ROC analysis based visualization of pathological brain regions in patients with epilepsy using multi-modal MR Imaging (DWI, T2 and CSI)

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Introduction

Multimodal MRI can be a valuable tool in the assessment of structural and metabolic deviations in patients with a certain cerebral disease. For example, diffusion and T2 weighted MRI may provide valuable structural information in terms of cell swelling or presence of edema, whereas spectroscopic imaging (CSI) provides metabolic information, e.g. one of the observable metabolites, NAA, is a (surrogate) marker for neuronal cell loss or dysfunction. For the assessment of the exact pathological state of local tissue, the outcomes of all three modalities have to be combined and interpreted as a whole (considering all possible combinations of either increased or decreased values). Therefore it is important to analyze the data from multiple modalities using a general method that is insensitive to the inherent differences between the modalities (e.g. contrast mechanism or spatial resolution). We implemented a receiver operating characteristic (ROC) curve analysis based visualization of abnormal brain regions in patients with epilepsy using three MRI modalities, namely diffusion and T2 weighted imaging and CSI.

Material and Methods

Thirteen healthy subjects (aged 23–57 years, median 26) and ten epilepsy patients with secondarily generalized seizures (aged 23–55 years, median 40) were included. Whole cerebrum imaging was performed with a clinical 1.5 T MRI system (Philips Intera, Philips Medical Systems), which was equipped with a standard quadrupolar head receiver coil. The protocol included a 3D T1-weighted fast field-echo sequence [TR 11 ms, TE 3.5 ms, flip angle 90°, matrix 256×256, 150 contiguous slices, 3.5×3.5×3.5 mm^3 sized voxels], a dual-echo turbo spin echo sequence (TSE-Dual) [TR 5211 ms, TE 11.9 ms/80 ms, matrix 256×256, FOV 204×112 mm^3], a DW multi-shot echo-planar imaging (EPI) sequence [EPI-factor 31, b-values 0/400/800/1200 s/mm^2, 3 orthogonal diffusion sensitizing directions, TR 2 cardiac cycles, TE 76 ms, matrix 128×128, FOV 230×230 mm^2], and a turbo spectroscopic sequence [turbo factor 3, 1 slice, 24×24 voxels per slice, FOV = 230×230 mm^2, slice thickness = 20 mm, TR = 2.5 s, TE = 272 ms, a nominal voxel size of 1.84 ml, localization PRESS, water suppression CHESS]. All images were co-registrated and spatially normalized to Talairach space. A percentile volume CSF map was created by attributing to each pixel a CSF percentage (λ_{CSF}) on a scale of 0-100%, based on their T2 relaxation times calculated from the dual-echo images. Tissue was segmented from CSF by incorporating the cut-off $\lambda_{CSF} \leq 10\%$. Maps of the apparent diffusion coefficient (ADC) were calculated by second order polynomial fitting of the direction averaged logarithmic signal intensities versus b-values. T2 maps were calculated on a pixel-by-pixel basis using the logarithm of the ratio of signal intensities at the two TE's. Mean metabolite ratios NAA/(Cr+Cho) maps were obtained through Gaussian fitting, and all voxels with a NAA peak linewidth >2 and <9 Hz were included for analysis. Analysis for the T2, ADC, and NAA/(Cr+Cho) maps was performed in predefined regions (left, right, and bilateral) in the frontal and temporal lobe. For the T2 and ADC maps of the patients statistical z-scores (defined as $[(x_i - x_{mc})/SD]$) maps were calculated on a pixel-by-pixel basis from the spatially normalized mean values (x_{mc}) of the controls. The NAA/(Cr+Cho) maps of the patients were converted into z-scores maps, using linear regression analysis (calculated for the control group) of the NAA/(Cr+Cho) values within the predefined regions using the white matter content in a voxel (obtained from segmentation of T1-weighted images) as an independent variable. The z-scores maps of the control group were based on the values of the other controls (n-1). To determine the cut-off z-score for which the most optimal separation is possible between the control and patient group, for each z-score map (corresponding to the T2, ADC and NAA/(Cr+Cho) maps) the fraction of abnormal voxels (number of 'deviating' voxels / total number of valid voxels within the predefined region) per subject (either patient or control) was used as input for ROC curves as function of z-score. The optimal z-score (e.g. the z-score where the separation between the patient and control group is maximal) was then determined by finding the z-score with the maximum area under the ROC curve, which corresponds with the z-score for which the statistical expression (H_0: true area under ROC curve = 0.5) yields the lowest p-value. This optimal z-score was then used to visualize per patient for each modality for each mask the 'deviating' voxels, which can be interpreted as pathological voxels.

Results

In Figure 1 the area under the ROC curve using the fraction of abnormal voxels within the left frontal lobe as function of z-score is shown, together with the statistical significance p, for all three modalities. Indicated with arrows are the optimal z-scores for the ADC, T2 and NAA/Cr+Cho data (within the left frontal lobe). Table 1 displays the fraction of abnormal voxels obtained for each MRI modality for all brain regions. A qualitative assessment might indicate that the sensitivity to detect abnormal tissue might decrease from CSI>T2>ADC. The pathological nature of detected abnormal voxels might be more confident from CSI<T2<ADC. In Figure 2, the pathological voxels (using these optimal z-scores in the left frontal lobe) for the three modalities are shown in a male, 56 year old patient with temporal lobe epilepsy. Within the region marked with a red circle in Fig.2a, one can observe many pathological voxels with increased ADC and T2 values, and decreased NAA/Cr+Cho levels, which is indicative of neuronal damage. Within the blue circle there are hardly any pathological voxels for ADC and none for NAA/Cr+Cho, which indicates that the diffusional and metabolic properties of this region are normal, whereas only the T2 map shows increased values, which are possible due to benign cell swelling.

Fraction of abnormal voxels		ADC	T2	CSI
Frontal lobe	left	0.15 ± 0.11	0.09 ± 0.13	0.22 ± 0.22
	right	0.01 ± 0.01	0.10 ± 0.12	0.44 ± 0.36
	total	0.01 ± 0.01	0.10 ± 0.12	0.32 ± 0.30
Temporal lobe	left	0.02 ± 0.02	0.15 ± 0.15	0.45 ± 0.37
	right	0.02 ± 0.02	0.06 ± 0.08	0.09 ± 0.12
	total	0.02 ± 0.02	0.05 ± 0.06	0.04 ± 0.06

Table 1: Fraction of abnormal voxels for each MRI modality.

Discussion

Using the developed method one can visualize abnormal, potentially pathological, regions as detected through inherently different MRI modalities, which enables an analysis of the local pathological state of brain tissue in a patient with a certain cerebral disease. Further research is required to investigate the exact synergy between the three modalities (e.g. importance of (non-)overlap of abnormal voxels) and their combined sensitivity to detect and characterize pathological brain regions.

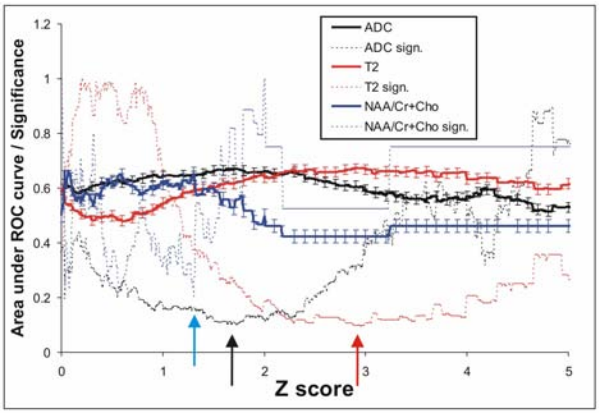

Fig.1: Area under ROC curve (obtained from the fraction of abnormal voxels within the left frontal lobe) (thick line) and statistical significance (p-value) (thin dotted line) as function of z-score, for the ADC (black), T2 (red) and NAA/Cr+Cho (blue) maps. The optimal z-scores are indicated with arrows. Error bars display SEM.

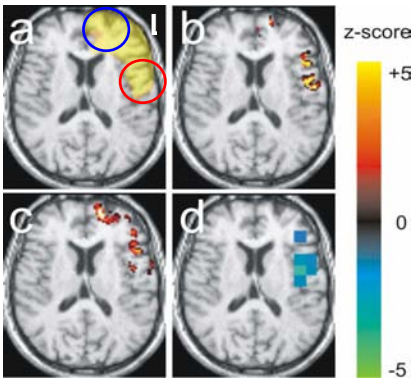

Fig.2: a) left frontal lobe mask (yellow) and pathological regions therein obtained from the b) ADC c) T2, and d) NAA/(Cr+Cho) maps overlaid on a tilted normalized transversal T1-weighted MR image of a TLE patient (male, 56 y).