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ORIGINAL PAPER

Does Greater Low Frequency EEG Activity in Normal Immaturity and in Children with Epilepsy Arise in the Same Neuronal Network?

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Abstract Greater low frequency power (<8 Hz) in the electroencephalogram (EEG) at rest is normal in the immature developing brain of children when compared to adults. Children with epilepsy also have greater low frequency interictal resting EEG activity. Whether these power elevations reflect brain immaturity due to a developmental lag or the underlying epileptic pathophysiology is unclear. The present study addresses this question by analyzing spectral EEG topographies and sources for normally developing children and children with epilepsy. We first compared the resting EEG of healthy children to that of healthy adults to isolate effects related to normal brain immaturity. Next, we compared the EEG from 10 children with generalized cryptogenic epilepsy to the EEG of 24 healthy children to isolate effects related to epilepsy. Spectral analysis revealed that global low (delta: 1–3 Hz, theta: 4–7 Hz), medium (alpha: 8–12 Hz) and high (beta: 13–25 Hz) frequency EEG activity was greater in children without epilepsy compared to adults, and even further elevated for children with epilepsy. Topographical and tomographic EEG analyses showed that normal immaturity corresponded to greater delta and theta activity at fronto-central scalp and brain regions, respectively. In contrast, the epilepsy-related activity elevations were predominantly in the alpha band at parieto-occipital electrodes and brain regions, respectively. We conclude that lower frequency activity can be a sign of normal brain immaturity or brain pathology depending on the specific topography and frequency of the oscillating neuronal network.

Keywords Spontaneous EEG · Theta · Alpha · Epilepsy · Brain immaturity · sLORETA

Abbreviations

BA	Brodmann area
BOLD	Blood oxygen level dependency
CE	Cryptogenic epilepsy
EEG	Electroencephalogram
ESM	Ethosuximide
FLAIR	Fluid attenuation inversion recovery
fMRI	Functional magnetic resonance imaging
GMV	Grey matter volume
HA	Healthy adults
HC	Healthy children
ICA	Independent component analysis

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ILAE	International league against epilepsy
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
LEV	Levetiracetam
LTG	Lamotrigine
sLORETA	Standardized low resolution brain electromagnetic tomography
TLE	Temporal lobe epilepsy
OXZ	Oxcarbazepine
VPA	Valproic acid

Introduction

In healthy subjects the low frequency EEG oscillations, i.e. delta (1–3 Hz) and theta (4–7 Hz), decrease with maturation in different brain regions (Gasser et al. 1988; Matousek and Petersen 1973; Whitford et al. 2007). Specifically, delta and theta oscillations dominate in childhood whereas alpha (8–12 Hz) oscillations dominate during adolescence (Benninger et al. 1984; Matthis et al. 1980; Clarke et al. 2001). In contrast, faster oscillations, i.e. beta (13–30 Hz) and gamma (>30 Hz) tend to become more prominent during adulthood (Whitford et al. 2007). Greater low frequency activity in children compared to adults or in younger compared to older children is a robust EEG marker of normal developmental immaturity (i.e., the opposite of normal development), and thus a marker of developmental lag within an age group.

However, low frequency activity is not only greater in healthy children compared to adults but also in patients suffering from a wide range of chronic functional brain disorders such as Parkinson's disease (Moazami-Goudarzi et al. 2008), pain (Sarnthein et al. 2006; Stern et al. 2006; Ray et al. 2009; Walton et al. 2010), tinnitus (Llinas et al. 1999; Moazami-Goudarzi et al. 2010), neuropsychiatric disorders (Jeanmonod et al. 2003), and epilepsy (Sarnthein et al. 2003; Clemens et al. 2000; Clemens 2004b; Sakkalis et al. 2008; Sterman 1981; Drake et al. 1998; Miyauchi et al. 1991; Gibbs et al. 1943). Epilepsy is one of the most common neurological diseases with typical abnormal patterns in the EEG or MEG (magnetoencephalogram). EEG/MEG changes in the period between seizure attacks (i.e., interictal state) are not accompanied by seizure symptoms but can be dominated by spiking activity. However, both spike-free and spike-dominated time windows of interictal interval can reveal EEG/MEG abnormalities (Clemens et al. 2007a; Lin et al. 2006; Pataraia et al. 2008; Hongou et al. 1993; Sakkalis et al. 2008). For example, spectral power elevations in lower and higher frequency bands have been reported in untreated children and adolescents with idiopathic generalized epilepsy and rare generalized spike-wave paroxysms (Clemens et al. 2007a; Clemens et al. 2000).

EEG Studies of Patients with Cryptogenic Epilepsy

Few studies have been performed in epileptic patients without radiological findings, i.e. in patients with cryptogenic epilepsy (Sakkalis et al. 2008; Hongou et al. 1993; Gelety et al. 1985). However, this is an important patient population to study since over two-thirds of epilepsies are of cryptogenic (or idiopathic) origin (Annegers et al. 1996). Spectral EEG analysis has shown greater alpha activity in adult patients with generalized cryptogenic epilepsy when compared to nonepileptic controls (Gelety et al. 1985). Sakkalis et al. (2008) reported in children with generalized cryptogenic epilepsy and drug-controlled epileptic seizures that the strongest resting EEG effects were in the alpha band. Further it has been reported that low frequency power was increased in children with cryptogenic partial epilepsy as compared to age-matched nonepileptic controls (Hongou et al. 1993). Although the latter indicates that the enhanced low frequency oscillatory activity might characterize epilepsy and not normal brain immaturity it is unclear whether this activity is linked to the same or to a different neuronal network than for nonepileptic controls.

Aims of the Study

This study aims to address the question whether low frequency oscillatory activity in normal children and in children with epilepsy arises in identical neuronal networks. To this end, this study systematically compared spectral EEG topography and source localization differences between children with generalized cryptogenic epilepsy and age- and gender-matched nonepileptic controls. Our hypothesis states that effects related to epilepsy (i.e., the comparison of children with epilepsy versus healthy children) are manifested in a different neuronal network than effects related to brain development (i.e., the comparison of healthy children versus healthy adults). This is because epilepsy-related effects should be present in brain regions linked to epilepsy, whereas developmental effects should be present in regions where major maturational processes are taking place. We specifically selected children with generalized cryptogenic epilepsy, because we wanted to test whether epilepsy-related effects can be differentiated from effects related to brain development even in the absence of a radiological diagnosis.

Materials and Methods

Subjects

Twenty four healthy children (HC from now on, 14 females, age ranges 9–11.2 years, average 10 years) and 15

healthy adults (HA from now on, 9 female, age ranges 20–30 years, average 26.3 years) participated in this study. All subjects were right-handed and had normal or corrected-to-normal vision. The study was approved by the local ethics committee and was conducted in accordance with the declaration of Helsinki. All participants gave written informed consent prior to participation. The subjects had no current or previous history of relevant physical illness and they were not currently taking drugs or medication known to affect their EEG. All EEG recording sessions were performed in the forenoon hours in order to exclude an impact of circadian factors on the EEG. Subjects were advised to abstain from caffeinated beverages on the day of recording to avoid the caffeine induced theta decrease in the EEG (Landolt et al. 2004). For children, IQ was estimated using the block design subtest of the HAWIK-III intelligence test (Tewes et al. 2000). Mean intelligence score was 110 (range 85–130). In addition, the children's behaviour profile (Achenbach and Edelbrock 1983) was analyzed. The average score across different subtests was normal (<60, mean value: 46.5 range 27.1–59.6). All parents filled out a questionnaire regarding children's handedness (Oldfield 1971).

Patients

Each patient gave written informed consent prior to participation. Ten right-handed children with generalized cryptogenic epilepsy (CE from now on, 4 females; age ranges 9–12 years, average 10.4 years; age ranges at onset of disease: 4–11 years, average: 7.4 years) were studied. Patients were right-handed and had normal or corrected-to-normal vision. All children had at least one high-resolution MRI (GE 3 Tesla scanner) of the head, according to the high recommendation standards of the ILAE (Serles et al. 2003), showing no epileptogenic lesion. MR images were acquired for the following sequences: FLAIR, T2*, 3D T1-weighted, and T2- weighted. For ethical reasons, PET imaging was not performed since none of the patients participated in a pre-surgical intervention program. Epilepsy syndrome and seizures were classified according to the ILAE recommendations (Engel 2001). Seizure burden and age of seizure onset are reported in Table 1. There were no tonic-clonic seizures for at least a week prior to EEG analysis. We focussed on spike-free EEG segments, since the spike-distribution was multiregional (>1 epileptogenic focus) and the spike rate was generally low (<0.5/min). Eight of the patients had been on pharmacological monotherapy or polytherapy, i.e. on multiple antiepileptic drugs (AEDs, Table 1). On the day before the study patients were all instructed to stop the treatment (apart from anticonvulsive treatment). All patients showed normal psychomotor development. IQ values differ ($P = 0.041$, unpaired t-test) between the HC group (mean IQ: 110.6 ± 10.3, range 85–130) and CE group (mean IQ 100.4 ± 12.8, range 83–120).

Table 1 Patients' characteristics including gender, age, clinical status, weight and medication

Patient Nr.	Gender	Age at EEG (years)	Age at seizure onset (years)	Seizure burden during daytime (n. of seizures within 1/2 year before the EEG)	Last seizure prior to EEG (in weeks)	Interictal events localization	Weight (kg)	Handedness	Etiology	Medication and dose (mg/d)
1	Female	10	6	~100	>1	Bifrontal	59	R	Cryptogen	LEV 3000
2	Female	11	10	100–130	>2	Multiregional	35	R	Cryptogen	OXZ 300, ESM 750
3	Male	10	7	~2	>12	Bifrontal	45.2	R	Cryptogen	LEV 1750
4	Male	10	2	~24	>5	Bitemporal, frontal	38.5	R	Mesial temp.	VPA 1000, LTG 200, LEV 2000
5	Female	9	2	~72	>3	Multiregional	37	R	Cryptogen	LTG 250
6	Male	12	11	~12	>1	Frontal	29.4	R	Cryptogen	LTG 225
7	Female	9	4	–(only during sleep)	>24	Temporal left	23.5	R	Cryptogen	VPA 525, LEV 1000
8	Female	10	8	~3	>15	Bifrontal	32	R	Cryptogen	LEV 2500, LTG 200
9	Male	12	10	100-130	>1	Bifrontal	38.4	R	Cryptogen	No
10	Female	11	5	–	>24	Multiregional	46	R	Cryptogen	No

LEV levetiracetam, *LTG* lamotrigine, *OXZ* oxcarbazepine, *ESM* ethosuximide, *VPA* valproic acid, *temp* temporal

Data Acquisition

For HC and HA, resting EEG (eyes closed) was recorded from 60 Ag/AgCl surface electrodes. All electrode positions of the 10–20 system plus the following 10–10 system sites were used: Fpz, Afz, FCz, CPz, POz, Oz, Iz, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5/6, TP7/8/9/10, P5/6, PO1/2/9/10, OI1/2. Electrode Fz served as reference electrode. Additionally, data from two electro-oculogram electrodes and two electro-cardiogram channels were measured. For CE, resting EEG was recorded from nineteen Ag/AgCl surface electrodes placed according to the international 10–20 system and from one electro-cardiogram channel. Common scalp electrodes were selected for the between-group analysis, including the following electrodes: FP1, FP2, F3, F4, F7, F8, Fz, T3, T4, T5, T6, C3, C4, Cz, P3, P4, Pz, O1, and O2. During recording, impedance was kept below 10 kΩ. A mean of 4.8 min (±0.9 min) EEG was recorded across all participating subjects.

Mean Spectral Analysis

EEG data were analyzed offline using the Brain Vision Analyzer Software (Brainproducts, Munich, Germany). Data were downsampled to 256 Hz and digitally lowpass filtered (0.5–70 Hz, 24 dB/octave), and visually inspected for eye movement-, muscle- and cardiac artefacts. After artefact rejection, EEG was decomposed into independent components for further removal of artefacts using an independent component analysis (S. Enghoff, http://www.cnl.salk.edu). Next, the EEG signal was reconstructed and transformed to average reference (Lehmann and Skrandies 1980). Since drowsiness may result in enhanced theta power, the level of vigilance was regularly checked during the recording by monitoring EEG parameters, such as slowing of the alpha rhythm or appearance of sleep spindles.

At least 38 2.5 s artefact-free EEG epochs reflecting relaxed-waking state of the subject were selected for spectral power analysis. No significant differences regarding the artefact-free EEG data length was found between the different groups (all $P > 0.8$, two-tailed unpaired *t*-tests). Only EEG epochs outside spiking periods were considered, i.e. outside a time window of one-second before and after the end of spiking activity. To check for a potential contamination of slow wave activity (1–3 Hz) following spikes discharges, we additionally analysed the data for spike-free EEG segments 3 s earlier and after the spike discharge (Supplementary Fig. 1).

Absolute spectral power across epochs was calculated by fast fourier transform (zero padded data with 384 zeros) for the following frequency bands: delta (1–3 Hz), theta (4–7 Hz), lower alpha (8–10 Hz), higher alpha (10–12 Hz) and beta (13–25 Hz).

Topographic Spectral Analysis

To investigate whether spectral band power EEG effects were related to brain immaturity or epilepsy, we first calculated the mean absolute spectral band power over all nineteen scalp electrodes for HC, CE, and HA. Next, we tested for significant topographic differences for the contrast CE-HC (i.e., effects related to epilepsy; one-tailed *t*-tests with $P < 0.01$, uncorrected) and for the contrast HC-HA (i.e., EEG effects related to brain immaturity; one-tailed *t*-tests with $P < 0.001$, uncorrected) for each frequency band. For the latter, a higher *P*-value was selected to obtain meaningful topographical maps. Between-group effects ((HC-HA)–(CE-HC)) were compared by *t*-tests ($P < 0.01$) and by a topographic analysis of variance (TANOVA, $P < 0.05$, corrected for multiple comparisons) (Strik et al. 1998). To test quantitatively for effects of different drug classes we calculated in a single-subject analysis the contribution of any given medication on each frequency band (for details see legend of Fig. 2).

Spectral Source Localization

We used standardized low resolution brain electromagnetic tomography (sLORETA), a distributed source solution based on spatial smoothness constraints (Pascual-Marqui 2002), to localize the generators of the scalp EEG power spectra for the contrasts CE-HC and HC-HA. The sLORETA solution space is restricted to the cortical gray matter in the digitized MNI atlas with a total of 6,239 voxels at 5 mm spatial resolution. We calculated tomographic sLORETA images corresponding to the estimated neuronal generators of brain activity within a given frequency range (Frei et al. 2001), i.e. in the range of 1–25 Hz. sLORETA images were statistically ($P < 0.05$, corrected for multiple comparisons) compared through multiple voxel-by-voxel comparisons using a non-parametric test for functional brain imaging (Nichols and Holmes 2002).

Results

Mean Spectral Analysis

As a starting point for the EEG analysis, we first quantitatively compared the spectral power for the three different groups: CE, HC, and HA. For the CE group, we observed the greatest absolute spectral power across all 19 electrodes in the delta to beta band (Fig. 1a, black curve). These

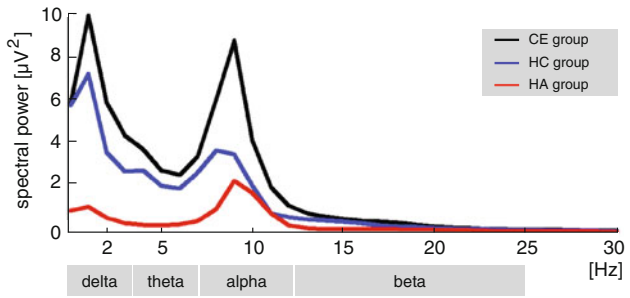


Fig. 1 Absolute spectral power averaged across all electrodes for children with cryptogenic epilepsy (CE group, *black curve*) and the healthy control groups: healthy children (HC group, *blue curve*) and healthy adult (HA group, *red curve*). The grey-shaded areas on the x-axis indicate the different frequency domains

increases in spectral band power cannot be explained by seizures, since the last seizure occurred at least a week before the EEG recording. Also for the HC group (blue curve) we found enhanced activity from delta to beta when visually compared to the HA group (red curve). The single subject data analysis revealed that the majority (8/10) of CE patients showed elevated alpha band power when compared to the HC group (Fig. 2a). This analysis also indicated that specific drug classes do not systematically lead to increases in power (Fig. 2b, c). The analysis for spike free longer EEG segments (i.e., EEG segments ± 3 s before and after spike occurrence) yielded no significant differences in any of the investigated frequency bands when compared to the above described spectral analysis ($|t - \text{values}| < 1$, Supplementary Fig. 1). Therefore, topographical and source localization analysis will be reported only for the original analysis.

Topographic Spectral Analysis

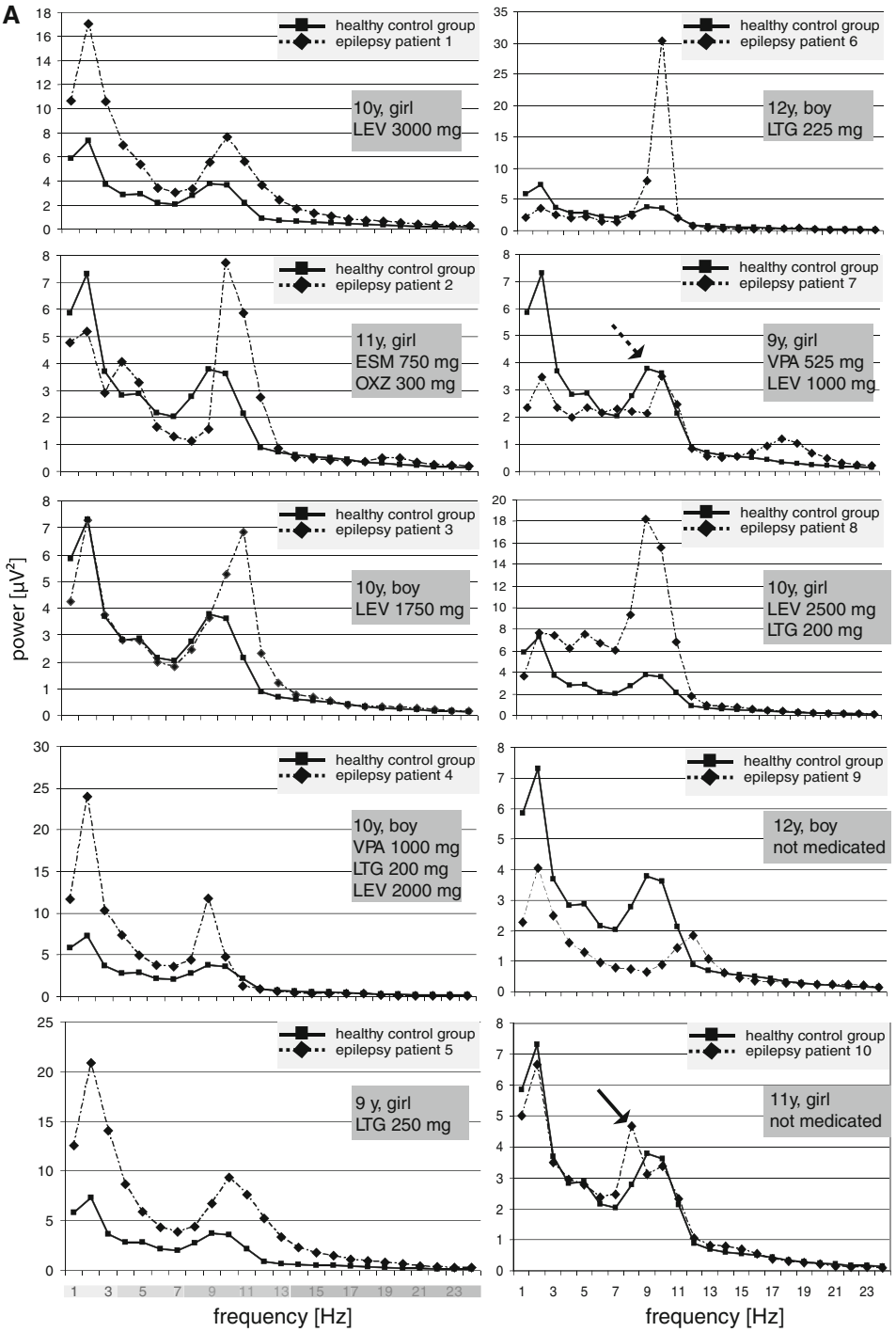
The topographical distribution of absolute spectral power is shown in Fig. 3a for the three different groups. For the HC group, absolute power was maximal in the delta and lower alpha band at fronto-parieto-occipital (delta) and parieto-occipital (lower alpha) electrodes (top panels). For the HA group, the absolute power peaked in the alpha band at parieto-occipital electrodes (middle panels). For the CE group, the absolute power was generally higher than in the two other groups (bottom panels). Specifically, the highest absolute spectral power values were visible in the delta and alpha band at parieto-occipital electrodes. To test for topographical effects related to brain development, we calculated an electrode-wise comparison for the contrast HC-HA. This contrast revealed spectral increases at fronto-central electrodes in delta and theta ($P \ll 0.001$, uncorrected) as shown in Fig. 3b (top panel). No significant effects were observed in the alpha (except at one temporal electrode) and beta band (not shown). To test for topographical effects related to epilepsy, we calculated an electrode-wise comparison for the contrast CE-HC. In contrast to HC-HA, the greatest differences ($P < 0.001$) occurred in the upper alpha band (10–12 Hz). The effects were most prominent at fronto-central and left parieto-occipital contacts (Fig. 3b, bottom panel). Additionally, few occipital electrodes showed significant effects in the delta and theta band ($P < 0.01$) and therefore at different locations than for the contrast HC-HA. No significant effects occurred in the beta band (not shown). To clarify whether developmental and epilepsy related effects are preserved both individual group contrasts were compared directly by calculating the contrast ((HC-HA)–(CE-HC)). The TANOVA in Fig. 4a indicates the significant and non-significant (grey bars) frequency points for this contrast. For example, all frequency points <12 Hz reflect significant ($0.05 > P > 0.01$) group differences. The topographical maps show the direction of these differences (Fig. 4b). Developmental effects (HC-HA > CE-HC, red colour code) occur in the delta and theta band at wide-spread locations, including fronto-central electrodes, as shown in the Fig. 4b (left panels). In contrast, effects related to epilepsy (CE-HC > HC-HA, blue colour code) were observed in the alpha band at fronto-parietal electrodes (Fig. 4b, right panels). This analysis therefore corroborates the effects observed on the individual group comparison level, namely that normal developmental immaturity effects are reflected in greater activations in the delta and theta band, whereas overactivations to epilepsy are manifested in the alpha band.

Spectral Source Localization

Significant source localization differences for the contrasts CE-HC and HC-HA are shown in Fig. 5. For the contrast HC-HA, delta and theta band activity increases occurred at fronto-central brain regions ($P < 0.01$, corrected for multiple comparisons). In contrast, differences for the CE-HC occurred only in the alpha band (8–12 Hz) and were manifested dominantly in parieto-occipital regions (all $P < 0.05$, corrected for multiple comparisons). As for the topographical spectral analysis, spectral source localization demonstrates no differences in the beta band.

Discussion

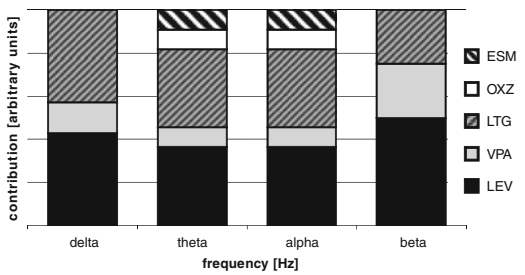
Our study revealed greater low frequency oscillatory activity in epileptic children (CE-HC) as well as in normally developing children compared to adults (HC-HA). However, topographical analysis and source localization demonstrated that these increases in spectral power originate from two different oscillatory neuronal networks.



B

medication (nr. of patients)	delta	theta	alpha	beta
	(quotient: nr. of patients/total nr. of patients [%])			
LEV (5/10)	30%	40%	40%	20%
VPA (2/10)	10%	10%	10%	10%
LTG (4/10)	30%	40%	40%	10%
OXZ (1/10)	0%	10%	10%	0%
ESM (1/10)	0%	10%	10%	0%

C



◀ **Fig. 2** **a** Average spectral power for the each of the patients with CE (cryptogenic epilepsy) and for the HC (healthy children) group. No systematic effect of a specific drug class on a specific frequency band could be observed. For example, it is unlikely that the delta and alpha band increases in patient four can be attributed to LEV or VPA, because patient seven does not show increased EEG power in these frequency bands (*dashed arrow*). In addition, patient 10 shows increased alpha band power (*solid arrow*) although not receiving any medication. **b** Overview of the medication distribution (%) for the individual patients (*left column*). To explore whether a specific drug class leads to increases in spectral power first mean band spectral power was calculated for each patient and across the HC group. Second, a quotient was calculated to express the spectral increase in each frequency band across the patient group. For example, in three of the five patients (30% of the whole patient group) that received LEV mean delta power was increased when compared to the mean band power for the HC group. **c** Contribution of drug classes on the different frequency bands. For example, LEV (*black bar*) contributes more to the beta band than to any other frequency bands, whereas OXZ and ESM contribute only on the theta and alpha band. *LEV* levetiracetam, *LTG* lamotrigine, *OXZ* oxcarbazepine, *ESM* ethosuximide, *VPA* valproic acid

We found a "developmental immaturity network" with greater power in delta and theta frequencies in frontocentral brain regions and an "epilepsy network" with predominantly elevated power in alpha frequency located in parieto-occipital brain regions.

The Role of Low Frequency Activity in Epilepsy

In general, our findings of greater low frequency power in CE patients extend the results from EEG studies that found predominantly increased low frequency activity for well-defined forms of epilepsy (Clemens 2004a, b; Clemens et al. 2000; 2007a; Kobayashi et al. 2009; Guye et al. 2006; Drake et al. 1998; Sterman 1981) but also for cryptogenic epilepsy (Hongou et al. 1993; Sakkalis et al. 2008). Initially, we had expected to observe the strongest epilepsy related effects in the delta-theta but not in the alpha band, because some but not all of these studies observed predominantly elevated delta-theta band activity.

Why Did We Observe Spectral Power Increases Predominantly in the Alpha Band in the CE Group?

It had been argued that the so called "posterior centre of gravity"-as visible from enhanced posterior alpha activity-might be a marker for patients with idiopathic generalized epilepsy (Clemens et al. 2007a; Rodin 1999). It is important to note that the study by (Clemens et al. 2007a) showed some similarities to our study: (1) they examined only EEG segments without epileptiform potentials; (2) patients had no generalized tonic–clonic seizures in a period of 5 days before the EEG investigation; and (3) their patients showed only rare spiking activity during the EEG recordings. Our data disclosed that this centre of gravity might be also a marker for children with generalized CE (Figs. 4, 5). Additionally, our results extend prior findings that demonstrated the existence of the posterior centre of gravity in the early course of ictal generalized spike-wave complex (Rodin 1999; Rodin and Cornellier 1989; Ferri et al. 1995). We suggest that our findings indicate that this region is hyperactive also in spike-free EEG epochs. One open question is whether low frequency activity increases in this region reflects the ictogenic property of the cortex, i.e. whether the cortex is per se ictogenic (van Gelder et al. 1983; Gloor et al. 1982) or whether there are other underlying pathophysiological mechanisms that might explain these overactivations.

One potential explanation for the dominance of alpha-band power in our CE group could be that alpha power elevations were induced by medications. Although some of these drugs (e.g. VPA) have only limited or no effect on spectral band power of patients with CE (Hongou et al. 1993) and in patients with primary generalized epilepsy (Benninger et al. 1985), the attenuation of frontal (theta and delta) activity is well documented (Clemens et al. 2007b). However, as the semi-quantitative single-subject analysis demonstrated there was no systematic contribution of any medication on the alpha band, i.e. none of the applied drugs could explain the observed alpha band power increases (Fig. 2a, c). It might be possible that the spectral power increases for the CE group do not directly reflect an underlying pathological mechanism, but are rather a sign of a developmental lag (e.g. a cognitive impairment). For example, it has been shown in several studies that the decrease of mean alpha frequency variability (by $\sim$0.5 Hz) predicts a cognitive impairment in healthy persons and epileptic patients as well (Frost et al. 1995; Salinsky et al. 2002). However, we did not observe a slowing of the mean alpha band power in the CE group (Fig. 1). Although IQ values differed between the CE and the HC groups, we found no significant correlation between the alpha peak power and IQ values (HC group: $r^2 = 0.005$, n.s.; CE group: $r = 0.11$; n.s.; Pearson correlations) for both groups, i.e. alpha band power was neither positively nor negatively linked to IQ.

To conclude, it is important to note also that delta and theta power was higher in the CE than in the HC group (Figs. 1, 3, 5). Thus, our results are not contradicting previous studies. One reason why we observed weaker effects in the delta and theta band than in the alpha band may be that the antiepileptic medication suppressed the low frequency increases. A second reason might be the young age of our child patient and control groups [as compared to Clemens et al. (2000) and Clemens et al. (2007a)], since greater power and high inter-subject variability in low frequency bands (Fig. 2) is typical for this age range.

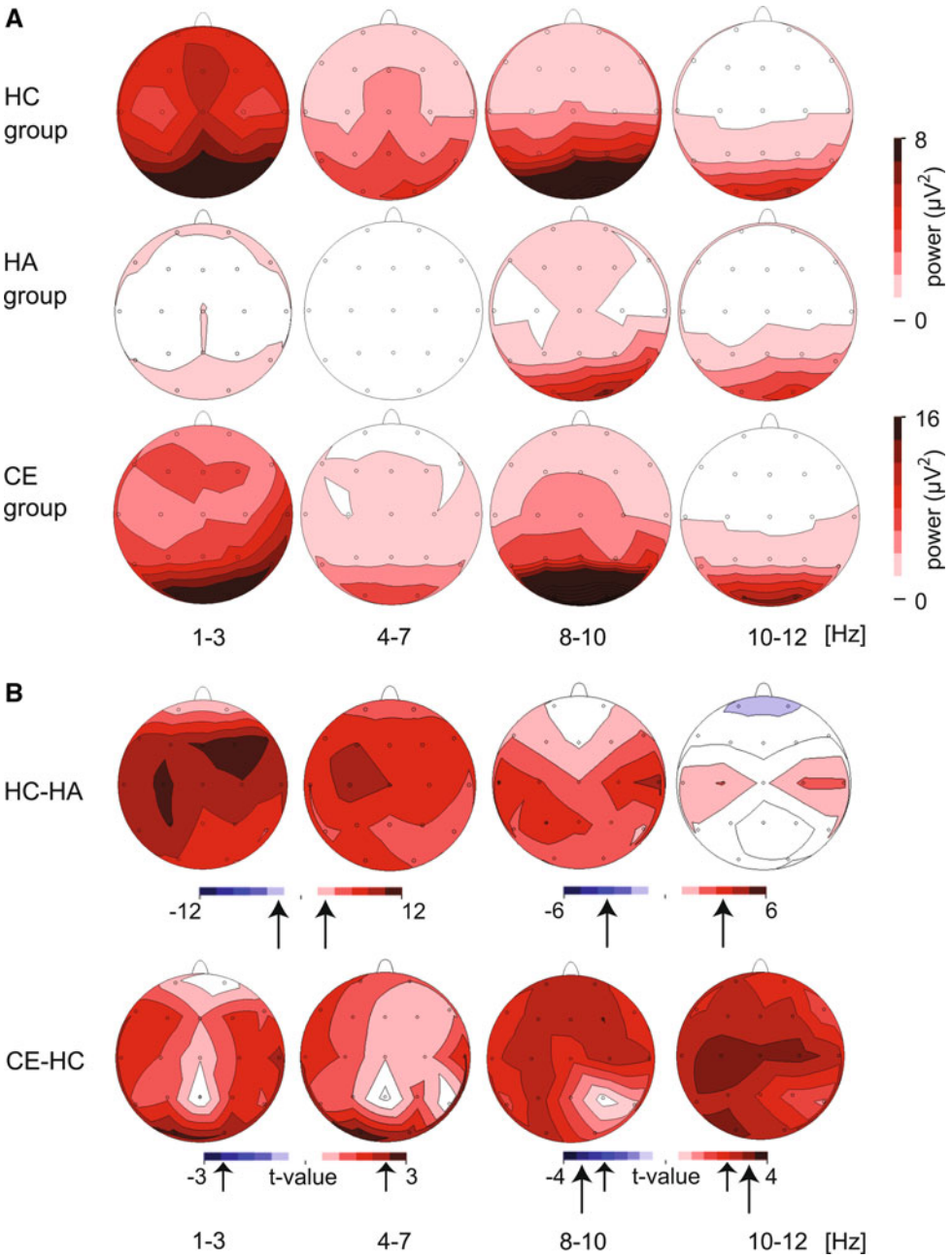


Fig. 3 **a** Topographic maps for the HC-, HA- and CE group between 1 and 12 Hz. The colour code on the right of each panel indicates spectral power (*light red*: low absolute power, *dark red*: high absolute power). Please note the different scaling for the CE group. **b** Results for the statistical comparison (t-maps) between HC-HA (*top panels*) and CE-HC (*bottom panels*). The *short black arrow* indicates $P < 0.01$ (*uncorrected*) and the *long black arrow* indicates $P < 0.001$ (*uncorrected*)

Spike-Triggered Versus Non-Spike Driven Analysis

Many brain imaging studies focussed on the time window at or around the onset of spiking activity. Lin et al. (2006) found the strongest increase in the alpha band in children with benign rolandic epilepsy during interictal spike occurrence using MEG at the approximate timing they observed an increase in 0.5–25 Hz oscillations over identical areas in the other hemisphere where no spike signals were found. This finding indicates that alpha power increases are not necessarily dependent on the presence of spikes. Our data extend the findings by Lin and co-workers in one aspect, namely that spike-unrelated alpha band changes characterize also patients without any radiological findings, i.e. with cryptogenic epilepsy. Our results are also in line with recent findings that reported increased low frequency activity -most prominent in the alpha band- in children with medically controlled epileptic seizures which show no neurophysiological abnormality (i.e., spikes) or any signs of brain dysfunction (Sakkalis et al. 2008).

EEG–fMRI recordings in patients with temporal lobe epilepsy and rare spikes revealed that parieto-occipital alpha band power showed negative correlations with the BOLD (Blood-Oxygen-Level-Dependent) signal, whereas

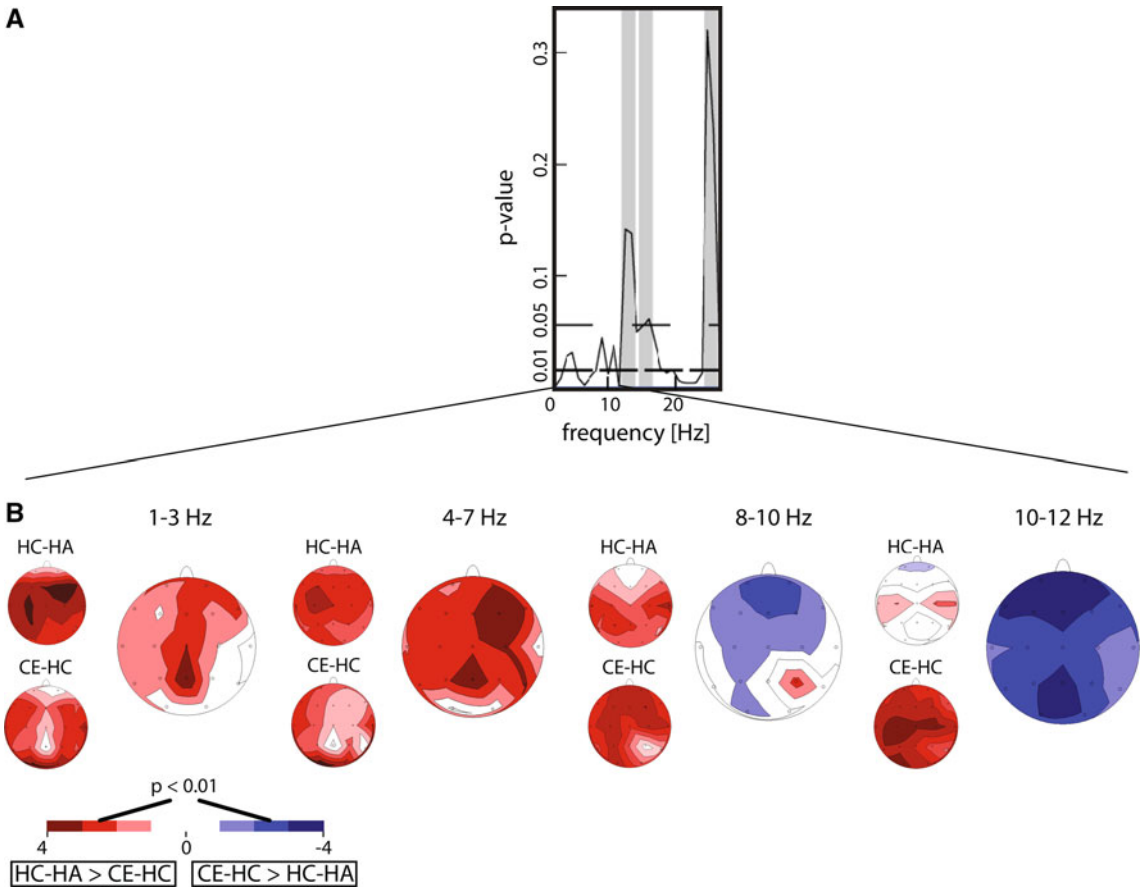


Fig. 4 Illustration of the direct comparison of the "developmental effect" and the "epilepsy effect": **a** Results of the topographical analysis of variance (TANOVA) for the contrast ((HC-HA)–(CE-HC)). Significant changes ($P < 0.05$, corrected for multiple comparisons) occur at <12 Hz and between 17 and 24 Hz. **b** Statistical comparison (t-test, $P < 0.01$) show the direction of these changes: Developmental effects (HC-HA > CE-HC, *red colour*-code) are present in the delta (1–3 Hz) and theta (4–7 Hz) band at widespread electrodes, including fronto-central electrodes. Epilepsy effects (CE-HC > HC-HA, *blue colour*-code) are present in the alpha (8–12 Hz) band at frontal and parieto-occipital electrodes

theta band power was positively correlated with the thalamic BOLD signal (Tyvaert et al. 2008). This indicates that EEG-fMRI signal correlations in cortical and sub-cortical areas are not exclusively dependent on the presence of spike epochs. In addition this EEG–fMRI study demonstrates that the spike-dominant region (i.e. increased temporal EEG power) does not necessarily overlap spatially with the underlying epilepsy-related hemodynamic changes. Recently, it has been reported that EEG–fMRI interactions may occur long before (5 s) or after (6 s) the spike onset (Jacobs et al. 2009), suggesting that the temporal coupling between spikes and hemodynamic responses is highly variable. We suggest that it would be interesting to use EEG–fMRI recordings in patients with cryptogenic epilepsy, first to investigate whether (parieto-occipital) alpha power is linked to hemodynamic changes and second to study the link between spike-related and spike-unrelated EEG epochs and hemodynamic changes, since this offers a way to examine neurophysiological interactions in patients with structurally unaffected cortical and sub-cortical regions.

The Relationship of Our Findings to the Type of Epilepsy

Deviations from other studies could be caused by the type of epilepsy diagnosis. For example, some studies described an increase in delta, theta, lower alpha (8–8.8 Hz), and beta but not in upper alpha (9–12.8) power in idiopathic, non-lesional and lesional partial epilepsy patients (Drake et al. 1998; Miyauchi et al. 1991). In contrast, patients with generalized cryptogenic epilepsy reveal predominately alpha band differences as compared to healthy individuals (this study, but see also Sakkalis et al. 2008). Once again it is important to note that delta and theta power was higher in the CE than the HC group (Figs. 1, 3, 5). However, we suggest that it is difficult to compare our results to other studies, since this would require a patient population with a similar diagnosis

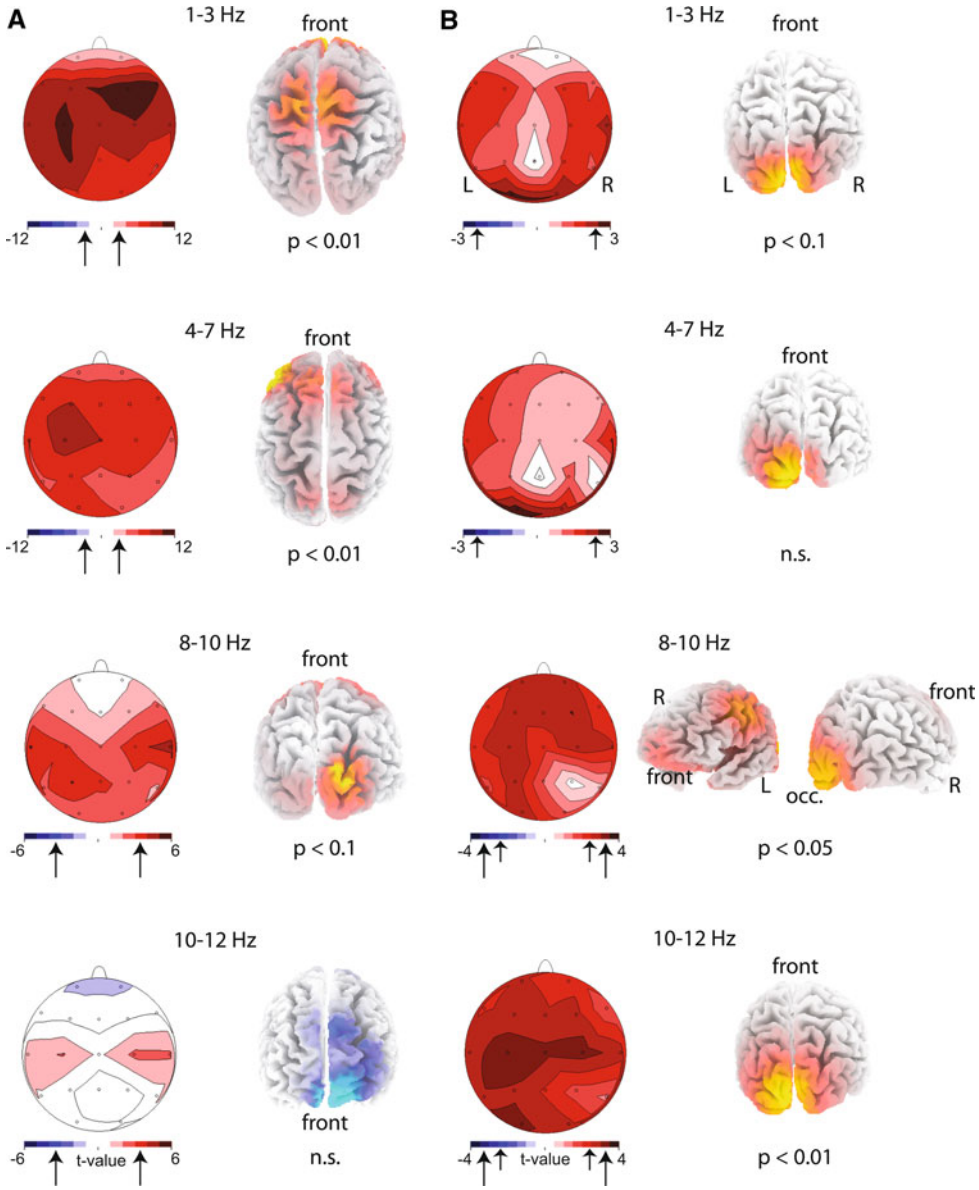


Fig. 5 Comparison of topographical- and source localization differences for the contrasts: **a** HC-HA and **b** CE-HC. For the topographical maps (*left panels* in **a** and **b**) the colour bar indicates statistical power differences with a red colour code for HC > HA and CE > HC and a blue colour code HC < HA and CE < HC. For the source localization maps (*right panels* in **a** and **b**), a *red–orange colour* code indicates HC > HA and CE > HC and a *blue colour* code indicates HC < HA and CE < HC. *L* left hemisphere, *R* right hemisphere, *n.s.* not significant. The *short black arrow* indicates $P < 0.01$ (*uncorrected*) and the *long black arrow* indicates $P < 0.001$ (*uncorrected*)

(i.e. patient with cryptogenic epilepsy and a similar multi-regional spike distribution), age- and gender distribution, behavioural values (e.g. IQ), medication, and a similar EEG recording and analysis setting. Patients with symptomatic epilepsy show altered EEG activity but this is related to structural brain abnormalities (Nunez 1995; Robinson et al. 2004), i.e. the observed findings are per se not directly comparable to our findings.

The Role of Oscillatory Activity During Development

For children compared to adults, we observed the greatest spectral power in the delta–alpha bands, in line with other studies (Whitford et al. 2007; Benninger et al. 1984). For example, Benninger et al. (1984) found that with development theta band power diminished as alpha band power increased, and that the speed of change in occipital regions is nearly twice that of central areas. Indeed, we found that the HC group showed enhanced alpha band power at occipital more than at central regions (Fig. 3a). A potential reason for the presence of greater low frequency activity during brain development might be that these frequencies mediate the establishment of long-range cortico–cortical connections, which are not fully developed during childhood (Fair et al. 2007; Supekar et al. 2010). In adults it has been shown that theta and alpha mediate long-range connections in a variety of task including visual perception and working memory (Sarnthein et al. 1998; von Stein and Sarnthein 2000).

A recent study using MRI and resting EEG recordings investigated the impact of maturation on both neuroanatomy and neurophysiology in the same healthy subjects

aged between 10 and 30 years (Whitford et al. 2007). The authors found that the reduction of low frequency power (0.5–7.5 Hz) correlated with a decrease of grey matter volume (GMV) with age in frontal and parietal cortices. Specifically, the EEG activity showed a curvilinear decline similar to GMV in corresponding cortical regions. An inverse pattern of curvilinearly increasing white matter volume was observed in the parietal lobe. Whitford and colleagues concluded that the reduction in GMV indicates a loss of neuropile and that the corresponding elimination of active synapses is responsible for the observed reduction in EEG power.

Conclusion

Our results demonstrate that EEG power in combination with source localization is a powerful tool to differentiate between immaturity during normal brain maturation and epilepsy. Our findings additionally indicate that the identification of separate neuronal networks can be achieved from spike-free EEG segments and in epilepsy patients in whom a clear radiological diagnosis is absent.

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