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**QUANTITATIVE EEG ABNORMALITIES IN PERSONS WITH "PURE" EPILEPTIC
PREDISPOSITION WITHOUT EPILEPSY. A LOW RESOLUTION ELECTROMAGNETIC
TOMOGRAPHY (LORETA) STUDY**

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Abstract

Objective. Epileptic predisposition means genetically determined, increased seizure susceptibility. Neurophysiological evaluation of this condition is still lacking. In order to investigate „pure epileptic predisposition” (without epilepsy) in this pilot study the authors prospectively recruited ten persons who displayed generalized tonic-clonic seizures precipitated by 24 or more hours of sleep deprivation but were healthy in any other respects.

Methods. 21-channel EEGs were recorded in the morning, in the waking state, after a night of sufficient sleep in the interictal period. For each person, a total of 120 seconds artifact-free EEG was processed to low resolution electromagnetic tomography (LORETA) analysis. LORETA activity (Amperes/ meters squared) was computed for 2394 voxels, 19 active electrodes and 1 Hz very narrow bands from 1 to 25 Hz. The data were compressed into four frequency bands (delta: 0.5-4.0 Hz, theta: 4.5-8.0 Hz, alpha: 8.5-12.0 Hz, beta: 12.5-25.0 Hz) and projected onto the MRI figures of a digitized standard brain atlas. The band-related LORETA results were compared to those of ten, age- and sex-matched healthy persons using independent t-tests. $p < 0.01$ differences were accepted as statistically significant.

Results. Statistically significant decrease of alpha activity was found in widespread, medial and lateral parts of the cortex above the level of the basal ganglia. Maximum alpha decrease and statistically significant beta decrease were found in the left precuneus. Statistically not significant differences were delta increase in the medial-basal frontal area and theta increase in the same area and in the basal temporal area.

Discussion. The significance of alpha decrease in the patient group remains enigmatic. Beta decrease presumably reflects non-specific dysfunction of the cortex. Prefrontal delta and theta increase might have biological meaning despite the lack of statistical significance: these findings are topographically similar to those reported in idiopathic generalized epilepsy in previous investigations.

Significance. Quantitative EEG characteristics of the genetically determined epilepsy predisposition were given in terms of frequency bands and anatomical distribution.

Key words

Epilepsy, epileptic predisposition, EEG, LORETA

Introduction

In his famous book William Lennox presented an autographic illustration named "The Epilepsy River". This widely known figure metaphorically shows that epilepsy is the result of flowing together of several, inherited and acquired sources (Lennox, 1960). In fact, older and recent genetic studies agree that epileptic predisposition (in other words, increased seizure propensity of genetic origin) contributes to the pathogenesis of most, if not all sorts of human epilepsy (Anderman, 1982; Ottman et al, 1985; Cavalleri et al, 2007; Helbig et al, 2008). Eminent epileptologists who outlined a comprehensive

framework for epilepsy strongly emphasized the importance of genetic predisposition in the etio-pathogenesis of the seizure disorders. They considered epileptic predisposition as a diffuse alteration of cortical neurochemistry resulting in increased cortical excitability (Gloor et al, 1982). Unfortunately, it seems that research (in particular, human research) got stuck at this step and no further efforts were done in order to highlight the nature of epileptic predisposition. Perhaps the main reason for this is that human genetic and electrophysiological studies were carried out in patients with epilepsy, or, at best, in their relatives (Metrakos and Metrakos, 1961). In other words, no persons with "pure epileptic predisposition" were investigated.

Pure epileptic predisposition (increased seizure propensity without epilepsy) can be investigated in otherwise healthy, non-medicated persons who display generalized tonic-clonic seizures (GTCSs) precipitated by natural, near-physiological events (Rodin, 1984). Knowledge about such persons stems from the Second World War and subsequent military crises. Healthy young soldiers and aircraftmen who had got a GTCS precipitated by 24 or more hours of sleep deprivation (SD) due to long-lasting sentry or air combats were reported by several authors (Schulte 1944; Bennett et al, 1963; Gundersohn et al, 1973). Later, it became widely accepted that young, otherwise healthy people, mostly in the second or third decades of their life, may suffer of single or repeated GTCSs on occasions of SD. The attribute "otherwise healthy" is supported by the fact that provoked GTCSs do not mean epilepsy. The GTCS is a non-specific response reflecting the supracritical load of the brain with seizure-promoting influences; in other words, there is no reason to postulate any epileptogenic cerebral pathology or significant network dysfunction (Aird et al, 1984). Experimental research disclosed that SD precipitates seizures by increasing the excitability of the CNS at several levels (Shouse, 1988). An additive seizure-provoking effect is the decreased and fluctuating level of vigilance after SD (Ellingson, 1984).

The common neurophysiological abnormality in epilepsy is increased neuronal (EEG) synchronization in the cerebral cortex in both ictal and interictal states. EEG is a proven tool to investigate neuronal synchronization at large spatial scales because even a small increase in the number of synchronized cortical EEG sources gives rise to significant increase of the EEG signal (Nunez, 1995). Animal experiments suggest that epileptic predisposition might occupy an intermediate position between the healthy condition and the epileptic cortex concerning the degree of neuronal synchronization (van Gelder et al, 1983; Kostopoulos, 1986). Based on the latter findings and the overall role of increased neuronal synchronization in epilepsy we postulated that pure epileptic predisposition is characterized by increased EEG synchronization as compared to that of completely healthy persons.

Patients and methods

The study design was approved by the Research Ethics Committee of Kenézy Kórház Ltd. and the University of Debrecen with the explicit statement that deviations from the accepted diagnostic and treatment protocols are not permitted; no diagnostic procedure or treatment should be indicated, refuted, or postponed for study purposes. The patients were prospectively selected out of those who were referred to the Epilepsy Outpatient Services at Debrecen or Pécs because of epileptic seizures. Potentially eligible persons were designated at the first visit by taking a detailed medical history, physical and neurological investigation. Inclusion criteria were: age of the first SD-provoked seizure between 10 and 30 years; normal ante- and perinatal history, normal developmental milestones and a credible report of one or more GTCSs precipitated by 24 or more hours of SD. Exclusion criteria were: recently active metabolic or inflammatory disease, a history of prior neurological and psychiatric

morbidity, unprovoked seizures (including other seizure types, absences or myoclonia in particular); regular alcohol intake or drug use except contraceptive pills; the use of excitant drugs or commercial products (for example, the so-called energy drinks) in the 48 hours before the seizure. Usual amounts of coffee or tea was permitted. The persons who had got a seizure in a discotheque were excluded because of the additional seizure provoking effects of flickering light and because the possibility of consuming some undetected drugs. Finally, patients with abnormal neurological and/ or psychiatric findings at investigation were excluded. The potentially eligible patients were further evaluated according to the routine protocol including EEG examination with hyperventilation and intermittent photic stimulation, and a cranial MRI. Persons who showed significant EEG abnormalities and/ or a pathological MRI finding indicating a focal epileptic or non-epileptic process were excluded at this step of evaluation. Interictal, generalized spike-wave paroxysms were acceptable because this finding was reported in healthy persons (Cavazutti et al, 1980) and in patients with SD-provoked seizures (Ellingson et al, 1984). According to our routine protocol the patients who were diagnosed as having "sleep deprivation seizures" did not receive medication but were instructed to avoid SD and to enter any further seizure and the suspected precipitating factor into a diary. They were followed at regular visits for at least two years. Follow-up was necessary because epilepsy may begin with a provoked seizure. Given that the first seizure is followed by the second within three months in most cases of beginning epilepsy (Sander and Sillanpaa, 1997), the lack of forthcoming non-provoked seizures in the long run is the best argument against epilepsy. Thus, the two-years period without spontaneous seizures excludes epilepsy with high probability. The patients who displayed one or more non-provoked seizures in this time period or those who escaped follow-up were excluded from the study. An age- and sex-matched control group composed of 10 healthy persons was selected from our normative EEG database. These persons had been recruited previously, for the sake of prior quantitative EEG studies. They had not had any neurological and psychiatric antecedents, metabolic disturbances, addictive habits (alcohol or drug use) and did not take legal drugs regularly (contraceptives were permitted).

EEG investigation

As to avoid the confounding effect of postictal slowing only EEGs recorded at least five days after the seizure were evaluated. All EEGs were carried out in the morning, after a night of sufficient sleep. Confounding, circadian EEG effects (Toth et al, 2007) and SD-related intrusion of slower frequencies (Borbély et al, 1981) were excluded in this way. All EEGs were recorded with the same sort of digital EEG equipment and recording protocol: 30 minutes EEG was recorded in relaxed-waking, eyes-closed state using the 19 monopolar derivations of the 10-20 system plus the earlobes against a sampling reference at Fpz; bipolar derivations detected oculographic and myographic artifacts. Impedances were < 10 kOhm; EEG was filtered at 0.1 and 33.6 Hz. Sampling rate was 128 per second, on-line analog-digital conversion was 12 bit. Given the Nyquist sampling rate (twice the maximum frequency of interest) and the desirable anti-aliasing effect of low-pass filtering these recording variables were appropriate to investigate the 1 to 25 Hz frequency range. Thereafter, all voltage differences were re-computed against a so-called mathematical linked ears reference. As to the quality of the records recommended standards were followed (Nuwer et al, 1994).

Epoch selection and LORETA analysis

EEGs of the patients and the control persons were recorded and analyzed in the same way. 30 x 2-sec epochs of spontaneous, waking activity characterized by continuous alpha rhythm with posterior voltage maximum were selected. Epochs containing any sort of transients, artifacts, or EEG patterns indicating shifts of the level of vigilance were excluded. Epoch selection was carried out by one of us and controlled by the senior author. Split-half reliability and test-retest reliability were checked and only samples with at least 95 per cent of these measures were analyzed. Fast Fourier Transform of the selected samples was carried out by means of the NeuroGuide 2.5.6. software (<http://www.appliedneuroscience.com>). Thereafter, the data were processed to the joined Low Resolution Electromagnetic Tomography (LORETA) software in order to quantitatively assess synchronized cortical activity in terms of frequency and the three-dimensional distribution of the sources.

LORETA is a recently developed method to localizes multiple distributed cortical sources of EEG activity in the three-dimensional space (Pascual-Marqui et al, 1994). The consistency of LORETA with physiology and localization has been validated for a lot of normal and pathological conditions (Pascual-Marqui et al, 2002). The scientific basis and comprehensive evaluation of LORETA can be found at the above specified website where free download of a lot of relevant papers is allowed. In brief, LORETA computes square root transform of the squared source current vectors (Ampers/meters squared) for 2394 voxels and for each very narrow band (VNB) from 1 to 30 Hz along the frequency axis. For the sake of brevity, this is called "activity" in this paper. LORETA projected these values onto structural magnetic resonance images according to the coordinate system of the Talairach Brain Atlas (Talairach and Tournoux, 1988) digitized at Montreal Neurological Institute. Individual LORETA results were averaged across the patients. The averaged results were compressed into frequency bands (delta: 0.5-4.0 Hz, theta: 4.5-8.0 Hz, alpha: 8.5-12.0 Hz, beta: 12.5-25.0 Hz). The patients and the controls were compared by independent t-tests. T-values corresponding to $p < 0.01$ were labelled as statistically significant. Correction for multiple comparisons was not done because it assumes that each voxel is independent of all other voxels and it is known that the Laplacian operator smooths voxels thus rendering them as "dependent" and not independent. The output of LORETA analysis was a tomographically arranged series of color-coded pictures displaying the algebraic difference and the statistical difference between the two groups. Localization was given in anatomical terms, the name of the gyrus, number of the Brodmann area, and the three-dimensional coordinates on the above mentioned brain atlas.

Results

Due to the multiple exclusion criteria only ten patients who were eligible in all respects were collected during a period of three years (2 males, 8 females, age limits: 18 and 29 years, average age: 21.7 year). They were students or workers who missed a night of sleep because of learning or night work. Out of them, four patients had a single GTCS after SD while six patients had got 2 or 4 seizures on repeated occasions of SD. EEG background activity was of alpha type and was within the normal limits in all the patients. Brief, interictal, generalized spike-wave paroxysms were recorded in two cases. Video recording or personal observation of one of us ensured that these paroxysms were not

accompanied by subtle seizure phenomena. The average age of the control persons was 21.1 years; the age difference between the two groups was statistically not significant ($p=0.6$).

LORETA results

Statistically significant decrease of alpha activity was found in the persons with epileptic disposition (as compared to the controls) in the medial and lateral parts of the cortex above the level of basal ganglia (Fig. 1). These alpha differences were distributed asymmetrically at the cortical convexity, being more widespread in the right hemisphere than in the left. However, maximal alpha difference was found in the left precuneus, BA 7. Interestingly, the only statistically significant beta difference was localized to the same area (Fig. 1) albeit statistically not significant decrease of beta activity was found everywhere in the temporo-parieto-occipital cortex.

No statistically significant difference between the two groups emerged in the delta and theta bands. However, an overall tendency for bilaterally increased delta and theta activity was found in the persons with epileptic predisposition as compared to the controls. Greatest delta differences were found bilaterally in the medial and basal prefrontal cortex (gyrus rectus, orbito-frontal gyrus, anterior-basal parts of the medial and middle frontal gyri, anterior cingulate, subcallosal gyrus). These areas correspond to BAs 10, 11, 34. Greatest theta differences were found in about the same parts of the frontal cortex and in the nearby basal temporal cortex (uncus, parahippocampal gyrus; BAs 20, 28, 36) and the anterior edge of the right insula, BA 13 (Fig 2).

Discussion

Alpha and beta frequency bands

This is the first quantitative EEG investigation of persons with "pure epileptic predisposition" as defined in the Introduction of the paper. The main findings of this study were that epileptic predisposition is characterized by a statistically significant decrease of alpha activity in a considerable part of the cortical mantle, and a statistically significant decrease of beta activity in a circumscribed part of the left parietal cortex, as compared to the control group. The left precuneus (BA 7) was the site of the maximal alpha and beta differences. However, these findings were like the top of the iceberg because smaller, statistically not significant but diffuse alpha decrease was found in the entire cortex and diffuse beta decrease was found in the temporo-parieto-occipital parts of it. The neurophysiological interpretation of decreased alpha and beta activity in the context of seizure liability is not easy. As far as is known, the relationship between alpha variables and seizure propensity has never been investigated. Beta decrease is usually interpreted as a non-specific sign of impaired cortical function (Kozelka and Pedley, 1990). Beta power was proposed as a biological marker of GABA-mediated anticonvulsive drug effects (Lopes da Silva, 2002) thus indirectly suggesting that beta decrease might be associated with increased seizure propensity. However, also opposite results were published (Pfersmann et al, 1993) and, in any case, drug-modified cortical GABA-ergic function is only one component of seizure liability.

Similarly, the significance of maximal alpha and beta decrease in the left precuneus remains uncertain. Concordantly with this finding, interictal dysfunction of the precuneus and posterior cingulate cortex in patients with generalized seizures was demonstrated in a functional MRI study (Lui

et al, 2008). The strategic role of this area in regulating physiological arousal processes and perhaps also epileptic activity argues for further, targeted investigations.

Delta and theta frequency bands

We found that delta activity was increased in the medial and basal frontal areas, theta activity was increased in the same areas and also in the basal temporal area in the persons with epileptic predisposition as compared to the controls. These differences were statistically not significant. However, the topographical similarity of increased delta and theta activity in these persons and in patients with idiopathic generalized epilepsy should be emphasized. From the clinical point, persons with SD-related GTCSs are most closely related to those who have idiopathic epilepsy exclusively with unprovoked GTCSs (Panayiotopoulos, 2005). A subtype of this epilepsy syndrome is labeled as "epilepsy with grand mal seizures on awakening", abbreviated here as EGMA (Janz, 1994). In these patients insufficient sleep is a frequent seizure-provoking factor thus underpinning the neurobiological similarity between them and the persons presenting with SD-provoked seizures only. Topographic analysis of the potential field indicated increased delta and theta activity in the prefrontal and parieto-occipital areas of unmedicated EGMA patients as compared to healthy controls (Clemens et al, 2000). Albeit the localizing precision of a classic topographic study and LORETA is limitedly comparable, prefrontal delta-theta excess seems to be a common feature of EGMA patients and persons with pure epileptic disposition. Furthermore, a LORETA study disclosed that unmedicated idiopathic generalized epilepsy patients display five cortical regions of increased delta-theta activity (Clemens et al, 2007). One of these areas, the so-called "prefrontal cluster" corresponds to the prefrontal delta and theta increase in the persons with pure epileptic predisposition. However, the degree of the abnormality was rather dissimilar. EGMA and other, idiopathic generalized epilepsy patients showed statistically significant increase of delta and theta synchronization in the prefrontal cortex and other cortical areas (Clemens et al, 2000, 2007). In contrast, the persons with pure epileptic predisposition showed statistically not significant delta and theta increase in the same cortical areas. This suggests that, concerning the amount of slow (delta, theta) EEG activity, persons with epileptic predisposition are nearer to healthy persons than to the patients with generalized epilepsy. This is in accord with the overall experience that persons with SD-related seizures only remain permanently seizure-free if sleep deprivation is avoided.

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Legend to Figures

Fig.1. Tomographically arranged LORETA figures for the statistically significant differences in the alpha and beta frequency bands. R and L indicate the right and left hemispheres, respectively. Each figure contains the Z-coordinate (millimeters) of the Talairach Atlas in the left lower corner. Blue color indicates significantly decreased alpha and beta activity in the persons with epileptic predisposition as compared to the controls. Black arrow points to the left precuneus where maximal alpha difference between the groups was found. Color scale: $t = \pm 2.88$ corresponds to $p=0.01$.

Fig.2. Tomographically arranged LORETA figures for the statistically not significant differences in the delta and theta frequency bands. R and L indicate the right and left hemispheres, respectively. Each figure contains the Z-coordinate (millimeters) of the Talairach Atlas in the left lower corner. Red color indicates statistically not significant increase of delta and theta activity in the persons with epileptic predisposition as compared to the controls. Color scale: $t = \pm 1.00$ corresponds to $p=0.3$.

