

Atrophy in rats induced with mild TBI and hemorrhagic shock: A TBM-based analysis

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Introduction

Mild traumatic brain injury (mTBI) leads to neurodegenerative changes that progress over time and can cause neurobehavioral and functional changes [1]. mTBI victims are also more susceptible to subsequent TBI or to secondary insults, such as hemorrhagic shock (HS) which can exacerbate the posttraumatic disorders. The main objective of this study was to assess the regional volumetric changes in rats subjected to mTBI, followed by HS. We determined regional volumetric changes using tensor-based morphometry (TBM) that has been shown to provide methodological improvements over the commonly used voxel-based morphometry (VBM) [2]. TBM identifies regional volume changes from the Jacobian Determinant (JD) of the deformation fields. Since the JD can be directly used in statistical analysis, it eliminates the need for comprehensive tissue segmentation.

Methods

Long Evans rats were used in these studies. To model mTBI aggravated by HS conditions, controlled impact injury (3 m/sec; 2.5mm deformation) was inflicted over the right parietal cortex (3mm±1mm posterior from bregma) of anesthetized rats, immediately followed by induced HS with mean arterial pressure (MAP) of 40mm Hg (group 1: mTBI+HS, n=15). Two additional sham injury groups: rats with impact injury but no induced HS (group 2: mTBI only, n=5) and rats with no impact injury, but induced HS (group 3: HS only, n=5) were also included for comparison. Soon after HS, the animals were resuscitated by re-infusion of blood and necessary fluids. Two weeks after injury, high resolution 3D RARE T2-weighted images were acquired on a Bruker 7T animal scanner after which the animals were sacrificed. Ten naïve rats were also included as control group. The images were manually stripped of the extra-meningeal tissues, bias corrected [3] and smoothed [4]. A custom template was generated by spatially normalizing the images of the control group using symmetric inverse consistent non-linear diffeomorphic registration [2]. All datasets were similarly registered to the template. The Jacobian obtained for each dataset following registration was normalized and the log Jacobian of the brain region was generated. The log jacobian maps for each of the groups 1, 2 and 3 were then compared with those of the control group for statistical differences. The two sample FDR-corrected unpaired *t*-tests were performed voxel-by-voxel for the whole brain using both parametric (<http://www.fil.ion.ucl.ac.uk/spm/>) and non-parametric (<http://www.sph.umich.edu/ni-stat/SnPM/>) methods [3, 5]. The resulting *t*-maps were overlaid on the template to identify regions with significant atrophy.

Results

The regions with significant atrophy in group 1: mTBI+HS compared to the naïve controls ($p < 0.05$ using FDR) are indicated by the blobs superimposed on the template (Fig. 1). As can be seen from this figure, significant atrophy was observed at the site of impact (yellow arrow), as well as regions away from the site of injury that include the contralateral parietal cortex and deep gray matter regions such as medial/cortical amygdaloid nucleus, and suprachiasmatic nucleus (green arrows). No significant atrophy was observed in groups 2 (mTBI only) or 3 (HS only) relative to the naïve controls.

Discussion and Conclusions

Our results indicate that mild traumatic brain injury aggravated by superimposed hemorrhagic shock causes local as well as global structural changes in the brain. Atrophy was detected with tensor-based morphometric analysis not only at the site of injury, but also in some deep gray matter regions far from the site of injury that otherwise appear normal on anatomical scans. The observed regional atrophy could perhaps explain the long-term cognitive deficits observed in mTBI subjects having secondary insults [6]. To the best of our knowledge, our analysis is the first TBM-based approach to detect injury induced atrophy in rat models.

References

[1] JW Huh, et al. *Exp Neurol*, 2008. [2] BB Avants, et al. *Med Imag Anal*, 2008. [3] J Ashburner and KJ Friston. *NeuroImage*, 2000. [4] SM Smith and JM Brady. *Int. Journal of Computer Vision*, 1997. [5] TE Nicholas and AP Holmes. *Human Brain Mapping*, 2001. [6] Schütz, et al. *Crit Care Med*. 2006.

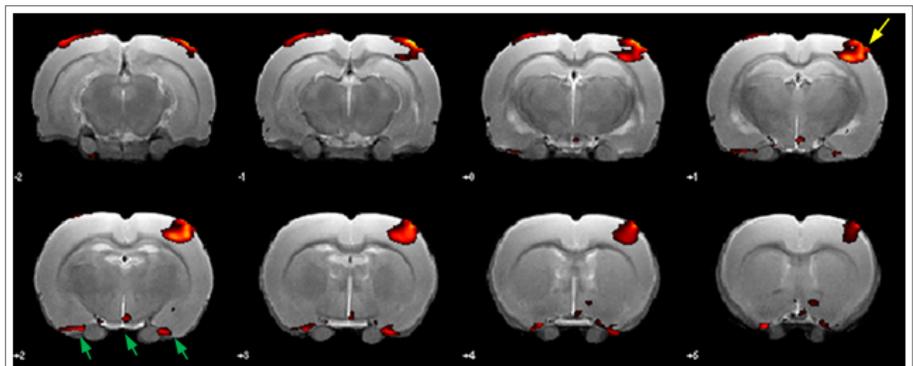


Figure 1: The *t*-map shown as red blobs overlaid on the anatomical images indicates significant atrophy ($p < 0.05$ on FDR) in group 1 (mTBI+HS) relative to naïve controls. The regions with significant atrophy include the ipsilateral parietal cortex and some regions in the contralateral parietal cortex, medial/cortical amygdaloid nucleus, and suprachiasmatic nucleus.