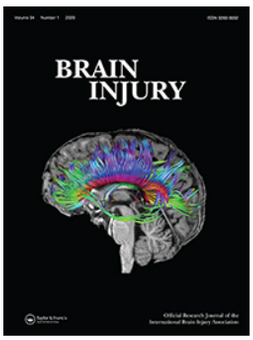

Brain Injury

ISSN: 0269-9052 (Print) 1362-301X (Online) Journal homepage: https://www.tandfonline.com/loi/ibij20

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To cite this article: David E. Ross, John D. Seabaugh, Jan M. Seabaugh, Claudia Alvarez, Laura Peyton Ellis, Christopher Powell, Christopher Hall, Christopher Reese, Leah Cooper & Alfred L. Ochs (2020) Patients with chronic mild or moderate traumatic brain injury have abnormal brain enlargement, Brain Injury, 34:1, 11-19, DOI: 10.1080/02699052.2019.1669074

To link to this article: https://doi.org/10.1080/02699052.2019.1669074

Published online: 25 Sep 2019.

BRAIN INJURY
2020, VOL. 34, NO. 1, 11–19
https://doi.org/10.1080/02699052.2019.1669074

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Patients with chronic mild or moderate traumatic brain injury have abnormal brain enlargement

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ABSTRACT

Introduction: Much less is known about brain volume abnormalities in patients with chronic mild or moderate traumatic brain injury (TBI) compared with patients with more severe injury. Commercially available software methods including NeuroQuant® are being used increasingly to assess MRI brain volume in patients with TBI.

Methods: 50 patients with mild or moderate TBI were compared to the NeuroQuant® normal control database (n = thousands) with respect to MRI brain volume.

Results: The patients had many areas of abnormal enlargement and fewer areas of atrophy, including abnormally small cerebral white matter (CWM) limited to the first 10 months after injury. Examination of correlations within the patient group between CWM volume and volumes of the abnormally enlarged regions showed multiple significant negative correlations, indicating that CWM atrophy correlated with enlargement of the other regions.

Discussion: The finding of many regions of abnormal brain enlargement was relatively new, although a couple of previous studies of patients with mild TBI found similar but more limited findings. The cause of the abnormal enlargement was unknown, but possibilities included: (1) hyperactivity and hypertrophy; or (2) chronic neuro-inflammation and edema.

Abbreviations: ADNI: Alzheimer's Disease Neuroimaging Initiative; CWM: cerebral white matter; GM: cerebral cortical gray matter; ICC: intraclass correlations coefficient; IFT: infratentorial; MRI: magnetic resonance imaging; mTBI: mild TBI; NQ: NeuroQuant®; SCN: subcortical nuclei; t0: time of injury; t1: time of first NeuroQuanted MRI scan after injury; t2: time of second NeuroQuanted MRI scan after injury; TBI: traumatic brain injury; VBR: ventricle-to-brain ratio; WBP: whole-brain parenchyma.

ARTICLE HISTORY
Received 14 April 2019
Revised 6 August 2019
Accepted 14 September 2019

KEYWORDS
Traumatic brain injury; magnetic resonance imaging; volumetry; asymmetry

Introduction

Decades of research have shown that traumatic brain injury (TBI) causes brain atrophy (1–3). However, most of this research was based on patients with moderate or severe TBI. Until recently, many investigators thought that brain volume was normal in patients with mild TBI, due in part to the normal appearance of MRI scans in those patients (4,5). However, when MRI brain volume is measured, patients with chronic mild or moderate TBI have been found to have volume abnormalities often (6–18) but not always (19).

Advancements in this area of research have resulted in clinically available software for helping clinicians understand the effects of injury on brain volume. Prominent among these is NeuroQuant®, FDA-cleared software for measuring MRI brain volume in human subjects (https://www.cortechslabs.com/products/neuroquant) (20,21). In recent years, the NeuroQuant® software was upgraded to version 2, which improved the identification of the brain regions and increased the number of regions analyzed and compared to normal control participants from three brain regions (NeuroQuant® 1.0) to approximately 60 (https://www.cortechslabs.com/neuroquant-2-0-update-available-now).

The aim of this study was to compare cross-sectional brain volumes between patients with mild or moderate TBI and normal controls.

Materials and methods

Patients

Selection criteria

The sample of patients was expanded from that studied previously (12). Patients included in this study were outpatients consecutively admitted to the Virginia Institute of Neuropsychiatry who met the following criteria: (1) diagnosed with traumatic brain injury according to the criteria of Menon et al. (22); (2) had a mild or moderate level of brain injury according to the criteria of Silver et al. (23); (3) agreed to be in the study and signed the informed consent form; (4) had no contraindications to obtaining an MRI, such as having magnetic metal in the head or being pregnant; (5) had an MRI without artifacts (e.g. motion artifacts)

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which would preclude accurate identification of brain structures by the NeuroQuant® software; (6) had no pre-injury history of brain disorder which could affect brain volume measurements; these included but were not limited to stroke, epilepsy, multiple sclerosis, inflammatory brain disorders, infectious brain disorders, active or prolonged substance use disorder, attention deficit hyperactivity disorder, autism, schizophrenia, bipolar disorder, Alzheimer's disease, other degenerative dementias, mental retardation, major depression which had not fully resolved before the index injury, obsessive compulsive disorder, obstructive sleep apnea, pre-injury posttraumatic stress disorder, and traumatic brain injury which had not fully resolved before the index injury; the majority of the patients included in the study had posttraumatic stress disorder due to the accident or injury, and mood disorders (e.g. depression, generalized anxiety or irritability) due to the accident or injury; (7) had no skull fractures which could interfere with measurement of intracranial volume; and (8) age 18 or older. This study was approved by the Sterling Institutional Review Board and satisfied the requirements of the Code of Ethics of the World Medical Association (Declaration of Helsinki) for human research.

Description of patient sample

Recruitment began in 2010. Two hundred and eighty-nine patients were screened by a physician board-certified in general psychiatry, neuropsychiatry and brain injury medicine (D.E.R.) with a thorough neuropsychiatric evaluation, including review of all available medical records, interview of the patient (and usually a family member or friend), mental status exam including some basic cognitive testing, and physical exam. Fifty patients (17.3% of those considered) were included in the study, and 239 (82.7%) were excluded based on the following reasons:

- 106 (36.7%) had pre-injury diagnoses which might have interfered with brain volume measurement.
- 60 (20.8%) did not have mild or moderate traumatic brain injury.
- For 25 (8.7%), it was not possible to obtain a NeuroQuantable MRI.
- 22 (7.6%) refused to participate in the research study.
- 26 (9.0%) were excluded for other reasons.

For the 50 patients who met the selection criteria, demographic characteristics were as follows: 26 men and 24 women; mean number of years of education was 14.3 (SD 3.0; range 10–21); mean age in years at the time of the injury was 46.7 (SD 12.5; range 16.9–80.2); mean age in years at the time of the MRI scan was 48.0 (SD 12.4; range 18.2–80.4); and mean interval between time of injury and time of MRI was 1.36 years (SD 1.14; range 0.11–5.68). 48.0% of the patients were referred by a physician or other clinician; 30.0% were referred by other sources (e.g. word of mouth); 16.0% were referred by an attorney; 6.0% were referred by our website. 80.0% of the patients were involved in litigation; 20.0% were not.

Causes of injury included motor vehicle accident (n = 41), train accident (n = 4), hit in head with object (n = 2) fell down steps (n = 1), mining accident (n = 1) and motor vehicle vs. pedestrian (n = 1).

Forty-five patients had mild TBI and five patients had moderate TBI. The mean GCS score was 14.7, median 15.0, range 11–15. The mean duration of loss of consciousness was 3.1 min, median 0, range 0–30 min. The median duration of posttraumatic amnesia was 0.17 h, range 0–264.00.

Regarding other neuropsychiatric symptoms due to the brain injury, in general, the sample of patients had a wide range of chronic symptoms including impaired cognition, impaired mood, impaired sleep and wakefulness, posttraumatic stress disorder and pain, which caused them to seek treatment at a TBI specialty outpatient clinic. The mean total score on the Kokmen Short Test of Mental Status (24) was 31.3 (SD = 3.6); 25.0% of the patients had abnormally low (≤30 (25)) total scores. The mean score on the Glasgow Outcome Scale-Extended version (GOS-E) (26) was 5.4 (SD = 0.6). The vast majority of patients had either GOS-E = 5 (consistent with Lower Moderate Disability [LMD]) or 6 (consistent with Upper Moderate Disability [UMD]). The main difference between patients with LMD and UMD was that most patients with LMD were unable to work, and most patients with UMD were able to work. 45.8% of the patients were able to return to work, and 54.2% of the patients were unable to return to work.

Brain imaging

Neuroquant® software was used for brain volume measurement

MRI brain volume was measured using NeuroQuant®, a computer-automated method. The US Food and Drug Administration (FDA) cleared NeuroQuant® for the routine clinical measurement of MRI brain volume in human subjects. This computer-automated analysis involved several steps, including stripping the brain of scalp, skull, and meninges; inflating the brain to a spherical shape; mapping the spherical brain to a common spherical space based on a dynamic atlas; identification of brain segments (that is, regions); and deflation of the patient's brain back to its original shape while retaining the identifying information for brain segments. NeuroQuant® has been reported to be reliable for measuring brain volume in normal subjects, patients with TBI, and other neuropsychiatric patients (8,27–33).

Magnetic resonance imaging

Each patient had a 3.0 Tesla MRI of the brain performed at one of various radiology centers using the scanning protocol recommended for allowing later NeuroQuant® analysis; this protocol is described in detail on the NeuroQuant® website (http://www.cortechs.net/products/neuroquant.php). In addition to the general requirements for having an MRI (e.g. having no magnetic metal in the head), the NeuroQuant® protocol required, at a minimum, the following:

- MRI scanner which supported the NeuroQuant® scanning protocol
- MRI scanning protocol based on the ADNI scanning protocol
- T1-weighted timing sequence

- Non-contrast
- Sagittal
- 3D
- Scan included nose, ears and vertex without wrap around artifact

Normal control participants from the NeuroQuant® normal control groups were scanned with either 1.5T or 3.0T scanners. NeuroQuant® is FDA-cleared to be used on 1.5T or 3.0T scanners, indicating good reliability between scanner strengths for the volume measurements (https://www.cortechslabs.com/resources/technical-information/recommended-scanner-settings).

Neuroquant® automated brain MRI segmentation

The brain MRI data for each patient or ADNI normal control were uploaded to the NeuroQuant® server, which processed and analyzed the brain imaging data. The output of the NeuroQuant® computer-automated analysis included one or more reports which contained volumetric information, and a set of DICOM-formatted brain images which were segmented, with each region identified by a distinctive color.

The NeuroQuant® segmented DICOM images were inspected for errors by one of the authors (D.E.R), in order to ensure accurate identification of brain regions by the software. If a region was identified inaccurately by the NeuroQuant®, it was omitted from the subsequent analyses. For the current study, 1.0% of brain regions were identified inaccurately and therefore the associated volumes were omitted from the analyses.

Neuroquant® brain volume analyses

All patients had NeuroQuant® 2.3 Triage Brain Atrophy analyses performed (https://www.cortechslabs.com/products/neuroquant/tba). For comparisons between the patients and the NeuroQuant® normal controls, the 44 regions from the Triage 2.3 analysis were used. These 44 regions included cortical gray matter, cerebral white matter, basal ganglia, infratentorial regions, and numerous cortical gray matter regions. These NeuroQuant® reports provided normative percentiles for each brain volume after adjusting the volumes for intracranial volume (by dividing by intracranial volume), matching for age (by comparing the volume to normal controls of the same age) and matching for sex (by comparing the volume to normal controls of the same sex). The volume data were averaged over left and right-sided counterpart brain regions.

Statistical analyses

Inspection of distributions of data

Distributions of data were inspected for outliers and distributional characteristics. All of the brain volume data were distributed at least approximately normally. Therefore, parametric statistics were used to compare groups with respect to brain volume.

Comparisons between groups

For comparing brain volumes between the patient group ($n = 50$) and the NeuroQuant® normal control group, Z tests were used, with the NeuroQuant® normal control group expected by design to have a mean of 0 and SD of 1 for each brain region volume.

Cohen's effect size d, defined as the difference in group means, divided by the pooled SD, were calculated and interpreted with reference to Cohen's scheme, where 0.2 is small, 0.5 is medium, and 0.8 is a large effect size difference between groups (34) pp. 25–26.

Statistical software

JMP Pro version 14.0.0 was used to perform all statistical analyses.

Results

Comparing brain volume between groups

The groups of patients and NeuroQuant® normal controls were compared with respect to MRI brain volume, and the results are shown in Table 1. The patients had many more regions of abnormal brain volume (28 out of 44) than would have been expected by chance alone (5% abnormally small +5% abnormally large = 10% abnormal; 10% x 44 regions = 4.4 regions). There were many more parenchymal regions that were abnormally large (24 regions) than abnormally small (four regions).

Graphs of volume versus time after injury

In order to explore the relationship between brain volume abnormalities and time after injury, we examined graphs of volume versus time after injury for several brain regions, including large brain regions (cerebral cortical gray matter and cerebral white matter) and regions that were found to have large effect size differences between patients and normal controls (cerebellar white matter and hippocampus) (Figures 1–4).

The graph of cortical gray matter volume (Z scores relative to NeuroQuant® normal controls) (Figure 1) showed that volume was quite large within the first 3 months after injury and was at a plateau at large volumes for 3 years or more.

The graph of cerebral white matter volume (Figure 2) showed that volume was quite small within the first 3 months after injury, was at a plateau at small values through the first 10 months after injury, then was larger and near normal volume by 3 years after injury. As an exploratory post hoc analysis, this observation was tested by comparing the cerebral white matter volume Z scores of the 20 patients with MRI data obtained closest to the time of injury (mean = 5.0 months after jury, $SD = 2.7$, range = 1.3–10.3) to the NeuroQuant® normal controls. The patients had significantly decreased volume of cerebral white matter (for patients, mean = −0.43, $SD = 0.77$; for normal controls, mean = 0.00, $SD = 1.00$; z = −1.94,$p = .05$) with a moderate effect size (Cohen's $d = -0.5$). As another exploratory post hoc analysis, correlations were examined between cerebral white matter volume and the 28 regions which had abnormal volume when compared to the NeuroQuant® normal controls; only correlations in the directions predicted by the results of the comparisons (e.g. smaller cerebral white matter correlating with larger cortical gray matter) were considered in order to reduce the risk of false-positive findings. Cerebral white matter volume correlated significantly with the volume of primary motor cortex ($R = -0.31$, $p = .03$), temporal lobe ($R = -.33$, $p = .02$), posterior superior temporal sulcus region ($R = -.38$, $p = .007$), and fusiform gyrus ($R = -0.43$, $p = .002$). The number of significant correlations (4) was greater than expected by chance alone (5% x 28 regions = 1.4).

Table 1. Comparisons of brain volume between patients and NQ normals.

Brain region	Mean	SD	Z-test statistic	df	Sig. (2-tailed)	Effect size d
Cerebral white matter	−0.22	0.92	−1.53	47	0.13	−0.23
Cortical gray matter	0.48	0.86	3.31	47	**0.001***	**0.51**
Ventricles	−0.01	1.00	−0.10	49	0.92	−0.01
Subcortical structures						
Cerebellar white matter	1.10	1.08	7.80	49	**<.0001***	**1.06**
Cerebellar gray matter	0.02	1.08	0.12	49	0.91	0.02
Brainstem	0.25	0.96	1.76	49	0.08	0.25
Thalamus	0.95	1.09	6.72	49	**<.0001***	**0.91**
Ventral diencephalon	0.30	0.88	2.13	49	**0.03***	**0.32**
Basal ganglia						
Putamen	0.06	0.92	0.39	48	0.70	0.06
Caudate	0.31	1.02	2.19	49	**0.03***	**0.31**
Nucleus accumbens	0.09	1.13	0.66	49	0.51	0.09
Pallidum	−0.51	0.74	−3.64	49	**0.0003***	**−0.59**
Cingulate	0.642	1.26	4.45	47	**<.0001***	**0.57**
Anterior cingulate	0.385	1.46	2.67	47	**0.01***	**0.31**
Posterior cingulate	0.746	0.97	5.17	47	**<.0001***	**0.76**
Isthumus cingulate	0.147	1.21	1.02	47	0.31	0.13
Frontal lobes	0.07	0.87	0.48	46	0.63	0.08
Superior frontal	−0.13	0.85	−0.87	46	0.38	−0.14
Middle frontal	0.528	0.87	3.62	46	**0.0003***	**0.57**
Inferior frontal	−0.14	0.81	−0.95	46	0.34	−0.15
Lateral orbitofrontal	−0.32	1.09	−2.19	47	**0.03***	**−0.30**
Medial orbitofrontal	−0.83	0.91	−5.73	47	**<.0001***	**−0.87**
Paracentral	0.441	1.00	3.02	46	**0.003***	**0.44**
Primary motor region	0.58	0.95	4.01	47	**<.0001***	**0.59**
Parietal lobes	0.864	0.84	5.98	47	**<.0001***	**0.94**
Primary sensory region	0.43	0.81	2.98	47	**0.003***	**0.48**
Medial parietal	0.74	1.02	5.14	47	**<.0001***	**0.74**
Superior parietal	0.34	0.97	2.37	47	**0.02***	**0.35**
Inferior parietal	1.06	0.74	7.38	47	**<.0001***	**1.22**
Supramarginal	0.24	0.83	1.64	47	0.10	0.26
Occipital lobes	0.392	0.96	2.72	47	**0.01***	**0.40**
Medial occipital	0.66	0.95	4.55	47	**<.0001***	**0.67**
Lateral occipital	0.08	0.81	0.54	47	0.59	0.09
Temporal lobes	0.263	0.90	1.82	47	0.07	0.28
Transverse temporal + superior temporal	0.26	0.81	1.79	47	0.07	0.29
Posterior superior temporal sulcus	0.30	0.97	2.06	47	**0.04***	**0.30**
Middle temporal	−0.19	0.94	−1.34	47	0.18	−0.20
Inferior temporal	−0.40	0.86	−2.78	47	**0.005***	**−0.43**
Fusiform	0.85	0.91	5.88	47	**<.0001***	**0.89**
Parahippocampus	0.09	0.95	0.63	47	0.53	0.09
Entorhinal	0.404	1.16	2.77	46	**0.01***	**0.37**
Temporal pole	0.07	0.97	0.46	47	0.64	0.07
Amygdala	0.97	0.95	6.83	49	**<.0001***	**0.99**
Hippocampus	1.00	0.89	6.93	47	**<.0001***	**1.06**

Table 1: Comparisons of brain volumes (Z scores) between patients and NeuroQuant® normal controls showed that the patients had many areas of abnormal volume. There were more parenchymal regions that were abnormally large than abnormally small. *Asterisks and **bold font** indicate regions associated with *P* value < .05.

Cerebellar white matter volume (Figure 3) was quite large within the first 9 months after injury, with some very large *Z* scores (often >2), then was smaller with *Z* scores around 0.5 more than 3 years after injury.

The hippocampus was quite large within the first 3 months after injury, then was smaller until reaching *Z* scores around 0.5 more than 3 years after injury (Figure 4).

Discussion

Abnormal brain volume

To our knowledge, this study was the first to find extensively increased brain volume in patients with chronic mild or moderate TBI. Total cortical gray matter and many cortical gray matter subregions were abnormally large. Also there was abnormal enlargement of multiple subcortical regions – including cerebellar white matter, thalamus, ventral diencephalon, amygdala and hippocampus–clarifying our previous find of enlarged subcortical nuclei + infratentorial regions (SCN+IFT) (12,16). In general, there were many more regions of abnormal enlargement than regions of abnormal diminution. Nevertheless, there were several abnormally small regions, including the pallidum, lateral and medial orbitofrontal gyri, and inferior temporal gyrus.

Furthermore, it seemed likely that abnormally small cerebral white matter was present in a subset of our sample of patients based on the following considerations. When compared to the NeuroQuant® normal controls, the patients had mildly decreased cerebral white matter volume (effect size $d = -0.23$) which was not statistically signicant ($p = .13$). When the subset of 20 patients within the first 10.3 months of injury was compared to the NeuroQuant® normal controls, the patients had significantly decreased volume of cerebral white matter ($p = .05$) with a moderate effect size ($d = -0.5$). Furthermore, smaller cerebral white matter volume correlated significantly and in the expected directions with several cortical gyral regions that were abnormally enlarged (primary motor cortex, temporal lobe, posterior superior temporal sulcus region, and fusiform gyrus). Finally, atrophy of cerebral white matter often has been reported in TBI (1,2) and cross-sectional atrophy of cingulate gyrus white matter has been reported in mild TBI (9).

Although there have been many reports of brain atrophy in patients with moderate to severe TBI (for review, see (1–3)), the pattern of volume abnormalities in mild to moderate TBI is less clear. Table 2 shows a brief review of 13 previous studies that were similar to the current study, that is, which involved adult patients with mild or moderate TBI, measured brain volume or cortical thickness, and involved mechanisms of injury such as motor vehicle accidents and falls, not military or sports injuries. In addition to reviewing studies that used cross-sectional volume measures, like the current study, studies with longitudinal volume measures also were included in the review and could be compared to the apparent changes in volume during the first year after injury described above and in Figures 1–5.

Two of the previous studies were published by the current authors (8,12,16). Compared to these previous studies, our current study was based on overlapping but significantly larger numbers of patients. Our first previous study found longitudinal atrophy of whole brain parenchyma, forebrain parenchyma, cerebral white matter, and cerebellum (8). But since the average time after injury was more than 2 years, these findings could not be readily compared to the volume abnormalities seen in the current study which appeared to have abnormal volumes within the first year or so after injury.

Our second previous study estimated volume at time 0 (t0), defined as the moment before injury, and compared it to volume measured at time 1 (t1), defined as the time of the first NeuroQuanted MRI after injury (12,16). The following findings from that study are relevant to the current study: (1) From t0-t1, whole brain parenchyma and cerebral white matter atrophied, and subcortical nuclei + infratentorial regions (SCN+IFT) enlarged. (2) Longitudinal enlargement of subcortical nuclei + infratentorial regions correlated significantly

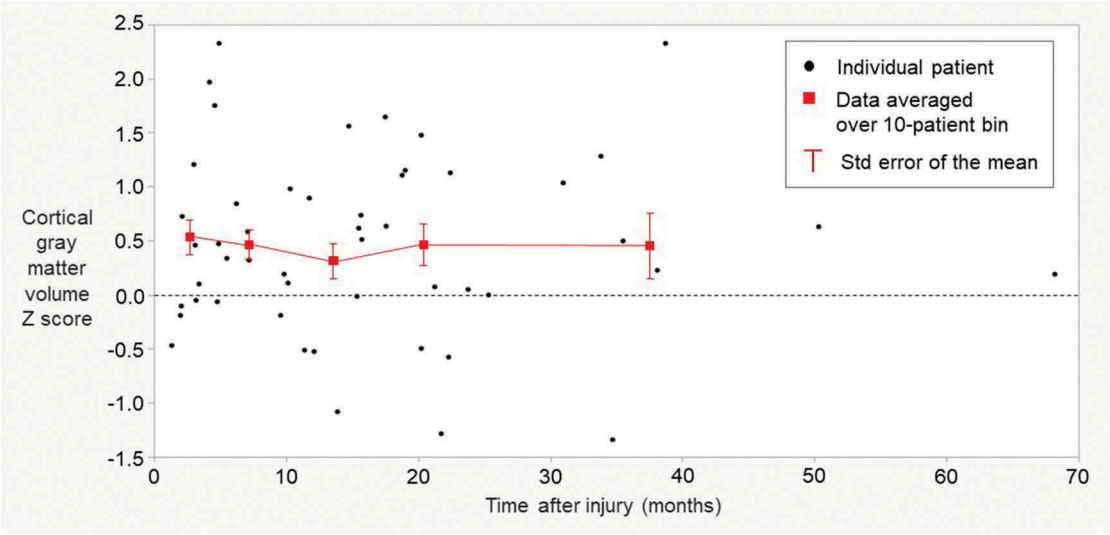

Figure 1. The graph of cerebral cortical gray matter volume (*Z* scores relative to NeuroQuant® normal controls) versus time after injury. The graph showed that volume was quite large within the first 3 months after injury and then was at a plateau at large volumes for 3 years or more.

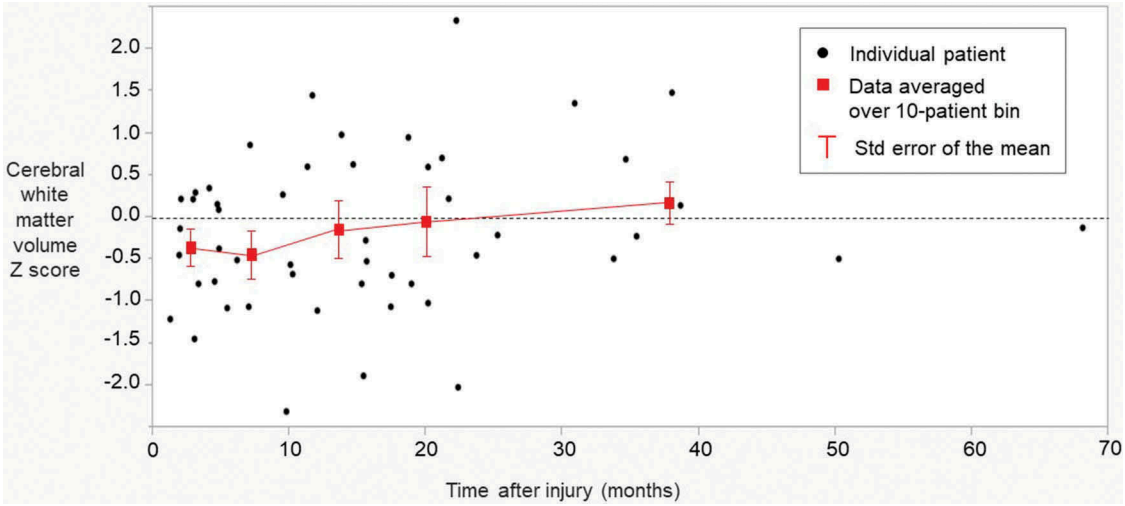

Figure 2. The graph of cerebral white matter volume (*Z* scores relative to NeuroQuant® normal controls) versus time after injury showed that volume was quite small within the first 3 months after injury, was at a plateau with small volumes through the first 10 months after injury, then was at normal volumes by 3 years after injury.

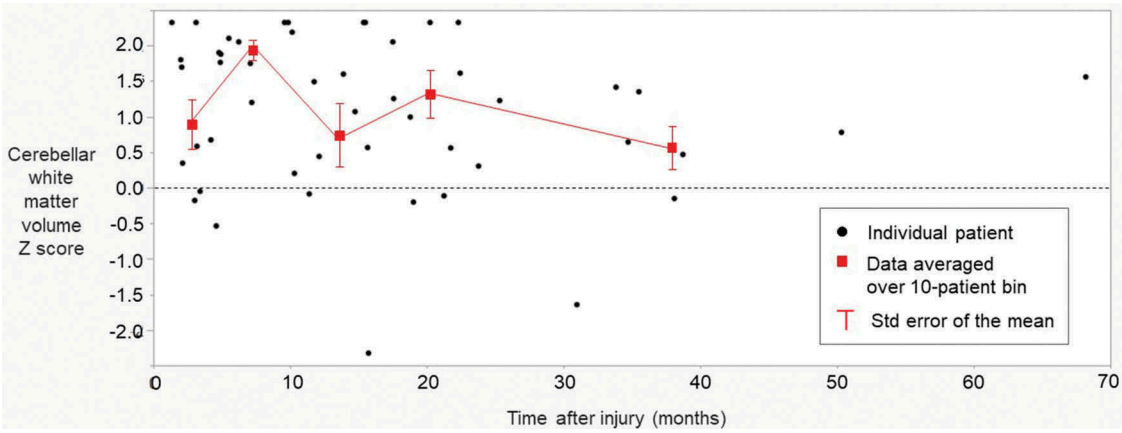

Figure 3. Cerebellar white matter volume was at large values within the first 9 months after injury, reaching very large *Z* scores (often >2), then was smaller with *Z* scores around 0.5 more than 3 years after injury.

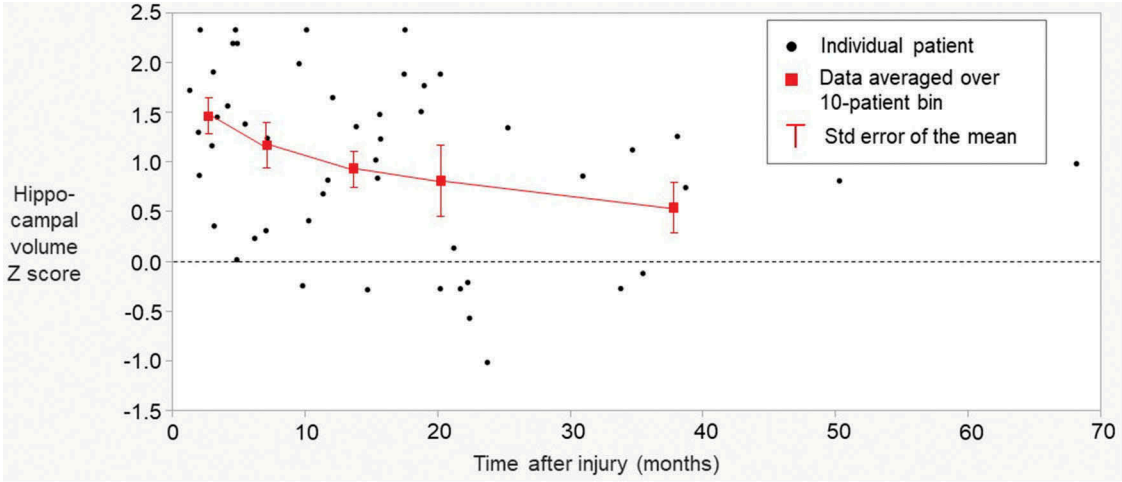

Figure 4. The hippocampus had large volumes within the first 3 months after injury, then had smaller volumes until reaching *Z* scores around 0.5 more than 3 years after injury.

with increased cerebellar volume at t1. And (3) t1 analyses found that whole brain parenchyma and cerebral white matter were abnormally small and that SCN+IFT was abnormally large. The previous finding of cerebral white matter atrophy was consistent with the current report of apparent cerebral white matter diminution within the first approximately 10 months after injury. The previous finding that enlargement of SCN+IFT correlated significantly with increased cerebellar volume was consistent with the current study's finding of abnormally large cross-sectional volume of cerebellar white matter which appeared to be quite large within the first several months after injury (Figure 3).

Regarding the other studies from our literature review, and regarding one of the main findings of this study–i.e. multiple abnormally large cortical gray matter regions–there have been two previous studies of patients with mild TBI that found abnormally thicker cerebral cortex (13,15). Theoretically, thicker cortex would correspond to increased volume of cortex.

Wang and colleagues found abnormal cortical thickening in the left rostral middle frontal (rMFG) and right precuneus gyri (13). Those findings were very similar to the current findings of abnormally large middle frontal gyrus and medial parietal cortex. However, Wang and colleagues also found thinner cortex in the left posterior middle temporal gyrus at 7.2 ± 3.1 days after injury; the current study did not find significantly abnormally small middle temporal gyrus although the effect was in the same direction as that of Wang and colleagues (effect size = −0.2).

Govindarajan and colleagues found cross-sectional abnormal cortical thickening in the cuneus (15), a finding which was very similar to our finding of abnormally large volume of the medial occipital region. They measured longitudinal change during the first 3 months after injury and found enlargement of the superior parietal cortex, a finding which was consistent with our finding of cross-sectional abnormally large volume of the superior parietal cortex. They also found longitudinal enlargement of the anterior cingulate cortex, a finding which was consistent with our finding of cross-sectional abnormally large volume of the anterior cingulate cortex. However, they found thinner middle temporal cortex (supporting the same finding by Wang and colleagues) and thinning of the supramarginal cortex (compared to no significant change of that structure in the current study). They also found longitudinal enlargement of the insula and middle temporal cortex.

However, other groups did not find abnormally large brain volume in patients with mild or moderate TBI. Of the remaining nine studies, most found atrophy, in some cases involving regions that were abnormally large in the current study.

Overall, these studies often found cortical gray matter and cerebral white matter atrophy, but a few studies (including the current one) found gray matter enlargement. The reasons for the different findings were unclear but may have been due to multiple differences in methods, including brain volumetry software, patient samples (including nature and severity of injury), cross-sectional versus longitudinal designs, and time after injury (for example, in the current study, some regions were quite large within the first few months, then were smaller after a year or more).

The volume findings of the current study can be summarized vis-à-vis the previous literature as follows. The current findings of abnormally large volume extended and partially replicated our earlier findings, which used a smaller subset of the current patient sample. The findings of increased cortical gray matter thickness in two other studies provided support for the findings of increased volume in the current study. In contrast, a greater number of studies found more atrophy than enlargement. However, the NeuroQuant® database used in the current study may have constituted a better normal control group than those of other studies because it was based on a much higher number of controls (thousands throughout the lifespan) and because it was the only one FDA-cleared for clinical use. Overall, it seemed likely that abnormally large volume of brain regions was a characteristic of at least some patients with chronic mild or moderate TBI.

Table 2. Literature review.

Study	Patients	Control partic-ipants	Methods	Significant cross-sectional findings	Significant longitudinal findings
Hofman 2001	21 patients with mTBI: 12 with MRI lesions visible on t1, and 9 with normal-appearing MRI	None	t1: around 4 days after injury. t1-t2 interval: around 6 months in duration. Semi-automated volumetry. tVBR = (t1_VBR/ t2_VBR)	Not applicable	Patients with abnormal-appearing MRIs had whole brain atrophy longitudinallly (based on decrease of tVBR).
MacKenzie 2002	t1: 14 patients with mild or moderate TBI. t2: Subgroup of 7 patients.	t1: 10 normal controls. t2: Subgroup of 4 normal controls.	t1: around 14 months after injury. t1-t2 interval: around 1 year in duration. Semi-automated volumetry.	None.	WBP atrophy and CSF enlargement.
Ross 2012	16 patients with mTBI	20 normal controls	t1 was around 2 years after injury. t1-t2 interval: around 1 year in duration.	Not applicable	Atrophy of WBP, forebrain parenchyma, CWM, and cerebellum.
Ling, 2013	t1: 50 patients with mTBI . t2: Subgroup of 26 patients.	t1: 50 normal controls. t2: Subgroup of 26 normal controls.	t1: around 14 days after injury. t2: around 4 months after injury. FreeSurfer was used to measure cortical thickness and volume.	None.	None.
Toth 2013	14 patients with mTBI	14 normal controls	t1: within 3 days and 1 month after injury. FreeSurfer was used for volumetry.	None.	Atrophy of gray matter and enlargement of ventricles and extracerebral CSF.
Zhou 2013	t1: 28 patients with mTBI . t2: subgroup of 19 patients	t1: 22 controls. t2: subgroup of 12 controls	t1: around 23 days after injury. t1-t2 interval: around 13 months in duration. FreeSurfer was used to measure volume.	At t2, atrophy of the anterior cingulate WM, the cingulate gyrus isthmus WM, and the precuneal GM.	Atrophy of the anterior cingulate WM, the cingulate gyrus isthmus WM, the precuneal GM, the inferior and medial orbital olfactory frontal regions.
Maller 2014	27 patients with mild or moderate TBI	23 normal controls	t1: varied from 6 weeks to 10 years after injury. FreeSurfer was used to measure cortical thickness and brain volume.	Atrophy of supramarginal, angular, lateral occipital, insular, pars triangularis and hippocampal regions.	Not applicable.
Ross 2014	26 patients with mild or moderate TBI	20 normal controls	t1: mean 1.7 years after injury. t2: mean 3.4 years after injury. Brain volume was estimated at time 0 (t0) = just before injury. NeuroQuant and NeuroGage were used to estimate (at t0) and measure (at t1 and t2) brain volume.	At t1, WBP and CWM were abnormally small, and SCN+IFT was abnormally large.	From t0-t1, WBP and CWM atrophied, and SCN+IFT enlarged. Enlargement of SCN +IFT from t0-t1 correlated with cross-sectional enlargement (at t1) of cerebellum and brainstem. For t1-t2, WBP and CWM atrophied.
Wang 2015	t1: 21 patients with mTBI . t2: Subgroup of 11 patients.	t1: 23 patients without TBI. t2: Subgroup of 12 patients without TBI .	t1: around 7 days after injury. t2: around 4 months after injury. FreeSurfer used to measure cortical thickness.	At t1, thicker cortex in the rostral middle frontal and precuneus gyri. Thinner cortex in the posterior middle temporal gyrus.	Rostral middle frontal gyrus cortical thickness decreased in the mTBI group but not in the non-TBI group
Epstein 2016	55 patients with mTBI	27 normal controls	t1: At least 1 year since injury. Mean years since injury = 8.9. FreeSurfer was used to measure cortical thickness and brain volume.	The cortical thinning of the right lateral OFC; however, after correction for multiple comparisons, this difference was no longer significant.	Not applicable.
Govindarajan 2016	33 patients with mTBI treated with atorvastatin. 38 patients with mTBI not-treated.	60 orthopedic controls.	t1: around 24 hours after injury. t2: around 3 months after injury. FreeSurfer was used to measure cortical thickness and brain volume.	At t1: Combined patient group had cortical thinning of middle temporal and supramarginal cortex. At t2: Combined patient group had cortical thinning of middle temporal cortex; non-treated patient group had cortical thickening of cuneus.	Combined patient group had cortical thinning of multiple cortical regions in the frontal, temporal and parietal lobes. Combined patient group had cortical thickening of insula, anterior cingulate and superior parietal regions. Non-treated patient group had thickening of middle temporal cortex.
Zagorchev 2016	44 patients with mTBI	29 normal controls	t1: around 2 months after injury. t2: around 15 months after injury. Computer-automated software was used for volumetry.	At t1 and t2, atrophy in caudate, putamen, thalamus, and amygdala.	Atrophy of the caudate, putamen, amygdala.
Rajesh 2017	12 patients with mTBI between 1–10 years after injury. 10 patients with mTBI between 20–65 years after injury.	12 normal controls matched to younger patient group. 10 normal controls matched to older patient group.	First group 1–10 years after injury. Second group 20–65 years after injury. FreeSurfer was used to measure cortical thickness and brain volume.	For younger patient group, thinner cortex in superior frontal and frontal pole regions; and smaller volume in middle frontal and frontal pole regions.	Not applicable.

Table 6: Review of previous studies of MRI brain volume in patients with chronic mild or moderate TBI. Only studies similar to the current study were reviewed. Some studies showed abnormal brain enlargement or cortical gray matter thickening, but more studies showed abnormal atrophy. Key: mTBI-mild TBI; VBR-ventricle-to-brain ratio.

Limitations

Limitations of the current study included that it was not a longitudinal study. Therefore, the graphs of brain volume versus time after injury did not show longitudinal change. Volumes were not measured before injury. Volume abnormalities could have been present before injury, although it seems unlikely given the careful screening of the patients. Future longitudinal studies will be needed to address this limitation.

As noted in the Methods section, normal control participants from the NeuroQuant normal control group were scanned with either 1.5T or 3.0T scanners. Each patient had a 3.0 Tesla MRI of the brain. It is possible that the different field strengths affected the results of our study. Nevertheless, NeuroQuant is FDA-cleared to be used on 1.5T or 3.0T scanners, indicating good reliability between scanner strengths for the volume measurements (https://www.cortechslabs.com/resources/technical-information/recommended-scanner-settings). Therefore, we think it is unlikely, although possible, that differences in field strength affected the results of this study.

Finally, the current study examined patients with mild or moderate TBI who had symptoms which persisted for months to years after the injury and sought treatment at a TBI specialty clinic. Therefore, these results may not apply to other patients with TBI, for example, patients with mild TBI who have complete resolution of symptoms within hours to days.

Conclusions

In contrast to previous studies which found brain atrophy in patients with TBI, the current study found more abnormal brain enlargement than brain atrophy. However, there was atrophy in some regions. The cause of the abnormal enlargement was unknown. Possibilities include: (1) hyperactivity and hypertrophy; and (2) chronic neuro-inflammation and edema. Further studies will be necessary to test these hypotheses.

Declaration of interest statement

Dr. Ross is CEO of NeuroGage LLC, a company which produces Neurogage® software, which is based on NeuroQuant® (however, Neurogage® was not used in the current study). In 2017, Dr. Ross was a paid consultant for CorTechs Labs, Inc., which produces NeuroQuant® software. None of the other authors had competing interests.

Contributors

David Ross designed the study, carried out much of the work, and wrote most of this paper.

John Seabaugh assisted with scheduling MRI scans and analysis of MRI brain volume data.

Jan Seabaugh assisted with clinicial evaluations of patients.

Claudia Alvarez, Laura Peyton Ellis, Christopher Powell, Christopher Hall, Christopher Reese and Leah Cooper assisted with organization and analysis of research data.

Alfred Ochs helped write this paper, including understanding the results and integrating them into the broader literature.

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