Single subject voxel-based analysis in mesial temporal lobe epilepsy

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Introduction: Voxel-based morphometry is a widely used clinical tool for detection of voxel-wise structural shape changes in subject groups using MRI. A related technique, voxel-based relaxometry (VBR), may be used to map changes in T2. Traditionally the techniques have been used to compare groups of subjects. In this context, the voxel-based techniques may not be used for the categorisation of individuals. A particularly useful application of these voxel-based techniques would be the ability to image patterns of abnormal tissue volume or T_2 in an individual. Such an application would be useful for classification of individuals into particular pathological groups or assessing the extent of structural or pathological damage associated with a neurological disorder. Although the statistical validity of comparing a single subject to a control group may be of concern given there is no voxel-wise variance estimate in the individual, we may observe patterns of expected change in individuals with a known tissue pathology. In this study we use a group of mesial temporal lobe epilepsy (mTLE) patients with hippocampal sclerosis to evaluate the presence of the expected pattern of tissue abnormality in HS and thereby determine the validity of single subject comparisons. Traditionally hippocampal atrophy is assessed using hippocampal volume measurements and T_2 changes are measured using manual region-of-interest based measurements. These two measurements will be used as markers the severity of hippocampal sclerosis, and will be used for assessing the ability of single subject VBM and VBR analysis to detect affected hippocampi in this subject group.

Methodology: *Imaging:* 40 mTLE patients (23 female) with hippocampal sclerosis (34 left-sided) and 209 controls (115 female) were imaged on a 3T GE LX Horizon scanner. T_1-weighted 3D coronal images were acquired using an inversion-recovery 3D Gradient Echo MR imaging sequence (voxel size $0.48 \times 0.48 \times 2$ mm). 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. *Hippocampal Volume measurement:* Hippocampal volumes were measured in the mTLE group by manually segmenting the right and left hippocampi from the 3D T_1-weighted images in the coronal plane, and summing the areas of these segmented slices. The total intracranial volume (TIV) of each subject was measured and the hippocampal volumes were measured as a percentage of TIV. *ROI-based T_2 measurement:* The representative T_2 for each hippocampi was measured by placing a circular region approximately 1 cm in diameter over the hippocampal head on the second echo (TE = 58 ms) from the multi-echo acquisition. This region was copied onto the T_2 map and the mean T_2 was measured. *VBR/VBM analysis*: The VBR methodology is outlined in [1]. Each individual mTLE subject was compared to our control population, using T_2 mapped data for the VBR analysis and structural T_1-weighted coronal images for the VBM analysis. The VBM analysis investigated decreases in gray matter in the patient group. A 6mm gaussian smoothing kernel was used in both analyses. The individual right and left hippocampi were used to inclusively mask the SPM t-score image that represented a volume decrease (VBM) and a T_2 increase (VBR) in these regions. The number of voxels that demonstrated a significant one-tailed t-score ($t > 1.65$) in each hippocampus was counted for both the VBM analysis and the VBR analysis.

Results: The volume of the ipsilateral hippocampus is significantly smaller than the contralateral hippocampus for this subject group ($p < 5E\text{-}9$). Similarly the T_2 of the ipsilateral hippocampus is significantly higher than the contralateral hippocampus for this subject group ($p < 5E\text{-}5$). Figure 1 shows a comparison between the single subject VBM analysis and the hippocampal volumes for each subject. The horizontal axis indicates the hippocampal volume for a hippocampus expressed as a percentage of the total intracranial volume. The vertical axis indicates the number of voxels with significantly decreased gray matter concentration in an inclusive mask of the hippocampus when the mTLE patient is compared to controls. The fitted line indicates there is a significant inverse relationship between these two parameters ($R = 0.173$, $p < 1E\text{-}4$). Figure 2 demonstrates the relationship between the single subject VBR analysis and the hippocampal T_2 for each subject. The horizontal axis indicates the characteristic T_2 for each hippocampus and the vertical axis indicates the number of voxels with a significantly increased T_2 in an inclusive mask of the hippocampus when the T_2 map for the mTLE subject is compared against the T_2 maps of controls. The fitted line indicates there is a significant positive relationship between these two parameters ($R = 0.484$, $p < 1E\text{-}7$). Figures 3 and 4 show the results of single subject VBM (Fig. 3) and VBR (Fig. 4) analyses of the same individual. The images are displayed in neurological orientation. Figure 3 indicates significant gray matter decrease ($p < 0.05$ uncorrected for multiple comparisons) in the left hippocampus, the left anterior temporal lobe and other small clusters in various cortical regions. Figure 4 indicates significant T_2 increases ($p < 0.05$, uncorrected for multiple comparisons) in the left hippocampus, left anterior temporal lobe, right hippocampus and other regions.

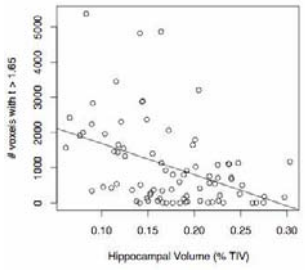

Figure 1. Number of significant voxels in the left and right hippocampi of single mTLE patient with HS compared with x number of controls against hippocampal volume.

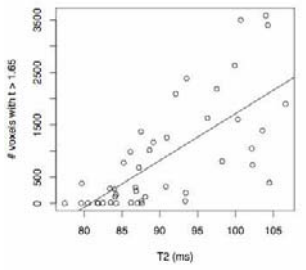

Figure 2. Number of significant voxels in the left and right hippocampi of single mTLE subject with HS compared with x controls against T_2 measured using manual ROI measurement.

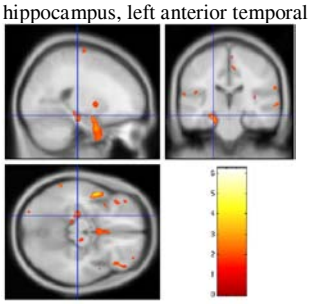

Figure 3. Example VBM analysis of subject 27 with left HS compared with x controls. The image is displayed at an uncorrected threshold ($p < 0.05$).

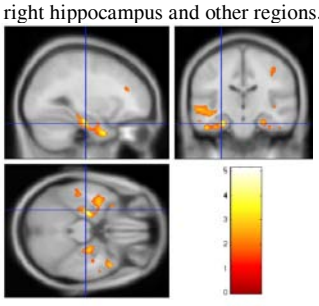

Figure 4. Example VBR analysis of subject 27 with left HS compared x controls. The image is displayed at an uncorrected threshold ($p < 0.05$).

Conclusions: Figure 1 indicates that a lower hippocampal volume, representing hippocampal atrophy, does result in more voxels reaching the threshold for display in the SPM output of the VBM analysis. Similarly higher hippocampal T_2 values are correlated with higher numbers of voxels over the minimum threshold in the VBR analysis (Fig 2). These results indicate that the SPM output of a single subject VBM and VBR analysis can detect regions in which there is known to be pathological tissue damage. Increased T_2 remote from the ipsilateral hippocampus (Fig 4), including the contralateral hippocampus, has been previously reported [2], and this result is reflected in the lower significance when comparing manual T_2 measurements of ipsi- and contralateral hippocampi as reported in the results section (compared to hippocampal volume decrease). Although the technique is able to detect regions of known tissue change, the results of this study do not address the issue of whether changes detected in regions remote from the hippocampi reflect a pathological difference in morphology (VBM) or T_2 (VBR). In spite of this caveat, the results of this study suggest that single subject VBM and VBR analysis may prove to be a useful diagnostic aid, particularly in epilepsy research, in which different epilepsy syndromes have different spatial patterns of seizure activity. Given an informed knowledge of the potential misinterpretation of single subject VBM and VBR analyses, this study demonstrates that single subject VBM and VBR may be used for clinical assessment of whole brain structural change in patients.

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