

## Longitudinal Regional Brain Volume Changes in Mild Traumatic Brain Injury

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**PURPOSE:** About 20% of patients have persistent post-concussive syndrome (PCS) within 6 months to 1-year after mild traumatic brain injury (MTBI), and there is recent evidence showing that these patients have microstructural, metabolic and functional changes to the brain using a variety of new neuroimaging techniques [1]. Whether a single concussive episode and the resultant microstructural, metabolic and functional changes that have been associated with such an injury culminate in chronic brain alterations such as atrophy is not known. The purpose of this study is to examine longitudinal changes in regional brain volume using automated whole brain parcellation in a well-defined cohort of MTBI patients and correlate regions of brain atrophy with quantitative neurocognitive assessment as well as clinical symptom scale measures.

**MATERIALS AND METHODS:** Of a group of 28 MTBI patients, 19 were followed for one year. These were compared with 22 matched controls, and 12 of whom were followed for one year. All MRI experiments were performed at the 3T Trio body MRI scanner (Siemens Tim Trio, Erlangen, Germany) using a 12-channel head coil. The 3D gradient echo T1-weighted MPRAGE protocol with the following parameters: (TR/TE/TI=2300/2.98/900ms, flip angle=9°, resolution=1x1x1mm<sup>3</sup>) was used to obtain structural images. In addition, T2-weighted fast spin-echo and high-resolution susceptibility-weighted imaging (SWI) sequences were also implemented to help detect hemorrhagic or other lesions. The DICOM format of the MPRAGE image of each image for each subject was analyzed using FreeSurfer (v.5.1.0) software (<http://www.surfer.nmr.mgh.harvard.edu>) to derive regional subcortical (45 regions), white matter (WM) volume (70 regions) and cortical gray matter (GM) (148 regions) [2]. To validate the results obtained using FreeSurfer, two additional commonly-used algorithms were used. For comparison between MTBI patients and controls, based on MPRAGE data, whole-brain voxel-based morphometry (VBM) package in FSL (<http://www.fmrib.ox.ac.uk/fsl/vbm>) was used for segmentation and gray matter density analysis. For longitudinal comparison of intra-subject initial and follow-up regional brain volume, after removing extracranial tissues using AFNI (<http://afni.nimh.nih.gov/afni/>), the boundary shift integral (BSI) method [3] was applied to measure the global atrophy rate and ventricular enlargement. BSI measures the longitudinal cerebral volume changes directly from voxel intensity projections, based on the volume change of the boundaries of a given cerebral structure or the whole brain of repeated registered structural images. BSI had been shown to be a robust measure of brain volume change by tightly correlated with the segmented volume of change; but with higher accuracy and less variability. Statistical correlation between FreeSurfer results (e.g. relative supratentorial volumetric change) and BSI results was performed. Pearson and Spearman rank correlation coefficients were computed between longitudinal brain volume changes and changes in neurocognitive scores over the same period or the measures at each time point.

**RESULTS:** In patients, there was significant decrease in WM volume of the bilateral anterior cingulate, the cingulate isthmus and GM of precuneus regions over one-year (corrected  $P < 0.05$ ). No volumetric differences were found between MTBI patients at the time of their initial visit and controls after normalization. Almost no changes in volume were detected in any regions in controls followed for one year (Figure 1A).

Corroborative results comparing patients at one-year follow-up to controls showed lower WM volume in the rostral anterior cingulate (rAC), caudal anterior cingulate (cAC) and left isthmus of cingulate, as well as lower GM volume in right precuneus (Figure 1B). These cross-sectional differences still remain after accounting for individual brain size differences and adjustment for multiple comparisons with Bonferroni correction (corrected  $P < 0.05$ ). Group analyses based on VBM method between MTBI patients at one-year follow-up and controls (corrected  $P < 0.05$ ) confirmed the pattern of regional atrophy seen using FreeSurfer (bilateral rAC and cAC, and posterior precuneus regions; Figure 1C). Consistent with FreeSurfer regional findings, group analyses based on VBM method between MTBI patients at initial visit and controls showed no significant group difference.

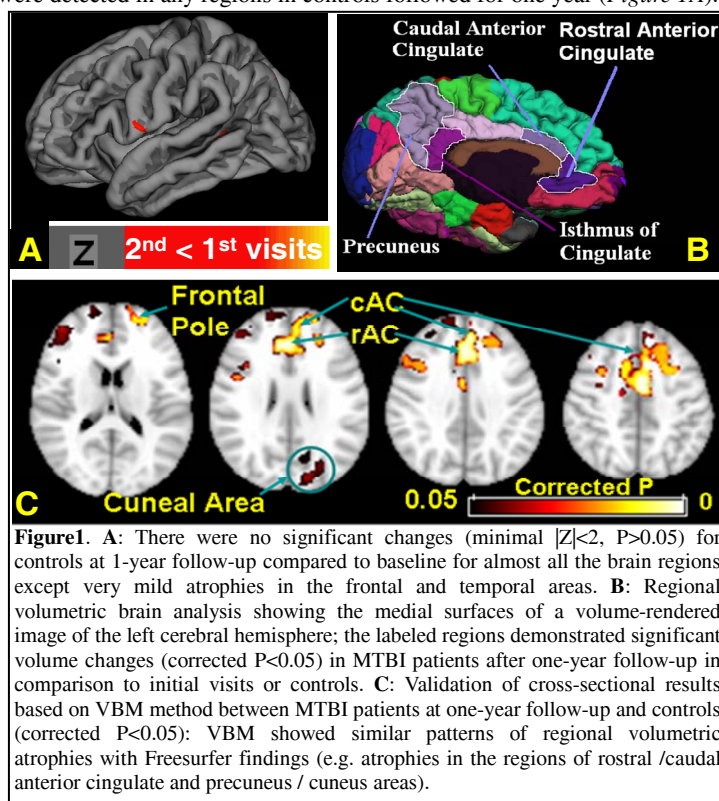
BSI results using longitudinal data in MTBI patients showed significant correlations between the whole-brain boundary shift and the ventricular enlargement ( $r = 0.62$ ,  $P = 0.003$ ). The average BSI between MTBI patients at one-year follow-up and initial visits is 7.6 CC (longitudinal atrophy), which is about two times the BSI of controls. And there was significant correlation between the supratentorial volumetric change measured from FreeSurfer and the whole-brain BSI ( $r = 0.54$ ,  $P = 0.042$ ).

Regarding association with neurocognitive performance, in the WM, loss of left rAC volume correlated with change in California verbal learning test (CVLT for memory encoding and recalling tests) score over time ( $r = 0.65$ ,  $P = 0.005$ ); and loss of right rAC volume correlated with change in Paced Auditory Serial Attention Task test (PASAT primarily for sustained attention tests) trial 2 score over time ( $r = 0.60$ ,  $P = 0.01$ ). At one-year follow-up, patients showed negative correlations between the left isthmus of cingulate WM volume and anxiety score (Spearman rank correlation  $r = -0.68$ ,  $P = 0.007$ ); as well as with the PCS ( $r = -0.65$ ,  $P = 0.01$ ).

**CONCLUSIONS:** Our observations demonstrate that regional brain atrophy is not exclusive to moderate and severe TBI, but may be seen following mild injury as early as one year after injury. The anterior and isthmus of the cingulum and precuneal regions may be distinctively vulnerable. We find an association between regional volume loss and neurocognitive performance / clinical symptom scores. Such associations may relate to dysfunction within these specific brain regions: the anterior cingulum is known to play a role in affective and cognitive domains and the precuneus is highly linked to associative cortex.

### References

- [1] Grossman et al. J Neurotrauma 2012. [2] Fischl et al. Cereb Cortex 2004. [3] Freeborough et al. IEEE Trans Med Imag 1997.



**Figure 1.** A: There were no significant changes (minimal  $|Z| < 2$ ,  $P > 0.05$ ) for controls at 1-year follow-up compared to baseline for almost all the brain regions except very mild atrophies in the frontal and temporal areas. B: Regional volumetric brain analysis showing the medial surfaces of a volume-rendered image of the left cerebral hemisphere; the labeled regions demonstrated significant volume changes (corrected  $P < 0.05$ ) in MTBI patients after one-year follow-up in comparison to initial visits or controls. C: Validation of cross-sectional results based on VBM method between MTBI patients at one-year follow-up and controls (corrected  $P < 0.05$ ); VBM showed similar patterns of regional volumetric atrophies with FreeSurfer findings (e.g. atrophies in the regions of rostral /caudal anterior cingulate and precuneus / cuneus areas).