Optimization of voxel based relaxometry parameters for the detection of focal T2 changes

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Introduction: The voxel-based approach has become a popular method for the objective analysis of various parameters. It relies on the warping of the MR images to a common space in which the parameter-of-interest can be compared in a voxel-wise manner. The original implementation was applied to the analysis of volume changes (voxel based morphometry, VBM (1)) but the methodology has been extended to the analysis of T2 data (voxel based relaxometry, VBR (2)) which has been implemented in an increasing number of studies (3,4). There are a considerable number of parameter choices to be made when setting up a VBR analysis which may influence the outcome of the analysis. These include the selection of the smoothing kernel, the covariates and the warping procedure through which the images are placed in standard space. This report examines the sensitivity of the VBR result to these parameter choices in a study of a homogenous group of subjects in which a focal area of mesial T2 increase is expected.

Methods 19 patients with unilateral left hippocampal sclerosis (HS) were recruited (mean age: 39 years; 11 men) and compared with a control group of 115 healthy subjects (mean age: 29; 56 men). T2 mapping was carried out with a multi-echo CPMG sequence (8 echoes, TE=29-231ms, TR=6sec, slice thickness=5mm, FOV=24cm, 256×128). T2 maps were fitted using the modified baseline approach in order to reduce CSF partial voluming effects (2). Structural scanning was performed on a 3T GE scanner using a T1-prepared high-resolution FSPGR sequence (voxel size: 0.5×0.5×2mm).

VBR analysis: VBR analysis was carried out using the approach of (2) with the T2 maps warped to standard space via the T2-w images. The VBR parameters that were manipulated in this study and their scope of variation were as follows:

(a) Smoothing kernel: (i) 4mm (ii) 6mm (iii) 8mm (iv) 10mm (iv) 12mm

(b) Covariates-of no-interest: (i) no covariates (ii) age (iii) gender (iv) age+gender. Regression analysis was also carried out for age and gender separately using the control T2 maps.

(c) Approaches for normalisation:

(i) via SPM T2 standard template (i.e., following (2))

(ii) via customized T2-w template: user-created templates generated by averaging and smoothing the normalised T2-w images obtained from scheme (i)

(iii) via customized T1-w template: T2-w images coregistered to the corresponding T1-w scan. The T1 images are taken over to standard space via a customized standard T1-w template created by a 2-pass registration scheme. T2-w images are then normalised via the T1-w-to-template normalisation

(iv) via customized T2-WM segment template: T2 images segmented in SPM. White matter (WM) segments are averaged and smoothed to form a WM template (T2-WM). All WM segments then renormalized to the new template and T2 maps taken over to standard space in this manner (similar to (3)).

Each of these choices were combined with each of the other choices to generate multiple alternative analysis pathways for the analysis of the HS subjects. All analyses were carried out using SPM2 (http://www.fil.ion.ucl.ac.uk). Results were compared at a statistical threshold of p=0.00005 (uncorrected). Comparison of the analysis pathways was undertaken by the assessment of the number of significant voxels in several areas of expected focal volume loss (ipsilateral hippocampus (HC), parahippocampal area (PHC) and the entire temporal lobe excluding the mesial area (TL)).

Results and Discussion: A smaller smoothing kernel was found to be more efficient at detecting the T2 increase in the hippocampal lesions (Fig. 1). This follows from the matched filter theorem and relates to the size of the expected change. The optimal kernel size for the detection of maximal signal in the expanse of the temporal lobe was, surprisingly, 8mm. The control T2 values were found to be strongly correlated (negatively) with age but not with gender (Fig. 2) This was confirmed by the VBR analysis which showed increased voxel counts in the presence of the age covariate with no further increase when the gender was added as a second covariate. The inclusion of the age covariate had a far greater impact on increasing the number of voxel counts that the inclusion of a gender covariate. The number of supra-threshold voxels was affected to a certain extent by the choice of the normalisation scheme (Fig. 3). A user-generated template for normalisation did not in general lead to a significant improvement in detection of temporal T2 changes with respect to the SPM template (Fig.3), however, the use of the T1-w template (approach (iii)) resulted in a marginal increase in voxel counts in the smaller structures. We identified the optimal combination over all of the analysis pathways for detection of hippocampal T2 increase with VBR. This optimal combination was: 6mm smoothing, 1 covariate (age), normalisation using either the SPM T2 template or via the T1-w images and corresponding T1 template.

Conclusions: This study has demonstrated the sensitivity of the VBR analysis method to the choice of several important parameters. It should be noted that the underlying basis of VBR is quite different to VBM in that T2 is a continuous whole-brain measure; this will influence the relative sensitivity of the two techniques to the preprocessing strategy. The optimal parameters choice is likely to be closely related to the size and characteristics of the area of T2 change.

References: (1) Ashburner J. et al., NeuroImage 8 :1105 (1997); (2) Pell G.S. et al, NeuroImage 21:707 (2004) ; (3) Specht K. et al., NeuroImage 25:287 (2005) ; (4) Townsend T. et al., NeuroImage 23:318 (2004)

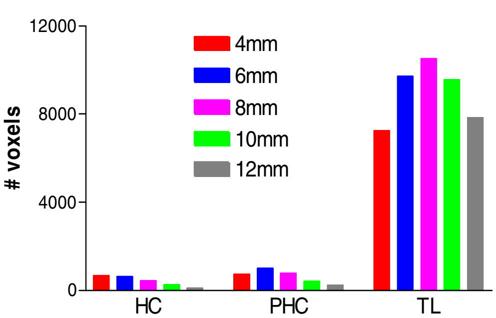

Fig.1: The effect of the smoothing kernel on the number of significant voxels observed in the ipsilateral hippocampus (HC), parahippocampal area (PHC) and temporal lobe (excluding mesial area, TL) areas (other parameters: 2 covariates, normalization via SPM T2 template).

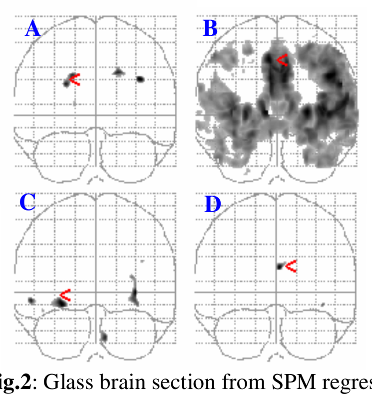

Fig.2: Glass brain section from SPM regression analysis of control T2 maps against the two covariates (i) age: positive contrast, (ii) age: negative contrast; (iii) gender: positive contrast, (iv) gender: negative contrast. Results shown for p=0.00005.

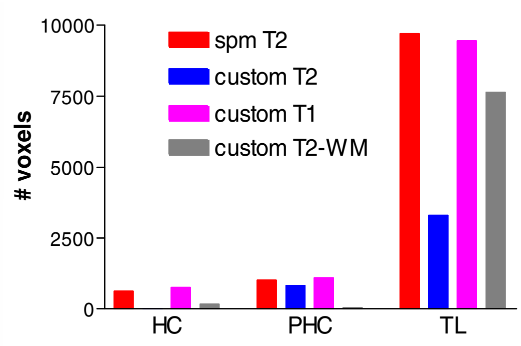

Fig.3: Effect of the 4 normalization schemes (see Methods) on the count of significant voxels in the brain areas described in Fig. 1 (other parameters: 6mm smoothing, 2 covariates).