Haircut: A method to reduce the dragging effect due to smoothing in voxel-based morphometry

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Introduction: Optimised voxel-based morphometry (VBM) *[1]* using the statistical parametric mapping (SPM) toolkit *[2]* is a popular method for assessing regional atrophy in patient cohorts. SPM5 attempts to identify regional differences between populations by normalising the structural images to the same standard space, segmenting the normalised images into grey (GM) and white matter (WM) and correcting for intensity non-uniformity (radio frequency bias) within the same unified model *[3]*. We recently performed a phantom study looking at the impact of skull-stripping and bias correction pre-processing on GM segmentation and warping *[4]* for VBM analysis in SPM5. Next, we were interested to assess the impact of these methods on real magnetic resonance (MR) data; however, testing with patient datasets is limited by the lack of a ground-truth *t*-map. We therefore created simulated lesions to the temporal lobes (right worse than left) and then evaluated several pre-processing method's ability to detect these lesions. Only the BET2 *[5]* + N3 *[6]* pipeline successfully detected bilateral lesions. However, the statistical effect was *dragged* out from the brain to the edge of the bounding box. As we knew that the only difference in GM segments for the *t*-map generation were in the temporal lobe, we hypothesised that the generation of low-probability voxels in the segmentation procedure meant that the statistical effect at the GM boundary could be dragged out of the brain by Gaussian smoothing. Here we report an experiment in which random noise was introduced to low-probability GM voxels to test the hypothesis that this would correct the observed artefactual displacement of significant clusters in the *t*-map.

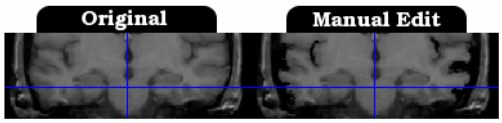

Figure 1: Original and manually edited control. The masking is more intense on the right insula and superior, middle and inferior temporal gyry.

Methods: Ten healthy controls were scanned on a 1.5T GE MRI scanner using a T_1-weighted 3D spoiled gradient-echo sequence (echo time: 4.2 ms, inversion time: 650 ms and flip angle: 20º) with voxel size: 0.84x0.84x1.5 mm. All scans were re-sampled to 256x256x256, 1-mm isotropic. The GUI tkmedit (Freesurfer *[7]* tool) was used to manually mask GM voxels in the temporal lobe and insula of all subjects; the removal being more intense on the right side as shown in Fig. 1. The two populations (original and manually edited) were skull-stripped prior to analysis using BET2 with fixed parameters: fractional intensity threshold, f, set to 0.4 and vertical gradient, g, set to 0. The stripped volumes were then bias-corrected using N3. Note that (i) pre-processing using the hybrid watershed algorithm (HWA) and N3, and (ii) no pre-processing (default SPM5) were also examined, but were inferior to BET2 in that they both failed to identify the left temporal lesion. All pre-processed volumes were normalised, segmented and modulated using the *unified segmentation* tool provided in SPM5. Ashburner et.al. *[3]* suggested that SPM5 is more accurate if it does not attempt to correct for intensity non-uniformities from unbiased images, hence bias regularisation was set to 10 and bias FWHM was increased to 150-mm cut-off. Subsequently, two procedures were followed: (i) *raw*. GM segments were smoothed using an 8-mm FWHM kernel; and (ii) *added noise/Haircut method*. Random noise was added to low-probability voxels from the GM segments prior to smoothing. An empirical threshold was set to 0.05, so that noise uniformly distributed between 0 and 0.05 was only added to probabilities lying under this threshold. The two populations (original vs. manually edited) were statistically compared by performing two-sample *t*-tests with default SPM5 settings for both procedures (raw & Haircut). Results were reported at a statistical threshold of p=0.001 (uncorrected). In addition, an average mask was employed in order to estimate the sensitivity of the results obtained using the method proposed in this study. The mask was generated by the sum of subtracted (original minus manually edited) binarised (threshold at 0.5) smoothed GM segments in standard space.

Results and Discussion: Comparing the VBM results from Fig. 2, it is clear that adding noise to low-probability voxels in GM segments prior to smoothing reduces the spreading effect from regions of significant differences located close to the external brain boundary. Fig. 3 compares the areas of significant atrophy obtained using the *Haircut* method with the average mask described in the methods section at four different coronal depths. It is encouraging to observe that the VBM clusters and the lesion mask are highly concordant. Although noise was also added to voxels within the brain boundary (WM tissue), the method neither improves nor worsens sensitivity in internal areas due to the mild severity of the artificial lesions compared to the size of the kernel (8-mm FWHM). However, studies of more severe atrophies might benefit from this technique by increasing sensitivity on both internal and external boundaries of GM tissue. The threshold and the noise amplitude were chosen empirically, but it was noticed that lower and higher thresholds resulted on larger spreading of the significant differences. This result suggests that there is an optimal threshold and noise amplitude that should be used for the volumes under study. Further work is needed to address this issue.

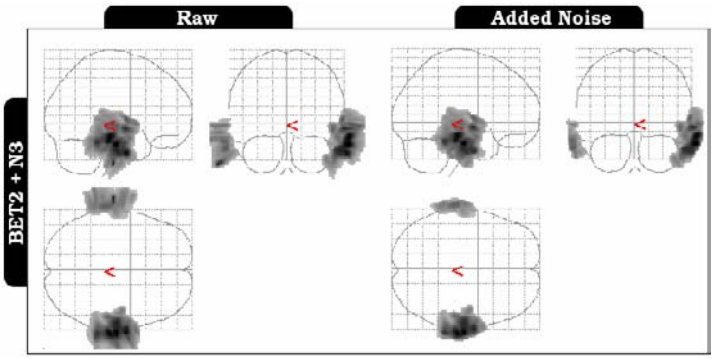

Figure 2: VBM results for the raw and added noise procedure. The spreading of significant atrophy is reduced by adding noise to the GM segments.

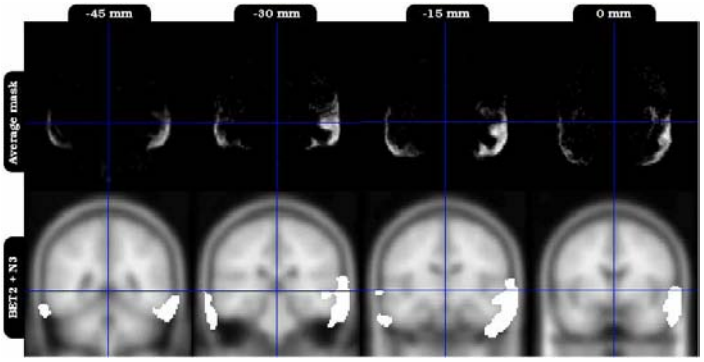

Figure 3: VBM results for the *Haircut* method compared to the average mask at four coronal depths.

Conclusions: Using the BET2 + N3 pre-processing pipeline has proven to be the most sensitive method to localise artificial bilateral lesions from real MRI datasets. Additionally, this study has demonstrated that the spreading of significant differences outside the GM boundary in VBM analyses due to the effect of the smoothing kernel can be reduced by adding random noise to non-GM voxels prior to the convolution with the Gaussian function. Applying this method to more severely atrophic cases might also result on VBM sensitivity improvements on internal GM boundaries.

References:[1] Ashburner J. et.al., Neuroimage 8:1105 (1997); [2] Available from http://www.fil.ion.ucl.ac.uk/spm; [3] Ashburner J. et.al., Neuroimage 26: 839 (2005); [4] Impact of bias-correction and skull-stripping pipelines on spatial normalisation using SPM5 in a phantom model, ISMRM-ESMRMB 2007 submitted abstract; [5] Smith S.M. Hum. Brain Mapp. 17: 143 (2002); [6] Sled J.G. et.al., IEEE Trans. Med. Imag. 17: 87 (1998); [7] Available from http://surfer.nmr.mgh.harvard.edu.