Individual white matter fractional anisotropy analysis on patients with MRI-negative partial epilepsy

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Revision of our manuscript ID#: JNNP/2008/160820 as a Short Report:
Individual white matter fractional anisotropy analysis on patients with MRI-negative partial epilepsy

Dear Prof. Scheltens,

Enclosed please find the revised manuscript entitled now "*Individual white matter fractional anisotropy analysis on patients with MRI-negative partial epilepsy*".

We are pleased that both authors had only minor suggestions for revision.
In the following paragraphs, we have addressed the remarks by the referees one by one, revised our manuscript accordingly and marked changes in the manuscript by underlining.

Following your suggestion, we now submit the manuscript as Short Report. After we have appended the relevant changes, the manuscript contains 1653 words and 18 references.

Sincerely,

Thomas Duning

Reviewer #1:

1.

The manuscript has gained a lot of clarity and readibility through the revision. Just one error should be corrected. The small sample size might lead to false-negatives, not true-negatives!! (in the discussion section).

We agree to this, our statement was incorrect. However, as recommended by Reviewer #2, we shortened the second paragraph of the Discussion (see 3., Reviewer #2) and deleted the sentence. The last sentence now reads:
Although our relatively small sample size does not allow us to conclude, this is at least consistent with studies showing no correlation with clinical factors and structural or metabolic abnormalities, suggesting that these extrafocal changes might be related to a more complex process of epileptogenesis.

Reviewer #2:

1.

This is now much better. A couple of minor points to improve clarity:
Discussion:
The first para begins by stating that there were two objectives of the study. The text then quotes a finding rather than an objective, which sounds a bit daft. Even if an objective were to be quoted, it would not fit very well with the statements about objectives in the abstract and introduction. I think the paragraph would be much better and clearer without the first and third sentences. The word 'Secondly' could be added to what would then be the second sentence.

We agree to this and changed the paragraph as recommended. The first paragraph of the Discussion now reads:

We report a symmetric widespread FA reduction in MRI-negative patients with CPE relative to controls, which provides further evidence for architectural brain abnormalities outside the epileptogenic zone in these patients. Secondly, we found significant reductions of FA in all patients, which occurred symmetrically in extratemporal regions. However, FA reduction in the temporal lobes was consistently identified ipsilateral to the seizure focus.

2.

“A functional correlative of the predominant temporal affection etc.”

This sentence had to be read three times before it finally became clear!! I suggest: The fact that the temporal lobe was predominantly affected may be a functional correlate of atypical language organization in patients with partial epilepsy.

We agree to this and changed the sentence accordingly.

3.

The sentence regarding negative correlations (end second para discussion) is too long and wordy. It would be simpler to add the words ' Although our relatively small sample size does not allow us to conclude, this is at least consistent with studies showing no correlation with...' etc and remove the last sentence of the paragraph.

We agree to this, changed the sentence as recommended by the reviewer and deleted the last sentence (see also 1., Reviewer #1).

Individual white matter fractional anisotropy analysis on patients with MRI-negative partial epilepsy

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Abstract:

Background: Conventional structural Magnetic Resonance Imaging (MRI) fails to identify a cerebral lesion in 25% of patients with cryptogenic partial epilepsy (CPE). Diffusion Tensor Imaging (DTI) is a MRI technique sensitive to microstructural abnormalities of cerebral white matter (WM) by quantification of fractional anisotropy (FA). The objectives of the present study were to identify focal FA abnormalities in patients with CPE who were deemed MRI negative during routine pre-surgical evaluation.

Methods: We performed DTI at 3 Tesla in 12 patients with CPE and normal conventional MRI and in 67 age-matched healthy volunteers. WM integrity was compared between groups on the basis of automated voxel-wise statistics of FA maps using an Analysis of Covariance. Volumetric measurements from high-resolution T1-weighted images were also performed.

Results: Significant FA reductions in WM regions encompassing diffuse areas of the brain were observed when all patients as a group were compared to controls. On an individual basis, voxel-based analyses revealed widespread symmetrical FA reduction in CPE patients. Furthermore, asymmetrical temporal lobe FA reduction was consistently ipsilateral to the electroclinical focus. No significant correlations were found between FA alterations and clinical data. There were no differences in brain volumes of CPE patients compared to controls.

Conclusion: Despite normal conventional MRI, WM integrity abnormalities in CPE patients extend far beyond the epileptogenic zone. Given that unilateral temporal lobe FA abnormalities were consistently observed ipsilateral to the seizure focus, analysis of temporal FA may provide an informative *in vivo* investigation into the localisation of the epileptogenic zone in MRI-negative patients.

Introduction:

Structural Magnetic Resonance Imaging (MRI) is a crucial tool routinely used for neuroanatomical pre-surgical evaluation of patients with refractory cryptogenic partial epilepsy (CPE) for the etiologic characterization of epileptogenic cortex. However, conventional MRI fails to identify cerebral lesions in approximately 25% of patients with CPE, and surgical treatment of MRI-negative patients is frequently associated with a poor post-surgical outcome.[1] Advanced MRI techniques provide the opportunity to identify subtle structural abnormalities that may underlie epileptogenic cortex, thus increasing the likelihood of successful surgical remediation of intractable seizures.

Diffusion Tensor Imaging (DTI) is a MRI technique that can indirectly evaluate white matter (WM) integrity by measuring the spatial directionality of water diffusion. Some DTI studies have suggested that structural abnormalities in patients with CPE are not only restricted to easily identified circumscribed lesions. However, there are few studies that have addressed the utility of DTI in patients with CPE and normal conventional MRI. Most studies include heterogeneous samples of patients with CPE, with and without hippocampal sclerosis or circumscribed lesions, and results were inconsistent.[2-6]

In the present study, we sought to combine DTI with statistical parametric mapping (SPM) to determine FA abnormalities across the entire brain in patients with CPE for whom conventional MRI revealed no structural pathology.

Methods:

Subjects:

For DTI analysis, 9 patients (6 women, mean age of 39 ± 11.7 years) with cryptogenic partial seizures and 67 healthy volunteers (24 women, median age 31.8 ± 4.1 years) with no history of neurologic disease were scanned. All epilepsy patients were recruited from our epilepsy monitoring unit. The conventional imaging sequences (T1, T2, FLAIR) of all examined patients did not show any abnormalities by visual inspection. All epilepsy patients underwent medical and neurological examination, interictal EEG, and long-term video EEG monitoring (at least 48 hours). All patients had refractory partial seizures evolving to secondarily generalized seizures and gave written informed consent prior to examination. CPE was diagnosed according to clinical and EEG features following the ILAE classification

system.[7] Seizures were classified according to the semiological seizure classification.[8] Detailed clinical characteristics of all patients are listed in Table 1.

MRI data analysis:

Image data were obtained on a 3.0 T system with a high resolution structural T1-weighted 3D turbo-field-echo sequence (reconstructed after zero filling to 512x410x320 cubic voxels, edge length 0.5 mm), as well as T2-weighted, and FLAIR imaging. For DTI we employed echo planar imaging (EPI) with 20 diffusion directions (36 slices, thickness 3.6 mm, matrix 128 x 128, inplane resolution 1.8 x 1.8 mm).

After correction for eddy currents, the EPI images were spatially normalized to the Montreal Neurological Institute (MNI) coordinate system following an optimized procedure.[9] The diffusion tensor and FA field maps of all participants were calculated from spatially normalized images (in-house software), normalized to an FA template image also corresponding to the MNI coordinate, and smoothed by a 8 mm isotropic Gaussian kernel. Differences in FA values between the patient group and healthy controls were evaluated using statistical parameter mapping (SPM5, ANCOVA, modeling age as a co-variate, $P < 0.001$). To assess the magnitude of regional FA alterations between patients and controls, we also performed additional quantitative region-of-interest (ROI) analyses (see Table 2). To define these subregions, we used an averaged and symmetrized (x-axis) mask of all healthy controls with FA-values > 0.4.

Due to the reported local FA alterations of CPE patients in the literature, we expected the most asymmetrical changes in the temporal lobes. To asses the asymmetry between the mean temporal lobe FA values, an asymmetry index was defined as AI = [100x(FA left temporal lobe - FA right temporal lobe) / (FA left temporal lobe + FA right temporal lobe)].

Brain tissue volumes, normalized for subject head size, were calculated from the high-resolution T1-weighted images, using the cross-sectional version of the Structural Imaging Evaluation of Normalized Atrophy (SIENA) software (SIENAx).[10]

Results:

Group-wise FA differences

Post-hoc t-tests of the SPM-ANCOVA revealed significant FA reductions in WM areas of patients, covering widespread parts of the brain, most prominent in the

frontal and temporal lobes, the corpus callosum, the corticospinal tracts, and the brainstem. In ROI analysis, only FA values of the cerebellum, the occipital lobe, the parietal lobes and the thalamus did not significantly differ from the control subjects (Table 2).

Individual FA analysis

Comparisons of individual CPE patients with control subjects revealed diffuse FA alterations as well as distinct circumscribed FA “drop-outs” in several WM regions (Figure 1). The extratemporal WM abnormalities occurred mainly symmetrically, while all CPE patients showed pronounced asymmetric FA reductions in the temporal lobes. In 5 patients, the FA was particularly reduced in the right temporal lobe, and in 7 patients primarily the left temporal lobe. Although only 4 patients had an electroclinical evidence of temporal lobe epileptogenic focus, the lateralization of the temporal FA changes concurred with the affected hemisphere in all patients where available evidence allowed lateralization of the presumed epileptogenic zone (Table 2). Two patients without a lateralized focus (patients 4 and 5) and one patient (patient 3) with a bitemporal seizure origin showed FA reductions lateralized to the left temporal lobe.

Asymmetry analysis

The group analysis of the asymmetry index (AI) showed significant asymmetric increased mean FA values of the temporal lobes of patients when compared to the healthy controls (p=0.015). Additionally, the individual AI values lateralized to the hemisphere of the epileptogenic zone in all 9 patients (Table 2) with defined focus. In three patients without a defined electroclinical focus, there was an asymmetric decrease of left temporal FA values.

Global volumetric differences

There were no differences in brain volumes of CPE patients (GM, WM, relative and normalized brain volumes) compared to the group of healthy controls.

Clinical correlations

No significant correlation was found between the mean FA reduction in any ROI or the asymmetry indices and duration of habitual epilepsy, frequency of

seizures, age of onset of epilepsy, the presumed localisation of the epileptogenic zone (by EEG or seizure semiology), number of generalised tonic-clonic seizures (GTCS), or duration of anticonvulsant therapy.

Discussion:

We report a symmetric widespread FA reduction in MRI-negative patients with CPE relative to controls, which provides further evidence for architectural brain abnormalities outside the epileptogenic zone in these patients. Secondly, we found significant reductions of FA in all patients, which occurred symmetrically in extratemporal regions. However, FA reduction in the temporal lobes was consistently identified ipsilateral to the seizure focus.

Our results are consistent with other neuroimaging studies that have indicated structural or functional abnormalities extending beyond the presumed epileptogenic zone.[4 6 11-14] Some authors have postulated that widespread microstructural changes in epilepsy patients could be related to seizure activity and thus disease severity, resulting in extensive and reversible changes of neurons.[11] We found no evidence of an association between FA alterations and duration or age of onset of habitual epilepsy, duration of the anticonvulsant medication, incidence of GTCS, or EEG localization. Although our relatively small sample size does not allow us to conclude, this is at least consistent with studies showing no correlation with clinical factors and structural or metabolic abnormalities, suggesting that these extrafocal changes might be related to a more complex process of epileptogenesis.[6 14]

Our findings extend previous studies that identified FA changes in heterogeneous samples of patients with and without known structural abnormalities. Using DTI and individual statistical comparison, we identified FA alterations in temporal lobe regions consistently ipsilateral to the putative seizure focus in patients with no observable brain abnormality on conventional MRI, which suggest that focal FA abnormalities may underlie the epileptogenic region that belies visual inspection of T1-weighted MRI. Various studies showed numerous anatomical and functional connection bundles of the temporal lobe.[11 14-16] The temporal FA changes of the affected hemisphere could be a sign of chronic remodelling of temporal structures due to repeated involvement in seizure originating from the epileptogenic focus, and

particularly the ipsilateral temporal WM might be vulnerable to such impulses.[17] The fact that the temporal lobe was predominantly affected may be a functional correlate of atypical language organization in patients with partial epilepsy.[18] Recently, a study revealed an association between these functional changes with temporal white-matter tract abnormalities in CPE patients.[5] Such anatomical and functional temporal changes may be clinically important because it may interfere with various routes of seizure propagation.

Lateralization of the affected hemisphere in patients with partial epilepsy, particularly cases without abnormal findings on high resolution MRI, remains a challenge for pre-surgical evaluation. An underlying MRI abnormality is a favourable prognostic indicator for seizure freedom after surgical treatment.[1] However, in this study the seizure focus of the partial epilepsy was located in the temporal lobe in only 4 patients. Thus, despite its sensitivity, DTI did not identify a direct clinical concordant abnormality in CPE patients with normal conventional MRI, and therefore this technique alone appears to have limited power in pre-surgical evaluation. Nevertheless, DTI might help to provide further information beyond what can be derived from standard epilepsy imaging protocols, i.e. identifying the hemisphere enclosing the epileptogenic focus in cryptogenic epilepsy, and particularly focussing on temporal changes might be helpful.

We suggest that WM FA analysis may represent an effective method of lateralising a neuroanatomical abnormality underlying the seizure focus during pre-surgical evaluation of CPE, in particular when supplemented by other neuroimaging techniques (MRS, FDG-PET, quantitative T2 mapping). In order for this potential to be realised, patients need to be further investigated to correlate pre-surgical FA alterations with post-surgical outcome, as only then will a direct relationship between microstructural alterations and the epileptogenic zone be established.

In conclusion, DTI seemed to be much more sensitive than conventional MRI in demonstrating white matter abnormalities in CPE. We did not find evidence to suggest that FA alterations were not associated with clinical factors, but such correlations may exist in larger samples. While it remains to be established whether FA alterations are a cause or a consequence of CPE - or both, they constitute an important step towards decrypting cryptogenic partial epilepsy.

Acknowledgements:

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Table 1: Clinical data of all patients

Pat. No.	*age*	*gender*	*age at epilepsy onset (years)*	*duration of disease (years)*	*presumed location of the epileptogenic zone (semiology and/or EEG)*	*seizure types ever*	*actual anticonvulsant therapy (per day)*	*all anticonvulsants ever used*	*last gtcs ... months ago*	*last seizure ... months ago*	*no. of gtcs ever*	*duration of anticonvulsant therapy (years)*
1	27	m	6	21	rt hem	sm mot, automot, gtcs	CBZ 1200mg	CBZ	0.3	0.1	100	21
2	40	f	16	24	lft temp	aura, automot, gtcs	OXC 1050mg PRG 600mg	CBZ, VPA, VGB, LEV, LTG, OXC, PHT, PRG	0.1	0.1	130	24
3	35	m	27	8	bilat temp	aura, automot, gtcs	VPA 2000mg LTG 300mg	CBZ, VPA, LTG, OXC, LEV, TOP	2	0.5	15	8
4	39	f	25	14	nonloc	sm mot, automot, gtcs	OXC 900mg TOP 350mg	TOP, LEV, GBP, LTG, CBZ, OXC	6	0.3	13	14
5	44	m	25	19	nonloc	aura, sm mot, gtcs	LEV 3000mg VPA 2000mg	GBP, VPA, LTG, LEV	23	14	17	19
6	21	f	13	8	lft hem	aura, automot, gtcs	LTG 375mg	OXC, LTG, GBP	n.a.	28	4	8
7	34	f	24	10	lft hem	aura, automot, gtcs	TOP 175mg	TOP, VPA, LTG	60	14	3	3
8	45	f	27	18	lft hem	aura, sm mot, gtcs	LTG 550mg	TOP, VPA, LTG	36	22	6	18
9	62	f	15	47	rt temp	hypermot, gtcs	LTG 300mg	CBZ, LTG	120	1	190	25
10	47	m	22	25	rt temp	aura, automot, gtcs	LTG 400mg	VPA, TOP, GBP	5	5	44	25
11	34	f	18	16	rt hem	automot, gtcs	LTG 500mg	VPA, LEV, PRD	4	4	19	14
12	43	f	25	18	rt hem	automot, sm mot, gtcs	LEV 3500mg VPA 2000mg	GBP, CBZ, OXC, TOP	2	2	49	16

f=female, m=male, rt=right, lft=left, hem=hemispheric, temp=temporal, bilat=bilateral, nonloc=non localizing, abs=absence seizure, automot=automotor seizure, sm mot= simple motor seizure, gtcs= generalized tonic clonic seizure, hypermot=hypermotor seizure, VPA=valproate, LTG= lamotrigine, TOP=topiramate, CBZ=carbamazepine, OXC=oxcarbazepine, LEV=levetiracetam, GBP=gabapentin, PHT=phenytoin, ETH=ethosuximide, PHB=phenobarbital, VGB=vigabatrine, PRD=primidone

	FA values (x1000) of Control group		FA values (x1000) of CPE patients		p - values
	Mean	± SD	Mean	± SD	
Whole brain	357.6	15.6	331.4	24.7	*<0.001**
Corpus callosum	414.3	37.0	351.2	44.9	*<0.001**
Genu	410.1	46.9	371.8	24.9	*0.008**
Splenium	457.0	40.9	413.3	64.4	*0.013**
Capsula interna	413.9	17.0	392.1	24.2	*0.010**
Cerebellum	311.8	21.8	299.7	32.4	0.218
Corona radiata	354.1	15.8	319.8	31.6	*<0.001**
Corticospinal tract	389.6	15.9	344.9	29.1	*0.001**
Brainstem	408.3	17.4	384.8	15.9	*0.003**
Frontal lobe	336.2	19.4	298.8	32.1	*<0.001**
Temporal lobes	367.1	16.1	334.7	31.4	*<0.001**
Left temporal lobe	368.2	17.8	329.7	29.4	*<0.001**
Right temporal lobe	366.0	16.2	340.4	18.1	*0.001**
Occipital lobe	336.0	26.2	332.8	40.2	0.232
Parietal lobes	354.5	17.7	348.4	19.6	0.163
Thalamus	438.6	36.8	428.2	31.5	0.755

Asymmetry indices [100x(FA left temporal lobe - FA right temporal lobe)/(FA left temporal lobe + FA right temporal lobe)]		**Difference to AI of healthy controls**
with left-hemispheric focus (n = 4)		
Patient 2	-7.0	-7.3
Patient 6	-9.7	-10.0
Patient 7	-7.6	-7.9
Patient 8	-2.7	-3.0
with right-hemispheric focus (n = 5)		
Patient 1	5.1	4.8
Patient 9	1.5	1.2
Patient 10	4.3	4.0
Patient 11	3.0	2.7
Patient 11	4.9	4.6
Non localizationg/ bilateral focus (n = 3)		
Patient 3	-0.4	-0.7
Patient 4	-2.0	-2.3
Patient 5	-1.5	-1.8

Table 2. Left: FA values (x1000) of different ROIs in epilepsy patients and healthy controls (n = 67). * significant FA reduction, $p < 0.05$ lower than healthy controls. **Right:** Asymmetry indices (AI) of temporal FA values in CPE patients and the deviation from the mean AI of the healthy controls. The lateralization of the temporal FA changes concurred with the hemisphere comprising the putative seizure focus in all patients.

Figure legends:

Figure 1: FA abnormalities observed in two patients with CPE relative to the cohort of control subjects (one-sample *t*-test, $p < 0.001$; uncorrected; 20 contiguous voxels). The statistical map was superimposed on an averaged FA template of the control group.

Examples of voxels with asymmetrical FA decrease. The presumed epileptogenic zone of Pat. 1 and Pat. 7 was localized in the right and left hemisphere respectively. The lateralization of the temporal FA changes concurred with the affected hemisphere in all patients with a defined electroclinical focus (9 patients). The circumscribed temporal (white arrows) and extratemporal (yellow arrows) FA reductions in the statistical maps were also clearly visible in corresponding color-coded FA-maps (framed figures).

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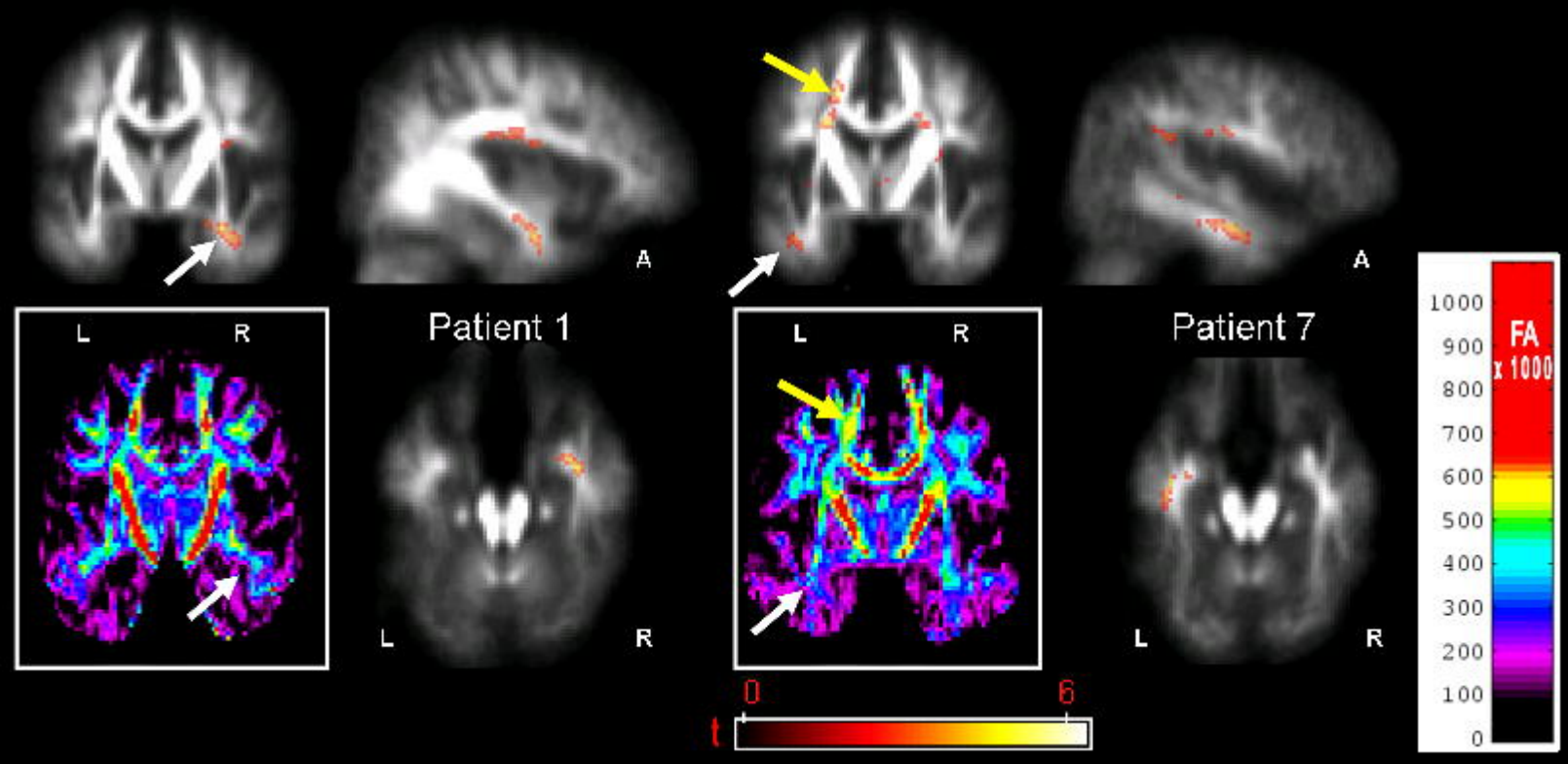
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