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Widespread neocortical abnormalities in temporal lobe epilepsy with and without mesial sclerosis

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ABSTRACT

Purpose: Extrafocal structural abnormalities have been consistently described in temporal lobe epilepsy (TLE) with mesial temporal lobe sclerosis (TLE-MTS). In TLE without MTS (TLE-no) extrafocal abnormalities are more subtle and often require region of interest analyses for their detection. Cortical thickness measurements might be better suited to detect such subtle abnormalities than conventional whole brain volumetric techniques which are often negative in TLE-no. The aim of this study was to seek and characterize patterns of cortical thinning in TLE-MTS and TLE-no.
Methods: T1 weighted whole brain images were acquired on a 4 T magnet in 66 subjects (35 controls, 15 TLE-MTS, 16 TLE-no). Cortical thickness measurements were obtained using the FreeSurfer software routine. Group comparisons and correlation analyses were done using the statistical routine of FreeSurfer (FDR, $p = 0.05$).
Results: TLE-MTS and TLE-no showed both widespread temporal and extratemporal cortical thinning. In TLE-MTS, the inferior medial and posterior temporal regions were most prominently affected while lateral temporal and opercular regions were more affected in TLE-no. The correlation analysis showed a significant correlation between the ipsilateral hippocampal volume and regions of thinning in TLE-MTS and between inferior temporal cortical thickness and thinning in extratemporal cortical regions in TLE-no.
Conclusion: The pattern of thinning in TLE-no was different from the pattern in TLE-MTS. This finding suggests that different epileptogenic networks could be involved in TLE-MTS and TLE and further supports the hypothesis that TLE-MTS and TLE-no might represent two distinct TLE syndromes.

Introduction

Temporal lobe epilepsy (TLE) is the most common form of partial epilepsy with a prevalence of 0.1% in the general population. Based on imaging and histopathological findings the following types of non-lesional TLE can be distinguished: TLE with mesial temporal lobe sclerosis (TLE-MTS, about 60–70%), i.e. atrophied hippocampus with MR signal abnormalities and severe neuronal loss in the histological examination, and TLE with normal appearing hippocampus on the MRI (TLE-no, about 30–40%) and no or only mild neuronal loss in the histological examination. Depth EEG exams show a relatively circumscribed epileptogenic zone in the hippocampus in TLE-MTS and more widespread, less well defined epileptogenic areas in the medial–lateral temporal lobe in TLE-no (Vossler et al., 2004). In both types however, seizures are not restricted to the temporal lobe but can spread to other regions as well. Accordingly, structural abnormalities are not restricted to the epileptogenic focus. In TLE-MTS for example, structural abnormalities have also been described in the entorhinal cortex, the parahippocampal and fusiform gyrus, thalamus, basal ganglia and frontal and parietal lobe (Jutila et al., 2001; Coste et al., 2002; Moran et al., 2001; Desay et al.; 2000; Dreifuss et al., 2001; Hagemann et al., 2002; Keller et al., 2004; Mueller et al., 2007). These abnormalities can be pronounced and are often detectable on visual inspection (Kim et al. 1995; Coste et al., 2002). In contrast, structural abnormalities in TLE-no tend to be more subtle and are often only detected by quantitative region of interest (ROI) approaches (Bernasconi et al., 2001; Bowers et al., 2003; Mueller et al., 2007).

Over the last few years several computational approaches for regionally unbiased whole brain cortical thickness measurements have been developed (Kim et al., 2005; Fischl and Dale, 2000; Thompson et al., 2005). Compared to traditional ROI analyses, these techniques have the advantage to assess the whole brain without requiring an a priori hypothesis regarding the localization of the abnormality. In addition to this, they are also less influenced by

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individual gyral variations than traditional voxel-based whole brain methods, e.g. voxel-based-morphometry (VBM). Recently, the first studies using cortical thickness measurements in TLE-MTS have been published showing a characteristic pattern of cortical thinning in the region of the superior frontal and precentral gyrus, operculum, inferior and medial temporal and occipital lobe (Lin et al., 2007; McDonald et al., 2008; Bernhardt et al., 2008). In this study we used cortical thickness measurements as provided by the FreeSurfer software routine with the following aims 1. To identify regions of cortical gray matter thinning beyond the hippocampus in TLE-MTS and to confirm the typical pattern of cortical thinning in TLE-MTS described by previous studies. Based on EEG and structural findings in TLE-MTS (Vossler et al., 2004; Mueller et al., 2006), we expected to find neocortical thinning in regions receiving hippocampal projections. 2. To identify regions of cortical thinning in TLE-no. We expected extrafocal thinning in TLE-no to affect neocortical regions in the inferior medial temporal lobe (Carne et al., 2007; Vossler et al., 2004; Mueller et al. 2007) and regions receiving projections from these regions, i.e., to show a different distribution than the one found in TLE-MTS.

Methods

Study population

The committees of human research at the University of California, San Francisco (UCSF), California Pacific Medical Center, San Francisco and VA Medical Center, San Francisco approved the study, and written informed consent was obtained from each subject according to the Declaration of Helsinki. Thirty-one consecutive TLE patients undergoing evaluation for epilepsy surgery were recruited between mid 2005 and end of 2007 from the Pacific Epilepsy Program, California Pacific Medical Center and the Northern California Comprehensive Epilepsy Center, UCSF. Fifteen patients (mean age 41.3 ± 10.4; left TLE/right TLE: 9/6, females/males 10/5) had evidence for mesial temporal lobe sclerosis on their 1.5 T MRI images (TLE-MTS) and 16 patients (mean age 37.8 ± 9.9; left TLE/right TLE: 8/8; females/males: 8/8) had normal appearing hippocampi (TLE-no) and normal MR reads at 1.5 T. So far, seven TLE-MTS and three TLE-no have had surgery and histopathological examination confirmed the presence (TLE-MTS), and absence (TLE-no) respectively of mesial temporal lobe sclerosis in all these patients. Age at onset of epilepsy was different between the two groups (TLE-MTS: 8.7 ± 6.9 years; TLE-no: 21.1 ± 9.2 years, $p<0.001$) as was duration of epilepsy (TLE-MTS: 31.5 ± 12.4 years; TLE-no: 14.7 ± 8.3 years; $p<0.001$). The identification of the epileptogenic focus was based on seizure semiology and prolonged ictal and interictal Video/EEG/Telemetry (VET) in all patients. The control population consisted of 35 healthy volunteers (mean age 37.9 ± 9.3; females/males: 23/12). Table 1 displays the patient characteristics.

Table 1
Patient characteristics

Patient no.	Age	Gender	Ictal VET	Precipitating Event/Risk Factors	Age at Onset of Seizures	1.5 T clinical MRI
1	46	Male	L mesial temporal	No	3	L MTS
2	35	Male	L mesial temporal	No	4	L MTS
3	50	Female	L mesial temporal	Febrile seizures	2	L MTS
4	24	Female	L mesial temporal	No	13	L MTS
5	35	Female	L mesial temporal	No	9	L MTS
6	54	Male	L mesial temporal	No	50	L MTS
7	44	Male	L mesial temporal	No	28	L MTS
8	48	Female	L mesial temporal	No	13	bil MTS
9	38	Female	L mesial temporal	Febrile seizures	6	bil MTS
10	46	Female	R mesial temporal	Post traumatic	6	R MTS
11	28	Female	R mesial temporal	Febrile seizures	13	R MTS
12	49	Female	R mesial temporal	No	7	R MTS
13	23	Female	R mesial temporal	Infection	5	R MTS
14	43	Male	R mesial temporal	No	5	R MTS
15	56	Female	R mesial temporal	No	12	R MTS
16	16	Male	L mesial temporal	No	14	Normal
17	27	Female	L mesial temporal	No	10	Normal
18	33	Female	L mesial temporal	No	10	Normal
19	35	Female	L mesial temporal	No	32	Normal
20	42	Female	L mesial temporal	No	21	Normal
21	38	Female	L mesial temporal	Post traumatic	37	Normal
22	33	Female	L mesial temporal	No	22	Normal
23	51	Male	L mesial temporal	No	18	Normal
24	29	Male	R mesial temporal	No	11	Normal
25	43	Female	R mesial temporal	Birth complications	20	Normal
26	45	Female	R mesial temporal	No	31	Normal
27	33	Male	R mesial temporal	No	23	Normal
28	45	Male	R mesial temporal	Post traumatic	30	Normal
29	39	Male	R mesial temporal	No	13	Normal
30	56	Male	R mesial temporal	Post traumatic	49	Normal
31	41	Male	R mesial temporal	Post traumatic	40	Normal

R, right; L, Left; MTS, mesial temporal sclerosis; No, none; Post traumatic, head trauma in history without temporal relationship to onset of seizures; infection, history of meningitis or encephalitis.

MRI acquisition

All imaging was performed on a Bruker MedSpec 4 T system controlled by a Siemens Trio™ console and equipped with a USA instruments eight channel array coil that consisted of a separate transmit coil enclosing the eight receiver coils. The following sequence, which was part of a larger research imaging and spectroscopy protocol, was acquired for cortical thickness measurements: volumetric T1-weighted gradient echo MRI (MPRAGE) TR/TE/TI = 2300/3/950 ms, 7° flip angle, $1.0 \times 1.0 \times 1.0$ mm^3 resolution, acquisition time 5.17 min.

Cortical thickness measurement

All T1 images were segmented in EMS (Van Leemput et al., 1999a, b). The bias field maps and tissue maps obtained during this process were used for bias correction and skull stripping of the T1 image. To allow for a combination of left and right TLE in the analysis, the T1 images of all patients with right TLE were side-flipped so that the focus was on the left side in all subjects. The same was done with all control images. FreeSurfer (version 3.05, https://surfer.nmr.mgh.harvard.edu) was used for cortical surface reconstruction and cortical thickness estimation of the original (controls and left TLE) and side-flipped (controls and right TLE) images. The procedure has been extensively