Patterns of altered functional connectivity in mesial temporal lobe epilepsy

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Summary

Purpose—In mesial temporal lobe epilepsy (MTLE) the epileptogenic area is confined to the mesial temporal lobe, but other cortical and subcortical areas are also affected and cognitive and psychiatric impairments are usually documented. Functional connectivity methods are based on the correlation of the blood oxygen level dependent (BOLD) signal between brain regions, which exhibit consistent and reproducible functional networks from resting state data. The aim of this study is to compare functional connectivity of patients with MTLE during the interictal period with healthy subjects. We hypothesize that patients show reduced functional connectivity compared to controls, the interest being to determine which regions show this reduction.

Methods—We selected electroencephalography–functional magnetic resonance imaging (EEG–fMRI) resting state data without EEG spikes from 16 patients with right and 7 patients with left MTLE. EEG–fMRI resting state data of 23 healthy subjects matched for age, sex, and manual preference were selected as controls. Four volumes of interest in the left and right amygdalae and hippocampi (LA, RA, LH, and RH) were manually segmented in the anatomic MRI of each subject. The averaged BOLD time course within each volume of interest was used to detect brain regions with BOLD signal correlated with it. Group differences between patients and controls were estimated.

Key Findings—In patients with right MTLE, group difference functional connectivity maps (RMTLE – controls) showed for RA and RH decreased connectivity with the brain areas of the default mode network (DMN), the ventromesial limbic prefrontal regions, and contralateral mesial

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Volumetric comparison (mm³) between right and left amygdala and hippocampus for LMTLE, RMTLE, and controls (boxplot representation). In the RMTLE group the RH is smaller than the LH, so the value of the difference RH–LH is negative. In the LMTLE the LH is smaller than the RH, so the value of the difference RH–LH is positive. This difference is smaller in LMTLE. No differences of volume were detected for amygdalae. In controls there were no differences between amygdalae and hippocampi.

Table S1. Clinical characteristics of patients with MTLE.

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temporal structures; and for LA and LH, decreased connectivity with DMN and contralateral hippocampus. Additional decreased connectivity was found between LA and pons and between LH and ventromesial limbic prefrontal structures. In patients with left MTLE, functional connectivity maps (LMTLE – controls) showed for LA and LH decreased connectivity with DMN, contralateral hippocampus, and bilateral ventromesial limbic prefrontal regions; no change in connectivity was detected for RA; and for RH, there was decreased connectivity with DMN, bilateral ventromesial limbic prefrontal regions, and contralateral amygdala and hippocampus.

Significance—In unilateral MTLE, amygdala and hippocampus on the affected and to a lesser extent on the healthy side are less connected, and are also less connected with the dopaminergic mesolimbic and the DMNs. Changes in functional connectivity between mesial temporal lobe structures and these structures may explain cognitive and psychiatric impairments often found in patients with MTLE.

Keywords

EEG-fMRI; Resting state functional connectivity; Mesial temporal lobe epilepsy; Default mode network

Mesial temporal lobe epilepsy (MTLE) is the most common focal epilepsy in adults, and hippocampal sclerosis the most frequent lesion in these patients. Seizures are often resistant to antiepileptic drugs, but many patients can be cured by resecting the epileptogenic zone (Thadani et al., 1995). To offer surgical resection, it is important to accurately localize the epileptogenic zone and understand the networks affected by it. Patients with left MTLE usually present verbal memory deficits, whereas those with right MTLE exhibit deficits of nonverbal (visual) memory (Kim et al., 2003). In addition to these dysfunctions related to damage in mesial temporal structures, other cognitive abilities are impaired: verbal comprehension, perceptual organization, academic achievement, language, and visuospatial function (Hermann et al., 1997; Jones-Gotman et al., 2010). Finally, patients often present psychiatric comorbidities, such as anxiety and depression (Shukla et al., 1979; de Oliveira et al., 2010).

Magnetic resonance imaging (MRI) can identify in vivo hippocampal sclerosis (atrophy and increased T₂ signal), but refined MRI analyses, such as voxel-based morphometry, have demonstrated that patients also exhibit abnormalities outside the hippocampus, not easily detectable by inspection of diagnostic images (Bonilha et al., 2010): decreased gray matter volume in other limbic structures (amygdala, fornix, entorhinal cortex), in the ipsilateral and contralateral temporal neocortex, and in extratemporal regions, such as thalamus, cerebellum, frontal lobe areas and cingulate gyrus, and occipital regions (Moran et al., 2001; Bernasconi et al., 2004; Riederer et al., 2008). Abnormalities affect a network of regions functionally or anatomically connected to the hippocampus, probably resulting in the complex cognitive and behavioral conditions. The mechanisms underlying brain damage in MTLE remain largely unknown. One theory hypothesizes that seizure propagation determines the distribution of damage (Riederer et al., 2008). Another suggests that loss of hippocampal connections results in deafferentation and neuronal damage; for instance, structures directly connected to the hippocampus, like the thalamus, show atrophy (Bonilha et al., 2010).

Changes in the level of neuronal activity are accompanied by changes in the concentration of deoxyhemoglobin in the blood; this is measured through the blood oxygen level-dependent (BOLD) effect with functional MRI (fMRI, Ogawa et al., 1992). Biswal et al. (1995) observed that functionally related brain regions show temporal correlations in the low frequency component of the BOLD signal and that such correlations occur during tasks and also at rest, revealing several functional networks (e.g., attention, vision, and motor system). Functional connectivity detects zones that exhibit correlated BOLD fluctuations and, as a result, belong to the same functional network (Greicius et al., 2003).

Reduced functional connectivity has been reported for several pathologic conditions including Alzheimer's disease, multiple sclerosis, and autism (Fox & Raichle, 2007). In MTLE, studies showed connectivity changes and impaired functional networks: in left MTLE, Waites et al. (2006), using language regions as seed, found disrupted connectivity in language areas. In unilateral MTLE, an impairment within and between hippocampi was shown by Pereira et al. (2010). Bettus et al. (2009) observed decreased connectivity within mesial structures in the affected temporal lobe and contralateral increased connectivity. Other studies have suggested that perceptual (Zhang et al., 2009a) and attention networks (Zhang et al., 2009b) are impaired in MTLE.

In this study, we compare fMRI connectivity of patients with MTLE with healthy subjects by using an approach more specific to mesial temporal structures than the ones used in previous studies. We expect that patients will show reduced connectivity, the interest being to determine in what regions.

Methods

Subjects

We selected patients with MTLE and the following inclusion criteria: (1) history of seizures with autonomic (e.g., epigastric sensation) or psychic features (e.g., déjà vu or dreaming state) as the first ictal symptom, followed by arrest of activity, staring, and automatisms, mainly oroalimentary; (2) interictal and ictal electroencephalography (EEG) epileptiform abnormalities over temporal or frontotemporal regions; and (3) unilateral epileptogenic temporal focus. The focus was lateralized based on clinical history, interictal and ictal video-EEG recordings, and neuroimaging. Patients with bilateral hippocampal atrophy or bilateral independent ictal EEG findings were excluded; (4) left hemispheric dominance for language determined by neuropsychological evaluations (and etomidate speech and memory test, eSAM, when indicated); and (5) availability of a 3 Tesla EEG-fMRI scan. For every patient we matched a healthy control subject for age, sex, and manual preference. Only the controls matched to the patients in the specific group (left or right MTLE) were used for the comparison with that group.

The study was approved by the institutional research ethics board. Each subject gave written informed consent in accordance with the Montreal Neurological Institute and Hospital Research Ethics Committee.

EEG-fMRI acquisition

EEG was continuously recorded inside a 3T MRI scanner (Siemens, Trio, Germany). No sedation was given. EEG was acquired with 25 MR-compatible scalp electrodes (Ag/AgCl) using the 10–20 (reference FCz) and the 10–10 (F9, T9, P9 and F10, T10, and P10) systems. Two electrodes were placed on the shoulder to record the electrocardiography. Data were transmitted from a BrainAmp amplifier (Brain Products, Munich, Germany; 5 kHz sampling rate) to the EEG monitor outside the scanner room via optic fiber. A T₁-weighted anatomic acquisition was obtained (1 mm slice thickness, 256 × 256 matrix; echo time [TE] = 7.4 msec and repetition time [TR] = 23 msec; flip angle 30 degrees) and used to superimpose functional images and for intersubject coregistration. The functional data were acquired in runs of 6 min using a T₂*-weighted echo-planar imaging (EPI) sequence, with two acquisition protocols (protocol 1: 64 × 64 matrix; either 25 slices, 5 × 5 × 5 mm, TE = 30 msec, TR = 1.7 s, or protocol 2: 33 slices, 3.7 × 3.7 × 3.7 mm, TE = 25 msec, TR = 1.9 s; flip angle 90 degrees; from protocol 1 to protocol 2 we increased the number of channel coils to improve signal quality). Patients were instructed not to move and to stay with eyes closed, resting.

EEG-fMRI processing

EEG—Brain Vision Analyser software (Brain Products) was used for offline correction of the gradient artifact (Allen et al., 2000). A 50-Hz low-pass filter was applied to remove the remaining artifact. The ballistocardiography artifact was removed by independent component analysis (Benar et al., 2003). For patients, a neurologist reviewed the EEG recording and marked the interictal epileptic discharges in order to exclude the runs including such events. Inclusion criteria for the connectivity study were the following: (1) one to four runs without any spike (fMRI recording includes 7–14 six-minute runs); (2) wakefulness proven by EEG during these runs; (3) motion of <1 mm as determined by the realignment of the preprocessing. The maximum number of runs was four for each subject in order not to bias the group analysis toward one subject.

fMRI—Preprocessing of the data was performed according to the NeuroImaging Analysis Kit (NIAC) fMRI preprocessing pipeline (<http://code.google.com/p/niak/downloads/list>) (Bellec et al., 2011). First, functional data were corrected for motion within each run using a rigid transformation (three rotations and three translations) and corrected for slice-timing. When multiple runs were used for a subject, each run was corrected for movement through coregistration with the first run. A high-pass filter was applied to remove slow time drifts (freq < 0.01 Hz). CORSICA (CORrection of Structured noise, Perlberg et al., 2007) was used for automatic detection and removal of structured physiologic noise. CORSICA uses a priori spatial information to automatically detect independent components containing physiologic fluctuations (especially cardiac and respiratory artifacts) to be removed before any functional connectivity study. Finally, the images corrected from physiologic structured noise were spatially smoothed (full width half maximum [FWHM] 6 mm), and the global average EPI was coregistered with the T₁-weighted anatomic sequence for each subject.

Functional connectivity analysis

Functional connectivity was assessed using the average BOLD signal of mesiotemporal structures as seed regions. Four volumes of interest (VOIs) in the left and right amygdalae and hippocampi (LA, RA and LH, RH) were manually segmented (Fig. 1) on each subject's T₁ MRI using Montreal Neurological Institute (MNI) Display software (v1.3, MacDonald, D. 1996, <http://www.bic.mni.mcgill.ca/ServicesSoftwareVisualization/HomePage>).

Because manual segmentation was done slice by slice, we had to spatially smooth each VOI before considering it a seed region. To do so we performed a morphologic closure on each VOI (consisting of a 3-mm dilatation followed by a 3-mm erosion). Every VOI was then resampled to the low-resolution fMRI space using trilinear interpolation. To avoid regions of low EPI signal resulting from susceptibility artifact, voxels of the EPI data falling outside of a functional mask, estimated from the mean EPI data of each run, were not considered when creating the seed signal. For every VOI, the signal of interest used for functional connectivity was the average EPI signal of the VOI in the low-resolution EPI space. A weighted average was calculated, wherein each voxel was weighted by the percentage of spatial overlap between the EPI space and the VOI defined in the T₁ high-resolution space. The resulting time course for each VOI was centered and scaled to a variance of 1 before being used as seed for functional connectivity.

The time course of each VOI was used as the regressor of interest in a general linear model analysis to detect regions with BOLD signal correlated with that VOI. This general linear model analysis was performed using the fMRIstat software package (Worsley et al., 2002). One to four runs were analyzed for each subject and results of all runs were combined using a fixed-effects model. To perform an intersubject group analysis, anatomic MRI scans of each subject were first spatially normalized in the stereotactic space of the average brain template from the Montreal Neurological Institute (Collins et al., 1994). The resulting geometric transformations were used to resample the results of individual fMRI analyses in the stereotactic space. In fMRIstat (as opposed to statistical parametric mapping [SPM]), the first level of analysis (individual level) is done in the original space and not in the template space, so we did not resample the VOIs in the template space. Intersubject group analysis was then performed using a mixed-effects analysis (Worsley et al., 2002). The two fMRI acquisition protocols were used as a confound in the intersubject group analysis, involving all controls, and RMTLE and LMTLE patients. t-Maps of group difference, that is, RMTLE patients minus controls and LMTLE minus controls, were estimated and thresholded at $|t| > 3.17$ ($p < 0.001$ uncorrected). Voxels passing this threshold were then selected for a cluster size test. Clusters showing a corrected $p < 0.05$ for spatial extent were considered significant and reported.

We computed the average volume of each VOI for RMTLE, LMTLE, and controls matched for each group. Every measurement was done after registration in the template space. Differences between right and left amygdalae and hippocampi for each group were computed using a paired *t*-test for left and right VOIs.

Results

Twenty-three patients with MTLE were selected: 16 with right and 7 with left MTLE (9 patients were male). The mean age at evaluation was 34.4 years (range 16–59 years), and mean age at seizure onset, 9.2 years (range 1–30 years). Clinical details are reported in Table S1. All patients were drug resistant. Anatomic MRI was normal in 3 patients, and showed mesial temporal sclerosis (MTS) (hippocampal atrophy plus and increased T₂ signal) in 12, mesial temporal atrophy in 7, and a mesial temporal cystic lesion in one. Twenty-three healthy subjects (mean age 34.2 years; range 18–55 years) were included but 2 of them (both belonging to the group matched with the right MTLE patients) were removed because the right amygdala VOI was outside the functional mask; therefore, 21 controls were analyzed.

The hippocampal VOIs were significantly smaller on the affected side compared to the contralateral side for RMTLE and LMTLE, but not for controls (Fig. S1). No difference was detected for amygdalae. Average functional connectivity maps for each VOI were more positive in controls than in patients. The differences of functional connectivity maps between patients and controls are described in Table 1.

Right MTLE

The main results for the RMTLE minus controls comparison are shown in Fig. 2. Among the four VOIs, the one with the largest number of affected voxels and the highest t-value was the RH (the affected one).

For the RA VOI, we found decreased connectivity with the posterior cingulate cortices (not illustrated), the right ventromesial prefrontal region, and left parahippocampal gyrus.

Results for the RH VOI showed decreased connectivity with the left amygdala and hippocampus, the ventromesial prefrontal regions, nucleus accumbens, the cortical areas involved in the DMN (posterior cingulate cortex and precuneus, anterior mesial prefrontal cortex, superior frontal gyrus, angular gyri bilaterally), and with the left anterior insula and right lateral cerebellum (not illustrated).

t-Maps for the LA VOI (contralateral to focus) showed decreased connectivity with the right and left posterior cingulate cortices (posterior DMN), the contralateral hippocampal body, and the ventral pons. An area of increased connectivity was present in the anterior part of the right middle frontal gyrus.

Finally, results for the LH VOI showed decreased connectivity with the cortical regions involved in the posterior and anterior DMN (right and left posterior cingulate cortices, and right and left superior frontal gyri and bilateral anterior mesial prefrontal cortices), the contralateral hippocampus (body and tail), the right ventromesial prefrontal region, and the left lateral middle frontal gyrus (not illustrated).

Left MTLE

The main results for the LMTLE minus controls comparison are shown in Figure 3. Again, among the four VOIs, the largest number of affected voxels showing the highest t-value corresponded to the abnormal LH.

t-Maps for the LA VOI showed decreased connectivity with the right hippocampal body, both ventromesial prefrontal regions, the left and right anterior mesial prefrontal cortices (anterior DMN), and the left nucleus accumbens (not shown).

t-Maps for the LH VOI showed decreased connectivity with the right and left ventromesial prefrontal regions and anterior mesial prefrontal cortices (anterior DMN) and bilateral posterior cingulate cortex (posterior DMN), the right hippocampal body and tail, the left nucleus accumbens, the right anterior parahippocampus, and the right inferior frontal gyrus (not shown).

There was no change in connectivity with the RA VOI. Results for the RH VOI showed decreased connectivity with the left amygdala and hippocampus, the right and left ventromesial prefrontal regions, the right and left anterior mesial prefrontal cortices (anterior DMN), and the left posterior cingulate cortex (posterior DMN, not shown).

Discussion

We compared fMRI functional connectivity of patients with unilateral MTLE with healthy subjects to measure interictally the disruption of neuronal connectivity between the epileptic focus and distant brain regions. Among patients with MTLE, mesial temporal structures can have different degrees of atrophy (Tasch et al., 1999). We therefore decided to define VOIs for each subject by visual segmentation of amygdala and hippocampus, allowing a realistic measurement of neuronal network changes in patients with MTLE. Previous studies that also looked at functional connectivity in epileptogenic temporal lobe networks, defined seed regions on anatomic atlas based on the anatomy of one healthy subject (Tzourio-Mazoyer et al., 2002), necessarily including regions outside the atrophic mesial temporal structures (Bettus et al., 2009; Pereira et al., 2010). The importance of choosing regions with homogeneous activity when defining seeds was suggested by Bellec et al. (2006); in this study we used anatomic priors to define subject-specific VOIs.

This study revealed four main findings. First we found that for seeds ipsilateral to the focus, patients with left or right MTLE presented important decreases of connectivity with the contralateral healthy mesial temporal structures, with regions of the DMN (especially with the side contralateral to the epileptic focus), and with the ventromesial limbic prefrontal regions. Second, we detected that for seeds contralateral to the focus, there is decreased connectivity with the diseased hippocampus, regions of the DMN, and the ventromesial limbic prefrontal regions. The t-values and cluster volumes indicate that this impairment was less severe for the healthy hippocampus compared to the affected one. Third, the amygdalae of the diseased and of the healthy sides have the same altered network as the hippocampus (i.e., abnormal connectivity with the same distant regions) even if these structures have different anatomic connections. Fourth, altered connectivity was demonstrated between

mesial temporal lobe structures and the reticular formation. To the best of our knowledge, decreases of connectivity between medial temporal lobe and mesolimbic network and brainstem have not been described before in this type of epilepsy.

The neural basis underlying BOLD functional connectivity is not completely understood. Shmuel and Leopold (2008) showed a correlation between BOLD slow fluctuations and underlying local neuronal activity, particularly fluctuations in the local field potential gamma band, in visual cortex of healthy monkeys by using simultaneous BOLD and intracortical electrophysiologic recording. The role of gamma oscillation in the electrophysiologic correlates of resting state networks has been demonstrated by recent studies using intracerebral EEG (Jerbi et al., 2010). Because of the presumed coupling between high gamma activity and BOLD signal (Logothetis et al., 2001), the investigation of gamma activity is important to understand the neural activity underlying resting state networks. A study by He et al. (2008) showed a correlation between slow cortical potentials (<4 Hz) and spontaneous BOLD fluctuations in patients with partial epilepsy, considering specifically regions without EEG abnormalities to study physiologic conditions. The interaction between different frequency bands (theta and gamma) has been proposed as the main model for the BOLD fluctuations, and has been used to explain internetwork communication (Dalal et al., 2011).

Decreased connectivity of the affected hippocampus

In patients with unilateral MTLE, impairment of functional connectivity of the affected hippocampus with the contralateral one has been reported (Pereira et al., 2010), and our results are in agreement with these findings. Some studies have investigated the role of epileptic discharge on functional connectivity. Guye et al. (2005) demonstrated that abnormal EEG is related to long-lasting metabolic dysfunctions measured by MR spectroscopy involving the epileptogenic and irritative zones, proving the existence of metabolic impairment in the interictal period; these metabolic impairments could be related to changes in connectivity. Bettus et al. (2011) studied directly the electro-physiologic correlates of BOLD signal fluctuations in structures exhibiting epileptiform discharges, by measuring correlations between intracerebral EEG and resting-state fMRI in five patients with TLE. They found an increase in connectivity measured from the intracerebral EEG but a decrease of connectivity measured from the BOLD signal in regions with epileptiform abnormalities relative to nonaffected areas, suggesting widespread neurovascular coupling alterations in TLE. Another cause of impairment of functional connections of the diseased hippocampus could be related to the anatomic injury of this region. A study that combined fMRI resting state functional connectivity and diffusion tensor imaging (Liao et al., 2011) showed altered functional and structural connectivity between the posterior cingulate cortex, precuneus, and mesial temporal lobe structures in patients with MTLE compared to healthy subjects, suggesting that the decreased functional connectivity with the DMN in MTLE results from structural degeneration and decreased connection density.

Decreased connectivity with the default mode network

Different imaging modalities have shown widespread cortical and subcortical abnormalities in MTLE, suggesting that this epilepsy is a network disease. fMRI studies have focused on

the default-mode function: Laufs et al. (2007) have shown that the deactivation in default mode regions is more frequent for IEDs in patients with TLE in patients with extra-TLE, suggesting that epileptic activity has an instantaneous effect on the interconnected DMN regions in TLE. Deactivation in the posterior cingulate has also been demonstrated in response to temporal spikes by Kobayashi et al. (2009). Frings et al. (2009) showed decreased functional connectivity between precuneus and hippocampus in MTLE patients compared to controls during an object-location memory task. Liao et al. (2010) investigated the resting state fMRI functional connectivity and showed that many areas in the DMN of patients with MTLE have decreased connections with other regions. Finally, an independent component analysis-based resting functional connectivity study has further indicated that the side of MTLE resulted in functional impairments in the DMN (Zhang et al., 2010).

Decreased connectivity with the dopaminergic mesolimbic network

The patients with right and left MTLE presented important decreases of functional connectivity with the ventromesial limbic prefrontal regions and with the nucleus accumbens. These regions belong to a dopaminergic mesolimbic network, involved in long-term memory for novel events and reward (Heimer et al., 1997). The hippocampus and amygdala have been often described as part of this network by neuroimaging studies (Koob & Volkow, 2010; Bunzeck et al., 2011), but the effects of MTLE on the dopaminergic mesolimbic pathway are not clear (Cifelli & Grace, 2011). The preferential seizure spread from mesial temporal lobes to mesial frontal lobes, especially the orbito-frontal cortex, has been demonstrated by ictal intracranial EEG in patients with MTLE, suggesting that mesial orbito-frontal cortex is strongly affected by mesial temporal activity (Lieb et al., 1991). We could hypothesize that these zones affected by seizure propagation are damaged and consequently show reduced connectivity. Conversely, dopaminergic alterations have been demonstrated in the pathophysiology of major depression, and dysfunctional activity of the mesolimbic dopaminergic system plays a crucial role in depressive behavior (Yadid & Friedman, 2008). The specific disconnection between mesial structures and mesolimbic network in MTLE could explain psychiatric impairments, such as anxiety and depression, often diagnosed in patients with this epilepsy.

Same impaired connectivity for hippocampus and amygdala

It is remarkable that in our study the amygdala and hippocampus have abnormal connectivity with the same regions, despite their different anatomic connections (Haines, 2008). A possible explanation is that the amygdaloid complex and the hippocampal formation play together a major role in the initiation and maintenance of seizures in TLE. The concept of MTLE as a syndrome involving both amygdala and hippocampus is strengthened from intracranial recordings in candidates for resective surgery and “selective amygdalo-hippocampectomy” results (Wieser, 1988). With this hypothesis, functional connectivity impairment may reflect the effect of epileptic activity spreading through preferential pathways, rather than anatomic connections.

Alteration of connectivity with the brainstem

The left amygdala shows decreased connectivity with the bilateral paramedian pontine area, a region of the brainstem that contains the reticular formation. Because of the low spatial

resolution of fMRI acquisitions ($3.7 \times 3.7 \times 3.7$ mm), accurate localization of small structures is difficult. Nevertheless, the pontine reticular formation is part of a network of structures involved in generalized epileptiform activity and may play a role in the pathophysiology of absence seizures (Carney et al., 2010). We found a similar decreased connectivity with the reticular formation for LH, RA, and RH in the RMTLE group; and for LA and LH in the LMTLE group, reaching a significant voxel-based t-value, but not passing the spatial extent threshold. The statistical methods used in fMRI are better adapted to the context of cortical responses, which usually encompass large areas, than to the small responses found in the brainstem. The detection of significant changes in small size regions is indeed limited because of partial volume effects, resulting in local decrease of the signal-to-noise ratio because of spatial smoothing. A hypothesis-driven analysis using anatomic spatial priors could improve the detectability in such small regions, but this was out of the scope of our study.

Decreased connectivity of the unaffected side

Of interest, our study shows that the healthy hippocampus (seed contralateral to the diseased hippocampus) also demonstrated decreased functional connectivity with the affected hippocampus, with regions of the DMN and with ventromesial limbic prefrontal areas. The t-values and spatial extent of connectivity maps indicate a less severe impairment for the healthy hippocampus than for the affected one. Previous studies suggest a functional impairment of the contralateral hippocampus in unilateral MTLE: Seeck et al. (1999) showed that decreased left hippocampal volume in patients with RTLE correlated with psychosocial functioning and age of onset. A MR spectroscopy study (Campos et al., 2010) demonstrated metabolic damage in bilateral hippocampi in patients with unilateral refractory TLE compared with controls and with patients with nonrefractory TLE, suggesting that patients with refractory TLE have a more extensive neuronal and axonal dysfunction. We found only one cluster with a positive value, suggesting that this area was more connected in patients than in controls (anterior part of the right middle frontal gyrus in left amygdala VOI for RMTLE group). Nevertheless, because of the position (border with the subarachnoid space) and the small volume, we are tempted to consider this cluster artifactual.

There are reports of increased function of the unaffected hippocampus in patients with unilateral MTLE, both in the resting state (Bettus et al., 2009) and during task-related (Addis et al., 2007; Powell et al., 2007) acquisitions. We do not have an explanation for the difference between these results and ours. Morgan et al. (2011) have shown that resting state cross hippocampal functional connectivity is disrupted at the beginning of the disease and then increases linearly with duration of epilepsy after 10 years.

Diffusion tensor imaging in TLE is associated with extensive bilateral white matter abnormalities, in patients with unilateral mesial temporal sclerosis (Concha et al., 2009). These diffusion tensor imaging changes are consistent with observations of extensive bilateral white matter abnormalities demonstrated with MR volumetry in unilateral TLE (Hermann et al., 2003; Seidenberg et al., 2005) and suggest that in this type of epilepsy the structural abnormalities involve a broad ipsilateral and contralateral network of structures (Gross, 2011).

Limitation of the study

All of our patients were drug-resistant, and this constitutes a selection bias from a tertiary epilepsy center. The relative contributions to alteration of neuronal connectivity of anatomic damage, seizure activity and propagation, antiepileptic drugs, and the comorbidity associated with MTLE is unknown, but these factors cannot be independent. Given the heterogeneity of antiepileptic drug therapy in our patients, we could not evaluate the effect of drugs on functional connectivity. Another limitation of this study is that we did not compare functional connectivity with neuropsychological findings and years of disease. Longitudinal studies in larger cohorts can address these issues.

Conclusions

In summary, our study suggests that even in unilateral MTLE both amygdalae and hippocampi (on the affected and on the “healthy” side) are less connected between them, with the brain areas of the dopaminergic mesolimbic network, and with regions of the DMN, this decrease being stronger for the affected hippocampus. The disrupted connectivity with the mesolimbic network could underlie the psychiatric impairments often observed in patients with this syndrome. Because the DMN participates in maintaining the baseline brain activities associated with cognition of self-awareness, episodic memory, and environmental monitoring (Buckner et al., 2008), the damage of the DMN in mesial temporal epilepsy may in part explain the pathophysiologic mechanism of some cognitive impairments in these patients (Zhang et al., 2010).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Example of manual segmentation of the four regions of interest (ROIs) in a single-subject MRI used to extract fMRI signal time courses during resting periods. Purple, left amygdala (LA); blue, left hippocampus (LH); yellow, right amygdala (RA); green, right hippocampus (RH). Patient with right mesial temporal sclerosis.

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Figure 2.

Group differences in VOI-based connectivity between patients with RMTLE and healthy controls. Color-coded statistical t-maps (corrected $p < 0.05$ for spatial extent) are displayed. For RA and RH, functional connectivity is significantly decreased in the brain areas of the DMN, the ventromesial limbic prefrontal regions, and the contralateral mesial temporal structures; and for LA and LH, a significant decreased connectivity is present in DMN and contralateral hippocampus. Additional decreased connectivity is found between LA and pons and between LH and ventromesial limbic prefrontal structures.

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Figure 3.

Group differences in VOI-based connectivity between patients with LMTLE and healthy controls. Color-coded statistical t-maps (corrected $p < 0.05$ for spatial extent) are displayed. For LA and LH, a significantly decreased connectivity is found with DMN, contralateral hippocampus, and bilateral ventromesial limbic prefrontal regions; for RH, there is decreased connectivity with DMN, bilateral ventromesial limbic prefrontal regions, and contralateral amygdala and hippocampus. No change in connectivity was detected for RA.

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Table 1

Summary of results of the intergroup functional connectivity maps (patients with RMTLE – controls; patients with LMTLE – controls)

VOI	Cluster	Volume (mm ³)	P-value (spatial extent)	Description (highest t-value)
RMTLE				
LA	1	960	<0.001	R posterior cingulate cortex (−3.7)
	2	848	0.001	R ventral part of the pons (−3.7)
	3	664	0.003	L posterior cingulate cortex (−4.1)
	4	656	0.004	R hippocampal body (−3.9)
	5	560	0.01	L ventral part of the pons (−4.7)
	6	496	0.019	R anterior part of the middle frontal gyrus (+3.9)
LH	1	4,952	<0.001	L (−4.7) > R (−3.3) posterior cingulate cortex
	2	3,880	<0.001	R ventro mesial prefrontal cortex (−4.6)
	3	1,032	<0.001	Bilateral anterior mesial prefrontal cortex (−3.8)
	4	984	<0.001	L superior frontal gyrus (−4.1)
	5	984	<0.001	R hippocampal tail (−4.6)
	6	928	<0.001	R hippocampal body (−4.4)
	7	912	<0.001	R superior frontal gyrus (−4)
	8	608	0.007	L lateral middle frontal gyrus (−3.7)
RA	1	1,160	<0.001	R ventro mesial prefrontal cortex (−4.45)
	2	448	0.025	L > R posterior cingulate cortex
	3	392	0.049	L parahippocampal gyrus (−4.2)
RH	1	26,440	<0.001	L hippocampus (−5.2), L (−6.11) > R (−4.8) posterior cingulate cortex and precuneus ^a
	2	16,544	<0.001	L (−4.8) > R (−4.6) anterior mesial prefrontal cortex, R (−5) > L (−3.7) nucleus accumbens ^a
	3	3,224	<0.001	L angular gyrus (−3.8)
	4	2,056	<0.001	R superior frontal gyrus (−4.4)
	5	1,584	<0.001	L superior frontal gyrus (−4.2)
	6	1,528	<0.001	L anterior insula (−4.3)
	7	1,432	<0.001	L amygdala (−3.64)
	8	760	0.006	R angular gyrus (−3.6)
	9	592	0.024	R lateral cerebellum (−3.7)
LMTLE				
LA	1	5,704	<0.001	R > L ventro mesial limbic prefrontal region (−4.8)
	2	1,024	<0.001	R hippocampal body (−3.8)
	3	928	<0.001	Bilateral anterior mesial prefrontal cortex (−3.9)
	4	672	0.003	L nucleus accumbens (−3.9)
LH	1	20,272	<0.001	Bilateral ventro mesial limbic prefrontal region (−5.7) and anterior mesial prefrontal cortex (−4.3) ^a
	2	3,120	<0.001	R hippocampal body and tail (−4.9)
	3	2,368	<0.001	Bilateral posterior cingulate cortex (−3.9)
	4	696	0.003	L nucleus accumbens (−3.4)

VOI	Cluster	Volume (mm ³)	P-value (spatial extent)	Description (highest t-value)
RA	5	664	0.004	R anterior parahippocampus (−4.9)
	6	496	0.024	R pars orbitalis inferior F gyrus (−3.7)
RH	—	—	—	—
	1	5,600	<0.001	L amygdala (−4.3) and hippocampus (−4.7)
	2	880	0.002	R > L ventro mesial limbic prefrontal region (−3.6)
	3	624	0.018	R (−4) > L (−3.6) anterior mesial prefrontal cortex
	4	512	0.049	L posterior cingulate cortex (−3.8)

^aLarge clusters in which two distant regions are connected by a small number of voxels.