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Epileptic diathesis: An EEG-LORETA study

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HIGHLIGHTS

- EEG theta activity reflects the degree of epileptic diathesis.
- Theta activity shows a common topographical pattern in generalized and focal epilepsy.
- Electroencephalography is correlated with epileptic diathesis, regardless of the syndrome.

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ABSTRACT

Objective: Epileptic diathesis is an inherited neurophysiological trait that contributes to the development of all types of epilepsy. The amount of resting-state electroencephalography (EEG) theta activity is proportional to the degree of cortical excitability and epileptic diathesis. Our aim was to explore the amount and topographic distribution of theta activity in epilepsy groups. We hypothesized that the anatomical distribution of increased theta activity is independent of the epilepsy type.
Methods: Patients with unmedicated idiopathic generalized epilepsy (IGE, n = 92) or focal epilepsy (FE, n = 149) and non-seizure patients with mild to moderate cerebral lesions (NONEP, n = 99) were compared to healthy controls (NC, n = 114). We analysed artifact-free EEG activity and defined multiple distributed sources of theta activity in the source space via low resolution electromagnetic tomography software. Age-corrected and Z-transformed theta values were compared across the groups.
Results: The rank of increased theta activity was IGE > FE > NONEP > NC. Both epilepsy groups showed significantly more theta activity than did the NC group. Maximum theta abnormality occurred in the medial-basal prefrontal and anterior temporal cortex in both epilepsy groups.
Conclusions: We confirmed the hypothesis outlined above.
Significance: The common topographical pattern of increased EEG theta activity is correlated with epileptic diathesis, regardless of the epilepsy type.

1. Introduction

The term "epileptic diathesis" appeared more than 150 years ago in medical writings (Shorvon, 2011). In the second half of the last century, prominent investigators agreed that epileptic diathesis denotes genetically determined seizure liability, which contributes to the development of epilepsy (Lennox, 1960; Gastaut, 1969; Gloor et al., 1982). Prior and recent research results support this concept. Syndrome-specific magnetic resonance imaging (MRI) abnormalities (Tashkandi et al., 2009) and syndrome-specific epileptiform discharges (Wandschneider et al., 2019) characterise patients with idiopathic generalized epilepsy (IGE) and their asymptomatic, first-degree relatives. This means that syndrome-specific pathology and electrical dysfunction do not necessarily cause epilepsy; individual predisposition is also needed to express the complete IGE phenotype. An investigation of the aetiology of focal epilepsy (FE) led to the same conclusion. For example, FE develops in 30–50% of patients with an open head injury (Giordano et al., 2011) and in approximately 33% of those with cerebral glioma (Gray and Bulstrode, 2011). Thus, individual predisposition also seems to be necessary for the development of FE. Furthermore, genetically determined individual seizure liability is a necessary aetiological factor for the broad spectrum of the so-called "seizure disorders" (Hauser, 1992). Family studies further support the genetic determination of epileptic diathesis. Epilepsy with a postnatal-acquired aetiology (head trauma, stroke) has a greater probability of developing in patients with a family history of epilepsy as compared to

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those without said family history (Perucca and Scheffer, 2021). Several authors conceptualized the epileptic diathesis as a quantitative trait, where the amount of epilepsy-susceptibility genes matters (Berkovic et al., 2006; Helbig et al., 2016).

The neurophysiological basis of epileptic diathesis is increased cortical excitability due to an altered balance of excitatory and inhibitory neuronal processes in favour of the former (Gloor et al., 1982). In fact, all epileptogenic genetic variations cause increased neuronal excitability (Thakran et al., 2020). Recently, a transcranial magnetic stimulation (TMS) study confirmed that increased cortical excitability is the physiological basis of epileptic diathesis (Badawy et al., 2013). The authors demonstrated that increased cortical excitability is heritable and concerns both hemispheres in patients with IGE and in asymptomatic siblings of patients with IGE and/or FE. They labelled this property of the cortex "the epileptic trait", which is synonymous to epileptic diathesis.

Cerebral field potentials reflect the degree of cortical excitability. A direct relationship exists between increased cortical excitability, increased synchronization of field potentials (electroencephalographic [EEG] oscillations, evoked potentials), and the occurrence of seizures in experimental settings (Gloor et al., 1982; van Gelder et al., 1983; Kostopoulos, 1986) and in human epilepsy (Tassinari and De Marco, 1985; Iwasaki et al., 2010; Brinciotti et al., 2020). A strong, band-specific correlation exists between TMS-defined increased cortical excitability and EEG spectral power in the theta band ($p < 0.0001$), in contrast to no correlation (p-values within 0.13–0.95) between cortical excitability and activity in the delta, alpha, and beta bands (Ly et al., 2016). Other authors demonstrated proportionality between theta band EEG oscillations and the degree of genetic determination of the main epilepsy types (Clemens et al., 2021).

A neglected area of research is the relationship of increased theta activity to gross cortical anatomy. Prior studies were carried out in the sensor space (Miyauchi et al., 1991; Diaz et al., 1988; Clemens et al., 2000), but no investigations to date addressed the distribution of increased theta activity in the source space. The aim of the present study was to explore and demonstrate the anatomical distribution of increased theta activity in IGE and FE in the source space. We set and tested the hypothesis that a common, three-dimensional pattern of increased theta activity characterises the two epilepsy types. This implies that the anatomical distribution of increased theta activity is independent of the epilepsy type. We based the hypothesis on the assumption that genetically determined seizure susceptibility is a basic, quantitative trait (Hauser, 1992) that is independent of the syndrome-specific epileptogenic gene variants (Thakran et al., 2020) and acquired causes of epilepsy.

2. Patients and methods

2.1. The "Epi-Stat" database

The investigation was based on the "Epi-Stat" epilepsy database developed at the Epilepsy Outpatient Service, Neurology Unit, Kenézy Campus, University of Debrecen. The database contains structured clinical, EEG, laboratory, neuroimaging, and other findings of patients with epilepsy, stemming from the patients' initial evaluation and follow-up. The University of Debrecen is the first referral centre for patients with epilepsy in Hajdú-Bihar County, Hungary. We evaluate children, adolescents, and adults with seizure disorders. We generally exclude those with an onset of epilepsy in the first four years of life, though we occasionally include such young patients. Patients with severe initial conditions are first referred to emergency units of Debrecen University. However, later treatment and follow-up takes place at the Outpatient Service, where we enter the data into Epi-Stat. The patient sample of Epi-Stat therefore mirrors the general epileptic population except the above-mentioned young cohort. Board-certified neurologists enter the data into Epi-Stat. The EEG Laboratory and the staff are also board-qualified. Epi-Stat therefore facilitates epilepsy and EEG research.

2.2. Patient selection

The research ethics committee of the institution approved the study protocol, which was based on the analysis of already accumulated results of Epi-Stat. Clinical, EEG, and other data were issued from a routine initial evaluation of the patients. For study purposes, we identified the patients by serial number and shielded personal identifiers. The workflow of evaluation was rapid and included a thorough medical history; urgent medical, laboratory and neurological evaluations; EEG; and imaging of cranial structures. The correct delineation of the epilepsy syndrome or, at least, the type of epilepsy (Scheffer et al., 2017) subserves successful drug treatment. We therefore started treatment after the acquisition of the main diagnostic findings. Exceptions were *de novo* severe epileptic conditions that needed immediate treatment, tailored to the individual circumstances.

We screened Epi-Stat for patients with IGE and FE as defined by the latest Classification (Scheffer et al., 2017) whose data entered the database in the period of January 2008 to December 2020. The flowchart shows our inclusion and exclusion criteria (Fig. 1). The inclusion criterion was an unequivocal IGE or FE diagnosis, based on clinical and paraclinical (EEG, MRI, and laboratory) findings. We did not include children younger than four years at the first seizure. The age limit was justified because of the composition of the database (Section 2.1) and poor cooperation of younger patients in the EEG setting. We did not include patients without IGE but with genetic generalized epilepsy (GGE) because these conditions (encephalopathy and/or mental retardation) frequently cause an excess of slow EEG activity. We did not include those patients with GGE (genetic generalized epilepsy) who were non-IGE patients because these conditions (encephalopathy and/or mental retardation) frequently cause an excess of slow EEG activity. We did not include patients with the so-called "combined" epilepsy who have focal and generalized seizures because they escaped the generalized versus focal epilepsy dichotomy of the study design.

The exclusion criteria were as follows: comorbidity as a metabolic disorder (for example, diabetes and endocrine disorders), central nervous system (CNS) disorders other than epilepsy including psychiatric comorbidity, clinically evident mental retardation, sleep apnoea syndrome, space-occupying cerebral lesions, and the use and abuse of neuroactive compounds that can modify the clinical presentation of epilepsy and alter EEG activity (Sannita, 2006). The EEG exclusion criteria ("inappropriate EEG record" in the flowchart) were a lack of waking activity in the record, poor quality of records, postictal EEG (recorded within 48 hours after a major motor seizure), and records without posterior rhythmic activity (including low voltage EEG). Of note, EEG records reflected cerebral activity at the first presentation of the patient. We circumvented potential confounders as detrimental effects of the long-lasting disease, effects of severe seizures, and drug effects in this way.

2.3. Study groups

Table 1 shows the demography and composition of the study groups. The IGE group ($n = 92$) comprised patients with childhood absence epilepsy ($n = 31$), juvenile absence epilepsy ($n = 7$), juvenile myoclonic epilepsy ($n = 29$), and epilepsy with generalized tonic-clonic seizures exclusively ($n = 25$). Patients in the FE group

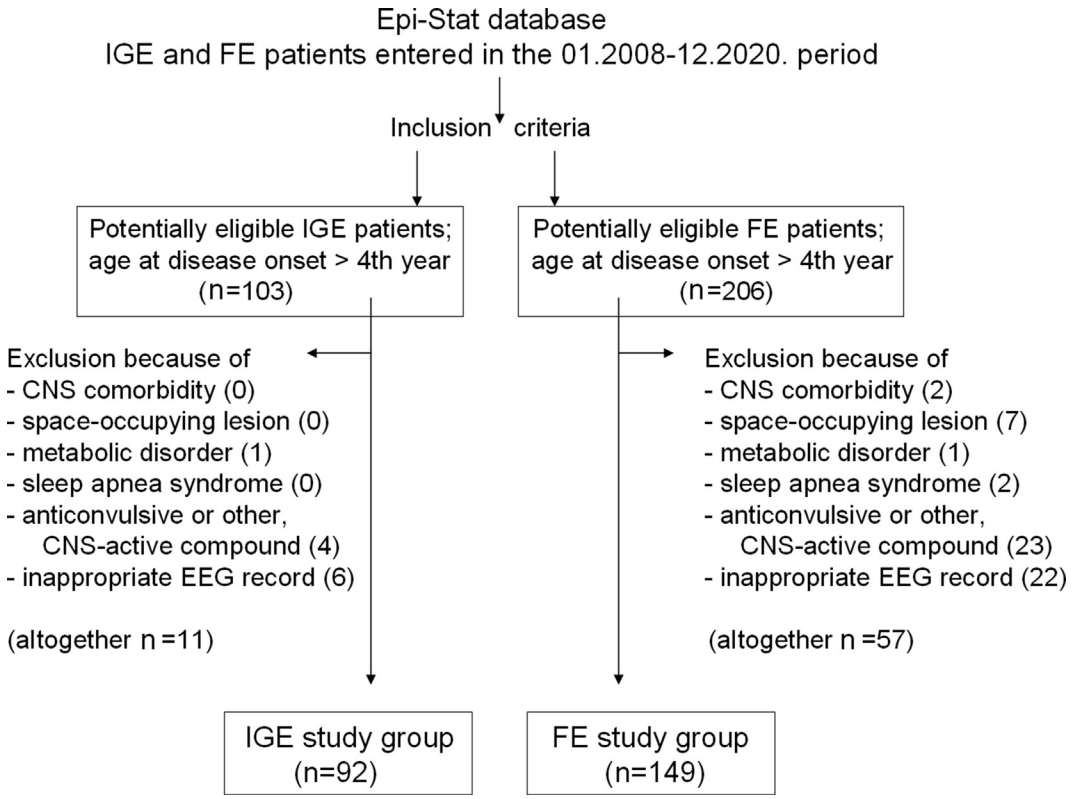

Fig. 1. Flowchart of the study. Inclusion and exclusion criteria. (IGE: idiopathic generalized epilepsy, FE: focal epilepsy, CNS: central nervous system.)

Table 1
Age- and sex composition of the study groups. M / F indicates male / female (IGE: idiopathic generalized epilepsy, FE: focal epilepsy, NONEP: non-seizure patients with mild to moderate cerebral lesions, NC: healthy controls).

Study Group	Number	Minimum Age (years)	Mean Age (years)	Maximum Age (years)	M/F Ratio
Idiopathic generalized epilepsy (IGE)	92	6.0	19.2	54.3	21/71
Focal epilepsy (FE)	149	4.6	28.8	92.6	69/81
Non-epilepsy (NONEP)	99	13	53.0	87.9	32/48
Normal controls (NC)	114	4.6	25.0	78.5	50/64

(n = 149) were classified according to the aetiology as defined by Scheffer (Scheffer et al., 2017): structural aetiology (n = 70), infection (n = 13), genetic (n = 7), immune (n = 2), and unknown aetiology (n = 57). As to the anatomic substrate of epilepsy, we sorted out "unifocal" patients with FE in whom ictal semiology and/or ictal EEG records argued for a single epileptic focus. We subdivided the 76 unifocal patients according to the lobar localisation of the focus. The anterior (ANT) group comprised patients with frontal, anterior, and medial temporal foci (n = 44). The posterior group (POST) comprised patients with parietal, posterior temporal, and occipital foci (n = 23). Nine unifocal cases escaped the ANT-POST dichotomy because the ictal data indicated simultaneous involvement of the pre- and postcentral areas (frontal and parietal lobes). All of the unifocal patients entered laterality analysis. Patients with unequivocally lateralising seizure symptoms and/or ictal EEG records were sorted into the LH (left hemisphere) group (n = 31) or the RH (right hemisphere) group (n = 45).

The non-epilepsy group (NONEP) was composed of outpatients who had a chronic cerebral disorder without seizures. The neurological conditions were non-severe multifocal vascular encephalopathy (n = 19); relapsing-remitting multiple sclerosis with 1.5 to 3.0 expanded disability status scale scores (EDSS) (n = 23); dementia due to Alzheimer's disease with 14 to 24 mini mental state examination scores (n = 18); and residual, mild to moderate post-stroke conditions (n = 19). Patients with objective symptoms of minor CNS dysfunction, normal MRI, and no definite diagnosis were also included in the NONEP group (n = 20). The patients did not take neuroactive medication except compounds that slowed down disease progression in the multiple sclerosis group and dementia due to Alzheimer's disease group. Cranial MRI showed mild to moderate abnormality as usual in the above-listed conditions or no abnormality at all.

The normative control group (NC) was composed of 114 healthy volunteers aged from 4 to 78 years who were recruited from nurses working at the hospital, their family members, friends, and the staff of the EEG laboratory. They had no history of neurological and psychiatric disorders, no painful or debilitating non-CNS disease, and did not take medication that might modify EEG activity. Their EEG activity was within the normal limits.

2.4. EEG recording, epoch selection, frequency analysis

We recorded 30 to 40 minutes of EEG in a semi-isolated room with digital EEG equipment. Silver-silver chloride electrodes were placed according to the 10–20 system positions and the earlobes. Electrode impedance did not exceed 10 kOhms. The physical reference was in the Fpz position, but we recomputed EEG against a mathematical linked ears reference. Filters were set at 0.1 and

33.6 Hz; the sampling rate was 256 per second, and on-line digitization was 12 bit. Samples were forwarded to the NeuroGuide software version 2.8. We selected the best 90 artifact-free two-second epochs for quantitative EEG analysis. The epoch selection criteria were as follows: presence of physiological posterior alpha activity; absence of artifacts, epileptiform potentials, and other non-stationary elements; and absence of patterns that indicated drowsiness or arousal. We computed spectral power via Fast Fourier Transform for the theta band (3.5 to 7.0 Hz). We used two reproducibility measures to minimize the effect of short- and long-term variability within the samples. Each sample showed at least 90% split-half and test–retest reliability (averaged over the 19 channels). The senior author supervised the selected epochs before low resolution electromagnetic tomography (LORETA) analysis.

2.5. LORETA analysis

LORETA is a widely used topographic analysis method that transforms the scalp electric potential field to current source density values (CSD, amperes per meters squared) for 2394 cortical voxels. The LORETA inverse solution is based on existing neuroanatomical and physiological knowledge and a mathematical constraint called the smoothness assumption, (Pascual-Marqui et al., 1994). A comprehensive evaluation of LORETA is available in several articles (Pascual-Marqui et al., 2009). The latest Guideline of the International Federation of Clinical Neurophysiology concluded that LORETA with the 19 standard electrodes of the 10–20 system is an appropriate method to estimate neuronal synchronization and localise generator sources at the lobar level when widely distributed resting-state activity is addressed (Babiloni et al., 2019). Human cortical theta is in fact a ‘‘diffuse and pervasive rhythm” (Puligheddu et al., 2005); therefore, LORETA analysis was an appropriate method in the setting.

Spectral data in the theta band (Section 2.4) were input into LORETA analysis in this study. We transformed voxel-wise raw CSD values into age-adjusted and Z-scored values according to the LORETA normative database (Thatcher et al., 2005). The software compared each raw CSD value of the evaluated person to the mean CSD of the topographically corresponding voxel and age group of the normative database. We expressed the degree of abnormality by Z-statistics. The Z-score indicated the statistical distance of the individual CSD value from the corresponding normative mean value ($Z = 0$). Positive and negative Z-values indicated increased ($Z > 0$) and decreased ($Z < 0$) theta activity, respectively. Colour-coded voxel-wise CSD values were projected on a T1 MRI template developed at Montreal Neurological Institute (https://link.springer.com/chapter/10.1007/978-1-4615-2546-2_48.). Three-dimensional localisation of the voxels was given by (x), (y), and (z) coordinates of the Talairach system (Talairach and Tournoux, 1988). A cursor helped read-off of the CSD value in the voxels of interest.

Normative EEG databases are independent of race and geography (John et al., 1983; Thatcher et al., 2005). However, hardware characteristics, minor differences in epoch selection, and other factors, including body position at EEG recording, can skew the results (Spironelli et al., 2016). To circumvent possible bias, we compared the patients' Z-scored data to those of our NC group (Section 2.3). We investigated NC persons in our laboratory, with the same equipment, in the same way we examined the patients.

2.6. Rationale of main group comparisons

We compared the amount of EEG theta activity in the IGE and FE groups to that of the NC group to assess the total difference between patients and healthy controls. We previously ascertained the relationship between resting-state EEG theta activity and clinical data that implied a greater and lesser degree of genetic determination of epilepsy. In concrete terms, a quantitative estimate of heritability of the epilepsies (Peljto et al., 2014) and positive family history of seizures (in our sample) were related to increased mean theta activity in an epilepsy cohort that was in gross overlap with the present study population (Clemens et al., 2021). The present study was an extension of our prior findings with the topographic aspect and introduction of a non-epilepsy (NONEP) group as follows.

Mild to moderate structural brain abnormality might contribute to increased theta activity (Cobb, 1976). In fact, some degree of structural abnormality also characterises patients with IGE and FE (Hatton et al., 2020). To estimate the theta-increasing effect of the lesional factor, we compared the NONEP and NC groups. The NONEP group was the best surrogate for lesional patients without epilepsy that were available in the database to form a control population. In addition, we compared the IGE and FE groups to the NONEP group. We expected that the epilepsy groups (that were characterised by genetic and presumed lesional theta-increasing effects) would show a greater amount of theta activity than would the NONEP group (with the presumed lesional theta increase alone).

2.7. Effect of unilateral epileptic dysfunction on theta activity

A neurophysiological analysis revealed that resting cortical excitability is greater in the hemisphere of the focus than in the opposite hemisphere in patients with FE (Badawy et al., 2007, 2013). Thus, we expected a greater amount of theta activity in the hemisphere of the focus than in the opposite one. To test this assumption, we compared the LH and RH groups to the NC group.

2.8. Effect of anterior versus posterior focus localisation on the distribution of theta activity

In theory, focal epileptic processes and epileptic activity might modify cortical excitability and electric activity; in concrete terms, theta activity. We therefore investigated the possible modification of theta topography in the ANT and POST groups (see Section 2.3).

2.9. Statistical analyses

Statistical analysis was carried out according to the Editorial ‘‘Statistical data analyses for clinical neurophysiology” (Stecker et al., 2017). To check the statistical normality of the voxel-wise LORETA-Z values, we applied Shapiro-Wilk normality tests (Shapiro and Wilk, 1965) to all of the voxels. After false discovery rate (FDR) corrections (Benjamini and Hochberg, 1995) of the p-values of the normality tests, we found that three to six percent of the voxels showed non-normality. Due to these low values, we decided to compute group differences via multiple Student's t-tests. FDR-corrected $p < 0.05$ values were accepted as statistically significant.

2.10. Demonstration of the results

LORETA figures (Figs. 2 and 3) were three-dimensional FDR-corrected t-maps that were generated automatically at the site (voxel) with maximum t-value. They allowed the visual localisation of the maxima and topographic gradients of theta activity across the study groups; for example, the IGE-NC and FE-NC comparisons. However, the selected planes did not demonstrate all of the cortical areas. We therefore used a different approach, numerically expressing the maximum abnormality (FDR-corrected t-values) in 10 anatomical areas in both hemispheres. We parcelled

the cortex into medial and lateral parts of the prefrontal, frontal, temporal, parietal, and occipital cortices, according to anatomical boundaries (Zilles, 2004). We identified maximum theta activity in each area and tabulated the findings.

3. Results

3.1. Main comparisons

Increased theta activity emerged in the IGE group as compared to the NC group. The difference was statistically significant in all of the voxels. FDR-corrected $p = 0.05$ corresponded to $t = 3.59$. Maximum abnormality ($t = 9.89$) occurred in the medial prefrontal cortex (Fig. 2, top), followed by the anterior medial temporal cortex ($t = 8.33$), and decreased towards the remaining cortical areas in both hemispheres (Table 2, top).

Increased theta activity characterised the FE group as compared to the NC group. The difference was statistically significant in all of the voxels. The magnitude of the abnormality was less than in the IGE group. FDR-corrected $p = 0.05$ corresponded to $t = 4.14$. Maximum abnormality occurred in the medial prefrontal cortex ($t = 6.61$), followed by the anterior temporal cortex ($t = 6.20$). The topography of the maximum abnormality was exactly the same as in the IGE group, as shown by the same Talairach coordinates (Fig. 2, bottom). The abnormality decreased in the remaining cortical areas (Table 2, bottom).

Apart from the two small areas in the right frontal and temporal cortices, all of the voxels showed a greater amount of theta activity in the NONEP than in the NC group. The differences were not statistically significant in any voxel ($p >$ FDR-corrected 0.05).

Increased theta activity characterised the IGE group as compared to the NONEP group in all of the voxels (Fig. 3, top). FDR-corrected $p = 0.05$ corresponded to $t = 4.24$. The difference was symmetrical and statistically significant in the frontal lobes and in the anterior part of the temporal lobes. Maximum abnormality occurred in the bilateral medial-basal prefrontal cortex ($t = 7.19$), followed by the right anterior temporal cortex ($t = 6.18$).

Increased theta activity emerged in the FE group as compared to the NONEP group in all of the voxels (Fig. 3, bottom). FDR-corrected $p = 0.05$ corresponded to $t = 4.34$. A statistically significant difference emerged in a limited cortical area in the right basal prefrontal cortex ($t = 4.37$), but not in the rest of the cortex.

3.2. Effect of lateralised epileptic processes on theta activity

A comparison of the topographic distribution of theta activity did not show a statistically significant difference between the LH and RH groups (uncorrected $p > 0.05$).

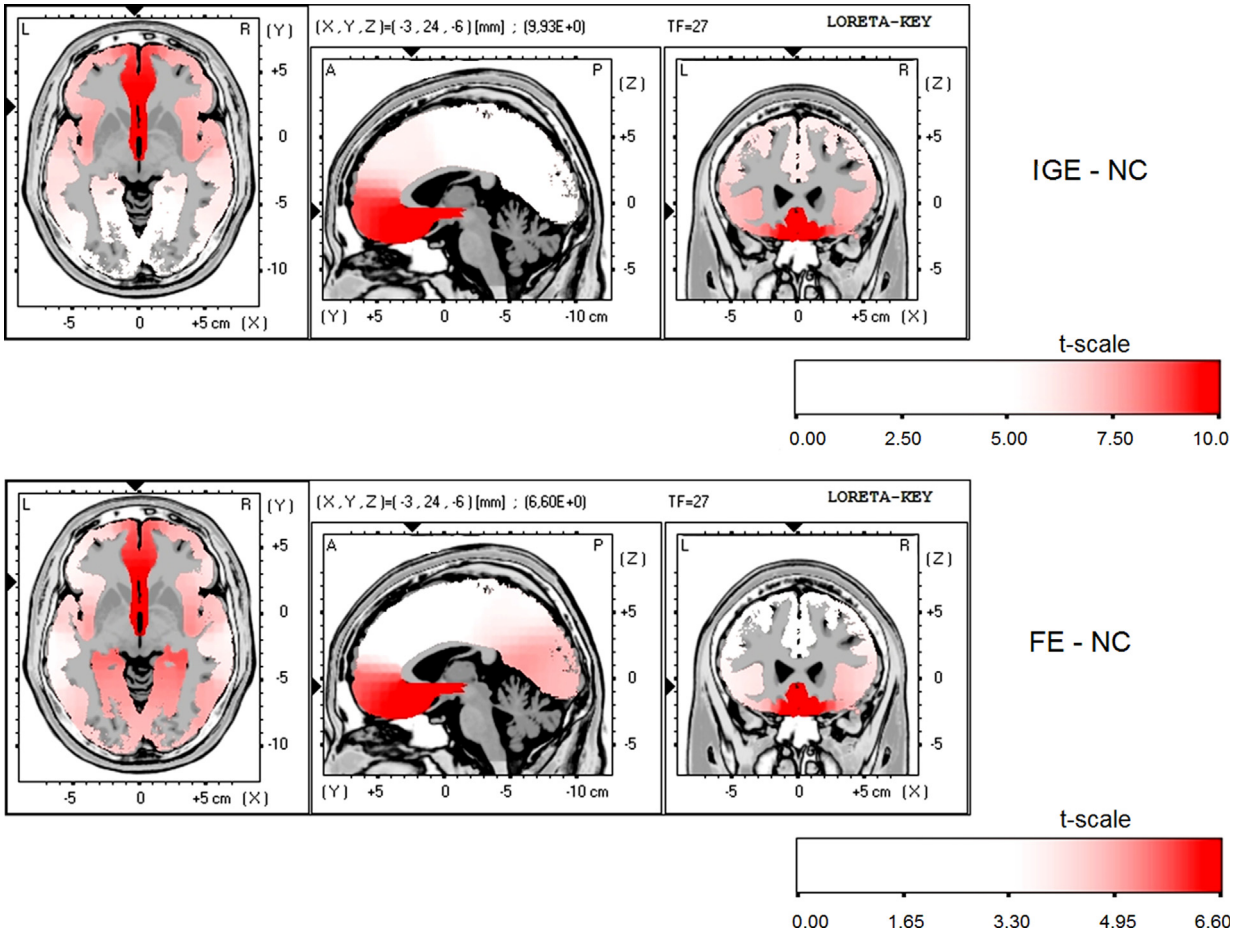

Fig. 2. Topographic distribution of increased theta activity in the epilepsy groups as compared to the NC group. Top: Increased amount of theta activity emerged in the IGE group as compared to the NC group. The difference was statistically significant in all of the voxels. FDR-corrected $p = 0.05$ corresponded to $t = 3.59$. The figure focuses on the area of greatest abnormality, in the inferior medial prefrontal cortex ($t = 9.98$). The degree of the abnormality decreased towards the anterior temporal cortex, insula, the rest of the frontal lobe, and the remaining cortical areas. Bottom: Increased amount of theta activity characterised the FE group as compared to the NC group. Overall, the magnitude of the abnormality was less than in the IGE group. However, the difference was statistically significant in all of the voxels. FDR-corrected $p = 0.05$ corresponded to $t = 4.14$. Maximum abnormality occurred in the medial prefrontal cortex ($t = 6.61$). The topography of the maximum abnormality was exactly the same as in the IGE group, as shown by the same Talairach coordinates. (IGE: idiopathic generalized epilepsy, FE: focal epilepsy, NC: healthy controls, CNS: central nervous system.)

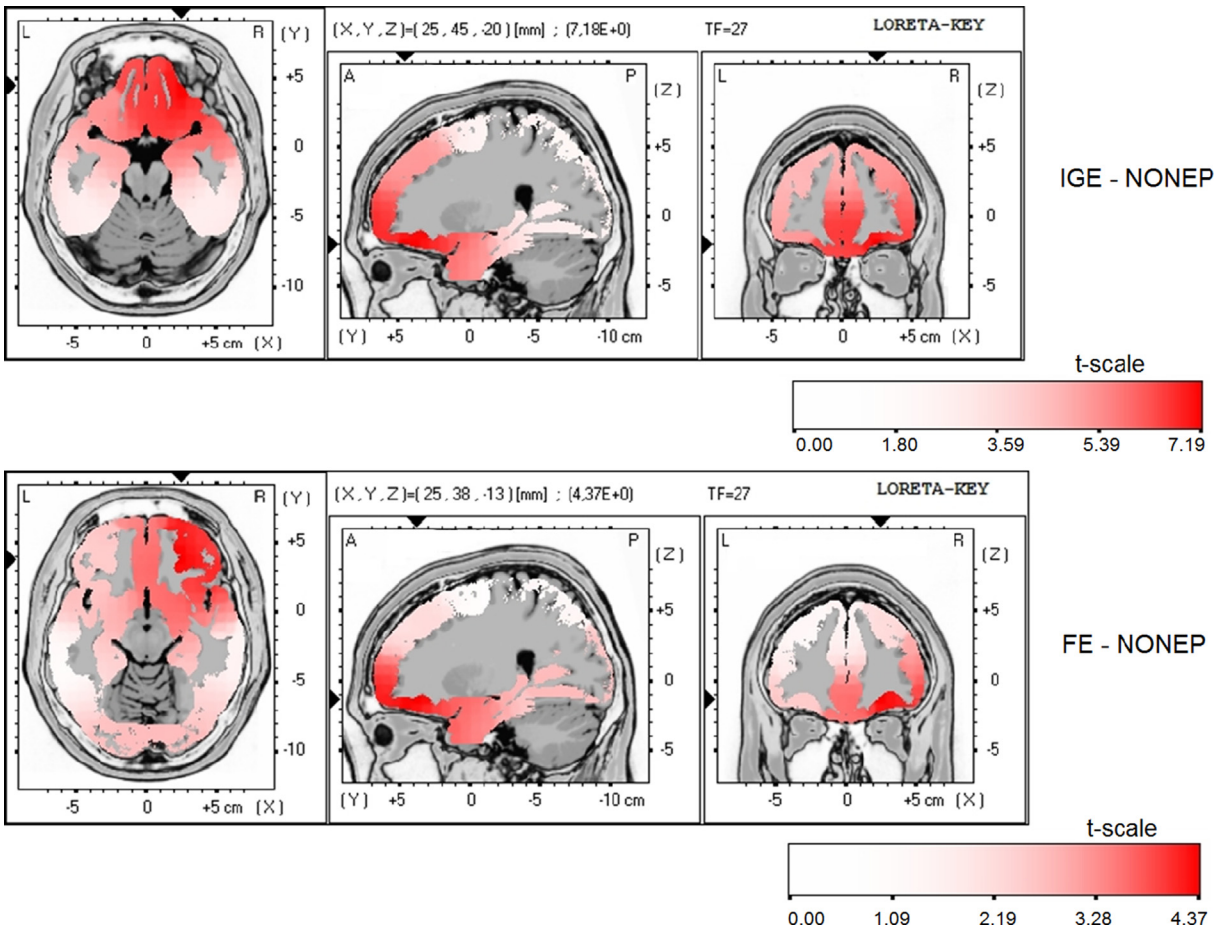

Fig. 3. Topographic distribution of increased theta activity in the epilepsy groups as compared to the NONEP group. Top: Increased theta activity characterised the IGE group as compared to the NONEP group in all of the voxels. FDR-corrected $p = 0.05$ corresponded to $t = 4.24$. The difference reached statistical significance in the frontal lobe and in the anterior part of the temporal lobe, symmetrically. Maximum abnormality occurred in the bilateral medial-basal prefrontal cortex ($t = 7.19$), followed by the right anterior temporal cortex ($t = 6.18$). Bottom: Increased theta activity emerged in the FE group as compared to the NONEP group in all of the voxels (Fig. 3, bottom). FDR-corrected $p = 0.05$ corresponded to $t = 4.34$. Statistically significant differences emerged in a limited cortical area in the right basal prefrontal cortex ($t = 4.37$) but not in the rest of the cortex. (IGE: idiopathic generalized epilepsy, FE: focal epilepsy, NONEP: non-seizure patients with mild to moderate cerebral lesions.)

3.3. Effect of anterior vs. posterior foci on theta activity

A comparison of the topographic distribution of theta activity did not show a statistically significant difference between the ANT and POST groups (uncorrected $p > 0.05$).

4. Discussion

We investigated the relationship of theta activity to cortical anatomy. Prior EEG topographic studies outlined diffuse distribution of increased theta activity in the sensor space, with moderate topographic resolution (Miyauchi et al., 1991; Díaz et al., 1998; Clemens et al., 2000). However, technical differences in EEG recording, analysis, and statistics did not permit a comparison of the FE and IGE findings. To date, this is the first known topographic investigation that evaluated all study groups by exactly the same methods and advanced statistics that allowed their straightforward comparison. In brief, we confirmed a diffuse excess of theta activity in the source space in both epilepsy groups as reported in the aforementioned prior studies. In addition to testing the hypothesis outlined in (Section 1), the aim of the study was to estimate the possible theta-modifying effect of structural abnormalities (Hatton et al., 2020) in the epilepsy groups. Finally, we investigated the effects of focal epileptic activity on theta topography.

4.1. Common pattern of increased theta activity

Despite the multitude of genetic and acquired aetiological factors in IGE and FE that are involved in the diversity of cerebral structure, metabolism, and electrical function, maximum theta abnormality emerged in exactly the same cortical areas in the IGE and FE groups (Fig. 2). This finding supported the hypothesis that the neurophysiological basis of the epileptic diathesis is independent of the epilepsy type. We localised the main generator ensembles of theta activity in the prefrontal and temporal limbic cortical areas, which are parts of the most epileptogenic network within the brain (Schwartzkroin and McIntyre, 1997; Bertram et al., 1998). Abnormal activity of this network is a shared feature of the epilepsy types and blurs the border between them (Bertram et al., 1998), as exemplified by many patients in clinical practice (Onat et al., 2013).

The magnitude of theta excess was greater in the IGE than in the FE group. This finding suggested that the degree of epileptic diathesis is greater in IGE than in FE. The results corresponded with a greater degree of genetic determination and heritability in IGE than in FE (Peljto et al., 2014). Besides non-specific epileptic diathesis, specific epileptogenic gene variants contribute to some IGE and FE syndromes as well (Takhran et al., 2020). There is some EEG-based evidence that at least IGE syndromes show in part dissimilar topographic patterns of increased theta activity (Clemens

Table 2
Regional results of LORETA analysis. IGE-NC comparison (top), FE-NC comparison (bottom). Student's *t*-values indicate maximum theta abnormality in ten cortical regions in the left and right hemispheres (LH and RH, respectively). *t*-values were not always symmetrical therefore rank of regional abnormality was based on (LH + RH)/2 values. Statistical significance (FDR-corrected $p < 0.05$) corresponded to $t = 3.59$ and $t = 4.14$ for the IGE-NC and FE-NC comparisons, respectively. (IGE: idiopathic generalized epilepsy, FE: focal epilepsy, NONEP: non-seizure patients with mild to moderate cerebral lesions, NC: healthy controls).

IGE - NC **Cortical region**	***t* max** **LH**	***t* max** **RH**	***t* max** **(LH + RH)/2**
medial prefrontal	9.89	9.89	9.89
medial temporal	8.33	8.33	8.33
lateral prefrontal	7.44	7.48	7.46
lateral temporal	7.44	7.44	7.44
lateral frontal	6.89	6.97	6.93
lateral parietal	4.98	5.76	5.37
medial frontal	5.30	5.30	5.30
lateral occipital	4.63	5.22	4.93
medial parietal	4.83	4.87	4.85
medial occipital	4.67	4.56	4.62
FE - NC **Cortical region**	***t* max** **LH**	***t* max** **RH**	***t* max** **(LH + RH)/2**
medial prefrontal	6.60	6.62	6.61
medial temporal	6.00	6.39	6.20
medial frontal	5.98	5.53	5.76
lateral occipital	4.81	5.20	5.01
medial parietal	4.81	5.01	4.91
medial occipital	4.75	4.86	4.81
lateral temporal	4.60	4.70	4.65
lateral prefrontal	4.14	4.78	4.51
lateral parietal	3.61	4.88	4.25
lateral frontal	3.59	4.10	3.83

et al., 2012). However, lack of consistent genetic testing did not permit the investigation of possible interactions between non-specific epileptic diathesis and syndrome-specific genetic effects in the present study.

4.2. Impact of the lesional factor on theta activity

Theta activity was greater in the NONEP than in the NC group in most voxels. However, no statistical significance emerged. If we accept that the NONEP group and the epilepsy groups are comparable with respect to the presence of mild to moderate cerebral lesions, the results indicate that the lesional factor of theta increase exists, though it does not significantly modify the main findings. The maximum difference (expressed by the maximum *t*-value) was greater for the IGE - NC comparison ($t = 9.98$) than for the IGE - NONEP comparison ($t = 7.19$). Similarly, the maximum difference for the FE - NC comparison ($t = 6.60$) was greater than for the FE - NONEP comparison ($t = 4.37$).

4.3. Focal epileptic processes do not modify theta topography

A TMS study disclosed unilaterally increased cortical excitability ipsilateral to the focus in patients with FE and bilaterally increased excitability in healthy siblings (Badawy et al., 2013). Lateralised epileptic processes modify the bilateral pattern and topographically restrict increased excitability to the ictogenic hemisphere by yet unknown mechanisms. Our findings support the relationship of EEG theta activity and TMS-defined cortical excitability in general and in patients with IGE. However, we did not find a theta-modifying effect of lateralised epileptic processes and anterior versus posterior localisation of the foci. The TMS and EEG findings are not actually contradictory because TMS reflects cortical excitability while EEG reflects the synchronization of oscillatory neuronal activity. As another possible explanation of the EEG-TMS divergence, increased theta activity is genetically determined and involves both hemispheres. On the contrary, lateralised TMS findings reflect acquired excitability due to lateralised epileptic activity. The investigation of the greater number of RH and LH patients might clear up the real relationship between genetically determined and acquired sources of cortical excitability.

5. Study limitations

A limitation of the study was the non-inclusion of young patients with their first presentation before they turn four years old. Thus, the conclusions are not necessarily relevant for that age group. Another limitation was that the assumed similarity of the NONEP group to the epilepsy groups with respect to the presence of "mild to moderate cerebral pathology". The retrospective study design did not allow the testing of this assumption by potentially available techniques; for example, assessing the amount of damaged white and grey matter by quantitative, MRI-based analyses.

6. Conclusions and perspective

The synthesis of already existing genetic and neurophysiological findings allowed the conclusion that the amount of theta oscillations in resting-state EEG background activity is correlated to the epileptic diathesis (in other words, an epileptic trait). In this investigation, we explored and demonstrated the three-dimensional anatomical distribution of theta activity across the cerebral cortex. The neurophysiological processes that underlie increased theta activity showed exactly the same symmetrical distribution in both epilepsy groups, with maximum values in medial-basal prefrontal and anterior temporal parts of the cortex. These findings support the concept that epileptic disposition (and its neurophysiological basis) is independent of the syndrome-specific aetiological factors in epilepsy. An analysis of the amount and anatomical distribution of theta activity might be a potentially useful method to estimate the degree of epileptic disposition, at least at the group level. The usefulness of estimating theta activity in individuals remains subject to further investigations.

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Conflict of interest

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

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