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Quantitative MR and cognitive impairment in cryptogenic localisation-related epilepsy

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ABSTRACT – For patients with chronic cryptogenic localisation-related epilepsy (CLRE), conventional MRI does not provide measures to discern between patients with or without cognitive complaints. We investigated, in a preliminary study, whether it is possible to detect cerebral biomarkers of cognitive impairment in patients with CLRE using sensitive quantitative MRI techniques. Neuropsychological assessment and quantitative 3.0 T MRI, comprising T2 relaxometry, diffusion tensor imaging, and spectroscopic imaging, were applied to 35 patients with CLRE and 21 healthy controls. Analysis included the left and right hippocampi, and frontal and temporal lobes. Differences between the groups and correlations with cognitive and clinical characteristics were assessed. Patients with epilepsy scored significantly worse on cognitive tasks compared to healthy controls. Significantly larger CSF fractions in the hippocampi and left temporal lobe, a longer T2 relaxation time in the left hippocampus, and a significantly higher concentration of glutamate/glutamine in the left frontal lobe were observed in patients with epilepsy. Moreover, poor memory performance was significantly correlated with larger CSF fractions in the right hippocampus and left temporal lobe in patients. In the temporal lobe, an association between subtle changes in morphology (indicative of atrophy) and memory performance was found, consistent with previous literature. These results may help to explain the alterations in brain functioning in patients with epilepsy.

Key words: cognition, diffusion tensor imaging, localization-related epilepsy, memory, MR spectroscopy, MRI-negative

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Cryptogenic localisation-related epilepsy is characterised by the presence of a localised seizure focus, without a visible lesion on structural brain MRI (MRI-negative). In addition to the disabling impact of recurrent seizures, cognitive impairment (including mental slowing and [working] memory impairment) often occurs at the same time in

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cryptogenic localisation-related epilepsy (Oyegbile *et al*., 2004; Oyegbile *et al*., 2006; Patrikelis *et al*., 2009). Currently, no clear evidence is available for which factors contribute to cognitive outcomes in patients with cryptogenic localisation-related epilepsy. Age at onset, seizure frequency, and disease duration (*i.e*. semiological characteristics that describe the chronicity of epilepsy) are most likely to be associated with cognitive impairment (Dikmen and Matthews, 1977; Upton and Thompson, 1997). However, none of these measures can sufficiently predict cognitive impairment in epilepsy.

MRI investigations may provide a better insight into the pathology of the cognitive comorbidity. MR techniques not only provide a means for a non-invasive procedure to study the macrostructural effects of epilepsy in the human brain, but also provide the opportunity to investigate cerebral damage in various ways (Tofts, 2003). As no macrostructural abnormalities underlying epileptic seizures are present in these patients, it remains to be revealed whether tissue biomarkers might account for this impaired brain function (Bernasconi *et al*., 2011).

Using quantitative MR analyses, it is possible to detect abnormalities at the microstructural and metabolic level, potentially related to cognitive decline and impaired brain function. For example, volumetric analyses provide indications of brain atrophy, T2 relaxometry provides information on the (free) water content and subtle morphology (Woermann *et al*., 1998), diffusion tensor imaging (DTI) provides a means to assess the integrity of specific white matter tracts in the brain, and proton MR spectroscopy (^{1}H-MRS) provides a window in which cell metabolism may be investigated (Jansen *et al*., 2007).

In the literature, the association between cognitive impairment in epilepsy and quantitative MR characteristics has been investigated mainly in studies of temporal lobe epilepsy. The excellent review by Bell *et al*. (2011) indicates that there is strong evidence that links structural changes to cognitive performances. For example, verbal memory decline has been associated with decreased hippocampal volume (Kälviäinen *et al*., 1997), longer hippocampal T2 times (Kälviäinen *et al*., 1997; Wood *et al*., 2000), reduced hippocampal concentration of the metabolite NAA (marker of neuronal integrity) (Sawrie *et al*., 2001; Hanoğlu *et al*., 2004), decreased NAA/(Cho+Cr) combined with strongly increased T2 relaxation time values in the hippocampus (Namer *et al*., 1999), decreased left hippocampal Cr/NAA ratio (Martin *et al*., 1999), decreased fractional anisotropy measures (*i.e*. microstructural integrity) of connections with the medial temporal lobe (Yogarajah *et al*., 2008), and altered mean diffusivity values in the uncinate fasciculus, parahippocampal cingulum, inferior fronto-occipital fasciculus, and arcuate fasciculus (McDonald *et al*., 2008). Working memory impairment is reported to be related to decreased caudate volume and reduced connectivity between the caudate and dorsal prefrontal cortex (Riley *et al*., 2011). However, others report non-significant findings after investigating similar relationships (Glikmann-Johnston *et al*., 2008; Vlooswijk *et al*., 2011).

These investigations suggest that detailed knowledge of the microstructure and metabolism may be useful in exploring the association between neuronal correlates of localisation-related epilepsy and cognition. The type of cognitive decline in most patients with epilepsy indicates that the dysfunctional brain region extends the temporal region (Jokeit and Ebner, 1999; Elger *et al*., 2004). It has been shown that abnormalities can be found not only in the epileptic zone, but also in regions extending the epileptic focus (*see review of* Bell *et al*. [2011]). However, most studies focus on patients with epilepsy with visible lesions on MRI (Bernasconi *et al*., 2011), whereas it remains to be seen what subtle abnormalities are present in patients with cryptogenic epilepsy.

As mental slowing and impaired (working) memory are commonly seen in these patients with epilepsy, it appears that both (pre)frontal and temporal lobes are affected (Jokeit *et al*., 1997; Hermann *et al*., 2003; Bonilha *et al*., 2007). We recently showed in patients with cryptogenic epilepsy, using functional MRI (Vlooswijk *et al*., 2011), that memory impairment was associated with prefrontal network dysfunction. Therefore, it is worthwhile to investigate tissue abnormalities in multiple regions of the brain, rather than only in the temporal lobe (Duning *et al*., 2010).

In the current investigation, multimodal, quantitative MRI techniques were studied in patients with cryptogenic/localisation-related epilepsy and healthy controls to explore cerebral microstructure, subtle morphology, and metabolism. Furthermore, in the patients with epilepsy, the relationships between quantitative MR measures, cognitive (memory) performance, and clinical characteristics were assessed.

Materials and methods

Study population

A total of 44 adult patients with chronic cryptogenic localisation-related epilepsy and 23 adult healthy volunteers gave written informed consent to participate in the investigation, which received ethical approval by the local Medical Ethical Committee (Vlooswijk *et al*., 2011). Both temporal and frontal lobe epilepsy patients were included, because both seizure types are likely to originate from, spread to, and affect the fronto-temporal regions (Manford *et al*., 1996).

Table 1. Clinical and neuropsychological characteristics.

	Patients with epilepsy	Healthy controls
Age	39.9 (12.0)	40.4 (13.5)
Gender (M/F)	19/16	9/14
Age at onset	23.1 (14.4)	-
Disease duration	16.7 (9.7)	-
Total PS	Median: 3, Modus: 7	-
Total SGS	24.5 (83.7)	-
Focus (T/F/FT)	9/13/13	-
Drug load (PDD/DDD)	1.62 (0.92)	-
Full Scale IQ	96.7 (15.5) **	113.3 (14.5)
Verbal IQ	98.3 (16.1) **	111.3 (13.9)
Performance IQ	95.0 (16.3) **	113.2 (15.0)
Figure recognition	11.9 (4.0) *	14.2 (3.8)

For age, age at onset, disease duration, total SGS, and drug load, results are reported as mean (SD), as assessed by a board-certified neuroradiologist. Categories of total PS are 0=0, 1=1-10, 2=11-20, 3=21-30, 4=31-40, 5=41-50, 6=51-100, 7=>100.
M/F: male/female; PS: partial seizures; SGS: secondary generalised seizures; T: temporal; F: frontal; FT: fronto-temporal; PDD/DDD: prescribed daily dose/defined daily dose of antiepileptic medication. Neuropsychological test results are reported as mean (SD).*$p<0.05$ and **$p<0.01$.

Nine patients and 2 healthy controls were excluded from further analyses because of significant clinical MR abnormalities (including medial temporal sclerosis and periventricular heterotopia), as assessed by a board of certified neuroradiologists. Final analyses were performed on data from 35 patients and 21 healthy volunteers. Average demographic and clinical characteristics of the participants are presented in *table 1*.

Inclusion criteria for the patients were: a confirmed cryptogenic (*i.e.* non-symptomatic) localisation-related epilepsy with an epileptic focus in the fronto-temporal brain region and no history of status epilepticus or any other disease that could cause cognitive decline. Healthy controls were family members and acquaintances of the patients without a history of brain injury or cognitive problems.

The following patient data were collected: age at onset, disease duration, total number of secondary generalised seizures (SGS), total number of partial seizures (PS), and drug load. Total number of SGS was calculated according to the patient record and seizure diaries. For those patients with relatively few SGS, the exact number could be withdrawn from the patient record. For those with a relatively large number of SGS (approximately 20 or more), the number was calculated according to the seizure frequency during subsequent periods, correcting for changes in seizure frequency (for example: weekly seizures during a few months followed by a period of seizure freedom). Hence, when a higher number of SGS had been experienced, the total number was an approximation. Since frequent PS are less likely to be recognised and are therefore less accurately reported, the estimation of the total number of PS is expressed in categories rather than in absolute numbers. Drug load was calculated by using the ratio of prescribed daily dose to defined daily dose (Vlooswijk *et al.*, 2010; Vlooswijk *et al.*, 2011).

Neuropsychological examination

All participants underwent extensive neuropsychological tests for intelligence, attentional functions, information processing, and memory function. Rather than self-reported, subjective complaints, we used objective neuropsychological assessments, as the latter method is more reliable (Helmstaedter *et al.*, 1998; Royall *et al.*, 2007). To test intelligence, the Wechsler Adult Intelligence Scale (WAIS-III) was used (Wechsler, 1997) with administration of all subtests in the majority of patients. As a measure for the central executive, involved in the early transient memory processes, the WAIS-III subtest digit-symbol substitution test (DSST) was used (Byrne, 1998). For the more stable components of working memory, we used the normalised scores from the WAIS-III subtests included in the Working Memory Index: digit span, letter-number sequencing, and arithmetic. Furthermore, two recognition tasks for words and figures from the FePsy test (Alpherts and Aldenkamp, 1994) were administered. Handedness was assessed using the Annett Handedness Questionnaire. All neuropsychological test results were evaluated by a clinical psychologist, and Full Scale IQ, verbal IQ, and performal IQ were determined (Vlooswijk *et al.*, 2011).

Magnetic resonance imaging

All participants underwent an MRI protocol using a 3.0-Tesla unit equipped with an 8-channel SENSE head coil and a transmit/receive head coil for the spectroscopy part (Philips Achieva, Philips Medical Systems, Best, The Netherlands), as described previously (Jansen *et al.*, 2007; Jansen *et al.*, 2008). No contrast was used. For anatomical reference, T1-weighted three-dimensional (3D) turbo field echo (TFE) images were acquired with the following parameters: repetition time (TR) of 9.91 ms, echo time (TE) of 4.6 ms, inversion time (TI) of 3 s, flip angle of 8°, $256 \times 256 \times 160$ matrix, $256 \times 256 \times 160$ mm^3 field of view (FOV), and 1-mm adjacent coronal slices. For T2 quantification, a 3D TSE-Dual was performed, using TR of 2,500 ms, TE_1 of 10 ms, TE_2 of 110 ms, $256 \times 256 \times 100$ matrix, $256 \times 256 \times 200$ mm^3 FOV, 2.0-mm adjacent coronal slices, and SENSE factor 1.5 left-right. Diffusion

tensor imaging (DTI) experiments were acquired using: 52 contiguous 2-mm thick slices, matrix size of 96 × 96, voxel size of 2 × 2x2 mm, TE of 62 ms, TR of 6,600 ms, and SENSE factor 2.5 anterior-posterior. Images were obtained along 15 non-colinear diffusion directions with a b-value of 800 s/mm^2; one b=0 image was acquired.

Two slices were selected for spectroscopic imaging, one accommodated in the temporal and one in the frontal lobe, using 20 × 20 voxels per slice, FOV of 256 × 256 mm^2, slice thickness of 20 mm, TR of 2.0 s, TE of 30 ms, a nominal voxel size of 3.3 ml, and echo acquisition half echo. Localisation and water suppression was achieved with PRESS and CHESS, respectively.

Image analysis

Data analysis was performed as described by Jansen *et al*. (2007). In short, 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, The Mathworks, Natick, MA, USA). From these values, a percentile volume pericortical cerebrospinal fluid (CSF) map was calculated. As the effect related to cognitive decline might depend on cerebral tissue types (Geinisman *et al*., 1990), grey matter and white matter were analysed separately in the frontal and temporal lobes, using specific maps obtained from segmentation of T1-weighted images (SPM, Wellcome department of Cognitive Neurology, London, UK). Each diffusion-weighted data set was spatially co-registered to the b=0 image with an affine transformation to correct for head motion and eddy-current distortions utilising CATNAP (Co-registration, Adjustment, and Tensor-solving, a Nicely Automated Program, version 1.3). The set of gradient vectors was adjusted according to the rotation of the individual images, as implemented in the CATNAP software. Based on the adjusted gradient tables, diffusion tensors were calculated and apparent diffusion coefficient (ADC) (in 10^{-6} mm^2/s) and fractional anisotropy (FA) (in %) maps were calculated (Tijssen *et al*., 2009). The T2, CSF, FA and ADC maps were co-registered and spatially normalised to MNI space using SPM2, to facilitate analysis of brain regions with masks. These masks, derived from the WFUpickatlas (http://fmri.wfubmc.edu/software/PickAtlas), included left and right frontal and temporal lobes and manually drawn hippocampi (Jeukens *et al*., 2009). Grey and white matter T2, CSF, ADC, and FA maps were smoothed using a Gaussian kernel with full with half maximum (FWHM) of 6 mm.

Metabolite quantification was performed using LCModel (Version 6.1-4), with which the *in vivo* MR spectra, as a linear combination of the separately recorded *in vitro* spectra of the individual metabolites, was analysed. The metabolite basis set (PRESS, TE 30 ms, 3.0 T) was kindly provided by Dr. Provencher (Provencher, 1993). Concentrations are reported and averaged over the region (left/right frontal/temporal) relative to creatine. The relative metabolite concentrations for choline (Cho), myoinositol (mI), *N*-acetyl-aspartate (NAA), and glutamate/glutamine (Glx) were determined. Metabolite estimates were excluded from analysis if the Cramer-Rao minimum variance exceeded the 20% range (Jansen *et al*., 2006). Additional quality measures included at least 10 voxels of sufficient quality to contribute to the average concentration of the brain region, and for analysis, at least 15 subjects per group were required to have valid concentrations.

Statistical analysis

Statistical analyses were performed using the SPSS 18.0 software package (SPSS Inc., Chicago, IL, USA). First, differences in neuropsychological test results and quantitative MR measures between patients with epilepsy and healthy controls were examined using linear regression analyses with group, age, and gender as independent variables. Age and gender were included as covariates in the regression analysis, as gender and age effects for quantitative MR measures have been described previously (Schmithorst *et al*., 2008). Second, to limit the number of statistical tests to only MRI measures with which significant group effects were found, non-parametric Spearman's correlation coefficients were obtained in order to examine the relationship between these MRI parameters, neuropsychological test results, and clinical epilepsy characteristics. Because of the exploratory nature of the analysis, we did not adjust for multiple testing. A p value of <0.05 was considered significant. The correlations were interpreted using the guidelines from Cohen (Cohen, 1988), with absolute correlations of <0.3 considered weak, 0.3-0.5 moderate, and 0.5-1.0 strong.

Table 2. Spearman's correlations between the neuropsychological test results and clinical epilepsy characteristics.

	Disease duration	Total PS	Total SGS	Drug load
Full Scale IQ	-0.17	-0.00	-0.26	-0.36 *
Verbal IQ	-0.09	0.01	-0.24	-0.16
Performance IQ	-0.18	-0.12	-0.13	-0.49 **
Figure recognition	-0.16	-0.24	0.00	-0.17

P values were obtained by using two-tailed tests.
* $p<0.05$ and ** $p<0.01$.

Results

Neurocognitive performance

The patient group displayed significantly lower verbal, performal, and total IQ, and significantly worse scores on the figure recognition task (*table 1*), as compared to controls. No significant correlations of neuropsychological performance with disease duration and frequency of partial, as well as generalised seizures, were found (*table 2*). However, significant negative correlations were found between drug load and full-scale IQ and performance IQ.

MR imaging

Visual inspection of all T2 and ADC maps did not reveal image artefacts; the obtained maps were therefore considered to be of good quality (both groups displayed similar MR quality characteristics). *Figure 1*

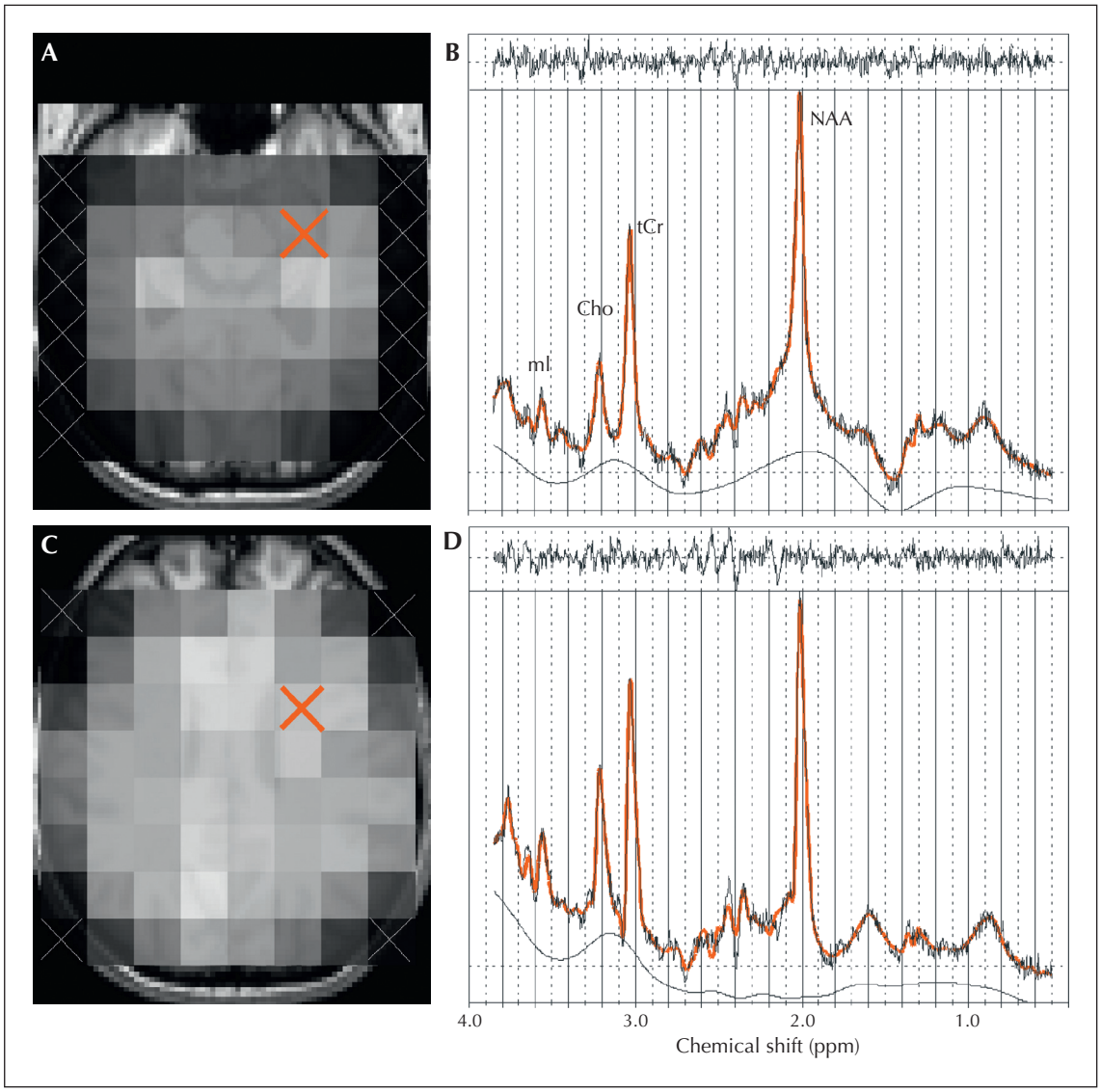

Figure 1. Metabolic images depicting the fitted NAA concentrations for (A) the temporal and (C) frontal slice of voxels of the patient, overlaid on oblique normalised transverse T1-weighted images.
Slice positions correspond to approximately z=-14 mm and +32 mm, in stereotaxic MNI coordinates, for the temporal (A) and frontal (C) slice, respectively.
From the voxels marked with red crosses in (A) and (C), the corresponding fits of *in vivo* spectra are shown in (B) and (D), respectively. The thin upper curves were estimated with the LCModel (Version 6.1-4) output (thick upper curves), and the difference of the spectra is plotted at the top. Underneath the *in vivo* spectrum, the baseline spline estimate, as determined by LCModel, is displayed.
NAA: N-acetyl-aspartate; tCr: total creatine; Cho: choline; mI: myo-inositol.

Table 3. MRI characteristics. Results of regression analyses with age, gender and group as independent variables and MRI characteristics as a dependent variable.

	Patients with epilepsy	Healthy controls
T2 values and segmentation results		
T2 (in ms) RH	84.6 (2.9)	83.4 (2.7)
T2 LH	86.6 (4.6)	84.1 (4.7)
T2 RT	81.4 (3.4)	80.3 (2.7)
T2 LT	82.9 (2.6) *	82.0 (2.2)
T2 RF	79.8 (2.0)	79.9 (2.5)
T2 LF	79.0 (2.2)	79.6 (1.9)
CSF fraction RH	0.14 (0.04) *	0.12 (0.03)
CSF fraction LH	0.10 (0.04) **	0.07 (0.02)
CSF fraction RT	0.08 (0.02)	0.07 (0.02)
CSF fraction LT	0.09 (0.02) *	0.08 (0.02)
CSF fraction RF	0.14 (0.05)	0.12 (0.03)
CSF fraction LF	0.16 (0.05)	0.14 (0.04)
White matter fraction RH	0.17 (0.03)	0.17 (0.03)
White matter fraction LH	0.29 (0.05)	0.26 (0.04)
White matter fraction RT	0.41 (0.02)	0.41 (0.03)
White matter fraction LT	0.39 (0.03)	0.39 (0.03)
White matter fraction RF	0.51 (0.03)	0.49 (0.03)
White matter fraction LF	0.50 (0.03)	0.50 (0.04)
Grey matter fraction RH	0.74 (0.05)	0.73 (0.02)
Grey matter fraction LH	0.67 (0.05)	0.68 (0.04)
Grey matter fraction RT	0.53 (0.04)	0.54 (0.03)
Grey matter fraction LT	0.53 (0.03)	0.53 (0.02)
Grey matter fraction RF	0.39 (0.03)	0.40 (0.04)
Grey matter fraction LF	0.38 (0.03)	0.38 (0.04)
DWI characteristics		
ADC (in $10^{-6}mm^2/s$) RH	977.2 (84.9)	1,001.1 (81.7)
ADC LH	966.1 (130.4)	954.7 (57.4)
ADC RT	9.04 (0.56)	9.07 (0.37)
ADC LT	9.41 (0.64)	9.51 (0.53)
ADC RF	8.53 (0.44)	8.38 (0.27)

	Patients with epilepsy	Healthy controls
ADC LF	8.55 (0.45)	8.53 (0.24)
ADC white matter RH	883.1 (68.7)	881.4 (43.6)
ADC white matter LH	849.5 (38.5)	847.2 (37.7)
ADC white matter RT	803.8 (27.1)	807.8 (22.0)
ADC white matter LT	800.0 (30.7)	798.3 (24.3)
ADC white matter RF	780.1 (29.5)	780.8 (23.4)
ADC white matter LF	781.7 (27.0)	773.7 (17.4)
ADC grey matter RH	913.9 (54.2)	921.1 (42.8)
ADC grey matter LH	904.5 (55.8)	903.3 (39.3)
ADC grey matter RT	855.9 (35.0)	845.1 (16.5)
ADC grey matter LT	862.4 (54.5)	842.1 (20.8)
ADC grey matter RF	872.2 (57.7)	864.5 (36.7)
ADC grey matter LF	880.2 (58.7)	856.0 (35.1)
FA (in %) RH	0.26 (0.07)	0.27 (0.06)
FA LH	0.24 (0.05)	0.25 (0.06)
FA RT	0.32 (0.02)	0.31 (0.02)
FA LT	0.28 (0.01)	0.28 (0.02)
FA RF	0.31 (0.02)	0.31 (0.01)
FA LF	0.32 (0.02)	0.32 (0.01)
FA white matter RH	0.37 (0.06)	0.37 (0.05)
FA white matter LH	0.45 (0.04)	0.45 (0.04)
FA white matter RT	0.41 (0.02)	0.41 (0.02)
FA white matter LT	0.44 (0.02)	0.44 (0.02)
FA white matter RF	0.40 (0.02)	0.41 (0.02)
FA white matter LF	0.40 (0.02)	0.41 (0.02)
FA grey matter RH	0.25 (0.02)	0.26 (0.02)
FA grey matter LH	0.26 (0.03)	0.27 (0.02)
FA grey matter RT	0.25 (0.02)	0.24 (0.01)
FA grey matter LT	0.25 (0.02)	0.25 (0.01)
FA grey matter RF	0.25 (0.02)	0.25 (0.02)
FA grey matter LF	0.25 (0.02)	0.24 (0.02)

Table 3. (*Continued*)

	Patients with epilepsy	Healthy controls
	MRS characteristics	
tNAA RT	1.49 (0.18)	1.57 (0.25)
tNAA LT	1.59 (0.18)	1.61 (0.18)
tNAA RF	1.58 (0.10)	1.57 (0.16)
tNAA LF	1.76 (0.14)	1.77 (0.19)
tCho RT	0.26 (0.04)	0.27 (0.03)
tCho LT	0.26 (0.04)	0.25 (0.03)
tCho RF	0.26 (0.03)	0.26 (0.03)
tCho LF	0.27 (0.03)	0.27 (0.03)
mI RT	0.65 (0.10)	0.67 (0.19)
mI LT	0.64 (0.09)	0.68 (0.15)
mI RF	0.57 (0.08)	0.57 (0.05)
mI LF	0.57 (0.09)	0.57 (0.06)
Glx RT	1.74 (0.46)	1.89 (0.84)
Glx LT	1.68 (0.37)	1.78 (0.53)
Glx RF	1.60 (0.12)	1.59 (0.20)
Glx LF	1.71 (0.14) *	1.61 (0.17)

Results are reported as mean (SD).
RH: right hippocampus; LH: left hippocampus; RT: right temporal; LT: left temporal; RF: right frontal; LF: left frontal; ADC: apparent diffusion coefficient; FA: fractional anisotropy. *$p<0.05$ and **$p<0.01$.

shows an example of the selected spectroscopic imaging slices of one patient, and the spectral fit of two voxels. Quantitative MR measures are presented in *table 3*. Significantly larger CSF fractions in the left and right hippocampus and left temporal lobe, a significantly longer T2 relaxation time in the left hippocampus, and a significantly greater concentration of Glx in the left frontal lobe were observed for patients compared to controls.

Correlations between the MR measures, neuropsychological test results, and clinical epilepsy characteristics

For the CSF fractions in the left and right hippocampus and left temporal lobe, the T2 relaxation time in the left hippocampus, and the concentration of Glx in the left frontal lobe, a correlation was obtained with neuropsychological and clinical characteristics in patients with epilepsy. There was a significant, negative moderate correlation between CSF in the right hippocampus and left temporal lobe or the figure recognition score (rho=-0.34; $p=0.02$, and rho=-0.36; $p=0.04$, respectively, *see figure 2*). Other correlations were not significant (*table 4*).

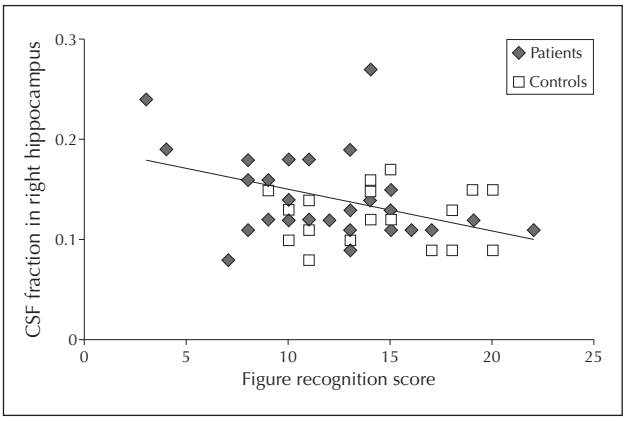

Figure 2. Scatter plot displaying the CSF fraction in the right hippocampus as a function of the figure recognition results for patients (black diamond) and controls (white square).
The difference between the two groups is statistically significant ($p=0.04$). The black line depicts a linear regression for the patients, which indicates a statistically significant correlation (rho=-0.34; $p=0.02$).

Discussion

To examine whether quantitative MR measures are associated with cognitive decline in patients with localisation-related epilepsy, neuropsychological test results and MRI examinations of patients with epilepsy were compared with those of healthy controls. Furthermore, within the epilepsy group, relevant quantitative MR measures were correlated with epilepsy characteristics, intelligence scores, and memory performance characteristics.

Major findings

First, this preliminary study showed that patients with epilepsy displayed significantly worse cognitive performance (IQ and memory) compared to healthy controls, which suggests that these patients indeed have cognitive problems. Second, the patients displayed significantly different quantitative MRI characteristics; CSF fractions of the left and right hippocampus and left temporal lobe were significantly larger, the T2 relaxation time in the left temporal lobe was significantly longer, and the concentration of Glx in the left frontal lobe was significantly greater, compared to healthy controls. Third, within the epilepsy group, the negative correlations between figure recognition and CSF

Table 4. Significant Spearman's correlations between the relevant MR parameters, clinical epilepsy characteristics, and neuropsychological test results.

	Disease duration	Total PS	Total SGS	Drug load	FS-IQ	VIQ	PIQ	Figure recognition
CSF RH	0.03	0.14	-0.15	0.07	-0.24	-0.16	-0.32	-0.39 *
CSF LH	0.14	0.31	-0.19	0.17	-0.04	0.05	-0.16	-0.27
CSF LT	0.15	-0.20	0.21	0.21	-0.22	-0.11	-0.32	-0.36 *
T2 LT	-0.16	-0.01	0.16	-0.13	-0.23	-0.28	-0.13	-0.16
Glx LF	0.14	-0.33	-0.07	0.04	-0.03	-0.04	0.00	0.14

RH: right hippocampus; LH: left hippocampus; LT: left temporal; LF: left frontal.
P values were obtained by using two-tailed tests. *$p<0.05$ and **$p<0.01$.

in the right hippocampus or left temporal lobe were statistically significant. Clinical epilepsy characteristics such as disease duration, seizure frequency, and drug load had no significant influence on the affected MRI measures.

Hippocampal damage and memory performance

Within the epilepsy group, the negative correlation between figure recognition and CSF in the right hippocampus or left temporal lobe was statistically significant. An increased CSF fraction is typically regarded as a sign of atrophy (Kuzniecky and Jackson, 2004). This hints at a relationship between subtle morphological brain damage and deteriorated memory performance in patients with epilepsy. These results are consistent with previous studies, in which a relationship was demonstrated between microstructural characteristics and cognitive (memory) performance in patients with epilepsy (McDonald *et al*., 2008; Yogarajah *et al*., 2008; Bell *et al*., 2011; Riley *et al*., 2011).

The hippocampal localisation of alterations in quantitative MR measures associated with impaired figure recognition was in accordance with previous findings by Helmstaedter *et al*. (Helmstaedter *et al*., 1997; Helmstaedter and Elger, 1998), who convincingly showed that hippocampal functioning is associated with memory impairment. However, in our previous functional imaging study, we observed an altered functional connectivity in the prefrontal (and not temporal) networks related to memory performance in patients with epilepsy (Vlooswijk *et al*., 2011). Apparently, subtle morphological abnormalities (*i.e*. larger CSF fractions) do not necessarily co-localise with regions of altered functional connectivity in this population with epilepsy, although both are associated with memory performance.

Neurotransmitter imbalance

The level of Glx in the left frontal lobe was significantly greater in epilepsy patients than in healthy controls. An elevated Glx concentration is in agreement with previous studies on patients with idiopathic generalised epilepsy (Helms *et al*., 2006; Doelken *et al*., 2010) and patients with refractory epilepsy associated with malformations in cortical development (Simister *et al*., 2007), in which all reported increased Glx levels in patients with epilepsy. As Glx is the major excitatory neurotransmitter, an increased level of Glx could indeed be a plausible explanation for the epileptic brain. Doelken *et al*. hypothesised that a disruption of the excitatory neurotransmitter balance (*i.e*. glutamate) and a disturbance of excitatory mediator turnover might underlie the seizures (Doelken *et al*., 2010). Interestingly, a recent experimental study with the pilocarpine-induced temporal lobe epilepsy rat model by Klatte *et al*. found that chronic epilepsy has a profound effect on the modulation of synaptic plasticity by the NMDA receptor, which is activated synaptically by glutamate (Klatte *et al*., 2013). A possible explanation as to why ^{1}H-MRS revealed significant Glx alterations in the frontal, but not the temporal lobe, is that ^{1}H-MRS using spectroscopic imaging in the frontal lobe is more robust than in the temporal lobe. We previously showed using the exact same ^{1}H-MRS protocol that the frontal lobe displayed far better quality characteristics (in terms of reproducibility) than the temporal lobe. An explanation for this is the increased lack of B0 homogeneity in the temporal lobe, which leads to a decreased quality of ^{1}H-MR spectra (Jansen *et al*., 2007).

Clinical implications and limitations

We observed altered subtle morphological brain characteristics in patients with epilepsy, however, no significant relationships with clinical disease variables were found. For example, drug load was negatively correlated with memory performance, but showed no significant associations with the quantitative measures of brain microstructure. Due to the limited number and heterogeneous nature of the patients included in this study, the results should be interpreted with caution. However, it is possible that cognitive

performance is influenced more by the use of medication than microstructure.
Performance of the figure recognition task and microstructural abnormalities did not correlate with total seizures of SGS and PS. This is in contradiction with previous literature, which clearly displays evidence of abnormalities and clinical characteristics (Hermann *et al*., 2003; Elger *et al*., 2004; Jansen *et al*., 2014). The results from our small study might suggest that seizures are not the sole cause underlying memory decline and brain abnormalities in this patient population. Furthermore, since no correlations with disease duration were observed, memory decline, as well as subtle morphological abnormalities, are unlikely to have a progressive character. Further (longitudinal) research with larger patient numbers is needed to clarify the causal relationship between memory decline and alterations in brain microstructure in epilepsy.

Conclusion

In this preliminary study, multimodal, quantitative MR techniques, including T2 relaxometry, DTI, and ^{1}H-MRS, were successfully applied to assess possible neuronal correlates of cognitive co-morbidity in patients with non-symptomatic localisation-related epilepsy. Associations of changes in subtle morphology, indicative of atrophy, with memory performance were found, consistent with previous literature (Bell *et al*., 2011). Clinical characteristics such as seizure frequency or drug load did not account for this association. Validation of our preliminary findings is necessary in order to draw definitive conclusions regarding the impact of localisation-related epilepsy on quantitative MR characteristics and cognitive function. □

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