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Back to the future: Estimating pre-injury brain volume in patients with traumatic brain injury

David E. Ross [a,b,*], Alfred L. Ochs [a,b], Megan D. Zannoni [a], Jan M. Seabaugh [a], for the Alzheimer's Disease Neuroimaging Initiative

[a] Virginia Institute of Neuropsychiatry, Midlothian, VA, USA
[b] Virginia Commonwealth University, Richmond, VA, USA

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ABSTRACT

Introduction: A recent meta-analysis by Hedman et al. allows for accurate estimation of brain volume changes throughout the life span. Additionally, Tate et al. showed that intracranial volume at a later point in life can be used to estimate reliably brain volume at an earlier point in life. These advancements were combined to create a model which allowed the estimation of brain volume just prior to injury in a group of patients with mild or moderate traumatic brain injury (TBI). This volume estimation model was used in combination with actual measurements of brain volume to test hypotheses about progressive brain volume changes in the patients.
Methods: Twenty six patients with mild or moderate TBI were compared to 20 normal control subjects. NeuroQuant® was used to measure brain MRI volume. Brain volume after the injury (from MRI scans performed at t1 and t2) was compared to brain volume just before the injury (volume estimation at t0) using longitudinal designs. Groups were compared with respect to volume changes in whole brain parenchyma (WBP) and its 3 major subdivisions: cortical gray matter (GM), cerebral white matter (CWM) and subcortical nuclei + infratentorial regions (SCN + IFT).
Results: Using the normal control data, the volume estimation model was tested by comparing measured brain volume to estimated brain volume; reliability ranged from good to excellent. During the initial phase after injury (t0–t1), the TBI patients had abnormally rapid atrophy of WBP and CWM, and abnormally rapid enlargement of SCN + IFT. Rates of volume change during t0–t1 correlated with cross-sectional measures of volume change at t1, supporting the internal reliability of the volume estimation model. A logistic regression analysis using the volume change data produced a function which perfectly predicted group membership (TBI patients vs. normal control subjects).
Conclusions: During the first few months after injury, patients with mild or moderate TBI have rapid atrophy of WBP and CWM, and rapid enlargement of SCN + IFT. The magnitude and pattern of the changes in volume may allow for the eventual development of diagnostic tools based on the volume estimation approach.

Introduction

Decades of research have shown that traumatic brain injury (TBI) causes brain atrophy (Bigler, 2005, 2011). Despite this impressive body of work, brain structural studies before and after injury are rare. To our knowledge, there have been only two studies published using quantitative structural brain imaging before and after injury. In total, the 2 studies examined 2 patients with severe TBI who showed progressive brain atrophy and 4 patients with mild TBI who did not (Bigler and Snyder, 1995; Gale et al., 1995). The small number of patients and limited (by today's standards) volumetric methods may have decreased the ability to detect abnormalities in the patient group. In contrast, more recent longitudinal studies of mild or moderate TBI patients, which examined brain structure at two points after injury, have consistently found abnormalities (Hofman et al., 2001; MacKenzie et al., 2002; Ross et al., 2012a, 2012b, 2012c; Zhou et al., 2013).

The lack of studies before and after injury is understandable for several reasons. Since it is not known when an accident will occur, usually an MRI cannot be obtained just before the accident. Also it would be impractical to get baseline MRI scans on large groups of normal subjects and then study the small percentage who would have a TBI afterwards. However, it would be possible to overcome these challenges, at least in part, if it were possible to reliably estimate brain volume just before injury.

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CWM, cerebral white matter; GM, cortical gray matter; ICV, intracranial volume; IFT, infratentorial; MRI, magnetic resonance imaging; SCN, subcortical; t0, time of injury; t1, time of first MRI scan after injury; t2, time of second MRI scan after injury; TBI, traumatic brain injury; WBP, whole brain parenchyma.

* Corresponding author at: Virginia Institute of Neuropsychiatry, 364 Browns Hill Court, Midlothian, VA 23114, USA. Fax: +1 866 586 8977.
E-mail address: DRoss@VaNeuropsychiatry.org (D.E. Ross).

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For many years, it has been known that normally the brain and skull change volume with a characteristic pattern throughout the life span (Courchesne et al., 2000). The brain and skull reach maximal volume around age 13, with the skull growing to be just big enough to cover the brain. Whole brain volume then changes relatively little overall until about age 35, when it begins to decrease. During later adulthood, the rate of atrophy progressively increases. In contrast, intracranial volume does not change during adult life. Based on these observations, Tate et al. (2011)—following the lead of Blatter et al. (1995)—showed that brain volume at an earlier point in life can be estimated reliably from intracranial volume measured later in life.

Further progress toward building a volume estimation model was achieved by Hedman et al., who conducted a meta-analysis of 56 studies (which included 2211 normal control subjects) of longitudinal change in MRI brain volume throughout the life span. Using curve-fitting regression techniques, they produced growth/atrophy curves for whole brain parenchyma (WBP), cortical gray matter (GM) and cerebral white matter (CWM). Thus, they created models which allow for accurate estimation of brain volume changes throughout the life span.

By considering combining the work of these researchers, it seemed possible to create a volume estimation method which could be used to test hypotheses about patients with traumatic brain injury (TBI). Intracranial volume could be measured in TBI patients (after the accident) and used to estimate brain volume for each patient just before the accident. The reliability of this method could be tested in a group of normal control subjects.

Accordingly, the aims of the current study were as follows: (1) develop methods for estimating brain volume throughout the life span; (2) use total intracranial volume (ICV), in combination with the Hedman growth/atrophy curves, to predict brain volume just before injury (t0); (3) compare TBI patients to normal control subjects, using longitudinal changes in brain volume (from t0 to t1), to test the hypothesis that patients have more rapid volume changes than normal control subjects; and (4) explore the relationship between longitudinal changes (t0–t1) and traditional brain volume measures (t1 cross sectional measures, and t1–t2 longitudinal measures).

Methods

Subjects

Patients

Selection criteria. Included in this study were outpatients consecutively admitted to the Virginia Institute of Neuropsychiatry who had mild or moderate TBI and no medical or neuropsychiatric disorders which would affect brain volume or its measurement with MRI. For details, see Ross et al. (2012a, 2012b, 2012c), or Inline Supplementary Methods 1.

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.

Description of patient sample. 26 patients met the selection criteria. Demographic characteristics were as follows: fifteen men and eleven women; mean number of years of education was 14.3 (SD 2.7; range 10–20); mean age in years at the time of the injury was 45.3 (SD 9.7; range 25.3–62.0); mean age in years at the time of the first MRI scan was 47.0 (SD 9.5; range 29.6–62.9).

A subset consisting of 21 patients had a second MRI scan. The mean age in years at the time of the second MRI scan was 48.7 (SD 9.1; range 30.1–63.7). The mean duration between the first and second MRIs was 0.70 years (SD 0.47; range 0.32–2.59).

A subset consisting of thirteen patients had a third MRI scan; mean age in years at the time of the third MRI scan was 50.7 (SD 8.0; range 33.8–64.2). The mean duration between the second and third MRIs was 0.65 years (SD 0.26; range 0.32–1.12).

Causes of injury included motor vehicle accident (N = 23), motor vehicle vs. pedestrian (N = 1), train accident (N = 1) and others (metal gate fell on head) (N = 1).

24 patients had mild TBI and 2 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 3.8 min, median 0, range 0–30 min. The mean duration of posttraumatic amnesia was 21.1 min, median 4.0, range 0–90.

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.

Normal control subjects

CorTechs Labs normal control subjects were not used in the current study. NeuroQuant® software, produced by CorTechs Labs, Inc., was used to analyze MRI brain volume in this study (see the NeuroQuant® software was used for brain volume measurement section). The NeuroQuant® program is associated with its own normal control database developed by CorTechs Labs. However, although the standard NeuroQuant® computer-automated analysis provided volume data on over 20 brain regions (http://www.cortechs.net/products/neuroquant.php and Brewer, 2009), it provided comparisons to the CorTechs normal control group for only 3 brain regions. Otherwise, the normal control data in the CorTechs Labs database were not publicly available and were not made available for the current study.

ADNI normal control subjects were used in the current study. Therefore, in order to assess NeuroQuant®'s ability to detect changes in other brain regions, this study used a group of normal controls different from the CorTechs Labs normal controls. The normal control data for the current study were obtained from a larger group previously studied as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Jack et al., 2008; Petersen et al., 2010; Weiner et al., 2010). The ADNI normal control data were obtained from an online database which had been made publicly available (http://adni.loni.ucla.edu).

For information required in publications based on ADNI data, see Inline Supplementary Methods 2.

The ADNI normal control subjects were selected to be healthy and free of cognitive problems. For details, see Jack et al. (2008), Petersen et al. (2010), and Weiner et al. (2010).

Description of normal control sample. For the NeuroQuant® analyses reported herein, a subgroup of 20 normal control subjects (10 men, 10 women) was chosen from the ADNI database. The mean age at the time of the first MRI scan was 68.3 years (SD 3.6 years; range 60.0–71.5), the mean interval between the first and second MRI scans was 1.13 years, and the mean number of years of education was 16.0 (SD 3.1; range 9–20).

Comparing patients and normal control subjects

The groups of patients and ADNI normal controls did not differ significantly with respect to sex (Pearson Chi-Square = .27, df = 1, P = .60).

Distributions of age data were not normal for the normal controls (Shapiro–Wilk statistic = 0.80, df = 20, P = .001). Therefore, in order to compare the two groups with respect to age, a nonparametric test (Wilcoxon) was chosen. The normal control subjects were significantly older than the patients (Chi-Square = 32.8, P < .0001).

The two groups did not differ significantly with respect to years of education (independent t-test, t = −1.87, df = 44, P = .07).