Regional cerebral blood volume (rCBV) bias voxel-based morphometry (VBM) in an animal study

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Target audience

Investigating neuroplasticity by means of imaging is one of the emerging fields in brain research. While long-term changes of brain volume are well understood and mainly explained by neurogenesis, and synaptogenesis, cell proliferation and apoptosis, 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) probability maps in the brain show changes in GM due to a change of environment or treatment over time. The drawback of VBM is that this method might be sensitive to changes in regional cerebral blood volume (rCBV). Therefore, for VBM findings, the possible influence of rCBV on VBM is essential to state. Reversible and rCBV induced effects may bias results in VBM without any effect on neuroplasticity.

Purpose

The purpose of this study was to investigate the hypothesis whether changes in rCBV partially explain the variance of VBM. This is because rCBV changes are one of the reversible short-term effects in the brain due to capillary swelling. Therefore, we compared the VBM results analysed in two different ways, one with rCBV as a covariate per voxel and one without, in order to state the influence of rCBV on GM probability maps.

Methods

Measurements were performed in 15 Sprague-Dawley rats (8 rats from the congenital learned helplessness (cLH) colony that we use as an animal model of depressive-like behaviour (2), and 7 from the colony not showing learned helplessness behaviour (cNLH)) 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 T_2-weighted RARE pulse sequence (factor 16) with (TR/TE_{eff}) 1200ms/50ms, and 150x150x300µm^3 voxel size. After resizing, bias-correction (30 mm cutoff) of the coregistered images, and skull removal, these data were segmented individually by the two-step segmentation procedure (3). 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 (0.4mm 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 (0.4mm isotropic). The statistical analysis of the GM maps was performed with a 2-sample t-test with weight as a covariate (SPM8).

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, normalized (SPM8) to the same group template as used for the VBM analysis, and then resized to VBM resolution to obtain a voxel correspondence between tissue maps and rCBV maps later on. The relative volume change of rCBV was calculated voxel-wise 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 smoothed rCBV maps (0.4mm isotropic) the mean rCBV of the whole measured brain volume was calculated for each individual animal, and the corresponding rCBV map was divided by this value for global standardization.

To investigate the influence of rCBV, we employed the Robust Biological Parametric Mapping toolbox (rBPM) (6,7). The toolbox uses the robust regression to model the relationship among multiple modalities, controlling the influence by outliers and anatomical variation. The calculated rCBV maps were entered as second covariate in the VBM analysis together with covariate weight.

Results

The VBM analysis results from SPM (without rCBV as a covariate) and rBPM (with rCBV as a covariate) are compared in 31 regions of interest extracted from the anatomical atlas (4), which are fully covered by all VBM and rCBV scans. The percentage of voxels with significant group effect ($p < 0.05$, cluster extent > 5) in VBM statistical analysis is used for the comparison. The comparison reveals that, in the VBM analyses of cLH > cNLH, the significant areas of 14 ROIs differ more than 5% of the ROI size between the SPM result and the rBPM result, while, in the VBM analysis of cLH < cNLH, the significant areas of 2 ROIs differ more than 5% of the ROI size (c.f. Figure 1).

Discussion and Conclusion

In our study GM statistics of more than a half of observed brain regions are biased significantly by rCBV. These findings indicate that the variance of VBM is partially explained by rCBV. This dependency between rCBV and VBM has to be investigated in greater detail in further studies.

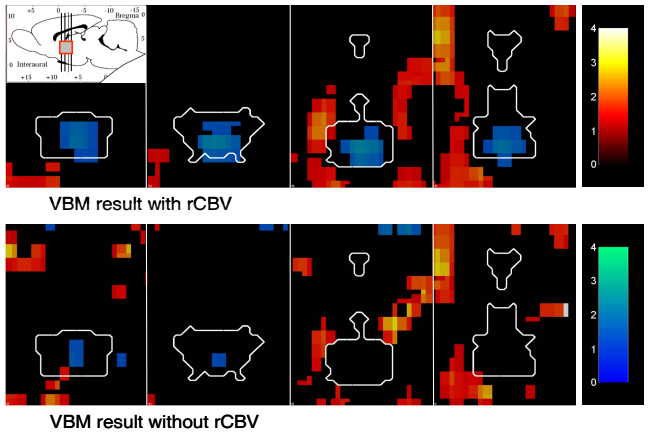

Figure 1: The VBM results around ventromedial thalamus (VMT). Top: SPM result; bottom: rBPM result; colour coding: -log10(p); yellow-red: cLH > cNLH; green-blue: cLH < cNLH; white contour: VMT.

References

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