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Association between seizure freedom and default mode network reorganization in patients with unilateral temporal lobe epilepsy

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ABSTRACT

Rationale: The spontaneous synchronized activity and intrinsic organization of the Default Mode Network (DMN) has been found to be altered because of epileptic activity of temporal lobe origin. Thus, the aim of the present study was to compare DMN's topological properties in patients with seizure-free (SF) and not seizure-free (NSF) temporal lobe epilepsy (TLE).
Methods: Functional connectivity within the DMN was determined from an 8-minute resting state functional magnetic resonance imaging (fMRI) in 27 patients with TLE (12 SF, 15 NSF) and 15 healthy controls (HC). The DMN regions of interest were extracted according to the automated anatomical labeling (AAL) atlas. Network properties were assessed using standard graph-theoretical measures.
Results: Analyses revealed, irrespectively of focus lateralization, borderline significance for longer paths ($p = 0.049$) and in trend reduced local efficiency within the DMN of SF when compared with that of NSF ($p = 0.075$). The SF and NSF patients did not differ in global network topology from HC ($p > 0.05$). At the nodal network level, the degree of central hubs was significantly reduced in SF when compared with that in NSF ($0.002 \le p \le 0.080$) and HC ($0.001 \le p \le 0.066$) while simultaneously, right anterior superior temporal gyrus revealed significantly higher degree in SF than in NSF ($p = 0.005$) and HC ($p = 0.016$).
Conclusion: Seizure freedom seems to be associated with hub redistributions that may underlie longer paths and (in trend) reduced local efficiency of the network. An associated slower system response might reduce the probability of a rapid spread of epileptic discharges over the whole network and may help to prevent hypersynchronous neuronal activity in brain networks that may result in epileptic seizures.

1. Introduction

With a prevalence of 0.1%, temporal lobe (TL) epilepsy (TLE) is the most common form of focal epilepsy [1]. Although classically considered as a focal disorder, TLE affects extended brain areas [2–6] involving broad contra- and ipsilesional brain networks [5–8]. Thereby, the core network nodes of the brain's Default Mode Network (DMN) [9,10] have been found to be highly involved within the cerebral network of patients with TLE, suggesting that the brain's DMN may be an integral part of the TLE seizure network [11,12]. The DMN is the most prominent resting state network (RSN) of the human brain that comprises structures of the medial prefrontal cortex (mPFC), the posterior cingulate cortex/retrosplenial cortex (PCC; precuneus), and the inferior parietal lobule (IPL). Mesial TL (mTL) structures and lateral temporal regions are also sometimes included in the definition of the DMN, especially considering that a high number of DMN regions are functionally correlated with the hippocampal formation [10]. The DMN has repeatedly been found to be active at rest and modulated in its activity under cognitive demands. On a functional level, it has become associated with internally oriented thinking [10,13–15], but also with higher order cognitive [16] (particularly regarding memory [15,17] and attention [18]) and psychological function [13,14,19]. An aberrant organization of the DMN has been related to cognitive [17,18,20] and psychiatric symptoms [13,14] in several pathological conditions [19].

Dyhrfjeld-Johnsen et al. proposed [21] that an increase of long-range connectivity, i.e., short(er) paths within brain networks, may contribute

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to the pathological lowering of the convulsive threshold and the rapid hypersynchronization of brain networks [21–24] that is assumed to underlie the recurrence of unprovoked seizures in epilepsy [25]. In contrast, reductions of long-range connectivity, i.e., longer paths particularly within networks that are somehow involved in or affected by the epileptic dysfunction, may be conducive to seizure freedom since these longer paths might be related to prolonged system response times that counteract the rapid spread of local epileptic discharges over the network. Since the spontaneous activity and intrinsic organization of the DMN have repeatedly been found to be altered because of epileptic activity of TL origin [2,26–31], we speculated that the intrinsic organization of the DMN might reflect the seizure state (seizure freedom vs. ongoing clinical seizures) in patients with TLE. The aim of the present study was therefore to compare global and nodal network properties of the DMN in nonoperated patients with unilateral TLE that had been free from any epileptic event for at least one year ("seizure-free" [SF]) and nonoperated patients with unilateral TLE with ongoing clinical seizures ("not seizure-free" [NSF]).

2. Methods

2.1. Participants

Patients with TLE that had not (yet) undergone epilepsy surgery were recruited from the patient pool of the Freiburg University Epilepsy Center based on their medical record. Inclusion criteria were the presence of unilateral TLE either confirmed by comprehensive presurgical assessment including video/electroencephalography (EEG) monitoring, high-resolution magnetic resonance imaging (MRI) and neuropsychological assessment [32,33] or — for patients who had not undergone any comprehensive presurgical assessment — according to the following criteria: a) lesion in high-resolution MRI, b) interictal EEG data pointing to an epileptic focus within one TL, and c) seizure semiology (for instance evidence for the occurrence of complex-partial seizures and typical seizure phenomena associated with TLE). Patients had to provide sufficient compliance and absence of contraindications for magnetic resonance imaging (MRI), absence of neurological comorbidities, and normal intellectual abilities (assessed via educational anamnesis or intelligence test data if available) in order to participate in the present investigation.

Additionally, a group of healthy controls (HC) (normal intellectual abilities, absence of neurological diseases, and cerebrovascular insults in their history) was recruited.

Outpatients and HC received a small expense allowance for their participation.

The study was approved by the boards of the ethical committee of Freiburg University, Germany (Declaration of Helsinki [34]). Informed written consent was gained from each participant.

2.2. Acquisition of functional data

All neuroimaging data were collected using a Siemens MAGNETOM® Trio (Siemens, Germany), 3-Tesla MRI scanner with a 12-channel head coil. An approximately seven-minute structural scan was performed using a standard T1-weighted magnetization prepared acquisition gradient echo (MPRAGE) with 160 slices covering the whole brain (field of view [FOV] 256 × 256 mm, matrix of 256 × 256, resulting voxel size 1 × 1 × 1 mm^3). Structural imaging was followed by the acquisition of an approximately eight-minute resting state functional magnetic resonance imaging (fMRI) (rs-fMRI) in order to investigate the functional connectivity within the DMN. Participants were asked to lie still and look at a fixation cross during the whole rs-fMRI session. The following parameters were used for rs-fMRI data acquisition: T2*-weighted Gradient-Echo Planar Imaging (EPI) sequence, TR = 1750 ms, TE = 30 ms, flip angle of 70°, FOV 192 × 192 mm, matrix 64 × 64. Individually, 290 volumes were acquired containing 28 axial slices per volume with a slice thickness of 5 mm and without an interslice gap (voxel size 3 × 3 × 5 mm^3). The slice position was tilted alongside the hippocampal axis in order to maximize brain coverage especially in temporomesial regions of interest (ROIs).

2.3. Image processing and data analysis

2.3.1. Preprocessing

Images were preprocessed in SPM 12 (Statistical Parametric Mapping; Wellcome Centre for Neuroimaging, London, UK) running in a Matlab R2014b environment (MathWorks, MA, USA).

Participants with head movements >3 mm during the scanning session were excluded from further analysis. The first five images per run were discarded to allow for steady-state T1 effects. Images were distortion-corrected and realigned to the first image of the scan run. Masks of gray and white matter as well as of cerebrospinal fluid (CSF) were generated via segmentation. Functional data was coregistered to the normalized T1-weighted structural image and smoothed with an 8-mm full-width half maximum (FWHM) Gaussian kernel.

2.4. Functional connectivity analysis

Functional connectivity analysis was performed using the CONN functional connectivity toolbox v14 (http://www.nitrc.org/projects/conn/). Confounding effects of the blood oxygenation level dependent (BOLD) signal from white matter and CSF masks, head movement and effects of the resting state paradigm convolved with hemodynamic response function were regressed out. Temporal correlations in the low frequency band (0.008–0.09 Hz) of the BOLD signal were computed within a subset of predefined ROIs (Fig. 1) [35,36]. (See Table 1.)

2.5. Construction of the DMN as a functional brain network

Thirteen ROIs – derived from the literature [10] and extracted from the AAL atlas [37] – were used for the construction of the DMN (Fig. 1). Each ROI was taken as a node. Values of the interregional correlation coefficients served as weights, i.e., strength of functional connections, between the nodes (i.e., ROIs) of the network resulting in a weighted symmetric functional connectivity (FC) matrix for each participant

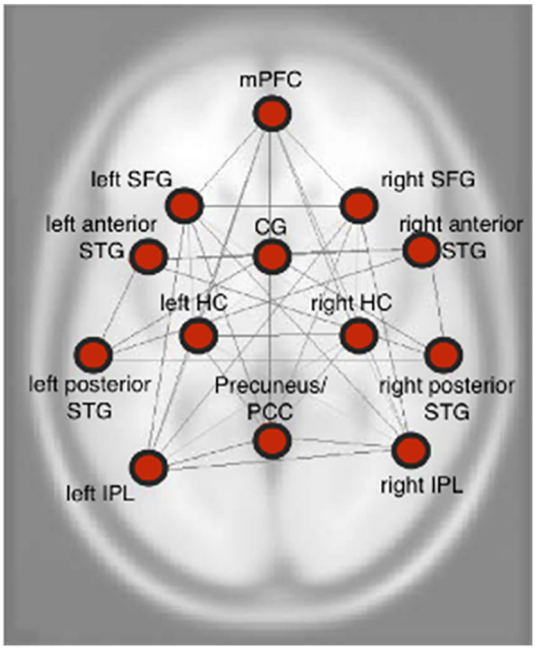

Fig. 1. Schematic overview of the nodes within the graph-theoretically constructed DMN (Ofer, 2015).

Table 1
MNI coordinates (mm) of anatomical regions used to construct the Default Mode Network.

	MNI coordinates (mm)		
Anatomical region	x	y	z
Precuneus (PCC)	0	−56	28
Mesial prefrontal cortex (mPFC)	0	54	−8
cingulate gyrus (CG)	0	6	40
Inferior parietal lobe (IPL)			
Left	−42	−68	38
Right	48	−60	38
Anterior superior temporal gyrus (ant. STG)			
Left	−44	4	−4
Right	54	8	−2
Posterior superior temporal gyrus (post. STG)			
Left	−60	−30	20
Right	60	30	24
Superior frontal gyrus (SFG)			
Left	−28	22	52
Right	30	22	52
Hippocampus (HC)			
Left	−20	−30	8
Right	24	−28	−10

[35]. To exclude nonsignificant connections, a threshold was set on the correlation coefficients according to a permutation test. For this purpose, surrogate data were generated by randomly shuffling the phases of the time series in the frequency domain, yielding a distribution of correlation coefficients under the null hypothesis of no connectivity [35]. After their transformation to Fisher's Z-scores, standard graph-theoretical measures [38,39] were calculated from FC matrix (adjacency matrix). Network edges were only preserved if their correlation coefficient exceeded a threshold of Fisher's $Z > 0.15$ in order to exclude values with insufficient strengths of functional connectivity between the nodes of the network [35,40].

2.6. Network analysis

For the assessment of global network properties and the evaluation of network properties, four standard graph-theoretical measures were chosen [41]: Global efficiency (E_{glob}), local efficiency (E_{loc}), clustering coefficient (C), and average shortest path length (L) (see [35,38,42,43]). Thereby, C was taken as a measure of local connectivity within the network since it reflects the probability that the neighbors of one node, i.e., all nodes connected to the particular node via one link, are also connected with each other. The length of a path, i.e., the number of edges that have to be traversed to connect two network nodes, on the other hand, was taken as an index for global network integration and long-range connectivity. The E_{loc} (measurement of the efficiency of a given node in communicating with the rest of the brain/network) and E_{glob} (indicator of network's ability for parallel information transfer) both encompass the inverse of L and were additionally chosen in order to assess the implications of network properties on network efficiency.

Nodal network analysis consisted of the assessment of E_{loc} (see above), betweenness centrality (B), which is an indicator of the centrality of a given node within a network, and degree (K) (number of edges that link a particular node to other nodes of the network and thus, an indicator for the "hubness"/interconnectivity of a given node) for each node of the network.

2.7. Sociodemographic data and disease variables

Sociodemographic data (e.g., educational level, occupational, and social situation) as well as information about disease history (medical and neurological diseases, comorbidities) and epilepsy-related variables in patients with TLE (e.g., age at epilepsy onset, seizure state (seizure freedom vs. ongoing clinical seizures), seizure type(s) (current and past)) were gathered via questionnaires and medical records. Seizure control was based on self-report, reports from patients´ relatives (if available) and medical documentation of the Freiburg University Epilepsy Center. Seizure freedom was defined as freedom from any epileptic event including auras for at least the past year.

2.8. Statistical analyses

Statistical analyses were conducted using SPSS version 22.0 (Statistical Package for Social Sciences, SPSS). Data were checked for normal distribution (Kolmogorov–Smirnov test) and homogeneity of variance (Levene's test). Since data did not meet the criteria for the calculation of parametric procedures (normal distribution and homogeneity of variance) [44], a rank-transform procedure was used to run multivariate analyses [45]. Subsequently to the application of the "joint ranking" method, rank-transformed global (C, L, E_{glob}, and E_{loc}) and nodal network parameters (E_{loc}, betweenness centrality (B), degree (K)) were entered into a multivariate analysis of variance (MANOVA) with the fixed factors *seizure state* (*SF* vs. *ongoing clinical seizures*) and *side of seizure onset* (*in the left* (*lTLE*) vs. *right* (*rTLE*) *TL*) (see [44]). Significant main effects and between-subject effects ($p < 0.05$) and trends ($p < 0.10$) were subsequently explored by calculating Tukey honest significant difference (HSD) posthoc tests for multiple comparisons.

3. Results

3.1. Descriptive statistics

In total, 27 patients with unilateral TLE were included in the study (15 female, 12 male, mean age ± SD = 43.07 ± 13.55 yrs., range 18–66 yrs.). Fourteen patients were assigned to the group of patients with left-sided TLE (lTLE) (8 female, 6 male; mean age ± SD = 44.93 ± 13.40 yrs., range: 18–66 yrs.); 13 patients were assigned to the group of patients with right-sided TLE (rTLE) (7 female, 6 male; mean age ± SD = 41.08 ± 13.96 yrs., range: 22–64 yrs.).

Twelve patients were SF according to the defined criteria (mean time of seizure freedom ± SD = 4.64 ± 3.67 yrs.; range: 1–10 yrs.). Fifteen patients continued to suffer from seizures or at least auras and were assigned to the group of NSF patients with TLE. Detailed information about both groups can be taken from Table 2. Individual clinical data for each patient are provided in Table 3.

Moreover, a group of 15 HC subjects (8 female, 7 male; mean age ± SD = 40.20 ± 15.49 yrs., range: 20–67 yrs.) participated in the study.

3.2. Retrospective analyses/follow-up

We subsequently gathered data about baseline seizure frequency and further course of TLE in SF and NSF patients for up to five years after their participation in our study.

3.3. Seizure-free patients

In order to validate our initial classification of seizure freedom for our participants, we additionally applied an alternative definition of seizure freedom [46]. According to this definition [46], "a patient should be considered "seizure-free" in response to a new antiseizure treatment (e.g., medication or surgery) once they have gone without a seizure for at least three times the duration of their longest preintervention interseizure interval in the preceding 12 months" [47]. Corresponding data could be retrospectively gathered in eight of our twelve SF patients. For the remaining four patients, required data were not available. Out of the eight patients in whom sufficient data were available, seven patients could also be classified as SF according to the alternative definition [46].

Table 2
Clinical and sociodemographical data of seizure-free and not seizure-free patients with TLE.

	Mean age ± SD	lTLE	rTLE	Female	Male	Mean age at onset ± SD	Mean active disease duration ± SD
Seizure-free patients with TLE	46.25 ± 10.86 yrs. (range: 25–66 yrs.)	7	5	6	6	30.21 ± 13.50 yrs. (range: 6.5–45 yrs.)	11.52 ± 12.18 yrs. (range: 0.7–37 yrs.)
Not seizure-free patients with TLE	40.53 ± 15.25 yrs. (range: 18–64 yrs.)	7	8	9	6	26.90 ± 16.29 yrs. (range: 0–58 yrs.)	13.75 ± 12.88 yrs. (range: 0.75–43 yrs.)

One patient missed the criterion by approximately 3 months (required duration of seizure freedom according to baseline seizure frequency: 2.25 yrs.; duration of seizure freedom at time of participation in the present study: 2 yrs.). However, in addition to the already considerable 2-year seizure freedom before the assessment, this patient remained SF for a further four years after study participation, justifying the former assignment to the group of SF patients.

In fact, all of the twelve "seizure-free" patients remained SF in the follow-up period. In one patient, three possible, but not confirmed, events resembling auras occurred one year after his participation in the study. Besides these three events, the patient reported no further (epileptic) events.

3.4. Not seizure-free patients

Among the NSF patients, two patients had undergone surgery (patient 1: resection of a ganglioglioma World Health Organization (WHO)° I, 12-month postop classification: Engel IVd, Wieser 5; patient 2: temporal pole resection with preservation of the hippocampus, 39-month postop classification: Engel Id, Wieser 2), and three patients became SF (according to [46]) under antiepileptic drug (AED) therapy approximately two years after their participation in our investigation. In these patients, seizure frequency ranged from 4 to 42 seizures/year at the time of participation. In patients in whom seizure control was achieved in the follow-up period, seizure freedom persisted for at least one year. The remaining ten NSF patients continued to suffer from clinical seizures with seizure frequencies ranging from one up to 27 seizures/month.

Our initial classification of seizure freedom is thus supported by follow-up data.

3.5. General results

Healthy controls and patients with TLE did not differ in age (*Kruskal–Wallis test*: χ^2 (2) = 1.155; p = 0.561), educational level ($\chi^2(6) = 5.898$; p = 0.435), occupational ($\chi^2(18) = 15.500$; p = 0.627) and social situation ($\chi^2(6) = 8.422$; p = 0.209), and gender distribution ($\chi^2(2) = 0.288$; p = 0.866).

There was also no difference in age at epilepsy onset and active disease duration, i.e., the duration of active TLE, neither between SF and NSF patients (*age at onset*: $U = -0.415$; p = 0.678; *active disease duration*: $U = -0.709$; p = 0.479) nor between patients with lTLE and patients with rTLE (*age at onset*: $U = -0.875$; p = 0.382; *active disease duration*: $U = -0.340$; p = 0.734).

There was no difference in side of seizure onset between SF and NSF patients with TLE ($\chi^2(1) = 0.363$; p = 0.547). Not seizure-free patients tended to report the prevalence of more than one seizure type as well as the coincidence of secondary generalization more frequently ($\chi^2(6) = 9.180$; p (*one-sided*) = 0.082), indicating a trend of a more complex history of epileptic seizures in NSF patients. Moreover, NSF patients tended to report the intake of a higher number of AEDs when compared with SF patients ($\chi^2(3) = 4.915$; p (*one-sided*) = 0.089). A significantly higher AED load under consideration of prescribed daily dose (PDD)/defined daily dose (DDD) ratios [48] was found in NSF patients when compared with SF patients ($U = -2.224$; p = 0.025).

3.6. Global network parameters

Multivariate tests (MANOVA) revealed a significant main effect of side of seizure onset (lTLE vs. rTLE) (F (4;34) = 4098; p = 0.008) and

Table 3
Table of clinical data of each participant.

Patient	Gender	Age	Age at onset	Side	Seizure-free?	MRI findings	Pathology	AED[a]
1	male	45	41	left	yes	temporolateral	focal lesion	none
2	male	66	20	left	yes	temporomesial	mTL atrophy	LEV
3	female	58	49	left	no	temporomesial	cavernoma, suspected hippocampal sclerosis	OXC
4	female	46	39	left	yes	temporomesial	cavernoma	LEV, OXC
5	male	49	42	left	yes	temporomesial	suspected focal cortical dysplasia (FCD)	LEV
6	female	56	43	left	no	no epileptogenic lesion		TPM
7	male	61	58	left	no	temporobasal	substance defect	LEV
8	female	25	24	left	yes	temporomesial	suspected FCD	ZNS
9	female	43	21	left	yes	no epileptogenic lesion		CBM
10	female	18	9	left	no	temporolateral	suspected FCD	LEV, LTG, PER
11	female	44	9	left	yes	no epileptogenic lesion		CBM
12	male	47	45	left	no	no epileptogenic lesion		LEV
13	male	38	< 1	left	no	subcortical extratemporal		LEV, LCS
14	female	33	27	left	no	temporomesiobasal	astrocytoma WHO° 1	LEV, LTG
15	male	47	45	right	yes	temporopolar and temporomesial	cavernoma, suspected FCD of right amygdala	OXC
16	male	64	21	right	no	temporolateral	suspected neuroglial tumor	LEV, LCS
17	female	46	33	right	no	temporomesial and temporopolar	suspected FCD	LEV, LCS, OXC
18	male	47	40	right	yes	temporolateral	cavernoma	LEV, LCS
19	female	31	6.5	right	yes	no epileptogenic lesion		LEV
20	female	39	23	right	no	no epileptogenic lesion		LTG, LCS, PER
21	female	29	21	right	no	temporolateral	ganglioglioma WHO° 1	LTG
22	male	25	24	right	no	temporolateral	lesion	LEV, LTG
23	male	58	40	right	yes	temporomesial	lipoma	LEV, OXC
24	female	22	22	right	no	temporolateral	suspected FCD	LTG
25	male	23	5.5	right	no	temporomesial	suspected hippocampal sclerosis	LEV
26	female	49	23	right	no	temporomesial	suspected neuroglial tumor	OXC, LEV
27	female	54	35	right	yes	temporobasal		LEV, OXC

[a] LEV = levetiracetam, OXC = oxcarbazepine, LTG = lamotrigine, TPM = topiramate, ZNS = zonisamide, CBM = carbamazepine, PER = perampanel, LCS = lacosamide.

a trend for seizure state (SF vs. NSF) (F (4;34) = 2.293; p = 0.080) (see below). The interaction *side of seizure onset* ∗ *seizure state* did not reach statistical significance (F (4;34) = 0.484; p = 0.747).

3.6.1. Seizure state

Between-subject effects revealed a significant main effect of *seizure state* for the global network parameters E_{loc} (F (1) = 4.294; p = 0.045) and L (F (1) = 5.565; p = 0.024). Posthoc tests revealed higher L in SF patients compared with that in NSF patients (p = 0.049), but comparable L to HC (p = 0.320). Not seizure-free patients did not differ from HC (p = 0.551) (Fig. 2). Posthoc tests revealed a trend for SF patients to have less E_{loc} than NSF patients with TLE (p = 0.075) and HC (p = 0.058). Not seizure-free patients with TLE did not differ from HC in DMN's E_{loc} (p = 0.991). No significant differences were found for DMN's E_{glob} (F (1) = 0.097; p = 0.757) and C (F (1) = 2.958; p = 0.094) (Fig. 3).

3.6.2. Side of seizure onset

A highly significant main effect of *side of seizure onset* could be revealed for E_{glob} (F (1) = 8.260; p = 0.007). Multiple comparisons revealed significantly increased E_{glob} in patients with lTLE compared with that in patients with rTLE (p = 0.020), but neither patients with lTLE nor with rTLE significantly differed from HC (all p > 0.05). The clustering coefficient marginally failed to reach statistical significance (F(1) = 4.078; p = 0.051). There was a trend of lower C in patients with lTLE compared with that in patients with rTLE (p = 0.082). Neither patients with lTLE nor with rTLE differed from HC regarding C (all p > 0.05). The E_{loc} (F(1) = 2.066; p = 0.159) and L (F(1) = 0.190; p = 0.665) did not reach significance with regard to side of seizure onset.

3.6.3. Seizure state ∗ side of seizure onset

Between-subject tests did not reveal any significant interaction effect (*seizure state* ∗ *side of seizure onset*: p > 0.668).

3.7. Nodal network parameters

The MANOVA revealed a significant main effect of seizure state (F (36;1) = 320.446; p = 0.044), but neither the factor side of seizure onset (F (36;1) = 1.142; p = 0.644) nor the interaction seizure state ∗ side of seizure onset (F (36;1) = 21.587; p = 0.169) reached statistical significance. When between-subject effects were explored, significant differences between the groups (SF vs. NSF vs. HC) could be revealed

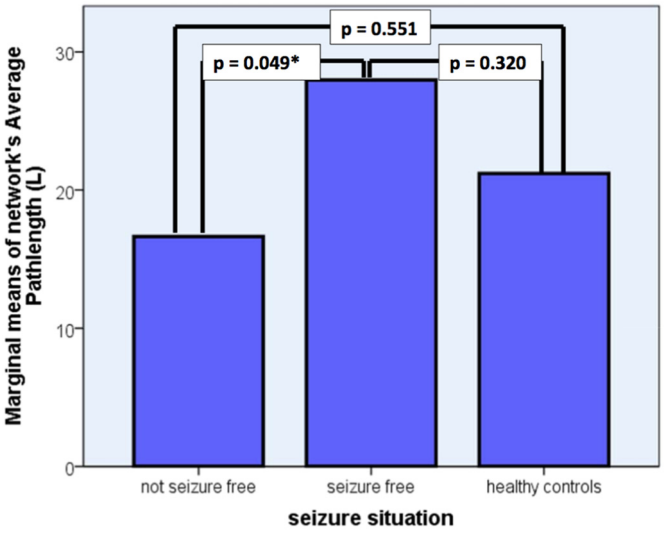

Fig. 2. Marginal mean ranks of the network's average shortest path length with regard to seizure state.

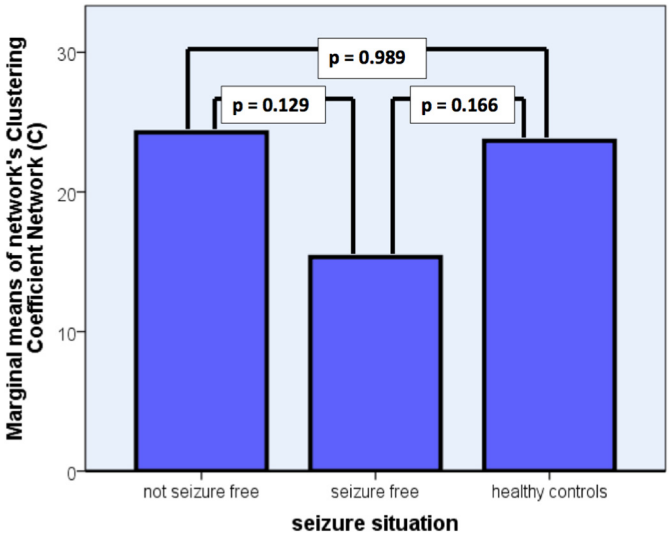

Fig. 3. Marginal mean ranks of the network's clustering coefficient according to seizure state

regarding the interconnectivity (Degree) of the following network nodes (Table 4, Fig. 4):

1. Degree of precuneus: F (1) = 13.350; p = 0.001
2. Degree of mPFC: F (1) = 4.623; p = 0.038
3. Degree of the right IPL: F (1) = 5.948; p = 0.020
4. Degree of the left IPL: F (1) = 7.653; p = 0.009
5. Degree of the right anterior STG: F (1) = 9.922; p = 0.003

4. Summary

The present findings indicate that longer paths within the network, i.e., more edges that need to be traversed to connect network nodes, and an associated trend of reduced local efficiency in network communication in SF patients might be associated with hub redistribution

Table 4
Significant results after correction for multiple comparisons for Degree of Precuneus, mPFC, left and right IPL, and right anterior STG according to seizure state: mean difference and significance according to the Tukey-HSD test.

Seizure state	Mean difference (I–J)	Tukey-HSD
Precuneus		
Not seizure-free (I) – seizure-free (J)	+14.330	p = 0.002**
Not seizure-free (I) – healthy controls (J)	−1.000	p = 0.956
Seizure-free (I) – healthy controls (J)	−15.300	p = 0.001**
mPFC		
Not seizure-free (I) – seizure-free (J)	+9.609	p = 0.080°
Not seizure-free (I) – healthy controls (J)	−2.300	p = 0.832
Seizure-free (I) – healthy controls (J)	−11.909	p = 0.024*
Right IPL		
Not seizure-free (I) – seizure-free (J)	+11.921	p = 0.028*
Not seizure-free (I) – healthy controls (J)	+2.267	p = 0.844
Seizure-free (I) – healthy controls (J)	−9.655	p = 0.088°
Left IPL		
Not seizure-free (I) – seizure-free (J)	+12.682	p = 0.012*
Not seizure-free (I) – healthy controls (J)	+3.000	p = 0.717
Seizure-free (I) – healthy controls (J)	−9.682	p = 0.066°
Right anterior STG		
Not seizure-free (I) – seizure-free (J)	−9.682	p = 0.005**
Not seizure-free (I) – healthy controls (J)	−1.300	p = 0.876
Seizure-free (I) – healthy controls (J)	+8.382	p = 0.016*

** p < 0.01.
* p < 0.05.
° p < 0.10.

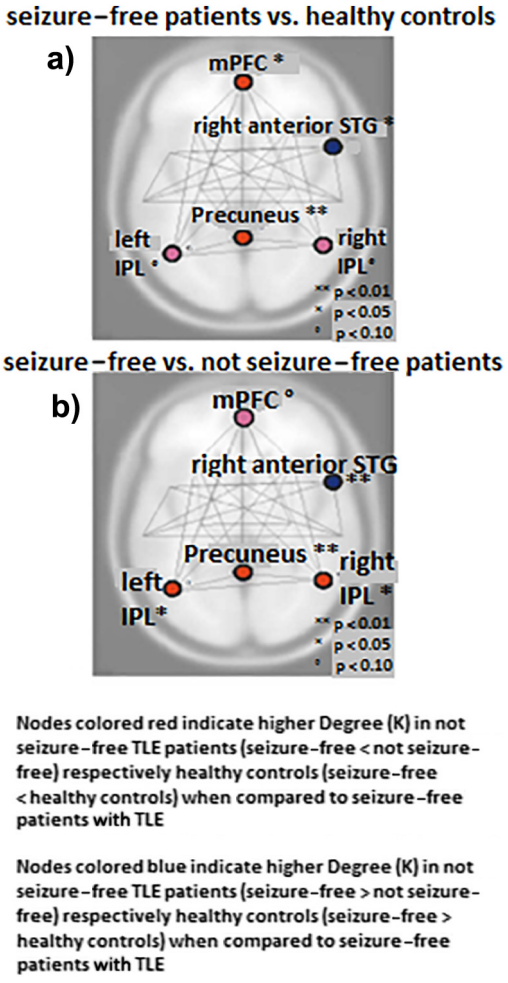

Fig. 4. Degree of DMN nodes for which seizure-free patients with TLE significantly differed from (a) healthy controls and (b) patients with TLE with ongoing clinical seizures.

processes and an altered interconnectivity at the nodal network level. Central hub regions of the DMN (precuneus, mPFC, IPL) showed a significantly lower number of direct links with other nodes of the network, i.e., reduced interconnectivity, in SF patients compared with that in NSF patients and HC. On the other hand, right anterior STG revealed significantly increased interconnectivity within the DMN in SF patients compared to NSF patients and HC (Table 4, Fig. 4). Healthy controls and NSF patients were not different neither with regard to global (Fig. 2) nor with regard to nodal (Table 4, Fig. 4) network properties.

The findings of the present study indicate that patients with TLE may show deviations and movements away from the "standard" configuration of the DMN in healthy subjects and that these differences depend on seizure state and focus lateralization in the left or right TL. With regard to seizure state, there was a trend of longer paths in SF patients and a trend of shorter or at least comparable path lengths in NSF patients compared with that in HC. Regarding focus lateralization, patients with lTLE and rTLE showed distinct deviations from HC with respect to global efficiency of the DMN, i.e., the network's ability for parallel information transfer, with patients with lTLE tending to show an increased global efficiency and patients with rTLE tending to show a decreased global efficiency compared with HC (see e.g., [11,30]).

5. Discussion

Most research on TLE has focused on seizure lateralization and its impact on network organization. Instead, and to the authors' best knowledge, the present investigation is the first to focus on the assessment of seizure state (seizure freedom vs. ongoing clinical seizures) and differences in network topological properties between SF and NSF patients with TLE. Considering that an increase of long-range connectivity, i.e., short(er) network paths, has been proposed to contribute to the pathological lowering of the convulsive threshold and the (rapid) hypersynchronization of brain networks [21–24] underlying epileptic seizures [25], we conversely speculated that reductions of long-range connectivity, i.e., longer paths particularly within networks involved in or affected by the epileptic dysfunction, may be conducive to seizure freedom. Longer paths within networks might be related to prolonged system response times that counteract the rapid spread of local epileptic discharges and the resulting hypersynchronous network activity. The spontaneous synchronized activity and intrinsic organization of the DMN have repeatedly been found to be altered because of epileptic activity of TL origin [2,23,26–30]. Thus, we speculated that DMN network properties might differ between patients with TLE with at least one year of seizure freedom including auras and patients with ongoing clinical seizures. Thus, the aim of the present study was to investigate these network properties in SF patients and patients with ongoing clinical seizures using a graph-theoretical approach.

According to the present findings, (alterations of) DMN properties associated with seizure freedom followed the same pattern in patients with lTLE and patients with rTLE. Thus, seizure freedom was found to be associated with an increase of the L, i.e., reductions of global connectivity, which might be mediated by hub redistribution processes at the nodal network level and accompanied by reductions of DMN's E_{loc}.

Findings from the nodal network level support that fewer DMN nodes are interlinked via short paths. Significant reductions of functional connections were revealed in important network nodes that regularly function as hubs within the network and its subsystems. Thus, the number of functional connections and thus the interconnectivity of the central hub of the network, the precuneus, as well as hub regions within the DMN's anterior and posterior subsystems, namely the mPFC and lPL [15], were significantly reduced in SF patients. Simultaneously, SF patients revealed significantly increased interconnectivity of the right anterior STG compared with NSF patients and HC, indicating that hub redistribution in SF patients with TLE may underlie and mediate longer communication pathways within the network. Alterations of hub regions in patients with TLE, particularly reductions of the "hubness" of the precuneus [11,12,39,49] within the DMN and a reduced FC between the anterior and posterior subsystems [30] have already been reported. Bernhardt et al. [12] found hub regions of the brain to be less evenly distributed over the four cerebral lobes and instead concentrated within the TL and paralimbic regions in patients with TLE. In line with these studies, the present findings also point to an increased "hubness" of nodes within the TL (right anterior STG) but also a simultaneous decrease in the interconnectivity of regular DMN hub regions. Interestingly and in contrast to other studies (e.g., [11,30,49]) that reported a general altered organization of functional brain networks in patients with TLE compared with that in healthy subjects, alterations of the DMN's organization could only be revealed in SF patients with TLE whereas patients with ongoing clinical seizures did not differ from HC in their global and nodal organization of the DMN. This likely underscores a particular status and involvement of the DMN within TLE's seizure network, as it has already been reported [11,26,27,50]. The "standard" organization and configuration of the DMN, but maybe also of other functional brain networks involved in the epileptic dysfunction, might therefore reflect (a part of) TLE's pathomechanism. As a consequence, seizure freedom might be related to deviations from this "standard" organization and configuration. In line with this assumption, Ponten et al. [23] reported an increase of local as well as global (i.e., long-range) connectivity in brain networks during epileptic seizures when compared to the interictal state. High local connectivity might thereby enhance the probability that local epileptic activity within one circumscribed pathologically altered network node entrains

synchronized activity in adjacent network nodes, further resulting in synchronization of the whole network if global connectivity is also high.

The ability for segregated processing within the subsystems of a network (high local connectivity; high C) as well as system integration (short paths, i.e., high global connectivity; low L) [41] is thought to represent the optimal network topology for information transfer. According to Ponten et al. [23], epileptic activity might be associated with drifts/alterations of topological properties that increase and optimize the efficiency of information transfer within the network when compared with the interictal state. The observed reductions of global connectivity in SF patients indicate a shift toward a "less efficient" network organization, which was additionally reflected as a trend of reduced E_{loc} of the DMN. Network efficiency crucially relies on short paths that enable a rapid information transfer and integration of information carried out by subsystems within the network [51]. Longer paths within networks might correspond to a slower system response contributing to seizure freedom by reducing the probability of a rapid spread of epileptic discharges over the whole network and therefore preventing hypersynchronous neuronal activity in brain networks [25]. Netoff et al. [24] reported the potential of self-annihilation processes of waves during their journey through networks. A slower system response due to longer paths might be conducive to self-annihilation of local epileptiform discharges before they spread over the whole network. Longer paths increase the number of edges that has to be traversed between network nodes and simultaneously increase the potential for "disturbances" and loss of "information" along the way. According to the present findings, seizure freedom might therefore be – irrespective of focus lateralization in the left or right TL – associated with hub redistributions at a nodal level that underlie the increased path lengths and decreased local efficiency at the global network level. Self-annihilation processes of local epileptiform discharges [24] might thus be enhanced by hub redistributional processes at the nodal level and longer paths at the global level, enabling seizure freedom or at least a reduced vulnerability of brain networks to the occurrence of epileptic seizures.

6. Limitations and outlook

As this was – to the authors' best knowledge – the first study that focused on seizure freedom and its associations with network properties of the DMN in patients with TLE, future studies are needed to validate its findings.

In the present investigation, seizure freedom was assessed preferentially via self-report. It is well-known that epileptic seizures due to TLE are frequently accompanied by postictal amnesia for the seizure event [52]. Furthermore, some patients may be reluctant to report the (re-)occurrence of seizures because of the possible consequences (e.g., restrictions in daily living and job execution such as losing their driver's license). The best possible means (e.g., consideration of medical reports) were used to ensure that participants' reports of seizure freedom were reliable before they were assigned to the group of SF patients with TLE. Apart from this, it remains a matter of debate how seizure freedom should be defined, particularly regarding the appropriate time period without clinically observable epileptic events to consider a patient SF [46,47,53–55]. Frequently, one year without the appearance of clinical seizures is considered to be sufficient to classify patients as SF. However, when using this criterion, biological distinctions between patients with epilepsy such as seizure frequency at baseline and thus disease severity might not sufficiently be taken into account. Considering that group differences in L were only borderline significant ($p = 0.049$) and that differences in the network's local efficiency were only observable in the form of statistical trends (SF vs. NSF: $p = 0.075$, SF vs. HC: $p = 0.058$), it is possible that clearer and less contestable differences could be obtained by using another definition of seizure freedom. In order to address this issue and to strengthen our findings and their interpretation, we gathered follow-up data from the patients who had been free of any epileptic event for at least one year prior to our assessment (range: 1–10 yrs.): All SF patients remained SF for four or even up to five years after their participation in our investigation. Moreover, the majority of our SF patients in whom sufficient data was available could still be classified as SF according to an alternative conceptualization [46]. Follow-up data confirm that our initial investigation compared truly SF patients with patients with ongoing clinical seizures and that group differences did not rely on an arbitrary time cut-off. Possibly, borderline significance and statistical trends may be due to small sample size and might have reached (higher) statistical significance in larger samples.

On the other hand, so far, it cannot be determined how (clinical) properties such as the heterogeneous underlying pathology and etiology of TLE in the sample might have influenced the results and partly contributed to divergent findings. This heterogeneity might be a limiting factor in the present investigation. Several authors have argued that particularly focus site (mesial vs. lateral) impacts the clinical characteristics and underlying pathomechanisms [56,57], and may thus have differential implications on network organization. Since the sample size did not allow the formation of subgroups (e.g., comparison between patients with mesial and lateral temporal pathologies and different underlying etiologies) because of partly too small sample sizes (see Table 3), it will be the topic of future investigations to unravel the impact of focus site, underlying pathology, and etiology of TLE on network organization, and how these aspects are linked with seizure freedom.

Moreover, patients of the present sample reported relatively late epilepsy onset (see Tables 2 and 3). Only five patients of the present sample reported epilepsy onset before the age of 10 years. The majority ($n = 22$) had epilepsy onset in adulthood (>20 years), a time period in which maturation processes of the DMN (and other brain networks) are usually completed [58]. The completion of these processes before the epilepsy onset in the majority of patients of the present sample might thus have contributed to the lack of differences between HC and the present group with TLE because of the higher robustness of mature brain networks against disturbances due to neurological diseases. The impact of age at epilepsy onset and disease duration on network development, its maturation, and its associations with clinical course and seizure freedom might be an interesting topic of future studies.

There was high heterogeneity in reported seizure types in NSF patients. Two patients (13.3% of the sample) reported simple partial seizures (SPS) as the only seizure type that recurred within the last three years. The impact of SPS and complex partial seizures (CPS) on the intrinsic organization of the brain and functional brain networks may differ from the impact of secondarily generalized seizures (SGS). Thus, for instance, Blumenfeld et al. [27] and Dupont et al. [26] were able to demonstrate reduced blood flow to regions of the DMN in patients with epilepsy during seizures that were accompanied by a loss or alteration of consciousness. Since the frequency and number of SGS were not included in the present analysis, future studies might be able to unravel the impact of different seizure types and their frequency on network's topological properties and the intrinsic organization of the brain as well as their relation to seizure freedom.

The present study only included patients with TLE prior to epilepsy surgery or patients in whom seizures could be successfully controlled by AED therapy. There might be differences in network properties (associated with seizure freedom) depending on whether seizure freedom was achieved pharmacologically or by epilepsy surgery. In a large percentage of patients, TLE cannot be successfully controlled by conservative pharmacological treatment [52]. Proven pharmacoresistance is one of the main criteria for considering patients for epilepsy surgery [59]. Based on the present data, it cannot be differentiated whether patients whose seizures could be successfully controlled by pharmacotherapy had network properties that made them respond to AEDs, or whether pharmacological treatment altered network properties in a way that led to successful seizure control. Therefore, network properties and disturbances that underlie the epileptic dysfunction in pharmacoresistant patients with TLE might differ from those in patients that respond to AED therapy. Longitudinal

studies on patients with TLE with new-onset epilepsy might be able to shed light on questions such as network alterations during the course of disease and how they are related to recurrent epileptic activity. Such studies may also enable the differentiation between responders and nonresponders to treatments and the prediction of seizure outcome based upon network properties.

Additionally, the impact of AEDs on organizational properties of functional brain networks is still unclear. Thus, AED effects cannot be ruled out from our findings, especially as patient groups (SF vs. NSF patients) differed significantly in daily drug dosage. A better understanding of the effects of AEDs on network properties in addition to how these network properties predict AED responsiveness may provide new perspectives and contribute to an optimization of a patient-centered treatment of epilepsies.

Graph-theoretical measures might be a good mean for this assessment. However, several pitfalls need to be taken into consideration when performing network analyses [60]: Differences in data acquisition modalities (e.g., EEG [61], MRI [12], fMRI [11]), network construction (e.g., semipartial correlations vs. bivariate correlations; whole-brain vs. circumscribed networks such as the DMN [38,60,62]), and analysis methods (e.g., extraction, number, and location of ROIs, use of midline structures, applied parameters, "small world" analysis [60,63–65]) may all contribute to divergent findings. For instance, Song et al. [66] proposed that epilepsy might be accompanied by a consistent pattern of brain efficiency alterations at the whole brain level, whereby alterations at the network and nodal level might exhibit variable patterns of efficiency changes. This would explain the divergent findings of the present investigation particularly from studies that focused on whole-brain connectivity (e.g., [11]). In the present investigation, network construction was derived from the literature [10]. Regions of interest [10] were extracted from the AAL atlas [37]. In patients with epilepsy, brain reorganization is a well-documented phenomenon (e.g., [56, 57]). Thus, standardized atlases of brain structures might not reflect the real anatomy and topology of functional brain networks in patients with epilepsy. Particularly midline structures might be differentially interconnected within the whole brain network according to their lateralization and may also depend on the underlying site and lateralization of the epileptogenic focus and etiology in TLE. This might even result in functional separations of the left and right lateralized portions of the same structure. Future studies might take this into consideration and use differential approaches for network construction, the extraction of regions of interest and their interconnectivity within the whole brain network in TLE (e.g., [65]).

The organization of brain functional networks has been found to typically follow a topological architecture known as a "small world" topology [12,40–42,67]. This network topology is characterized by high local connectivity within its components and high global (i.e., long-range) connectivity between them [41,51,68]. In line with previous studies that have found "small worldness" of functional brain networks to be maintained in patients with TLE [12,16,39,49], the present study indicates that the "small worldness" of the DMN seems to be maintained in SF patients as well as in patients with ongoing clinical seizures. The observed reductions of global connectivity in SF patients may indicate a shift toward a "less efficient "network organization termed network regularization [41] albeit within the range of "small worldness". On the other hand, the observation that SF patients and patients with ongoing clinical seizures differed from one another, but not from HC, may also indicate a movement of both groups away from HC in different directions. Thereby, SF patients tended to show longer paths whereas patients with ongoing clinical seizures tended to have shorter or rather comparable path lengths compared to HC. This would be in line with the findings of Ponten et al. [23] who observed an increase of "small world" properties in the course of epileptic activity. This additionally supports the idea of seizure freedom being associated with deviations from "standard" network organization albeit "small worldness" per se might be maintained. Since the present study did not encompass a direct of measure of "small worldness" [39,60,65], it might be the topic of future investigations to assess the architecture of the DMN and other functional brain networks in SF patients and patients with ongoing clinical seizures.

Future studies may profit from the use of combined EEG–fMRI procedures and/or the use of dynamic FC analysis [69]. Interictal epileptiform discharges (IEDs), especially due to TLE, have been found to alter DMN's resting state-activity and topological properties of brain networks [23, 26,50]. While this was not controlled in the present study, it is likely that patients with ongoing clinical seizures showed more epileptic activity in their EEG than SF patients. To evaluate the effect of IEDs in the group of patients with ongoing clinical seizures that might in turn be related to higher local and global connectivity [23], combined EEG–fMRI procedures along with the use of dynamic FC analysis [69] may help provide insight into the dynamics of interictal networks and unravel the effects of IEDs on interictal network organization in patients with epilepsy.

The DMN has become largely associated with internally oriented thinking as well as higher-order cognitive and psychological functioning. All of this encompasses (autobiographical) memory processes as well as self-referential processes [15]. An aberrant organization of the DMN has been related to cognitive and psychiatric symptoms in several pathological conditions [19]. In TLE, (autobiographical) memory deficits as well as depressive symptoms are more frequently found than in other epileptic syndromes [70–73]. Future studies might be able to shed light on the question of how alterations of DMN topological properties associated with seizure freedom might be linked to cognitive and psychiatric symptoms in patients with TLE.

7. Conclusion

Despite the aforementioned limitations, the present data give hint that seizure freedom in patients with TLE seems to be associated with "deviations" from a standard configuration of the DMN toward a "less efficient" network organization. This seems to be independent of focus lateralization in the left or right TL. Seizure freedom was found to be associated with hub redistributions at the nodal level that may underlie longer paths and a trend of reduced local efficiency at the global network level. Longer paths within networks, i.e., a higher number of edges that has to be traversed between network nodes, elevate the risk for "disturbances" and loss of "information" along the way. An associated slower system response might therefore contribute to seizure freedom in that it reduces the probability of a rapid spread of epileptic discharges over the whole network (self-annihilation processes) and therefore help to prevent hypersynchronous neuronal activity that may result in epileptic seizures.

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Disclosure of conflicts of interests

None of the authors has any conflict of interest to disclose.

Ethical publication statement

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.

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