Validation of voxel-based relaxometry using manual region-of-interest measurements

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***Introduction*:** Structural morphometric changes in groups of patients can be assessed by voxel-based morphometry (VBM). The voxel based approach has been extended to include the analysis of T_2 maps, termed voxel-based relaxometry (VBR) [1]. Traditionally, analysis of T_2 mapping data is based on manual placement of a region-of-interest over an anatomically defined area. The aim of this study is to determine the relationship between the results obtained with manual T_2 measurements and VBR analysis. We have used a group of mesial temporal lobe epilepsy patients with left hippocampal sclerosis to address this relationship. The patient group is ideally suited for the purpose of the study, as they have defined abnormalities in T_2 relaxation time, including markedly increased T_2 relaxation time in the affected hippocampus, as well as changes remote from the left hippocampus, particularly affecting the anterior temporal lobe white matter (ATL), amygdala, and contralateral hippocampus [2].

***Methodology*:** 24 patients with left sided hippocampal sclerosis and 24 age and gender matched controls were imaged on a 3T GE LX Horizon scanner. The T_2 mapping sequence was a standard Carr-Purcell-Meiboom-Gill (CPMG) multi-echo acquisition [8 echoes, echo times, TE = 28.875–231 ms (spaced at equal intervals); repetition time, TR = 4 s; slice thickness = 6 mm; slice gap = 1.5 mm; 10 slices; image matrix: 256 × 128; field-of-view, FOV = 24 cm; scan time, Tscan = 6.5 min]. The slices were acquired in a plane, perpendicular to the long axis of the hippocampus. T2 maps were generated by fitting to a mono-exponential model of T2 relaxation, that is, $S(t) = S(0) \exp(-t/T2) + k$, where S(t) is the signal acquired at each echo time, t. The baseline signal level, k, allows for small amounts of cerebrospinal fluid (CSF) to be present even in regions such as predominantly grey matter to help to reduce partial voluming errors.

ROI-measurements: Regional measurements of T_2 values were delineated on the second T_2-weighted image of the multi-echo acquisition, TE = 55 ms. Regions selected were the thalamus, the hippocampal head, temporal lobe white matter in the same plane as the hippocampal head, the parahippocampal gyrus, the hippocampal tail, the temporal lobe white matter in the same plane as the hippocampal tail, the amygdala, the anterior temporal lobe, the caudate nucleus and the frontal white matter. The hippocampal head was selected as the anterior hippocampal slice with the maximal area. The hippocampal tail was selected by choosing the most posterior slice without partial volume artefact where the hippocampal tail curves upward from an anterior-posterior direction to an inferior-superior orientation. *VBR analysis:* Details of the VBR methodology can be found in [1]. The output of the VBR analysis was a statistical parametric map of significant differences in T_2 between the two subject groups. The same regions listed above were delineated on the standard T_2-weighted MNI ICBM152 template. These delineated regions differed from the previous regions in that they were defined in standard space; therefore the segmentation was done once for each region rather than on an individual-by-individual basis as detailed in the previous section. The regions in standard space were used to inclusively mask the SPM output of the VBR analysis to give a regional measure of differences between the subject groups.

Results: Figure 1 shows the VBR results of regions with increased T2 in the patient group ($p < 0.05$, FWE). Increased T_2 was found in the left hippocampal head, and tail, and in the ATL . Table 1 shows the corresponding results for the manual analysis. For comparative purposes the final column in the table indicates whether the region is observed in the VBR analysis. Significant T2 increase was detected in the left hippocampal head and tail, the left parahippocampal gyrus, the left amygdala and the ATL. Significant increases were also observed in the contralateral, right hippocampus and ATL. Figure 2 shows a comparison of the regional test statistic for the manual analysis (x-axis) and the VBR-based analysis (y-axis). The figure demonstrates a significant linear fit between the manual and automated measurement of T_2 differences (solid line, $R = 0.538$, $p < 0.0005$).

Region	p-value	Observed in SPM image
Left Thal	0.259	
Right Thal	0.604	
Left Hipp Head	3.083E-7**	††
Right Hipp Head	0.097	
Left Hipp Head TL	3.035E-4**	††
Right Hipp Head TL	0.0207*	†
Left ParaHippG	0.0168*	†
Right ParaHippG	0.1495	
Left Hipp Tail	1.871E-4**	††
Right Hipp Tail	0.0475*	
Left TL Hipp Tail	0.0223*	
Right TL Hipp Tail	0.114	†
Left Amyg	4.064E-8**	†
Right Amyg	0.1042	
Left ATL	1.711E-7**	††
Right ATL	0.039*	†
Left Caud	0.819	
Right Caud	0.889	
Left FWM	0.041*	
Right FWM	0.077	

Table 1. p values for differences between manual ROI-based mean T_2 times of patients and controls using one-sided Student's t-test. *Statistically significant difference in means at 95% confidence level uncorrected for multiple comparisons ($p < 0.05$). **Statistically significant difference in mean T_2 at 95% confidence level using Bonferroni correction for multiple comparisons ($p < 0.0025$). † indicates the region was observed on the SPM image ($p < 0.001$ uncorrected) †† indicates the region was observed on the SPM image ($p<0.05$ FWE correction)

***Conclusions*:** The significant linear relationship between the test statistic obtained using automated VBR analysis and manual roi-based analysis indicates that regions of significantly increased T_2, as detected using VBR, also show increased T_2 in manual roi-based measurements. The VBR technique has the advantages of objectivity and ease of scalability. Additionally the ability to map T_2 changes on a voxel-by-voxel basis allows for improved spatial specificity – this is inevitably lost in region-of-interest based analyses due to the fact that regions consisting of a number of voxels are chosen for analysis. The ROI method is, however, more sensitive to detecting T_2 changes in some regions, such as the left amygdala. Table 1 indicates that although differences in T_2 in this region are highly significant when measured using a manual approach, these differences are only observed in the SPM output when the thresholds are not corrected for multiple comparisons. It is possible that these variations are due to slight misregistration when each image is warped to the standard template in the voxel-based analysis. It should be noted that the warping routine was developed for voxel-based morphometry. The aim of the warping step in the VBM approach is to maintain local structural differences whilst correcting for global differences in head/brain shape. For the VBR approach we are more interested in achieving exact (or as exact as possible) correspondence between the same brain regions in different subjects. The results of the VBR analysis may be improved by using a different warping routine.

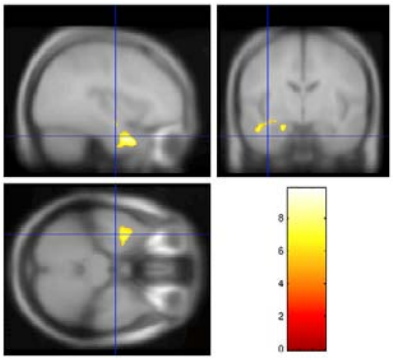

Figure 1: Statistical parametric map of significantly increased T_2 in mTLE patients with left-side hippocampal sclerosis ($p < 0.05$, FWE). The images are displayed in neurological orientation.

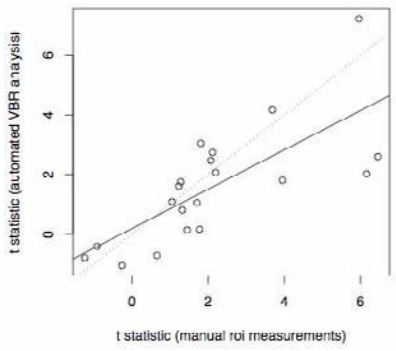

Figure 2: Comparison of differences in T_2 determined using manual roi-based measurements and automated VBR analysis. The solid line shows the line of best fit through the data, the dashed line indicates a line through the origin with slope = 1.

References:

[1] Pell, G.S., Briellmann, R.S., *et al* 2004. Voxel-based relaxometry: a new approach for analysis of T_2 relaxometry changes in epilepsy, NeuroImage 21, 707-713.
[2] Briellmann, R.S., Jackson, G.D. *et al* 2004. Structural abnormalities remote from the seizure focus: a study using T_2 relaxometry at 3 T, Neurology 28, 2303-8