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Inter-ictal network of focal epilepsy and effects of clinical factors on network activity

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HIGHLIGHTS

- Inter-ictal EEG functional connectivity in focal epilepsy differs from that of healthy persons.
- Abnormal functional EEG connectivity (EEGfC) selectively occurs in narrow EEG frequency bands.
- EEGfC is influenced by etiology, seizure type, duration of illness and treatment.

ABSTRACT

Objective: Aim of the study was to explore the inter-ictal, resting-state EEG network in patients with focal epilepsy (FE) and to specify clinical factors that influence network activity.
Methods: Functional EEG connectivity (EEGfC) differences were computed between 232 FE patients (FE group) and 77 healthy controls. EEGfC was computed among 23 cortical regions within each hemisphere, for 25 very narrow bands from 1 to 25 Hz. We computed independent effects for six clinical factors on EEGfC in the FE group, by ANOVA and post-hoc *t*-statistics, corrected for multiple comparisons by false discovery rate method.
Results: Robust, statistically significant EEGfC differences emerged between the FE and the healthy control groups. Etiology, seizure type, duration of the illness and antiepileptic treatment were independent factors that influenced EEGfC. Statistically significant results occurred selectively in one or a few very narrow bands and outlined networks. Most abnormal EEGfC findings occurred at frequencies that mediate integrative and motor activities.
Conclusions: FE patients have abnormal resting-state EEGfC network activity. Clinical factors significantly modify EEGfC.
Significance: Delineation of the FE network and modifying factors can open the way for targeted investigations and introduction of EEGfC into epilepsy research and practice.

1. Introduction

Extremely dense structural connectivity of the human brain is the anatomical basis of neuronal network activity (Sporns et al., 2005). Recently developed methods of analysis allow exploration of network activities in many cerebral disorders including epilepsy. Investigators often label epilepsies as "network disorders" albeit meaning of the term varies across authors and articles. It was suggested that preferred neuronal paths of ictal spread and topography of inter-ictal dysfunction delineate the so-called epileptic network (Spencer, 2002). In other words, the "epileptic network" refers to parts of the total cerebral network that work abnormally because they are in some way related to the epileptic process. Concepts, methods and main results of network studies in epilepsy have been summarized in recent works (Engel et al., 2013; Centeno and Carmichael, 2014; Yaffe et al., 2015; Gleichgerrcht

Abbreviations: AE, antiepileptic drug; EEGfC, EEG functional connectivity; FE, focal epilepsy; ILAE, International League Against Epilepsy; LORETA, Low Resolution Electromagnetic Tomography; LSC, LORETA Source Correlation; NAE, without antiepileptic drug; PS, partial seizure; PSSG, partial and secondary generalized seizure; ROI, region of interest; SG, secondary generalized seizure; SPN, statistical parametric network.

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et al., 2015) while other reviews discuss fundamentals of connectivity and network analysis (Friston, 2011). Network activity in focal epilepsies (FE) is particularly interesting because the network concept overcomes several shortcomings of the classic FE concept. Essence of the new concept is that widespread epileptic network activity, not the circumscribed epileptic focus, is responsible for ictal and inter-ictal epileptic dysfunction (Spencer, 2002). A useful method to analyze network activity is computing EEG functional connectivity (EEGfC) between cortical areas. Prior studies disclosed global EEGfC differences between FE patients and healthy controls (Horstmann et al., 2010; Vecchio et al., 2015). Abnormal EEGfC is consequence of widespread structural abnormality that extends far beyond the so-called epileptic focus (Riederer et al., 2008). Impaired structural integrity of cerebral white matter is particularly important in this respect because it is the anatomical substrate of EEGfC (Chu et al., 2015; Nunez et al., 2015). A few EEGfC studies suggested that EEGfC findings might have relevance for research and clinical practice as well. Network analysis can help to understand neurophysiology of ictal and interictal states (Kramer and Cash, 2012; Iannotti et al., 2016). EEGfC analysis might contribute to epilepsy diagnosis (Douw et al., 2010). Analysis of magnetoencephalography-based functional connectivity shed light on evolution of cognitive dysfunction in FE (Ibrahim et al., 2014). Antiepileptic drug treatment results in seizure freedom and parallel network normalization in generalized epilepsy (Clemens et al., 2014), and similar clinical-EEGfC relationship might exist in FE as well. Unfortunately, research results are not applicable to clinical practice at present. Clinical variables (etiology of epilepsy, duration of the illness and antiepileptic treatment) presumably modify EEGfC (Douw et al., 2010; Horstmann et al., 2010). Unknown effect of these factors on EEGfC hinders correct interpretation of the findings and blurs the clinical perspective. Aim of this study was to investigate impact of the above-mentioned clinical factors on resting-state EEGfC in a large cohort of FE patients.

2. Patients and methods

2.1. The "Epi-Stat" database

Epi-Stat is structured database that contains all the available clinical, EEG and neuroimaging data of the patients with epilepsy referred to Kenézy Gyula University Hospital Department of Neurology, a first referral center for epilepsy patients in Hajdú-Bihar county of Hungary. As a rule, general practitioners refer all epilepsy patients to a neurologist in Hungary. Composition of the database therefore roughly reflects that of the general epilepsy population, except for patients with early childhood epilepsies. The sample is somewhat skewed by moderate over-representation of severe epilepsy patients who came from other localities for consultation and treatment. Epilepsy expert neurologists enter the data into Epi-Stat. The EEG laboratory and the EEG readers are board-certified.

2.2. Patient selection

We retrieved data of FE patients from "Epi-Stat". This means that we based this investigation on already pooled data, the results of routine clinical and EEG investigations of epilepsy patients. Research Ethics Committee of Kenézy Gyula University Hospital approved the study protocol. Personal identifiers were hidden; patients were identified by serial number.

All cryptogenic and symptomatic FE patients evaluated after the 4th year of life, between 2008 and 2016, were potentially eligible for the study. We defined FE according to the International Classification (ILAE, 1989). Patients with idiopathic focal epilepsy of childhood, non-classifiable epilepsy and special syndromes (ILAE, 1989) were not included. The senior author reviewed clinical files and digitally stored EEG records of the potentially available patients and excluded patients who had (i) incomplete medical documentation, (ii) metabolic disorder, neurological and psychiatric comorbidity and medication that can modify the clinical picture of epilepsy and/or EEG activity (Sannita, 2006). We excluded patients with low voltage EEG and poor quality EEG record.

2.3. Composition of the sample, patient groups

The total sample contained 232 patients, 96 males and 136 females. Age range and median age of the patients at EEG investigation were 5–93 and 31 years, respectively. There was convincing evidence of a single, left or right hemispheric seizure onset in 47 and 37 patients, respectively. The remaining patients had uncertain laterality of seizure onset or presented with multiple foci.

We investigated the influence of six factors on EEGfC. Definition and corresponding patient groups were as follows.

"Etiology": patients were classified as cryptogenic (n = 104) or symptomatic (n = 128), according to the ILAE Classification (ILAE, 1989).
"Family": patients with or without seizure disorder in the family were labelled as "family positive" (n = 50) or family negative (n = 182), respectively.
"Onset": we defined onset as age of the patient at the first seizure. Patients were classified as having epilepsy onset between the 1–10 years of life (A1 group, n = 61), between 11–20 years (A2 group, n = 83), and between 21–100 years (A3 group, n = 88).
"Seizure": patients with exclusively partial seizures (PS group, n = 98), patients with partial and secondary generalized seizures (PSSG group, n = 74), patients with exclusively secondary generalized seizures (SG group, n = 60) were distinguished, according to the ILAE seizure classification (ILAE, 1981).
"Duration": we defined duration as number of years that elapsed between the first seizure and the EEG record analyzed in this study. Patients were classified as having disease duration of <1 year (D1 group, n = 62), 1–10 years (D2 group, n = 54), 11–20 years (D3 group, n = 54) and >20 years (D4 group, n = 62).
"Treatment": patients with new-onset epilepsy who did not receive drug treatment so far composed the NAE group (n = 80). Patients who were investigated later in the course of the illness and were treated with appropriately selected drugs composed the AE group (n = 152). Most patients were on carbamazepine monotherapy, fewer patients received so-called newer generation antiepileptic drugs or combination of two anticonvulsive compounds.

In addition, we investigated 77 healthy control persons. We recruited them from the medical staff, friends and their relatives. They had no neurological items in medical history and did not take medication except contraceptive pills in some women. We recorded and analyzed EEG in the same way as in the patients. Quantitative EEG variables are independent of race and geography (John et al., 1983), therefore one can compare patient data to normative quantitative EEG databases developed in other countries. However, little differences in electrographic definition of the waking state (Bente, 1979) and body position at EEG investigation can modify the EEG spectrum (Spironelli et al., 2016). Therefore, comparison of the FE and healthy control groups increased reliability of the findings.

2.4. EEG recording and epoch selection

In Sections 2.4–2.6 we describe recording and analysis methods that were used by our research group and were described several times as follows. 'We recorded EEG in a semi-isolated room, with

the same digital EEG equipment. Silver-silver chloride electrodes were placed according to the 10–20 System, fixed by appropriate adhesive and conductive gel. Impedances did not exceed 10 k Ohms. 30–40 min of 19-channel EEG was recorded in the eyes-closed, waking-relaxed state from standard scalp sites and the earlobes against Fpz sampling reference. Thereafter we recomputed EEG against a mathematical linked ears reference. Filters were set at 0.1 and 33.6 Hz, sampling rate was 256 per second, on-line digitization was 12 bit. Thereafter we selected the "best" 90 epochs (each 2 s, a total of 3 min EEG) for quantitative analysis by means of the NeuroGuide software Version 2.8. (www.applied-neuroscience.com). Our standard epoch selection protocol included: (1) presence of continuous physiological alpha activity with voltage maximum in posterior regions, (2) absence of artifacts, epileptiform potentials and other non-stationary elements, (3) absence of patterns indicating drowsiness or arousal. This electrographic definition of the relaxed-waking state refers to a narrow window of vigilance level (Bente, 1979). We used two reproducibility measures to minimize the effect of short- and long-term variability within the samples. Each sample showed at least 90 percent split-half and test-retest reliability (calculated as the average of the 19 channels). The senior author reviewed the selected epochs. NeuroGuide allowed transmission of the samples to the Low Resolution Electromagnetic Tomography (LORETA) and LORETA Source Correlation (LSC) software' (Clemens 2008; Clemens et al., 2013, 2014, 2016; Dömötör et al., 2017a,b).

2.5. LORETA analysis

'LORETA is a widely used method to localize multiple distributed cortical sources of EEG activity in the three-dimensional space (Pascual-Marqui et al., 1994). In other words, LORETA demonstrates synchronously activated EEG generators by computing their cortical localization from the scalp distribution of the electric field. The LORETA inverse solution is based on existing neuroanatomical and physiological knowledge and a mathematical constraint called smoothness assumption. The cortical grey matter compartment (including the hippocampi) was subdivided into 2394 voxels. LORETA computes current source density (amperes/meters squared) for each voxel. Three-dimensional position of the voxels is given according to Talairach coordinates (Talairach and Tournoux, 1988). Several authors validated the consistency of LORETA with physiology and localization in physiological and pathological conditions as summarized in (Pascual-Marqui et al., 2002). Comprehensive evaluation of the method is available in (Pascual-Marqui, 2009)' (Clemens et al., 2013, 2014, 2016; Dömötör et al., 2017a,b).

2.6. Analysis of resting-state EEG functional connectivity

'Correlating activity of localized sources is a useful alternative to correlate quantitative EEG variables measured at scalp electrodes and offers a deeper understanding of intra-hemispheric cortico-cortical connectivity (Thatcher et al., 2007a; Schoffelen and Gross, 2009). LSC analysis means computing the temporal covariance or correlation of LORETA-defined current source density time series between two cortical areas (region of interest, ROI), across successive 2-seconds epochs over the investigated sample. Pearson product correlation coefficient ("r") is a valid measure of EEGfC, in other words, oscillator coupling" (Thatcher et al., 2007a). Authors who compared the sensitivity and reliability of several methods concluded that Pearson correlation is a robust method being sensitive to all the investigated coupling parameters and does not depend on the model (Wendling et al., 2009). (Clemens et al., 2013, 2014, 2016; Dömötör et al., 2017a,b).

We computed "r" for very narrow bands of 1 Hz bandwidth from 1 to 25 Hz. Nearby voxels were clustered into 23 ROIs in each hemisphere (Table 1). Using only 46 ROIs compensates for potential localization error of LORETA with 19–21 electrodes as calculated by (Thatcher et al., 2007b). Number of electrodes, number and location of the ROIs are fixed in Z-statistics of the LORETA software and database (Thatcher et al., 2005) and cannot be changed by users. Some ROIs do not correspond to standard anatomical nomenclature; anatomical location of them is given in (Thatcher et al., 2007b). "r" values were generated between each ROI and all the other ROIs in the same hemisphere. This meant $[(23 \times 23) - 23]$ "r" values for one hemisphere and one very narrow band. Raw "r" values were adjusted for age and were Z-transformed according to the LSC Normative Database (Thatcher et al., 2005) that is part of NeuroGuide software package. Correction for age and Z-statistics were necessary to overcome age-dependence of quantitative EEG variables. So, each "r" value indicated the distance of that value from Z = 0, the normative mean of the corresponding age group. Positive and negative Z-values indicated increased and decreased EEGfC, respectively. We graphically demonstrated statistically significant EEGfC values in "glass brain" figures, generated by "BrainCon" software developed at Department of Medical Imaging, University of Debrecen (Spisák et al., 2013).

2.7. Statistical analysis

We computed FE - control group differences by Student's *t*-tests for each connection and very narrow band by the software specified above. Correction for multiple comparisons was carried out by false discovery rate (Benjamini and Hochberg, 1995) and the corrected $p < 0.05$ values were accepted as statistically significant group differences.

In the patient group, the effects of the investigated factors (etiology, family, onset, seizures, duration, and treatment) on EEGfC were analyzed separately by mass (all connections in all very narrow bands) variance analysis (ANOVA) using mixed-effect models. In these models next to the subject-specific random effect, we represented the hemisphere, the band and the investigated factor as fixed effects, which did not vary over subjects. After the ANOVA calculations we used post-hoc Tukey tests to characterize the

Table 1
The 23 ROIs selected for analysis. ROIs are anatomically identical in the two hemispheres.

Anterior Cingulate
Medial Frontal-Subcallosal Gyrus
Superior Frontal Gyrus
Orbital-Rectal Gyrus
Middle Frontal Gyrus
Inferior Frontal-Extra Nuclear Gyrus
Cingulate Gyrus
Insula
Uncus
Pre-Para Central Lobule
Parahippocampal Gyrus
Superior-Transverse Temporal Gyrus
Postcentral Gyrus
Inferior Temporal Gyrus
Middle Temporal-SubGyral Gyrus
Fusiform Gyrus
Posterior Cingulate
Inferior Parietal Lobule
Angular-Super Parietal-Supramarginal Gyrus
Precuneus
Lingual Gyrus
Cuneus
Inferior-Middle-Superior Occipital Gyrus

Table 2
The table summarises the results of the 10-times repeated 10-fold cross-validation procedures. The "R^2 maximum" column shows the R^2 values of the "best" model in the appropriate factor. The "R^2 mean" and "R^2 SD" columns show the mean and standard deviation of 10×10 fold averaged R^2 values both for all and FDR-selected connections.

		All connections		FDR selected connections	
Factor	R^2 maximum	R^2 mean	R^2 SD	R^2 mean	R^2 SD
Etiology	0.206	0.060	0.033	0.071	0.031
Family	0.205	0.056	0.033	0.067	0.031
Onset	0.202	0.054	0.032	0.064	0.031
Seizure	0.208	0.057	0.033	0.072	0.032
Duration	0.203	0.054	0.033	0.065	0.032
Treatment	0.210	0.062	0.033	0.074	0.032

patient group differences by Student-*t* values for all connections of all very narrow bands. Using this procedure, we evaluated 15 statistical parametric networks (SPNs) corresponding to the factor related patient group arrangements and comparisons. We analyzed the effect of etiology, family and treatment parameters by one comparison per parameter (cryptogenic vs. symptomatic, family positive vs. family negative and NAE vs. AE, respectively) according to the group definitions. Because the onset and the seizure parameters divided the investigated population into three groups, we generated three SPNs per parameter for group comparisons: A1 vs. A2, A1 vs. A3 and A2 vs. A3; PS vs. PSSG, PS vs. SG and PSSG vs.SG, respectively. According to the four patient groups defined by the duration parameter, we studied the group differences by six SPNs: D1 vs. D2, D1 vs. D3, D1 vs. D4, D2 vs. D3, D2 vs. D4 and D3 vs. D4.

For delineation the significant group differences in the SPNs we used false discovery rate technique to adjust all *p*-values attached to all Student-*t* values of all SPNs. Using these adjusted *p*-values, we determined a Student-*t* threshold (T0) that emphasized from the SPNs only those differences, which corrected *p*-value was less than 0.05 (T0 = +−4.4).

In the case of all factors, we used 10-times repeated 10-fold cross-validation technique to estimate the accuracy of model fitting of our mixed effect models (Gareth et al., 2013). Because of the vast number of EEGfC values we reported the results of the validation procedure by the maximum, the mean and the standard deviation of the R-square values (Table 2). Mean and standard deviation were calculated twice: once for all connections, then again for only those connections where the false discovery rate-corrected *p*-value of any group difference was less than 0.05.

3. Results

3.1. EEGfC in the total FE sample

We estimated abnormal EEGfC by the number of statistically significant group differences and magnitude of the abnormality expressed by the color-coded *t*-values (Fig. 1). Sporadically occurring EEGfC values did not outline networks, therefore we concentrated on maps that showed at least 10 abnormal connections with the same sign (positive or negative). This number of statistically significant connections separated very narrow bands with rich abnormal connectivity from those with sporadic findings. With this restriction, increased EEGfC emerged in the FE group, in the 3–7 Hz range, with the maximum number of abnormal connections at 6 Hz. The findings delineated a diffuse network that connected ROIs across the cortex, with greater involvement of the anterior than the posterior areas. The network at 6 Hz (at maximum topographical extension) included medial frontal ROIs (anterior cingulate, cingulate gyrus, medial frontal-subcallosal gyri, orbital-rectal gyri, lateral frontal ROIs (middle and superior frontal gyri, inferior frontal-extranuclear), pre-paracentral lobule, insula, medial and lateral temporal ROIs (uncus, parahippocampal gyrus, superior-transverse temporal gyrus, inferior temporal and medial temporal-subgyral gyri), parietal ROIs (postcentral and angular-super parietal-supramarginal gyri, inferior parietal lobule). In contrast to the above-mentioned, densely connected ROIs, medial parietal and occipital ROIs (posterior cingulated, precuneus, lingual gyrus, cuneus) and the lateral occipital and fusiform gyri had a few or no abnormal connections with ROIs in frontal and temporal cortices.

The posterior network of decreased connectivity emerged at 11 Hz and was composed of ROIs that corresponded to the cuneus, lateral temporal cortex and lateral parietal (angular-supramarginal) cortex. The findings showed considerable difference between the hemispheres.

3.2. Influence of clinical factors on EEGfC

Post-hoc tests showed that four factors had statistically demonstrable effect on EEGfC as follows. The ten-fold cross-validation technique showed that the used statistical model was accurate on EEGfC values that were associated with the investigated factors (Table 2).

3.2.1. Etiology

Symptomatic epilepsies showed less EEGfC than cryptogenic epilepsies in the 10–15 Hz range. The difference appeared as network effect at 11–13 Hz, between medial frontal, temporal and parietal areas in both hemispheres. EEGfC in prefrontal and occipital areas did not differ between the two FE groups (Fig. 2, left panel).

3.2.2. Seizure

Greater EEGfC emerged in the SG group than in the PS and PSSG groups at 10 and 11 Hz. Bilateral, frontal, central, temporal and anterior parietal areas were involved. The figure demonstrates the SG-PS difference (Fig. 2, right panel). Topographically very similar findings emerged in the SG-PSSG comparison.

3.2.3. Duration

Comparison of the four groups showed that EEGfC at 6–7 Hz increased with increasing duration of epilepsy, particularly after 10 years of duration. Maximal difference emerged between the D4 and D1 groups at 6–7 Hz in frontal, central and parietal areas. Occipital EEGfC did not significantly change as a function of duration. EEGfC decreased as a function of duration in the D4-D1 comparison at 11–18 Hz, but network effect emerged at 12 Hz only, in the left hemisphere (Fig. 3, left panel).

3.2.4. Treatment

The untreated group showed less EEGfC at 5–7 Hz (maximum at 6 Hz) as compared to the treated group. The network effect was marked and occurred in all cortical areas. On the contrary, more EEGfC emerged in the untreated group compared to the treated group at 11 Hz in the left hemisphere and at 20 Hz bilaterally (Fig. 3, right panel).

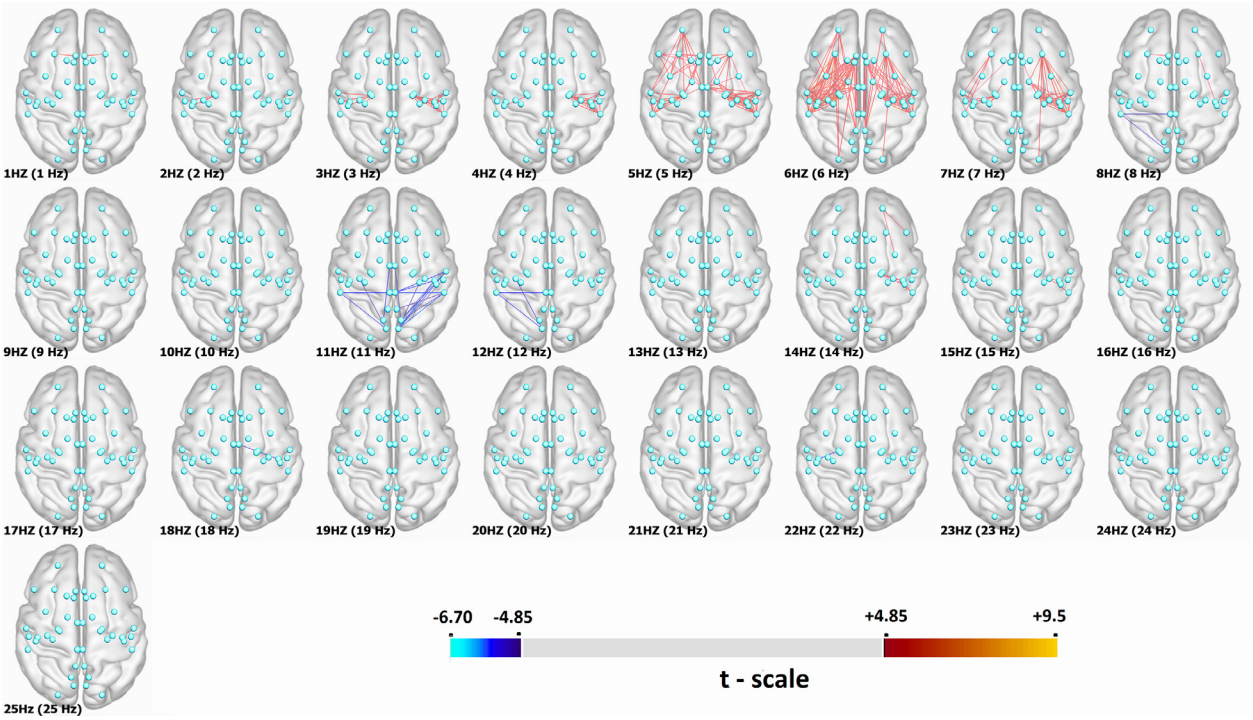

Fig. 1. Increased EEGfC (brown-yellow connections) and decreased EEGfC (blue connections) in the FE group as compared to the healthy control group. Right side of the glass brain corresponds to the right hemisphere. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

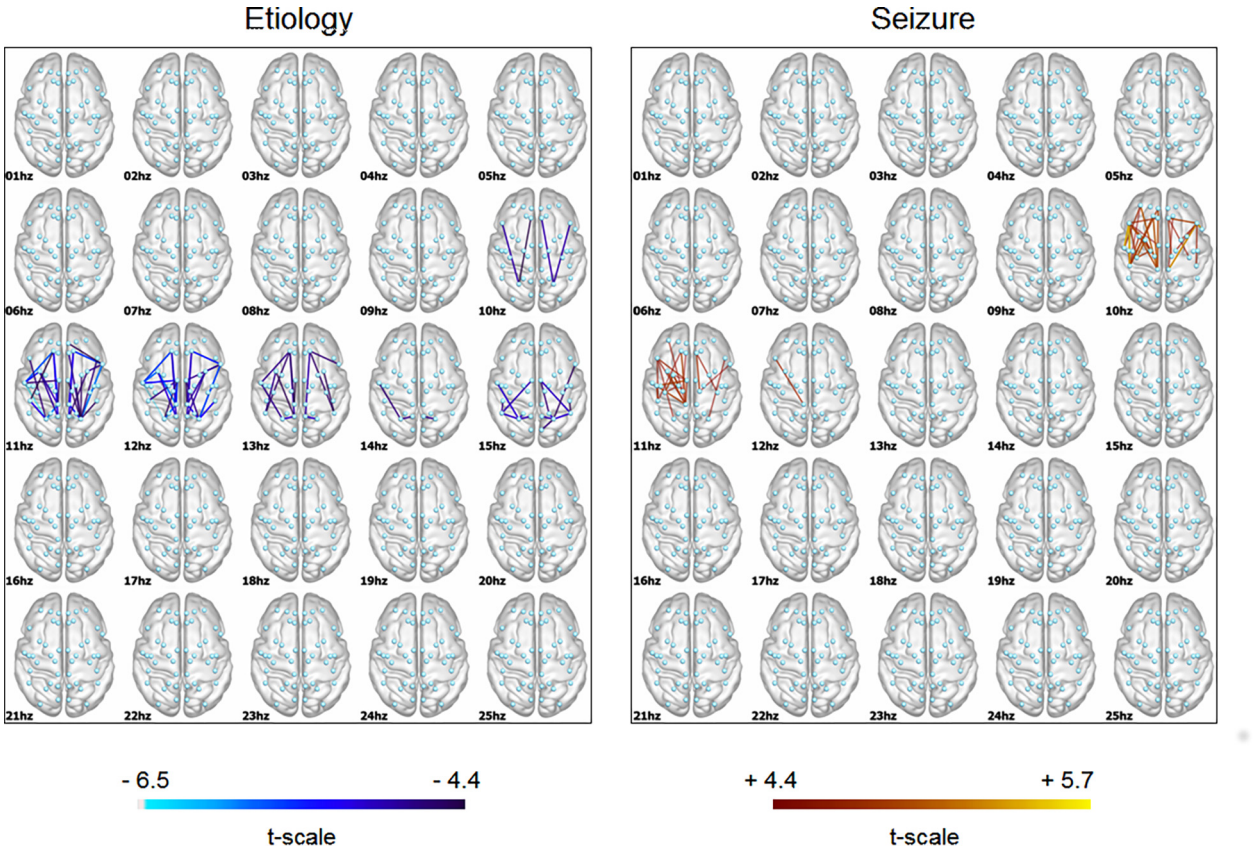

Fig. 2. Impact of clinical factors on EEGfC. The glass brain panels (each showing results from 1 to 25 Hz) demonstrate the results of post-hoc *t*-tests. The software automatically generated *t*-scales for each comparison. Colors of the *t*-scales demonstrate statistically significant group differences. Left panel: "Etiology", difference between the cryptogenic and symptomatic groups. Right panel: "Seizure", difference between the secondary generalized and focal (without generalization) seizure groups. Right side of the glass brain corresponds to the right hemisphere.

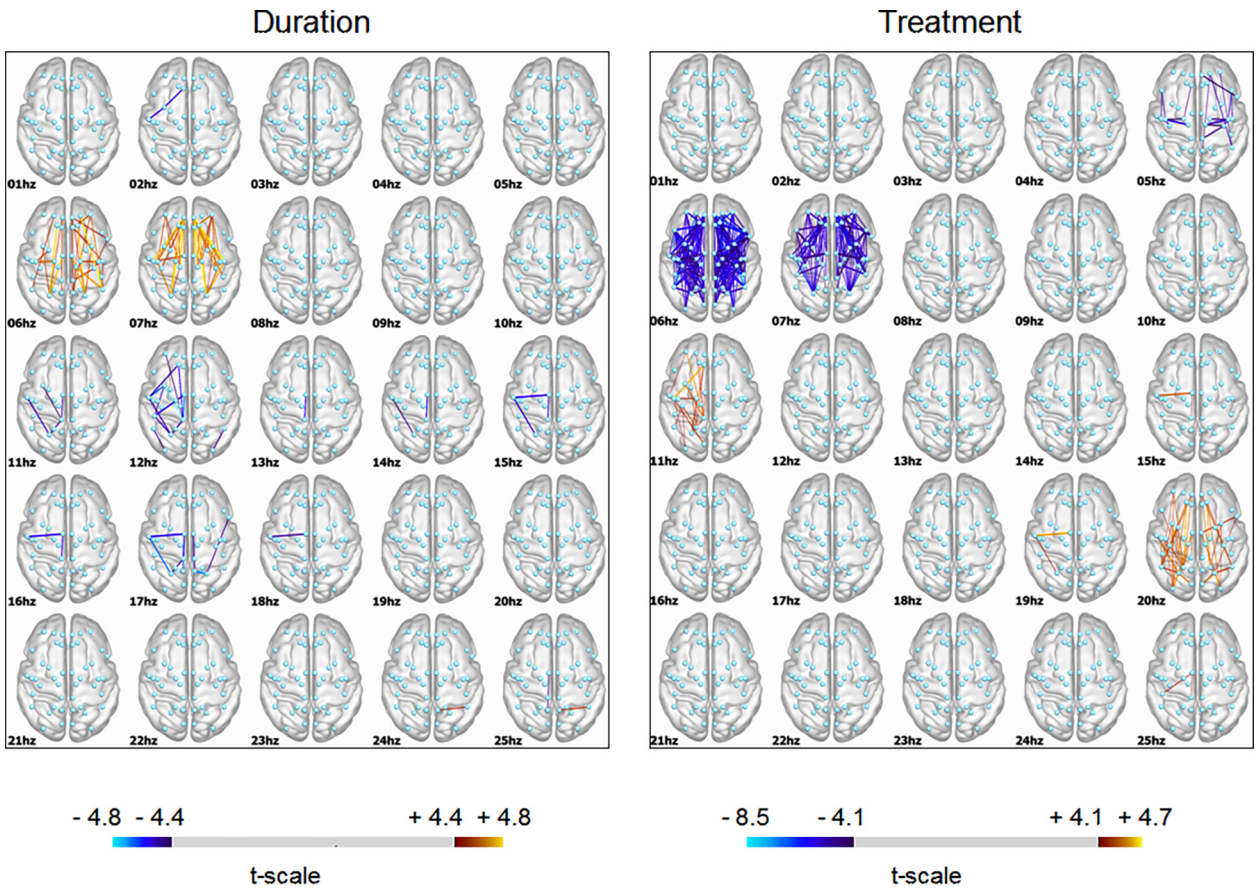

Fig. 3. Impact of clinical factors on EEGfC. The glass brain panels (each showing results from 1 to 25 Hz) demonstrate the results of post-hoc *t*-tests. The software automatically generated *t*-scales for each comparison. Colors of the *t*-scales demonstrate statistically significant group differences. Left panel: "Duration"; difference between the D4 (>20 years) and the D1 (<1 years) groups. Right panel: "Treatment", the untreated group compared to the treated group. Right side of the glass brain corresponds to the right hemisphere.

4. Discussion

As far as is known, this is the first study to explore very narrow band EEGfC in FE patients and to investigate modifying effect of clinical factors on resting-state EEGfC. Composition of the patient sample suggested that the findings reflected EEGfC of the general FE population, except benign childhood epilepsy. Our patients belonged to the so-called "common epilepsy" category (Sisodiya and Mefford, 2011) that is the most common sort of epilepsy in neurological practice. Its other name is "non-syndromic epilepsy" because the patients do not belong to either of the well-delineated epilepsy syndromes. The epileptic network is also individual and develops under influence of timing, localization and biological characteristics of the epileptogenic process (Wolf, 2011). Our findings demonstrated that common patterns of network organization exist despite great inter-individual variability of clinical, EEG and MRI findings. We do not think that the network outlined in the global comparison (Fig. 1) corresponds to any physiological network or specific brain function (Wolf, 2011). Increased EEGfC in the theta band and in the frontal-temporal-lateral parietal network seems to be a common, yet unexplained phenomenon that was found in lumped EEGfC analysis of 259 patients with diverse neurological disorders including epilepsy syndromes and non-epileptic disorders (Dömötör et al., 2017a,b). Decrease in alpha EEGfC in posterior areas in the above-mentioned sample has been a common finding as well (Dömötör et al., 2017a,b).

4.1. EEGfC in the FE group

A few authors reported abnormal resting-state network activity in FE patients in the delta band (Horstmann et al., 2010) and alpha band (Vecchio et al., 2015) as compared to healthy controls. They computed EEGfC for broad frequency bands and used global graph metrics to evaluate functional segregation and integration within the cortico-cortical network. They interpreted the results as overall increase of EEGfC in FE. We computed EEGfC with greater resolution in the frequency domain. Computing EEGfC for very narrow bands is more physiological approach than dealing with broad frequency bands because natural oscillations of the brain actually happen in narrow bands of 1–2 Hz bandwidth (Lopes da Silva, 2013). Some of the results would be presumably lost using the broadband approach. Another shortcoming of the global approach is that topography of abnormal connectivity was lost. Topographically characterized widespread network changes in FE were reported in other network studies (Spencer, 2002; Bartolomei et al., 2006). In this study, we demonstrated topographical patterns of abnormal (increased and decreased) network activity in the FE group as compared to the healthy control group. Increased and decreased EEGfC indicates increased and decreased coupling between great neuronal pools. Intuitively, complexity of cerebral organization suggested that co-occurrence of increased and decreased coupling is realistic scenario of epileptic network modification.

The network of increased EEGfC showed increased number of abnormal connections from 3 to 7 Hz and maximum number of them at 6 Hz. This range roughly corresponds to the theta broad band that is involved in physiological integration of cerebral functions (Basar and Schürmann, 1999; Buzsáki, 2006). Increased theta connectivity seems to be characteristic to epilepsy (Douw et al., 2010). Altered theta activity may be associated with epilepsy including the natural course of it and treatment effects as well (Colom et al., 2006). We suggest that theta connectivity (with particular emphasis to the 6 Hz frequency) should be addressed in forthcoming studies.

From the topographical point of view, we discuss abnormal EEGfC patterns at 6 Hz. This network of increased EEGfC included all temporal and all but one frontal ROIs. This distribution might correspond to the well-known, increased propensity of the frontal and temporal cortices to generate seizures. On the contrary, minor or no involvement of posterior ROIs in this network might correspond to lesser propensity of posterior areas in epileptogenesis (as compared to anterior sites).

4.2. Modifying effect of the clinical factors

Four of the six clinical factors independently influenced EEGfC while two factors had no statistically detectable effect on it. Interestingly, effects of biologically diverse factors converged to a few very narrow bands. Four factors (etiology, seizure, duration, treatment) affected the upper alpha band, two factors (duration, treatment) the upper theta band. Again, the findings suggested that the bulk of epilepsy-related network modification happened at EEG frequencies that are involved in cerebral integration (Basar and Schürmann, 1999; Buzsáki, 2006).

4.2.1. Etiology of epilepsy

Epilepsies have genetic and acquired etiological factors. The former comprises hundreds or thousands of genes of small effect in common epilepsy (Helbig et al., 2016). We therefore postulated that total impact of epilepsy susceptibility genes was greater in the family positive than in the family negative group. However, the "family" factor did not differentiate between EEGfC in the two groups. Age composition of the FE group was a possible cause for not detecting the postulated difference. The majority of the patients were older than 20 years at EEG investigation. Epidemiological studies disclosed that weight of genetic influence decreases and weight of acquired factors increases in epileptogenesis that starts after the second decade (Hauser, 1997).

Symptomatic etiology was associated with decreased EEGfC in the upper alpha band as compared to the cryptogenic epilepsy group. Symptomatic etiology means presence of localized or diffuse epileptogenic lesion. Epileptogenic and non-epileptic, localized and diffuse cerebral lesions are typically associated with decreased EEGfC in the alpha frequency band (Dömötör et al., 2017a,b). We therefore concluded that decreased alpha EEGfC in symptomatic FE was due to the hemispheric lesions.

4.2.2. Onset of the disease

Epileptogenesis is a chronic process and implies transformation of normal networks toward epileptic networks (Bragin et al., 2000). One can suppose that early epileptogenic insults cause profound network abnormality of the developing central nervous system as compared to lesions acquired in later life. Our results did not support this idea. As a possible bias, we defined "onset" as age at the first unprovoked seizure. In reality epileptogenesis and network transformation starts beforehand the first clinical seizure occurs. Onset of epileptogenesis is evident in many patients, for example, in epilepsy that follows a major stroke. On the contrary, onset of epileptogenesis remains hidden if the epileptogenic abnormality developed indefinite months or years before the first seizure. It is possible to investigate this issue in controlled, experimental setting and in human epilepsy where timing of the epileptogenic lesion is unequivocal.

4.2.3. Seizure

Electrical seizure activity tends to spread from the seizure onset area towards neighboring and remote sites. Several patients are prone to diffuse and bilateral spread of ictal activity that ends in a generalized tonic-clonic seizure. Initial phase of this evolution is cortico-cortical spread (Spencer, 1988) we therefore assumed that liability for secondary generalization is associated with increased cortico-cortical EEGfC. If so, greatest EEGfC would appear in the SG group where all the patients had exclusively secondary generalized seizures. The results confirmed this assumption. Neuronal basis of the oscillatory alpha system is diffuse (Nunez et al., 2001), therefore it might be ideal substrate to dissipate electrical seizure activity. It is possible that our results reflect diffusely decreased feedforward inhibiton that is main cause of rapid secondary generalization (Trevelyan et al., 2007).

4.2.4. Duration of epilepsy

Epileptic dysfunction causes long-lasting and cumulative impairment of brain structure and function. Functional MRI demonstrated network transformation as function of disease duration in FE patients (Wang et al., 2014). Most investigators emphasize the deleterious effect of seizures. However, many processes, for example, altered neuronal plasticity (Pitkänen and Sutula, 2002) and inter-ictal epileptiform discharges (Staley et al., 2005) contribute to derangement of brain functions. In this study, the "duration" factor comprised seizure-related and non-seizure effects as well. We confirmed diffuse network derangement as a function of duration of the illness. Relationship of increased theta and decreased alpha EEGfC to the many aspects of epilepsy-related cerebral dysfunction should be addressed in forthcoming investigations.

4.2.5. Treatment

Anticonvulsive drugs have therapeutic and neurotoxic effects. In theory, both influences can modify the epileptic network. According to principles of pharmaco-EEG, successful treatment restores clinical and EEG variables in parallel (Saletu et al., 2005). In fact, drug treatment normalized EEGfC in all frequency bands in generalized epilepsy (Clemens et al., 2014). By analogy, similar situation might emerge in FE as well. Theta band differences are of particular interest because an experimental study suggested relationship between modification of EEG theta activity and seizure control (Colom et al., 2006). Factor analysis disclosed less EEGfC in the untreated than in the treated group, which indicated independent effect of drug treatment on EEGfC. However, prospective, self-control studies are necessary to explore relationship between network modification at special frequencies and therapeutic and neurotoxic influences of dissimilar antiepileptic compounds.

5. Conclusions

Resting-state, interictal EEGfC in FE patients differs from that of healthy persons. The differences were due to four factors (etiology, seizure type, duration of the illness and antiepileptic treatment) that independently influenced EEGfC. Our work can be starting point to plan further studies to investigate FE networks in relation to neurophysiological, pharmacological and clinical issues.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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