Classification of Alzheimer's disease using T_2 distribution parameters from 3T MRI

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Introduction

Reports have suggested a relationship between abnormalities of brain iron metabolism and neurodegenerative diseases [1]. The newly available, high-field, high-resolution 3T scanners enhance the iron dependent MR contrast, the major effect being a reduction in T_2 with little effect on T_1 [2]. Simultaneously, increased T_2 values have been seen in studies [3] and histopathological examinations have confirmed this increase to be associated with increased water content. In this study, we define features that measure T_2 shortening and T_2 lengthening on 3T MRI and establish their role in characterizing Alzheimer's disease (AD).

Methods

The study involved 24 probable AD patients and 20 age-matched cognitively healthy controls. Dual spin-echo images (TE=18,80ms) and registered T1-weighted images on these patients were acquired using a 3T scanner. Fifty-four coronal slices with continuous coverage from the temporal pole to the dentate nucleus were obtained in a 12-minute scan. Five ROIs (intracranial space, hippocampus, caudate, putamen, nucleus basalis/ventral pallidum area) were manually segmented using the T_2-weighted SE images and T_2 histograms were generated for each ROI.

Features extracted were related to the lower and upper tails of the T_2 distributions: lower tail probabilities (% of voxels in the ROI with T_2 less than empirically derived thresholds), the 5th (P5) and 10th percentiles, upper tail probabilities and 90th (D9) percentiles. The T_2 histograms were smoothed using a Γ-variate [4] function [$f(T_2) = A(T_2 - B)^C \exp(-(T_2 - B)/D))$]. A hybrid three-component (H3C) model, with an exponential in the left and the right tails, and a Γ-variate in the middle was developed. This three-component model is consistent with the hypotheses of reduced T_2 due to increased brain iron from voxels in the lower tail and increased T_2 due to increased water content in the voxels in the upper tail. Hierarchical clustering of normalized features was used to determine correlated groups of features. A graphical display is used to convey the clustering and the significance of the features simultaneously in a manner that is easily understood by clinicians. A classifier was built using features selected from among the low tail, high tail, C and D and other shape parameters by stepwise discriminant analysis and further validated using leave-one-out cross-validation.

Results and Discussion

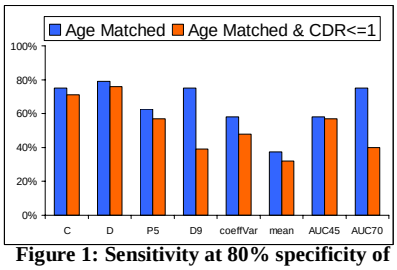

Figure 1: Sensitivity at 80% specificity of selected features from hippocampus

The mean (sd) of age in the AD group was 69.7 (6.9) years and 46% were female. In the control group, the mean (sd) of age was 68.2 (8.1) years and 60% were female. The mean (sd) Median Absolute Percentage Error from the Γ-variate fit to the hippocampus T_2 histogram was 76% (9%) and this was reduced to 46% (9%) with the H3C model. Figure 1 shows the sensitivity at 80% specificity of the H3C model parameters (C and D), along with low (P5 and AUC45) and high tail features (D9 and AUC70) found significant in earlier studies [5] and other statistical measures of mean and spread from the hippocampus T_2 histogram. Figure 1 suggests that the shape parameters C and D of the T_2 distribution are robust discriminators between AD and controls. There was a significant drop in sensitivity of the high tail features D9 and AUC70 when the analysis was restricted to a subset of subjects with CDR known <=1 (21 AD and 19 controls). This is consistent with earlier histopathological findings [3] that increase in T_2 is associated with increased water content as seen in more advanced stages of the disease.

Figure 2: T_2 distribution in hippocampus regions (yellow–T_2<= 45ms, green– T_2 > 70ms)

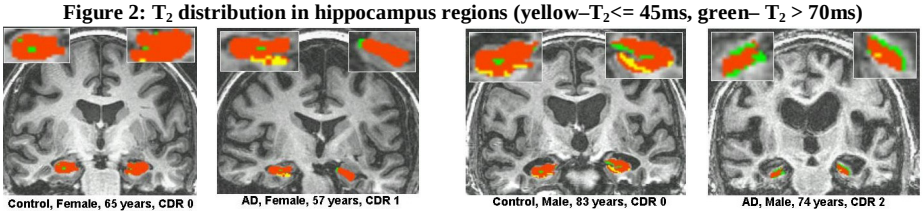

Figure 2 shows the T_2 distribution with regions of low T_2 (yellow) and high T_2 (green) highlighted in the hippocampus. In the younger AD and control (left panels), the difference is in the low T_2 (yellow) while in the older AD and control (right panels), the difference is in the high T_2 distributions (green). Of the large number of features extracted from all the ROIs, more than 50 features were found to be statistically significantly different in ADs and controls (see Figure 3, left panel). The most significant features appear red in AD and a mixture of red and green in the controls. Hierarchical clustering shows that the significant features fall into 4 main groups (see Figure 3, right panel): whole brain, Γ-variate, low T_2, and a mixture of spread and high T_2 measures. Using stepwise discriminant analysis, the selected features from the 5 ROIs included C, D and exponential rate parameters from the H3C model for the hippocampus T_2 histogram, C from Putamen, D from caudate, as well as Putamen and hippocampus volumes. The best performance was achieved with a k-nearest neighbor classifier (k=5). The misclassification rate following cross-validation was 7% on the age-matched data and 10% on the CDR <=1 subset.

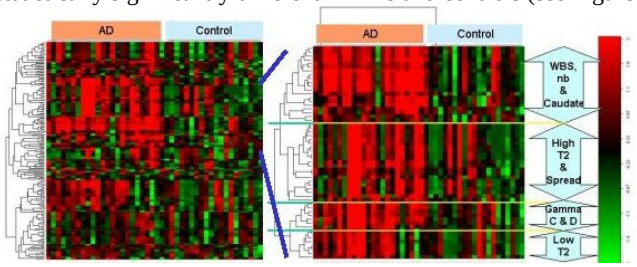

Figure 3: Heat map showing feature clustering

Conclusions

Our analyses show that descriptors of T_2 histograms such as those that capture lower tails, upper tails, spread and overall shape parameters are particularly relevant to the presence of AD. The visualization technique also provides a uniquely intuitive mechanism to integrate a panoply of other marker information: behavioral, cognitive, genetic etc and also identify individuals at risk for AD. These techniques offer a promising method of using T_2 histogram analysis for a wide variety of neurological diseases.

References

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