Large-Scale Brain Networks Are Distinctly Affected in Right and Left Mesial Temporal Lobe Epilepsy

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Abstract: Mesial temporal lobe epilepsy (MTLE) with hippocampus sclerosis (HS) is associated with functional and structural alterations extending beyond the temporal regions and abnormal pattern of brain resting state networks (RSNs) connectivity. We hypothesized that the interaction of large-scale RSNs is differently affected in patients with right- and left-MTLE with HS compared to controls. We aimed to determine and characterize these alterations through the analysis of 12 RSNs, functionally parceled in 70 regions of interest (ROIs), from resting-state functional-MRIs of 99 subjects (52 controls, 26 right- and 21 left-MTLE patients with HS). Image preprocessing and statistical analysis were performed using UF2C-toolbox, which provided ROI-wise results for intranetwork and internetwork connectivity. Intranetwork abnormalities were observed in the dorsal default mode network (DMN) in both groups of patients and in the posterior salience network in right-MTLE. Both groups showed abnormal correlation between the dorsal-DMN and the posterior salience, as well as between the dorsal-DMN and the executive-control network. Patients with left-MTLE also showed reduced correlation between the dorsal-DMN and visuospatial network and increased correlation between bilateral thalamus and the posterior salience network. The ipsilateral hippocampus stood out as a central area of abnormalities. Alterations on left-MTLE expressed a low cluster coefficient, whereas the altered connections on right-MTLE showed low cluster coefficient in the DMN but high in the posterior salience regions. Both right- and left-MTLE patients with HS have widespread abnormal interactions of large-scale brain networks; however, all parameters evaluated indicate that left-MTLE has a more intricate bihemispheric dysfunction compared to right-MTLE. Hum Brain Mapp 37:3137–3152, 2016. © 2016 The Authors Human Brain Mapping Published by Wiley Periodicals, Inc.

Key words: functional connectivity; functional magnetic resonance imaging; default mode network; salience network; hippocampus; visuospatial network

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abnormal behavior, or secondary to neurological diseases. Could improve the identification of changes related to study of these patterns and the interaction of its subareas specific task or at rest [Egu... inherent patterns of areas dynamically correlated during a access to alterations on the cerebral functional organiza...The use of functional parcellation aims to improve the difference between right and left MTLE groups in com...acal parcellation to functional maps and compared [Bernhardt et al., 2011; Liao et al., 2010]. Most of the previ...s characterized by reduced specificity and global efficiency hub distribution, demonstrating alterations in MTLE char...vations of these patients on cognitive tasks as memory and language, as well as on auditory and visual naming activities [Alessio et al., 2006; Vannest et al., 2008].

Given the characteristics of a network-level pathology in MTLE [Spencer, 2002], other studies have examined graph-theory properties [Bullmore and Sporns, 2009] of both structural [Bernhardt et al., 2011; Bonilha et al., 2013] and functional data [Chiang et al., 2014; Liao et al., 2010; Vlooswijk et al., 2011]. These studies evaluated the relationships between the syndrome alterations and properties such as degree of connectivity, clustering coefficient and hub distribution, demonstrating alterations in MTLE characterized by reduced specificity and global efficiency [Bernhardt et al., 2011; Liao et al., 2010]. Most of the previous graph theory studies in MTLE have applied anatomical parcellation to functional maps and compared differences between right and left MTLE groups in comparison to controls [Bettus et al., 2009; Wang et al., 2009]. The use of functional parcellation aims to improve the access to alterations on the cerebral functional organization. Since we can define the brain functional networks as inherent patterns of areas dynamically correlated during a specific task or at rest [Eguiluz et al., 2005], the direct study of these patterns and the interaction of its subareas could improve the identification of changes related to abnormal behavior, or secondary to neurological diseases.

Despite the information about specific RSNs in MTLE, there is no current data about how these networks interact in this condition and whether this interaction differs between patients with right or left HS. As mentioned before, it is well-known that patients with left MTLE have worse performance in memory tasks and distinct structural damage of cerebral gray and white matter than patients with right MTLE [Besson et al., 2014; Keller et al., 2002; Riederer et al., 2008]. These data put together implies that right and left MTLE could have different pathological mechanisms. Although previous studies have focused on the differences in functional connectivity between these groups of patients, these analyses were restricted to specific brain nodes, more often including the hippocampal region [Morgan et al., 2012; Pereira et al., 2010; Zhang et al., 2010]. However, today it is accepted that in order to understand the brain function and its disruptions, we must move forward from looking at specific brain regions and try to understand how the different areas interact and the possible abnormalities of this interaction. Therefore, the study of intercorrelations among RSNs in right and left MTLE might improve the understanding of the underlying mechanisms associated with these conditions.

We hypothesized that internetwork and intranetwork connectivity of RSNs is differently altered in patients with right and left MTLE compared to controls. In order to investigate that, we studied connectivity between RSNs using regions of interest (ROIs) derived from a functional parcellation in homogeneous groups of MTLE patients with unilateral HS.

**METHODS**

**Subjects**

All patients and controls included in this study signed an informed consent, approved by the Ethics Committee of the University of Campinas.

We included 47 consecutive adult patients with clinical and electroencephalographic diagnosis of drug-resistant MTLE and MRI signs of unilateral HS followed at the Epilepsy Clinic of the University of Campinas. The clinical diagnosis of MTLE was based on ILAE criteria [Berg et al., 2010]. All patients had seizure semiology compatible with seizure onset in the mesial temporal structures and had failed at least two antiepileptic drugs at the moment of the enrollment in this study. All underwent extensive interictal and/or ictal scalp EEG recordings, with epileptiform abnormalities restricted to the anterior and medial temporal electrodes. MRI scans acquired with a protocol for epilepsy were reviewed by two different epileptologists (FC and ACC) looking for signs of HS (clear loss of internal structure and volume reduction on T1 weighted image (WI) and signal hyperintensity on T2 WI/FLAIR). Second, MRI signs of HS were confirmed through quantification of volume and T2 signal according to our center protocol...
TABLE I. Demographic and clinical information

| Group          | Controls | R-MTLE   | L-MTLE   |
|----------------|----------|----------|----------|
| Age (years)    | 43 (±13) | 46 (±7)  | 47 (±6)  |
| Female         | 52%      | 58%      | 48%      |
| Seizure onset  | 12 (±9)  | 8 (±7)   |          |
| Epilepsy duration (years) | 33 (±11) | 39 (±9) |
| Familiar history of epilepsy | 50%     |          | 45%      |
| Protocol type (P1/P2) | 26/26   | 20/6     | 15/6     |

For "Age," "Seizure Onset," and "Epilepsy Duration," the values represent the mean and the standard deviation. In the fields "Female" and "Family History," the values represent the percentage of occurrence of these factors in each group.

[Cowan et al., 2014b]. In this study, patients classified with bilateral HS were not selected. According to the side of the HS and the ictal/interictal EEG abnormalities, patients were classified as right (R-MTLE) or left (L-MTLE) MTLE. Only patients with concordant laterality on MRI and EEG were selected.

MRI Acquisitions

All patients and controls underwent 3-tesla MRI (Philips Achieva) according to the following protocol:

1. Structural images: T1 WI with isotropic voxels of 1 mm, acquired in the sagittal plane, 180 slices, 1 mm thick, no gap, flip angle = 8°, TR = 7.0 ms, TE = 3.2 ms, FOV = 240 × 240 mm².

2. Functional images: patients and controls were submitted to either one of two distinct functional protocols: P1) echo planar image (EPI) with isotropic voxel of 3 mm, acquired on the axial plane with 32 slices, gap of 0.3 mm, matrix = 80 × 80, flip angle = 75°, TR = 2 s, TE = 30 ms, in a 6 min scan resulting in 180 dynamics; P2) EPI with isotropic acquisition voxel of 3 mm, acquired on the axial plane with 39 slices, no gap, matrix = 80 × 80, flip angle = 90°, TR = 2 s, TE = 30 ms in a 6 min scan resulting in 180 dynamics. The main difference between protocols was the coverage of inferior cerebellar regions. Therefore, we did not include the inferior cerebellum in the analyses as described below.

In total, we selected 99 subjects according to clinical, demographic and MRI parameters (Table I): 52 controls, 26 patients with R-MTLE, and 21 patients with L-MTLE.

There was no difference between the groups considering age and gender. Significant differences were observed only between controls and R-MTLE group on the proportion of the protocol types (pairwise Fisher’s Exact Test, two-tailed P-value = 0.028); therefore, this was considered as a covariate on the analysis.

Additionally, we found no differences between patients groups regarding age at seizures onset, duration of epilepsy and family history of epilepsy.

Functional Connectivity

The UF²C—user friendly functional connectivity toolbox

The UF²C toolbox (http://www.lni.hc.unicamp.br/app/uf2c/) was developed by the author (Campos, BM) aiming to standardize and facilitate connectivity studies through a straightforward graphical user interface and validated preset parameters. The toolbox runs within MATLAB platform (2014b, The MathWorks) with SPM12 (Statistical Parametric Mapping 12, http://www.fil.ion.ucl.ac.uk/spm/) and it is freely available for download.

We preprocessed and performed the statistical analysis (first and second level) according to the UF²C standard pipeline. The preprocessing was based on: fMRIs dynamics realignment (using mean image as reference), images coregistration (fMRI mean image with T1 WI), spatial normalization (MNI-152), smoothing (kernel of 6 × 6 × 6 mm³ at FWHM) and T1 WI tissue segmentation (gray matter [GM], white matter [WM], and cerebral spinal fluid [CSF]) and normalization (MNI-152). The segmented GM maps were interpolated to match the functional images and used to mask the analysis, removing non-GM regions. Additionally, we detrended (removed linear trends) and band-pass filtered (0.008–0.1 Hz) the time-series. The Figure 1 is a flowchart representing all the processing steps.

ROI and cross-correlation matrices

For the first level analysis, we generated individual matrices based on ROIs derived from a functional parcellation. Instead of applying anatomical parcellation as seen in previous studies, we used 70 ROIs from 12 functional networks previously created and described by Shirer et al [2012]: Anterior Salience (network code = n1, number of ROIs = 5), Posterior Salience (network code = n2, number of ROIs = 10), Basal Ganglia (network code = n3, number of ROIs = 4), Dorsal DMN (network code = n4, number of ROIs = 9) Ventral DMN (network code = n5, number of ROIs = 9) left executive-control network (ECN) (network code = n6, number of ROIs = 5), right ECN (network code = n7, number of ROIs = 5), Auditory (network code = n8, number of ROIs = 2), Visual (network code = n9, number of ROIs = 3), Language (network code = n10, number of ROIs = 6), Sensorimotor (network code = n11, number of ROIs = 4), and Visuospatial/Dorsal Attention (network code = n12, number of ROIs = 8). We selected these ROIs to evaluate functional connectivity in widespread brain areas considering distributed relevant functional networks. The Visual network in this study is the...
union of the ROIs from the High and Prime visual networks described by Shirer et al. (2012).

As we observed FOV variations between functional protocols in the inferior portion of the cerebellum, no ROIs from this area were included to avoid data from the bottom of the images. Therefore, in our analysis, we excluded the following ROIs due to their positioning on the inferior portion of the cerebellum: two ROIs from the Anterior
Salience network (ROIs 6 and 7); two from the Posterior Salience (ROIs 8 and 11); one from Basal Ganglia (ROI 5); one from Language (ROI 7); one from LECN (ROI 5); one from RECN (ROI 5); two from Sensorimotor (ROIs 4 and 6); one from ventral DMN (10); and three from Visuo-spatial (ROIs 9, 10, and 11). Additionally, one ROI was excluded due to its small size: Visual (prime visual 2) with four voxels.

Time-series were consistently extracted from each ROI of each subject. For a specific ROI, we used the average time series of all ROI voxels that matched two consecutive criteria:

a. Being included on the subject GM mask;  
b. The UF²C correlates each single ROI voxel time series with the average ROI time series (GM-masked). The voxel was included (to the average) if its correlation value is within the average ± standard deviation of all correlations between the ROI-masked voxels.

The cross-correlation matrices were created by performing Pearson’s correlation tests (2,415 tests, pairwise combination of all the 70 ROIs, removing auto [diagonal] and symmetric correlations). These individual correlation matrices were subsequently converted to z-score (Fisher’s Z-transformation) and taken to a second level analysis to investigate differences between controls and patients groups.

**Group comparisons**

The second level analyses were performed also using an appropriate modality on UF²C toolbox. As a first step, to evaluate confounding effects induced by the two different fMRI acquisition protocols, we performed an additional test, comparing only control subjects, who were divided into two groups with pure protocol types (26 controls with protocol type “P1” and 26 with protocol type “P2”). No significant differences were detected between these groups of control subjects (alpha = 0.05, false discovery rata [FDR] corrected).

In order to evaluate and characterize how right or left MTLE functionally affects the RSN behaviors and interactions, we evaluated inter-ROIs connectivity considering the internetwork (among ROIs of different networks) and intranetwork (among ROIs of a same network) interactions. For that, we performed MANCOVA tests, with a protocol type variable as covariate and alpha = 0.0375 (due to the two multiple pairwise group comparisons – FDR correction). All tests between ROIs (2,415 tests) were also corrected for multiple comparisons using the FDR procedure [Benjamini, and Hochberg, 1995] and only corrected sub threshold results ($P < 0.0375$) were considered significant.

It is important to highlight and clarify some terms applied in this study. “Relative decreased connectivity” (Fig. 2A,B) and “relative increased connectivity” (Fig. 2C,D) indicate lower or higher absolute Person’s correlation scores of patients compared to the control group’s respective scores. In this sense, the idea of “decreased” or “increased” means that the Person’s correlation values are, respectively, farther or closer to zero when compared to controls, regardless of whether the correlation is positive (Fig. 2A,C) or negative (Fig. 2B,D). Interestingly, we also detected some situations in which the correlation scores from patients presented opposite signals compared to controls. Despite the usage of absolute r-score values to define the direction of the differences among groups, the statistical tests were performed with the original values (trans-formed to z-score, but keeping the original signals), making sure that comparisons among correlations in opposite directions (Fig. 2E,F) have been considered accordingly in the statistical analysis. For these scenarios, the graphical results (Fig. 3) do not show these alterations as decreased or increased, but just indicate them with dashed lines.

Aiming to characterize how the connectivity alterations are laterally distributed, we calculated a laterality index (LI). We subtracted the number of contralateral altered connections (CAC), from the number of ipsilateral altered connections (IAC) and divided it by the total number of altered connections [Coito et al., 2015]:

$$LI = \frac{IAC-CAC}{IAC+CAC}$$

The interpretation of the LI value could be summarized as follows: if the alterations are completely restricted to the ipsilateral side, its LI value is 1. Values between 0 and 1 reveals that the majority of the alterations is ipsilateral and the value oscillates within this range according to the weight (number) of the contralateral alterations. Analogously, the LI is negative if the majority of the alterations is on the contralateral side, varying between $-1$ and 0 according to the weight (number) of the ipsilateral alterations. If all alterations are restricted to the contralateral side, the LI value would be $-1$. It is important to clarify that in the case of alterations including a interhemispheric ROI and a non-interhemispheric ROI, we consider the alteration side to be the same as the non-interhemispheric ROI. Another important observation is that since the LI uses the total number of alterations as equation denominator, the resultant LI value quickly decreases (non-linearly) due to the less altered side weight.

**Graph theory parameters**

We performed an additional analysis to extract three graph theory parameters of altered connectivity. We calculated them using the results of the statistical differences between groups, generating graph information related to the connectivity alterations for R-MTLE and L-MTLE. (1) The ROIs degree of altered connectivity (RDAC), which
means the total number of significant altered connections of each ROI, calculated for each patient group separately. The RDAC provides an overall idea about the significance of a specific altered node, illustrating if it is merely an affected part of a net of alterations (low RDAC) or a center of these alterations (high RDAC). In line with that, the RDAC can be understood as a measure of centrality. (2) The average degree of altered connectivity (ADAC) which considers the RDACs of both patient groups together, calculating an overall average among them:
Figure 3.
Altered connections on right and left MTLE when compared to control group (ANCOVA test, $P < 0.0375$ false discovery rate [FDR] corrected). (A) Altered connections on R-MTLE. The blue lines indicate pairs of ROIs with relative decreased connectivity. The dashed lines (or yellow on the 3D brain) indicate connections with opposite correlation signal in R-MTLE when compared to controls. (B) Altered connections on L-MTLE. The blue lines indicate pairs of ROIs with decreased connectivity. The red lines indicate pairs of ROIs with relative increased connectivity. The dashed lines (or yellow on the 3D brain) indicate connections with opposite correlation signal on L-MTLE when compared to controls. The spheres sizes are in function of the degree of altered connectivity and their colors represent the different networks. R-MTLE: right mesial temporal lobe epilepsy; L-MTLE: left mesial temporal lobe epilepsy; Corr: correlation; L: left side; R: right side; DMN: default mode network; LECN: left executive control network; RECN: right executive control network.
where $i$ and $j$ are the indexes of the ROIs with altered connections for R-MTLE and L-MTLE respectively; and the $n_1$ and $n_2$, the total number of altered ROIs for R-MTLE and L-MTLE respectively. For further reference, we considered a ROI as a hub of alterations, if its RDAC was greater than the ADAC value. (3) The clustering coefficient of altered connectivity (CCAC):

$$CCAC_i = \frac{t_i}{\text{RDAC}_i \times \frac{\text{RDAC}_i + 1}{2}},$$

where $i$ is the ROI index and $t_i$ the total number of triangles (connections between ROI $i$ neighbors'). The CCACs, similarly to the RDACs are calculated for each altered

### TABLE II. Relative decreased connectivity Hubs on R-MTLE

| Hub (ROI/Region) | ROI name | Network | Anatomical regions | ROI (%) | Voxel (n) |
|------------------|----------|---------|--------------------|---------|-----------|
| r4n2             | r1n4     | Dorsal DMN | Medial Frontal Gy. | 42      | 2233      |
| L. Supramarginal Gy. |          |         | Anterior Cingulate | 21      | 1148      |
| L. Inf. Parietal Gy. (Post. Salience) | r4n4    | Dorsal DMN | Post. Cingulate | 33      | 525       |
|                  |          |         | Precuneus          | 31      | 497       |
|                  | r2n2     | Post. Salience | R. Insula | 35      | 134       |
|                  |          |         | R. Sup. Temporal Gy. | 14      | 19        |
| r8n2             | r1n4     | Dorsal DMN | Medial Frontal Gy. | 42      | 2233      |
| R. Poscentral Gy. |          |         | Anterior Cingulate | 21      | 1148      |
| R. Supramarginal Gy. (Post. Salience) | r3n4    | Dorsal DMN | R. Sup. Frontal Gy. | 90      | 124       |
|                  | r9n4     | Dorsal DMN | R. Hippocampus | 97      | 139       |
| Sup. Frontal Gy. | r4n2     | Post. Salience | L. Supramarginal Gy. | 50      | 660       |
| Medial Frontal Gy. (Dorsal DMN) | r8n2     | Post. Salience | L. Inf. Parietal Gy. | 32      | 389       |
|                  | r9n4     | Post. Frontal Gy. | R. Poscentral Gy. | 32      | 327       |
|                  | r1n5     | Dorsal DMN | R. Supramarginal Gy. | 11      | 112       |
|                  | r5n5     | Ventral DMN | R. Supcentral Gy. | 11      | 112       |

The “voxel (n)” indicates the number of voxels of the respective anatomical region and the “ROI (%)” the percentage of this region within the original ROI mask. R: right; L: left; r: ROI number; n: Network number; Gy: gyrus; DMN: default mode network; Sup: superior; Post: posterior.

### TABLE III. Opposite connectivity Hubs on R-MTLE

| Hub (ROI/Region) | ROI name | Network | Anatomical regions | ROI (%) | Voxel (n) |
|------------------|----------|---------|--------------------|---------|-----------|
| r1n4             | r2n2     | Post. Salience | R. Insula | 35      | 134       |
| Sup. Frontal Gy. |          |         | R. Sup. Temporal Gy. | 14      | 19        |
| Medial Frontal Gy. (Dorsal DMN) | r3n2    | Post. Salience | L. Middle Frontal Gy. | 91      | 93        |
|                  | r9n4     | Dorsal DMN | R. Hippocampus | 97      | 139       |
|                  | r2n6     | L. ECN | L. Middle Frontal Gy. | 60      | 264       |
|                  | r3n7     | R. ECN | L. Inf. Frontal Gy. | 22      | 98        |
|                  | r1n4     | Dorsal DMN | R. Angular Gy. | 38      | 715       |
|                  |          |         | R. Supramarginal Gy. | 12      | 228       |
| r9n4             | r1n4     | Dorsal DMN | Medial Frontal Gy. | 42      | 2233      |
| R. Hippocampus (Dorsal DMN) | r3n4    | Dorsal DMN | Anterior Cingulate | 21      | 1148      |

The “voxel (n)” indicates the number of voxels of the respective anatomical region and the “ROI (%)” the percentage of this region within the original ROI mask. R: right; L: left; r: ROI number; n: network number; Gy: gyrus; DMN: default mode network; Sup: superior; Post: posterior; Inf: inferior; ECN: executive control network.
ROI, from each patient group separately. The CCAC indicates how an altered ROI and its neighbors (via altered connections) are segregated (low CCAC) or interlaced (high CCAC) among themselves. It may indicate the existence of a net of alterations. The standard definition of these and other several graph parameters were fully described by Rubinov and Sporns [2010].

**RESULTS**

Table I shows the detailed clinical characteristics of MTLE patients. No significant differences (alpha = 0.03 FDR corrected) were observed between R-MTLE and L-MTLE regarding distribution of gender ($P = 0.609$), age ($P = 0.675$), age of seizure onset ($P = 0.0798$), epilepsy duration ($P = 0.072$), or family history of epilepsy ($P = 0.743$).

Compared to controls, both patients groups (R-MTLE and L-MTLE) presented functional connectivity alterations on the pairwise ROIs analysis (alpha = 0.0375 FDR corrected). From the 12 studied networks, just the auditory and visual networks did not present alterations, although for the R-MTLE group, the anterior salience and sensorimotor networks were also preserved. Tables (II–VI) show the results organized in hubs of alterations. The ROIs anatomical labeling was performed using xjView toolbox (http://www.alivelearn.net/xjview).

**Brain Networks in Right and Left MTLE**

| Hub (ROI/Region) | ROI name | Network | Anatomical regions | ROI (%) | Voxel (n) |
|------------------|----------|---------|--------------------|---------|-----------|
| r4n2             | r1n4     | Dorsal DMN | Medial Frontal Gy. | 42      | 2233      |
| Sup. Frontal Gy. |          |         | Anterior Cingulate | 21      | 1148      |
| L. Supramarginal Gy. |          |         | Post. Cingulate | 33      | 525       |
| L. Inf. Parietal Gy. |          |         | Precuneus | 31      | 497       |
| (Post. Salience) |          |         | L. Hippocampus | 87      | 342       |
| r8n2             | r1n4     | Dorsal DMN | Medial Frontal Gy. | 42      | 2233      |
| R. Poscentral Gy. |          |         | Anterior Cingulate | 21      | 1148      |
| R. Supramarginal Gy. |          |         | R. Sup. Frontal Gy. | 90      | 124       |
| (Post. Salience) |          |         | Posterior Cingulate | 33      | 525       |
| r4n4             | r8n2     | Dorsal DMN | Medial Frontal Gy. | 35      | 1632      |
| Post. Cingulate  |          |         | R. Sup. Frontal Gy. | 32      | 537       |
| Precuneus        |          |         | R. Supramarginal Gy. | 11      | 112       |
| (Dorsal DMN)     |          |         | L. Hippocampus | 87      | 342       |
| r6n12            | r1n4     | Visuospatial | L. Supramarginal Gy. | 50      | 660       |
| Post. Salience   |          |         | L. Inf. Parietal Gy. | 32      | 389       |
| r8n2             | r8n2     | Visuospatial | R. Sup. Frontal Gy. | 32      | 327       |
| r8n4             | r8n4     | Dorsal DMN | R. Supramarginal Gy. | 32      | 327       |
| r7n12            | r8n2     | Visuospatial | L. Hippocampus | 87      | 342       |
| r8n4             | r4n2     | Visuospatial | R. Sup. Frontal Gy. | 61      | 201       |
| r8n4             | r4n2     | Visuospatial | L. Supramarginal Gy. | 50      | 660       |
| r8n4             | r8n4     | Visuospatial | L. Inf. Parietal Gy. | 32      | 389       |
| r8n4             | r8n4     | Visuospatial | R. Supramarginal Gy. | 32      | 327       |
| r9n4             | r9n4     | Dorsal DMN | L. Hippocampus | 97      | 139       |
| r1n5             | r1n5     | Ventral DMN | R. Hippocampus | 97      | 139       |
| r5n5             | r5n5     | Ventral DMN | Post. Cingulate | 54      | 251       |

The “voxel (n)” indicates the number of voxels of the respective anatomical region and the “ROI (%)” the percentage of this region within the original ROI mask. R: right; L: left; r: ROI number; n: network number; Gy: gyrus; DMN: default mode network; Sup: superior; Inf: inferior; Post: posterior.

ROI, from each patient group separately. The CCAC indicates how an altered ROI and its neighbors (via altered connections) are segregated (low CCAC) or interlaced (high CCAC) among themselves. It may indicate the existence of a net of alterations. The standard definition of these and other several graph parameters were fully described by Rubinov and Sporns [2010].

Compared to controls, both patients groups (R-MTLE and L-MTLE) presented functional connectivity alterations on the pairwise ROIs analysis (alpha = 0.0375 FDR corrected). From the 12 studied networks, just the auditory and visual networks did not present alterations, although for the R-MTLE group, the anterior salience and sensorimotor networks were also preserved. Tables (II–VI) show the results organized in hubs of alterations. The ROIs anatomical labeling was performed using xjView toolbox (http://www.alivelearn.net/xjview).

**R-MTLE Connectivity**

In total, 21 ROIs linked by 21 connections showed alterations on R-MTLE group when compared to controls. We found significant connectivity decreases in R-MTLE mainly on the right hippocampus (r9n4) connections with dorsal and ventral DMN (n4 and n5) and posterior salience.
network (n2) (Table II and Fig. 3A in blue lines). Three other hubs presented relative decreased connectivity, including frontal portion of DMN (r1n4) and right and left posterior salience (r8n2 and r4n2).

In summary, by a network perspective, we observed decreased intranetwork connectivity between the posterior salience (n2) ROIs and also between dorsal DMN (n4) ROIs. Decreased internetwork connectivity were observed between posterior salience (n2) and dorsal DMN (n4) and also between dorsal DMN (n4) and ventral DMN (n5).

The R-MTLE group also showed opposite connectivity relative to controls including: frontal portion of the dorsal DMN (r1n4), the right hippocampus (r9n4), left and right ECN ROIs (r2n6 and r3n7), and anterior salience (r3n2). By a network perspective, we observed opposite intranetwork connectivity only between dorsal DMN (n4) ROIs and opposite internetwork connectivity affecting just the dorsal DMN (n4) and some of its connections with the posterior salience (n2), left ECN (n6), and right ECN (n7) (Table III and Fig. 3A in dashed lines).

### Graph theory properties

On the R-MTLE, the ipsilateral hippocampus and the frontal portion of the DMN (r1n4) presented the highest

**TABLE V. Relative increased connectivity Hubs on L-MTLE**

| Hub (ROI/Region) | ROI name | Network | Anatomical regions | ROI (%) | Voxel (n) |
|------------------|----------|---------|--------------------|---------|-----------|
| r4n2             | r5n4     | Dorsal DMN | Bilateral Thalamus | 47      | 105       |
| L. Supramarginal Gy. | L. Inf. Parietal Gy. (Post. Salience) |           |                    |         |           |
| r4n4             | r4n11    | Sensorimotor | Cerebelum | 75      | 2015      |
| Post. Cingulate Precuneus (Dorsal DMN) | | | | | |
| r5n4             | r4n2     | Post.Salience | L. Supramarginal Gy. | 50      | 660       |
| Bilateral Thalamus (Dorsal DMN) | | | L. Inf. Parietal Gy. | 32      | 389       |

The “voxel (n)” indicates the number of voxels of the respective anatomical region and the “ROI (%)” the percentage of this region within the original ROI mask. R: right; L: left; r: ROI number; n: network number; Gy: gyrus; DMN: default mode network; Sup: superior; Inf: inferior; Post: posterior; L: left; Gy: gyrus; DMN: default mode network; Post: posterior; Inf: inferior.

**TABLE VI. Opposite connectivity Hubs on L-MTLE**

| Hub (ROI/Region) | ROI name | Network | Anatomical regions | ROI (%) | Voxel (n) |
|------------------|----------|---------|--------------------|---------|-----------|
| r1n4             | r2n2     | Post.Salience | R. Insula | 35      | 134       |
| Sup. Frontal Gy. | | | R. Sup. Temporal Gy. | 14      | 19        |
| Medial Frontal Gy. (Dorsal DMN) | r6n5 | Ventrall DMN | Precuneus | 88      | 1703      |
| r3n7             | R. ECN   | | R. Angular Gy. | 38      | 715       |
| r3n12            | Visuospatial | | R. Supramarginal Gy. | 12      | 228       |
| r7n12            | Visuospatial | | L. Inf. Frontal Gy. | 67      | 748       |
| r5n4             | r2n6     | L. ECN  | L. Mid. Frontal Gy. | 60      | 264       |
| Bilateral Thalamus (Dorsal DMN) | | | L. Inf. Frontal Gy. | 22      | 98        |
| r5n4             | r3n12    | Visuospatial | L. Inf. Frontal Gy. | 67      | 748       |
| r2n7             | r1n5     | Ventrall DMN | Post. Cingulate | 54      | 251       |
| R. Mid. Frontal Gy. | | | L. Calcarine | 46      | 214       |
| R. Sup. Frontal Gy. (R. ECN) | r5n5 | Ventrall DMN | Post. Cingulate | 58      | 345       |
| r6n5             | Ventrall DMN | | R. Precuneus | 47      | 278       |

The “voxel (n)” indicates the number of voxels of the respective anatomical region and the “ROI (%)” the percentage of this region within the original ROI mask. R: right; L: left; Gy: gyrus; DMN: default mode network; Post: posterior; Inf: inferior; ECN: executive control network Sup: superior; Mid: Middle.
RDAC (seven connections or 33% of the total number of alterations for each) whereas a relative low CCAC (0.1 for both). Conversely, posterior salience ROIs (r2n2, r4n2 and r8n2) and the ipsilateral superior frontal gyrus (DMN, r3n4) presented highest CCAC whereas lower RDAC. The LI of the R-MTLE group was 0.190 indicating that the majority of the R-MTLE alterations is ipsilateral, but also there are altered connections on the contralateral side.

**L-MTLE Connectivity**

In total, 29 ROIs linked by 28 connections showed alterations on L-MTLE group when compared to controls. We found five hubs with relative decreased connectivity including left hippocampus (r9n4), affecting connections with ventral and dorsal DMN ROIs (r4n4, r9n4, r1n5, and r5n5) and ipsilateral posterior salience (r4n2). The frontal portion of DMN (r1n4) and the bilateral inferior parietal gyrus of the posterior salience network (r8n2 and r4n2) were also hubs with deceased connections.

By a network perspective, we observed decreased internetwork connectivity only between dorsal DMN (n4) ROIs. We found reductions on internetwork connectivity between posterior salience (n2) and dorsal DMN (n4) ROIs and also between dorsal DMN (n4) with ventral DMN (n5) and visuospatial/dorsal attention network (n12) (Table IV and Fig. 3B in blue lines).
ROIs graph theoretical results. In “A,” the degree of altered connectivity (RDAC) and in “B” the cluster coefficient values (CCAC). The horizontal dashed lines in A, represents the ADAC that we used to define a ROIs with higher values as a hub of alterations. The dashed blue and yellow lines were used to indicate overlapping between groups lines. Conn.: connectivity; R-MTLE: right mesial temporal lobe epilepsy; L-MTLE: left mesial temporal lobe epilepsy; R: right; L: left; Gy: gyrus; Infe: inferior; Mid.: middle; Supe.: superior; Ant.: anterior; Post. Posterior; DMN: default mode network; LECN: left executive control network; RECN: right executive control network.
Three hubs presented relative increased connectivity: two dorsal DMN regions, the posterior cingulate (r4n4), bilateral thalamus (r5n4), and the ipsilateral inferior parietal gyrus (r4n2) of posterior salience. We observed increased internetwork connectivity between dorsal DMN (n4) and posterior salience (n2) ROIs and between sensorimotor (n11) and dorsal DMN (n4) ROIs (Table V and Fig. 3B in red lines).

We also observed opposite connectivity (relative to controls) on the R-MTLE group, which included a hub of the right ECN (r2n7) and only its connections with ventral DMN ROIs (r1n5, r5n5 and r6n5). Additionally, we found opposite connectivity on the frontal portion of dorsal DMN (r1n4) with bilateral inferior parietal gyri of the visuospatial/dorsal attention network (r3n12 and r7n12), ventral DMN (r6n5), right ECN (r3n7), and left posterior salience (r2n2). The thalamus (r5n4) was also considered a hub with opposite connections, which included visuospatial (r3n12) and left ECN (r2n6) networks ROIs (Table VI and Fig. 3B in dashed lines). By a network perspective, we found internetwork opposite connectivity alterations that involved the dorsal DMN (n4) with the posterior salience (n2), ventral DMN (n5), left and right ECN (n6 and n7), and visuospatial (n12). Additionally, we observed alterations between the right ECN (n7) and the ventral DMN (n5). The average connectivity values of all described altered connections are shown on Figure 4.

**Graph theory properties**

The L-MTLE group presented relevant RDAC on the frontal portion of the DMN (r1n4), in the posterior cingulate cortex (r4n4) and in the ipsilateral hippocampus (r8n4) (Fig. 5A). The CCAC in this group, revealed low clustering values with the highest score on the ipsilateral inferior parietal lobule (r4n2) (Fig. 5B); The LI for the L-MTLE group was 0.035 indicating that the majority of the L-MTLE alterations is ipsilateral but with a very similar quantity on the contralateral side.

**DISCUSSION**

Using resting-state fMRI, we investigated the patterns of connectivity alterations in patients with left and right MTLE. We performed several approaches of validated methodologies to extract clear information about each MTLE type separately. We demonstrated that patients with right and left MTLE have widespread abnormal interactions of large-scale networks. Despite the vast alteration in both patients groups, all evaluated parameters indicate that L-MTLE is a more intricate bilateral functional syndrome than R-MTLE. Moreover, ipsilateral hippocampi of both groups behave as central hubs of decreased functional connectivity.

The large-scale networks interaction abnormalities of L-MTLE and R-MTLE can be summarized as follows: (i) both R-MTLE and L-MTLE patients presented decreased connectivity and inversion of the correlation signal between the dorsal DMN and the posterior salience network (compared to controls); (ii) both R-MTLE and L-MTLE patients presented inversion of the correlation signal between the dorsal DMN and the ECN; (iii) L-MTLE patients presented decreased connectivity and inversion of the correlation signal between the dorsal DMN and the visuospatial/dorsal attention network; (iv) in patients with L-MTLE, a relative increased connectivity was observed between the bilateral thalami and the posterior salience network.

Differences on connectivity alterations between left and right MTLE have been previously described in the literature [Haneef et al., 2015; Pereira et al., 2010; Waite et al., 2006]. Through diversified methodologies, these studies explored distinct aspects of brain functional connectivity using anatomical or functional relevant ROIs, independent component analysis and graph theoretical information. Our study unified some of these methodologies, applying consecutive techniques with an unbiased pipeline, providing robust results through an innovative point of view.

**Abnormal Connectivity in Right and Left MTLE**

For both groups, we found abnormal DMN connections, with the superior and middle frontal gyri as important hubs of alterations. The ipsilateral hippocampus was also highlighted as a central area of abnormalities, as expected due to its dominant importance in MTLE underlying physiopathology.

**Differences of abnormal connectivity between right and left MTLE**

With the exception of the ipsilateral hippocampi (that are altered according to the group lateralization), all hubs with relative decreased connectivity observed on R-MTLE patients were also observed on L-MTLE. In addition, patients with L-MTLE presented as hubs of relative decreased connectivity the dorsal DMN (r4n4) and the right ECN (r2n7). The idea that the L-MTLE patients are more susceptible to bilateral and diffuse structural alterations was already described in the literature [Ahmadi et al., 2009, Coan et al., 2009] and our study suggests that these patterns occurs also with the functional organization, involving contralateral networks. These findings are sustained by the laterality index that showed more ipsilateral-restricted alterations on R-MTLE, while the L-MTLE presented a more bilateral pattern of alterations.

In addition to the diffuse and bilaterally affected connectivity, the cluster-coefficient on the L-MTLE proved to be lower than in R-MTLE. This finding suggests that despite L-MTLE patients having a higher ADAC and widespread alterations, these abnormal connections presented low interactions between themselves. These facts could be related to the cognitive abnormalities presented in patients.
with MTLE and in an ineffective attempt to restore these functionalities. On the R-MTLE patients, the ADAC was lower than in L-MTLE, with more restricted pattern of alterations including eight networks. Conversely, these alterations demonstrated to be integrated between themselves, with higher cluster coefficients and more ipsilaterally distributed as mentioned above. The clinical relevance of these findings, at this point, can only be speculative. Nevertheless, it is widely known that patients with L-MTLE have worse cognitive performance than R-MTLE [Alessio et al., 2006; Hermann et al., 1997]. As also suggested by intracranial EEG studies, the abnormal connectivity in the hemisphere contralateral to the epileptogenic zone in L-MTLE could be an attempt to compensate the functional deficit, as the performance of working memory scores have been correlated to this increased contralateral connectivity [Bettus et al., 2009]. However, in our study while regions of increased connectivity were only observed in L-MTLE, the graph theory parameters showed low interactions between these nodes, which could indicate an ineffective connectivity. Therefore, we believe that, at this point, the hypothesis of the occurrence of areas of increased connectivity in L-MTLE as a compensatory mechanism requires further investigation.

The connectivity within DMN ROIs is extensively reduced, with the ipsilateral hippocampus as a main hub of alterations for both groups, differing only on the opposite connectivity with the frontal portion of DMN (r1n4 and r3n) on the R-MTLE. The connectivity reduction between these areas could be secondary to the structural abnormalities as well as both ictal and interictal activities, closely related to the hippocampal damage [Zhang et al. 2010].

We also observed several internetwork alterations in R-MTLE and L-MTLE. Differently from previous studies, we assessed the internetworks abnormalities looking at positive and negative correlations and also at the inversion of the correlation directions between patients and controls, providing a full characterization of the abnormal interaction of the different brain regions in MTLE. In our study, both R-MTLE and L-MTLE patients presented altered correlations involving the DMN, the salience network and ECN, showing an inversion of the correlation signal between them in comparison to the control group. The Figure 3B reveals, for example, that an ECN hub (r2n7) of L-MTLE patients worked positively correlated with the DMN during rest, in opposite to the controls. Accordingly, both inferior frontal gyrus (both sides, r3n12 and r7n12) and the frontal portion of the DMN (r1n4) proved to be positively correlated, also in contrast to controls. The relationship between DMN, salience and ECNs is under investigation, but recent studies defined that DMN and salience work oppositely, meaning that the increase of the first is followed by a decrease in the second, and vice-versa [Balthazan, et al., 2014]. Some authors suggest that this mechanism involves a mediation of activity executed by the salience network guiding the focus on internal (DMN) or external (ECN) process and stimulus [Liang et al., 2016].

Other internetwork alterations were observed exclusively in L-MTLE, more specifically between DMN and visuospatial/dorsal attention network, which also presented an inversion of correlation signal. Previous studies demonstrated that the relation between DMN and visuospatial/dorsal attention network is supposedly anti-correlated [Tomasi et al., 2009], once the DMN should deactivate when the visuospatial is required to focus in a task. Since our study performed the functional acquisitions during rest, we can determine that visuospatial/dorsal attention network regions (r3n12 and r7n12) are misleadingly recruited by DMN, corroborating the evidence of a more disorganized functional behavior on L-MTLE. Additionally, only in patients with L-MTLE an increased connectivity was observed between the bilateral thalami and the posterior salience network, more specifically, the left inferior parietal region.

Although extensively described, the causes of diffuse abnormal functional and structural abnormalities in MTLE are unknown. One possible factor involved on RSN disruption in MTLE patients may be the underlying interictal activity. Although we do not have concomitant EEG recordings to this data, previous studies described the functional alterations caused by interictal spikes [Coan et al., 2014a]. However, there is no evidence that the characteristics of interictal epileptiform discharges, including rate, localization or extent, differ between right or left MTLE and, accordingly, these differences were also not observed between our groups of patients. Therefore, while the epileptiform discharges might affect the overall connectivity in MTLE patients, it might not contribute specifically to the differences between right and left MTLE. Similarly, while the chronic use of anti-epileptic drugs (as described for patients in use of topiramate [Yasuda et al., 2013]), as well as the natural disease evolution may also be relevant factors influencing connectivity abnormalities in MTLE, they may not necessarily impact the differences between right and left MTLE described in our study. These characteristics were balanced between the patients groups. Further prospective studies will be necessary to address the influence of these factors on connectivity alterations in MTLE.

Methodological Considerations

ROI-based studies applied to diseases with structural alteration such as hippocampal atrophy, should have additional attention during the time-series extractions. Misleading co-registration between the ROI mask and the cortex could include extra cortical tissues or regions with extensively altered cellular constitution that are not functionally representative. Although we did not include an atrophy mask as covariate in our model, the methodology applied for extraction of time series avoided confounding voxels through the tissue segmented mask and the required homogeneity among time-series from ROIs voxels.
The Figure 4 shows the average correlation values for each altered connection for each group. It is possible to identify means close to values related to noise (or non-significant average correlations: $P > 0.05$ or $r < 0.145$; with 180 degrees of freedom—number of dynamics for each run). Our aim was to include all possible not connected regions in the analysis, since we considered the possibility of the occurrence of conversion of absent connections into significant ones and vice-versa in MTLE. For instance, the connection between regions r1n4 and r3n7 is almost absent in controls subjects but it is consistently present in the R-MTLE and L-MTLE groups.

In this study, we applied established approaches as cross-correlation between series and graph theoretical parameters, but we also quantified these graph properties with the difference between MTLE groups and controls as a third level step. This method characterizes the patterns of alterations directly, avoiding arbitrary successive thresholds commonly applied on graph-theoretical studies.

The networks parcellation and nomination can vary among authors. Since we decided to use the Shirer's parcellation in our study, we strive to respect that organization with few exceptions (described on the “Methods”). These divergences are usually secondary to chosen parameters during the process to create the functional templates such as, for example, the defined number of components to be determined during an Independent Component Analysis. In our study, the dorsal attention network is represented by the Visuospatial (n12). Differently, a network exclusively composed by ROIs of the Ventral Attention network (VAN) is missing. We concluded that the regions composing the VAN are represented by ROIs included on the perceptual networks (e.g., sensorimotor, auditory). Therefore, despite not including the VAN, the relevant anatomical regions associated to it are considered in our ROI-wise analysis. We understand that the results presented on Tables (II–VI), can assist these interpretations, since they “translate” the functional ROI name to specific anatomical region.

The UF2C toolbox demonstrated to be an efficient and straightforward tool to investigate functional connectivity. The minimalistic user interface and the standard settings enable reliable assessment of functional information through a consistent and validated preprocessing pipeline.

**CONCLUSION**

Patients with right and left MTLE have widespread abnormal interactions of large-scale networks. Despite the vast alteration in both patients groups, all evaluated parameters indicate that L-MTLE has a more intense bihemispheric dysfunction compared to right-MTLE.

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