Assessing the Effect of Age on Voxel-Based Relaxometry of Epileptic Patients

R. Sharkey[1,2], R. K. Kosior[1,3], P. Federico[1,2], and R. Frayne[1,2]

[1]Seaman Family MR Research Centre, Foothills Medical Centre, Calgary, AB, Canada, [2]Radiology and Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada, [3]Biomedical Engineering, University of Calgary, Calgary, AB, Canada

INTRODUCTION

T2 weighted MR imaging can be helpful in locating epileptogenic lesions since a correlation has been found between the presence of epileptogenic tissue and elevated T2 relaxation time.[1] T2 relaxometry (quantitative assessment of T2 relaxation time) is a sensitive tool for identifying T2 abnormalities.[2] T2 Voxel Based Relaxometry (VBR) is a technique which performs a voxel-level statistical comparison of quantitative T2 maps to identify regions with significantly elevated T2 relaxation time.[3] VBR may thus depict the locations and extents of T2 abnormalities. This whole brain, objective technique has been shown to be useful both as a research tool for examining groups of patients and for clinical evaluation of single patients[4], and also in cases of cryptogenic focal epilepsy where the seizure focus is uncertain[5]. With T2 relaxometry and VBR, one important consideration is that causes other than epilepsy may also produce increased T2, leading to false-positive T2 changes attributed to epilepsy. The process of aging, for instance, in healthy individuals may lead to tissue changes that manifest as T2 changes. There is some evidence that T2 relaxation time changes with age.[6, 7] This may have important implications considering the broad age range of studied patients. To this end, our objective was to assess the effect of age on T2 for VBR analysis using an expanded group of healthy controls with voxel-based statistical analyses.

METHODS

We scanned 44 healthy volunteers (controls) and 25 right temporal lobe epilepsy (RTLE) patients who provided written informed consent. A modified Carr-Purcell-Meiboom-Gill (CPMG) sequence was performed at 3 T (Signa VH/i; GE Healthcare, WI). The CPMG sequence parameters were: 8 echoes, TE 30 ms to 240 ms, TR = 2175 ms, 256 x 128 matrix, 24 cm FOV, 15 to 24 slices, 5 mm thick, 1 mm gap. T2 maps were generated using a Levenberg-Marquardt non-linear fitting routine with a baseline to account for cerebrospinal fluid partial-volume. The T2 maps were spatially normalized (T2-weighted template) and smoothed (Gaussian filter, 6 mm full width half maximum) with SPM2 (FIL Methods Group, UK, 2004) using previously described methods.[3, 4] To ascertain whether age could be correlated with T2 relaxation time, two simple regressions of age and T2 were run with SPM2 at thresholds of $\alpha = 0.001$ and $\alpha = 0.05$. The normalized 3rd-echo images from all 44 controls were averaged to produce an average anatomical brain map and then regions of interest (ROIs) were placed in 13 regions (Fig 1). ROI measurements were averaged from ROIs placed on both the left and right side of the brain and on both axially and coronally sliced image (4 per location) to increase the sample size and minimize ROI placement variability. These results were plotted against age and a linear regression was performed from which the slope, R^2 value and *P* value were obtained for comparison between regions. To determine the impact of age VBR analysis a single-subject VBR assessment was carried out for the controls and for the RTLE patients. Statistical analysis of the smoothed T2 maps was performed using a two-sample student's t-test between individual controls and the remainder of the controls, and between individual patients and the control group using SPM2 ($\alpha = 0.05$). For each subject, VBR was performed once with age included as a nuisance variable, and once without. The number and location of significant T2 elevations on VBR maps were recorded based on the presence of VBR significance in the same regions assessed for the ROI analysis, except both grey matter and white matter were considered for those lobes where only white matter ROIs were placed.[4]

RESULTS

There were 44 controls studied, with a mean age of 37 yr ± 15 yr (standard deviation, SD), a range of 18–70 yr, composed of 24 females (55%). There were 25 right temporal lobe epilepsy (RTLE) patients studied with a mean age of 42 yr ± 13 yr (SD), a range 20–67 yr, composed of 17 females (68%). We broke down our control group into age groups of < 20 yr, > 60 yr, and 5 yr age groups in between. Each age group had a minimum of 2 patients. Age regression at $\alpha = 0.001$ showed small localized regions of significance, most notably in the putamen and hippocampus (Fig 1). When the regression was repeated at $\alpha = 0.05$ the areas of significance were much more extensive, covering much larger areas surrounding the putamen and hippocampus and stretching into the amygdala and large significant areas were also present in the frontal lobe white matter. A large degree of significance was detected around the edges of the brain and near areas of CSF. Analysis of the ROIs showed variable slope and R^2 values across the brain, but revealed a general trend for white matter T2 to increase with age and grey matter T2 to decrease with age (Fig 1). The trend was significant ($p < 0.05$) in the frontal lobe white matter, hippocampus, caudate and putamen. Controls had, on average, a reduced occurrence of significant regions and greater variability between individuals than did the RTLE group. A graph of the discrepancies between the two VBR scores shows increased discrepancy between the young and old, with a greater degree of correlation closer to average age (Fig 2).

DISCUSSION

The areas of significance found in the voxel-based linear regression correspond to those regions found to be significant by the ROI-based linear regression. There is good corroboration between the results of the linear regression and the VBR severity scores. Most previous reports have failed to identify any correlation between age and T2 relaxation time. However a previous study found a significant negative relationship between age and T2 time in the caudate, putamen and hippocampus in healthy controls at a significance of $\alpha = 0.01$ with stepwise and simple regression, which is an agreement with our findings.[6] The age related increase in T2 time in the frontal lobes could possibly be a result of normal age related microvascular white matter changes.[8] The insular ribbon is discordant with the other findings, though partial volume effects with adjacent CSF may be a confounding factor. As expected, both ends of the age range in Fig 2 exhibit a higher rate of discrepancies between the two VBR scores with those closer to average age showing comparatively few. The variability of T2 changes throughout the brain suggests that a global scaling factor is not sufficient to adjust for age, and that age should be adjusted for at the voxel-level in VBR analysis, especially since highly epileptogenic regions such as the hippocampus show a significant correlation with age.

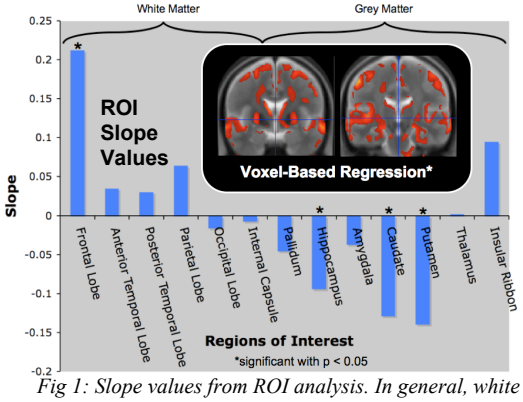

Fig 1: Slope values from ROI analysis. In general, white matter regions show increased T2 with age while grey matter regions show decreased T2. The insular ribbon is discordant with the other findings, though partial volume effects with adjacent CSF may be a confounding factor.

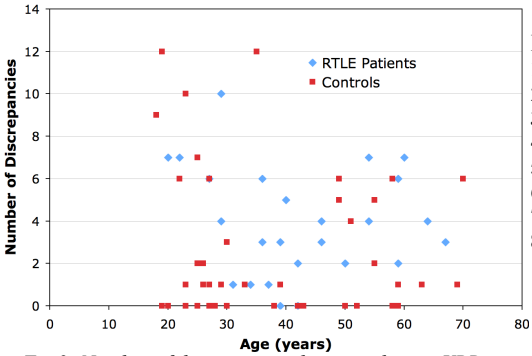

Fig 2: Number of discrepancies between the two VBR severity scores (with and without age as a nuisance variable) for each patient and control. As expected, the graphs show the greatest discrepancies at the younger and older ages.

References

1. Bernasconi A, *et al*. Neuroimage 2000;12:739
2. Jackson GD, *et al*. Neurology 1993;43:1793
3. Pell GS, *et al.* Neuroimage 2004;21:707
4. Kosior RK, *et al*. Epilepsy Res 2009;86:23
5. Rugg- Gunn FJ, *et al*. Neurology 2005;64:318
6. Briellman RS, *et al*. Neurology 2004;63:2303
7. Scott RC, *et al*. Brain 2003;126:1968
8. Yoshita M, *et al*. Top Magn Reson Imaging 2005;16:399