Original article

Epileptic Disord 2020; 22 (5): 623-32

Functional connectivity analysis of patients with temporal lobe epilepsy displaying different ictal propagation patterns*

Nermin Gorkem Sirin [1,2], Elif Kurt [2,3], Cigdem Ulasoglu-Yildiz [2,3], Ani Kicik [4], Ali Bayram [2,3], Zerrin Karaaslan [1,2], Nerses Bebek [1], Betul Baykan [1,2], Tamer Demiralp [2,5], Candan Gurses [1]

[1] Departments of Neurology and Clinical Neurophysiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
[2] Aziz Sancar Institute of Experimental Medicine, Department of Neuroscience, Istanbul University, Istanbul, Turkey
[3] Hulusi Behçet Life Sciences Research Laboratory, Istanbul University, Istanbul, Turkey
[4] Department of Physiology, Faculty of Medicine, Demiroğlu Bilim University, Istanbul, Turkey
[5] Department of Physiology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Received September 02, 2019; Accepted July 27, 2020

ABSTRACT – *Aims*. The pathophysiology of switch-of lateralization and bilateral temporal asynchrony, which are scalp EEG ictal propagation patterns (iPP) in temporal lobe epilepsy (TLE), is poorly understood. We aimed to analyse functional connectivity (FC) of the temporal lobe and related areas in patients with TLE with iPP (iPP-TLE) and without iPP (non-iPP TLE).

Methods. Twelve patients with iPP-TLE, 13 patients with non-iPP TLE, and 13 healthy controls (HC) underwent resting-state functional MRI (fMRI). Seed-based FC was analysed between the homologous insulae, hippocampi, amygdalae, parahippocampal, superior temporal, and middle temporal gyri.

Results. FC was reduced between homologous temporal lobe areas in patients with TLE compared with HCs. Patients with non-iPP TLE displayed decreased FC between the homologous parahippocampal and superior temporal gyri, and patients with iPP-TLE had lower FC between the homologous insulae, parahippocampal and superior temporal gyri compared with HC. Furthermore, patients with iPP-TLE tended to have lower FC between the bilateral insulae when compared with patients with non-iPP TLE.

Correspondence:
Nermin Gorkem Sirin
Istanbul University Istanbul Faculty of Medicine,
Department of Neurology,
Capa, Fatih, Istanbul,
34390, Turkey
<gorkemsirin@yahoo.com.tr>

doi:10.1684/epd.2020.1210

*This paper was presented in 16th European Congress of Clinical Neurophysiology in Budapest in 2017.

Conclusions. Reduced FC of interhemispheric connections between temporal lobes and related areas might be an adaptive change to protect contralateral areas in seizure propagation. The insula showed decreased FC between two hemispheres in patients with iPP-TLE, assuming a role in ictal scalp propagation pattern changes in TLE.

Key words: temporal lobe epilepsy, ictal scalp EEG propagation patterns, switch-of lateralization, bilateral asynchrony, functional connectivity

Although the lateralization of ictal EEG is mainly based on the first appearance and amplitude difference between the two hemispheres at seizure onset, a number of ictal propagation patterns (iPP) may emerge along the progressing seizure (Steinhoff *et al*., 1995; Napolitano *et al*., 2008; Napolitano *et al*., 2010). 'Switch-of lateralization' and 'bilateral asynchrony' are two such interesting iPPs observed on scalp EEG of patients with temporal lobe epilepsy (TLE) (Steinhoff *et al*., 1995; Schulz *et al*., 2000; Sirin *et al*., 2013). According to the original description by Steinhoff *et al*. (1995), switch-of lateralization consists of ictal activity initially lateralized to one hemisphere followed by ictal discharges lateralized to the contralateral hemisphere, and bilateral asynchrony is described as ictal discharges showing more than 1-Hz difference between the two hemispheres after seizure onset. It is known that some patients with iPP, despite their consistently lateralized side of seizure onset, may display bilateral interictal discharges (Steinhoff *et al*., 1995). Although the first paper on iPP reported only patients who were seizure-free after surgery (Steinhoff *et al*., 1995), later studies claimed that the presence of iPP might lead to false ictal lateralization and worse surgical outcome (Schulz *et al*., 2000; Kang *et al*., 2005; Lee *et al*., 2006; Sirin *et al*., 2013). Both the discrepancies between the ictal and interictal EEG findings and the uncertainties in predicting the surgical prognosis point to the importance of a detailed investigation of the underlying mechanisms in iPP.

Resting state functional magnetic resonance imaging (RS-fMRI) is widely used for the assessment of basal functional connectivity (FC) in the brain. In patients with TLE, altered FC between the homologous and intra-hemispheric regions related to the epileptogenic zone were reported to provide information about lateralization of the epileptogenic zone and the pathophysiological features of epileptic and compensatory connections within brain networks (Bettus *et al*., 2010; Morgan *et al*., 2010; Pereira *et al*., 2010; Morgan *et al*., 2011; Pittau *et al*., 2012; Ji *et al*., 2013; Haneef *et al*., 2014; Haneef *et al*., 2015; Morgan *et al*., 2015; Su *et al*., 2015). However, iPPs have not yet been specifically investigated in fMRI studies.

We hypothesized that FC between the homologous areas, representing the most direct interactions of both temporal lobe structures by means of shortest paths, might provide information about iPPs. Increased FC between homologous temporal lobes in patients with TLE with iPP might indicate unilateral epileptogenic focus with discharges easily spreading over the contralateral temporal lobe, whereas reduced FC might support the existence of bilateral independent epileptogenic foci in the temporal lobes. The aim of this study was to investigate the FC alterations in homologous areas of the temporal lobes in patients with these iPPs.

Methods

Patients

Among 258 consecutive patients with TLE who had undergone video-EEG monitoring between 1999 and 2017 in our epilepsy centre, 24 patients had 'switch-of lateralization' and/or 'bilateral asynchrony' on ictal scalp EEG. Twelve patients underwent surgery for epilepsy at the time of the study and were excluded because the regions investigated in this study included parts of the temporal lobes. The remaining 12 patients were recruited to the study and grouped as TLE and iPP (iPP-TLE). Thirteen patients showing only unilateral ictal discharges during the seizure were also included in the study and grouped as TLE without iPP (non-iPP TLE). All patients had drug-resistant epilepsy, *i.e*. treatment with two appropriately chosen antiepileptic drugs with adequate doses, either as monotherapy or in combination, that failed to provide seizure freedom. As a third group, 13 healthy controls (HC) who had no history of epilepsy and normal neurological examination also participated in the study.

EEG findings

Ictal EEG. Patients with at least one seizure displaying 'switch-of lateralization' and/or 'bilateral asynchrony' were classified as part of the iPP-TLE group. The ictal scalp EEG propagation patterns were determined according to the previous description by Steinhoff *et al*. (1995). Bilateral asynchrony consisted of ictal activity lateralized to one hemisphere followed by ictal discharges showing more than 1 Hz difference between two hemispheres and lasting for at least 10 seconds (*figure 1*). Switch-of lateralization was determined as ictal activity lateralized to one hemisphere followed

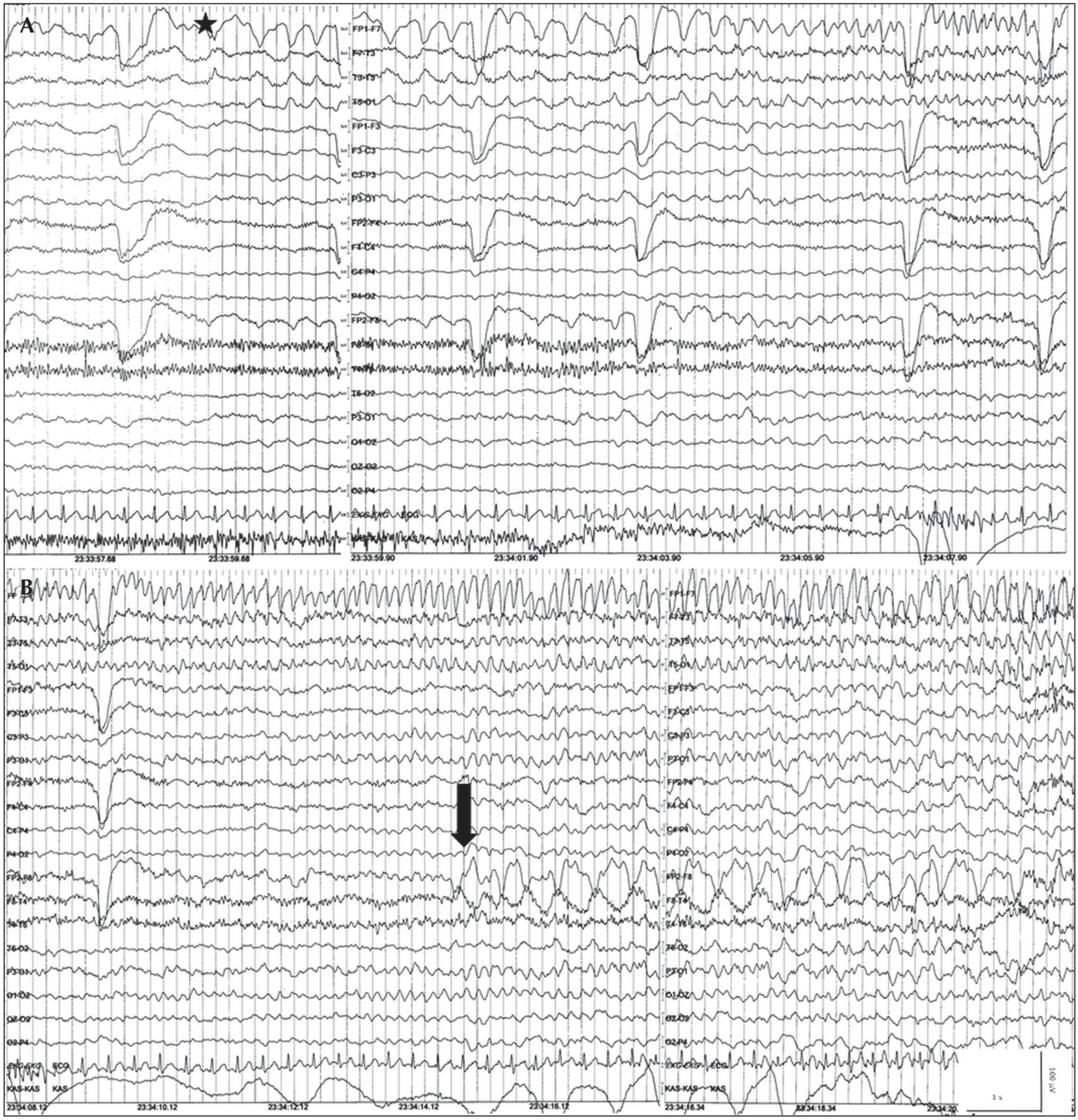

Figure 1. Bilateral asynchrony. (A) Ictal activity starts at the left frontotemporal region with delta frequency (star) and evolves into theta frequency. (B) Fifteen seconds after onset, an activity occurs at the right frontotemporal region with delta frequency (arrow) showing a frequency difference of more than 1 Hz between the two hemispheres.

by ictal discharges lateralized to the contralateral side lasting for at least 10 seconds (*figure 2*).

In patients with non-iPP TLE, ictal discharges were lateralized to unilateral temporal or hemisphere electrodes at seizure onset without any switch-of lateralization and/or bilateral asynchrony during the remaining epileptic activity.

Interictal EEG. Interictal findings were classified as unilateral when more than 90% of the recorded epileptiform discharges were lateralized to one temporal lobe. When more than 10% of the interictal epileptiform discharges were seen over both hemispheres, patients were grouped as showing bilateral interictal discharges.

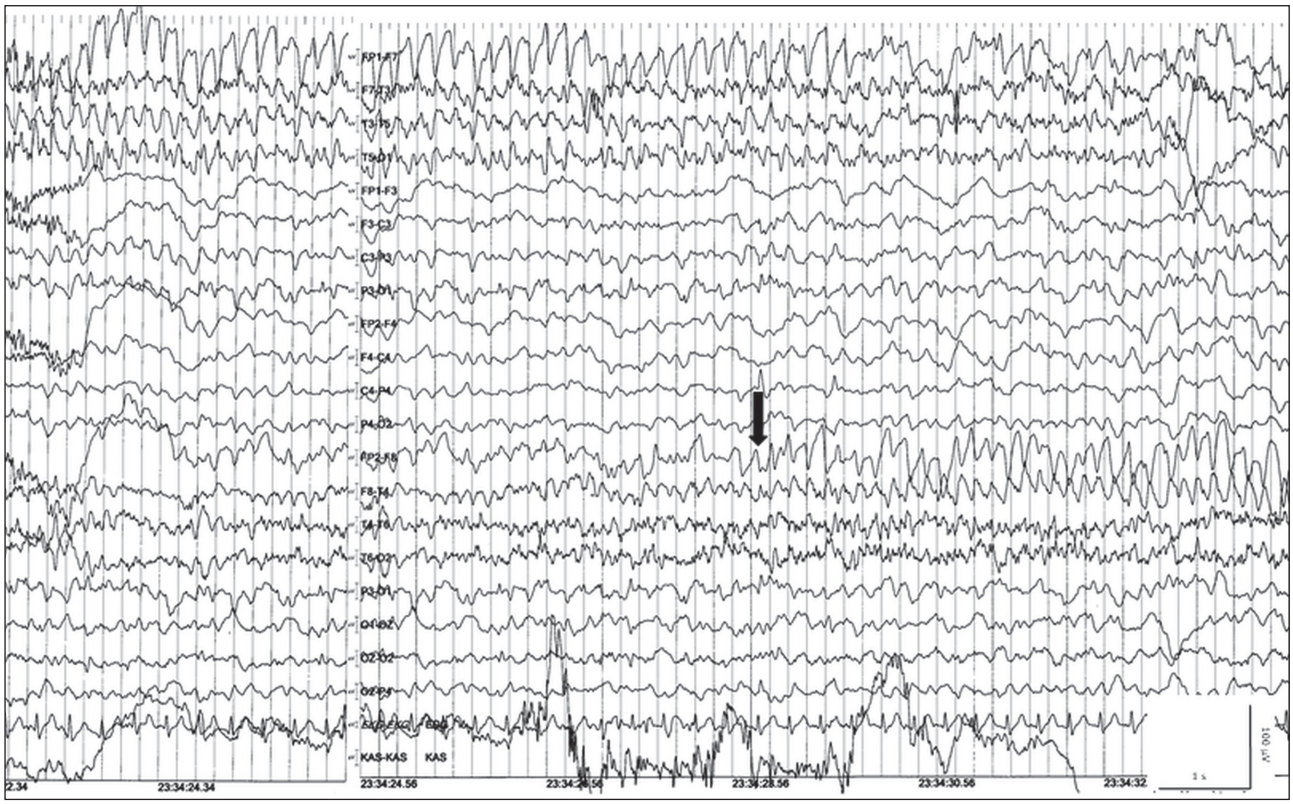

Figure 2. Switch-of lateralization. After several seconds, the ictal discharges lateralizing to the right frontotemporal electrodes show 'switch-of lateralization' (arrow).

MRI acquisition and data analysis

Structural and functional MRI data were acquired on a Philips 3 Tesla MRI system equipped with a SENSE-32 channel head coil (Philips Achieva, Best, The Netherlands). T1-weighted structural 3D turbo field echo (TFE) images were collected using the following parameters: 250 × 250-mm field of view (FOV), 180 axial slices, voxel size of 1 mm^3 isotropic, and flip angle of 8°. RS-fMRI data were collected using an EPI sequence with the following parameters: repetition time (TR) = 2 s, echo time (TE) = 30 ms, flip angle = 90°, FOV = 224 × 240 mm, 36 axial slices, voxel size = 2 × 2 x 4 mm. Following ten dummy volumes, 214 volumes were collected, and the total scan duration was 7.5 minutes. All subjects were asked to keep their eyes closed and not to sleep during the functional scanning.

The pre-processing steps were performed using the SPM8 toolbox (Statistical Parametric Mapping software, www.fil.ion.ucl.ac.uk). Functional images were first realigned to the first scan to correct for head motion. The anatomical image was co-registered to the mean functional image and segmented and normalized to the Montreal Neurological Institute (MNI) standard space. The realigned functional images were spatially normalized to the MNI space and resampled to 2-mm^3 voxels. Finally, the functional images were spatially smoothed (full-width half maximum=8 mm).

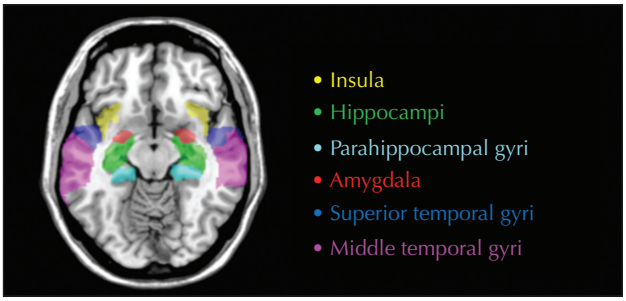

Figure 3. Region of interests were assigned according to the Automated Anatomical Labelling (AAL) Atlas, as shown with coloured pairs.

FC analyses were performed using the CONN-fMRI FC toolbox v13 (http://www.nitrc.org/projects/conn). Homologous temporal lobe structures comprising the left and right insulae, hippocampi, parahippocampal gyri, amygdalae, and superior temporal and middle temporal gyri were defined as regions of interest (ROIs) corresponding to the Automated Anatomical Labelling (AAL) Atlas (*figure 3*). These ROIs were particularly chosen for investigating the temporal lobe and related areas in patients who represented a

clinical presentation of TLE. The FC between homologous ROIs were analysed because these iPPs were suggested to be related to bilateral epileptogenic activity (Steinhoff *et al*., 1995; Schulz *et al*., 2000; Sirin *et al*., 2013).

In the denoising step, signal was bandpass filtered between 0.01 and 0.1 Hz and the effects of the white matter, cerebrospinal fluid, rest condition, and the six head motion parameters obtained from spatial motion correction were used as confounds to remove the potential sources of noise.

After the denoising step, the time series of voxels within each ROI were averaged, and the average time series were correlated with those of the homologous ROI in the contralateral hemisphere. The resulting correlation coefficients were Fisher z-transformed to obtain normal distribution.

Statistical analysis

Demographic and clinical data were compared using non-parametric tests. For statistical testing of fMRI data, individual ROI-to-ROI z-values of the HC and patient groups were compared using three one-way multivariate analysis of variance (MANOVA) designs with SPSS software (21.0. Armonk, NY: IBM). In the first design, all FC in patients with TLE between homologous temporal lobe structures was compared with that of healthy controls. To overcome the statistical power problems due to the limited size of the iPP-TLE and non-iPP TLE groups, we tested the effect of ictal propagation pattern on patients with right or left ictal seizure onset separately. For this purpose, analysis based on second and third MANOVA designs was performed to reveal the significance of the FC differences among the HC, iPP-TLE, and non-iPP TLE groups independent of the EEG seizure onset side, and among the HC group and patients with left or right ictal seizure onset independent of the ictal scalp EEG propagation pattern. In this way, the gross effects of the iPP and the ictal discharge initiation side were handled using two separate MANOVA designs. For the second and third MANOVA designs, any significant multivariate group effect was detailed by ANOVA contrasts between pairs of groups. The ethics committee of Istanbul University and Istanbul Faculty of Medicine approved this study and all subjects provided written informed consent.

Results

There was no significant age difference among the HCs, and iPP-TLE and non-iPP TLE groups (*table 1*). Additionally, age at disease onset and seizure frequency did not differ significantly between the two patient groups, but disease duration was significantly longer in patients with iPP-TLE than in those with non-iPP TLE (*table 1*). Among the patients with iPP-TLE, six had right and six had left-sided seizure onset according to ictal scalp EEG patterns observed at onset, whereas in the non-iPP TLE group, seven had left-sided and six had right-sided seizure onset. The interictal and ictal electrophysiological and anatomical neuroimaging features of the patient groups are summarized in *table 2*. Within the iPP-TLE group, 10 of 12 patients showed only 'switch-of lateralization' as the propagation pattern and two of 12 patients had 'bilateral asynchrony' on ictal scalp EEG. None of the patients had both of these iPPs on their recordings.

In the first step, the resting-state FC values of all patients with TLE were compared with those of the HCs. The group means of z-transformed correlation coefficients were positive for all ROI pairs. The MANOVA test between the HCs and patients with TLE revealed a statistically significant overall difference ($F(6,31)= 5.45$, $p=0.001$; Wilk's $\Lambda=0.49$, partial $\eta^2=0.51$); patients showed reduced FC compared with the HCs. Univariate comparisons revealed that the FC of the

Table 1. Demographic and clinical features of patients and healthy controls.

	iPP-TLE*n* = 13	**Non-iPP TLE*n* = 12**	**HC *n* = 13**	**Stats**
Age (years)	33.4±8.8	34.6±7.2	35.2±6.6	$\chi^2=0.285$ $p=0.867$
Disease duration (years)	15.2±11	25.2±9.4	–	U=31 $p=0.011$
Age at disease onset (years)	20.7±11	13.5±8.8	–	U=46.5 $p=0.086$
Seizure frequency (number per month)	9.2±9.3	3.2±1.9	–	U=47.5 $p=0.094$

TLE: temporal lobe epilepsy; iPP: ictal scalp propagation patterns; HC: healthy controls.

Table 2. Electrophysiological and anatomical imaging features of the patients with TLE.

	iPP-TLE *n* = 12	Non-iPP TLE *n* = 13
Interictal EEG		
Unilateral	10	11
Bilateral	2	-
Normal	-	2
Ictal EEG onset		
Left	6	7
Right	6	6
Interictal EEG concordant with ictal onset side		
Yes	7	11
No	5*	-
Normal interictal EEG	-	2
Unusual propagation pattern		
Switch-of lateralization	10	-
Bilateral asynchrony	2	-
MRI		
HS	10‡	9
Normal	2	3
Other†	-	1

TLE: temporal lobe epilepsy; iPP: ictal scalp EEG propagation patterns; HS: hippocampal sclerosis. *Two patients had bilateral interictal discharges and three patients had contralateral interictal discharges to the seizure onset side. †Patient had right temporal glioma. ‡Three patients had bilateral hippocampal sclerosis.

patients with TLE was significantly reduced between the right and left insulae ($F(1,36)=7.37$, $p=0.01$), parahippocampal gyri ($F(1,36)=21.31$, $p<0.001$), and superior temporal gyri ($F(1,36)=9.7$, $p=0.004$) (*figure 4A*).

The second MANOVA design, for which the differences of FC among the HCs and iPP-TLE and non-iPP TLE groups were analysed, also revealed an overall significant group effect ($F(12,60)=3.09$, $p=0.002$; Wilk's $\Lambda=0.38$, partial $\eta 2=0.38$). All correlations between homologous ROIs were positive for all of the three groups. ANOVA contrasts revealed that patients with non-iPP TLE displayed a lower FC between the homologous parahippocampal gyri ($p=0.001$) and superior temporal gyri ($p=0.042$) compared with the HCs (*figure 4B*), whereas the patients with iPP-TLE had lower FC between the homologous insulae ($p=0.001$), homologous parahippocampal gyri ($p<0.001$), and homologous superior temporal gyri ($p=0.002$) compared with the HCs (*figure 4C*). Furthermore, the comparison between the patients with iPP-TLE and non-iPP TLE showed a decrease of FC between the bilateral insulae in patients with iPP-TLE, but the difference was at a trend level ($p=0.053$) (*figure 4D*).

The third MANOVA design for HCs and patients with TLE with left or right-sided seizure onset (independent of the propagation pattern) also revealed a significant group effect ($F(12,60)=2.4$, $p=0.013$; Wilk's $\Lambda=0.46$, partial $\eta 2=0.32$). The ANOVA contrasts showed that the patients with TLE with both left and right-sided seizure onset displayed reduced FCs between homologous insulae (left: $p=0.046$, right: $p=0.014$), parahippocampal gyri (both $p<0.001$), and the superior temporal gyri (left: $p=0.008$, right: $p=0.019$), and patients with left-sided TLE further displayed reduced FC between the homologous middle temporal gyri ($p=0.029$).

Discussion

Our results reveal significantly reduced FC between homologous temporal lobes and related areas; i) in all patients with TLE compared with HCs, ii) in patients with non-iPP TLE compared with HCs, and iii) in patients with iPP-TLE compared with HCs. Additionally, patients with iPP-TLE displayed reduced FC between homologous insulae compared with patients with non-iPP TLE, however, the difference was not significant. This pattern of insular involvement is further supported by the fact that the FC between the left and right insulae was significantly reduced in patients with iPP-TLE compared with HCs, while such difference was absent in the non-iPP vs. HC comparison.

FC in TLE

Previous resting-state fMRI studies on patients with TLE showed reduced FC within the temporal lobe ipsilateral to the seizure onset, accompanied by enhanced FC within the temporal lobe, contralateral to the seizure onset (Bettus *et al.*, 2009; Bettus *et al.*, 2010; Pereira *et al.*, 2010; Morgan *et al.*, 2012; Maccotta *et al.*, 2013; Haneef *et al.*, 2015). However, analyses of FC between homologous temporal lobe and limbic areas showed controversial results in patients with TLE. Although a larger group of studies on patients with mesial TLE revealed reduced FC between homologous hippocampi and the temporal lobes (Pereira *et al.*, 2010; Pittau *et al.*, 2012; Maccotta *et al.*, 2013; Morgan *et al.*, 2015), there were a few other studies that demonstrated increased FC between the homologous temporal lobe and limbic areas in TLE (Haneef *et al.*, 2014; Maneshi *et al.*, 2014). Another study claimed that longer disease duration, specifically more than 10 years, was associated with increased FC between bilateral hippocampi (Morgan *et al.*, 2011). In short, the fMRI-based FC studies in TLE generally point to a reduced connectivity between the two hemispheres,

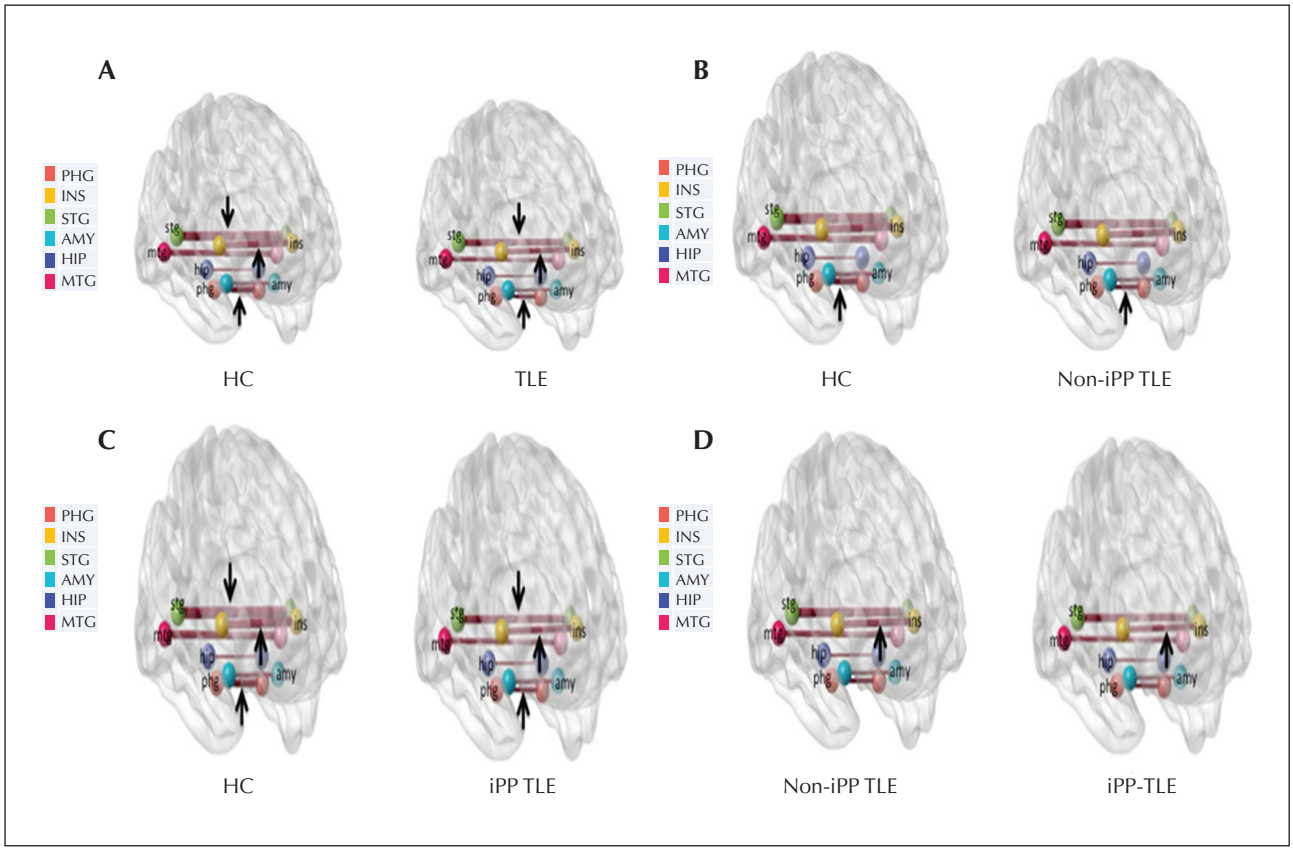

Figure 4. (A-D) Seed-based correlation maps between homologous areas. (A) Comparison between patients with temporal lobe epilepsy (TLE) and healthy controls (HCs); (B) Comparison between patients showing unilateral lateralized ictal discharges (non-iPP TLE) and HCs. (C) Comparison between patients with TLE showing unusual ictal propagation patterns (iPP-TLE) and HCs. (D) Comparison between patients with non-iPP TLE and iPP-TLE.

as in our results, but there are also controversial results suggesting increased inter-hemispheric connectivity.

FC in TLE with varying electrophysiological ictal propagation

The main goals of our study were to reiterate the interhemispheric connectivity changes in TLE, but additionally, by stratifying patients with TLE in terms of the presence of iPP, to clarify whether this electrophysiological pattern relies on a specific inter-hemispheric difference in FC during the interictal stage. It may be suggested that these atypical and rare patterns of seizure propagation are generated at one side and spread to contralateral hemisphere electrodes, previously defined as a 'mirror focus' (Gupta *et al.*, 1973; Morrell, 1985), or arise from two independent epileptogenic foci in homologous areas of temporal lobes (Janszky *et al.*, 2005). According to the above description of iPP and the two contrasting hypotheses regarding its development, fMRI-based interhemispheric FC differences between the iPP and non-iPP groups provided important information about the inter-hemispheric interactions in TLE. The consistent finding in our study is reduced FC between homologous areas in the temporal lobe in patients with TLE regardless of ictal propagation patterns compared with HCs. Although the exact mechanism for this decreased FC is obscure, a protective mechanism for the non-epileptic temporal lobe was suggested in previous studies (Pereira *et al.*, 2010; Maccotta *et al.*, 2013; Morgan *et al.*, 2015). According to the hypothesis of reduced FC, which is a result of protection of the contralateral temporal lobe in TLE, bilateral epileptogenic foci in temporal lobes should cause a more pronounced loss in FC between homologous areas compared with those in a unilateral epileptogenic focus. However, in the present study, there was no significant difference in connectivity between homologous temporal lobes in TLE with or without iPP. This finding could be explained in two ways. Firstly, iPP is not related to 'bilateral independent' epileptogenic foci. The fact that this was reported by other studies revealing good postsurgical outcomes in some of these patients with iPP further supports the lack of two foci (Steinhoff *et al.*, 1995; Sirin *et al.*, 2018). Secondly,

reduced FC might not reflect a mechanism related to protection of the contralateral temporal lobe, but rather a destruction by the disease process *per se*. It is also tempting to speculate that the patterns of connectivity of the epileptogenic brain could be entirely different from healthy subjects.

The reduced FC, at a non-statistically significant level, in homologous insulae of patients with iPP-TLE compared with patients with non-iPP TLE demonstrates the importance of the insula, which is not part of the temporale lobe, but is anatomically close to and has strong functional connections with temporal lobe structures, especially with the amygdala (Gloor, 1997). In insular epilepsy, ictal and interictal activity could be restricted to temporal lobe electrodes on scalp recordings, indicating a close relationship (Freri *et al.*, 2017; Levy *et al.*, 2017; Obaid *et al.*, 2017). Increased FC was reported between the insula and temporal lobe structures (hippocampus and superior, middle and inferior temporal gyri), ipsilateral to the seizure focus, in a well-designed study of patients with TLE (Maccotta *et al.*, 2013). All these different findings indicate that the insula plays an important role in the pathophysiology of TLE. Thus, considering it as a hub within the TLE network, reduced FC between the two insulae might be one of the determinants for the unusual propagation of ictal discharges to the contralateral hemisphere.

In one study focusing on interictal EEG findings and FC in patients with TLE, Tracy *et al*. reported increased anti-connectivity between the temporal lobes in patients with TLE who had unilateral interictal epileptiform discharges, compared with HCs. Intriguingly, however, patients with bilateral interictal epileptiform discharges did not show this anti-connectivity, which was interpreted as lack of a protective mechanism by the authors (Tracy *et al.*, 2014). There are currently no data on the FC of ictal propagation patterns. Remarkably, our study is unique in investigating the FC patterns of patients with these rare but important ictal scalp EEG propagation patterns, to understand their clinical value and related mechanisms.

Connectivity analysis among patients with right and left-sided TLE

The connectivity analysis of our patients with TLE with right-sided seizure onset showed reduced FC between homologous parahippocampal gyri, insulae, and superior temporal gyri. Patients with TLE with left-sided seizure onset showed reduced FC between the same homologous structures as well as middle temporal gyri. This finding is consistent with previous studies that showed more noticeable connectivity changes between homologous temporal lobes in left-sided TLE for still unknown reasons (Pereira *et al.*, 2010; Maneshi *et al.*, 2014; Haneef *et al.*, 2015).

Limitations

Patients with iPP had a longer duration of epilepsy than the non-iPP TLE control group. The reason for this unexpected difference may relate to the fact that patients with iPP are known to have poor surgical outcomes (Steinhoff *et al.*, 1995; Schulz *et al.*, 2000), which restricts their access to early surgery, leading to prolonged disease duration for these rare cases. However, our control TLE group without iPP tended to undergo epilepsy surgery within a short time. Therefore, we could not exclude the effect of epilepsy duration on our groups. Previous studies showed that patients with a longer duration of epilepsy might have reduced connectivity regardless of the side (Haneef *et al.*, 2014; Morgan *et al.*, 2015; Chiang *et al.*, 2015).

Within the iPP-TLE group, we were unable to analyse patients showing 'switch-of lateralization' and 'bilateral asynchrony' separately because of the small number of patients in each group (two patients with 'bilateral asynchrony' and 10 patients with 'switch-of lateralization'). Although these patterns were previously suggested to be related to bilateral independent ictal activity (Steinhoff *et al.*, 1995; Schulz *et al.*, 2000; Sirin *et al.*, 2013), the underlying mechanism might be different for each.

Another possible limitation of our study is that subgroup analysis could not be performed among patients with TLE with right and left-seizure onset with different iPPs due to the low number of patients. In the present study, ROIs were defined as the related areas of temporal lobes using an automated atlas. Unfortunately, most of our patients had neither intracranial monitoring nor a seizure-free period after epilepsy surgery in order to be able to clearly determine the epileptogenic zone.

Conclusion

Our findings further emphasize that FC is reduced between homologous temporal lobes in patients with TLE compared with HCs. Moreover, different ictal scalp EEG propagation patterns, such as switch-of lateralization and bilateral asynchrony might be related to decreased FC between homologous insulae, playing a possible role in the pathophysiology of these unusual patterns. □

Acknowledgements and disclosures.
This project was supported by the Turkish Ministry of Development, project #2010K120330 and by the Scientific Research Projects Unit of Istanbul University, project #21336.
None of the authors have any conflict of interest to declare.

References

Bettus G, Bartolomei F, Confort-Gouny S, *et al*. Role of resting state functional connectivity MRI in presurgical investigation of mesial temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2010; 81(10): 1147-54.

Bettus G, Guedj E, Joyeux F, *et al*. Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. *Hum Brain Mapp* 2009; 30(5): 1580-91.

Chiang S, Stern JM, Engel Jr. J, Haneef Z. Structural-functional coupling changes in temporal lobe epilepsy. *Brain Res* 2015: 161645-57.

Freri E, Matricardi S, Gozzo F, Cossu M, Granata T, Tassi L. Perisylvian, including insular, childhood epilepsy: Presurgical workup and surgical outcome. *Epilepsia* 2017; 58(8): 1360-9.

Gloor P. *The Temporal Lobe and Limbic System*. New York: Oxford University Press, 1997.

Gupta PC, Dharampaul PC, Pathak SN, Singh B. Secondary epileptogenic EEG focus in temporal lobe epilepsy. *Epilepsia* 1973; 14(4): 423-6.

Haneef Z, Chiang S, Yeh HJ, Engel Jr. J, Stern JM. Functional connectivity homogeneity correlates with duration of temporal lobe epilepsy. *Epilepsy Behav* 2015: 46227-33.

Haneef Z, Lenartowicz A, Yeh HJ, Levin HS, Engel Jr. J, Stern JM. Functional connectivity of hippocampal networks in temporal lobe epilepsy. *Epilepsia* 2014; 55(1): 137-45.

Janszky J, Janszky I, Schulz R, *et al*. Temporal lobe epilepsy with hippocampal sclerosis: predictors for long-term surgical outcome. *Brain* 2005; 128(2): 395-404.

Ji GJ, Zhang Z, Zhang H, *et al*. Disrupted causal connectivity in mesial temporal lobe epilepsy. *PLoS One* 2013; 8(5): e63183.

Kang SY, Lee SA, Yim SB, Lim YM, Kang JK, Lee JK. Factors contributing to clinical seizure lateralization in patients with mesial temporal lobe epilepsy. *Eur Neurol* 2005; 54(4): 191-8.

Lee SA, Yim SB, Lim YM, Kang JK, Lee JK. Factors predicting seizure outcome of anterior temporal lobectomy for patients with mesial temporal sclerosis. *Seizure* 2006; 15(6): 397-404.

Levy A, Yen Tran TP, Boucher O, Bouthillier A, Nguyen DK. Operculo-insular epilepsy: scalp and intracranial electroencephalographic findings. *J Clin Neurophysiol* 2017; 34(5): 438-47.

Maccotta L, He BJ, Snyder AZ, *et al*. Impaired and facilitated functional networks in temporal lobe epilepsy. *Neuroimage Clin* 2013: 2862-72.

Maneshi M, Vahdat S, Fahoum F, Grova C, Gotman J. Specific resting-state brain networks in mesial temporal lobe epilepsy. *Front Neurol* 2014: 5127.

Morgan VL, Conrad BN, Abou-Khalil B, Rogers BP, Kang H. Increasing structural atrophy and functional isolation of the temporal lobe with duration of disease in temporal lobe epilepsy. *Epilepsy Res* 2015: 110171-8.

Morgan VL, Gore JC, Abou-Khalil B. Functional epileptic network in left mesial temporal lobe epilepsy detected using resting fMRI. *Epilepsy Res* 2010; 88(2-3): 168-78.

Morgan VL, Rogers BP, Sonmezturk HH, Gore JC, Abou-Khalil B. Cross hippocampal influence in mesial temporal lobe epilepsy measured with high temporal resolution functional magnetic resonance imaging. *Epilepsia* 2011; 52(9): 1741-9.

Morgan VL, Sonmezturk HH, Gore JC, Abou-Khalil B. Lateralization of temporal lobe epilepsy using resting functional magnetic resonance imaging connectivity of hippocampal networks. *Epilepsia* 2012; 53(9): 1628-35.

Morrell F. Secondary epileptogenesis in man. *Arch Neurol* 1985; 42(4): 318-35.

Napolitano CE, Orriols M. Two types of remote propagation in mesial temporal epilepsy: analysis with scalp ictal EEG. *J Clin Neurophysiol* 2008; 25(2): 69-76.

Napolitano CE, Orriols MA. Graduated and sequential propagation in mesial temporal epilepsy: analysis with scalp ictal EEG. *J Clin Neurophysiol* 2010; 27(4): 285-91.

Obaid S, Zerouali Y, Nguyen DK. Insular epilepsy: semiology and noninvasive investigations. *J Clin Neurophysiol* 2017; 34(4): 315-23.

Pereira FR, Alessio A, Sercheli MS, *et al*. Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: evidence from resting state fMRI. *BMC Neurosci* 2010: 1166.

Pittau F, Grova C, Moeller F, Dubeau F, Gotman J. Patterns of altered functional connectivity in mesial temporal lobe epilepsy. *Epilepsia* 2012; 53(6): 1013-23.

Schulz R, Luders HO, Hoppe M, Tuxhorn I, May T, Ebner A. Interictal EEG and ictal scalp EEG propagation are highly predictive of surgical outcome in mesial temporal lobe epilepsy. *Epilepsia* 2000; 41(5): 564-70.

Sirin NG, Gurses C, Bebek N, Dirican A, Baykan B, Gokyigit A. A quadruple examination of ictal EEG patterns in mesial temporal lobe epilepsy with hippocampal sclerosis: onset, propagation, later significant pattern, and termination. *J Clin Neurophysiol* 2013; 30(4): 329-38.

Sirin NG, Yilmaz E, Bebek N, Baykan B, Gokyigit A, Gurses C. Unusual ictal propagation patterns suggesting poor prognosis after temporal lobe epilepsy surgery: Switch of lateralization and bilateral asynchrony. *Epilepsy Behav* 2018: 8631-6.

Steinhoff BJ, So NK, Lim S, Luders HO. Ictal scalp EEG in temporal lobe epilepsy with unitemporal versus bitemporal interictal epileptiform discharges. *Neurology* 1995; 45(5): 889-96.

Su L, An J, Ma Q, Qiu S, Hu D. Influence of resting-state network on lateralization of functional connectivity in mesial temporal lobe epilepsy. *AJNR Am J Neuroradiol* 2015; 36(8): 1479-87.

Tracy JI, Osipowicz K, Spechler P, *et al*. Functional connectivity evidence of cortico-cortico inhibition in temporal lobe epilepsy. *Hum Brain Mapp* 2014; 35(1): 353-66.

TEST YOURSELF

(1) What are the electrophysiological characteristics of switch-of lateralization and bilateral asynchrony?

(2) What information does resting-state functional connectivity provide in patients with epilepsy?

(3) What are the main alterations in functional connectivity between homologous temporal lobes in patients with TLE?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".