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ORIGINAL ARTICLE

## Progressive brain atrophy in patients with chronic neuropsychiatric symptoms after mild traumatic brain injury: A preliminary study

DAVID E. ROSS<sup>1,2</sup>, ALFRED L. OCHS<sup>1,2</sup>, JAN M. SEABAUGH<sup>1</sup>, MICHAEL F. DEMARK<sup>1</sup>, CAROLE R. SHRADER<sup>1</sup>, JENNIFER H. MARWITZ<sup>2</sup>, & MICHAEL D. HAVRANEK<sup>3</sup>, for the Alzheimer's Disease Neuroimaging Initiative

<sup>1</sup>Virginia Institute of Neuropsychiatry, Midlothian, VA, USA, <sup>2</sup>Virginia Commonwealth University, Richmond, VA, USA, and <sup>3</sup>Amicus Visual Solutions, Richmond, VA, USA

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### Abstract

**Introduction:** NeuroQuant<sup>®</sup> is a recently developed, FDA-approved software program for measuring brain MRI volume in clinical settings. The aims of this study were as follows: (1) to examine the test-retest reliability of NeuroQuant<sup>®</sup>; (2) to test the hypothesis that patients with mild traumatic brain injury (TBI) would have abnormally rapid progressive brain atrophy; and (3) to test the hypothesis that progressive brain atrophy in patients with mild TBI would be associated with vocational outcome.

**Methods:** Sixteen patients with mild TBI were compared to 20 normal controls. Vocational outcome was assessed with the Glasgow Outcome Scale-Extended (GOSE) and Disability Rating Scale (DRS).

**Results:** NeuroQuant<sup>®</sup> showed high test-re-test reliability. Patients had abnormally rapid progressive atrophy in several brain regions and the rate of atrophy was associated with inability to return to work.

**Conclusions:** NeuroQuant<sup>®</sup> is a reliable and valid method for assessing the anatomic effects of TBI. Progression of atrophy may continue for years after injury, even in patients with mild TBI.

**Keywords:** Traumatic brain injury, magnetic resonance imaging, volumetry, cortical atrophy, longitudinal study, medicolegal, vocational outcome, NeuroQuant<sup>®</sup>

### Introduction

Decades of research have shown that traumatic brain injury (TBI) causes brain atrophy [1, 2]. In recent years, with advances in technology, there has been a shift from qualitative descriptions to measurement of the volume abnormalities. Despite the advances in the research settings, magnetic resonance imaging (MRI) brain volumetry generally was not available in routine clinical practice.

This situation changed in 2007 with the introduction of NeuroQuant<sup>®</sup>, a computer-automated

method for measuring brain MRI volume (<http://www.cortechs.net/products/neuroquant.php>). The US Food and Drug Administration (FDA) approved NeuroQuant<sup>®</sup> for the routine clinical measurement of brain MRI volume in human subjects. In addition to the evidence supplied in the FDA application, several peer-reviewed studies have supported the reliability and validity of NeuroQuant<sup>®</sup> for measuring brain volume in patients with neuropsychiatric disorders and normal control subjects [3–7]. These included an examination of inter-method reliability

[5] and one previous peer-reviewed study in which NeuroQuant<sup>®</sup> detected hippocampal atrophy in a patient with mild TBI [3]. There have been no reports of NeuroQuant's test-re-test reliability in the scientific peer-reviewed literature. One of the goals of the current study was to address that limitation.

A recent review of the literature found that the longitudinal design (obtaining more than one scan) was more powerful than the cross-sectional design (obtaining only one scan) for detecting brain volumetric differences between normal controls and patients [8]. Most of the 10 studies included in the review performed follow-up MRI scans within less than a year after injury. The review found several studies in which progressive brain atrophy correlated with vocational outcome in TBI patients [9–11]. Of the 10 studies, only one was limited exclusively to patients with mild TBI [12]. That study included only mild TBI patients with lesions found on initial MRI scan and it did not include vocational measures.

Accordingly, in an effort to extend the knowledge in this field, other goals of the current study were to test the hypotheses that a group of mild TBI patients (not limited to those with lesions identified on initial MRI scan) would have greater progressive brain atrophy than normal controls, that the atrophy would persist for more than 1 year after injury and that the rate of atrophy would be associated with vocational outcome.

## Methods

### Subjects

**Patients.** Included in this study were outpatients consecutively admitted to the Virginia Institute of Neuropsychiatry who met the selection criteria. Selection criteria required that each patient (1) was diagnosed with traumatic brain injury by a board-certified neuropsychiatrist according to the criteria of Menon et al. [13]; (2) had a mild level of brain injury according to the criteria of Silver et al. [14] (including Glasgow Coma Scale score in the range of 13–15; duration of loss of consciousness <30 minutes; and duration of post-traumatic amnesia <1 day); (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 (such as motion artifacts) which would preclude accurate identification of brain structures by the NeuroQuant<sup>®</sup> software; and (6) had no history of stroke, pre-accident traumatic brain injury, substance abuse or other brain disorder which could affect brain volume measurements. This study was approved by the

New England Institutional Review Board and satisfied the requirements of the Code of Ethics of the World Medical Association (Declaration of Helsinki) for human research.

Sixteen patients met the selection criteria. Demographic characteristics were as follows: Six men and 10 women; mean age in years was 48.1 (SD = 10.9; range = 19.9–62.9); mean number of years of education was 13.4 (SD = 2.9; range = 8–18). The mean duration from date of injury to the first MRI was 2.0 years (SD = 1.4; range = 0.4–5.7). The mean duration between the first and second MRIs was 1.0 years (SD = 0.4; range = 0.4–2.6). Causes of injury included motor vehicle accident ( $n = 13$ ), motor vehicle vs pedestrian ( $n = 1$ ), train accident ( $n = 1$ ) and other (large water jug fell on head) ( $n = 1$ ).

For the sample of patients, the mean GCS score was 14.4, median was 15.0 and range was 11–15. Only two of the 16 patients (12.5% of the sample) had witnessed loss of consciousness and the duration for those were unavailable but probably less than 30 minutes each. The majority (93.8%) of the sample had post-traumatic amnesia; with duration mean = 11.9 hours, median = 1.5 hours and range = 2–48 hours. Two of the 16 patients had a focal neurological sign (quadrantopsia).

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, post-traumatic stress disorder and pain.

More specifically, all of the patients had cognitive impairment, with the most common types (other than those mentioned above) as follows: impaired concentration 93.8%, distractibility 81.3%, impaired short-term memory 93.8%, bradyphrenia 87.5% and executive dysfunction 56.3%. Most (93.8%) of the patients had mood disorder, with the most common types as follows: major depression 56.3%, generalized anxiety 43.8% and irritability 43.8%. Only 12.5% of the sample had psychotic symptoms, which in all cases were mild and did not require treatment with anti-psychotic medication.

All the patients had impaired sleep or wakefulness, with the most common types as follows: insomnia 87.5%, fatigue 87.5%, hypersomnolence 62.5% and restless legs syndrome 56.3%. Most (81.3%) of the patients had impaired sensory filtering, including photophobia (81.3%) and sonophobia (75.0%); 31.3% of the sample had motor impairment due to brain injury, with the most common types including impaired motor sequencing (18.8%) and bradykinesia (18.8%).

The majority (81.3%) of the sample had post-traumatic stress disorder and 81.3% had

post-traumatic visual syndrome; 56.3% of the sample had vertigo and 37.5% had tinnitus. All but one patient (93.8% of the sample) had headaches, with the most common types including neuropathic (68.8%), migraine (37.5%) and cervicogenic (31.3%). Most patients (87.5% of the sample) had pain in body areas other than the head.

*Normal control subjects.* The standard NeuroQuant<sup>®</sup> computer-automated analysis provides volume data on over 20 brain regions (<http://www.cortechs.net/products/neuroquant.php>) [4]. However, it provides comparisons to a normal control group for only three brain regions. In order to assess NeuroQuant<sup>®</sup>'s ability to detect atrophy in other brain regions, this study used a group of normal controls different from the NeuroQuant<sup>®</sup> normal controls. These normal control data were obtained from a larger group, previously studied as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI) [15–17]. The ADNI normal control data were obtained from an online database which had been made publicly available (<http://adni.loni.ucla.edu>).

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([adni.loni.ucla.edu](http://adni.loni.ucla.edu)). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California-San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations and subjects have been recruited from over 50 sites across the US and Canada.

For the NeuroQuant<sup>®</sup> extended analyses reported herein, a sub-group of 20 normal control subjects (10 men, 10 women) were chosen from the ADNI database. The mean age was 68.3 years (SD = 3.6 years; range = 60.0–71.5) and the mean number of years of education was 16.0 (SD = 3.1; range = 9–20).

The groups of patients and ADNI normal controls did not differ significantly with respect to sex (Pearson Chi-Square = 0.56,  $df = 1$ ,  $p = 0.45$ ).

Distributions of age data were not normal for the patients (Shapiro-Wilk statistic = 0.88,  $df = 16$ ,  $p = 0.04$ ) or normal controls (Shapiro-Wilk statistic = 0.80,  $df = 20$ ,  $p = 0.001$ ). Therefore, in order to compare the two groups with respect to age, a non-parametric test (Mann-Whitney U-test) was chosen. The two groups differed significantly with respect to age ( $p < 0.001$ ), with ADNI normal controls older than the patient group. The two groups also differed significantly with respect to years of education (independent  $t$ -test,  $t = -2.49$ ,  $df = 34$ ,  $p = 0.02$ ), with the ADNI normal controls having more years of education than the patient group.

#### *Brain imaging*

*Magnetic resonance imaging.* Each patient had a 3.0 Tesla MRI of the brain performed at one of four local radiology centres using the scanning protocol recommended for allowing later NeuroQuant<sup>®</sup> analysis; this protocol is described in detail on the NeuroQuant<sup>®</sup> 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<sup>®</sup> protocol required, at a minimum, the following:

- Supported MRI scanner (GE, Siemens, or Phillips),
- MRI scanning protocol based on the ADNI scanning protocol,
- T1 timing sequence,
- Non-contrast,
- Sagittal,
- 3D, and
- Scan included nose, ears and vertex without wrap around.

*NeuroQuant<sup>®</sup> automated brain MRI segmentation.* The brain MRI data for each patient or ADNI normal control was uploaded to the NeuroQuant<sup>®</sup> server, which processed and analysed the brain imaging data. 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 shared with the Talairach atlas brain [18]; 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. The output of the NeuroQuant<sup>®</sup> computer-automated analysis included a report which



contained volumetric information and a set of DICOM-formatted brain images which were segmented, with each region identified by a distinctive colour.

The NeuroQuant<sup>®</sup> segmented DICOM images were inspected for errors, a step recommended by the makers of NeuroQuant<sup>®</sup> in order to ensure accurate identification of brain regions by the software. The segmentation results for each region were visually inspected by two of the authors. If a region was identified inaccurately by the NeuroQuant program, it was omitted from the subsequent analyses. Few errors were identified. For example, no errors were found for whole brain parenchyma or forebrain parenchyma.

For each brain region, the percentage volume difference was determined by subtracting the volume at scan 1 from the volume at scan 2, dividing the result by the volume at scan 1 and expressing the resulting proportion as a percentage. The annual rate of volume change was calculated by dividing the percentage volume difference by the duration between scans (measured in years).

#### *Vocational outcome*

Vocational outcome was measured by the Glasgow Outcome Scale-Extended version (GOSE) and Disability Rating Scale (DRS). Three-way consensus ratings for each GOSE and DRS scale were performed by a neuropsychiatrist, Master of psychology and Master of vocational rehabilitation.

The GOSE is an 8-point ordinal scale designed to measure a wide range of outcomes. Higher scores indicate better outcome. Categories include 'death', 'persistent vegetative state', 'severely disabled', 'moderately disabled' and 'good recovery', with the three higher level categories sub-divided into upper and lower levels (e.g. upper good recovery and lower good recovery) [19]. Scores are based on a structured interview that includes questions related to ability to follow commands, perform activities of daily living, work, travel and participate in leisure activities. Individuals are also asked about emotional disturbance and injury-related difficulties. Using the GOSE, of the 16 patients in the current study, eight were classified as Upper Moderate Disability (UMD) and eight were classified as Lower Moderate Disability (LMD). The key difference between these two groups was that the UMD patients, although impaired at work, were able to continue working, whereas the LMD patients were unable to work.

The DRS [20] is an 8-item functional rating scale with demonstrated reliability and validity [21, 22]. Each DRS item is rated by the clinician on a scale from 0 to 3, 4 or 5, designating impairment,

disability and handicap. Higher scores denote greater levels of disability [23]. The items most relevant to the current study included a rating of overall functioning (cognitive and physical levels of independence) and an estimate of employability (ability to work or attend school). The total score indicates whether disability is absent (0), mild (1–3), moderate (4–6) or severe (>6) [20]. The DRS is used to track individuals from coma to community, providing consistency of measurement over time [24]. For the patients in the current study, the mean DRS total score was 3.4 (SD = 1.2, range = 1–5).

#### *Statistical analyses*

SPSS version 20 was used to perform the statistical analyses.

*Evaluating test-retest reliability in normal controls.* Each normal control had repeat MRI testing ~1 year after the first MRI. Although this period was longer than ideal for examining test-re-test reliability (e.g. a 1-day period would have been better), it was potentially useful insofar as it would provide a lower boundary on the test-re-test reliability if performed under ideal conditions. If the test-re-test reliabilities were good, it would be safe to assume that they would be good or better under ideal conditions. Test-re-test reliabilities were calculated for each brain region using intra-class correlations coefficients. To interpret ICC values, the following guidelines were used:  $ICC < 0.4$  represented poor reliability,  $0.4 \leq ICC \leq 0.75$  represented fair-to-good reliability and  $ICC > 0.75$  represented excellent reliability [25].

*Comparisons between groups.* Independent samples *t*-tests were used to test for between-group differences (patients vs normal controls and patient GOSE sub-groups vs each other). For each comparison, Levene's test was used to test for equality of variances between groups. If variances differed significantly, then an unequal-variance *t*-test, which did not assume equality of variances, was used.

*Correlations with vocational outcome.* As noted above, for the patient sample, the DRS total scores ranged from 1 (better vocational outcome) to 5 (worse vocational outcome). Therefore, (non-parametric) Spearman's rho coefficients were used to test the hypotheses that rates of volume change correlated with vocational outcome, as assessed by DRS total scores.

**Results**

*Test-re-test reliability in normal controls*

The first objective of this study was to examine test-re-test reliability for measurement of brain volume. Test-re-test analyses showed excellent reliability for all brain regions except the ventral diencephalon, which showed fair-to-poor reliability (Table I). Figure 1 shows examples of NeuroQuant® segmented images from the MRI at time 1 and the MRI from time 2 for a normal control subject.

*Comparisons between patients and normal controls*

In order to test hypotheses about the relationship between brain volume change and TBI, whole brain parenchyma was chosen first, based on its common use and strong support in the literature [1, 2, 8]. Furthermore, several other regions were chosen, as follows: total cerebrospinal fluid (CSF), forebrain parenchyma, cortical grey matter, cerebral white matter, cerebellum and brainstem. These regions were chosen based on the strength of evidence from the previous literature (for example, total CSF volume increases when whole brain parenchymal volume decreases) [1, 2, 8] and the virtual dissection of the whole brain parenchyma into its major

Table I. Test-re-test reliability for NeuroQuant® volumetric measures. Normal controls had MRI scans performed ~1 year apart. Analyses showed excellent reliability for all brain regions except the ventral diencephalon, which showed fair-to-poor reliability.

Region	Intra-class correlation coefficient		
	Left	Right	Total (=left + right)
Total intracranial volume			0.99
Brain parenchyma	0.99	0.99	1.00
Cerebrospinal fluid	1.00	1.00	1.00
Forebrain parenchyma	1.00	1.00	1.00
Cortical grey matter	0.99	0.98	0.98
Cerebral white matter	0.97	0.97	0.97
Lateral ventricle	1.00	1.00	1.00
Inferior lateral ventricle	1.00	0.97	1.00
Caudate	0.96	0.97	0.97
Putamen	0.94	0.87	0.95
Pallidum	0.78	0.76	0.85
Thalamus	0.94	0.91	0.95
Amygdala	0.93	0.95	0.95
Hippocampus	0.95	0.98	0.98
Cerebellum	0.98	0.97	0.98
Brainstem	0.98	0.96	0.98
Third ventricle	0.80	0.94	0.97
Fourth ventricle	0.98	0.98	0.98
Ventral diencephalon	0.48	0.38	0.42
Exterior cerebrospinal fluid	0.97	0.91	0.96

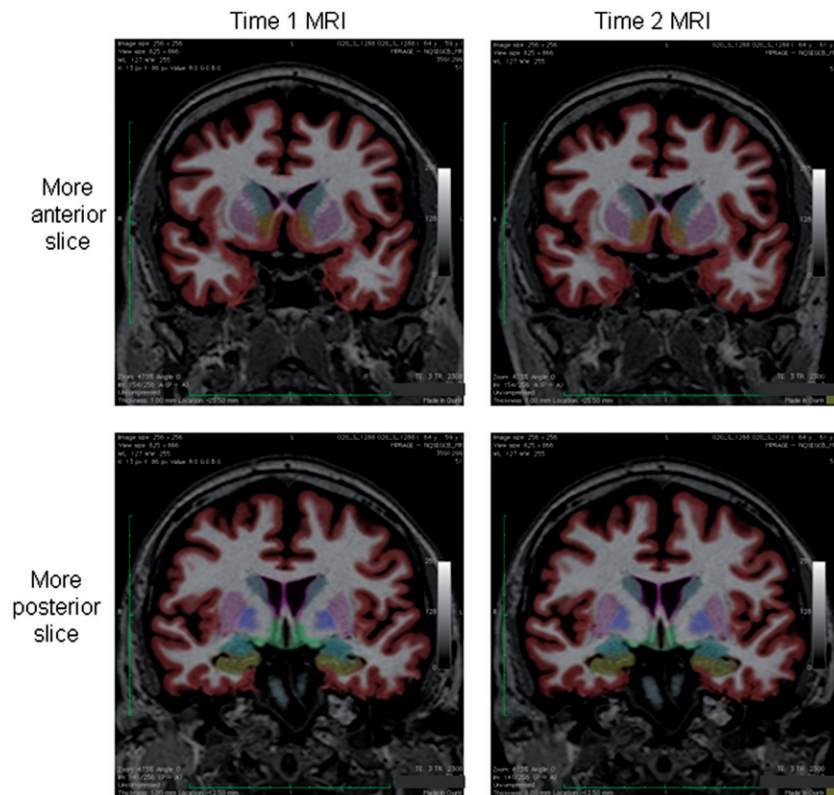


Figure 1. NeuroQuant® segmented images from a normal control subject were used by the automated software program to measure volume regions used for test-re-test reliability. Visual inspection of these two images, taken from MRI scans done 1-year apart, shows little variation over time.

Table II. Comparisons between patients with mild TBI and normal controls. The patients showed significantly greater progressive brain atrophy in several regions. Effect size  $d$  was calculated per Cohen [29].

Brain regions	Group	(% volume change/year)		Independent samples $t$ -tests			
		Mean	SD	$t$	df	Sig. (2-tailed)	Effect size $d$
Whole brain parenchyma	Patient	-3.36	3.92	-3.50	16.24	0.003*	1.5
	Normal	0.14	0.89				
Forebrain parenchyma	Patient	-3.34	3.97	-3.44	16.12	0.003*	1.4
	Normal	0.14	0.86				
Cortical grey matter	Patient	-2.28	6.62	-0.57	13.71	0.579	0.2
	Normal	-1.20	2.18				
Cerebral white matter	Patient	-3.62	4.78	-4.15	31.00	< 0.001*	1.4
	Normal	1.67	2.55				
Cerebrospinal fluid	Patient	3.12	10.53	0.25	13.02	0.805	-0.1
	Normal	2.37	2.68				
Cerebellum	Patient	-5.69	6.23	-3.45	14.38	0.004*	1.5
	Normal	0.21	1.71				
Brainstem	Patient	-2.03	3.73	-1.93	14.55	0.074	0.8
	Normal	0.07	1.50				

\* indicates a statistically significant  $p$  value ( $\#0.05$ ).

anatomic sub-regions (for example, NeuroQuant<sup>®</sup> defined whole brain parenchyma as the sum of forebrain parenchyma, brainstem and cerebellum).

A series of independent samples  $t$ -tests revealed that the patients had significantly more progressive atrophy than the normal controls (Table II). Most of the effect sizes were very large.

#### *Associations between brain volume change and vocational outcome*

A series of independent samples  $t$ -tests revealed that the patient GOSE sub-group with Lower Moderate Disability had significantly more progressive atrophy than the patient sub-group with Upper Moderate Disability (Table III). Most of the effect sizes were very large. Figure 2 shows an example of progressive ventricular enlargement in a patient with Lower Moderate Disability. As would be expected based on these findings, correlations between DRS Total scores and brain volume changes showed a pattern similar to that described just above for the comparisons between GOSE sub-groups. However, effect sizes were more modest, ranging mostly from moderate to large, with two correlations being associated with  $p$ -values < 0.05 (Table IV).

## Discussion

### *Test-re-test reliability*

The present study showed that the NeuroQuant<sup>®</sup> software measured brain regions with high test-re-test reliability. In fact, test-re-test reliability for large volume structures—including intracranial space,

whole brain parenchyma, CSF and forebrain parenchyma—were almost perfect. Previously, NeuroQuant<sup>®</sup> was found to have good inter-method reliability [5]. Furthermore, since NeuroQuant<sup>®</sup> is fully computer-automated, its reliability for measuring the same MRI data more than once is perfect (a mistaken second NeuroQuant<sup>®</sup> analysis on the same MRI in the clinic provided empirical data in support of this conclusion). Although, therefore, usually there would be no need to perform NeuroQuant<sup>®</sup> twice on the same MRI data, it may be useful for researchers who wanted to check their results by comparing them to those of other researchers, for example using a publicly available MRI database. The promising results from these reliability studies, in addition to the data supporting the FDA application, bode well for the use of NeuroQuant<sup>®</sup> to measure MRI brain volume in human subjects.

### *Comparisons between patients and normal controls*

The between-group comparisons showed that the patients with mild TBI had abnormally rapid progression of atrophy in whole brain parenchyma, forebrain parenchyma, cerebral white matter and cerebellum. These findings were consistent with several previous reports in the literature (for review, see Ross [8]).

The present study extends knowledge about progressive brain atrophy after TBI because it contained data which generally were much later after injury (mean = 2.44 years after injury) than data from earlier studies (range 0.27–0.83 years after injury) [11, 26–28]. The persistence of progressive

Table III. Comparisons between patient GOSE sub-groups based on vocational outcome. The patients with poorer vocational outcome showed significantly greater progressive brain atrophy in several regions. Effect size  $d$  was calculated per Cohen [29].

Brain region	Group	(% volume change/year)		Independent samples $t$ -tests			
		Mean	SD	$t$	df	Sig. (2-tailed)	Effect size $d$
Whole brain parenchyma	UMD	-1.15	2.68	2.68	14	0.018*	-1.4
	LMD	-5.57	3.83				
Forebrain parenchyma	UMD	-1.07	2.66	2.74	14	0.016*	-1.4
	LMD	-5.61	3.86				
Cortical grey matter	UMD	1.03	4.31	2.26	11	0.045*	-1.3
	LMD	-6.15	7.04				
Cerebral white matter	UMD	-3.32	5.71	0.24	11	0.817	-0.1
	LMD	-3.98	3.93				
Cerebrospinal fluid	UMD	-2.02	8.80	-2.78	11	0.018*	1.6
	LMD	11.34	7.73				
Cerebellum	UMD	-2.37	2.80	2.30	12	0.04*	-1.3
	LMD	-9.01	7.11				
Brainstem	UMD	-3.29	2.94	-1.36	11	0.201	0.8
	LMD	-0.56	4.28				

LMD, Lower Moderate Disability sub-group; UMD, Upper Moderate Disability sub-group.

atrophy for 2 years or more after injury was surprisingly long and raised a question about the nature of the underlying pathophysiology. Was it due to one of the following: (1) direct effects of the TBI; (2) common co-morbid conditions such as chronic pain, insomnia or psychosocial stress; or (3) an interaction between the TBI and co-morbid conditions? Furthermore, to the authors' knowledge, there has been no longitudinal study of longer duration to determine when the brain stops atrophying after TBI. In other words, a key unanswered question in this field is the following: when does the brain stop atrophying after traumatic brain injury? Further research will be needed to answer these questions.

From a more clinical perspective, of course, it is concerning that patients have brain atrophy which continues to progress as late as 2 years or more after injury. The flip side of that coin is that it raises the possibility for treatment or rehabilitation interventions to eliminate the progressive atrophy and improve the patient's clinical outcome.

#### *Association between brain atrophy and vocational outcome*

Progressive brain atrophy was associated with vocational outcome, when measured with the GOSE or DRS. Essentially, patients who had remained able to work (although impaired at work) had significantly less atrophy than those who became unable to work.

The associations between progressive atrophy and vocational outcome were supported by several previous studies [10, 11, 26–28]. This well-replicated finding provides validity for the findings of progressive atrophy. In other words, one might ask:

'Although it seems bad that the brain atrophies after TBI, are you sure that it is bad?' The answer is clearly 'yes', because increased atrophy predicts inability to return to work, which in many cases can be years after injury or indefinitely, even in patients with technically 'mild' TBI. For at least some patients with mild TBI who also have persistent neuropsychiatric complications, it seems that there are progressive and important brain changes.

#### *Practical considerations*

Although brain volumetry has been performed for a few decades, it has been confined mostly to researchers working in university settings. In the last few years, two breakthroughs led to the availability of brain volumetry in practical clinical settings. The first was a series of software developments allowing the automatic identification and measurement of brain regions. Perhaps the leading examples of this approach include FreeSurfer and NeuroQuant<sup>®</sup>. It is remarkable that these computer-automated programs are able to accomplish in ~15 minutes what human operators (with computer assistance) required 15 hours or more to do a mere decade ago.

The second breakthrough was the development of a commercially-available program (NeuroQuant<sup>®</sup>) which is based on FreeSurfer. Since FreeSurfer was developed for researchers, it has a somewhat steeper learning curve than NeuroQuant<sup>®</sup>. NeuroQuant<sup>®</sup> was developed to be relatively easy to use (although, in the authors' experience, it still requires some training for novice users). Perhaps more importantly,



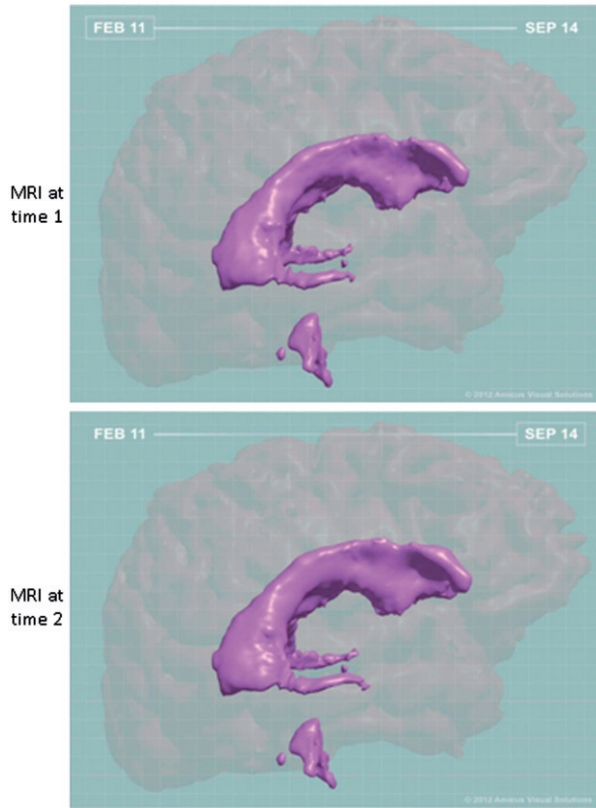


Figure 2. Three-dimensional reconstruction of NeuroQuant<sup>®</sup> segmented images shows the ventricles overlaid on the cortical surface of the brain. This patient was a 49 year old woman who suffered a mild traumatic brain injury from a motor vehicle accident. She had multiple persistent neuropsychiatric problems, was never was able to return to work and was rated as having Lower Moderate Disability on the GOSE. The first MRI was obtained 9 months after the accident and the second was obtained 2.6 years after the first. From time 1 to time 2, her cerebrospinal fluid volume increased by 8.6% per year (97th normative percentile) and her whole brain parenchyma decreased by 2.9% per year (0.2 normative percentile). Visual comparison of the changes in these images over time revealed that the temporal horns (especially on the right) elongated and the lateral ventricles appeared as if they had inflated. These 3-dimensional images were reconstructed from the Neuro Quant segmented 2-dimensional images by one of the authors (MDH), a board-certified Medical Illustrator.

Table IV. Correlations between rate of brain volume change (%/year) and vocational outcome measured by the Disability Rating Scale total score. Progressive brain atrophy correlated with worse vocational outcome in several regions, reaching significance in two regions.

Brain region	Spearman's rho	<i>p</i>
Whole brain parenchyma	-0.51	0.044*
Forebrain parenchyma	-0.56	0.023*
Cortical gray matter	-0.44	0.129
Cerebral white matter	-0.18	0.549
Cerebrospinal fluid	0.49	0.087
Cerebellum	-0.34	0.236
Brainstem	0.35	0.238

\* indicates a statistically significant *p* value (#0.05).

although FreeSurfer is publicly available and (as the name implies) free, it is prohibited from being used for commercial purposes. Therefore, its use is markedly limited in clinical settings. In contrast, NeuroQuant<sup>®</sup> was developed for commercial application and received FDA approval for the measurement of MRI brain volume in human subjects, greatly enhancing its applicability in typical clinical settings.

*Limitations*

Although all the patients in this study had mild TBI, they also had chronic symptoms which led them to seek neuropsychiatric treatment. Therefore, they probably did not reflect many patients with mild TBI who have good or complete resolution of symptoms after TBI. On the other hand, they probably were a good representative sample of the minority of patients with mild TBI who have persistent symptoms for months to years after injury.

The normal control group in this study was significantly older than the patient group. Since the brain atrophies more quickly in older subjects, this study may have failed to find some differences that actually exist in the populations of age-matched normal controls and mild TBI patients with persistent symptoms. This limitation makes it more striking that multiple differences, with very large effect sizes, were found nonetheless.

**Conclusions**

This study extends previous knowledge of progressive brain atrophy after TBI in the following ways: (1) Previous studies examined patients no more than 1 year, on average, after the date of injury. The current study found that patients with TBI had progressive atrophy more than 2 years, on average, after the date of injury. (2) The only previous study of progressive brain atrophy in patients with mild TBI was restricted to those with lesions on initial MRI [12]. In the current study, the group of patients with mild TBI was not restricted to those with lesions on the initial MRI; nevertheless, they still showed abnormally rapid progressive atrophy. (3) Previous studies which found an association between progressive brain atrophy and vocational outcome were not limited to patients with mild TBI. The current study included only patients with mild TBI but still found significant associations between progressive brain atrophy and vocational outcome. (4) Previous group studies of patients with TBI have used methods for brain volumetry which are limited to research settings, markedly limiting their applicability to clinical settings. The current study tested NeuroQuant<sup>®</sup>, a computer software program which

is FDA-approved and commercially available, and found it to be reliable and valid for measuring brain volume in normal controls and patients with TBI.

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