

**Clinical Neurophysiology 2010;121:848-858.****Theta EEG source localization using LORETA in partial epilepsy patients with and without medication**

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**Abstract**

Objective. To investigate and localize the sources of spontaneous, scalp-recorded theta activity in patients with partial epilepsy (PE).

Methods. 9 patients with beginning, untreated PE (Group1), 31 patients with already treated PE (Group2), and 14 healthy persons were investigated by means of spectral analysis and LORETA, low resolution electromagnetic tomography (1 Hz very narrow band analysis, age-adjusted, Z-scored values). The frequency of main interest was 4 to 8 Hz

Results. **Group analysis.** Group1 displayed bilateral theta maxima in the temporal theta area (TTA), parietal theta area (PTA), and frontal theta area (FTA). In Group2, theta activity increased all over the scalp as compared to the normative mean (Z=0) and also to Group1. Maximum activity was found in the TTA, PTA, and FTA. However, in the PTA and FTA the centers of the abnormality shifted towards the medial cortex. **Individual analysis:** all the patients showed preferential activation (maximum Z-values) within one of the three theta areas.

Conclusion. EEG activity in the theta band is increased in anatomically meaningful patterns in PE patients, which differs from the anatomical distribution of theta in healthy persons.

Significance. The findings contribute to our understanding of the sources of theta rhythms and the pathophysiology of PE.

## Introduction

Electroencephalographic theta activity in humans is usually defined as activity in the 4-7 Hz frequency range. The neurophysiological significance of theta activity has been highly enigmatic from the beginning of the EEG era. The main cause of uncertainty was its intermediate position between the two, bordering frequency bands with apparently clear-cut significance: alpha, that was considered as a normal waking EEG rhythm and delta, that was frequently associated with cerebral pathology. The old German synonym for theta ("Zwischenwelle") is perhaps the best reflection of this ambiguity (Neundörfer, 1975). Even the integration of EEG and magnetic resonance imaging methods did not substantially improve the understanding and interpretation of altered (mainly, increased) theta activity in pathological states. Theta power or activity was reported to be surprisingly independent of cerebral pathomorphology in quantitative studies. Unlike delta and alpha activities, theta activity is not significantly correlated with advancing age after the first two decades (Babiloni et al, 2006a) suggesting that it is not influenced by lifetime cumulative cerebral pathology. T2 relaxation time, a sensitive indicator of brain injury, correlates positively with delta amplitude, negatively with alpha and beta amplitudes, but is not significantly correlated with theta amplitude (Thatcher et al, 1998). Significant negative correlation exists between the amount of lobar white matter and delta but not theta activity across the continuum of subjects with mild cognitive impairment and Alzheimers' dementia (Babiloni et al, 2006b). However, regional theta power correlates positively to the volume of cerebral edema around brain lesions (Fernandez-Bouzas et al, 1997) and negatively to hippocampal volumes in Alzheimer's disease (Grunwald et al, 2001).

Several pieces of evidence suggest that increased theta activity might require a more functional interpretation. Pathologically increased theta oscillations exist in thalamo-cortical networks in patients with generalized and partial epilepsy (Llinás et al, 1999, Clemens et al, 2000; Clemens, 2004). Midparietal rhythmic theta activity is a genetic marker of increased seizure liability in myoclonic-astatic epilepsy of childhood (Doose and Baier, 1988). Valproate and lamotrigine decreased theta oscillations in successfully treated generalized epilepsy patients as compared to the untreated state (Clemens et al, 2007a, 2008). On the other hand, experimental data argue for the seizure-gating effect of increased theta activity in animal epilepsy (Miller et al, 1994; Colom et al, 2006). The above data suggest that understanding the neuronal mechanism of theta rhythms in epilepsy might be of theoretical and practical importance in epilepsy.

Concerning partial epilepsy (PE), a yet not emphasized contradiction exists between the prior quantitative EEG studies and the general concept of PE. One would expect that PE that is caused by a more or less localized epileptogenic process in one hemisphere (ILAE 1989) presents with theta increase localized to the affected part of the cortex. In fact, visual EEG analysis often detects some focal theta activity nearby the epileptogenic process. Surprisingly, quantitative EEG studies outlined a different picture. Increased theta power was found all over the scalp in both nonlesional and lesional PEs (Drake et al, 1998; Miyauchi et al, 1991) and in idiopathic benign PE of childhood as well (Braga et al, 2000). The diffuse theta increase was independent of the localization of the epileptic focus and was not significantly altered by antiepileptic medication (Diaz et al., 1998). Thus, the origin and significance of theta increase in PE remains rather enigmatic. For the present study we recorded

resting EEG from the scalp and analyzed the cortical generators. While we have reported the results in patients with generalized epilepsy earlier (Clemens et al, 2007b), we now investigate the sources of theta activity from patients with PE with or without medication.

### **Patients, healthy control persons and methods**

The design of the study was approved by the Research Ethics Committee of Kenézy Hospital Ltd. The patients were collected from three epilepsy outpatient services in Hungary. Group1 was recruited from newly diagnosed, untreated PE patients. Standard neurological investigation, EEG and MRI (epilepsy protocol, at 1.5 Tesla magnetic field strength) was performed in these patients as parts of the routine epilepsy evaluation protocol. Group2 was recruited from chronic, already treated PE patients who attended the outpatient service for follow-up visits. These patients had fulfilled the same evaluation protocol previously. Exclusion criteria were the same for both groups: diffuse structural encephalopathy or, prior neurological disease or surgery distorting the gross anatomy of the brain as assessed by cranial MRI; any comorbidity, metabolic disorder or drug use or abuse and that is known to significantly alter EEG spectra; a history of complex partial or secondarily generalized seizures in the 5 days before investigation. The patients were instructed not to drink coffee or other stimulant products in the morning before EEG investigation. PE was diagnosed and classified according to generally accepted criteria (ILAE 1989). The clinical data (including the number and severity of the seizures) have been continuously entered into the medical records of the patients as part of the routine follow-up. Overall, the patients were treated and followed as usual. Healthy persons were recruited at the Department of Neurology, University of Pécs, under the approval of that Local Ethics Committee (Toth et al, 2007).

#### EEG recording

EEG was recorded for 30 minutes while subjects were relaxed-waking with their eyes closed. Using the BQ 3200 EEG System manufactured by Micromed, Treviso, Italy (bandpass filter from 0.1 to 33.6 Hz, sampling rate 128 1/s, 12 bit A/D conversion), we recorded signals from the 19 electrodes of the 10-20 system and both earlobes against Fpz as a reference. Oculographic and myographic artifacts were detected with bipolar derivations. Electrode impedance was < 10 kOhm. Signals were re-referenced offline to digitally averaged ears. EEG records that did not fit the general quality criteria for quantitative EEG analysis (Nuwer et al, 1994) were excluded from further analysis.

#### Quantitative EEG analyses

The same EEG samples underwent spectral and LORETA analyses. Conventional spectral analysis was used to assess the scalp distribution of absolute spectral power across the 1.0 to 12.0 Hz frequency range. Low resolution electromagnetic tomography (LORETA) was used as a magnifying glass that permitted a detailed analysis of activity within the theta frequency band including the localization of the theta generators to anatomical structures. Age-adjusted, Z-scored data were used in spectral analysis and LORETA alike. The difficulties inherent to the age-dependency of the EEG variables were circumvented in this way. Z-transformation permitted the estimation of the statistical degree of the abnormality. Age-adjusted, Z-scored EEG variables are independent of age, sex and race. The validated databases for spectral power and LORETA ensured that the findings are reliable even in the absence of a rigorously matched control population (John et al, 1983, Thatcher et al,

2003). The overall reliability of the quantitative EEG databases was further confirmed in a comparative study showing that the Thatcher database replicated the results of the John database (Trudeau et al, 1999).

#### Epoch selection and EEG spectral analysis

30 x 2-sec epochs of spontaneous, waking activity characterized by continuous alpha rhythm with posterior voltage maximum were selected. Epochs containing epileptiform transients, artifacts and EEG patterns indicating shifts of the level of vigilance were excluded. Epoch selection was carried out blindly without knowing the patients' data and was controlled by the senior author. Reliability measures of the sample (split-half reliability and test-retest reliability) were checked and samples with < 95 per cent of these measures were excluded from further analysis. Fast Fourier Transform of the selected samples and spectral analysis was carried out by means of the NeuroGuide software of Thatcher (<http://www.appliedneuroscience.com>). Frequency resolution was 0.5 Hz. Cross-spectral absolute power for the 19 derivations was computed for each frequency point. The raw data were averaged across the selected epochs, adjusted for age, and Z-transformed (Thatcher et al, 2003). In our study the averaged results of two, neighbouring frequency points were compressed into a very narrow band (VNB, 1 Hz resolution). For example, Z-scored power at 7 Hz was the average of the 6.5 and 7.0 Hz values. Spectral analysis was focused on the theta band (defined here as 4.5-7.5 Hz) but also the neighbouring bands: delta (1.0-4.0 Hz) and alpha (8.0-12.0 Hz) were considered. The spectral results were displayed as absolute and Z-scored power spectra for individual analysis and were compressed into output files (.tdt) of NeuroGuide. Importing the latter files into Microsoft Excel and the Prism3 statistical package (<http://www.graphpad.com>) allowed further statistical elaboration of the results including group analysis. Given that not all datasets passed the Kolmogorov-Smirnov normality test, Wilcoxon signed rank one-sample test was used to evaluate the deviation of the spectral data from the theoretical median ( $Z=0$ ) of the healthy population.

#### LORETA analysis

LORETA is a recently developed method to localize multiple distributed cortical sources of EEG activity in the three-dimensional space (Pascual-Marqui et al, 1994; Pascual-Marqui et al, 2002). LORETA computes square root transform of the squared source current vectors ( $A / m^2$ ) for each voxel. For the sake of brevity, this is called "activity" in this paper. Each individual LORETA analysis was performed at the frequency of the maximum positive Z-scored theta value within the 4.5-8.0 Hz frequency range as established in the individual EEG spectrum (Fig-1). Raw LORETA values underwent age-adjustment and Z-transformation as described in the LORETA Normative EEG Database (Thatcher et al, 2005). The use of statistical mapping was reported to be superior to the raw LORETA results in detecting EEG abnormalities (Zumsteg et al, 2005). The output of LORETA analysis was a tomographically arranged series of pictures displaying the color-coded Z-scored activity in the selected 1 Hz VNB for each voxel. The maximum positive Z-score for the left and right hemisphere were found by means of the LORETA Viewer. The individual results (maximum Z-values) were tabulated according to laterality and localization, specifying the name of the gyrus and the Brodmann area (BA). Descriptive LORETA group analysis was carried out by averaging of the individual LORETA analysis (.lia) files to LORETA group analysis (.lga) file format. Averaged LORETA pictures were analyzed in the same way than the individual LORETA pictures. In order to estimate the topographic distribution of theta activity in healthy persons, the 6.5 to 8 Hz averaged absolute (raw)

LORETA results of 14 healthy persons were given. These data came from a prior study where they had not been explicitly published (Toth et al, 2007).

## Results

Serial number of the patients, demographics, MRI findings and treatment were summarized in Table-1. Group1 patients with newly diagnosed, untreated epilepsy (N= 9, age limits: 13-43 years, average age: 22.6) differed from Group2 patients (N= 31, age limits: 13-56 years, average age: 27.0 years). The members of the latter group had difficult-to-treat epilepsy albeit there was considerable dispersion regarding the duration of the disease (interval: 2-17 years, average: 12.3 years) and the frequency of the seizures (1 to 30) in the last 6 months. Two patients (No 27. and 28.) had very frequent but mild sensory or focal motor seizures. Four patients did not regularly enter the number of seizures into the diary. In this group 24 patients were treated with carbamazepine monotherapy, 7 patients with other drugs or bitherapy. None of the patients presented with complaints or neurological signs indicative of drug-related neurotoxicity. The average age of the healthy persons was 23,6 years.

### Spectral findings

Split-half reliability and test-retest reliability were greater than 95 per cent in every EEG sample. The theta peak was separable from the delta and alpha peak values in the individual spectra. The theta spectrum showed simultaneous increase, peak, and decrease of power in most or all derivations in the majority of the patients, suggesting a topographically diffuse process ( Fig-1.)

VNB spectral data for the two groups are summarized in Table-2. All the Group1 patients showed Z-scored power within the  $\pm 1$  Z range. Remarkably, the scalp-averages in the theta range and at the border frequencies were scattered around zero

On the contrary, all Z-scored theta values in Group2 were positive, and the medians differed considerably from Z=0. There was a stepwise increase of the Z-scores from 1 Hz to 7 Hz as demonstrated by the scalp-averages and the increasing number of the Z>1 values in the individual derivations in Table-2. All but one values returned below the Z=1 level at 9 Hz and the further frequencies in the alpha range. Comparison of the two groups showed that spectral power in the 3 to 9 Hz range was higher in Group2 than in Group1.

### LORETA group analyses

Healthy persons. Group analysis showed the distribution of raw (absolute) LORETA activity in the 6.5 to 8 Hz narrow band. (Fig-2). Maximum values were found bilaterally in medial parts of the cortex: precuneus (BA 7) and posterior cingulate (BA 31) in the parietal lobes, anterior cingulate (BA 32) and medial frontal gyrus (BA 11) in the frontal lobes. Intermediate values were found in the temporal lobes and at the temporo-parietal junction. The remaining parts of the cortex showed lesser amount of activity, with minimum values at the frontal convexity. Individual LORETA analysis disclosed individual variability in the localization of the maximum abnormality. Six patients showed parietal maxima, five patients frontal maxima, and 3 patients frontal and parietal maxima. Remarkably, no maximum theta values were found outside the specified, medially located areas.

Unmedicated patients (Group1). Contiguous areas consisting voxels of increased ( $Z>0$ ) or decreased ( $Z<0$ ) activity in the 4-9 Hz range were found in both hemispheres. Areas of increased theta activity were roughly symmetrical and were separated by areas of lesser activity. The former areas were labelled as the frontal theta area (FTA), temporal theta area (TTA), and parietal theta area (PTA) as depicted in Fig-3. Anatomical localization and the degree of the maximum abnormality (greatest Z-score) from 4 to 8 Hz within these areas were given numerically in Table-3. Activity in the left and right PTA rose from 4 to 7 Hz and decreased with further increase of frequency. Maximum activity across this frequency range was consistently found in the superior parietal lobule. The degree of abnormality gradually decreased towards the precuneus, postcentral gyrus, and inferior parietal lobule. The PTA showed some asymmetry in that the lower part of the inferior parietal lobule and the temporo-parietal junction showed moderately higher Z-scores on the left than on the right side. Activity in the left and right FTA increased from 4 to 8 Hz and decreased with further increase of frequency. Maximum activity was confined to the superior and medial frontal gyri (BA 8) and a limited part of the cingulate gyrus below the medial frontal gyrus. Maximum abnormality in the TTA was located in the fusiform gyri bilaterally and decreased towards the parahippocampal and inferior temporal gyri. However, the left and right maxima emerged at different frequencies.

Patients under medication (Group2). The amount of theta activity showed an overall increase across the entire cortex with respect to the statistical baseline ( $Z=0$ ) and also when compared to Group1. No voxel showed negative values at 7 Hz (Fig-4). The TTA, PTA, and FTA were identifiable also in Group2 as given in details in Table-3. The degree of abnormality increased as a function of frequency from 4 to 7 Hz in the PTA and TTA and tended to decrease at 8 Hz. The degree of the maximum theta abnormalities at 7 Hz was about two to four times greater in Group2 than in Group1. In addition, in the PTA and FTA the center of the abnormality shifted toward the midline cortex (precuneus and cingulate gyrus) as compared to the loci of the maximum abnormalities in Group1.

#### LORETA individual analysis

LORETA individual analysis was carried out in all the patients. Table-4. shows heterogeneity concerning the localization and the frequency of the maximum abnormality. The most interesting finding was that one of the three theta areas was preferentially activated (that is, showed greater Z-values than the remaining theta areas) in all but three patients. Patients showing preferential activation of the TTA, PTA, and FTA were found in both Group1 and Group2. Regarding frequency, maximum theta values were found at 6 or 7 Hz in most patients. However, these patients displayed lesser values of activity in the same anatomical distribution at 5 Hz and even at 4 Hz or, rarely, 3 Hz. At the other end of the theta range, the pattern of activity at 6-7 Hz frequently extended into the VNB at 8 Hz but not at 9 Hz.

#### Effect of the lesion on theta activity

In order to investigate the potential effect of the MRI-defined lesion on theta activity the nonlesional group ( $n=20$ ), the left hemisphere lesion group ( $n=10$ ) and the right hemisphere lesion group ( $n=8$ ) were compared. Patients No. 39. and 40. with multiple cerebral lesions escaped this analysis. Averaged maximal individual Z-scores in the nonlesional group were 2.04 in the left hemisphere and 1.87 in the right one. The group with left hemisphere lesions showed 1.35 and 1.39 scores ipsi- and

contralaterally, respectively. The group with right hemisphere lesions showed 1.82 and 2.13 scores ipsi- and contralaterally, respectively. No statistically significant differences emerged between the three groups ( $p=0.38$ ) suggesting that the presence and laterality of the lesion did not significantly influence the emergence and degree of the theta abnormality.

The patients with preferential activation of the TTA had normal MRI ( $n=9$ ), or a single lesion in the temporo-parieto-occipital area ( $n=5$ ), or multifocal abnormalities ( $n=2$ ). No single frontal lesion was found in this group. The PTA patients had normal MRI ( $n=7$ ) or a single lesion in the temporo-parietal area ( $n=2$ ). The FTA patients had normal MRI ( $n=4$ ), or a single lesion in the frontal lobes ( $n=4$ ), temporal lobes ( $n=2$ ), or multifocal lesions ( $n=1$ ). These findings raise the possibility that preferential activation emerges in the theta center nearby to the epileptogenic process. However, the number of the lesional cases is too small to perform statistical analysis to prove or refute this possibility.

## Discussion

### The advantage and the results of VNB spectral analysis

The authors who investigated broad-band power in PE (Drake et al, 1998; Miyauchi et al, 1991; Braga et al, 2000; Diaz et al., 1998) did not address the problem that the theta band comprises an uncertain number of rhythmic oscillations. As a corollary their results reflect compound activity implying significant blurring regarding the exact frequencies of the large scale theta oscillations. Narrow band analysis was recommended to improve the resolution of frequency analysis (Szava et al, 1994). In fact, in this study VNB analysis resulted in novel findings. We found that activity (that is, the intensity of synchronous oscillations) increased as a function of frequency from 4 to 7 or 8 Hz and rapidly fell at 8 or 9 Hz. However, this phenomenon reflected a group effect composed of at least two constituents. First, the frequency-dependence of activity was observed in most individual spectra and LORETA analyses suggesting that, defining sharp borders between neighbouring frequency bands poorly reflects physiological reality. Second, the individual dispersion of the VNBs with maximum activity indicates biological variability concerning the working frequency of that theta network. The individual peak frequencies should be emphasized in planning targeted studies and in the evaluation of individual persons (Klimesch, 1999).

### Unmedicated patients (Group1)

This was the first quantitative EEG study carried out in a group of PE patients with beginning, untreated epilepsy. Albeit this group was small, analysis of the spectral results disclosed that the overall increase of theta activity is not characteristic to beginning, untreated PE. However, this finding was greatly refined by source analysis. LORETA demonstrated that some parts of the cortex showed increased while others showed decreased activity (as defined in the Results section). In this study we focussed on areas of increased activity because they reflect increased neuronal synchronization, the basis of epileptic malfunctioning. Discrete maxima of increased theta activity were found in three, anatomically separated cortical areas in both hemispheres. The falling gradients of activity from these areas in any direction suggest that the TTA, PTA, and FTA are "theta centers" playing an important role in generating spontaneous cortical theta activity. In anatomical terms, the fusiform gyrus, superior parietal lobule, and the superior and medial frontal gyri were the sites of the main theta generators. These centers of activity clearly differed from the theta centers found in the 14 healthy persons. Our findings: the medial frontal and parietal theta maxima in healthy persons confirmed prior results as

follows. A single-dipole magnetoencephalographic analysis localized the main theta source in the posterior cortex near the mid-sagittal plane (Puligheddu et al, 2005). A top view LORETA figure published in another paper demonstrated the presence of theta activity all over the cortex with parietal midline maxima in healthy young and healthy old persons. Unfortunately, detailed quantitative results and the medial view of the hemispheres were not presented in that paper (Babiloni et al, 2006a). We concluded that the PTA and FTA are anatomically not identical to the centers of theta activity in healthy persons. Theta maxima outside the normal theta centers (in particular, those located at the cortical convexity) seem to be clearly abnormal findings. The same holds true for the TTA because healthy persons never showed theta maxima in the temporal lobe. The functional significance of these findings is not self-evident and going into details is beyond the scope of this study. Thus we only briefly mention that the three theta areas correspond to unimodal and heteromodal association cortices (Mesulam, 1985; Zilles, 2004). All but two patients in Group 1 showed bilateral, rather symmetrical theta increase, independent of the presence and lateralization of the epileptogenic lesion. This fact indicates a functional origin of theta increase rather than a lesional interpretation of it. Our findings weakly suggest that the localization of the epileptogenic process might influence preferential activation, favouring activation of the anatomically nearby theta system. In particular, frontal lobe lesions were associated with activation of the FTA but not the TTA and PTA. A recent study seems to support this suspicion. More or less rhythmic interictal theta activity in the frontal derivations was frequently found in patients with frontal epilepsy but rarely in temporal lobe epilepsy patients (Beleza et al, 2009). In any case, the relationship between the epileptogenic process and the activated theta network might contribute to understand the functional meaning of theta increase in PE.

#### Patients under medication (Group2)

Our spectral results confirmed the presence of diffuse theta increase in patients with chronic, treated PE as described in prior studies (Drake et al, 1998; Miyauchi et al, 1991; Braga et al, 2000a; Diaz et al., 1998). Again, the VNB spectral findings were greatly refined by LORETA analysis. Greatest activity was found at 7 Hz in the TTA (fusiform and parahippocampal gyri), PTA (precuneus and superior parietal lobule), and the FTA (anterior cingulate). The reason for this theta increase is not clear because several causes might exist and interfere with one another. First, one component of it is the "baseline" theta abnormality discussed in the previous paragraphs. However, theta maxima in the TTA and PTA in Group2 were somewhat shifted towards the midline cortex as compared to the theta maxima of Group1, further indicating the complexity of the causes.

The difference between the unmedicated and medicated patients is demonstrable with the difference between the extension and degree of the abnormality in Fig-2. versus Fig-3. This effect is due to medication, particularly carbamazepine. This drug is known to increase theta power (Clemens et al, 2006), as confirmed in this study. Both spectral findings and LORETA showed that drug-related increase was present across the entire theta range in all voxels. However, maximum difference between the two groups was detected at 7 Hz in the posterior and medial parts of the cortex as opposed to lesser theta increase in the frontal and anterior temporal cortex. The anatomically uneven distribution of the cortical effect of carbamazepine is a new finding that seems to be worthy to investigate in prospective studies.

In theory, the role of mild but distributed progressive cortical damage cumulating in the course of the illness cannot be excluded. All the Group2 patients had difficult-to-treat epilepsy giving rise to this possibility. However, the reported morphological alterations: the anatomical patterns of reduced neocortical thickness (Lin et al, 2007) and neocortical volume loss in T1 weighted MRI images (Liu et al, 2003) did not resemble the anatomical distribution of the TTA, PTA, and FTA. An intermediate

possibility between the direct lesional and the network-related theta increase is that slowly evolving neuronal loss in critical structures like the thalamus and hippocampus might affect network synchronization. In fact, progressive neocortical and hippocampal atrophy were described in PE patients (Mathern et al, 2002; Cendes, 2005) but hippocampal quantitative MRI data and the theta measures have never been correlated in PE. This was done in Alzheimer's disease where negative linear correlation was found between hippocampal body volume and theta power over the frontal regions (Grunwald et al, 2001).

### Localizing accuracy

The relatively small number of electrodes is a frequently criticized point in LORETA studies. In fact, localizing accuracy considerably increases from 19 to about 64 electrodes. However, inaccuracy decreases when the electrodes are evenly distributed over the scalp (Michel et al, 2004), as in this study. Furthermore, the LORETA literature suggests that 19 to 23 scalp electrodes permit correct sub-lobar localization of verified sources of activity. Using this number of electrodes LORETA solutions were sometimes blurred or uninterpretable but never clearly incorrect (Zumsteg et al, 2005, 2006). Furthermore, the accuracy of the method should be discussed in terms of the spatial scale of the task and the signal-to-noise ratio as well. We investigated theta, a pervasive and robust rhythm (Puligheddu et al, 2005) that was increased in large cortical areas. The theta centers were described in terms of relatively large anatomical units (gyrus, BA) that tolerate some mislocalization without significant blurring of the findings

### **Conclusions**

Interictally recorded EEG theta rhythms have practical significance in relation to clinically very important issues: seizure propensity, seizure control, and drug-related neurotoxicity. In this paper we verified that LORETA may be a useful investigation tool to address the above mentioned problems. The importance of this fact is supported by the inability of other neuroimaging methods (magnetic resonance imaging methods, positron emission tomography) to address these problems. Our findings completed the existing knowledge regarding theta oscillations with anatomical aspects. The investigation of newly diagnosed, untreated PE patients resulted in findings that are not confounded by antiepileptic drug effects and other factors related to long-lasting epilepsy. Our findings might be utilized in planning forthcoming, targeted studies addressing the relationship between clinical variables and corresponding theta oscillations in selected parts of the cortical mantle.

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### Legends to Figures

Fig-1. Patient No.15., member of Group2. Three seconds of the linked-ears referenced EEG trace on the left. Absolute power spectrum (right, top) and age-adjusted, Z-scored spectrum (right, bottom). The theta peak at 7 Hz is clearly separable from delta activity and the alpha peak at 10 Hz. Near parallel rise and fall of most values across the 5 to 8 Hz frequency range indicate a diffuse theta process. In this patient LORETA analysis was carried out at the theta peak.

Fig-2. Three-dimensional anatomical localization of the generators of the 6.5-8 Hz narrow band activity in the 14 healthy control persons. Absolute (raw) activity values. Areas of greatest activity (most intense red color) are in the medially located cortical areas of the parietal and frontal lobes.

Fig-3. Group1. Unmedicated patients. Three-dimensional anatomical localization of the temporal, frontal, and parietal areas of increased theta activity at 7 Hz. Comparison is performed against the LORETA Normative Database. Red and blue color indicate voxels with  $Z > 0.3$  and  $Z < 0.3$  activity, respectively. End points of the color scale are set at  $Z = \pm 0.48$ .

Fig-4. Group2. Patients under medication. Three-dimensional anatomical localization of the temporal, medial frontal, and parietal areas of increased theta activity at 7 Hz. Comparison is performed against the LORETA Normative Database. The color scale begins with light pink at  $Z = 1$ . End points of the color scale are set at  $Z = \pm 1.37$ .