Decreased Basal fMRI Functional Connectivity in Epileptogenic Networks and Contralateral Compensatory Mechanisms

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Abstract: A better understanding of interstructure relationship sustaining drug-resistant epileptogenic networks is crucial for surgical perspective and to better understand the consequences of epileptic processes on cognitive functions. We used resting-state fMRI to study basal functional connectivity within temporal lobes in medial temporal lobe epilepsy (MTLE) during interictal period. Two hundred consecutive single-shot GE-EPI acquisitions were acquired in 37 right-handed subjects (26 controls, eight patients presenting with left and three patients with right MTLE). For each hemisphere, normalized correlation coefficients were computed between pairs of time-course signals extracted from five regions involved in MTLE epileptogenic networks (Brodmann area 38, amygdala, entorhinal cortex (EC), anterior hippocampus (AntHip), and posterior hippocampus (PostHip)). In controls, an asymmetry was present with a global higher connectivity in the left temporal lobe. Relative to controls, the left MTLE group showed disruption of the left EC-AntHip link, and a trend of decreased connectivity of the left AntHip-PostHip link. In contrast, a trend of increased connectivity of the right AntHip-PostHip link was observed and was positively correlated to memory performance. At the individual level, seven out of the eight left MTLE patients showed decreased or disrupted functional connectivity. In this group, four patients with left TLE showed increased basal functional connectivity restricted to the right temporal lobe spared by seizures onset. A reverse pattern was observed at the individual level for patients with right TLE. This is the first demonstration of decreased basal functional connectivity within epileptogenic networks with concomitant contralateral increased connectivity possibly reflecting compensatory mechanisms. *Hum Brain Mapp* 30:1580–1591, 2009. ©2008 Wiley-Liss, Inc.

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INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common form of partial epilepsy in which seizures originate primarily from one or several anatomical divisions of the temporal lobe and propagate through interconnected neuronal networks (Bartolomei et al., 2004). In cases of drug-resistant TLE, the only curative therapy currently available is surgical

TABLE I. Clinical characteristics of the MTLE patients

Patient No.	Sex	Age	Epilepsy onset (year)	Epilepsy duration (year)	Seizures frequency (per week)	MRI visible lesion
Left MTLE patients						
1	M	39	33	6	1.5	Left HS
2	F	35	16	19	8	Left HS
3	F	23	13	10	1.5	Left HS
4	M	40	26	14	2	Left HS
5	F	48	14	34	2	Left HS
6	F	25	16	9	4.5	Left HS
7	F	41	27	14	1.5	Left amygdala hypersignal
8	F	25	18	7	2.5	Left parahippocampal FCD
Right MTLE patients						
9	F	24	17	7	0.5	Right HS
10	M	39	8	31	6	Right MTL CD
11	F	54	13	41	4	Right HS

HS, hippocampal sclerosis; FCD, focal cortical dysplasia; MTL, medial temporal lobe; CD, cortical dysplasia.

resection of the epileptogenic zone (EZ). To offer an appropriate surgical resection, it is crucial to localize the EZ and thus better understand the brain networks involved in seizure generation. Recent electrophysiological studies using depth EEG recordings have demonstrated a hypersynchrony between structures participating to the epileptogenic networks during seizures (Guye et al., 2006), as well as during interictal periods (Bettus et al., 2008; Schevon et al., 2007). A better understanding of the interstructure relationship sustaining these pathologic networks is important not only to better define these networks in a surgical perspective but also to better understand the potential consequences on cognitive functions (mainly memory impairment) usually associated with medial TLE (MTLE).

Interpretation of resting state BOLD (blood oxygen level dependant) signal is not yet fully understood, especially in pathological states such as in epilepsy where the neurovascular coupling could be altered (Lemieux et al., 2008). However, resting state fMRI can be used to assess basal functional connectivity inside networks by computing temporal correlations of BOLD signals between remote brain areas during a resting period (Biswal et al., 1995; Lowe et al., 1998; Waites et al., 2005). This method has been shown to provide enough sensitivity to evidence altered functional connectivity between temporal lobe structures in patients with Alzheimer's disease (Greicius et al., 2004; Wang et al., 2006) or in networks sustaining language in patients presenting with TLE (Waites et al., 2006).

To our knowledge, no assessment of basal functional connectivity has yet been conducted in MTLE patients concerning medial and neocortical temporal structures related to the memory system involved in this type of epilepsy. We hypothesize that, relative to controls, MTLE patients show altered temporal basal functional connectivity in relation to the lateralization of their epilepsy during the interictal period. Therefore, we aimed to assess the ability of resting

state fMRI to evidence specific altered profiles of temporal lobe basal functional connectivity during the interictal period in right-handed subjects presenting with left or right MTLE.

MATERIALS AND METHODS

Subjects

Eight right-handed patients with left MTLE and 26 healthy right-handed subjects matched for age and sex gave their informed consent to be included in this study approved by the local Ethics Committee of Marseille Public Hospital. Laterality of all subjects was controlled (all subjects were right handed) to limit the potential bias related to possible variations in structural and functional asymmetries of temporal lobes. The eight patients with left MTLE (six females, two males, age = 34.9 ± 9.3 years) were selected after a comprehensive noninvasive presurgical phase evaluation including detailed history and neurological examination (Table I), neuropsychological testing, conventional MRI, and surface video-EEG. Six out of the eight MTLE patients had a left hippocampal sclerosis, one patient had hypersignal in the left amygdala on FLAIR images, and the last one had a left parahippocampal focal cortical dysplasia. Although exhibiting two types of pathology, all patients presented with homogeneous electro-clinical features compatible with a pure MTLE as defined in a previous work using SEEG (Maillard et al., 2004). Normative evaluation of memory capacity and intelligent scale of patients were assessed by the Wechsler Memory Scale, third edition (WMS III), and the WAIS III (Wechsler adult intelligent scale) (Table II).

The 26 right-handed healthy controls (12 females, 14 males), matched for age (age = 28.5 ± 8.5 years, $P = 0.087$, Kruskal-Wallis test) and sex ($P = 0.661$, Kruskal-Wallis test) and were free of neurological disease and cog-

TABLE II. Neuropsychological evaluation of MTLE patients

	Left MTLE (<i>n</i> = 8)			Right MTLE (<i>n</i> = 3)		
	Mean	Range		Mean	Range	
		Upper	Upper		Upper	Lower
WMS III						
Immediate memory quotient	95.87	110	77	91	107	63
Diff memory quotient	91.12	109	76	91.33	111	67
Work memory quotient	82*	66	97	87	105	79
WAIS III						
Verbal intelligence quotient	82.75*	95	62	73*	94	62
Performance intelligence quotient	81.75*	98	63	68*	80	55
Full Scale intelligence quotient	81.75*	90	66	69.67*	87	58

WMS III: Wechsler memory scale Third Edition and WAIS III: Wechsler adult Intelligent scale-Third Edition.

* Under 1.5 SD; normal mean = 100.

nitive complaints. No abnormal findings on conventional brain MRI were observed in controls.

To test the ability of resting-state fMRI to evidence subtle basal connectivity disturbance relative to the laterality of epilepsy and limit the probability of a chance finding, we have also explored three patients with right TLE (two females, one male, age = 39 ± 15 years, all right-handed). According to the small $n = 3$, only individual results were considered in these subjects.

All subjects underwent an MRI examination (duration 80 min), in the framework of a multimodal MRI protocol on a 1.5T Magnetom Vision plus MR-scanner (Siemens, Erlangen, Germany).

Conventional MRI

Conventional MRI included T₁-weighted images (TE/TR = 15 ms/700 ms, 23 contiguous slices, 5-mm slice thickness, field of view (FOV) 240 mm, matrix 256) acquired in the AC-PC plane, T₂-weighted images (TE/TR = 112/7308 ms, FOV 240 mm, matrix 256, 23 contiguous slices, 5-mm slice thickness) acquired in the bihippocampal plane, T₁-weighted inversion recovery images (TE/TR = 60/8,000 ms, TI = 350 ms, FOV = 240 mm, matrix 512, 5-mm slice thickness), FLAIR images (TE/TR = 110/8,000 ms, TI = 2,500 ms, FOV = 240 mm, matrix 256, 5-mm slice thickness) acquired in a coronal axis perpendicular to the bihippocampal plane, and sagittal 3D-MPRAGE images (TE/TR = 4/9.7 ms, isotropic voxel of $1.25 \times 1.25 \times 1.25$ mm³).

Resting State fMRI

Data acquisition

Two hundred brain volumes (time-elapsd between blocks: 4 s) were acquired in the transverse AC-PC plane, using a single-shot multislice gradient-echo echo-planar imaging (GE-EPI) sequence (TE 55 ms, TR 4 s, 30 contiguous slices, 4-mm thickness, matrix 64, FOV 256 mm).

During resting-state fMRI, subjects were instructed to simply keep their eyes closed and not fall asleep.

Data processing

Resting-state fMRI acquisitions were preprocessed using the SPM2 software (Wellcome Institute, London, UK). After slice timing correction, images were realigned before spatial normalization (16 nonlinear registration $7 \times 6 \times 7$ basis functions) and smoothing (12 mm). Sources of spurious or regionally nonspecific variance related to physiological artefacts (CSF pulsations, head motions, etc.), were removed by regression including the signal averaged over the lateral ventricles, and the signal averaged over a region centered in the deep cerebral white matter to reduce nonneuronal contributions to BOLD correlations (Bartels and Zeki, 2005; Vincent et al., 2006).

Choice of the regions of interest

According to previous studies using depth electrodes in TLE patients (Bartolomei et al., 2001, 2004), we defined 10 regions of interest (ROI; five in each hemisphere) usually involved in epileptogenic networks of medial TLE. These regions were automatically defined on a digital Talairach atlas (Pick_atlas toolbox, SPM2) and consisted of amygdala (Amy), entorhinal cortex (EC), anterior hippocampus (AntHip), posterior hippocampus (PostHip), and the temporal pole (Brodman area 38, BA38). These ROIs were used as masks (see Fig. 1) applied onto the residual images to extract the mean signal time-courses from each predefined ROI.

To determine functional interactions between ROIs in each temporal lobe, correlation coefficients between pairs of signal time-courses were computed (JMP statistical software). Correlation coefficients were then normalized using the Fisher transformation ($rN = 0.5 \log [(1 + r)/(1 - r)]$) to reflect basal functional connectivity and to perform subsequent statistical analyses.

Within-Group Analyses of Resting State Functional Connectivity in the Temporal Lobe

For each group (controls and left MTLE patients), unilateral temporal basal functional connectivity, values were tested against the null hypothesis for each link (Mann

Figure 1.

Regions of Interest (ROIs) defined in bilateral temporal lobes used to extract fMRI signal time courses during resting periods. ROIs (posterior hippocampus: brown; anterior hippocampus: red; entorhinal cortex: orange; amygdala: yellow; temporal pole (Brodmann area 38): blue) were automatically defined on a digital Talairach atlas and applied on the coregistered and spatially normalized EPI images for each subject.

Whitney test, corrected $P < 0.005$; 10 comparisons per group) to determine the statistical significance of each correlation. Basal functional connectivity values for nonsignificant correlations were set to zero.

For each group (controls and left MTLE patients), differences in basal functional connectivity values between contralateral links were also tested (Wilcoxon rank test, corrected $P < 0.005$; 10 comparisons per group).

Within-group effect of functional connectivity was tested for controls and left MTLE for each hemisphere (Wilcoxon signed rank, relative for the mean). Within-group analysis was not performed on the right MTLE patients relative to the small $n = 3$

Between-Group Comparisons (Controls Versus Left MTLE Patients)

For each hemisphere, between-group comparisons of basal functional connectivity values were performed for each link using a Mann Whitney test. A corrected $P < 0.005$ was considered for 10 comparisons.

In text and figures, P -values annotated with * referred to statistical values surviving to multiple comparison correction.

Individual Results

To evaluate the added value of basal functional connectivity at the individual level, z -scores were calculated for patients relative to the mean and standard deviation of controls. Patients have been classified as abnormal for z -score values above or below 2.

Correlations

In the left MTLE group, pairwise correlations were done to determine (i) balance of functional connectivity between the normal and the affected temporal lobe, (ii) impact of increased connectivity on altered memory scores, (iii) impact of seizure frequency on altered connectivity, and (iv) impact of disease duration on altered connectivity. We considered that each test aimed at answering one different question; consequently, no multiple comparison corrections were applied (Spearman Rho, $P < 0.05$).

RESULTS

Within-Group Analysis of Basal Functional Connectivity in Controls

No effect was observed for the global functional connectivity of each hemisphere (Wilcoxon rank test, left lobe $P = 0.5$; right lobe $P = 0.5$).

During resting state, controls showed significant basal functional connectivity values in both hemispheres for the links Amy-BA38 ($P < 0.0001^*$), Amy-EC ($P < 0.0001^*$), Amy-AntHip ($P < 0.0001^*$), Amy-PostHip ($P < 0.0001^*$), BA38-EC ($P < 0.0001^*$), BA38-AntHip ($P < 0.0001^*$), BA38-PostHip ($P < 0.0001^*$), EC-AntHip ($P < 0.0001^*$), and AntHip-PostHip ($P < 0.0001^*$) (Mann Whitney test, corrected $P < 0.005$). In contrast, correlations between EC-PostHip were not significant in the two hemispheres.

Left-right asymmetry in basal functional connectivity was present, with a left predominance for the links AntHip-PostHip ($P < 0.001^*$), Amy-AntHip ($P < 0.002^*$), and Amy-PostHip ($P < 0.001^*$), while a right predominance was observed for the link Amy-EC ($P < 0.001^*$) (Wilcoxon rank test, corrected $P < 0.005$) (Fig. 2, top)

Within-Group Analysis of Basal Functional Connectivity in Left MTLE Patients

No effect was observed for the global functional connectivity of each hemisphere (Wilcoxon rank test, left lobe $P = 0.5$; right lobe $P = 0.5$).

Similar to controls, patients showed significant basal functional connectivity in both sides for the links Amy-BA38 ($P < 0.0001^*$), Amy-EC ($P < 0.0001^*$), Amy-AntHip ($P < 0.0001^*$), Amy-PostHip ($P < 0.0001^*$), BA38-EC ($P < 0.0001^*$), BA38-AntHip ($P < 0.0001^*$), BA38-PostHip ($P < 0.0001^*$), AntHip-PostHip ($P < 0.0001^*$), and the right EC-AntHip link ($P < 0.0001^*$) (Mann Whitney test, corrected $P < 0.005$) (Fig. 2 bottom). No significant correlation was observed for the links EC-PostHip in both sides. In addition, left MTLE patients (Fig. 2 bottom and Fig. 3) showed disruption of the functional link EC-AntHip in the left hemisphere.

Patients showed trends of right predominance for two links, Amy-EC ($P = 0.039$) and AntHip-PostHip ($P = 0.039$) (Wilcoxon rank test, corrected $P < 0.005$).

Figure 2.

Basal functional connectivity of the medial temporal lobes in controls (top) and in left MTLE patients (bottom). Connecting lines correspond to significant basal functional connectivity. Links thickness reflects correlation values. Normalized correlation coefficients and standard deviation (brackets) are indicated in

squares. In patients, epileptogenic zone is outlined. Hemispheric predominance of correlation coefficients are marked by grey background squares (uncorrected $P < 0.05$) and stars stand for surviving P values to multiple comparison correction (Mann Whitney test, corrected $P < 0.005$).

Between-Groups Analysis (Left MTLE Patients Versus Controls)

Due to multiple comparison corrections, a trend of decrease in basal functional connectivity was observed for

the left link AntHip-PostHip in MTLE patients ($P = 0.015$), accompanied by a trend of increased basal functional connectivity for the contralateral link AntHip-PostHip relative to controls ($P = 0.040$) (Mann Whitney test, corrected $P < 0.005$).

Figure 3.

Differences in basal functional connectivity between the left MTLE patients and controls. Relative to controls, MTLE patients showed disruption (entorhinal cortex—anterior hippocampus, crossed dashed line) and decreased functional connectivity (ante-

rior—posterior hippocampi, dotted line) inside the left temporal lobe and increased basal functional connectivity inside the right temporal lobe (anterior—posterior hippocampi, bold line) (Mann Whitney test, corrected $P < 0.005$). Epileptogenic zone is outlined.

The comparison between patients and controls showed also a trend of differences in asymmetry for the link AntHip-PostHip ($P < 0.039$) with a predominance of the left hemisphere in controls and a predominance of the right hemisphere in MTLE patients (Wilcoxon rank test, corrected $P < 0.005$) (see Fig. 3).

Individual Results in MTLE Patients

Left MTLE

Seven out of the eight left MTLE patients (nos. 1, 2, 3, 5, 6, 7, 8) showed at least one abnormal basal functional connectivity value, while only one patient (no. 4) had a normal basal functional connectivity profile during the interictal period.

Decreased or disrupted basal functional connectivity was observed in both hemispheres for two patients (nos. 1 and 2), was restricted to the left hemisphere in two patients (nos. 3 and 5), and was restricted to the right hemisphere in two patients (nos. 6 and 7).

In the left hemisphere, disconnections involved preferentially the left EC (nos. 1, 2, 3, 5) and the left anterior hippocampus (nos. 1, 3, 5). In one case (no. 2), a significant but negative correlation was observed between the left EC and AntHip (no. 2).

In the right hemisphere, decreased connectivity or disconnection involved various structures in a less specific way (two subjects with disruption for EC-AntHip, two for Amy-PostHip, and one for BA38-PostHip).

In contrast, increased basal functional connectivity (2 SD above the mean values of controls) was observed in four out of the eight left MTLE patients (nos. 1, 2, 3, 8) but was restricted to the right nonepileptogenic temporal lobe, while no such increase was observed for these patients in the left temporal lobe. This increased connectivity involved consistently the links including the right posterior hippocampus (see Fig. 4).

Right MTLE

The three right MTLE patients showed at least one abnormal basal functional connectivity value. Two out of the three right MLTE patients had decreased functional connectivity, in both hemispheres for one patient (no. 10) and restricted to the side of the epilepsy for the other patient (no. 9). In these two patients, the affected link was the right Amy-PostHip.

Increased functional connectivity was observed in two patients (nos. 10, 11) restricted to the left hemisphere contralateral to epilepsy. One patient (no. 10) had increased connectivity involving the left BA38-PostHip link, and the

Figure 4.

Individual patterns of basal functional connectivity observed in left MTLE patients. Links with normal basal functional connectivity values are displayed in grey. Relative to the mean and standard deviation of controls, patients have been classified as abnormal for z-score values above or below 2 SD. Increased connec-

tivity are reported in bold and decreased connectivity with crossed dashed line. One patient had a normal profile. Seven patients had at least one decreased or disrupted connection. Four patients had at least one increased connection in the right temporal lobe.

Figure 5.

Individual patterns of basal functional connectivity observed in right MTLE patients. Links with normal basal functional connectivity values are displayed in grey. Relative to the mean and standard deviation of controls, patients have been classified as abnormal for z-score values

above or below 2 SD. Increased connectivity are reported in bold and decreased connectivity with crossed dashed line. Two patients had interrupted connectivity in one or both lobes. Two patients had at least one increased connection in the left lobe.

other patient (no. 11) showed increased connectivity for the left Amy-AntHip, Amy-PostHip, and AntHip-PostHip links (see Fig. 5).

Balance of Functional Connectivity Between the Normal and the Affected Temporal Lobe in MTLE Group

The abnormally increased connectivity between right AntHip-PostHip was correlated with the number of links with decreased connectivity in the left hemisphere (Spearman Rho = 0.792, $P = 0.019^*$) (see Fig. 6).

Relationship Between Increased Connectivity and Altered Memory Scores in the Left MTLE Group

In the left MTLE group, a significant positive correlation ($R = 0.711$, $P = 0.048^*$) was observed (see Fig. 7) between increased connectivity values of the right AntHip-PostHip links and the working memory quotients of the WMS III battery.

Impact of Seizure Frequency on Altered Connectivity in the Left MTLE Group

No significant correlation was found between seizure frequency and decreased ($R = 0.213$, $P = 0.611$) or increased ($R = -0.263$, $P = 0.528$) functional connectivity.

Figure 6.

Reorganization of functional connectivity in left MTLE patients. Correlation between basal functional connectivity values between the right anterior and posterior hippocampi and the extent of disconnection inside the left hemisphere reflected by the number of links with abnormal connectivity values (Spearman Rho = 0.792, $P = 0.019$).

Figure 7.

Compensatory effects of functional reorganization in left MTLE patients. Significant positive correlation ($R = 0.711$, $P = 0.048$) between the increase in basal functional connectivity values between the right anterior and posterior hippocampi link and the memory scores (working memory quotients of the WMS III battery).

Impact of Disease Duration on Altered Connectivity in the Left MTLE Group

No significant correlation was found between disease duration and decreased ($R = 0.491$, $P = 0.216$) or increased ($R = -0.207$, $P = 0.623$) functional connectivity.

DISCUSSION

Using resting-state fMRI, we investigated the properties of neural networks involved in the epileptogenic zone of MTLE, by studying basal functional connectivity within temporal lobe structures during the interictal period. We observed (i) in controls, higher functional connectivity within the left temporal lobe relative to the right, (ii) in MTLE patients, decreased connectivity within the epileptogenic zone relative to controls, and (iii) increased connectivity within the contralateral temporal lobe correlating to memory scores that suggests a compensatory mechanism.

Rationale of the Network Studied

The MTLE network model holds that limbic seizures may result from a more extensive alteration of limbic networks within the temporal lobe (Bartolomei et al., 2001; Bertram et al., 1998), where the ictal discharge is limited to the medial limbic structures and may propagate secondarily to the cortex. We have chosen to study the interrelationship between five ROIs, i.e., the temporal pole (BA38), the amygdala, the entorhinal cortex, and the anterior and the posterior hippocampi highly supposed to participate to the epileptogenic network in MTLE. Indeed, constant unidirectional or bidirectional coupling were observed

between amygdala, hippocampus, and entorhinal cortex using SEEG (stereo-electroencephalography) signal (Bartolomei et al., 2001). In MTLE network, privileged links were recorded in limbic structures of the temporal lobe, which are characterized by a significantly high correlation during the period preceding the appearance of rapid epileptic discharges (Bartolomei et al., 2004).

Moreover, anterior and posterior hippocampi were separated according to the antero-posterior functional dichotomy supported by several studies: (i) in animals, showing unique afferents from the entorhinal cortex to different regions of the hippocampus (Dolorfo and Amaral, 1998; Witter et al., 1989), and showing different degrees of neuron recruitment between posterior and anterior hippocampi during selective tasks (Colombo et al., 1998); (ii) in humans, demonstrating a dissociation of activation between anterior and posterior hippocampi subject to different kinds of mnemonic stimulations relative to object recovery (Kohler et al., 2005; Lee et al., 2006; Pihlajamäki et al., 2004) or visuo-spatial memory (Burgess et al., 2001; Maguire et al., 1996; Parslow et al., 2004).

It is noteworthy that these networks are extending outside the temporal lobes, especially to the parietal and the prefrontal regions (Vincent et al., 2006). However, we have chosen to restrict this preliminary study to regions most likely to be candidate to resection during treatment of intractable partial MTLE.

Basal Functional Connectivity of Temporal Networks in Controls

In the 26 right-handed normal subjects, we found an asymmetrical organization of basal functional connectivity between medial and neocortical structures inside the temporal lobes. A left predominance was observed in basal functional connectivity within medial temporal lobe network. This was especially the case for the left connections involving the hippocampus (anterior and posterior) and amygdala with three links significantly higher in the left hemisphere relative to the right hemisphere (AntHip-PostHip, AntHip-Amy, Amy-PostHip). This left predominance of connections inside the temporal lobe appears in line with previous structural data obtained by quantitative diffusion tensor tractography showing asymmetry in the relative patterns of fiber density such as in the arcuate fasciculus that provides the basis of a neural system model for language lateralization (Nucifora et al., 2005). In addition, functional studies using autobiographic memory tasks as paradigm also demonstrated a stronger left lateralization of activity and effective connectivity inside the left temporal lobe (Addis et al., 2007).

The basal functional connectivity values between Amy-EC have been found here to be higher in the right hemisphere in controls as well as in patients. These two structures are reported to play a key role in emotion processing of which some aspects are considered as being rather lateralized in the right hemisphere (Baas et al., 2004).

Basal Functional Connectivity of Temporal Networks in Left MTLE

In this homogenous population of right-handed patients presenting with left MTLE, decrease in basal functional connectivity was observed preferentially in the left hemisphere, while increase in basal functional connectivity appeared restricted to the right hemisphere spared by seizures onset, at the group level as well as at the individual level.

These results suggest that epilepsy affects the integrity of temporal lobe networks by decreasing basal functional interactions during interictal periods. Decreased functional connectivity between medial temporal structures and interconnected neocortical areas (BA38) is in line with previous data reported on language network (links between frontal and parietal areas) also recorded at rest in TLE patients (Waites et al., 2005). In addition, combined SEEG-MR spectroscopic imaging studies have demonstrated that not only temporal but also frontal regions with interictal and/or ictal paroxysmal events recorded by SEEG were characterized by a decrease in *N*-acetyl-aspartate (NAA) level, a marker of neuronal function integrity (Guye et al., 2002, 2005). In the present study, disconnections involved preferentially the entorhinal cortex and the anterior hippocampus in the left hemisphere affected by seizures. Hippocampus and entorhinal cortex constitute a transmodal node establishing, for explicit memory, a directory that guides the binding of the modality and category-specific fragments of individual events into coherent multimodal experiences, also promoting the stable encoding of new associations in other parts of the neocortex (Mesulam, 1998). Presence of decreased connectivity at rest between these structures in left MTLE patients emphasizes the decrease in basal functional connectivity affecting this neural system. Despite the fact that two MTLE patients presented with a different pathology (i.e., focal cortical dysplasia), electroclinical patterns were homogeneous in the whole group. Thus, these results suggest that the functional connectivity alterations observed in these patients are more linked to the epileptic processes itself than to the type of associated lesion. In addition, we did not observe a within-group effect regarding the hemispheric temporal functional connectivity. Preliminary results in patients with right MTLE add further evidence for a similar pattern of altered functional connectivity characterized by a decreased connectivity in the epileptic temporal lobe and an increased connectivity in the contralateral side.

Increased Resting State Functional Connectivity in the Hemisphere Contralateral to Seizures Onset

Concurrent to decrease in basal functional connectivity, we have also observed at the group level as well as at the individual level a significant increase in basal functional connectivity for at least one link, always located in the right hemisphere, contralateral to the EZ. In four out of

the eight patients with such a profile, the increase in basal functional connectivity involved the connection linking the anterior to the posterior hippocampus. In two patients (nos. 2 and 3), increased connectivity involved supplementary links including BA38 and amygdala.

This contralateral-increased functional connectivity has also been reported in two of three patients with right MTLE (mirrored profiles). In right MTLE patients, left posterior hippocampus was also particularly involved in this increased connectivity (present for the two patients).

This increased connectivity at rest suggests increased wiring inside networks that could sustain compensatory mechanisms. This is supported by the significant correlation between increased functional connectivity of the right AntHip-PostHip link and the extent of disconnection affecting the left temporal lobe in the left MTLE group. Noteworthy is that the increased functional connectivity was also correlated to working memory scores in patients, reinforcing the hypothesis of an efficient compensatory mechanism related to stronger functional connectivity.

Compensatory mechanisms have been already evidenced during tasks involving the memory network with increased brain activity observed inside various structures such as the left medial prefrontal cortex, bilateral hippocampi, medial parietal cortices, parahippocampal gyri, and temporal lobe of TLE patients (Addis et al., 2007; Maguire et al., 2001; Powell et al., 2007; Thivard et al., 2005). An overall reorganization has been reported very recently during an autobiographical memory task in the hierarchical interactions between temporal, parietal, and frontal structures (effective connectivity), showing the presence of brain plasticity in response to pathological damage induced by MTLE (Addis et al., 2007).

Pathophysiological Hypothesis

It is now well demonstrated that seizures are not only the result of excitatory/inhibitory imbalance but also alterations of mechanisms supporting neural synchrony (Bartolomei et al., 2004; Bragin et al., 1999; Uhlhaas and Singer, 2006; Wendling et al., 2003). Electrophysiological studies in animal models as well as human studies using intracranial recordings have shown an increased synchronization in the epileptogenic zone during seizures and interictal state (Bartolomei et al., 2004; Bragin et al., 1999; Guye et al., 2006; Bettus et al., 2008; Schevon et al., 2007). However, dynamic modifications of synchronization may occur during transition phases between interictal state and seizure, depending on the discharge frequency. During the rapid discharge at seizure onset, desynchronization between signals recorded inside the epileptogenic network has been demonstrated in neocortical seizures (Wendling et al., 2003).

Nevertheless, literature provides evidence of increased functional EEG connectivity between structures forming the EZ. Conversely, in this article, we have found a decreased basal functional connectivity during interictal period.

It then remains to explain the apparent discrepancy between EEG and fMRI connectivity in epileptic patients. We hypothesize that pathophysiological alterations associated with epilepsy (i.e., metabolic and hemodynamic changes) may affect the neurovascular coupling responsible for a correlation between BOLD signal and neuronal activity (directly measured by EEG) in healthy subjects (Logothetis et al., 2001; Schwartz, 2007). Thus, whereas increased EEG connectivity could be related to pathologically reinforced links between hyperexcitable structures forming the epileptogenic network, decreased fMRI connectivity during rest could be more related to metabolic or perfusion defects. This is in accordance with the observation that abnormal electrical activities can induce (or can be due to) long lasting metabolic alterations observed during interictal periods, affecting both the epileptogenic zone network (source of the seizures) and the connected brain regions (Guye et al., 2005). In addition, we postulate that whereas increased EEG connectivity is probably not related to an improvement of the functions sustained by the networks involved in the EZ, decreased fMRI connectivity is clearly related to an impairment of cognitive functions (Waites et al., 2006). We have also demonstrated that basal functional connectivity could be increased in the hemisphere spared by seizure in MTLE patients, preferentially involving connections including the hippocampus. We infer that this increase in basal functional connectivity of the hippocampus contralateral to epilepsy is related to compensatory mechanisms aiming at functionally limiting the effects of brain injury inside the temporal lobe involved in MTLE. We think that the results of this preliminary study provide convincing elements of the impact of epilepsy on basal functional connectivity, whenever these results have to be replicated on larger cohorts, in other types of epilepsy and with gold standard measurements such as SEEG recordings.

CONCLUSION

Using resting-state fMRI performed in MTLE patients, we have showed for the first time the presence of decreased basal functional connectivity within epileptogenic networks potentially associated with concomitant increased contralateral connectivity, suggestive of compensatory mechanisms.

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