Quantitative MR at 3.0 T of patients with non-symptomatic localization-related epilepsy: association with generalized and partial seizures

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Introduction

Decline of cognitive function is the most frequent co-morbid disorder in epilepsy, particularly in patients with non-symptomatic localization-related epilepsy [1]. Whether repeated brief seizures induce neuronal damage, and whether they are related to possible cognitive deterioration is still unknown and remains to be elucidated [2]. In recent years evidence is growing that localization-related epilepsy with partial seizures alone may also constitute a risk factor for cognitive impairment [3]. Currently, no clear evidence is available which factors contribute to cognitive impairment in localization-related epilepsy. Characteristics that describe the chronicity of epilepsy, such as duration and number of seizures, are most likely related to the deterioration of the mental status. Not much is known about the brain-behavior relationships, i.e. what neuronal mechanisms underlie the cognitive changes. Emerging experimental studies in chronic (animal) models and human MRI and neuropsychological studies are providing new information about adverse long-term consequences of seizures (e.g. [2,4]). To determine which neuronal correlates are identifiable for cognitive impairment in living human patients, MR techniques such as T2 relaxometry, diffusion tensor Imaging (DTI), and chemical shift imaging (CSI) seem most suited. This research was devised to explore a neurobiological and microstructural explanation for cognitive deficits in patients with non-symptomatic epilepsy, and to assess the relationship with seizures.

Material and Methods

Subjects The study population included 44 patients with non-symptomatic (i.e. no MRI visible lesions at 3 T) epilepsy (21F, 23M, age 40±12y), and 23 healthy volunteers (14F 9M, age 40±14y). For patients, seizure focus, as obtained from EEG was frontal = 17, temporal 14, and frontotemporal = 13. The total number of secondarily generalized seizures experienced (SGS) and partial seizures (PS) during life-time were tabulated for all patients. All subjects underwent extensive tests for intelligence (WAIS-III). ***MRI*** MRI was performed with a 3.0-Tesla whole-body unit (Philips Achieva [software release 1.5.4.0], Philips Medical Systems, Best, The Netherlands. Each session consisted of an imaging part using an 8 channel SENSE head coil and a spectroscopy part using a T/R head coil. For anatomic reference, first T1-weigthed three-dimensional (3D) turbo field echo (TFE) images were acquired with the following parameters: repetition time (TR) 9.91 ms, echo time (TE) 4.6 ms, inversion time (TI) 3 s, flip angle 8°, matrix 256x256x160, field of view (FOV) 256x256x160 mm3, 1 mm adjacent coronal slices. For T2 quantification a 3D TSE-Dual was performed, using: TR 2500 ms, TE_1 10 ms, TE_2 110 ms, matrix 256x256x100, FOV 256x256x200 mm_3, 2.0 mm adjacent coronal slices, SENSE factor 1.5 left-right. DTI images were obtained with a EPI-SE sequence, using: b-values 0 and 800 s/mm_2, TR 6600 ms, TE 62 ms, 15 gradient directions for diffusion sensitization (gradient overplus on), matrix 128x128x66, FOV 256x256x132 mm^3, 2 mm adjacent transverse slices, SENSE factor 2.5 anterior-posterior. Two slices were selected for spectroscopic imaging, one accommodated in the temporal and one in the frontal lobe, respectively, using: 20x20 voxels per slice, FOV 256□256 mm_2, slice thickness 20 mm, TR 2.0 s, TE 30 ms, a nominal voxel size of 3.3 ml, echo acquisition half echo. Localization and water suppression was achieved with PRESS and CHESS, respectively. ***Analysis*** The T2 was calculated (in ms) on a voxel-by-voxel basis using the signal intensities of the images obtained at the two echo times (Matlab). From these values also a percentile volume cerebrospinal fluid (CSF) map was calculated [5]. The ADC (in $10^{-6}mm^2/s$) and FA (in %) maps were calculated utilizing CATNAP. The T2-, CSF-, FA- and ADC-maps were co-registrated and spatially normalized to MNI space using SPM2, to facilitated analysis of brain regions with masks. These mask included left and right frontal and temporal lobes and manually drawn hippocampi [6]. Grey matter (GM; containing neurons) and white matter (WM; containing axons) were analyzed separately in the frontal and temporal lobes, using specific maps obtained from segmentation of T1-weighted images (SPM2). Metabolite quantification was performed using LCModel (v6.1-4). Concentrations are reported averaged over region (left/right frontal/temporal) relative to creatine. The metabolite estimations for choline (Cho), myoinositol (mI), n-acetyl-aspartate (NAA) and glutamate/glutamine (glx) were analyzed. Metabolite estimates were excluded from analysis, if the Cramer-Rao minimum variance exceeded the 20% range. Additionally, at least 10 voxels had to contribute to the average of a region. T2-, CSF-, ADC-, and FA-maps were smoothed using a Gaussian kernel with FWHM of 6 mm.

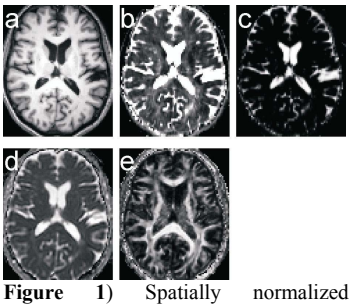

Figure 1) Spatially normalized transverse (a) T1-weighted, (b) T2-, (c) CSF-, (d) ADC-, and (e) FA maps of a patient with epilepsy.

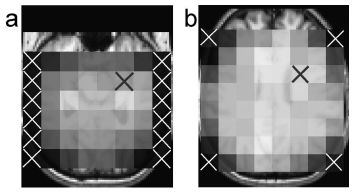

Figure 2) CSI data of the same patient. The NAA map in (a) the temporal and (b) frontal slice of voxels satisfying the quality control requirements, overlaid on T1-weighted images.

Statistics Differences between patients and controls were calculated with two-tailed Student's t tests, where ($p<0.05$) indicated statistical significance. Additionally, MR parameters and IQ were correlated with seizure total (SGS and PS) using the non-parametric Spearman correlation. Firstly, correlations between PS and SGS were calculated for the selected significant different MR parameters ($p<0.05$), secondly SGS and PS were correlated with the full set of MR parameters ($p<0.01$ to compensate for multiple corrections).

Results and Discussion

Patients with epilepsy displayed significantly lower IQ values (96±15), compared to healthy controls (113±15), which indicates that the patients indeed have cognitive problems. Furthermore, quantitative MRI revealed a significantly higher CSF fraction in the left (0.10±0.04 vs 0.07±0.02) and right hippocampus (0.15±0.04 vs 0.12±0.03). The ADC of the GM fraction of left frontal (886±58 vs 856±35 $10^{-6}mm^2/s$) and temporal lobe (868±56 vs 842±21 $10^{-6}mm^2/s$) was significantly higher than in controls. These findings are consistent with studies that show that chronic neuronal damage due to seizures can be associated with increased water content, leading to increased pericortical CSF fractions, and ADC values [7]. And finally, glx in the left frontal lobe (1.7±0.1 vs 1.6±0.2) was significantly higher than in controls. As glx contains the excitatory neurotransmitter glutamate, a higher glx could indeed be plausible for the epileptic brain. Within the patient group, IQ did not correlate with seizure totals SGS and PS ($p>0.19$), which indicates that cognitive decline is not entirely caused by seizures. We set out to address whether the observed microstructural and metabolic differences between patients and controls could be correlated with seizure total. It was found that the ADC of the GM fraction of left frontal displays a positive correlation with PS total ($\rho=0.41$, $p=0.012$), suggesting a causal relationship between PS and ADC values. However, glx in the left frontal lobe displayed a negative correlation with PS ($\rho=-0.37$, $p=0.025$). This apparent conflicting result could be due to the fact that glx is not purely glutamate, but also contains glutamine. SGS did not show significant correlation with the selected MRI measures. For the full set of MR parameters, SGS showed a negative correlation with the CSF fraction of the right temporal lobe ($\rho=-0.44$, $p=0.005$), and PS showed a positive correlation with the T2 of the WM fraction of left temporal lobe ($\rho=0.44$, $p=0.005$) and with the ADC of the WM fraction of left frontal lobe ($\rho=0.40$, $p=0.09$). The observed positive associations of PS with T2 and ADC are consistent with PS-induced increased water content [7]. In contrast, SGS displays a negative correlation with CSF, which is not consistent with that finding.

Conclusion

Quantitative MR techniques, including T2 relaxometry, DTI, and CSI, can be successfully applied to assess possible neuronal correlates for cognitive co-morbidity in patients with non-symptomatic localization-related epilepsy. Associations of PS with quantitative MR are consistent with previously reported chronic neuronal damage (i.e. increased water) due to seizures [7]. Associations of SGS with quantitative MR seem to be conflicting and might hint at a different underlying mechanism which requires further investigation.

References

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