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Connectivity and tissue microstructural alterations in right and left temporal lobe epilepsy revealed by diffusion spectrum imaging

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ABSTRACT

Focal epilepsy is increasingly recognized as the result of an altered brain network, both on the structural and functional levels and the characterization of these widespread brain alterations is crucial for our understanding of the clinical manifestation of seizure and cognitive deficits as well as for the management of candidates to epilepsy surgery.

Tractography based on Diffusion Tensor Imaging allows non-invasive mapping of white matter tracts in vivo. Recently, diffusion spectrum imaging (DSI), based on an increased number of diffusion directions and intensities, has improved the sensitivity of tractography, notably with respect to the problem of fiber crossing and recent developments allow acquisition times compatible with clinical application.

We used DSI and parcellation of the gray matter in regions of interest to build whole-brain connectivity matrices describing the mutual connections between cortical and subcortical regions in patients with focal epilepsy and healthy controls. In addition, the high angular and radial resolution of DSI allowed us to evaluate also some of the biophysical compartment models, to better understand the cause of the changes in diffusion anisotropy.

Global connectivity, hub architecture and regional connectivity patterns were altered in TLE patients and showed different characteristics in RTLE vs LTLE with stronger abnormalities in RTLE. The microstructural analysis suggested that disturbed axonal density contributed more than fiber orientation to the connectivity changes affecting the temporal lobes whereas fiber orientation changes were more involved in extratemporal lobe changes. Our study provides further structural evidence that RTLE and LTLE are not symmetrical entities and DSI-based imaging could help investigate the microstructural correlate of these imaging abnormalities.

1. Introduction

Patients with temporal lobe epilepsy (TLE) suffer from dysfunctions affecting large-scale brain networks rather than a single focal region (Laufs, 2012). Functional and structural brain imaging studies, as well as invasive electrophysiology studies (Engel et al., 2013; Bernhardt et al., 2013; Van Diessen et al., 2013) have shown that this so-called epileptic network involves temporal and extratemporal regions of both hemisphere (Fahoum et al., 2012). The mapping of these abnormal neuronal networks is an important prerequisite for a better understanding of this condition, particularly when evaluating patients who are candidates for epilepsy surgery.

The development of diffusion-based Magnetic Resonance (MR) imaging and the tractography of white matter fiber tracts have allowed the investigation of the structural alterations underlying these abnormal brain functions (Gross, 2011). MR diffusion-based studies have initially demonstrated local alterations in diffusion measures in the white matter using voxel-based morphometry, however without integration of these abnormalities into identified tracts or networks. This was followed by the mapping of alterations in specific user-defined white matter tracts (limbic circuitry, uncinate fasciculus, arcuate fasciculus) with some correlation to cognitive measures (Aarts et al., 1984; Yogarajah et al., 2008; Concha et al., 2009). Tract-Based Spatial Statistics and similar techniques have revealed widespread bilateral temporal and extratemporal alterations in major white matter tracts (Focke et al., 2008; Voets et al., 2012). Very recently, in an effort to bridge the gap between cortical functional and subcortical structural connectivity studies, a few studies have investigated which cortical regions are

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affected by these subcortical white matter abnormalities. Using graph analysis applied to structural networks in patients with TLE, they found an altered distribution of connectivity hubs in left TLE vs controls (Liu et al., 2014). In addition, preoperatively increased connectivity in a temporal and extratemporal network was associated to persistence of post-operative seizures (Bonilha et al., 2013).

Fractional Anisotropy (FA) is the measure usually applied to describe white matter tract abnormalities but its microstructural biological correlates remain insufficiently understood. Recent studies have proposed MR-based measures of Intra-cellular Volume Fraction (ICVF) and Orientation Dispersion Index (ODI) as important components of the Fractional Anisotropy (Zhang et al., 2012; Kunz et al., 2014). Diffusion spectrum imaging (DSI) is a recently developed high angular resolution diffusion technique (Wedeen et al., 2005). DSI has been shown to better resolve the ambiguity of fiber crossing encountered in tractography (Cammoun et al., 2012; Granziera et al., 2009) and to provide increased sensitivity towards the detection of short range cortico-cortical connections (Gigandet et al., 2008; Granziera et al., 2012). Due to its multiple b-value properties, DSI also allows estimating finer microstructural properties such as ICVF and ODI to investigate the factors influencing GFA (Generalized Fractional Anisotropy) changes.

Here, we used DSI to estimate the structural connectivity and network properties in right (RTLE) and left TLE (LTLE) patients compared to healthy controls at whole-brain and regional level. We investigated three different structural connectivity matrices, averaging GFA (Tuch, 2004), ICVF and ODI (Zhang et al., 2012) along the tracts. Using a graph theory framework, we then identified cortical regions that significantly contributed to alterations in typical network indices such as the Strength, Efficiency, Shortest Path and Clustering.

2. Materials and methods

2.1. Patients and controls

22 patients with pharmacoresistant unilateral TLE (13 females and 9 males, age = 33.8 ± 10.1 years, 12 right-sided and 10 left) participated in this study and were recruited from the joint Epilepsy Surgery Program of Geneva and Lausanne, Switzerland. 15 patients had HS (hippocampal sclerosis), 7 patients had no apparent MRI lesion. The clinical diagnosis of TLE was made according to concordant electro-clinico-imaging data by experienced epileptologists (SV, MS). In 9 patients, invasive validation with intracranial EEG and/or seizure-freedom following anterior temporal lobe resection was available. In the remaining HS patients, a concordant non-invasive work-up was obtained. See Table 1 for more detailed information.

Table 1
The clinical data of patients used in this study.

Patient	Gender	Age	Onset	Focus side	MRI	Intracranial EEG	ILAE OP outcome (follow-up in years)
1	F	32	9	R	HS	Yes	I (2 y)
2	F	42	20	R	HS		I (3 y)
3	F	37	25	R	HS		I (3 y)
4	F	36	12	R	HS	Foramen ovale	na
5	M	28	2	R	HS		I (3 y)
6	F	50	12	R	None	Yes	I (1 y)
7	M	38	2	R	HS		na
8	M	22	17	R	HS		I (3 y)
9	M	40	22	R	None	Yes	na
10	F	30	27	R	HS		na
11	M	36	20	R	HS		I (1 y)
12	F	20	5	R	HS		I (2 y)
13	F	15	4	L	HS	Yes	I (3 y)
14	M	18	8	L	None	Yes	I (3 y)
15	M	44	17	L	HS		I (1 y)
16	F	40	16	L	HS		na
17	F	43	37	L	HS		I (2 y)
18	F	25	13	L	None	Yes	II (1 y)
19	M	25	15	L	HS		na
20	F	48	36	L	None	Yes	III (6 m)
21	F	46	41	L	None		na
22	M	27	23	L	None	Yes	I (2 y)

In addition, 21 healthy volunteers (8 females and 13 males, age = 31.2 ± 4.8 years) were included. The subjects were acquired on two different sites where a reproducibility study previously showed no scanner bias in the analysis. The two scanners used in the current study are referred to as scanners A and B in Lemkaddem et al. (2012). None of these control subjects had a history of neurological or psychiatric disorders. The ethical committee of two hospitals involved in this work approved this study and a written informed consent was obtained from each participant.

2.2. Imaging acquisition

MRI acquisition was performed on a 3 T Trio A Tim System (Siemens, Erlangen, Germany) using a 32-channel head coil. The imaging protocol included a DSI acquisition using a twice refocusing spin-echo with EPI read-out and diffusion gradient scheme minimizing eddy-current induced effects (Reese et al., 2003). The acquisition parameters were: TR/TE = 8500/154 ms; acquisition matrix = 96 × 96; in-plane resolution = 2.2 × 2.2 mm; slice thickness = 3 mm; 44 axial slices; acceleration factor = 2 and partial phase encoding factor = 6/8. It was acquired according to aq4-half protocol, which consists of 128 measurements in a 3D Cartesian grid comprised by the q-space points of a cubic lattice within the hemisphere of 4 lattice units in radius, with a maximum b-value of 6400 s/mm^2 (Wedeen et al., 2008).

Anatomical images were acquired for cortex parcellation with a T1-weighted MPRAGE (TR/TE = 2300/2.86 ms) and T2-weighted 3D SPACE (TR/TE = 3200/408 ms) with both an acquisition matrix = 256 × 256; voxel size = 1 × 1 × 1.2 mm; 160 sagittal slices; acceleration factor = 2; variable flip angle. The total scanning time was 30 min.

2.3. Pre-processing

84 cortical and subcortical regions with anatomical landmarks were mapped from MPRAGE image using Freesurfer 5.0 software (http://surfer.nmr.mgh.harvard.edu). These regions of interest (ROIs) are then co-registered to the diffusion image space using a nonlinear registration tool of FSL (FNIRT) (http://fsl.fmrib.ox.ac.uk).

In order to cope with geometric distortions due to the diffusion Echo Planar Image (EPI) read-out, the T2-weighted image was used for registering the MPRAGE image to the diffusion image. This procedure has the advantage that the T2-weighted image shares the same contrast as the b0 image but is much less distorted. Whole brain tractography was performed in the white matter areas using an in-house streamline-based algorithm adapted to work with DSI data (Daducci et al., 2012; Lemkaddem et al., 2012).

2.4. Diffusion model reconstruction and connectivity computation

An ODF (Orientation Distribution Function) was evaluated for a set of vectors representing the vertices of a regular polyhedron, the 362 vertex 6-fold geodesated icosahedron, of mean nearest-neighbor separation = 0.16, rad = 9°. Next, the GFA (Tuch, 2004) that is defined as an analog for q-ball imaging of the FA in DTI was computed from the ODFs. The GFA is expressed as:

$$\mathrm{GFA} = \frac{SD(ODF)}{RMS(ODF)},$$

where $SD(ODF)$ is the standard deviation of the ODF and $RMS(ODF)$ is its root mean square. Beside the usual indices derived from the ODF such as the GFA, we used a biophysical multi-compartment diffusion model, the Neurite Orientation Dispersion and Density Imaging (NODDI) model