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# Longitudinal changes in global brain volume between 79 and 409 days after traumatic brain injury:

## relationship with duration of coma

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## Abstract

Neuropathological and experimental animal studies indicate that traumatic brain injury (TBI) results in long-term, neurodegenerative changes. Structural image evaluation using normalization of atrophy (SIENA) offers an automated analysis of the subtle changes in percent brain volume change (%BVC) associated with TBI. In the present study, SIENA was used to evaluate %BVC in individuals who had sustained a mild to severe TBI. We obtained 3D-T1 weighted anatomical MRI scans approximately 79 days and again 409 days post-injury. TBI patients (n= 37) displayed significantly greater decline in %BVC (-1.43%) relative to a normal comparison group (+ 0.1%, n=30). Greater %BVC was associated with longer duration of post-injury coma. These results confirm previous findings from cross-sectional studies, and suggest that the brain undergoes structural changes for several months after TBI.

### Keywords

SIENA; injury severity; brain volume change

## INTRODUCTION

Traumatic brain injury (TBI) is often associated with pervasive neuropsychological, physical and behavioral changes, which can lead to long-term disability that may or may not diminish over time. Quantitative structural neuroimaging techniques such as magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and computed tomography (CT) have been used successfully to identify both local and diffuse neuropathological changes associated with TBI such as wallerian degeneration, which has been shown to last for weeks after injury in

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experimental animals and over several months post-injury in humans (see Graham et al., 2002 for reviews, see Bigler, 2005).

Recent advances in quantitative MRI analysis such as structural image evaluation using normalization of atrophy (SIENA) (Smith et al., 2001, Smith et al., 2002) offer relatively straightforward, automated analysis of longitudinal changes in global brain volume. This procedure is automated, unbiased, and reliable, and may also be useful at characterizing global changes in brain volume after TBI. Enzinger et al. (2005) used SIENA to evaluate longitudinal changes in global brain volume in middle-aged individuals over a six-year follow-up period, and reported an annualized percent brain volume change (%BVC) of -0.40% ± 0.29.

In the present study we used SIENA to examine the longitudinal effects of TBI on %BVC between 79 days (range = 39-109 days) and 409 days (range = 352-530 days) post-injury. We also sought to determine whether or not %BVC was associated with duration of post-injury coma measured by the time to reach a Glasgow Coma Scale motor score of 6 (GCS-6), and other demographic variables such as age, education and gender. Based on prior quantitative MRI studies, we hypothesized that TBI patients would display greater %BVC over time relative to a comparison group that had not sustained any brain trauma. We also hypothesized that greater %BVC would be associated with longer duration coma, but not with the age, education, or gender.

# METHODS

## Research Participants

**TBI patients—**All TBI patients were referred from the departments of Neurosurgery, Trauma, and/or Rehabilitation at the University of Wisconsin Medical School. Exclusion criteria for all patients in the TBI group included diagnosis of substance abuse disorder or an undiagnosed history of long-term substance abuse. Additional exclusion criteria for all TBI patients included pre-injury diagnosis of a major psychiatric disorder or a prior history of head trauma. Mild post-injury adjustment issues in TBI patients (e.g., depression or anxiety) and intoxication at the time of injury were not considered exclusion criteria for TBI patients.

The inclusion criteria for TBI patients consisted of all of the following criteria: 1) involvement in an incident involving a blunt injury to the head (e.g., a motor vehicle accident or fall) resulting in loss of consciousness severe enough to require immediate medical attention at a level one trauma center; 2) visual presence of trauma related lesion(s) on CT or MRI scan verified by a radiologist; 3) altered consciousness and available 24-hour GCS scores. The 24-hour GCS score was used to rate injury severity because admission GCS scores are commonly reduced iatrogenically through intubation and sedation procedures necessary for patient transport and emergency medical care.

The final number of subjects in the TBI group included 37 TBI patients (mean age = 29.3 ± 10.9; mean education 13.2 ± 1.6; 27 men and 10 women). Of the 37 TBI patients included in this study, 11 patients suffered a mild TBI (24 hour GCS score ≥ 13), 10 patients suffered a moderate TBI (24hour GCS score of 9 – 12), and 16 patients suffered a severe TBI (24 hour GCS score ≤ 8). The mean GCS-6 score was 121.5 ± 170.5 hours (range = 0-730 hours). Eleven of the TBI patients were intoxicated at the time of injury. The mechanism of injury included: motor vehicle accident (29 patients), a fall (5 patients), pedestrian versus automobile (1 patient), and being hit in the head by an object (2 patients). Visit 1 occurred approximately 79 days post-injury and visit 2 was approximately 409 days post-injury (mean time between MRI scan 1 and 2 was 329.5 ± 54.5 days).

**Normal comparison group—**To examine the measurement error associated with the longitudinal analysis of %BVC, a normal comparison (NC) group (n = 30) underwent two structural MRI scan approximately 6 months apart (mean time between MRI scan 1 and 2 was 190.3 ± 116.9 days). The NC group (mean age = 24.5 ± 6.4; mean education 14.9 ± 1.5; 13 men and 17 women) was recruited from the community via advertisement. The inclusion criteria consisted of the following: 1) no current diagnosis of major psychiatric disease (including substance abuse disorder) or other major medical conditions (e.g., diabetes or recent history of cancer), 2) no history of head trauma, and 3) no impairment in cognitive functioning.

**Structural MRI—**Structural MRI was performed using a General Electric 3.0 Tesla SIGNA (Waukesha, WI) MRI system. A 3D IR-prepped fast gradient echo pulse sequence was administered to provide high-resolution T1-weighted spoiled gradient echo (SPGR) structural images. The whole brain was imaged in the axial plane with the following parameters: inversion time = 600 ms, fast gradient echo read-out with TR/TE/flip = 9 ms/1.8 ms/20°; acquisition matrix = 256 × 192 × 124 (axial 256 × 192 in-plane, interpolated to 256 × 256); field of view = 240 mm; slice thickness = 1.2 mm (124 slices); ± 16 kHz receiver bandwidth; acquisition time ~ 7.5 minutes. A neuroradiologist reviewed all structural MRI images to identify the location and extent of lesions associated with the TBI, and to identify non-injury related brain abnormalities that might exclude subjects from the statistical analyses. In addition, TBI patients with inadequate imaging or excessive motion during the scan that resulted in poor brain extraction were excluded from the analysis (n = 4).

**Structural image evaluation using normalization of atrophy (SIENA) analysis—**Structural image evaluation using normalization of atrophy (SIENA) within the FMRIB Software Library (FSL) 3.2 software suite (www.fmrib.ox.ac.uk/fsl) was used for the automated assessment of longitudinal %BVC. The detailed processing steps involved in SIENA have been described previously (Smith et al., 2001, Smith et al., 2002). SIENA segments brain from nonbrain tissue, and estimates the skull surface from anatomical images acquired at 2 separate time-points from the same subject. The result of the segmentation procedure is then used to coregister the two images, while normalizing for changes in geometric shape. The coregistered, segmented brain images are then used to evaluate local changes in brain volume between the two anatomical scans based on movement associated with image edges. The results are presented as %BVC between the 2 time points. SIENA has previously been used to evaluate longitudinal changes in brain volume in normal aging and in several neurological disorders with high accuracy (approximately ± 0.20% error in the measurement of brain volume change) (Smith et al., 2002).

**Data Analysis—**The nonparametric Mann-Whitney U-Test was used to evaluate differences in demographic variables between the TBI patients and the normal comparison group using an alpha level set at 0.05 (two-tailed). The mean demographic data for both groups can be seen in Table 1. Group differences in %BVC were also conducted using the Mann-Whitney U-Test using an alpha level set at 0.05 (two-tailed). Spearman's nonparametric correlations were performed to determine the relationship between %BVC and GCS-6, education, gender, and age. The %BVC data between visits 1 and 2 for the NC group was included primarily to evaluate measurement error associated with the SIENA %BVC technique (previously estimated to be near ± 0.20 %BVC). Presumably, individuals in the second to fourth decades of life would show little change in brain volume in the absence of brain trauma (Blatter et al., 1995,Enzinger et al., 2005).

# RESULTS

## Demographic variables

The results of the statistical analyses of the demographic data can be seen in Table 1. The Mann-Whitney U-Tests for the demographic variables revealed that the two groups did not significantly differ in terms of age ($p > 0.10$), however the NC group was significantly more educated (mean = 14.9 years) relative to the TBI group (mean = 13.2 years) ($p < 0.01$).

## SIENA analysis

The Mann-Whitney U-Test revealed significantly greater %BVC between visits 1 and 2 in TBI patients (-1.43 ± 1.20 %) relative to the control subjects (0.09 ± 0.37 %) ($z = -5.95$, $p < 0.0001$). Importantly, the %BVC displayed by the NC group was less than the range of %BVC reported over serial MRI scans in healthy subjects (i.e., ±0.20%) as part of the SIENA validation study (Smith et al., 2002), suggesting little to no change in brain volume within the NC group between visits 1 and 2. Fig. 1 depicts the %BVC for both the TBI patient and NC groups.

## Correlation analyses

The Spearman's correlation analysis revealed significant associations between GCS-6 and % BVC ($r = -0.52$) (see Fig. 2) and education and %BVC ($r = -0.36$). There were no significant correlations between any of the other predictor variables.

# DISCUSSION

TBI is associated with both local and diffuse brain damage. The most common site of local cortical damage includes the anterior and inferior frontal and temporal lobes (Bigler, 1990). Although several studies have described more diffuse changes in brain structure after TBI, few longitudinal studies exist (see Povlishock and Katz, 2005 for review). In the present study, we used SIENA to evaluate longitudinal changes in global brain volume in individuals that had sustained a mild to severe TBI relative to a group of individuals that had not sustained brain damage. We also sought to determine whether %BVC was associated with duration of coma and other demographic variables.

We found that TBI patients displayed significantly greater longitudinal reduction in brain volume (-1.43 %BVC) relative to the NC group (+0.09 %BVC). Importantly, the %BVC displayed by the NC group was within the measurement error reported in the SIENA validation study (Smith et al., 2002), thereby indicating very little change in brain volume in the NC group. Furthermore, the %BVC change displayed by TBI patients was greater than that observed over a 6-year period in middle-aged individuals (mean age = 60 years), who were found to display an annualized %BVC of -0.40 ± 0.29 (Enzinger et al., 2005).

The results of the present study are also consistent with previous studies of brain volume changes after TBI. In a cross-sectional study, Blatter et al. (1997) found that TBI patients displayed significantly less total brain volume concurrently with significantly greater lateral and third ventricle volumes. MacKenzie et al. (2002) extended these findings, and reported a significantly greater longitudinal rate of decline in brain parenchymal volume in TBI patients (-2.0%) relative to normal control subjects (-0.6%) between 4 and 16 months post injury. The results of the present study confirm the findings of MacKenzie et al. (2002), suggesting that TBI is associated with more long-term changes in brain volume several months after the initial injury. The %BVC found over a 1-year period in the TBI patients was significantly greater than the %BVC measured over a similar time frame during normal aging. The results of the present study also suggest that longer duration post-injury coma (a measure of injury severity) is associated with greater longitudinal %BVC. Taken together, these results suggest that

SIENA might offer a relatively straightforward, automated method for examining longitudinal changes in brain volume after TBI, and also might be useful in determining factors associated with recovery of function after TBI.

Several experimental studies have elucidated the mechanisms associated with some of the long-term, cellular and molecular changes that underlie brain volume reductions associated with TBI. For example, long-term changes in brain volume may be associated with disruption of the intracellular cytoskeletal network or WM fiber tracts (Povlishock and Christman, 1995). Deafferentation of WM fiber tracts can result in the downstream disconnection of the axon from the cell soma resulting in wallerian degeneration that can last for weeks after injury in experimental animals and over several months post-injury in humans (Graham et al., 2002).

There are several limitations to the present study. First, the time interval between visits 1 and 2 was substantially shorter in the NC group relative to the TBI group, although individuals who had not sustained a brain injury would not be expected to display a significant amount of brain volume change in the absence of brain injury. Future studies should utilize longer duration follow-up intervals in normal comparison groups to determine the generalizability of the findings from the present study. Second, it is possible that the clearing of brain edema over time might be responsible for the substantial %BVC observed in the TBI group. It is likely that the majority of the clearing of brain edema would have occurred in the acute phase after the brain injury, whereas all of our TBI patients received their first MRI scan greater than 1 month after the initial brain trauma. However, acute brain edema results in decreased cerebral perfusion and brain oxygenation that can initiate a series of longer duration pathophysiological events that eventually leads to brain herniation and death (Unteberg et al., 2004), and was likely a contributing factor to the changes of brain volume observed in the present study.

## SUMMARY

In the present study, TBI patients were found to display significantly greater declines in % BVC over an approximately 1-year period than is observed over the same time during normal aging. Greater %BVC was found to be associated with a longer duration of coma. These changes might be due to long-term cellular and molecular changes such as Wallerian degeneration, which may last for several months post-injury. Prior studies suggest that these long-term changes in brain volume occur concurrently with recovery of function and behavioral improvement that is often observed in TBI patients. More studies with larger sample sizes are needed to confirm and extend the findings of the present study to determine whether the extent to which %BVC is associated with longitudinal functional and neuropsychological recovery after brain damage.

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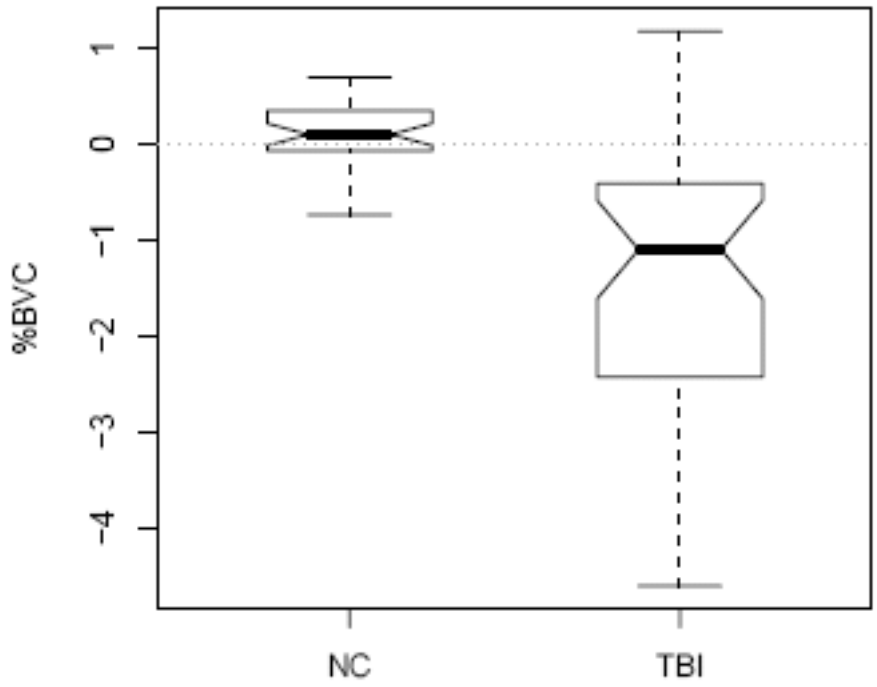


**FIG. 1.**

Results of the SIENA analysis of percent brain volume change (%BVC) between visits 1 and 2 for the TBI patients and the NC group. The figure represents a notched boxplot of the %BVC for both groups. The plot contains the mean of each group, the 95% confidence interval about the mean represented by the notch in each box, and the 5th, 25th, 75th and 95th percentiles, representing the range of variability in %BVC for both groups.

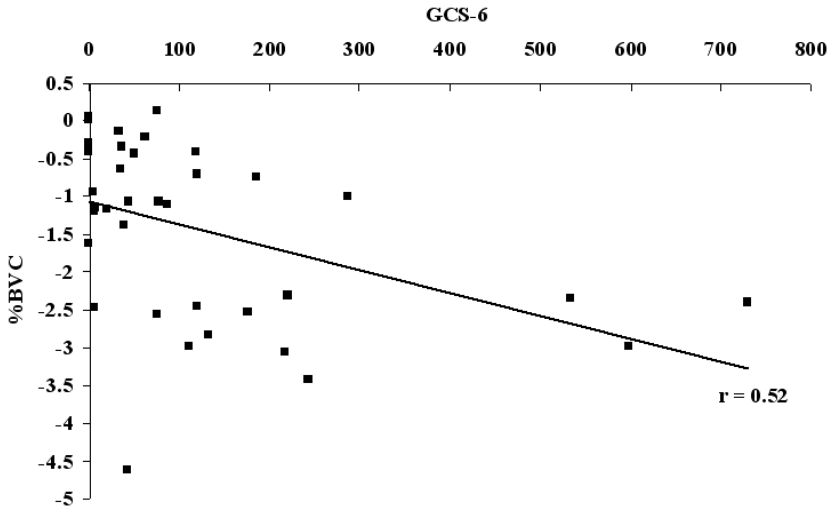


**FIG. 2.**

A scatter plot of the association between GCS-6 and %BVC prior to adjustment to a 12-month scale with Spearman's rank correlation coefficient (r).

## Table 1

Demographic Data

| Demographics | NC group | TBI visit 1 | *p*-value |
|---|---|---|---|
| | *M (SD)* | *M (SD)* | |
| Gender | 13 M / 17 F | 27 M / 9 F | -- |
| Age | 24.5 (6.4) | 29.3 (10.9) | > 0.10 |
| Education | 13.2 (1.6) | 14.9 (1.5) | < 0.01 |
| GCS-6 | -- | 121.5 (170.5) | -- |
| %BVC | 0.09 (0.4) | -1.43 (1.2) | < 0.0001 |

**Notes:** GCS-6 = time to a GCS motor score of 6. %BVC = percent brain volume change. Data are presented as raw scores unless otherwise noted. All p-values represent the results of the Mann-Whitney U-Test.