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EEG-LORETA endophenotypes of the common idiopathic generalized epilepsy syndromes

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Summary
Objective: We tested the hypothesis that the cortical areas with abnormal local EEG synchronization are dissimilar in the three common idiopathic generalized epilepsy (IGE) phenotypes: IGE patients with absence seizures (ABS), juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic—clonic seizures exclusively (EGTCS).
Patients and methods: Groups of unmedicated ABS, JME and EGTCS patients were investigated. Waking EEG background activity (without any epileptiform potentials) was analyzed by a source localization method, LORETA (Low Resolution Electromagnetic Tomography). Each patient group was compared to a separate, age-matched group of healthy control persons. Voxel-based, normalized broad-band (delta, theta, alpha, and beta) and very narrow band (VNB, 1 Hz bandwidth, from 1 to 25 Hz) LORETA activity (=current source density, A/m^2) were computed for each person. Group comparison included subtraction (average patient data minus average control data) and group statistics (multiple *t*-tests, where Bonferroni-corrected $p < 0.05$ values were accepted as statistically significant).
Results: Statistically not significant main findings were: overall increased delta and theta broad band activity in the ABS and JME groups; decrease of alpha and beta activity in the EGTCS group. Statistically significant main findings were as follows. *JME group*: bilaterally increased theta activity in posterior (temporal, parietal, and occipital) cortical areas; bilaterally

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increased activity in the medial and basal prefrontal area in the 8 Hz VNB; bilaterally decreased activity in the precuneus, posterior cingulate and superior parietal lobule in the 11 Hz and 21—22 Hz VNBs. *ABS group*: bilaterally increased theta activity emerged in the basal prefrontal and medial temporal limbic areas. Decreased activity was found at 19—21 Hz in the right postcentral gyrus and parts of the right superior and medial temporal gyri. *EGTCS group*: decreased activity was found in the frontal cortex and the postcentral gyrus at 10—11 Hz, increased activity in the right parahippocampal gyrus at 16—18 Hz.
Discussion: Increased theta activity in the posterior parts of the cortex is the endophenotype for JME. Increased theta activity in the fronto-temporal limbic areas is the endophenotype for ABS. Statistically not significant findings might indicate diffuse biochemical abnormality of the cortex in JME and ABS.
Significance: EEG-LORETA endophenotypes may correspond to the selective propensity to generate absence and myoclonic seizures in the ABS and JME syndromes.

Introduction

Childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with generalized tonic—clonic seizures exclusively (EGTCS) are common epilepsy syndromes classified as idiopathic generalized epilepsy (IGE). By definition, this term implies that they are genetically determined nonlesional disorders, in which the seizures start in both hemispheres simultaneously (ILAE, 1989). From the point of neurophysiology, the ''mild diffuse epileptogenic state'' of the cortex was appointed as the pathological basis of seizure liability, while the generalized seizures were realized as transient, abnormal, bilateral-synchronous thalamo-cortical oscillations (Gloor, 1979). Clinical and EEG reports demonstrating focal epileptogenic abnormality or focal onset of the so-called generalized seizures were not weighty enough to influence mainstream thinking until 1998 when two magnetic resonance imaging (MRI) studies disclosed morphological cerebral abnormalities in IGE patients (Woermann et al., 1998; Savic et al., 1998). After this breakthrough, modern imaging studies increasingly made the scientific community to re-conceptualize IGE as a group of disorders where structural abnormalities may contribute to etiology, and the role of focal abnormalities should be emphasized in ictogenesis (Koepp and Duncan, 2004).

Two issues are particularly important within this new framework. First, which part of the cortex is the seizure-onset area and which parts of the brain are involved in the course of the seizures? Second, what cortical abnormality is responsible for ictogenicity, in other words, the seizure-prone state of the brain in IGE syndromes? Most functional imaging studies addressed the first issue leading to increasing knowledge regarding the ictal anatomy of absence, myoclonic, and generalized tonic—clonic seizures (Blumenfeld et al., 2003; Holmes et al., 2004, 2010; Gotman, 2008; Stefan et al., 2009; Carney et al., 2010; Moeller et al., 2010; Sakurai et al., 2010). However, most studies demonstrated that a few, topographically dissimilar cortical sites are involved at seizure onset, in addition to the syndrome-specific, main seizure onset area. Furthermore, the seizures are preceded by electromagnetic changes in topographically non-contiguous areas far beyond the seizure onset zone (Aarabi et al., 2008; Amor et al., 2009). These results indicate that IGE is similar to the focal epilepsies insofar as the epileptogenic zone (Lüders and Awad, 1991) or epileptic network (Spencer, 2002; Nair et al., 2004) that is the anatomical—physiological substrate of the seizure-prone condition is topographically more extended than the seizure onset zone. This important matter is always addressed when surgical treatment of focal epilepsy is considered (Lüders et al., 2006). However, its neurobiological significance reaches far beyond planning resective surgery. As to the IGE syndromes, the anatomical—physiological substrate of ictogenicity remains a neglected issue that has never been critically revised in the light of recent findings. At best, the results of the imaging studies were interpreted as being potentially related to ictogenicity in some way. This is actually correct because morphological, metabolic and biochemical abnormalities do not permit any conclusive inference regarding the neuronal substrate of ictogenicity. In other words, morphological, metabolic and biochemical alterations do not automatically indicate that the abnormality contributes to ictogenicity.

On the other hand, abnormal patterns of the electromagnetic oscillations of the brain are direct markers of ictal and interictal epileptic malfunctioning (McCormick and Contreras, 2001; Timofeev and Steriade, 2004). Microelectrophysiology detects epileptic malfunctioning at small spatial scales while EEG and magnetoencephalography (MEG) detect it within great neuronal ensembles. Multiple pieces of experimental and clinical evidence indicate that EEG- and MEG-detected local cortical dysfunction and altered cortical connectivity characterize the neuronal substrate of ictogenicity albeit the concepts are far from being definite (Spencer, 2002; Nair et al., 2004; Timofeev and Steriade, 2004). As a corollary, both local cortical dysfunction and remote cortical connectivity should be investigated in order to understand the neuronal substrate of ictogenicity (McCormick and Contreras, 2001; Steriade, 2001). About ten years ago we suggested that the seizure-prone state of the brain can be grasped by means of EEG background activity analysis in IGE syndromes (Clemens et al., 2000). Since then, further evidence confirmed this statement. Briefly, the main electrophysiological characteristics of the seizure-prone state are increased cortical excitability and increased EEG synchronization. These traits are interrelated in IGE models (van Gelder et al., 1983; Kostopoulos, 1986) and in human IGE. Seizures, increased cortical excitability and increased EEG synchronization in the delta and theta