of vendor or field strength [12, 32]. The younger ages in our cohort compared to the normal database raises the possibility that atrophy may have been underestimated. Another limitation of this study is the differing sensitivities of MMSE and MoCA, with one study showing greater sensitivity of MoCA compared to MMSE in detecting cognitive impairment in relation to TBI [24]. Finally, we do not evaluate distinct white matter tracts in this study and did not find abnormally low white matter volumes in the TBI group. However prior work has shown the importance of white matter analyses in capturing the cognitive deficits in TBI [33]. Thus, future studies should incorporate combined longitudinal volumetric and white matter diffusion MR imaging analyses for maximal sensitivity in detecting TBI related brain abnormalities.

This study demonstrates total reduction of gray matter volume in TBI compared to controls with focal areas showing greater areas of volume loss. This work may form the basis for future studies that not only utilize these regions for improved accuracy of TBI related brain damage but may also serve as biomarkers for treatment response for cognitive rehabilitation programs [34]. Future studies with clinical trials will be necessary for such additional validation.

ACKNOWLEDGMENTS

Supported by McLoughlin Cognitive Health Gift Fund. Dr. Raji is supported in his research by grants from the WUSTL NIH KL2 Grant (KL2 TR000450 – ICTS Multidisciplinary Clinical Research Career Development Program) and the Radiological Society of North America Research Scholar Grant and the Foundation of the American Society of Neuroradiology Boerger Research Fund for Alzheimer's Disease and Neurocognitive Disorders.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-0708r1).

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