Encephalopathy with Electrical Status Epilepticus in Slow Wave Sleep – a review with an emphasis on regional (perisylvian) aspects

Peter Halász [1], Márta Hegyi [2], Zsuzsa Siegler [2], András Fogarasi [2]

[1] National Institute of Clinical Neurosciences, Budapest
[2] Bethesda Children Hospital Epilepsy Center, Budapest

Correspondence

Peter Halász
National Institute of Clinical Neuroscience
Budapest, Hungary
e-mail: halasz35@gmail.com
Phone: +361 70 370 8401

SUMMARY

Aim. The aim of this article is to review criticaly the Electrical Status Epilepticus in Slow Sleep (ESES) phenomenon from a neurophysiological mechanisms aspect as well as terminological and classification issues.

Methods. The review includes all the relevant papers published during the last 43 years on the subject of ESES and Continous Spike – Wave in Sleep (CSWS).These papers were identified in various large databases via the internet.

Rewiev and remarks. ESES/CSWS phenomena can be held as a common final pathway originating from different etiologies, including patients with early brain damage (probably involving thalamic structures), but also patients without structural pathology as in atypical evolution of idiopathic regional childhood hyperexcitability syndromes (with Rolandic epilepsy as a prototype). There are hints that genetic predisposition might be an important factor in the development of this process. The two large patient groups (lesional and non-lesional) show the same EEG evolution and encephalopathic cognitive consequences. The sleep EEG activation can be held as a common endophenotype. ESES represents an extreme sleep activation/potentiation of the local/regional interictal discharges, enhancing them in frequency, territorial extension, intra and trans-hemispherial propagation, synchrony and continuity. This process is most probably not identical with the development of bilateral spike-wave pattern in „generalized" epilepsies which involves primarily or secondarily the thalamo-cortical system as it had been explored by Gloor (1979) for idiopathic generalized rpilepsy and Steriade and Amzica (2003) for different types of generalized spike and wave discharges.

Conclusions and syndromological embedding of ESES. In an overwhelming majority of the investigated cases, the maps of the single discharges constituting sleep activation are identical; with focal/regional interictal spikes followed by slow closing wave, as it is seen in childhood regional age dependent hyperexcitability syndromes (prototype of the centro-temporal spikes of Rolandic epilepsy). The main mechanism of the developing cognitive impairment is most probably the consequence of interference with plastic function of slow wave sleep by obliterating synaptic decline during sleep. Presently, the consensus and co-operative research is highly obstacled by the terminological chaos, the controversial definitions and views around this still striking and enigmatic phenomenon.

Keywords: Electrical Status Epilepticus in Slow Sleep • Continuous Spike-Wave in slow Sleep • perisylvian epileptic network • cognitive impairment • sleep plastic functions • synaptic decline during slow wave sleep • atypical Rolandic epilepsy • early thalamic lesions

Review paper

Abbreviations

ADHD – Attention Deficit Hyperactivity Disorder

BOLD (signal) – Blood Oxygen Level Dependent contrast imaging

CSWS – Continuous Spike - Wave in Sleep

CTS – Centro-Temporal Spike(s)

ELP4 – Elongator Protein Complex 4 gen (involved in cell motility, migration, and adhesion)

ESES – Electrical Status Epilepticus in Slow Sleep

fMRI – functional Magnetic Resonance Imaging

GRIN2A – NMDA receptor subunit gen (involved in cell adhesion)

IED – Interictal Epileptiform Discharge

IQ – Intelligence Quotient

LKS – Landau-Kleffner Syndrome

MRI – Magnetic Resonance Imaging

NR2A – NMDAR subunit gen (involved in development of dentritic arborisation)

PET – Positron Emission Tomography

SRPX2 – Sushi Repeat-containing protein X-linked 2 gen (promotes synaptogenesis)

TMS – Transcranial Magnetic Stimulation

INTRODUCTION

The enigmatic phenomenon of "Electrical Status Epilepticus in Slow Sleep" (ESES) or "Continuous Spike and Wave during Sleep" (CSWS) represents a great challenge for clinical experts dealing with child epileptology and also for neuroscientists involved in their research. During the almost 45 year history of this topic the unresolved questions around the syndrome came closer to research problems as how sleep activates epilepsy, how epilepsy interferes with cognitive functioning and how sleep plays a role in plastic functions. In recent years there has been a large increase in interest toward ESES/CSWS and several excellent reviews and summaries have been published (Loddenkemper et al., 2011; Tassinari et al., 2012; Sánchez Fernández et al., 2012). An international conference on Encephalopathy with Electrical Status Epilepticus during Slow Sleep was also held in March, 2014 in Soro (Denmark). We are still facing several unresolved questions; some could be aswered by systematic co-operation among instutions and gathering databases for detailed follow up studies based on standard criteria.

AIM

The aim of this article is to review criticaly the ESES phenomenon from a neurophysiological mechanisms aspect as well as terminological and classification issues. We will discuss the history and etiology of ESES, the terminological and conceptual chaos around ESES/CSWS and its causes, the mechanism of the discharges (are they generalized spike-and-waves or regional discharges?), what is their spatial distribution, synchrony and amount, the functional imaging (fMRI and PET) data, the genetic aspects and role of endophenotypes, the relationship with neuropsychological impairment and lastly the mechanisms of sleep enhancement and interrelationship with cognitive impairment. Finally we provide a recommendation as to what should be done so as to learn more about the encephalopathy with ESES.

METHODS

The review includes all the relevant papers published during the last 43 years on the subject of ESES and CSWS. These papers were identified in various large databases via the internet.

REVIEW AND REMARKS

History and etiology of ESES

In 1971 Patry, Lyagoubi and Tassinari, described a "Peculiar EEG pattern occuring almost continously during sleep, characterized by apparently subclinical spike-and-waves, for a variable length of time (months to years)" in six children with cognitive deficit. After this first publication, Tassinari et al., (1977) introduced the term "Encephalopathy related to electrical status epilepticus during slow wave sleep". They suggested that "the condition of a protracted (years) status epilepticus in sleep can be the factor leading to severe mental deterioration and psychic disturbances". At the beginning the ESES syndrome was considered to be rare (Tassinari et al., 2000). However, subsequently more and more patients were recognized with different etiologies.

One of the first recognized patient group was Rolandic epilepsy with centro-temporal spiking (CTS), where ESES was considerd to be a possible deviant evolution of the disease. The concept was broadened to all variants of idiopathic focal childhood epilepsy (Dalla Bernardina et al., 1978, 1991; Lerman and Kivity, 1991; Panayiotopoulos, 1999) as an age dependent transitory (for years) idiopathic regional hyperexcitability syndromes

underlain by a genetically based maturational abnormality (Doose and Baier, 1989; Panayiotopoulos, 1999).

Since Kellerman (1978) first documented that patients with acquired epileptic aphasia or Landau-Kleffner Syndrome (LKS) had an extreme activation of spike-and-wave discharges during slow-wave sleep consistent with ESES, LKS is considered by several authors as a clinical variant, or a subtype of ESES (Dulac et al., 1983; Deonna and Roulet-Perez, 2010; De Negri, 1997; Galanopoulou et al., 2000; Halász et al., 2005; Van Bogaert et al., 2006; Nickels and Wirrel, 2008; Rudolf et al., 2009; Garcia-Peńas, 2010; Overvliet et al., 2010)

Fejerman (2009) also recognised the "atypical evolution of Rolandic epilepsy", defined by the appearance of severe neuropsychological impairments and continuous spike-and-waves during slow sleep. A very similar concept has been published by our group (Halász et al., 2005). We provided evidences for a unifying concept for the syndromes of benign focal childhood epilepsies, LKS, and ESES, treating them as a spectrum of a disorder with a common transient, age dependent, non lesional, genetically based epileptogenic abnormality.

Recently, a retrospective study which included 196 patients with benign childhood epilepsy with centrotemporal spikes, suggested that an "atypical" evolution into ESES or to LKS is more common than previously reported; accounting for 6.6% of patients and representing 65% of all "atypical" presentations of CTS (Tovia et al., 2011). Other reports have shown that patients with a previous diagnosis of idiopathic partial epilepsy account for about one-third of the Electrical Status ESES cases (Saltik et al., 2005; Kramer et al., 2009).

These epilepsies are characterized by the abundance of regional epileptiform discharges in sharp contrast with the rare, and in several cases lacking, seizures. The nature and severity of interictal cognitive symptoms are closely related to localization, amount and persistence of epileptic interictal discharges within the perisylvian network. The frequent epileptic discharges alters the evolution of the perisylvian cognitive network developing late and being vulnerable for any interference in this imprinting time for speech and other cognitive functions.

Another group of patients with evolution to ESES are children with structural abnormalities. In a series of 20 children, reviewed by Bureau (1995), neuroimaging was abnormal in more than 60% of cases. Polymicrogyria, particularly perisylvian, has been reported in up to 81% of patients (Guerrini, 2007). Teixeira

et al. (2009) reported, in their series of 40 patients with polymicrogyria, that 6 children (15%) presented with continuous epileptiform abnormalities over a focal area in wakefulness, which became bilateral and synchronous during sleep; the observation of this electrical status correlated with worsening of school performance. Patients with shunted hydrocephalus, represented approximately 30% of cases of reported by Veggiotti et al. (1999) and by Caraballo et al. (2008). Early thalamic lesions seemed to be also strongly associated with sleep-enhanced epileptiform discharges (Monteiro et al., 2001; Kelemen et al., 2006; Guzzetta et al., 2005; Andrade-Machado et al., 2012; Sánchez Fernández et al., 2012; Loddenkemper et al., 2012; Quigg and Noachtar, 2012).

Hegyi et al., (2014) in their study of 33 patients with ESES attending the Bethesda Hospital, Budapest, identified sleep EEGs in 171 records, on average 5/patient and wake recordings in 492 records, on average 15/patient). From the etiological point of view there were 15 patients without and 18 patients with structural abnormalities. In the Guzzetta et al. (2005) study of the 32 patients identified, all but 3 patients had early thalamic lesion ESES like activation, while in the Bethesda study of the 32 patients with ESES only 4 patients had thalamic lesions (among them an isolated thalamic lesion was present in only one patient).

Terminological and conceptual chaos around ESES, CSWS

Beside the etiological diversity there is an embarassing terminological and conceptual chaos around ESES phenomenon (Sánchez Fernández et al., 2013). Tassinari (1977) was the first to use the name ESES, but later he changed it to "Encephalopathy with Status Epilepticus during Sleep" (ESES), to emphasize the cognitive impairment as a sequel of the nightly recurring near-continuous discharges. Another used term was „Continuous spikes and waves during sleep" (Tassinari et al., 1985); whilst The Commission on Classification and Terminology of ILAE used the term: „Epileptic Encephalopathy with continuous spike and wave during sleep" (Engel, 2006; Berg et al., 2010).

According to the excellent survey of Sánchez-Fernández et al. (2013) 55–60% of child neurologists and epileptologists in North America used ESES and CSWS acronyms synonymously, but the majority of the responders (more than 60%) considered CSWS as a devastating epileptic encephalopathy with seizures and severe neu-

rocognitive sequels even if treated correctly, and used ESES only for the EEG pattern regardless of the clinical epileptic and cognitive symptoms. This convention behind the seemingly almost identical acronyms is accepted practice by several authors (Sánchez Fernández et al., 2012, Liukkonen et al., 2010). The same survey showed that appart from nomenclature, oppinions about the course, outcome and diagnostic criteria were also very heterogenous. We can assume that the situation is the same among experts throughout the world.

There is confusion around the characteristics of the EEG discharges, the morphological and functional features of the discharges and also around the diagnostically required amount and spatial distributions of the discharges. One of the biggest difficulty lies in the lack of continuous long term follow-up data

In this review we will use ESES when writing about the EEG evolution process and „Enecephalopathy with status Electricus in Slow Sleep" when meaning the whole complex age dependent clinical picture, with cognitive impairment and epilepsy with different etiologies. The terms of CSWS will not be used in this article, as it is missleading, because the term „spike-and-wave" pattern is not really well defined and is used with different syndromic connotations. Therefore, we think that the term CSWS should be abandoned.

What is the mechanism of the discharges? (Generalized spike-and-wave or regional discharge? Focal or secondary generalized?)

The first publications were refering explicitly about generalized spike-and-wave discharges (Tassinari et al., 2012, fig. 2) and it was not highlighted that these discharges differ from the classical „generalized spike and wave" pattern associated with idiopathic generalized epilepsies. The criteria of the Comission on Classification and Terminology of ILAE in 1989 were accordingly written. Not only the electro-morphology was considered to be "spike-and-wave" but the recent interpretations about the pathomechanism of the discharges also went back to the classical generalized spike wave pattern. For example, Loddenkemper et al. (2011) and Sánchez Fernández et al. (2012) trying to explain the association of ESES and early thalamic lesion, refer to the Steriade model of spike-wave network, related to the interrelationships within the cortico-thalamic system. Similarly, Tassinari et al. (2012) relies on the secondary bilateral synchrony mechanism which was assumed to work classically (Tükel and Jasper, 1952) by

involving secondarily thalamic and thalamo-cortical circuitry. However, asymmetric, unilateral, or more focal/regional discharges were frequently reported (Bureau, 1995; Saltik et al., 2005; Van Hirtum-Das et al., 2006; Kramer et al., 2009; Liukkonen et al., 2010; Sánches Fernández et al., 2012). The sleep discharges in LKS were also found almost always asymmetric, with a dominant hemispheric and regional distribution congruently to the language disturbances. Beaumanoir as early as 1995 pointed out that „during ESES, the interictal EEG abnormalities during wakefulness are similar to those before ESES, but are usually more marked".

The North American survey by Sánchez Fernández (2013) has shown that 20% of child neurologists and epileptologists quantify "bilateral epileptiform activity" even if the discharge is not synchronous between the two hemispheres, and around 40% of the responders quantify more or less continuous unilateral epileptiform discharge as Electrical Status Epilepticus in Sleep pattern.

The last overview of the Tassinari group (2012) summarizes as follows: *The EEG during wakefulness shows usually focal, or multifocal, slow spikes with frequent associated diffuse slow spikes and waves. In a proportion of cases, the EEG can show similar features to what one observes in "idiopathic" focal ("Rolandic", frontal or, less frequently, parieto-occipital) epilepsies or syndromes. In other cases, a clear background asymmetry, the presence of fast spikes, or other lesional features can be seen together with organic pathologies (e.g., disorders of neuronal migration).* Tassinary et al. (2012) in their Figure 9 show a clear cut map of a focal/regional parieto-temporal discharge, nothing to do with the classical bilateral spike-wave pattern.

Thus, doubts can be raised about the existence of an unitary mechanism of ESES because discharges show heterogenic forms; they are either bilateral spike-waves or are focal/regional discharges like in Rolandic or in other focal idiopathic childhood epilepsies, or even more, they can have more diverse characteristics in dysgenetic lesional cases.

The literature is astonishingly poor in studies analysing the potential fields of the ESES discharges. In our study (Hegyi et al., 2014) of the 33 (18 lesional and 15 non-lesional) children with ESES only three (bellow 10%) (two non-lesional and one lesional) showed the classical generalized spike and wave field. It was characterized by bilateral more or less symmetric distribution, with an uniform dipole (anterior negative and

posterior positive half-fields) without unihemispheral phase reversal. All the other patients, regardless of lesional or non-lesional etiology, showed unihemispheral peaks of their discharges with anterior, medial and posterior localisation along the Sylvian – fissure as an axis, almost equally distributed (fig. 1, 2) Thus we can conclude that in our patient series that showed lesional and non-lesional cases in a ratio of 54.5:46.5%, the overwhelming majority of patients had spike fields similar to what is observe in focal/regional childhood idiopathic hyperexcitabilitysyndromes. This finding enlightens our lack of detailed knowledge about the nature of discharges, and highlights the possibility that the majority of the discharges might be focal/regional, and their electro-morphology, spatial distribution and functional properties do not obviously follow the classical generalized spike-wave pattern.

Spatial distribution, synchrony and the amount of the discharges

Encephalopathy with ESES is conceptualized as a more or less uniform age dependent electroclinical syndrome, starting in early childhood and terminating before puberty, leaving variable degree of permanent cognitive impairment. The common features of the syndrome are: marked activation or potentiation of epileptiform discharges during non rem slow wave sleep (NREM), leading to a (near)-continuous pattern with variable distribution over the scalp, covering a „significant proportion" of NREM sleep, the cut-off ranging 25–85% (Sanchez et al., 2013). The cognitive impairment depends on the percentage of NREM sleep occupied by the discharges and the duration of the electrical pattern.

One of the main obstacles in the understanding the evolution of ESES is the lack of systematic assessment of the electrical-cognitive correlations in this evolution process. Only a few patiens had been followed longitudinally with concurrent description of the evolution in the key EEG and clinical features (Morikawa et al., 1995; Praline et al., 2006; Liukkonen et al., 2010; Sánchez Fernández, 2012b; Hegyi et al., 2014). Presently we have mainly only cross-sectional data.

In children with syndromes of idiopathic focal epilepsy before the electrical status epilepticus develops, the individual discharges of the sleep EEG pattern are very similar to the interictal ones. The difference lies in the extension of the region they cover, in the increased number and amplitude of the discharges, their length and continuity and furthermore in the increased with-

in- and trans-hemispheral propagation and their synchrony. Sleep potentiated activation of the discharges followed longitudinally have an increasing phase, they reach a plateau and later show a stepwise regression before puberty. The discharge regression is not synchronous with seizure propensity which usually stops earlier, while the electrical discharges continues (Sánchez Fernández et al., 2012b). The augmentation of discharges during the increasing phase, and later during the whole course of the ESES process, shows a fluctuating course. We can observe several variations in the spatial (topical) configuration of the discharges (fig. 3)

The increase in abundance of discharges seems to be parallel with their increase in propagation of the discharges. There is also an increase in the synchrony of the discharges within one and between both hemispheres. The regression shows the same patchy and stepwise character (fig. 4). The evolution of the discharges has always a „leading hemisphere" where changes appear first and during the regression lasts longer (Kobayashi et al., 1994). If propagation to the contralateral hemisphere occurs, it appears first over the homologous territories, and the propagated discharges usually lag behind the leading hemisphere (Kobayashi et al., 1994; Morrell et al., 1995; Tassinari et al., 2000). This feature was designated by several authors (Kobayashi et al., 1994; Tassinari et al., 2000) as „secondary bilateral synchrony (SBS)". However SBS was coined in the classical work of Tükel and Jasper (1952) and later Jasper used it in several works together with Wilder Penfield, for a special way of bilateralisation. According to them an originally unilateral cortical discharge occurs after assumed involvement of the thalamic structures projects via the „thalamo-cortical system" and back toward wide bilateral cortical territories (Penfield and Jasper, 1954).

The required amount of discharges in ESES and the methods of estimating it are different; "a significant proportion" of the non-REM sleep is defined from 25% to 85% (Beaumanoir, 1995; Boel and Casaer, 1989; Bureau, 1995; Dalla Bernardina et al., 1978; Hirsch et al., 1990; Inutsuka et al., 2006; Laurette and Arfel, 1976; Loddenkemper et al., 2009; Patry et al., 1971; Saltik et al., 2005; Tassinari et al., 2000, Van Hirtum-Das et al., 2006; Yan Liu and Wong, 2000; Yasuhara et al., 1991).

The most frequently used methodology to measure the spike frequency is the "spike-wave index" as the percentage 1-second bins in non-REM sleep (Aeby et al., 2005; Tas et al., 2009). The discharge amount is usually
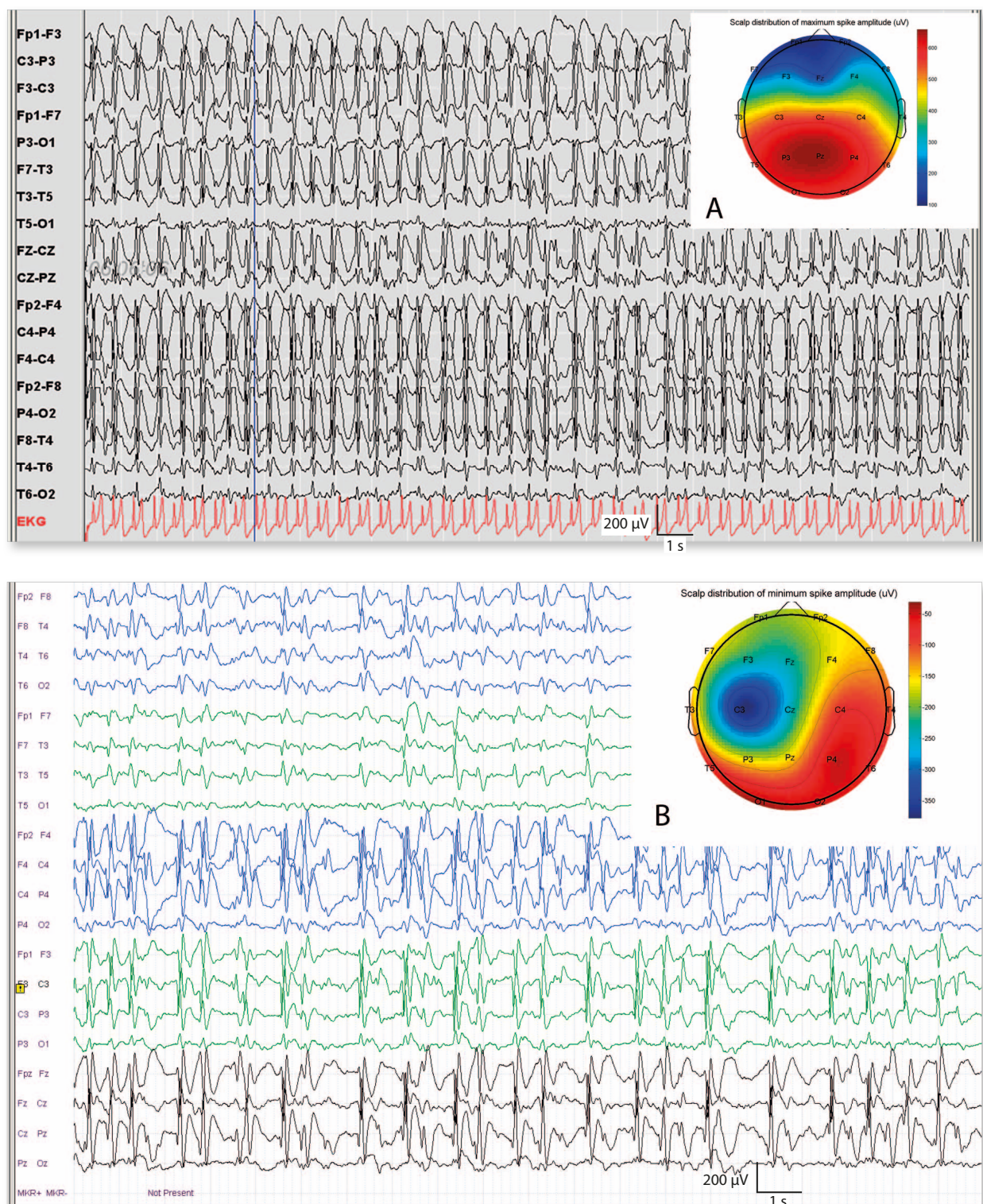
Figure 1. Two types of average discharge maps: **A** – Bilateral synchronous spike-wave discharges with uniform bilateral symmetric dipole map (anterior negative and posterior positive half-fields) at the peak of the spikes, without unihemispheral phase reversal, observed in 3 cases; **B** – unihemispherial regional discharge with perisylvian phase reversal, observed in 29 cases. The axis of the dipole is in the rectangular position to the Sylvian fissure.
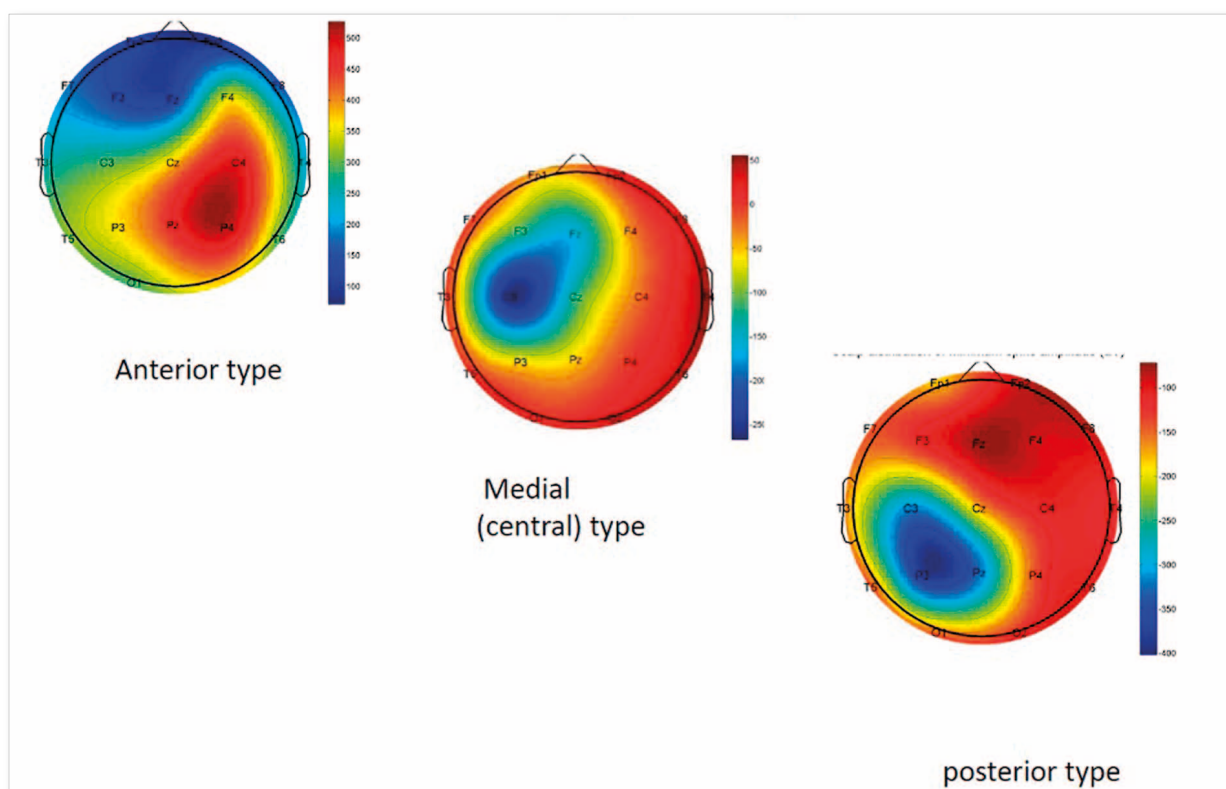
Figure 2. Typical anterior-medial and posterior spike field variants with perisylvian localisation. The axis is perpendicular to the Sylvian fissure. All maps represent averages of several hundreds of individual discharges.

higher in the first sleep cycle and progressively decreases through the night. A modification of this measure is to count spike frequency expressed as the number of spikes per time interval, which seems to be more sensitive (Loddenkemper et al., 2011). Measuring spike frequency during sleep and wakefulness, and comparing the differences between them, provides a measure for sleep potenciation factor (Sánches Fernández, 2012). No consensus exists on the specific portion of sleep used for the calculation of epileptiform activity. Some authors calculate it during the complete nocturnal sleep, whereas others use the total duration of each cycle of slow-wave sleep; some use the first 30 minutes of NREM sleep of the first and last sleep cycle, whilst some use at least one sleep-wake cycle, or the first 5 minutes of nonrapid eye movement sleep.

The original description of ESES requires that at least 85% of the total duration of slow-wave sleep should be occupied by slow spike-waves (Patry et al., 1971; Tassinari et al., 2000). This cutoff value has been largely followed in the majority of publications. However several authors used lower cutoff values (Van Hirtum-Das, 2006; Inutsuka et al., 2006; Kevelam et al., 2012). In patients with clinically evident continuous discharges during sleep, a value of less than 85% is accepted in more than one third of cases, and the values varies 25–85% (Beaumanoir et al., 1995). Difficulties increase if we consider that the specific values of epileptiform activity vary over time (Sánchez Fernández, 2012b).

Functional imaging: fMRI and PET studies
PET and SPECT studies have revealed hypermetabolism and hypoperfusion in the perisylvian region and temporo-parietal cortex associated with ESES without and with LKS (Fueki et al., 1988; Gaggero et al., 1995; Maquet et al., 1995; Maquet et al., 2000) and lesional cases also; how unilateral perisylvian dominance with MRI and fMRI (Hegyi et al., 2009; Siniatchkin et al., (2010). The early FDG-PET study of Maquet et al. (1995) showed that among six patients studied during the active phase of ESES, five had unilateral, focal/regional increase of glucose metabolism in the cortex. The pattern of neuropsychological deterioration was in good agreement with the topography of the distur-
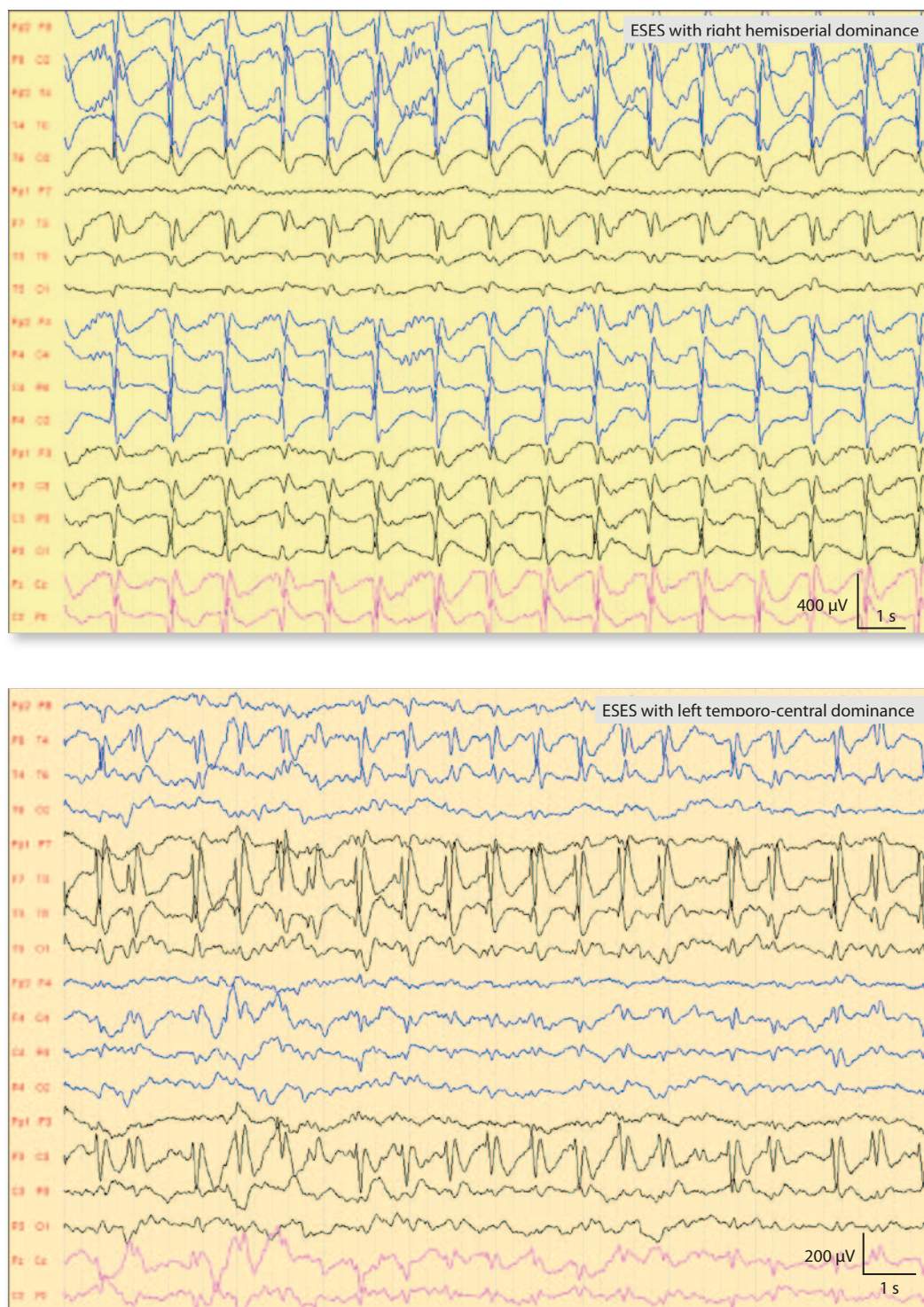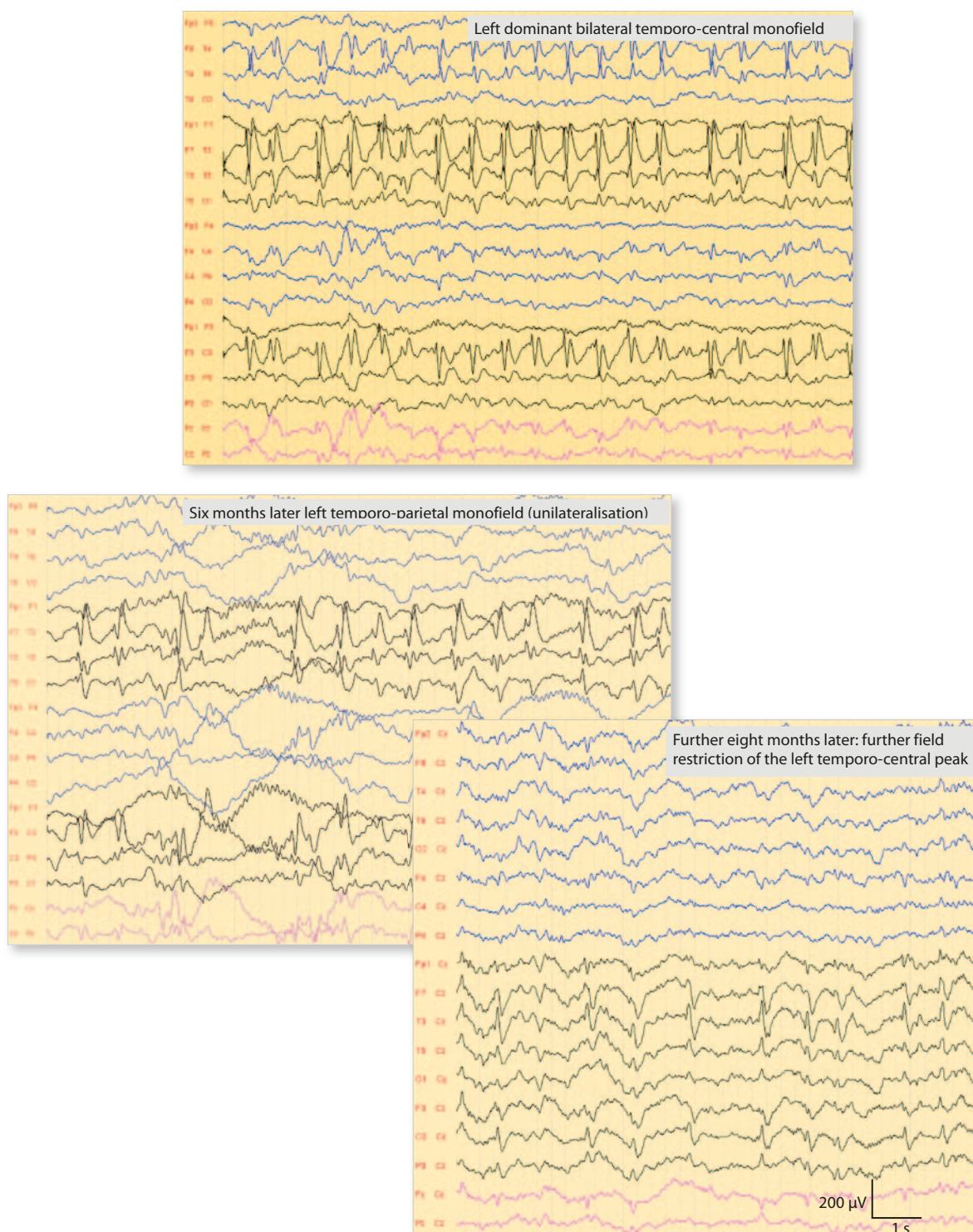
Figure 3. Variations in the spatial distribution of the Electrical Status Epilepticus in Slow Sleep (ESES) pattern.

Figure 4. Regression of ESES pattern in time: tendency of changes from diffuse toward more regional in PM patient.

bances of cortical glucose metabolism. The metabolism of the cortical mantle was higher than in the subcortical structures, especially in the thalamic nuclei, suggesting a cortical dominance. *The thalamic nuclei remained symmetrical despite significant cortical asymmetries, suggesting either that cortico-thalamic neurons do not participate in the generation of spike-and-wave discharges or that they are inhibited by the pathologic mechanisms.*

Siniatchkin et al. (2010) in a series of 12 patients with continuous electrical pattern simultaneously performed fMRI and EEG source analysis. They have found a common neuronal network activated during the discharges. This activation involved bilateral perisylvian regions, the insula, cingulate and prefrontal cortices, and the thalami. In parallel, a deactivation occurred in the precuneus, bilateral parietal cortices, and caudate nuclei. This pattern of common activation and deactivation was independent of the original focus of the discharge and the underlying etiology.

De Tiége et al. (2004, 2013) using FDG-PET and time sensitive magnetic source imaging studies demonstrated in six patiens with LKS and atypicl Rolandic epilepsy during active phase of electrical discharges, significant focal hypermetabolic network over the perisylvian cortex and thalamus, which was common to different syndromes, regardless of underlying etiologies and locations of the primary discharging focus. Beside this finding congruent with other studies, they recognised large frontal fields of hypometabolism not involved in the epileptic network as such and probably related to a mechanism they called as „remote inhibition", Hypofunction in these inhibited areas was assumed to contribute to the neuropsycological deterioration.

Moeller et al. (2013) evaluated EEG-fMRI data in atypical benign partial epilepsy and observed a combination of features seen in Rolandic epilepsy (focal BOLD signal changes in the spike field) and patterns observed in ESES (distant BOLD signal changes in cortical and subcortical, structures).

These findings underline the role of the perisylvian network and shed some light on the thalamic involvement and support the idea of a focal epileptic origin with secondary bilateralisation in ESES. However, the direction of impulse traffic between the cortex and thalamic non-specific system might be initiated firstly by the cortex entraining the thalamic structures secondarily after the discharges became more and more frequent and synchronized over wide fields of the cortex

in one and after propagating trough the corpus callosum to both hemispheres. This mechanism seems to be different from what was assumed to occur in the SBS mechanism of Jasper and Penfield. New studies of the thalamocortical sytem established, that the thalamic nuclei are not in direct connection with other thalamic nuclei; co-operation and entrainment of the thalamic system is allways organized under the primateship of the cortex (Rovó et al., 2012).

Genetic aspects, the role of endophenotypes

After a long time without any major breaktroughs in the genetic research of idiopathic focal childhood epilepsies and the spectrum diseases involving ESES and LKS, recent reports support the involvement of SRPX2 and ELP4 genes in the inheritance of the tendency toward marked activation in sleep; with possible roles in cell motility, migration and adhesion (Rudolf et al., 2009). Lemke et al. (2013) showed alterations of the gene encoding the N-methyl D-aspartate (NMDA) receptor NR2A subunit as a major genetic risk factor for idiopathic focal childhood epilepsies including their atypical variations. New heterozygous mutations in GRIN2A in 27 of 359 affected individuals have been found from two independent cohorts with increasing frequency toward the ESES end of the spectrum.

Increased copy number variations have been reported by Lesca et al. (2012) in Rolandic epilepsy – ESES (including LKS) spectrum in the genomic architecture of several genes (encoding cell adhesion proteins) involved also in autism spectrum disorders.

Endophenotypes are genetically based common modules of phenotypicaly different complex disorders (like schizophrenia, autism, ADHD and certain epilepsies). The CTSs is an example of the endophenotype of Rolandic epilepsy, expressing focal hyperexcitability and local/regional cognitive deficits with the same localisation; this may also occur in autism spectrum disorder and in ADHD patients (fig. 5) Similarly, we can assume that a critical increase in sleep activation of CTS like interictal discharges is also a common endophenotype for the spectrum disorders containing atypical Rolandic Epilepsy with development of ESES (including LKS). It would be interesting to search for genetic markers in the lesional cases as well. Since only a small number of the children affected by early brain damage show increased electrical discharges during sleep, it might be possible that these lesional children also cary a kind of genetic predisposition.
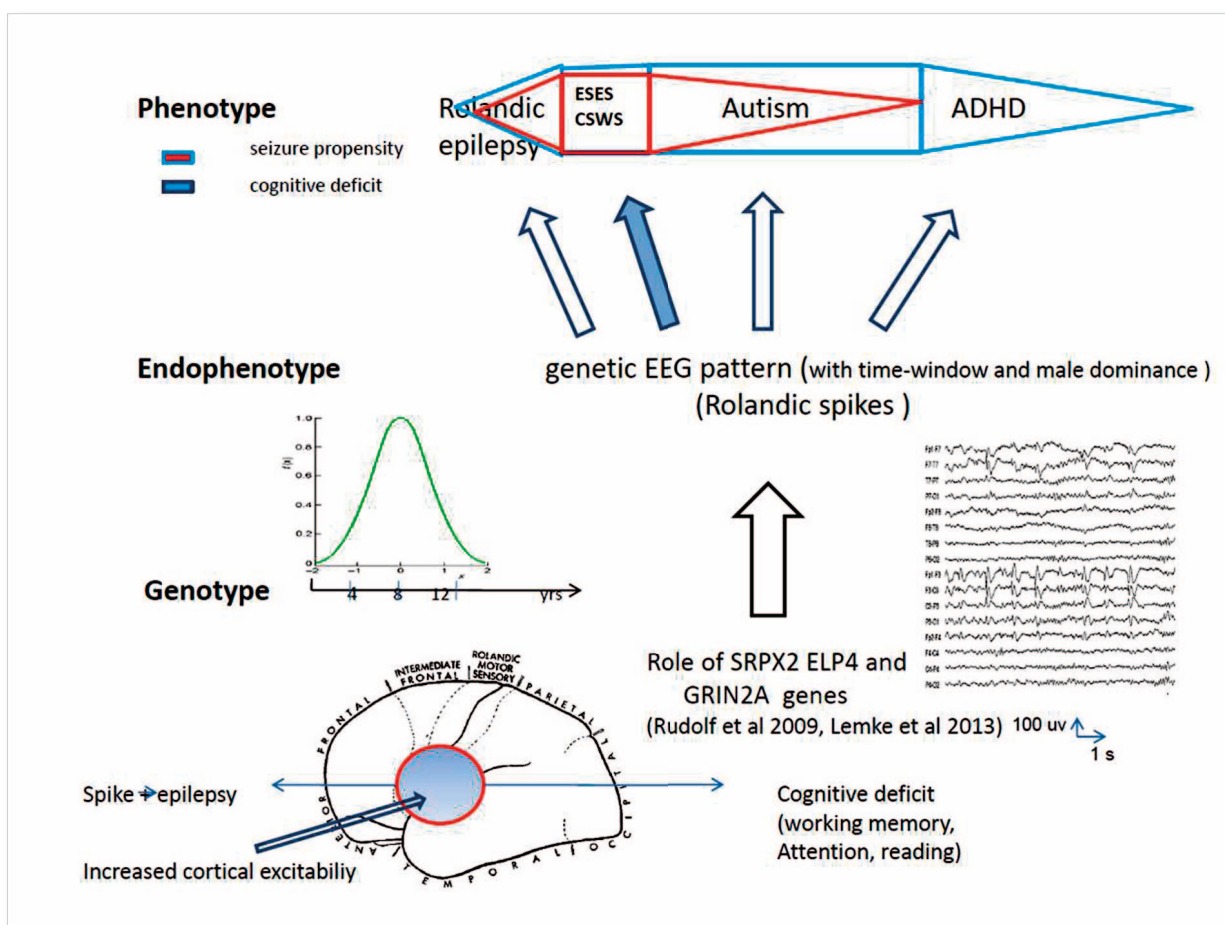
Figure 5. Endophenotype of centro-temporal spikes in slow wave sleep is present in different clinical phenotypes (Rolandic epilepsy, Electrical Status Epilepticus in Slow Sleep (ESES)/ Continous Spike – Wave in Sleep (CSWS), autism, Attention Deficit Hyperactivity Disorder (ADHD). The severity of cognitive impairment is indicated by blue lines and the different level of seizure propensity by red lines. The green curve illustrates the age window of centro-temporal (Rolandic) spikes and the EEG insert the morphology of spikes. References to the genetic background is shown under the white arrow. The blue colored red circle points to the common territory of spikes and cognitive deficit symptoms and increased epileptic exitability.

The basic identity in spike morphology and distribution of the elctrical discharges regardless of the etiology and localisation of the early brain damages (Hegyi et al., 2014) supports this idea. Further genetic research is needed to confirm t this assumption.

Relations with neuropsychological impairment

The degree of cognitive decline depends on the duration of electrical discharges. Usually there are no residual deficits when the period of discharging is shorter than 13 months and it develops as a rule when it persists for more than 18 months (Garcia-Penas, 2010; Kramer et al., 2009). At least 50% of patients remain severely impaired (Loddenkemper et al., 2011; Tassinari et al., 2000; Nickels and Wirelli, 2008). A good correlation exists between the cortical localisation of discharges and the disrupted function (Tassinari et al., 2009).

According to Loddenkemper et al. (2011) overview *Neuropsychologic regression involves a wide spectrum of developmental and cognitive milestones in varying but often severe degrees. Language regresses in the form of a subacute and progressive aphasic disorder, with spontaneous fluctuations over time. Behavior becomes disruptive with the appearance of hyperactivity, impulsivity, and even aggressive behavior. A neuropsychologic examination frequently reveals learning disorders, impairment in temporospatial orientation, memory problems, and reduced attention span. Social developmental delay, emotional lability, and disinhibition interfere with day-today social interactions. The deterioration of*

fine and gross motor skills may also be observed. Dystonia, dyspraxia, ataxia, and unilateral and negative myoclonus further contribute to functional neuropsychologic regression. An overall decrease in intelligence quotient is frequently evident, and a marked discrepancy between verbal and performance quotients may also occur. a tendency toward impairments of intelligence quotient during the acute phase, and a recovery of baseline intelligence during the residual phase.

Several studies attempted to correlate nuropsychological deficits in chidhood regional idiopathic hyperexcitability syndromes. The temporary and mild impairments often observed in the natural history of Rolandic epilepsy is different from the more long-lasting and more specific neuropsychological deficits associated with ESES.

Metz-Lutz and Filippini (2006) investigated a cohort of 44 children that were enrolled in a study from the onset of Rolandic epilepsy, between 4 and 7 years to complete remission at about 12 years. They were divided into a „typical" (with traditional benign course) and to an „atypical" group. They evaluated neuropsychological achievements twice yearly with a neuropsychological test-battery (verbal abilities, visuospatial skills, memory, executive functions; and made a Wechsler intelligence test scale every 18 months, together with a 2 hours EEG in wake time and a full night EEG every year. The atypical group showed significantly lower full-scale IQ and verbal IQ than the typical group from the onset of epilepsy until recovery. Performance IQs were significantly lower only at the onset and during the period of active electrical discharges during sleep The verbal IQs resulted in sifnificantly lower scores with respect of information, problem solving, similarity, and vocabulary. Performance on the short term memory and verbal learning test appeared significantly worse in the atypical group. These findings suggested that attention and behavioral control are particularly sensitive to the discharges during sleep. The differences between the two groups were present from the beginning, suggesting that in atypical forms the cognitive impairment might be due to another pathophysiological mechnism. This could be for example another expression (genetic variation?) of a common maturational disturbance as suggested by Doose et al. (1989).

Mechanisms of sleep enhancement – interrelationship with cognitive impairment

In recent years several studies reported that slow wave sleep inreases learning, and one of the possible roles of slow wave sleep would be to provide a nest for plastic changes (Stickgold et al., 2000; Huber et al., 2004, 2006; Vyazovskiy et al., 2008.)

The most coherent and well-established hypothesis of sleep function is presently the so-called "synaptic homeostasis hypothesis" proposed by Tononi and Cirelli (2003). The higher the amount of potentiation in cortical circuits during wakefulness, the higher is the increase of slow wave activity during subsequent sleep. The homeostatic increase in slow activity is shown to be valid for regional involvement in special localization related tasks, and especially the frontal lobe is sensitive for this homeostatic drive (Huber et al., 2007; Massimini et al., 2007). During developmental periods of early childhood, when plastic changes are the most abundant, synaptic potentiation is associated with high amount of delta activity, while decay of potentiation in the elderly is associated with important decrease of slow waves and these characteristics fit very well into the hypothesis. The hypothesis was supported by studies that applied transcranial magnetic stimulation (TMS) before sleep onset to manipulate slow wave oscillations during sleep. Results showed that TMS-evoked responsiveness, representing synaptic potentiation, prior to sleep enhanced local slow wave activity whereas TMS-evoked decrease in cortical responsiveness reduced slow wave activity locally during subsequent sleep.

The exponential decrease of slow wave activity across the sleep cycles described by Borbély (1982) represents the strong electrophysiological fingerprint of this downscaling process. Downscaling probably provides a certain cleaning and refreshing synaptic capacity for new learning. Tononi and Cirelli (2003) stated that space and energy savings as well as increases in signal-to-noise ratio are functions of the slow wave-related synaptic downscaling process.

It is well known, that NREM sleep activates epileptic interictal discharges (IEDs) (Foldvary-Schaefer et al., 2006) and REM sleep does not. In childhood idiopathic focal epilepsies IEDs show an important activation in the number of discharges and also the scalp territory where they appear. Clemens and Majoros (1987) showed that the activation is the largest during slow wave sleep (stage 3–4) more in the first cycle and during the descending slope of the cycles. From the work of Besagliere and Acherman (2010) we know that these sleep states are characterized by high homeostatic pressure leading to the production of greater than 1 Hz

slow waves with high amplitudes and steep slopes of down states.

Sleep activation (potentiation) in ESES far exceeds sleep activation experienced in idiopathic regional hyperexcitability syndromes. It's peculiar characteristics is state dependency. As activation of the discharges starts with stage 2, earlier than slow oscillations become overwhelming, not only slow waves, but spindles should be important factors (similarly to CTE spikes of Rolandic epilepsy (Nobili et al., 1999; Kelleway 2000; Beelke et al., 2000).

Hyperexcitability described in deconnected cortical structures (Echlin and Battista, 1963; Schaul, 1998) may explain how different early brain damages (among them thalamic injuries) may contribute to precipitating ESES.

We still do not know exactly what dynamic forces promote the progressive activation. Kindling phenomenon was the first to show us that epileptic excitation can be exagerated by a learning process. It seems to be plausible to assume, that the abundant spiking initiates an involvement of the neighbouring territories and via corpus callosum the opposite hemisphere similarly to kindling like learning process (Majkowski, 1989). By this process more and more wider regions participate and in the same time the transitory events turn to be more and more enduring. As it was shown for other learning processes, we can assume that sleep slow oscillation may promote importantly these plastic changes. At the beginning of the evolution the epileptic learning process leading to a progression of epileptic discharges is overwhelming. Later the discharges turn to interfere more and more with the slow wave downscaling process and in that way impair normal plastic sleep function. (Bölsterli et al., 2011; Bigna et al., 2014). Possibly by certain learning experiments during sleep it might be possible to measure the relation of the degree of discharges and the related decrease of learning capacity and memory. In this way we hope to learn more about the important milestones of this harmful process in the future.

Encephalopathy with ESES interferes with sleep EEG functions like spindling and slow wave oscillation and by this way interferes with learning capacities and memory consolidation of the young brain. Although this condition is reversible and disappears before puberty, certain imprinting processes needed for the development of the young brain are not possible to substitude later. Therefore the early recognition and effective intervention would be crucial in this disorder.

What should we do to learn more about the encephalopathy with ESES

We propose that first of all a committee should clarify all the terminological controversies and missleading terms, and establish a better nomenclature, and a followup protocol with standard requirements staging the clinical, EEG and neuropsychological conditions during different steps of evolution. Genetic studies might also be useful in the lesional group as well. A study with these goals could be readily undertaken in institutions having enough number of patients, facilities and manpower;and led by an international leading board. The follow up procedure should involve epileptological, neuroimaging, sleep EEG and neuropsychological data.

CONCLUSIONS AND SYNDROMOLOGICAL EMBEDDING OF ESES

We have seen that ESES is a common final pathway originating from different etiologies, including patients with early brain damage (probably involving thalamic structures), but also in patients without structural pathology as in atypical evolution of idiopathic regional childhood hyperexcitability syndromes (with Rolandic epilepsy as a prototype). We have hints that genetic predisposition might be an important factor in the development of this process. The two big group of patients show the same EEG evolution and encephalopathic cognitive consequences sleep EEG activation, so can be held as a common endophenotype. In the lesional group the possible genetic factors have not been explored as yet.

The type of cognitive functions impairment is in close relationship with the localisation, amount and persistence of epileptic discharges in slow wave sleep. Distribution and electro-morphological analysis of the constituting discharges shows that ESES represents an extreme sleep activation/potentiation of the local/regional interictal discharges, enhancing them in frequency, territorial extension, intra and trans-hemispherial propagation, synchrony and continuity. This process is most probably not identical with the development of bilateral spike-wave pattern in „generalized" epilepsies which involves primarily or secondarily the thalamo-cortical system as it had been explored by Gloor (1979) and Steriade and Amzica (2003). An majority of the investigated cases, the maps of the single discharges constituting sleep activation are identical with focal/regional interictal spikes followed by slow closing wave; we see in childhood regional age depen-

dent hyperexcitability syndromes (prototype the CTS of Rolandic epilepsy).

EEG, neuropsychological and neuroimaging (fMRI and PET) data provide more and more evidence supporting that the slow sleep dependent discharge storms involve preferentially the perysilvian network responsible for the cognitive function impairment. If the process has a posterior dominance, impairment of speech functions are overwhelming (LKS).

Neuroimaging data support that electrical discharges propagate to several other subcortical structures and to thalamic nuclei, but the latter is not involved in that way as we seen in idiopathic generalized epileptic patients.

The mechanism of the extreme potentiation of the discharges during NREM sleep is not fully understood. We can assume that the development is a stepwise procedure in which kindling like learning process take place and the enduring persistence of the discharges interferes with memory consolidation and obstacle plastic function of NREM sleep (Tassinari et al., 2009; Cantalupo et al., 2011; Bölsterli et al., 2011; Bigna et al., 2014).

CONFLICT OD INTEREST DISCLOSURE
The authors have no conflict of interest to declare

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