Do Regional Cerebral Blood Volume (rCBV) Effects Partially Explain Short-Termed Changes of Voxel-Based Morphometry (VBM)?

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Introduction

The option to reflect neuroplastic effects of the brain by means of imaging is still an emerging field in brain research. While long-term changes of brain volume may be well interpreted by cell proliferation or apoptosis, neurogenesis, and synaptogenesis, short-term effects within several hours have also been found recently (1), but their explanation remains unclear.

One non-invasive tool for investigating neuroplasticity is voxel-based morphometry (VBM) based on segmented T_2-weighted MR images. The obtained gray matter (GM) and white matter (WM) probability maps for each tissue compartment in the brain can be used to visualize the changes in GM or WM due to an applied task or treatment. One drawback of VBM could be that this method is partially sensitive maybe to changes in regional cerebral blood volume (rCBV). Reversible short-term effects may bias results in VBM without any underlying effect due to neuroplasticity.

The aim of this study was to investigate the hypothesis that rCBV partially explains the variance of VBM changes, because the changes in rCBV are one of the main reversible short-term effects in the brain due to capillary swelling. Therefore, we intended to analyze region-based correlations between rCBV and tissue probability maps obtained with VBM.

Methods

Measurements were performed in 8 Sprague-Dawley rats (from the congenital learned helplessness colony that we use as an animal model of depressive-like behavior at our institute (2)), anesthetized with medetomidine. The imaging experiments were performed at a 9.4T MRI system (Bruker) equipped with a body coil for transmission and a phased array rat brain coil for signal receiving.

For VBM measurement 3D structural data were acquired using a high-resolution T2-weighted RARE pulse sequence (factor 16) with (TR/TE_{eff}) 1200ms/ 50ms, and 150x150x300µm^3 voxel size (3). After resizing by a factor of 10, bias-correction (30 mm cutoff) of the coregistered images, and skull removal, these data were segmented individually by the two-step segmentation procedure. From these data the group templates of tissue probability maps were created with all animals using the SPM Dartel routine. The group templates were smoothed (4mm isotropic), normalized (SPM8) to a template in the same space as in an anatomical rat brain atlas (4), and used as priors for the SPM-based segmentation of all structural 3D data. The individual tissue class maps were also smoothed (4mm isotropic), and standardized on the intracranial volume.

For rCBV measurement 10mmol/kg gadolinium-based contrast agent (Gd-DTPA) (5) was administered intraperitoneally. For data acquisition a RARE pulse sequence (with 116x116µm^2 in-plane resolution) was used with 1 mm slice distance. 10 slices were measured in midbrain. The cerebral volume was acquired two times: firstly - without any contrast agent, and secondly – 40 min after contrast agent administration in the steady state of the contrast agent (5). Images were motion-corrected, smoothed (0.5mm isotropic) and also normalized (SPM8) to the same group template in the same space as the anatomical rat brain atlas (4). The relative volume change rCBV was calculated voxel-based using the following equation:

$rCBV \sim \ln(SI(t)/SI_{pre})/TE$, where SI(t) is the signal intensity in a voxel after injection of contrast agent at the time t, SI_{pre} is the native signal intensity of the observed voxel. For standardization of the rCBV maps only the 4 largest rCBV values of the posterior cerebral vein (PCV) were used as a reference (3).

Voxel-wise correlation (Matlab R2009b) was performed between rCBV and GM and WM maps for 43 bilateral regions of interest (ROI) in midbrain obtained from the atlas (4) in each animal. Group statistics over animals were done with one sample t-tests (IBM SPSS Statistics, version 20.0.0) per ROI, and the p-values were FDR corrected.

Results

We found a highly significant positive correlation between GM and rCBV in 20 distinct brain regions, only for amygdala and lateral geniculate nucleus we detected a significant negative correlation (Figure 1). 15 of these significant ROIs showed negative correlation for WM and rCBV. Significant positive correlation between WM and rCBV was found in orbitofrontal cortex, diagonal band, periaqueductal grey, septum, and hypothalamus. Septum and hypothalamus showed trends for positive correlation between rCBV and GM, too.

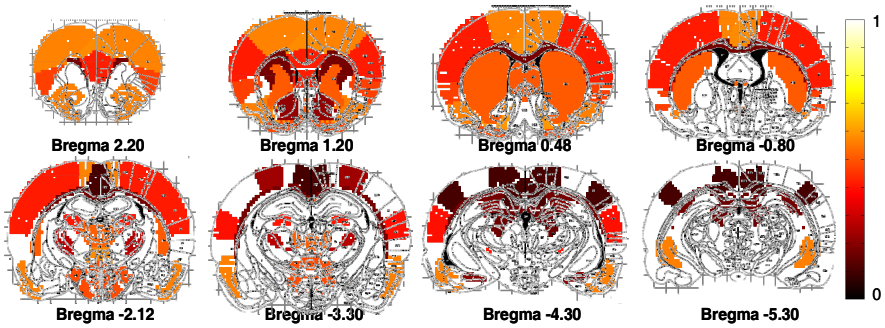

Figure 1: Correlation coefficient of significant ROIs for positive correlation ($p<0.05$) between rCBV and gray matter probability maps tested over all animals (from rostal to caudal)

Discussion

RCBV correlates significantly with GM maps for many brain regions covering large areas of the brain cortex, whereas it correlates negatively with WM maps. These findings indicate that rCBV partially explains the variance of VBM, and further studies are urgently needed to understand this relationship in greater detail.

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