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Differences in subcortical functional connectivity in patients with epilepsy

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ABSTRACT

Introduction. Epilepsy is a disease characterized by abnormal paroxysmal bioelectrical activity in the brain cortex and subcortical structures. Seizures per se change brain metabolism in epileptic focus and in distal parts of the brain. However, interictal phenomena can also affect functional connectivity (FC) and brain metabolism in other parts of the brain.

Aim of study. We hypothesised that epilepsy affects functional connectivity not only among cortical, but also between subcortical, structures of the brain in a resting state condition.

Clinical rationale for study. Investigating functional connectivity in patients with epilepsy could provide insights into the underlying pathophysiological mechanisms. Better understanding may lead to more effective treatment strategies.

Material and methods. Functional connectivity was analysed in 35 patients with epilepsy and in 28 healthy volunteers. The group of patients was divided into generalised and focal epilepsy (temporal and extratemporal subgroups). Each patient and healthy volunteer underwent an fMRI resting-state session. During the study, EEG signals were simultaneously recorded with fMRI to facilitate the subsequent detection of potential interictal epileptiform discharges (IEDs). Their potential impact on BOLD signals was mitigated through linear regression. The data was processed and correlation coefficients (FC values) between the BOLD signal from selected structures of the central nervous system were determined and compared between study groups. The results were presented as significant differences in correlation coefficients between brain/subcortical structures in the epilepsy and control groups.

Results. Lower FC values for the epilepsy group compared to the control group were shown for connections related to the MPFC, hippocampus, thalamus, amygdala, and the parahippocampal gyrus.

Conclusions. Epilepsy alters the functional connectivity of resting state subcortical networks. Patterns of pathological changes of FC differ between epilepsy subtypes, with predominant lower FC between the hippocampus, parahippocampal gyrus, amygdala and thalamus in patients with epilepsy.

Clinical implications. This study suggests that epilepsy affects subcortical structures. Identifying distinct patterns of altered FC in epilepsy subtypes may help to tailor treatment strategies. Changes in FC detected by fMRI may precede clinical symptoms, aiding in the early diagnosis of cognitive and emotional disorders in focal epilepsy.

Keywords: epilepsy, resting-state functional magnetic resonance imaging (rs-fMRI), functional connectivity, subcortical, interictal

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Introduction

Epileptic seizures are likely to occur as phenomena related to the dynamics of brain networks [1]. Therefore, understanding the characteristics of these networks in patients with epilepsy is vital to gain insight into the dynamics that may give rise to the propagation of seizures and other dysfunctions/comorbidities observed in epilepsy.

Functional connectivity (FC) is the statistical relationship between the levels of deoxygenated blood in different areas of the brain over time. It can be measured with the use of stimulation-free variant of functional magnetic resonance imaging (fMRI) known as resting state fMRI (rs-fMRI) [2]. By recording blood-oxygenation level-dependent (BOLD) signals, rs-fMRI can give valuable insights regarding the functional connections within the brain. The first correlations between resting-state BOLD signals originating from distant brain structures were noted as early as 1995 [3]. The spatial pattern of such connections between specific structures of the brain creates a functional connectivity network.

Numerous studies have revealed the presence of such networks, encompassing both grey matter and subcortical structures [4] including those associated with default mode network [5], dorsal and ventral attention [6], and the central executive network [7].

Given the above, we decided to consider the relationship between epilepsy and functional connectivity. It has been shown that epilepsy may affect the functioning of the network of functional connections in the brain [8]. For instance, it has been demonstrated that patients with temporal lobe epilepsy had reduced functional connectivity between the hemispheres, but increased locally on the side of the epileptic focus [9]. The relationship between epilepsy and the disturbances of functional connectivity networks has also been established in frontal lobe areas, which are part of the default mode network. An illustrative case in recent literature is the 2023 study by Bacon et al. [10], which explored the functional connectivity patterns in individuals suffering from drug-resistant epilepsy. Their findings revealed substantial changes in crucial brain networks, including the default mode and dorsal attention networks.

Epilepsy can have a profound impact on a patient's overall functioning due to its commonly associated emotional [11–13], attention-related [14–16], and memory-related [17–19] disorders. When considering the influence of epilepsy on a patient's functioning, it is important to acknowledge its potential implications for functional connectivity. A review of mapping cognitive and emotional networks [20], published in 2020, highlighted the potential to employ rs-fMRI for identifying critical yet traditionally non-eloquent brain networks involved in cognitive and emotional processing. It is obvious that during seizures or interictal epileptiform discharges (IEDs), the physiological functional connectivity of the brain is disrupted [21]. However, during interictal periods, FC may also be altered in patients with epilepsy, which may influence other brain functions.

Taking this into account, it can be concluded that epilepsy significantly impacts upon the functional networks in the brain. It is therefore reasonable to study the changes in brain function caused by epilepsy, in terms of emotions, memory, and attention deficit disorder, but also depending on the type of disease. In recent years, several methods have been used to analyse the functional connectivity of patients with epilepsy. In order to study regional interaction between predefined anatomical brain structures, seed-based analysis is used by calculating and comparing correlation coefficients (FC values) between BOLD signal pairs derived from these regions. The analysis can reveal correlated regions (ROI-to-ROI analysis) and voxel clusters that are correlated with the selected seed (Seed-to-Voxel). The former method was used, among others, by Roger et. al. [22] for the study of mesial temporal lobe epilepsy. One can conclude that many functional connectivity studies are based on determining functional connectivity values between signals coming from different areas of the brain. This has been done in order to study, among others, temporal lobe epilepsy [22, 23] or the ganglia-thalamo-cortical network [24]. Brain regions of interest (ROIs) for such studies are usually chosen *a priori* [25], as was the approach taken in our study.

The purpose of this study was to investigate whether functional connectivity between both cortical and subcortical structures could be altered in patients with epilepsy. We aimed to explore whether functional disorders in epilepsy extend beyond seizure to also include interictal periods.

Investigating FC in patients with epilepsy could provide insights into the underlying pathophysiological mechanisms. Such knowledge might lead to more effective treatment strategies. By examining the correspondence between different brain regions and their communication patterns, one can also gain valuable insights into the impact of seizures on cognitive and emotional functions, helping to address the broader impacts of epilepsy beyond just seizure control.

Material and methods

In this study, we defined functional connectivity as the correlation coefficient value between the BOLD signals from defined brain regions. These correlations were analysed at the group level in order to decipher FC patterns specific for studied populations. Group differences were inferred from within the general linear model (GLM) statistical framework on a given confidence level.

Subjects and fMRI data recording

This study was approved by the local bioethics committee and was performed according to Declaration of Helsinki guidelines. All participants gave their written consent for participation. The mean time from the onset of epilepsy of 35 patients

(12 M, 23 F; mean age 33.3) was 6.2 years. Nine patients (six with focal epilepsy and three with generalised) had drug-resistant epilepsy. None of the participants experienced a seizure during or immediately surrounding the study period. Each patient underwent up to three sessions of rs-fMRI acquisition (GE Discovery MR750w, TR = 2.5 s, TE = 25 ms, voxel size 3 mm x 3 mm x 3 mm) and a structural scan (T1-weighted: TR = 6.94 ms, TE = 2.97 ms, FA = 11, voxel size 1 mm x 1 mm x 1.2 mm). EEG data was recorded simultaneously to remove the influence of possible IEDs on spontaneous fluctuations of the BOLD signal (Neuroscan SynampsRT 64-channel EEG system). After rejecting the outlier data, subjects were divided into a group of generalised epilepsy (seven patients), and a group of focal epilepsy (10 temporal epilepsy and 18 extratemporal epilepsy patients). The characteristics of the patient groups are set out in Table 1. All of the patients received antiepileptic treatment: levetiracetam, valproate, lamotrigine and lacosamide were used in study participants. The majority of patients were on monotherapy. There were no significant differences in the use of anti-seizure medications (ASMs) between subgroups of patients with epilepsy. 28 healthy volunteers (16 M, 12 F; mean age 28.1) underwent a 10-minute resting-state fMRI scan with the same acquisition parameters as patients, serving as the control group.

Table 1. Clinical and demographic characteristics of all patients

	Generalised	Temporal	Extratemporal
Number of subjects	7	10	18
Sex (M/F)	6/1	3/7	3/15
Mean age (years)	29.9	34.2	34.1

Data processing

The fMRI data underwent a standard preprocessing pipeline (realignment, coregistration, normalisation and smoothing) using SPM12 [26], while the EEG data was processed with CURRY7 software. Manual detection of IEDs was performed by an experienced neurologist. Subsequent preprocessing of MRI data in CONN [27] involved outlier detection and denoising, specifically regressing out the influence of IEDs on the spontaneous fluctuations of the BOLD signal. For this purpose, information on the occurrence and duration of possible IEDs obtained from the EEG recording was used.

Functional connectivity analysis

Resting-state analysis was performed, comparing functional connectivity (FC) values between patients with epilepsy and a group of healthy subjects. The preliminary analysis, conducted for connections encompassing 164 ROIs from the Harvard-Oxford Cortical Atlas proposed by CONN software, revealed various cortical and subcortical regions of altered functional connectivity.

For the purpose of this study, we chose mainly subcortical structures which may be associated in the pathogenesis of epilepsy and comorbidities (Fig. 1A). These structures are related to the default mode, central executive and salience networks [28]. The thalamus (L/R — left/right) was selected as the first region of interest, being an integrating brain structure receiving sensory information and synchronising pathological epileptic activity. The hippocampus (L/R — left/right) and the parahippocampal gyrus (anterior/posterior, left/right — aPaHC (L/R), pPaHC (L/R)) were selected as elements of the limbic system that are a potential location of the epileptogenic focus, which may be related to short-term memory disorders. The medial prefrontal cortex (MPFC) was the next structure of interest, given its association with the working of memory and attention processes. The MPFC is also a component of the extensively studied default mode network. The final region of interest was the amygdala (left/right — L/R), a structure crucial for emotional responses. Amygdala dysfunction seems to be related to the coexistence of depressive disorders in epilepsy [12].

Functional connectivity values were computed for each patient across pairs of ROIs, serving as the basis for subsequent group analysis. The group analysis consisted of determining the differences in functional connectivity between the epilepsy subgroups and the healthy group (parametric multivariate statistics — cluster level inferences, cluster threshold $p < 0.05$, FDR corrected, connection threshold: $p < 0.05$, FDR corrected).

Results

The analysis of functional connectivity between the epilepsy and control groups revealed notable differences, particularly a loss in FC values among patients between selected brain regions, including the hippocampus, parahippocampal gyrus, amygdala, and MPFC (with the highest t-score of –6.35, $p = 0.000001$, for FC between the left and right hippocampus). These findings are depicted in Figure 1B, where regions of interest (ROIs) are aggregated into clusters through hierarchical clustering methods.

The results for each comparison were presented in the form of a connectivity matrix (cluster threshold $p < 0.05$, FDR corrected, connection threshold: $p < 0.05$, FDR corrected). The detailed results of the statistical analysis are included in Tables 2–6 in the supplementary materials.

The examination of functional connectivity between the focal epilepsy group and healthy subjects unveiled substantial differences. Specifically, a decrease in FC values was observed for structures akin to those observed in the comparison between the overall epilepsy group and the healthy group (with max. t-score of –6.19, $p = 0.000001$, between the left and right hippocampus). These findings are demonstrated in Figure 1C. The investigation into functional connectivity between the generalised epilepsy group and healthy subjects revealed

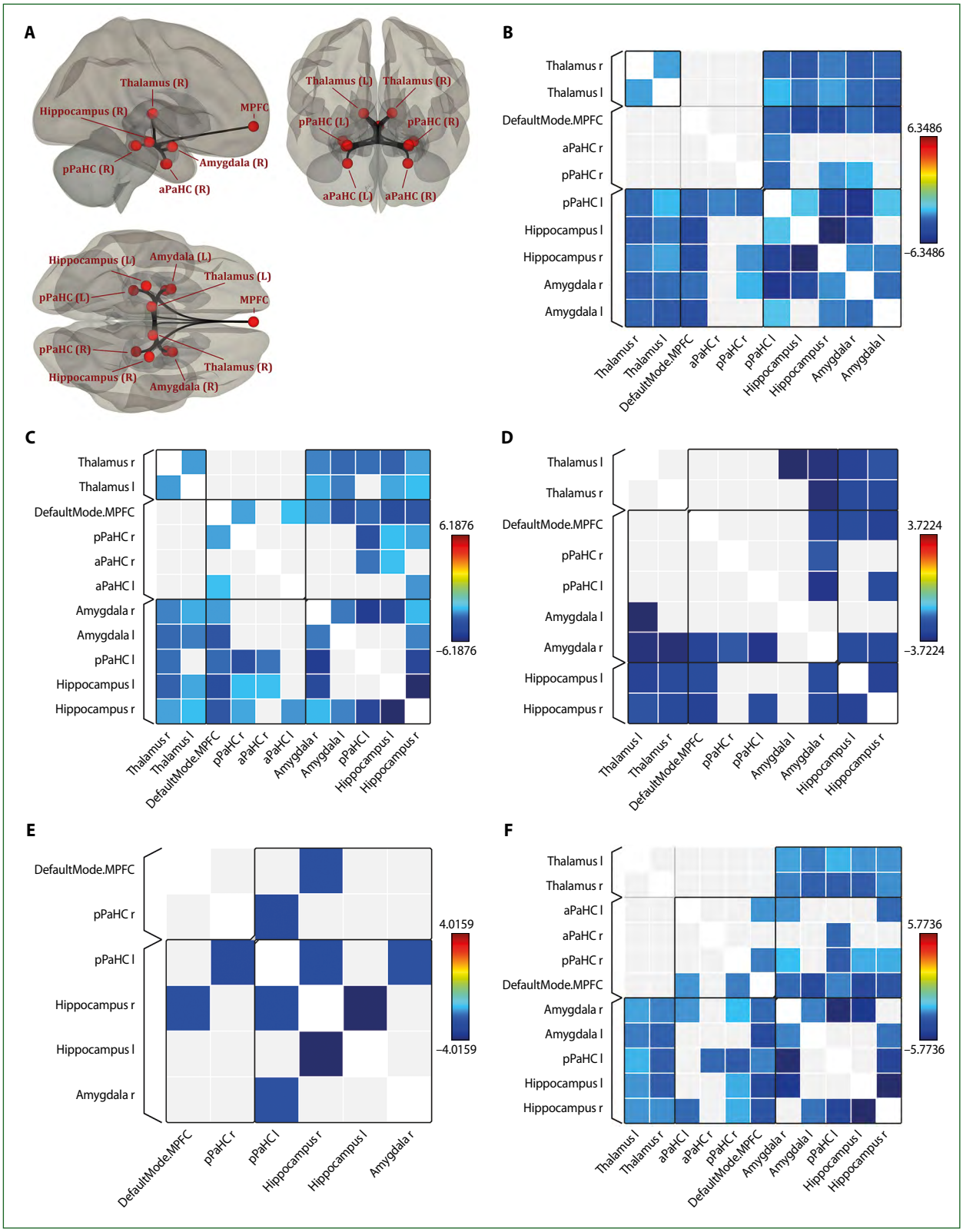

Figure 1. A. Selected regions of interest: medial prefrontal cortex (MPFC), parahippocampal gyrus (anterior/posterior, left/right – aPaHC (L/R), pPaHC (L/R)), thalamus (L/R – left/right), hippocampus (L/R – left/right), amygdala (L/R – left/right); **B–F.** Differences in functional connectivity values between epilepsy(B)/focal epilepsy(C)/generalised epilepsy(D)/temporal epilepsy(E)/extratemporal epilepsy(F) and healthy groups in selected ROIs shown in form of connectivity matrix. Colour scale represents T value resulting from parametric multivariate statistics (cluster threshold $p < 0.05$. FDR corrected, connection threshold: $p < 0.05$, FDR corrected). Developed using CONN [27]

notable differences, specifically a decrease in FC among brain regions such as the thalamus, amygdala, and hippocampus (with the highest t-score of –3.72, p = 0.005977, for FC between the left thalamus and left amygdala). These findings are presented in Figure 1D.

The focal epilepsy group was divided into temporal and extratemporal subgroups. Upon comparison of the temporal epilepsy subgroup with healthy subjects, significant differences in FC were observed among brain regions such as the hippocampus, parahippocampal gyrus, and amygdala (with the highest t-score of –4.02, p = 0.037218, for FC between the left and right hippocampus). These findings are visually represented in Figure 1E. The examination of functional connectivity between the extratemporal epilepsy group and healthy subjects revealed notable distinctions, particularly a decrease in FC among brain regions such as the hippocampus, parahippocampal gyrus, amygdala, and MPFC (with the highest t-score of –5.77, p = 0.000007, for FC between the left and right hippocampus). These findings are illustrated in Figure 1F.

Discussion

Epileptic pathological hypersynchronous activity causes excessive release of neurotransmitters, resulting in active hyperemia and increased blood flow and deoxygenation. This is the pathomechanism of the change of BOLD signal in fMRI. It is well established that a seizure per se changes brain metabolism in epileptic focus and distal parts of the brain [29]. But seizure is only the final effect of the pathomechanisms of altered brain activity. There is a continuum of pathological changes in bioelectrical activity in epilepsy in the epileptic focus. Most of these changes are clinically 'silent' in terms of seizures but they can affect functional connectivity and brain metabolism in the vicinity and in other parts of the brain.

The hypothesis of our study was that epilepsy, not only seizures, affects functional connectivity between cortical and subcortical regions of the brain. These altered functional connectivities in a resting state condition may underlie the pathomechanism of comorbidities in epilepsy such as cognitive and emotional disturbances. Thus, we analysed the resting state functional connectivity in patients with epilepsy compared to healthy volunteers. The main finding of the presented study is that epilepsy is a disease of cortical and subcortical networks, not only during epileptic seizures, but also in resting conditions. Our findings clearly show that functional connectivity of the resting state of the brain is altered in patients compared to healthy controls. The most affected connectivities are changed in patients between subcortical structures crucial for the working memory and emotions structures, such as the hippocampus and amygdala. These findings align with previous studies on resting state in epilepsy [28, 30] and may be the pathomechanism of the emotional disturbances in the condition. However, this hypothesis requires further investigation. Surprisingly, functional connectivity is much more affected in focal epilepsy than in generalised epilepsy. This finding may, paradoxically, lead to the conclusion that focal (extratemporal) epilepsy exhibits a broader or more widespread impact than generalised epilepsy. However, this surprising result of FC analysis may reflect some clinical observations. Firstly, focal epilepsy is more often complicated by emotional disorders and cognitive dysfunction than is generalised epilepsy. One study examining functional connectivity and its impact on cognitive processes in patients with epilepsy, specifically temporal lobe epilepsy (TLE) and neuroticism [31], found a significant association. It highlighted that higher neuroticism scores in TLE patients are linked to atypical patterns of resting-state connectivity between mesial temporal and frontal regions. Some of these aberrant connectivity patterns are specific to neuroticism, while others align with increased symptoms of depression and anxiety. Secondly, epileptogenesis in generalised epilepsy usually develops in early childhood or even in the foetal period. The plasticity of the central nervous system is most efficient in the first decade of life, which probably allows for the development of compensatory mechanisms for recurrent epileptic discharge. Epileptogenesis in focal epilepsy usually develops later, in the second and third decades of life. In this developmental period, the plasticity of the central nervous system is less effective and the possibility of developing compensatory mechanisms is limited. As a result, subclinical disturbances of the resting state of the central nervous system may be more pathogenic, which may explain the more frequent co-occurrence of emotional disorders in patients with focal epilepsy.

Most previous studies have focused on intracortical functional connectivity dysfunction in patients with epilepsy. The novelty of our study is the analysis of FC of subcortical structures. The alterations of subcortical functional connectivity may partly explain and contribute to the emotional comorbidities in epilepsy, although differences of cortical networks' functional connectivity may also contribute to the general pathomechanism of epilepsy, a possibility which demands further investigation.

Limitations

The major limitation of our study is the limited size of epileptic subgroups. However, significant differences were found between these small populations of patients. Therefore, one can assume that an increase in the number of patients would only strengthen the statistical power of our results.

We cannot exclude the effect of ASMs on resting-state activity in patients with epilepsy. The mechanism of action of medications used by patients in our study is different, but the eventual effect is to reduce the hyperexcitability of neurons. The effects of ASMs are not brain structure-specific, and therefore we assume that observed differences in functional

connectivity of certain brain regions in patients are not related to the medications itself, but are rather the effect of pathophysiology of epilepsy.

Our analysis was performed only on a selected group of structures (mainly subcortical) for the purpose of targeted statistical analysis. Analysis of the remaining cortical structures identified as a result of the preliminary analysis will be performed in a subsequent study.

Clinical implications/future directions

The main conclusions of our study are:

1. Epilepsy alters the functional connectivity of resting state subcortical networks
2. The pattern of pathological changes in functional connectivity may differ among epilepsy subtypes. Given the small sample size of individual groups, further studies with larger cohorts of patients with epilepsy are necessary to confirm this hypothesis, and to draw more robust conclusions.

Our findings may indicate that pathological alterations in subcortical networks in epilepsy possibly contribute to comorbidities such as cognitive and emotional disorders. These observations warrant further investigation into the appropriate evaluation of emotional and cognitive functions in patients with epilepsy. Alterations in FC during rs-fMRI may precede the clinical symptoms, and could be useful in early diagnosis of presymptomatic cognitive and emotional disorders in focal epilepsy.

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Ethics statement: *The study was approved by the Bioethics Committee at the Military Institute of Aviation Medicine in Warsaw — Decision no 6/2021.*

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