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Default mode function in patients with generalised epilepsy syndromes: from generalised to focal findings

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ABSTRACT

Introduction. Many recent studies have suggested that generalised epilepsy is associated with cortical epileptogenic focus, and therefore distinguishing between focal and generalised often becomes difficult.

Aim of study. We aimed to detect differences between default mode function in patients with idiopathic generalised epilepsy who have discharges on EEG, and healthy persons.

Material and methods. This was a case-control study; we performed EEG analysis with LORETA in 17 patients with a type of generalised epilepsy and a control group represented by 17 healthy age-matched persons. We performed statistical non-parametric tests for current density electrical distribution for our two groups ('t-statistic on Log transformed data') and we defined regions of interest (ROIs) from the default mode network. In the second part, we compared the average activation for each ROI for each timeframe in the epoch for the group with epilepsy, and for controls (we performed a Wilcoxon rank-sum test for two means).

Results. In the first part, we obtained that in the medial frontal gyrus (BA 9) delta oscillations significantly differed in patients with epilepsy who had electrical discharges on EEG in resting state conditions compared to healthy controls (medial frontal gyrus in this group had a greater number of synchronously oscillating neurons than did the controls). In the second part, we ran statistics on our localised activity from the default mode network (defined ROIs) and we obtained statistically significant differences in the left medial frontal gyrus (the values were higher for the group with epilepsy, p-value = 0.0066).

Conclusions and clinical implications. It may be possible to move from a 'generalised theory' about epilepsy to a 'focused theory' by understanding how various areas of interest are activated within default mode networks. Insights into the pathophysiology of generalised epilepsy may lead to new treatment options.

Keywords: idiopathic generalised epilepsy, resting state electroencephalography (EEG), low-resolution brain electromagnetic source tomography (LORETA)

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Introduction

The idiopathic generalised epilepsy group includes childhood absence epilepsy (CAE), juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE), and epilepsy with generalised tonic-clonic seizures alone (EGTCS) [1].

Regardless of the idiopathic generalised epilepsy subtype, evidence has been provided that functional connectivity is reduced. In all subtypes, the default mode network is most affected [2].

Functional resting-state MRI has demonstrated that default mode network activity in EGTCS patients differs from

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normal controls at rest. Results suggest that EGTCS patients have reduced functional integrations of the default mode network, which might provide insight into the neural correlations of impaired consciousness in these patients [3].

In other studies, a decrease in functional connectivity has been found in the self-referential, somatosensory, visual, and auditory networks, as well as increases and decreases in functional connectivity in the default-mode and dorsal attention networks in EGTCS patients compared to healthy subjects [4].

Other studies that have used dynamic methods in functional connectivity have detected specific disruptions in patients with generalised tonic-clonic seizures, with many functional abnormalities in the default mode network. The authors concluded that dynamic functional network connectivity could distinguish patients with generalised tonic-clonic seizures (idiopathic generalised epilepsy) from controls (defined in the study as age-, gender-, and handedness-matched healthy controls) with an accuracy of 77.91% ($p < 0.001$). Functional connectivity between resting state networks may aid in understanding the pathological aspects of idiopathic generalised epilepsy [5].

Electrical source localisation uses temporal and spatial information derived from an EEG to find the source of potentials recorded on the scalp. These techniques, including LORETA (low resolution electromagnetic tomography), have been validated for ictal and interictal studies [6].

Studies that have used routine EEG examination and imaging methods have concluded that epilepsy is a network disease, with cortical and subcortical disturbance; identifying epileptic networks may provide new insights into a better characterisation of epileptic syndromes and individualised treatment [7, 8].

The idea that the pathological basis of idiopathic generalised epilepsy involves the entire cortex has evolved over time, and many ictal and interictal studies have found abnormalities in frontal lobes in these patients. These studies concluded that there are frontal areas that play an important role in generating generalised seizures [9].

Studies during interictal EEG epochs in focal epilepsies have revealed alterations in global brain functional connectivity and in specific resting-state networks. This can provide a chronic effect on pathological mechanisms involving these structures, and could increase the sensitivity of scalp EEG in detecting abnormalities in the absence of interictal discharges [10].

Compared to other functional imaging methods, investigating functional connectivity via EEG has many advantages i.e. a higher temporal resolution, lower cost, ease of obtaining EEG data in epileptic patients, and being part of a routine investigation [11].

Exact low resolution brain electromagnetic tomography (eLORETA) can be used to compute the cortical distribution of current density [12].

In LORETA, there are measures applied to pairs of EEG signals between time series that correspond to different spatial locations. In other words, at each voxel in the cortical grey matter, a vector time with three components is computed, and this corresponds to a density vector with dipoles moments along the X, Y, and Z axes. This method is linear; it has zero localisation error and low spatial resolution [13].

There is comprehensive literature data available based on different algorithms that solve the electromagnetic inverse problem for LORETA. This is a noninvasive method that can determine the distribution of active neurons in time, and it can help to study the dynamics of neural networks in the brain [14].

Material and methods

Subjects

We selected 17 consecutive right-handed patients diagnosed with a type of generalised epilepsy syndrome (JME, JAE, EGTCS) who had undergone an EEG in our unit within the last three years, and 17 age-matched healthy subjects.

The characteristics of the patient group are set out in Table 1. The control group was composed of healthy age-matched subjects. There were no statistical differences in the mean ages or gender balance of the two groups, obtaining a p-value of 0.55 in the Chi square test.

This study was in accordance with the tenets of the Helsinki Declaration and received institutional and ethical consent.

EEG scalp recording

The EEG was performed in an isolated room using 19 scalp electrodes (Cadwell, Kennewick, WA, USA), placed according to 10–20 international montages, with a sampling rate frequency of 256 Hz. The impedances were kept below 5kΩ.

We included only patients who had typical interictal/ictal discharges on EEG, i.e. generalised spike-wave discharges (GSW), multispike-wave/multispike discharges, ictal 3Hz GSW discharges, or generalised spikes/sharp waves. The EEG selection criteria were the following: a) presence of posterior alpha rhythm; b) absence of drowsiness/sleep; c) absence of winking or other artifacts; and d) absence of epileptic discharges, with a mean distance of at least five seconds from them. A certified EEG neurologist selected the EEG data during wakefulness between discharges according to selection criteria.

Processing signals

The selected EEG data was imported in MATLAB R2022b (MathWorks, Natick, MA, USA) toolbox EEGLAB v2020, and the following steps were followed: high- and low-pass filtered at 0.5 and 40 Hz; other types of artifacts removed; re-referenced to average reference. From the EEG data, 60 epochs (each 2 s, a total of 120 s) were selected for each patient. These pre-processing steps were carefully followed by decomposition of the signals with independent component analysis (ICA) and the removal of data that did not contain brain activity. The ICA components with artifacts were manually removed. The obtained data was exported in LORETA (Low Resolution

Table 1. Characteristics of patients

Patient	Age (years)	Epilepsy type	EEG duration (min)	Discharges type (IED/ID)	Medication
1	21	EGTCS	90.5	GSW	Lamotrigin 100 mg/day
2	22	EGTCS	24	GSW	Lamotrigin 400 mg/day
3	22	EGTCS	158	GSW/Sharp waves	Levetiracetam 1,500 mg/day
4	21	JME	636	Multispike-wave discharges	Levetiracetam 1,000 mg/day
5	45	JAE	152	3–3.5 Hz ictal GSW discharges	Sodium valproate 1,500 mg/day
6	18	EGTCS	59	GSW	Levetiracetam 1,000 mg/day
7	24	JME	598	Multispike-wave discharges	Levetiracetam 1,000 mg/day
8	28	EGTCS	40	GSW	Sodium valproate 900 mg/day
9	34	JME	35	GSW/multispike-wave discharges	Levetiracetam 2,000 mg/day Lamotrigin 100 mg/day
10	23	JME	180	Multispikes/multispike-wave discharges	Levetiracetam 1,000 mg/day
11	23	EGTCS	150	GSW	Topiramate 150 mg/day Levetiracetam 500 mg/day
12	26	JAE	66	3 Hz ictal GSW discharges	No medication
13	24	EGTCS	160	Generalised spikes/sharp waves	No medication
14	21	EGTCS	149	Pseudofocal frontal discharges	Levetiracetam 1,000 mg/day
15	42	EGTCS	180	Bilateral frontal spike wave discharges	No medication
16	47	EGTCS	26	GSW	Sodium valproate 1,000 mg/day
17	19	EGTCS	30	GSW	Levetiracetam 1,000 mg/day

EGTCS — epilepsy with generalised tonic-clonic seizures only; IED — interictal discharges; ID — ictal discharge; GSW — generalised spike-wave; JAE — juvenile absence epilepsy; JME — juvenile myoclonic epilepsy

Electromagnetic Tomography). This is one of the many methods of electrical source localisation that computes the 3D cortical distribution of current density.

LORETA

eLORETA (exact low resolution brain electromagnetic tomography) represents an improvement over previously developed LORETA tomographies and the standard version of LORETA (sLORETA) [14, 17]. eLORETA is a real inverse solution (not simply a linear imaging method) with zero error localisation in the presence of measurement and structured biological noise [15].

In eLORETA, we compared the cortical distribution of electric activity from the two groups to see the default mode function in patients with epilepsy who had discharges on EEG and control subjects. Practically, the oscillatory activity in eight EEG frequency bands was analysed: delta (0.5–4 Hz), theta (4–8 Hz), alpha 1 (8–10 Hz), alpha 2 (10–12 Hz), beta 1 (12–16 Hz), beta 2 (16–20 Hz), beta 3 (20–24 Hz) and gamma (32–80 Hz) [16].

The head model used in LORETA is the MNI152 template, with a three-dimensional solution space restricted to cortical grey matter. A total of 6,239 voxels at 5 mm spatial resolution represents the intracerebral volume [12, 17].

We defined five ROIs (regions of interest) to estimate the electrical activity from defined regions from the default mode network. The regions selected from the default mode network using MNI (Montreal Neurological Institute) space are described in Table 2. These regions of interest were selected for both hemispheres, and every ROI contained Talairach coordinates for these regions from the default mode network (the selection can be adjusted if a small number of voxels are defined).

We created ROIs in eLORETA from the following five brain regions belonging to the default mode network: posterior cingulate cortex from BA31 (PCC), medial prefrontal cortex from BA9 (MPFC), parahippocampal gyrus from BA36 (HF), inferior parietal cortex from BA40 (IPC), and middle temporal gyrus from BA39 (MTL). All voxels belonging to the same ROI were averaged in the transformation matrix.

Table 2. Regions of interest selected for default mode network

Lobe	Structure	Brodmann area	X-MNI	Y-MNI	Z-MNI
Limbic lobe	Parahippocampal gyrus	36	25	–35	–20
Limbic lobe	Parahippocampal gyrus	36	25	–30	–20
Temporal lobe	Middle temporal gyrus	39	–60	–60	10
Temporal lobe	Middle temporal gyrus	39	–55	–75	10
Limbic lobe	Posterior cingulate	31	–20	–65	15
Limbic lobe	Posterior cingulate	31	–10	–70	15
Parietal lobe	Inferior parietal lobule	40	–65	–40	25
Parietal lobe	Inferior parietal lobule	40	–65	–35	25
Frontal lobe	Medial frontal gyrus	9	–10	35	35
Frontal lobe	Medial frontal gyrus	9	–10	45	35

Table 3. Log of F ratio of spectral densities; LnF: Log of F ratio of spectral densities with 'Cohen's d' effect size: low = 0.2; med = 0.5; hi = 0.8

	LnF (0.01)	LnF (0.05)	LnF (0.10)	Extreme P
One-tailed (A > B):	0.786	**0.726**	0.696	0.01040
One-tailed (A < B):	–0.793	–0.731	–0.691	0.65700
Two-tailed (A < > B):	0.810	0.760	0.729	0.02360

The average activation for each region of interest for each timeframe in the epoch was computed. We obtained a matrix with five columns and 256 rows for each group.

We performed a statistical test known as a 't-statistic on Log transformed data' test in LORETA for independent groups A = B for all timeframes (frequencies). We conducted a voxel-by-voxel analysis of the current density distribution between the two groups with the help of statistical nonparametric mapping. We applied a log of F-ratio statistics for independent groups, a variance smoothing parameter of 0, and 5,000 randomisations for multi-comparison correction.

In these tests, threshold values were calculated ('log F-ratio') and a file was generated with extremes of probability (ExtremePs), the corresponding maximal thresholds, and thresholds at values of $p < 0.01$, $p < 0.05$ and $p < 0.10$ with $p < 0.05$ for statistical significance.

These statistical analyses are included in the sLORETA/eLORETA software package. The methodology, which is non-parametric, is based on estimating, via randomisation, the empirical probability distribution for the max-statistic (e.g. the maximum of a *t* or an *F* statistic), under the null hypothesis. There are also corrections for multiple testing [18].

Results

We obtained differences in our groups applying voxel-by-voxel F-ratio tests (Log of ratio of averages current densities in each frequency band). We obtained a value of 0.726 for LnF (0.05) corresponding to a p-value of 0.01040 (statistical significance for $p < 0.05$) one-tailed threshold, and a value of 0.760 for LnF (0.05) corresponding to a p-value of 0.02360 ($p < 0.05$) two-tailed threshold result (Tab. 3).

In LORETA, this value corresponded to the medial frontal gyrus (BA 9), meaning that generators of delta oscillations (low frequency band) are significantly different in epileptic patients who have electrical discharges in resting state conditions compared to healthy controls. This means that neurons from the medial frontal gyrus in epileptic patients oscillate more strongly than controls (Fig. 1).

In the second part, we obtained in LORETA a matrix for each group, with a column corresponding to each ROI defined and a line for each timeframe. The Wilcoxon rank-sum test for equality of medians (this test is a non-parametric version of the t-test for independent samples) was applied for all five features of interest (5 ROIs = 5 columns).

The null hypothesis (H0) was that the group with epilepsy (Epi) and the control group (C) had equal means, and the alternative hypothesis (H1) was that Epi features had different medians (two-tailed test), H1 Right was that Epi features had higher medians (one-tailed test), while H1 Left was that Epi had lower medians (one-tailed test). We obtained statistically significant values ($p = 0.0066$) for ROI 5, the one that corresponded to the left medial frontal gyrus (Fig. 2).

Discussion

We statistically compared the default mode function between patients with generalised epilepsy and healthy age-matched persons. We found differences in the middle frontal gyrus in the delta band for epileptic patients compared to controls, meaning that epileptic patients had a larger number of synchronous neurons in this region for delta oscillations than controls (with statistics for each frequency, for each voxel). For regions of interest defined from the default mode

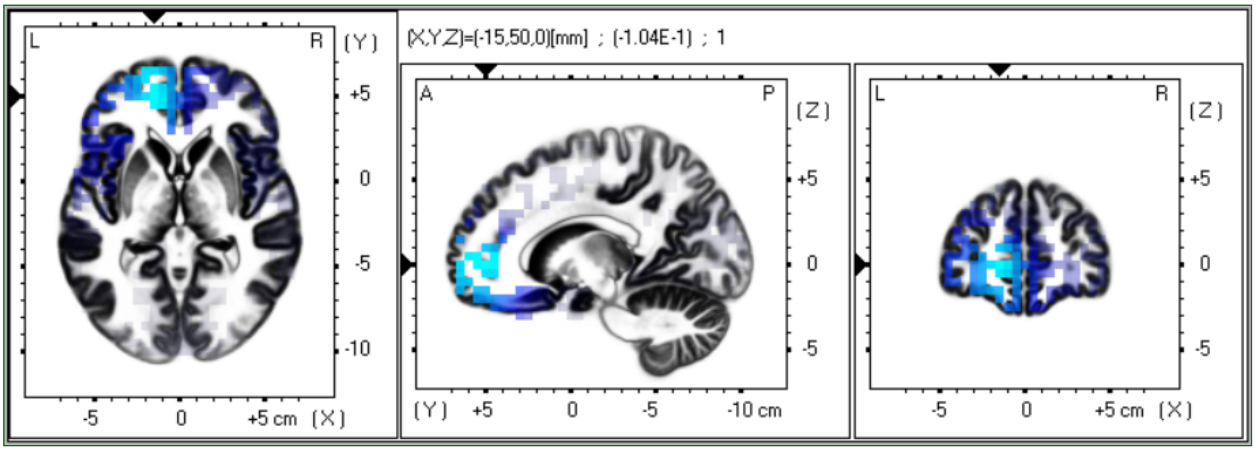

Figure 1. Log of F ratio statistics, for each frequency and each voxel. Electric neuronal activity corresponds to a colour scale

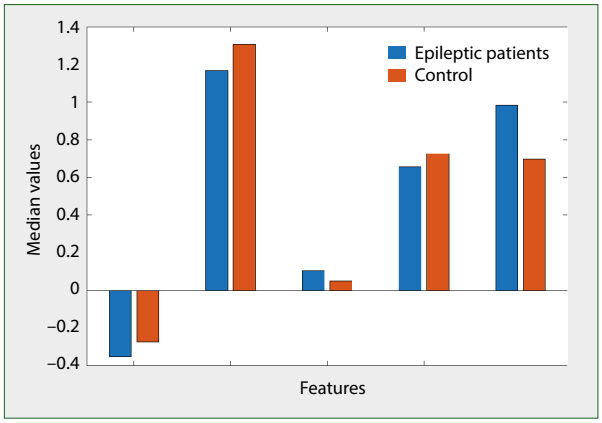

Figure 2. Results from Wilcoxon rank-sum test for two means after comparison of every matrix obtained (for epileptic group and control group) that contained values at specified ROIs; a significant difference (p = 0.0066) between ROI 5 corresponded to left medial frontal gyrus

network, we found statistically significant values for the left medial frontal gyrus.

As a result of these findings, we may be able to hypothesise a common mechanism underlying generalised epilepsy syndromes, but we can also speculate about the particularities of each type.

It has been demonstrated that regions from the default mode network (medial prefrontal cortex) are involved in focal activation of generalised spike-wave discharges in juvenile absence epilepsy. Using magnetoencephalography (MEG), these studies have pointed out that absences do not involve generalised cortical networks, but instead involve selected regions such as the orbital frontal and medial frontal regions [19].

Some data suggests that ictal discharges propagate through selective cortical networks, including orbital frontal and mesial frontal regions, rather than being truly 'generalised' in primary generalised epilepsy with absences. It has been clear since the early neurophysiological studies of fronto-thalamic enhancing responses that orbital and frontopolar control the thalamic regulatory mechanisms [20, 21].

Other MEG studies that use graph theory and coherence have compared focal and generalised epilepsies in a resting state. They have demonstrated increased network connectivity in bilateral mesial-frontal and motor regions in patients with idiopathic generalised epilepsy [22, 23].

Another fMRI-EEG study on 12 patients with genetic generalised epilepsy that used dynamic causal modelling found that DMN can be considered a gateway to generalised spike-wave discharges. The authors analysed the interactions between DMN, dorsal attention network, salience network and thalamus to see what role they played in down-regulation of consciousness. It was concluded that DMN had a driving role in this mechanism, although there were many differences between patients and there was heterogeneity in the results [24].

Other EEG-fMRI studies in IGE have revealed BOLD changes in posterior cingulate, lateral parietal and frontal cortices a few seconds before the onset of generalised spike-wave discharges. This suggests an essential role of DMN in GSWDs mechanism [25].

Network studies such as integrated value of influence have found an important role played by nodes such as the insular gyrus and left inferior parietal gyrus at 3-4 Hz during spike-wave activity in patients with generalised tonic-clonic seizure alone, suggesting that some nodes of a particular network may play a crucial role in generating GSWDs [26].

Some EEG-fMRI studies have attempted to find specific brain regions activated prior to generalised discharges; they found inconsistently activated regions prior to generalised spike-waves such as the precuneus, prefrontal and parietal cortical regions [27–29]. A high sensorimotor synchrony and a low posterior network synchrony before generalised spike-wave discharge has been shown; this is speculated to be a predisposing state for discharges [30].

According to some authors, network analysis might be a way to predict seizures. Clinical application of functional connectivity analysis could impact upon epilepsy diagnosis and treatment, but validated results are required [31]. Some researchers even believe that network analysis could be superior to conventional EEG in the diagnosis of epilepsy [32, 33].

Many recent studies have suggested that generalised epilepsy causes increased focal epileptogenic hubs that trigger generalised epileptic discharges. 'Cortical focus theory' describes an epileptogenic focus that entails generalised discharges through corticothalamic and corticocortical networks. These findings may have an impact on physiopathology and treatment options [23].

One of the brain regions particularly related to cognition and execution is the medial frontal gyrus, a part of the prefrontal cortex [34]. It has been found that patients with idiopathic generalised epilepsy have increased grey matter abnormalities in their medial fontal gyrus, and that the thalamo-frontal network has abnormalities in generalised epilepsy subtypes [35]. These particularities may be useful in patients resistant to antiepileptic drugs.

For the most part, generalised epilepsies respond well to treatment, but remission probability decreases as more antiepileptic drugs are used [36]. Increasing understanding of pathophysiology and connectivity may lead to new approaches in such cases.

Neuromodulation is an alternative treatment for patients with drug-resistant genetic generalised epilepsy after the failure of multiple anti-seizure medications. Various factors influence the outcome of neurostimulators (mainly DBS) including electrode placement, stimulation parameters, the subtype of epilepsy, and the individual cortical-subcortical connectivity profile [36, 37].

Numerous advanced noninvasive studies have supported this view by highlighting the importance of early cortical involvement, particularly in the frontal and the parietal cortex [23].

Limitations

Several limitations should be considered with regard to the current study. Firstly, we included a small number of patients limited to specific non-parametrical statistical tests. Secondly, it is difficult to divide patients into groups with specific generalised epileptic syndrome. Thirdly, larger studies may compare these parameters found in default mode network with other networks such as the dorsal attention network, and salience network. To confirm the present findings, future studies should include more patients and healthy subjects.

Our study was also limited by the small number of electrodes used for electrical source imaging, especially in the temporal region. The influence of gender on the default mode network was not described, and this represents another limitation of the study.

Conclusions

Our study supports the idea of a move away from a generalised theory to a more focused one in generalised epilepsies. We found that the left medial frontal gyrus synchronises more easily, and we hypothesise that this could be more than a co-activation during generalised epileptic activity.

Searching for subtle interictal epileptiform discharges that are not recognised by visual inspection on EEG might be an interesting research area in defining focal abnormalities in generalised epileptic syndromes. New insights into physiopathology will continue to improve treatment options regarding generalised epilepsy.

Article information

Data availability statement: *Datasets analysed in this study are available from the corresponding author upon reasonable request.*
Ethics statement: *Due to the retrospective nature of this study, institutional consent was obtained prior to the study.*
Authors' contributions: *CEB and DIC designed study; CEB collected and analysed data; IS compiled statistics; CEB wrote manuscript. All authors approved final manuscript.*
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