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ELECTRICAL STATUS EPILEPTICUS DURING SLEEP

CONTINUOUS SPIKES AND WAVES DURING SLEEP

Maria Peltola

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To my Family

ABSTRACT

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Electrical status epilepticus during sleep – Continuous spikes and waves during sleep

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Background: Electrical status epilepticus during sleep (ESES) is an EEG phenomenon of frequent spikes and waves occurring in slow sleep. ESES relates to cognitive deterioration in heterogeneous childhood epilepsies. Validated methods to quantitate ESES are missing. The clinical syndrome, called epileptic encephalopathy with continuous spikes and waves during sleep (CSWS) is pharmacoresistant in half of the patients. Limited data exists on surgical treatment of CSWS.

Aims and methods: The effects of surgical treatment were studied by investigating electroclinical outcomes in 13 operated patients (nine callosotomies, four resections) with pharmacoresistant CSWS and cognitive decline. Secondly, an objective paradigm was searched for assessing ESES by the semiautomatic quantification of spike index (SI) and measuring spike strength from EEG.

Results: Postoperatively, cognitive deterioration was stopped in 12 (92%) patients. Three out of four patients became seizure-free after resective surgery. Callosotomy resulted in greater than 90% reduction of atypical absences in six out of eight patients. The preoperative propagation of ESES from one hemisphere to the other was associated with a good response. Semiautomatic quantification of SI was a robust method when the maximal interspike interval of three seconds was used to determine the "continuous" discharge in ten EEGs. SI of the first hour of sleep appeared representative of the whole night SI. Furthermore, the spikes' root mean square was found to be a stable measure of spike strength when spatially integrated over multiple electrodes during steady NREM sleep.

Conclusions: Patients with pharmacoresistant CSWS, based on structural etiology, may benefit from resective surgery or corpus callosotomy regarding both seizure outcome and cognitive prognosis. The semiautomated SI quantification, with proper user-defined settings and the new spatially integrated measure of spike strength, are robust and promising tools for quantifying ESES.

Keywords: Electrical status epilepticus during sleep, ESES, continuous spikes and waves during sleep, CSWS, epilepsy surgery, spike index, spike strength, RMS

TIIVISTELMÄ

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Unenaikainen sähköinen status epilepticus

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Tausta: Sähköinen status epilepticus unessa (ESES) on aivosähkökäyrä (EEG)-ilmiö, jossa hidasaaltounen aikana esiintyy tiheä piikkihidasaaltopurkaus. ESES:n kvantifioimiseen ei ole olemassa validoituja menetelmiä. ESES on liitetty kognitiivisen tason laskuun ja tällöin puhutaan CSWS (continuous spikes and waves during sleep) -oireyhtymästä. CSWS ei vastaa lääkehoitoon puolella potilaista ja sen epilepsiakirurgisesta hoidosta on olemassa vain vähän tietoa.

Tavoitteet ja menetelmät: Selvitimme retrospektiivisesti epilepsiakirurgian vaikusta elektrokliinisiin löydöksiin 13:lla lääkeresistenttiä CSWS-oireyhtymää sairastavalla lapsella, joilla oli rakenteellinen aivojen poikkeavuus. Toinen tavoite oli löytää objektiivinen puoliautomaattinen tapa mitata purkauksen määrää ja piikkien voimakkuutta EEG:stä.

Tulokset: Kognitiivisen tason jatkuva heikentyminen loppui 12 (92 %) potilaalla leikkauksen jälkeen. Kolme neljästä resektiopotilaasta tuli kohtauksettomaksi. Kallosotomian jälkeen kuudella kahdeksasta potilaasta päivittäiset kohtaukset vähenivät yli 90 %:lla. Purkauksen leviäminen leikkausta edeltävästi vain yhdestä hemisfääristä toiseen liittyi hyvään leikkaushoitovasteeseen. Piikki-indeksi, jossa käytetään jatkuvan purkauksen määritelmänä maksimissaan kolmea sekuntia piikkien välillä, osoittautui luotettavaksi menetelmäksi ESES:n kvantifioimiseen. Useammasta elektrodista integroitu piikkien neliöllinen keskiarvo oli piikin voimakkuuden vakaa mitta häiriintymättömässä NREM-unessa.

Päätelmät: Lääkehoidolle vastaamatonta CSWS:ää sairastavat potilaat, joilla on rakenteellinen aivopoikkeavuus ja yhdensuuntainen purkauksen leviämismalli, näyttävät kohtausten vähenemisen lisäksi hyötyvän epilepsiakirurgiasta kognitiivisesti. Puoliautomaattinen piikki-indeksin kvantifiointi sopivilla käyttäjäasetuksilla ja uusi spatiaalisesti integroitu piikin voimakkuuden mittari ovat stabiileja ja lupaavia ESES:n kvantitatiivisia mittareita.

Avainsanat: Unenaikainen sähköinen status epilepticus, ESES, CSWS, epilepsia-kirurgia, piikki-indeksi, piikin voimakkuus, neliöllinen keskiarvo

TABLE OF CONTENTS

ABSTRACT **4**

TIIVISTELMÄ **5**

ABBREVIATIONS **9**

LIST OF ORIGINAL PUBLICATIONS **10**

1 INTRODUCTION **11**

2 REVIEW OF THE LITERATURE **13**

2.1 EEG Basics 13

2.2 Epileptiform spikes 13

2.3 Spike analysis 14

2.4 Spikes and cognition 16
2.4.1 Transient cognitive impairment 16
2.4.2 Long-term cognitive impairment 17

2.5 Electrical status epilepticus during sleep 19
2.5.1 Definition 19
2.5.2 Pathophysiological mechanisms of ESES 20
2.5.3 EEG diagnostics of ESES 21

2.6 Continuous spikes and waves during sleep 24
2.6.1 Definition 24
2.6.2 Etiology 24
2.6.3 Electroclinical presentation 25
2.6.4 Treatment 27
2.6.5 The role of ESES in cognitive impairment 30

3 AIMS OF THE STUDY **33**

4 MATERIAL AND METHODS **34**

4.1 Subjects 34

4.2 Surgical procedures 35

4.3 Clinical evaluation 36
4.3.1 Neurocognitive outcome in Study I 36
4.3.2 Seizure outcome in Study I 36

4.4 Neurophysiological methods 37
4.4.1 EEG recordings 37
4.4.2 Spike localization and propagation 38
4.4.3 Computer aided spike search 38
4.4.4 Quantification of ESES 40

4.5 Data analyses and statistics 42
4.5.1 Study I 42
4.5.2 Study II 42
4.5.3 Study III 44

4.6 Ethical considerations 45

5 RESULTS 46

5.1 Outcome of callosotomy and resective surgery in pharmacoresistant ESES with symptomatic etiology (Study I) 46
5.1.1 Clinical outcome 46
5.1.2 Pre- and postoperative EEG findings 48
5.1.3 Semiautomatic quantification of SI –the search for the optimal paradigm (Study II) 50
5.1.4 Comparison of methods to measure spike strength in CSWS (Study II) 52

6 DISCUSSION 55

6.1 Epilepsy surgery may be beneficial in selected patients of pharmacoresistant CSWS with symptomatic etiology 55
6.1.1 Clinical outcome 55
6.1.2 EEG outcome 56
6.1.3 Factors associated with the outcome 57

6.2 Semiautomatic quantification of SI is a promising tool 58
6.2.1 General aspects on quantification of SI 58

6.2.2 User defined parameters affecting the semiautomated quantitation SI 58
6.2.3 Temporal variability of SI....59

6.3 Spike strength – a good candidate for a complementary quantitative EEG measure in CSWS 60
6.3.1 New EEG measures needed for ESES 60
6.3.2 Challenges of measuring the spike amplitude....60

6.4 Future considerations 61

7 SUMMARY AND CONCLUSIONS....62

8 ACKNOWLEDGMENTS....64

9 REFERENCES....66

ORIGINAL PUBLICATIONS I-III....79

ABBREVIATIONS

Ampl-Q	Highest quartile of amplitude values
BECTS	Benign epilepsy with centrotemporal spikes
CSWS	Continuous spikes and waves during sleep
DQ	Developmental quotient
EEG	Electroencephalography, electroencephalogram
ESES	Electrical status epilepticus during sleep
FDG-PET	Fluorodeoxyglucose - positron emission tomography
FFT	Fast Fourier transform
GABA	Gamma-aminobutyric acid
GRIN2A	Glutamate receptor, ionotropic, N-metyl D-aspartate 2A
fMRI	Functional magnetic resonance imaging
IQ	Intelligence quotient
ISI	Interspike interval
LKS	Landau-Kleffner syndrome
maxISI	Maximum interspike interval
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
NMDA	N-methyl-D-aspartate glutamate
NREM	Non-rapid eye movement
PCA	Principal component analysis
PDS	Paroxysmal depolarization shift
RMS	Root mean square
RMS-Q	Highest quartile of root mean square
SI	Spike index
TCI	Transient cognitive impairment

LIST OF ORIGINAL PUBLICATIONS

This thesis is based in the following publications, which are referred to in the text by Study I-III. The original communications have been reproduced with permission from the copyright holders.

I Peltola ME, Liukkonen E, Granström ML, Paetau R, Kantola-Sorsa E, Valanne L, Flack B, Blomstedt G, Gaily E. The effect of surgery in encephalopathy with electrical status epilepticus during sleep. *Epilepsia* 2011; 52:602–9.

II Peltola ME, Palmu K, Liukkonen E, Gaily E, Vanhatalo S. Semiautomatic quantification of spiking in patients with continuous spikes and waves in sleep: sensitivity to settings and correspondence to visual assessment. *Clin Neurophysiol* 2012; 123:1284–90.

III Peltola ME, Sairanen V, Gaily E, Vanhatalo S. Measuring spike strength in patients with continuous spikes and waves during sleep: Comparison of methods for prospective use as a clinical index. *Clin Neurophysiol* 2014; 125: 1639-1646

1 INTRODUCTION

Electrical status epilepticus during sleep (ESES) is a phenomenon characterized by spikes and waves, which are activated by sleep and become very frequent or continuous during non-rapid eye movement (NREM). In 1971, Patry, Lyagoubi, and Tassinari first described ESES in six mentally retarded children in whom discharges were "very characteristic of petit mal seizure." Five of the children had epileptic seizures and two were lacking speech. ESES was not related to overt clinical symptoms during sleep, but an association between the ESES and cognitive decline was suspected and was confirmed later (Tassinari et al., 1977).

Nomenclature used for the encephalopathy with ESES has been and currently is extremely variable (Cantalupo et al., 2013; Eeg-Olofsson & Larsson, 2013; Fernández et al., 2013). Most authors agree that it would be necessary to unify the nomenclature and separate the EEG pattern from the clinical syndrome, but consensus on terms is lacking. In this thesis, ESES is used for the EEG phenomenon and the "continuous spikes and waves during sleep" (CSWS) for the clinical syndrome with epilepsy-related neurocognitive impairment. Initially, CSWS included "during slow sleep", but the current tendency to shorten terms has made the spelling "continuous spike-waves during sleep" increasingly popular.

The exact incidence of CSWS is not known. In pediatric neurology clinics, a reported frequency of 0.2% of childhood epilepsies (Kramer et al., 1998) most probably underestimates the incidence of CSWS. Although rare, CSWS is a devastating syndrome, which requires prompt treatment, the efficacy of which is checked with regular intervals, e.g. three or six months (Veggiotti et al., 2012). Pharmacological treatment terminates CSWS in only half of the patients and this results in a permanent cognitive impairment in two-thirds of the patients (Liukkonen et al., 2010). Thus, alternative treatment possibilities need to be considered. Preliminary results on resective epilepsy surgery suggest good seizure and cognitive outcomes in patients with CSWS with unilateral structural lesions (Kallay et al., 2009; Battaglia et al., 2009; Loddenkemper et al., 2009; Roulet-Perez et al., 2010; Fournier-Del Castillo et al., 2014). However, treatment options for patients, unsuitable for resective surgery, have

not been explored. Corpus callosotomy is beneficial against frequent drop attacks and absence seizures and may improve cognition secondarily (Sunaga et al., 2009; Lee et al., 2013), but its effect on CSWS is unknown.

Pathophysiological mechanisms of ESES are unknown and the correlation between the quantity of spikes and waves during slow sleep and clinical symptoms remains elusive. Quantifying methods of spikes and waves are laborious and variable (Hommet et al., 2000; Aeby et al., 2005; Sánchez Fernández, Loddenkemper et al., 2012). Automated or semiautomated spike quantifying methods were introduced, only recently, in diagnostics of ESES/CSWS, and need to be validated and established for clinical use (Larsson et al., 2009; Nonclercq et al., 2009; Chavakula et al., 2013). Studies have focused less on other qualitative and quantitative parameters of ESES, such as the amplitude of spikes and propagation area (Aeby et al., 2005; Larsson, Eeg-Olofsson, et al., 2010). Simple, repeatable, and sensitive measures are highly needed for monitoring the ESES, in the clinic, and for further understanding of the role that of increased spike burdens play in cognitive impairment.

2 REVIEW OF THE LITERATURE

2.1 EEG Basics

Electroencephalogram (EEG) is a measure of brain electrical activity. The main source of cortical EEG signals is synaptic activity of pyramidal neurons that causes an active ion current at a cell membrane, close to the synapse (i.e., a transmembrane current) followed by a distributed passive return current (Buzsáki et al., 2003; Nunez, 2006). The polarity of potential field generated by the proximity of the pyramidal cell, depends on whether the ion current flow is caused by excitatory or inhibitory synapses. The pyramidal cells are organized into vertical columns perpendicular to the cortical surface. When a large number of pyramidal cells become active, synchronously, their potential fields summate in various geometries, depending on the size and location of activated area (Ebersole, 2003; Nunez, 2006). The relationship is complex between electric potentials within the brain and on the scalp. In most modelling works, the extracellular field potentials are conventionally represented by equivalent current dipoles that correspond to the local orientation of activated cortical neurons and the location is equivalent to a center of net extracellular field potentials (Scherg & Ebersole, 1993).

2.2 Epileptiform spikes

A spike is a characteristic EEG pattern in patients with epilepsy, but not a specific marker for epilepsy. By graphical definition, a spike is a transient, which is clearly distinguishable from background activity, and has a duration between 20 ms and less than 70 ms. The sharp wave is a blunter transient with a duration of 70 to 200 ms (Noachtar et al., 1999). Spikes and sharp waves are used interchangeably and are equivalent in epilepsy diagnosis. In this thesis, the term spike is used for both spikes and sharp waves.

Pathophysiological mechanisms underlying spikes are heterogeneous and incompletely understood. In humans, laminar recordings with microelectrodes have shown that at the neuronal level, spikes were initiated by large postsynaptic potentials consistent with

paroxysmal depolarization shift (PDS) found in animal studies (Ulbert et al., 2004; Alvarado-Rojas et al., 2013). However, the relationship between spikes recorded in EEG and activity of individual neurons is heterogeneous and much more complex than simple PDS (de Curtis & Avanzini, 2000). Non-synaptic mechanisms and synaptic connections between cells may intervene to build up fast and effective synchronization within the neuronal network and generate sources that are large enough to be recorded in EEG. Simultaneous intracranial and scalp EEG recordings, along with mathematical simulation studies, suggest that synchronous activation of neurons, over a relatively large cortical area (6-30 cm^2), is essential that a spike can be recorded at the scalp (Cooper et al., 1965; Kobayashi et al., 2005; Tao et al., 2005; Cosandier-Rimélé et al., 2008). The spike amplitude reflects the size of activated cortical source area and degree of neuronal synchronization. The spatiotemporal relationship between intracortical spike sources and scalp EEG is unclear. In the brain, different locations of epileptic cortical sources may lead to similar voltage fields in the scalp (Scherg & Ebersole, 1993; Cosandier-Rimélé et al., 2008). In contrast, changes within a small area of a cortical source may explain the majority of variation in spatiotemporal properties of spikes, which are recorded in the scalp.

2.3 Spike analysis

The evaluation of spike properties; e.g., polarity, amplitude, location, propagation, and frequency is one of the basic goals in EEG clinical reviews. Digital EEG recording has enabled remontaging and processing of data with different algorithms. Spherical spline interpolation of scalp potentials enables the computation of topographical voltage maps over the whole head surface for the graphical visualization of potential distribution. Also, estimates of current source densities and virtual reference-free montages can be computed (Hjorth, 1975, 1991; Perrin et al., 1987; Pascual-Marqui et al., 1988; Nunez & Pilgreen, 1991). This has improved the localization of EEG phenomena (Rosenzweig et al., 2014). Another type of recomputed montages is source montages, which are based on linear inverse modeling and multiple source analysis (Scherg & Ebersole, 1994; Scherg & Berg, 1996). Source montages are similar to spatial filters because they increase the sensitivity of EEG for focal activity from different brain areas with various orientations (Figure 1). Furthermore, the averaging of spikes can be used to improve the signal-to-noise ratio for a more precise localization of the spike

onset area (Ebersole, 2000; Bast et al., 2004). All these methods extend the traditional review of EEG and can be implicated in EEG clinical interpretation.

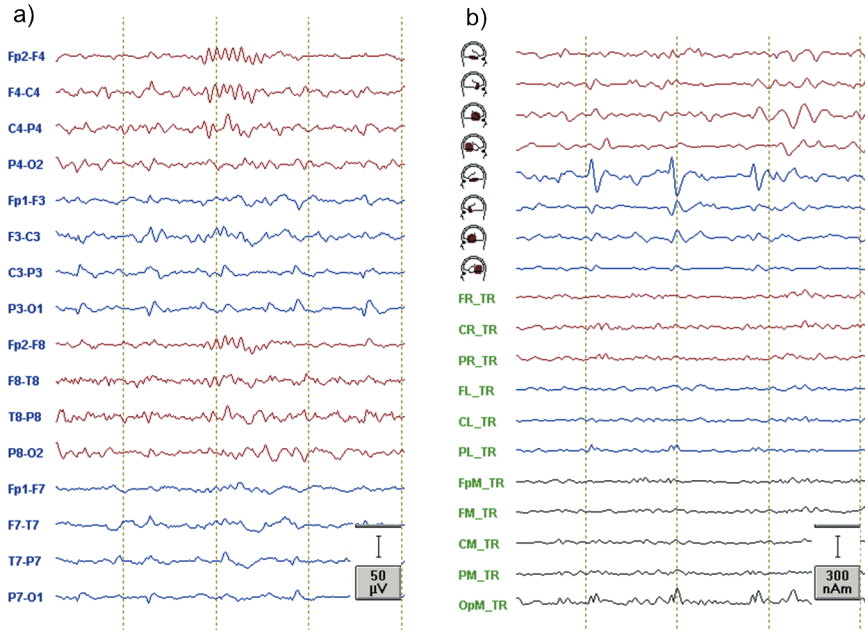

Figure 1. A bipolar montage (a) shows small amplitude spikes in the left temporal-parietal area that are emphasized and better localized by the spatial filter of temporal source montage (TR) and 1-sec intervals are between vertical lines (b). TA=temporal anterior, TP=temporal posterior, F=frontal, C=central, P=parietal, Fp=fronto-polar, Op= occipito-polar, L=left hemisphere, R=right hemisphere, M=midline.

The visual detection of spikes from the EEG recording of several hours is a time consuming task and requires skilled personnel. The manual marking of all spikes for further quantitative analysis is a challenging task in the clinical environment. Therefore, several automated algorithms for faster spike detection exist (Wilson & Emerson, 2002; Halford, 2009). The oldest and most common methods are based on one-channel recognition of morphological spike attributes, such as duration, slope, and peak amplitude (Gotman & Gloor, 1976; Frost 1979). Also, spike characteristics can be extracted for temporal and spatiotemporal matching by complex mathematical algorithms, such as frequency domain analysis, wavelet analysis, neural networks or principal component analysis (PCA) (Gabor & Seyal, 1992; Scherg et al., 1999, 2012; Wilson et al., 1999; Goelz et al., 2000).

The average sensitivity of algorithms, compared to human spike detection, range from 57 to 95% and selectivity from 25 to 87% (Wilson & Emerson, 2002). Artefacts, high intra- and interpatient variation of spike morphology, and EEG background patterns challenge automated detection. Some semiautomated methods have attempted to solve this problem by using a spike sample chosen by an skilled user and "teaching" the algorithm to be sensitive for a particular EEG (Chavakula et al., 2013). Another approach towards an adaptive algorithm is to exploit the spatial characteristics of spikes and base the detection on source analysis. A hierarchical multichannel clustering, which detects and classifies spikes corresponding to different foci, is a promising tool for a clinical use (Van Hese et al., 2008; Nonclercq et al., 2012; Scherg et al., 2012). However, all clustering methods are not intended for the exact quantitation of spikes, but for the identification and profiling of different types of spikes.

2.4 Spikes and cognition

2.4.1 Transient cognitive impairment

Interictal spikes, during the awake state, are potentially associated with a transient cognitive impairment (TCI) without the overt clinical symptoms of seizures (Mirsky & Vanburen, 1965; Aarts et al., 1984; Binnie et al., 1987; Kasteleijn-Nolst Trenite et al., 1988). TCI occurs in half of the patients with focal or generalized interictal discharges (Binnie et al., 1987; Siebelink et al., 1988). An association, based on functional neuroanatomy, exists between the laterality and location of spikes and the type of impairment. Right-sided spikes are more often related to TCI in spatial tasks and left-sided spikes to verbal tasks (Aarts et al., 1984). In a small, but a detailed study of two patients with frequent posterior spikes, Shewmon and Erwin (1989) found that the increased reaction time, during a visual task, coincided with the duration of a spike-wave complex or a slow wave in the absence of clear spike. During intracranial recordings in patients with suspected temporal lobe epilepsy, the effect of hippocampal spikes on memory specific processes were evaluated. The spikes in a healthier hippocampus; i.e., contralateral to epileptogenic area, or bilateral spikes, impaired the memory retrieval (Kleen et al., 2013). However, the reaction time was not affected and the total quantity of spikes, in a given test session, was not related to overall performance.

2.4.2 Long-term cognitive impairment

In epileptic encephalopathy, the epileptic activity itself may contribute to progressive cerebral dysfunction beyond what might be expected from the inherent underlying pathology, alone (Holmes & Lenck-Santini 2006; Berg et al., 2010; Filippini, Arzimanoglou, et al., 2013; Lado et al., 2013). Epileptic encephalopathy may occur in any type of epilepsy, but it is especially associated with certain epilepsy syndromes of childhood, including early myoclonic encephalopathy, Ohtahara syndrome, West syndrome, Dravet syndrome, Lennox-Gastaut syndrome, Landau-Kleffner syndrome (LKS), and CSWS. Functional imaging and genetic studies have recently offered new insights into the pathophysiology of epileptic encephalopathies, but our understanding still remains incomplete. Cognitive deficits may arise from several mechanisms that differ from one type of epileptic encephalopathy to another (Avanzini et al., 2013; Lado et al., 2013). Progressive encephalopathy may arise from diffuse cortical interneuronal dysfunction caused by genetic lesions, abnormal subcortical regulation of cortex, or from the disruption of cortical networks and brain plasticity due to epileptic activity. The latter is thought to be the most important mechanism of cognitive decline in CSWS and LKS. LKS can be recognized as a subtype of CSWS manifested by an acquired aphasia and ESES in a child without a structural brain abnormality (Landau & Kleffner, 1957; Rossi et al., 1999; Van Bogaert, 2013).

The long-term consequences of interictal spikes are less clear and remain under debate in epilepsies with mild cognitive and behavioral problems and less abundant (and not necessarily sleep activated) spike-wave activity compared to epileptic encephalopathies. Interictal spikes, occurring either during awake or sleep, may contribute to cognitive and behavioral difficulties in some patients (Binnie, 2003; Aldenkamp et al., 2004; Hughes, 2010; Ebus et al., 2012; Verrotti et al., 2014). However, only one double-blinded, placebo-controlled, crossover study on the treatment effect of spikes on cognition in patients with epilepsy exists. The study was conducted using 48 children with well-controlled or mild epilepsy and behavioral problems (Pressler et al., 2005, 2006). They showed that a significant reduction in interictal discharges obtained by add-on lamotrigine was accompanied with improved behavior, but there was no improvement in general intelligence.

Benign epilepsy with centrotemporal spikes (BECTS) is the most common benign focal epilepsy of childhood (Larsson & Eeg-Olofsson, 2006) and is characterized by centrotemporal spikes, which are enhanced by drowsiness and sleep. Seizures are well-

controlled, nocturnal focal seizures with orofacial sensory-motor symptoms (Aicardi, 1979; Guerrini & Pellacani, 2012). Patients have normal intelligence, but they have an increased risk for verbal and non-verbal memory deficits associated with executive, language, and behavioral problems. (Metz-Lutz et al., 1999; Hommet et al., 2001; Lindgren et al., 2004; Verrotti et al., 2014). Several retrospective studies (Nicolai et al., 2007; Piccinelli et al., 2008; Filippini, Boni, et al., 2013) and one small prospective study (Baglietto et al., 2001) suggest that an increased burden of nocturnal interictal discharges has an impact on mild cognitive impairments in BECTS, however, these results remain unconfirmed (Northcott et al., 2005; Pinton et al., 2006; Schneebaum-Sender et al., 2012).

A higher incidence of language, attention, and short- and long-term verbal memory impairments occur in siblings of the patients with BECTS. This questions the causal role of frequent nocturnal spikes in specific cognitive impairments (Verrotti et al., 2013). Similar debate has been going on the role of interictal spikes on cognition in patients with regressive autism spectrum disorders and frequent nocturnal spikes without epilepsy (Chez et al., 2006; Deonna & Roulet-Perez, 2010). However, there is no evidence for treatment of spikes and a continuing debate remains on whether "to treat or not to treat" (Binnie, 2003; Hughes, 2010). In a recent, double-blind, placebo-controlled crossover study, levetiracetam reduced significantly sleep-related spike activity during NREM sleep (from 57.1% to 34.1% in NREM sleep time) on a group level, but this had no clear effects on behavior, vigilance, or learning and memory (Bjørnæs et al., 2013). Nevertheless, at baseline, lower scores in verbal learning tasks were correlated positively with the quantity of spikes. The group consisted of 21 patients who were referred to the National Centre for Epilepsy in Norway mainly because of concerns about attention, behavior, school performance, autism or ADHD. At the baseline of study, the mean IQ of the patients was 90.8 (range: 69-114).

Typical BECTS may evolve into an atypical form with varying severity of new clinical symptoms; e.g., diurnal-only seizures, atonic-astatic seizures, atypical absences, and negative myoclonias (Aicardi & Chevrie, 1982; Wirrell et al., 1995; Tovia et al., 2011). Early age (< 4 years) at the onset of epilepsy may predispose individuals to atypical evolution (Fejerman, 2009). Patients have more frequently learning and behavioral disabilities compared to typical BECTS (45.5% *vs.* 7.8%, respectively) (Verrotti et al., 2002). In this patient group, behavioral and cognitive impairments associate with increased EEG abnormalities; e.g., the emergence of multifocal spikes, bilateral

propagation of spikes, increased spike frequency during sleep and awake states, temporary ESES, or focal slowing (Massa et al., 2001; Saltik et al., 2005; Metz-Lutz & Filippini, 2006; Filippini, Boni, et al., 2013).

Rarely, progression into the epileptic encephalopathy, either to CSWS or LKS occurs. CSWS may also evolve from heterogeneous focal childhood epilepsies with structural brain abnormalities. Currently, we have no definite electroclinical markers to predict the encephalopathy. In a retrospective study of 196 patients from pediatric neurology outpatient clinics in Israel, 5% of patients with typical BECTS developed CSWS (Tovia et al., 2011) and 2% LKS. It has been proposed that LKS, CSWS, and atypical BECTS belong to a single continuum of disorders with varying severity and profile (Galanopoulou et al., 2000; Rudolf et al., 2009; Deonna & Roulet-Perez, 2010). Indeed, recent genetic studies demonstrate that BECTS, LKS, and CSWS may have a common genetic origin sustained by *de novo* or inherited mutations in the *GRIN2A* gene (Lesca et al., 2012, 2013; Lemke et al., 2013; Carvill et al., 2014) (Refer to Chapter 2.6.2.). The CSWS incidence in focal childhood epilepsies with structural etiology is unknown.

2.5 Electrical status epilepticus during sleep

2.5.1 Definition

ESES has multiple definitions. According to the original criteria, spikes and waves must comprise at least 85% of NREM sleep to be considered as ESES (Patry et al., 1971; Tassinari et al., 2000) (Figure 2). However, thresholds set from 25% to greater than 85 percent are applied because of the observation that the clinical symptoms of CSWS can be related to less frequent spikes and waves in some patients (Van Hirtum-Das et al., 2006; Kramer et al., 2009; Liukkonen et al., 2010). As a consequence, the abandonment of the fixed thresholds in the diagnosis of CSWS (Van Bogaert et al., 2006; Tassinari et al., 2009; Sánchez Fernández, Loddenkemper, et al., 2012) has been proposed. ESES may be defined as frequent spikes and waves activated markedly during sleep compared to wakefulness.

The original definition of ESES states that ESES has to be recorded at least on three occasions over a period of at least one month (Patry et al., 1971). This criterion was not included in the guidelines for EEG in CSWS, which were proposed after the

symposium “Fifty Years from Laundau-Kleffner syndrome” in 2009 (Scheltens-de Boer, 2009).

ESES can be focal, multifocal, unilateral, asymmetric bilateral, or diffuse/bilateral (labeled occasionally as generalized) (Morikawa et al., 1985; Eriksson et al., 2003; Scheltens-de Boer, 2009; Margari et al., 2012; Fortini et al., 2013).

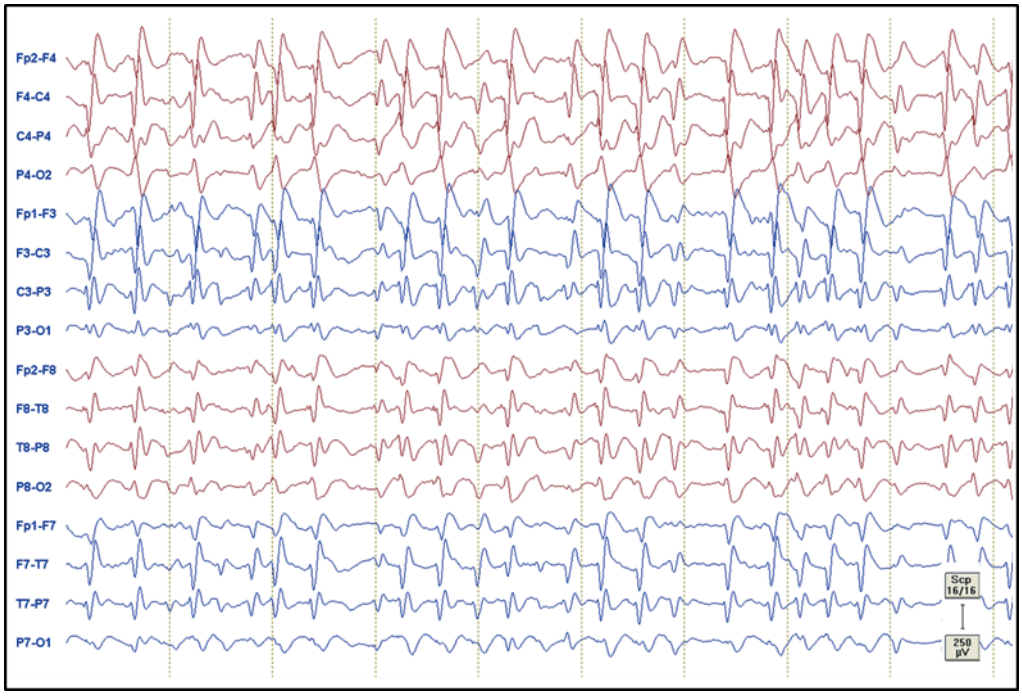

Figure 2. Electrical status epileptic during sleep presenting as bilateral spikes and waves**.** Patient is an eight years old girl with a right hemisphere polymicrogyria.

2.5.2 Pathophysiological mechanisms of ESES

Mechanisms causing ESES are poorly understood. Kobayashi et al. (1994) showed that in traditional EEG montages apparently generalized spikes and waves in ESES were generated by secondary bilateral synchronization (Kobayashi et al., 1994). Later source analysis studies have strongly supported the focal cortical onset of ESES (Smith, 2004; Larsson, Eeg-Olofsson, et al., 2010; Siniatchkin et al., 2010). Recent metabolic and EEG/MEG studies have provided new insights to propagation patterns of ESES (See the Chapter 2.6.5.). The latest findings revealing possible genetic mechanism in ESES-related epileptic encephalopathies manifesting as speech and language dysfunction

(Refer to Chapter 2.6.2) will offer new possibilities to study ESES in animal models and may help us to better understand the pathophysiology of ESES.

Thalamus may play an additional role in synchronizing of ESES. Earlier animal studies have shown that thalamus potentiates cortically generated spikes and waves (Steriade et al., 1988). In humans, thalamic injury and early developmental lesions may predispose to ESES (Guzzetta et al., 2005; Kelemen et al., 2006; Sánchez Fernández et al., 2012; Kersbergen et al., 2013). However, mechanisms of thalamic potentiation remain elusive. Current hypothesis is that intracortical lesion would disrupt the activation of thalamic GABA(A) and GABA(B) receptors and transform the physiological oscillation in corticothalamic network to the slow paroxysmal oscillation and spikes and waves discharges (Blumenfeld & McCormick, 2000; Beenhakker & Huguenard, 2010).

2.5.3 EEG diagnostics of ESES

Spike index and spike frequency

In the clinical EEG review, diagnosis of ESES is based often on a rough visual estimate of the quantity of spikes and waves and with a dichotomous assessment ESES/no-ESES. Spike index (SI) is a more elaborate measure, which indicates the percentage of NREM sleep covered by the spikes and waves (Guey et al., 1969). The main problem in use of SI is a lack of validated methods to quantitate. In addition to the SI, the spike frequency; i.e., the absolute number of spikes and waves per time unit, has been proposed for the assessment of ESES (Fernandez et al., 2012).

Two different strategies are used to calculate the SI. In the first one, the SI is calculated by first counting bins (typically one second or minute) with spikes (Hommet et al., 2000; Aeby et al., 2005; Fernandez et al., 2012). In the second one, the interspike interval; i.e., spike-free period of certain length is used to determine the continuous spike-wave discharge (Larsson et al., 2009) and the SI is the proportion of time with continuous discharge.

EEG samples with different durations are used to quantify the SI: the whole night sleep or NREM sleep (Tassinari et al., 2000; Inutsuka et al., 2006; Larsson et al., 2009; Liukkonen et al., 2010), at least one sleep cycle (Massa et al., 2000; Saltik et al., 2005), the initial 30 minutes of NREM sleep (Aeby et al., 2005), and five minutes sample

during NREM sleep (Fernandez et al., 2012). Earlier studies of Nobili et al. (1999) showed that spike density peaks during the first ten minutes of each sleep cycle. The spike number per minute in consecutive NREM periods did not differ significantly (Nobili et al., 1999, 2001). However, the minimum duration of sleep needed for a repeatable calculation of SI is not known.

Visual quantification of spikes is time-consuming and practically impossible to do from a whole night recording in clinical practice. Several automated and semiautomated spike detection algorithms exist, but due to methodological limitations and time needed to learn to use them, they have not yet been implemented widely in clinical use (Halford, 2009). Few computerized methods are used for spike recognition in a context of enhanced nocturnal spiking or ESES (Larsson et al., 2009; Nonclercq et al., 2009, 2012; Martín Miguel et al., 2011; Chavakula et al., 2013). Spikes are detected by either template matching or cluster analysis. In the semiautomated method, the user defines the correlation threshold for template matching and thus, regulates the sensitivity and specificity of spike recognition (Scherg et al., 1999; Larsson et al., 2009). One automated method using the template matching showed a sensitivity of 43 to 78% and a selectivity of 64 to 96% in different EEG sets when compared to visual spike detections (Chavakula et al., 2013). A recently published algorithm, based on cluster analysis, had only 0.3% higher sensitivity and 0.4% lower selectivity compared to visual spike detections (Nonclercq et al., 2012).

In automated methods, SI quantification is based on counting the SI by bins of one second. The semiautomated approach of Larsson et al. (2009) is different because it implements the concept of continuous discharge that will be discussed in more detail in the Methods section, Chapter 4.4.4.2.

None of the current methods of calculating the SI has been widely implemented in clinical work for several reasons. First, most of the analysis tools are not commercially available. Second, there is no consensus on calculating method of SI. Third, there is no agreement whether a whole night recording is needed or a shorter duration of sleep EEG would be sufficient to obtain the SI comparable to the whole night SI.

The automated spike detection by an overnight EEG is rapid, but the quality of sleep and EEG recording is easier to control during shorter periods of sleep. Economic aspects must not be overlooked, either. Recently, Larsson, Evsiukova, et al. (2010) showed a good correlation between the SI calculated from a morning nap after sleep deprivation and that from the ambulatory whole night EEG.

Spike amplitude and propagation

Spike amplitude is rarely considered in ESES, although few results suggest that reduction of spike amplitude may be related to favorable treatment response (Veggiotti et al., 2001; Aeby et al., 2005; Larsson, Eeg-Olofsson, et al., 2010). Larsson, Eeg-Olofsson et al. (2010) showed that response to levetiracetam treatment was demonstrated by total suppression of spikes or by decreased SI and/or diminished maximal source amplitude or propagation of spikes in patients with increased nocturnal focal epileptiform activity.

Physiologically, the spike amplitude is considered to express the strength of the epileptic source by combining both the spatial extent and the density of synchronously acting neuronal networks (Cosandier-Rimélé et al., 2008). It is intuitively used in a clinical EEG analysis, but before implementation in further clinical studies of CSWS, the methodological workup of spike amplitude needs to be established in terms of temporal stability and repeatability of the measures.

Definitions for the distribution of ESES (focal, multifocal, unilateral, asymmetric bilateral or diffuse/symmetric bilateral) are rarely mentioned. In clinical EEG reviews, the distribution of spikes are in general expressed by the area, where electrodes record the amplitude within 50% of the maximal spike amplitude (Foldvary et al., 2001).

Analyzing spike propagation in ESES is challenging because of fast propagation. Kobayashi et al. (1994) estimated interhemispheric time differences during spike-wave activity by coherence and phase analysis in EEG and showed that ESES had unilateral onset. Recently, source imaging methods based on a distributed linear inverse solution have been applied to quantify the propagation or explore the propagation pathways (Siniatchkin et al., 2010; Larsson, Eeg-Olofsson, et al., 2010). The quantification of a propagation area may be useful in assessing the treatment response in ESES (Larsson, Eeg-Olofsson, et al., 2010).

Visual semiquantitative and qualitative classification of ESES combining several EEG features offers a more multifaceted view of ESES than previous approaches focusing on SI (Aeby et al., 2005; Saltik et al., 2005). However, for clinical use, validated and simple semiautomated/automated quantitative measures should be preferred.

2.6 Continuous spikes and waves during sleep

2.6.1 Definition

CSWS is an age-related epileptic encephalopathy, where an acquired cognitive impairment other than aphasia is associated with the ESES (De Negri, 1997; Veggiotti et al., 1999; Van Bogaert et al., 2006). ESES alone should not define the clinical syndrome (Veggiotti et al., 1999).

2.6.2 Etiology

With rare exceptions, CSWS is a disorder of the developing brain where ESES remits spontaneously during puberty (Mariotti et al., 2000; Bensalem-Owen & Fakhoury, 2008; Lucey & Duntley, 2008). CSWS may occur in previously normal children with normal brain imaging or be related to developmental impairment and structural brain abnormalities.

In larger series, structural defects occur in 45%-59% of the patients (Van Hirtum-Das et al., 2006; Buzatu et al., 2009; Liukkonen et al., 2010; Caraballo et al., 2013). The most common underlying causes for these are thalamic and vascular lesions (Guzzetta et al., 2005; Kelemen et al., 2006), hydrocephalus (Veggiotti et al., 1999) and malformations of cortical development (Guerrini et al., 1998; Teixeira et al., 2007). The patients with normal MRI and unknown etiology of ESES usually present with an evolution from Landau-Kleffner syndrome, atypical BECTS, or more rarely from atypical forms of Panayiotopoulos syndrome or late onset childhood occipital epilepsy (Gastaut type) (Rossi et al., 1999; Galanopoulou et al., 2000; Liukkonen et al., 2010; Caraballo et al., 2013).

An earlier study has reported the coexistence of BECTS and CSWS in two families (De Tiège et al., 2006). Recent genetic studies suggest that new heterozygous mutations in *GRIN2A* (encoding the N-methyl-D-aspartate glutamate (NMDA) receptor a2 subunit) are a possible cause for ESES-related epileptic encephalopathies manifesting as speech and language dysfunction (Lemke et al., 2013; Lesca et al., 2013; Carvill et al., 2014). The *GRIN2A* mutations of altering activity of NMDA receptors have a potential role in disrupting synaptic transmission, plasticity, and facilitating epileptogenic processes (Kalia et al., 2008).

2.6.3 Electroclinical presentation

Latent phase preceding ESES

Before the development of ESES, 80-90% of patients have seizures. Mean age at the epilepsy onset is 3.5-5 years (range: 0.2-12 years) (Scholtes et al., 2005; Liukkonen et al., 2010; Raha et al., 2012). Patients with a structural brain lesion have seizures at a younger age compared to patients with an unknown etiology of CSWS (Bureau, 1995; Tassinari et al., 2000; Liukkonen et al., 2010). First, seizures are typically nocturnal and half of the patients have focal motor seizures that evolve into hemiclonic status epilepticus in 6 to 20% of patients. Other frequent seizure types are atypical absence seizures, dyscognitive seizures with automatisms, and generalized clonic or tonic clonic seizures. Eight percent of the patients have initially one seizure type and seizures are usually infrequent. Cognitive development, prior to ESES, is normal in 67% of patients (Kramer et al., 2009).

Patients with structural brain lesions may show background slowing in EEG. More than half of the patients present with focal or multifocal spikes during the awake stage that propagates bilaterally in 15% of patients (Caraballo et al., 2013). Sleep increases the frequency of spikes and waves markedly.

Active phase during ESES

The beginning of severe symptoms is approximately time-related to the onset of ESES with a mean delay of one to two years from seizure onset (Scholtes et al., 2005; Liukkonen et al., 2010). However, because of the limited number of available EEG recordings, the exact time relation between the onset of ESES and clinical symptoms is usually unknown. Several studies have reported the onset of ESES between 0.4 and 13.2 years with a peak at four to five years (Scholtes et al., 2005; Liukkonen et al., 2010; Seegmuller et al., 2012; Fortini et al., 2013). The duration of ESES varies from two months to 10.1 years.

In most patients, seizures become more frequent and severe, and new additional seizure types emerge at the onset of ESES (Scholtes et al., 2005; Liukkonen et al., 2010; Caraballo et al., 2013). Typical new seizure types are negative myoclonus and atypical absence. Motor impairments are frequent, including dyspraxia, ataxia, worsening of pre-existing hemiparesis and oromotor dysfunction (Tassinari et al., 2000). Tonic seizures are regarded as an exclusion criterion if they are a prevalent seizure type. Seventy percent of the patients have multiple daily seizures and more than half of the

patients present with several seizure types (Bureau, 1995; Liukkonen et al., 2010).

In a multicenter long-term study of 117 patients with CSWS, 66% of patients manifested with attention deficit hyperactivity disorder, 34% language deterioration, 38% aggressiveness, 15% memory deficit, 20% impaired temporospatial orientation, and 25% non-verbal communication deficit (Caraballo et al., 2013). Global cognitive deterioration was observed in 64% of patients. These results agree with studies of smaller patient groups (Margari et al., 2012; Raha et al., 2012; Seegmuller et al., 2012).

In our earlier series, the most prominent presenting symptom of CSWS was motor in 20 out of 32 (63%) patients. Seventeen (53%) patients manifested with behavioral symptoms, 16 (50%) with language impairment and 10 (31%) with cognitive problems (Liukkonen et al., 2010). The worsening of seizures or emergence of new seizure types was seen in 13 (41%) patients.

Bilateral/diffuse ESES is the originally described and most common type of spike-wave discharge in CSWS (Tassinari et al. 2000). However, lateralized or unilateral and focal forms have also been related to acquired cognitive deficits (Morikawa et al., 1985; Eriksson et al., 2003; Margari et al., 2012; Fortini et al., 2013). Unilateral ESES is strongly associated with structural etiology (Fortini et al., 2013). Independent focal spikes may emerge among the bilaterally propagated spikes (De Tiège et al., 2013). During the active phase of ESES, SI may vary from 25% to 100% (Beaumanoir, 1995; Van Hirtum-Das et al., 2006; Kramer et al., 2009; Tovia et al., 2011; Caraballo et al., 2013). Spikes and waves usually repeat at the frequency of one to three Hz, but faster spike-wave bursts and polyspikes may occur particularly in patients with structural etiology (Beaumanoir, 1995; Caraballo et al., 2013). Occasionally, rhythmic discharges superpose on spike-and-waves. Sleep spindles, vertex waves and K-complexes are rarely visible, but the cyclic organization of NREM-REM sleep is preserved and spike frequency usually decreases markedly during REM sleep (Nobili et al., 2001; Bölsterli et al., 2011).

Long-term outcome of CSWS

Long-term prognosis of seizures is typically favorable in patients with unknown etiology. Seizure freedom is less common when CSWS is related to structural etiology (Caraballo et al., 2013). If ESES is not terminated by the treatment, spontaneous resolution is seen by the puberty (Morikawa et al., 1985; Tassinari et al., 1985).

Long-term studies with standardized neuropsychological measurements are scarce. We showed that only 10 out of 32 (30%) children with CSWS regained the cognitive level they had before ESES (Liukkonen et al. 2010). In 9 out of these 10 patients, ESES was terminated by the treatment. Another study followed patients up to adulthood and found that behavioral symptoms affecting social life were resolved in 90% of patients (Seegmüller et al. 2012). Forty percent of patients had recovered borderline-normal intelligence. However, the cognitive recovery was markedly slower compared to the behavioral improvement. A younger age and lower IQ, at the time of CSWS diagnosis, and lack of treatment response correlate with unfavorable cognitive outcome (Scholtes et al. 2005, Liukkonen et al. 2010).

2.6.4 Treatment

Pharmacological treatment

Treatment goals are to prevent the cognitive deterioration and to control the seizures. No antiepileptic drug is found superior to others and relapses occur frequently.

High-dose valproate (VPA) is used as a first-line therapy in CSWS, but the results are disappointing (Inutsuka et al., 2006; Kramer et al., 2009; Liukkonen et al., 2010). As a second line treatment, a combination of VPA and ethosuximide was efficient in 18 to 43% of patients (Kramer et al., 2009; Liukkonen et al., 2010). After treatment failure with VPA and ethosuximide, clobazam was beneficial in nine of 30 (30%) patients (Kramer et al., 2009). High-dose diazepam abolished ESES, temporarily, in 50 to 100% of patients, in a small studies of five to 15 patients without long-term response (De Negri et al., 1995; Inutsuka et al., 2006; Kramer et al., 2009; Sánchez Fernández, Hadjiloizou, et al., 2012). Recently, add-on sulthiame was shown to abolish seizures and ESES in ten out of 28 patients with CSWS with structural etiology and in 21 of 25 patients with CSWS without structural abnormalities (Fejerman et al., 2012). Among the new generation antiepileptic drugs, levetiracetam is used alone or as an add-on treatment with favorable clinical or both clinical and EEG response in half of the patients of the small series, most of them with structural etiology (Aeby et al., 2005; Wang et al., 2008; Atkins & Nikanorova, 2011). Carbamazepine, phenobarbital, lamotrigine and phenytoin are generally avoided because of exacerbation of ESES found in some cases (Caraballo et al., 2013).

If antiepileptic drugs have proven ineffective, immunotherapy may be used. Corticosteroid treatment is useful in some patients with well-preserved cognitive

functions, particularly in patients with LKS (Sinclair & Snyder, 2005; Buzatu et al., 2009; Kramer et al., 2009; Liukkonen et al., 2010). Immunoglobulins or ketogenic diet has been tried in small number of patients with modest results (Kramer et al., 2009).

Electrical stimulation

Transcranial direct current stimulation was applied in one patient with CSWS without benefit (Varga et al., 2011). There are no reports on the effect of vagal nerve stimulation in CSWS.

Epilepsy surgery

Hemispherectomy, lobar, or multilobar resection is effective for selected children and adolescents with a congenital or early-acquired brain lesion, despite abundant generalized or bilateral epileptiform discharges on EEG (Wyllie et al., 2007).

Twelve functional hemispherectomies or hemispherotomies and two resections have been applied in medically refractory patients with symptomatic CSWS and unilateral brain lesions (Table 1). Resolution of ESES, good seizure, and cognitive outcome was observed in all (Kallay et al., 2009; Battaglia et al., 2009; Loddenkemper et al., 2009; Roulet-Perez et al., 2010; Fournier-Del Castillo et al., 2014). Eight out of 11 patients with comparable pre- and postoperative IQ/DQ measurements obtained a cognitive catch-up with increment of IQ or DQ with greater than or equal to 10 points. The minimum duration of postoperative follow-up was 18 months. A recent case report found the resolution of ESES, cognitive improvement, and seizure freedom after temporal lobectomy in a child with unilateral thalamic infarcts and CSWS (Moseley et al., 2012), but the postoperative follow-up was only three months. A limitation of most studies is a missing preoperative IQ trajectory that would verify the cognitive decline caused by the ESES.

There are no previous reports on callosotomy in CSWS. The patients with frequent severe drop attacks, generalized tonic seizures, atypical absence seizures and bilateral, or generalized discharges may obtain a marked reduction in seizure frequency after corpus callosotomy (Gaily et al., 1999; Sunaga et al., 2009). Callosotomy decreases usually bilateral synchronous discharges with less effect on the total quantity of spikes and waves (Gates et al., 1984; Fiol et al., 1993; Oguni et al., 1994; Matsuo et al., 2003). Cognitive and behavioral outcomes after callosotomy remain unclear. Behavioral improvement was seen in patients with favorable seizure outcome and decreased bilateral discharges in the postoperative EEG after callosotomy (Yonekawa et al., 2011).

Table 1. Previous studies on epilepsy surgery in CSWS.

Study	Type of surgery (number of patients)	Age at surgery	Dur. of ESES before surgery	Cognitive outcome ≥18 mo. postop	Preop. seizure types (No. of pats. when >1)	Seizure outcome ≥ 18 mo. postop.	Preopera-tive MRI lesion	Preopera-tive EEG	Postopera-tive EEG
Kallay et al. 2009	Hemispher-otomy (1)	5.3 y	1.3 y	Catch-up*	Focal sz AA drops	Sz-free	Unilateral	Bilateral ESES	Cessation of ESES
Battaglia et al. 2009	Functional hemispher-ectomy (2)	6.8 y 11 y**	2.3 y 8.5 y	Catch-up (2 pats.)	Focal sz (2) AA (2)	Sz-free	Unilateral	Bilateral ESES	Cessation of ESES
Lodden-kemper et al. 2009	Hemispher-ectomy (6) ---------- TPO dis-connection (1) ---------- Frontal lobectomy (1)	3.6 – 16.2 y (med. 8.2 y) --------- 4.8 y --------- 14.9 y	Un-known	Catch-up (2 pats.) Halted decline (4 pats.)	Atonic GTCS (4) Hypom. (2) Dialeptic (4) Focal clonic Myoclonic ---------- Bilateral asymmetric tonic ---------- Automotor	Sz-free (4 pats.) Engel II (2 pats.) ---------- Sz-free (1 pat.) ---------- Sz-free (1 pat.)	Unilateral (4 pats.) Bilateral (2 pats.) ---------- Unilateral (1 pat.) ---------- Unilateral (1 pat.)	Bilateral ESES	Cessation of ESES
Roulet-Perez et al. 2010	Hemispher-otomy (1)	5.3 y	Un-known	Catch-up	Drop, focal sz AA (2)	Sz-free	Unilateral	Bilateral ESES	Cessation of ESES
Fournier-Del Castillo et al. 2014	Hemispher-ectomy (2)	6.9 y 6.8 y	1.3 y 1.3 y	Catch-up (1 pat.) Halted decline (1pat.)	Asymmetric tonic (1) Unilateral tonic (1)	Sz-free	Predomi-nantly left (1 pat.) Unilateral (1 pat.)	Bilateral ESES	Cessation of ESES

Pat., patient; med., median; m., motor; sz, seizure; AA, atypical absence sz; GTCS, generalized tonic clonic sz; hypom., hypomotor; PNV, perinatal vascular; PoNV, postnatal vascular, TPO, temporoparieto-occipital; *increment of IQ/DQ by ≥ 10 points, ** previous parietotemporal resection of porencephalic area at 7 y without cessation of ESES. Drop**;** i.e., sudden tonic or atonic seizure with loss of balance.

2.6.5 The role of ESES in cognitive impairment

Underlying pathophysiological mechanisms of cognitive impairment in ESES remain elusive. Several factors have made it difficult to understand the relationship between the ESES and clinical symptoms: the small size of patient groups, heterogeneous etiologies, a spectrum of clinical symptoms, and a lack of quantitative measures of ESES. However, there is a good consensus on time-related relationship between the beginning of ESES and cognitive deterioration. Further evidence for a causal relationship is that significant cognitive improvement is possible after successful treatment of ESES (Battaglia et al., 2009; Loddenkemper et al., 2009; Liukkonen et al., 2010; Seegmuller et al., 2012). In addition, the spike focus and profile of cognitive dysfunction have shown functional association in some studies. Frontal spikes relate to dysexecutive symptoms, temporal to language problems and posterior to visual agnosia (Roulet Perez et al., 1993; Rousselle & Revol, 1995; Veggiotti et al., 2001; Eriksson et al., 2003). In line, patients with generalized ESES are more likely to have global or more severe deterioration compared to those with more focal ESES (Van Hirtum-Das et al., 2006). To the contrary, other studies have not found the association between profile of neuropsychological deficit and spike focus (Hommet et al., 2000; De Tiège et al., 2004; Caraballo et al., 2013) or distribution of ESES (Raha et al., 2012; Sánchez Fernández et al., 2013).

The duration of ESES is correlated with the outcome (Scholtes et al., 2005; Seegmuller et al., 2012), but that was not confirmed in our earlier study suggesting that several factors determine the prognosis in CSWS (Liukkonen et al., 2010). The intraindividual quantity of spiking fluctuates considerably during the course of CSWS (Tassinari et al., 2009; Fernández, Loddenkemper et al., 2012). Contrary to the findings in patients with atypical BECTS, the SI was not correlated to the severity of cognitive decline or seizures in CSWS in retrospective longitudinal studies (Hommet et al., 2000; Fernández, Loddenkemper et al., 2012; Caraballo et al., 2013). However, the results may be biased by sparse and asynchronous EEG and IQ measurements and variable methods to quantify SI.

Several hypotheses of pathophysiological mechanisms of cognitive impairment related to ESES have been proposed. Currently, a very popular theory is that ESES interferes with the normal neural processes during slow sleep resulting in abnormal synaptic homeostasis and impaired memory consolidation (Tassinari & Rubboli, 2006; Bölsterli et al., 2011; Bölsterli Heinzle et al., 2014). In slow sleep, membrane potentials of

cortical neurons alternate between a depolarized upstate and a hyperpolarized downstate (Steriade et al., 1998). Highly synchronized activity of several neurons is seen as slow wave activity during NREM sleep in the EEG. According the synaptic homeostasis hypothesis (Tononi & Cirelli, 2006), synaptic plastic processes occur during wakefulness and result in increase in synaptic strength in brain circuits. Synaptic potentiation is linked to the homeostatic regulation of slow wave activity that is associated with synaptic downscaling. During sleep, the synaptic strength is downscaled or returned to a baseline that is needed for efficient neural function, and for learning and memory. In rat and human EEG, the slope of slow waves was correlated with the degree of synchrony of firing cortical neurons, and synaptic strength and density that normally decreases overnight (Riedner et al., 2007; Vyazovskiy et al., 2007). Bölsterli et al. (2011, 2014) measured the slow wave properties in patients with CSWS and found that the overnight decrease in the slope of slow waves corresponding to downscaling was absent focally or multifocally at the sites with a maximal amplitude of spikes and waves. However, selecting "true" slow waves among frequent spikes and waves may be challenging. Theory of impaired memory consolidation is further supported by a pilot study of four children with MRI negative focal epilepsy with unknown etiology and ESES (SI 35-97%) (Urbain et al., 2011). Authors observed that recall performance was decreased overnight in all patients with epilepsy compared to healthy controls. In one patient with CSWS, a total resolution of ESES was achieved by hydrocortisone treatment resulting in the normalization of overnight memory performance.

FDG-PET studies have found different metabolic patterns during awake in patients with CSWS and concordance between the localization of spikes and hypermetabolic areas (Maquet et al., 1995; De Tiège et al., 2004; De Tiège et al., 2008; DeTiège et al., 2013). This is contrary to typical interictal hypometabolic pattern attributed to neuronal loss in focal epilepsy and may be related to sustained high neuronal energy consumption in ESES. A study combining FDG-PET and MEG showed that areas with hypermetabolic changes at the awake state were concordant with the spike onset (De Tiège et al., 2013). However, no specific metabolic pattern was representative of spike propagation suggesting that the mechanisms by which ESES impairs neuronal function are not solely related to the spike propagation. Most of the hypometabolic areas were outside the spike onset or propagation area (De Tiège et al., 2008, 2013). Authors interpreted this as remote inhibition of neurons in distant brain areas documented earlier in animal models (Witte & Bruehl, 1999).

Similarly, in simultaneous EEG-fMRI studies increased brain perfusion was consistent with the spike onset, but not always with the propagation area (Siniatchkin et al., 2010). A common pattern of cortical activation for all patients with CSWS was bilateral perisylvian-insular, independently of the etiology of CSWS. The areas corresponding to the default mode network showed deactivation. These findings further suggest dysfunction of networks, which are involved in behavioral and cognitive processes in patients with CSWS.

3 AIMS OF THE STUDY

This study's objective was to assess benefits of epilepsy surgery in CSWS and to improve EEG diagnostics of ESES.

The specific aims of this thesis were:

I To explore the effect of epilepsy surgery on electroclinical outcomes in CSWS (Study I).

II To search for an objective paradigm for quantification of ESES by defining appropriate parameter settings for semiautomatic quantification of spike index (SI) (Study II).

III To compare methods of measuring the spike strength for the prospective use of clinical index in CSWS (Study III).

4 MATERIAL AND METHODS

4.1 Subjects

This thesis was a part of research project coordinated by the Epilepsy Unit of the Helsinki University Central Hospital The prospective parent study investigated the long-term prognosis of medically treated 32 CSWS patients (Liukkonen et al., 2010).

The first study of this thesis (Study I) evaluated the clinical and neurophysiological effect of epilepsy surgery on CSWS and was a direct continuum to the parent study, although retrospective in nature. Thirteen of 52 children, who were diagnosed with CSWS during 1991 to 2005 at our Epilepsy Unit, had epilepsy surgery and were included in the study. The indications for surgical treatment were completely drug-resistant bilateral ESES, on-going cognitive regression, or cognitive stagnation with or without frequent seizures, and EEG or MEG findings suggesting that discharges were spreading between hemispheres. Patient characteristics are shown in Table 2. During the year preceding surgery, the most common seizure type was an atypical absence status, observed recurrently in ten patients. Severe behavioral disorders with aggressiveness, irritability, and hyperactivity were present in all except one child.

The second study (Study II) was retrospective and included nine patients (ten EEG recordings) with more recent EEG recordings between the years 2006 and 2010. Overnight EEGs were pulled blindly from the database of the video-EEG unit of the Epilepsy Unit of the Helsinki University Central Hospital among the 168 EEG recordings that were made because of previously diagnosed CSWS (spikes and waves occupying at least 85% of NREM sleep on overnight video-EEG and developmental regression) or the suspicion of CSWS in a routine EEG with a short nap sleep. Five of ten overnight EEGs were diagnostic and five were recorded to monitor treatment response. Characteristics of the selected patients are shown in Table 2.

The third study (Study III) included ten patients (ten EEGs) from the Study I in whom a digital pre- and postoperative EEG was available (dataset 1) and all nine patients (ten EEGs) from the Study II (dataset 2).

Table 2. Clinical characteristic of the patients in Study I and II.

	Study I	**Study II**
Target group	Surgically treated patients with CSWS	Patients with suspected CSWS
N	13 (24 EEGs)	9 (10 EEGs)
Gender, N	Female 9, male 4	Female 3, male 6
Etiology, N	Perinatal vascular, 6 Postnatal vascular, 1 Bilateral MCD, 4 Unilateral MCD, 2	Perinatal vascular, 4 Unknown 3* Genetic, 2
MRI, N	Structural lesion, 13 Unilateral lesion, 7	Structural lesion, 4 Unilateral lesion, 1 Normal, 5
Age at the seizure onset, years	Range: 0.2 – 4.7 Median: 2.3	Range: 2.3 – 5.6 Median: 3.8
Age at 1st EEG with ESES, years	Range: 1.3 – 6.6 Median: 3.9	Range: 2.8 – 9.2 Median: 6.0
Age at EEG studied here (preoperative in Study I), years	Range: 2.5 – 7.0 Median 4.3	Range: 3.1 – 12.9 Median 6.9
Seizure type at EEG studied here (preoperative in Study I), N	Atypical absences, 10 (Tonic-)clonic seizures, 2 Dyscognitive seizures with automatisms, 3 Atonic seizures, 3 No documented seizures, 2	Atypical absences, 4 (Tonic-)clonic seizures, 5 Dyscognitive seizures with automatisms, 6

N, number of patients; CMV, cytomegalovirus; MCD, malformation of cortical development.
* , based on a T2 MRI and a special epilepsy protocol with a phase array coil.

4.2 Surgical procedures

Focal resection was selected for patients with focal or lobar lesions consistent with focal abnormalities in neuroimaging and ictal onset zone or onset zone of ESES when patients had no documented seizures. Patients with unihemispheric lesions with hemiparesis on the contralateral side and ictal onset zone (or onset zone of ESES when patients had no documented seizures) on the side of lesion were eligible for

hemispherotomy. Callosotomy was considered for patients not suitable for focal resection or hemispherotomy. Total callosotomy was selected for patients who showed evidence of bilateral or generalized ictal onsets, were severely intellectually impaired and had no speech, or who had a large hemispheric destructive lesion but only mild hemiplegia. Anterior callosotomy was chosen for patients with preserved speech with unknown lateralization.

4.3 Clinical evaluation

4.3.1 Neurocognitive outcome in Study I

Patients in Study I underwent neurological and neuropsychological evaluation at 0.3 to 7.2 months (median 1.8) before surgery. Intelligence was measured with the age-appropriate Wecshler scale or with Bayley-R in severely impaired patients (Wechsler, 1984, 1995; Bayley, 1993). Postoperative evaluation was done at six months and at two years after surgery. A significant postoperative change in cognition was defined as a change of ten or more IQ points compared to the preoperative level. Cessation of cognitive deterioration was considered as a favourable outcome.

4.3.2 Seizure outcome in Study I

Seizure and clinical outcome was assessed at six months and at two years after surgery. Seizure outcome was classified by Engel class I-IV (Engel, 1987) (Table 3) and was defined favorable if an Engel class I-II was obtained at two years after surgery.

Table 3. Engel Epilepsy Surgery Outcome Scale (Engel, 1987).

Class I	Free of disabling seizures
Class II	Rare disabling seizures ("almost seizure-free")
Class III	Worthwhile improvement
Class IV	No worthwhile improvement

4.4 Neurophysiological methods

There are several unknown factors is spike quantification that determined the methods and workflow used in this thesis (Figure 3).

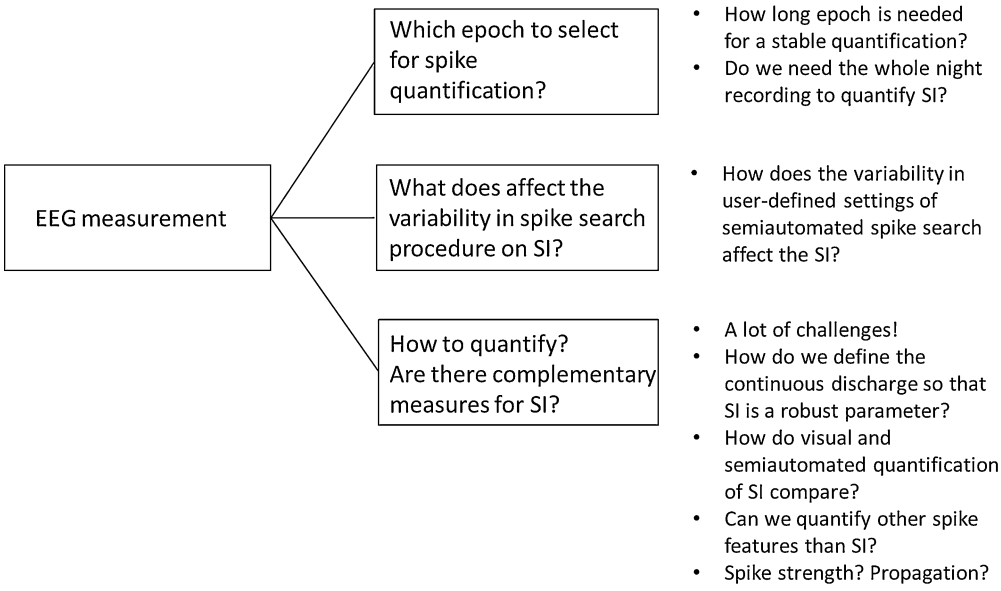

Figure 3. Basis of the neurophysiological workflow and methods.

4.4.1 EEG recordings

The video-EEG recordings were made as a part of clinical epilepsy evaluation by using 26 to 35 scalp electrodes placed according to the International 10-20 system with additional electrodes of a 10-10 system. Data was recorded at 200 Hz. The duration of each recording was 13 to 24 hours. In total, approximately 520 hours of EEG data were included.

In Study I, preoperative video-EEG was recorded 0 to 4.0 months (median 0.9) before surgery from all patients. Eleven patients underwent a postoperative video-EEG recording 0.3-5.6 months (median 1.9) months after surgery. In two patients, there was no clinical need for the postoperative EEG.

4.4.2 Spike localization and propagation

First, EEGs were interpreted by reading the EEG signal with traditional bipolar and referential montages: spikes were identified, the number of spike foci was analyzed in awake, and sleep EEG.

Second, spikes were evaluated with Laplacian montage, virtual montages, and brain region source montages. These were all analyzed by BESA Research Software® MEGIS GmbH, Gräfelfing, Germany (Scherg et al., 2002). The BESA source montages are derived from multiple dipole or regional source models. Virtual average montage estimates the voltage at defined locations of a sphere using spherical spline interpolation from the original EEG signal. Reference free voltage maps, sensitive to dipole orientation, were used particularly for propagation studies of spikes. The onset area and the propagation of ESES were assessed by measuring time delays of spike onsets between brain regions and by evaluating dipole topography over time on voltage maps. Analysis was based on the first emerging spikes after a pause of at least one second in the continuous discharge during the first hour of NREM sleep. Depending on the number of foci and the complexity of propagation, ten or more single discharge onsets were analyzed.

The extent of spike propagation was estimated by dividing the scalp area into six regions: right and left frontal, centrotemporal, and parieto-occipital. The magnitude of propagation was given a value from one to six, according to the number of areas with spike propagation.

4.4.3 Computer aided spike search

In Study II, the standard spike search was based on a spatio-temporal search function of BESA Research® (Scherg et al., 2002; Bast et al., 2004) applicable to one channel or a selected number of channels. In one channel search function, the spike template from one channel was correlated with the ongoing EEG of the same channel. In the multichannel search, BESA Research® computed PCA over the chosen template in selected channels and used the five largest (or the number of selected channels if less than five) PCA components and corresponding waveforms to calculate correlation with ongoing EEG. The strictness of spike detection criteria depended on the user-defined threshold of the Pearson correlation coefficient (%).

Before the spike search, EEG was filtered with a combination of 1.6 Hz (6 dB/oct.; forward) low cutoff and 35 Hz (24 dB/oct.; zerophase) high cutoff filters. One representative prototype spike was chosen for a template. Spikes were searched from the whole EEG recording in two steps by using an initial template from one channel and a final template from all channels. In one channel search, the search was performed with a correlation threshold of 75%, using the whole length of the prototype spike. An average spike waveform (n~100) was created from the first hour of sleep. This average spike served as a final template for the further search of spikes that were done over all channels from the whole night recording with a correlation threshold of 50%. The quality of spike search was assessed by visual inspection of ten segments of ten seconds of EEG and spike search was continued with new prototype spikes/templates until 80% of spikes were detected. Detections were exported from BESA® in event files (ASCII) to be processed further with PS script (v.2, courtesy of Dr. Larsson, (Larsson et al., 2009) running in Matlab®.

In addition to standard spike search described above, additional spike searches were performed in a subset of data consisting of four EEGs to examine the robustness of semiautomated SI calculation (see Chapter 4.5.2, Figure 6). First, we studied how the variation in spike search strategy affected the SI by altering the correlation thresholds, but still aiming to tag at least 80% of the spikes. This mimics user and EEG dependent variation of search strategies. For example, large spikes with mild spatiotemporal variation are easy to search compared to small, instable spikes. Experienced EEG analyzers may choose template spikes more optimally compared to inexperienced ones. Second, we examined how the goodness of spike search affected the SI by making spike searches that included less than 80% or close to 100% of the spikes.

In Study III, the spike search was conducted with one spike template from the virtual average montage over all channels with a correlation threshold of 60%. All spikes were then averaged using a window of ±150 ms around the peak of the largest spike for further analysis. Baseline was defined from the first 50 ms of the averaging window. Averaged spikes were exported to Excel® or Matlab® by event files (ASCII) for further analysis. Because the search was conducted in one step over all channels, the average consisted of spikes with a fairly similar propagation and spatiotemporal evolution over time that increased the stability of spike average.

4.4.4 Quantification of ESES

4.4.4.1 Visual scoring

In Study I, the SI was approximated by counting the overnight proportion of the discharge free episodes of minimum duration of ten seconds. The criterion for ESES was a SI of greater than 85%.

In Study II, two experienced clinical neurophysiologists (M.P. and S.V.) tagged manually all ISIs of approximately three seconds or more from the first hour of sleep independently in all ten EEGs, using similar filter settings, montages, as well as time (15 s/window) and amplitude (400 nAm to 2.5 μAm) scaling. Tags (i.e., time points) were imported to Excel® and akin to the semiautomated SI analysis, SI was then calculated as the proportion of continuous discharge (for details, see the next paragraph). The mean SI of the two readers was taken as the gold standard.

4.4.4.2 Semiautomated quantification

The SI quantifies the proportion of time with continuous discharges in the given epoch. The definition of "continuous" is critical and based on the maximal interspike interval (maxISI), which is allowed between consecutive spikes (Figure 4). In this study, we examined the effect of ISI on SI, in detail, and calculated the SI with the maxISIs from 1 to 7 s (maxISI1-maxISI7, respectively). The output of SI in 2 min epochs was imported from PS/Matlab® to Excel® for further calculations. The SI was calculated from the first hour of sleep and whole-night sleep. Following the original papers (Larsson et al., 2009; Larsson, Evsiukova, et al., 2010), the whole-night SI was calculated by including only SIs that were above the mean SI level, which was considered to mainly represent NREM periods of sleep. The SI of the first hour of sleep was calculated without such epoch selections after it was visually verified to correspond to NREM sleep. Finally, the semiautomated SI obtained by the spike search with moderate correlation percentages and max ISI3 of the first hour of sleep was compared with the gold standard.

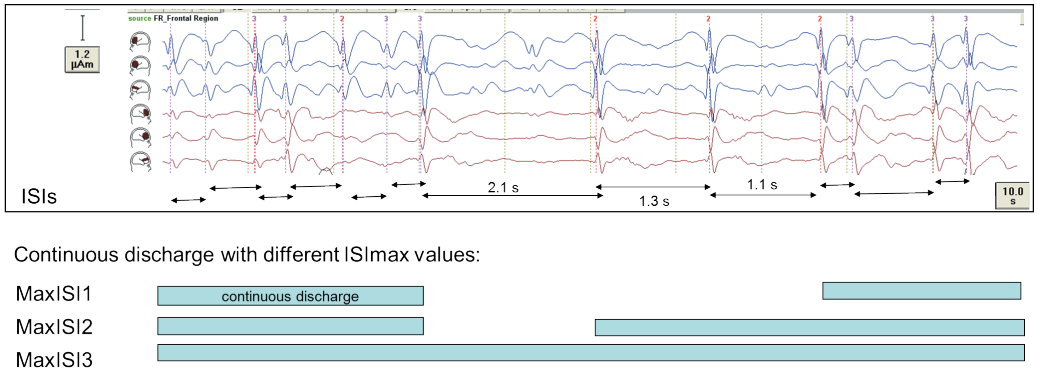

Figure 4. Effect of maxISI on the quantification of SI. The user-defined parameter maxISI of the quantification algorithm determines how long pauses between successive spikes are allowed in what is considered a continuous discharge. In the lower part of this picture, the light blue bars depict the time, which would be considered as "continuous discharge" from the EEG shown above when the maxISI is varied between 1s, 2s, and 3s (Reprinted from Peltola et al. 2011, The effect of surgery in encephalopathy with electrical status epilepticus during sleep, Clinical Neurophysiology, 123; 7, Supplementary e-data, with permission of Elsevier).

4.4.4.3 Measurements of spike strength

In Study I, the spike-wave strength was measured by calculating a mean Fast Fourier Transformation (FFT) of one minute of artefact free EEG from all channels of brain region source montage filtered with 5 Hz high-pass and 15 Hz high low-pass filters. The peak value of spectral source amplitude (nAm) was referred here as source strength. A 50% increment or decrement in source strength was defined as a significant change in postoperative EEG compared to preoperative. The spike propagation was explored from the source montages and spline maps.

In Study III, the spike strength measurement was studied, in detail, in order to find a simple and repeatable method. EEG was filtered with 2Hz forward low-cut filter (6dB/oct) and 40 Hz zero-phase high-cut filter (24dB/oct). Four measures were employed: amplitude and RMS of spike from a single channel, and two measures from the combination of channels that together accounted for the highest quartile of spike strength. The latter measures, Ampl-Q and RMS-Q, were introduced in order to compensate for spatiotemporal instability of spikes.

Single channel measures

Spike amplitude (uV/cm^2) was measured from baseline to peak in the Laplacian montage. Traditional peak amplitude measurements are sensitive to variations in spike morphology and electrode locations. To see if we could improve stability, we calculated RMS (μV/cm^2) over the time period ±150 ms around the highest peak in the Laplacian montage.

Spatially integrated measures

Spatiotemporal variation of spikes causes instability to the measures of amplitude and RMS. In order to strengthen repeatability, cumulative amplitude and RMS were computed over the highest quartile (i.e., from seven out of 27 electrodes), and called Ampl-Q and RMS-Q, respectively. The choice for the highest quartile of electrodes was pragmatic because we were not able to find any inclination point when the cumulative amplitude and RMS were plotted against the number of ranked channels.

4.5 Data analyses and statistics

4.5.1 Study I

Pre- and postoperative EEG parameters, seizure type, frequency, and neuropsychological measures were compared. Associations between pre- and postoperative EEG findings, seizure and cognitive outcome, type of surgery and clinical characteristics were examined. Due to a small group size, descriptive statistics were used. Binomial probability was calculated for the cognitive outcome (unpublished data).

4.5.2 Study II

Natural distribution of ISIs in ESES was analyzed from the overnight EEG. SI was calculated from the first hour of sleep and whole night sleep by varying the length of the time epoch of calculation to study the temporal stability of SI (Figure 5). In addition, the dependency of SI on maximal interspike interval (maxISI) and sensitivity of SI to variations in spike search protocol were studied (Figure 6). Finally, the semiautomatic method was compared with the quantification based on visual scoring by two neurophysiologists.

Statistical analysis was performed with the IBM SPSS® software version 20.0 (IBM Corp., Armonk, NY, USA). Differences between the two groups were evaluated with a Mann-Whitney U test, and considered significant if $p<0.05$ (two-tailed). The pair-wise correlation between scorings was analyzed with the Spearman rank correlation test.

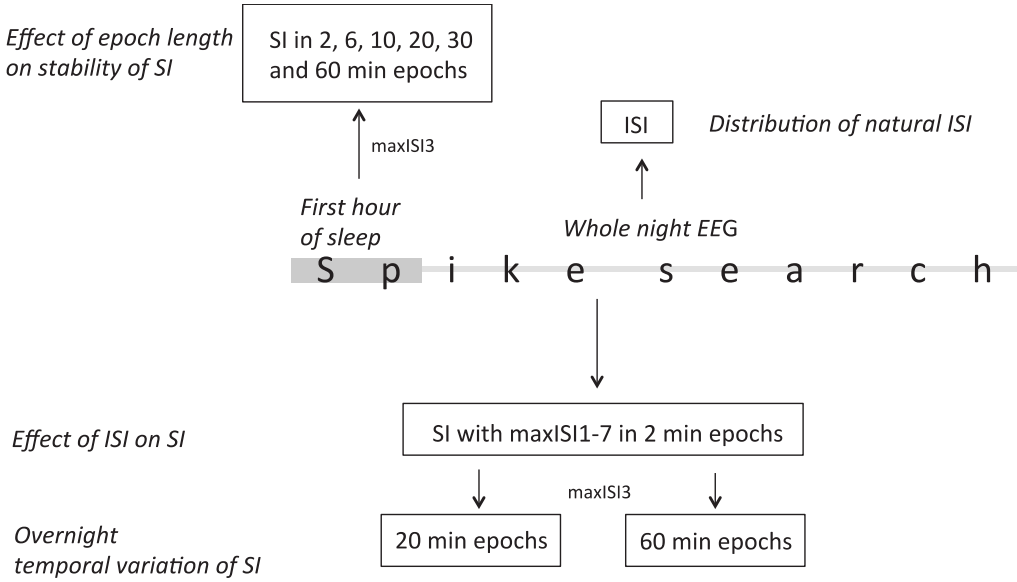

Figure 5. The study design to examine the temporal variation of SI and related factors in Study II.

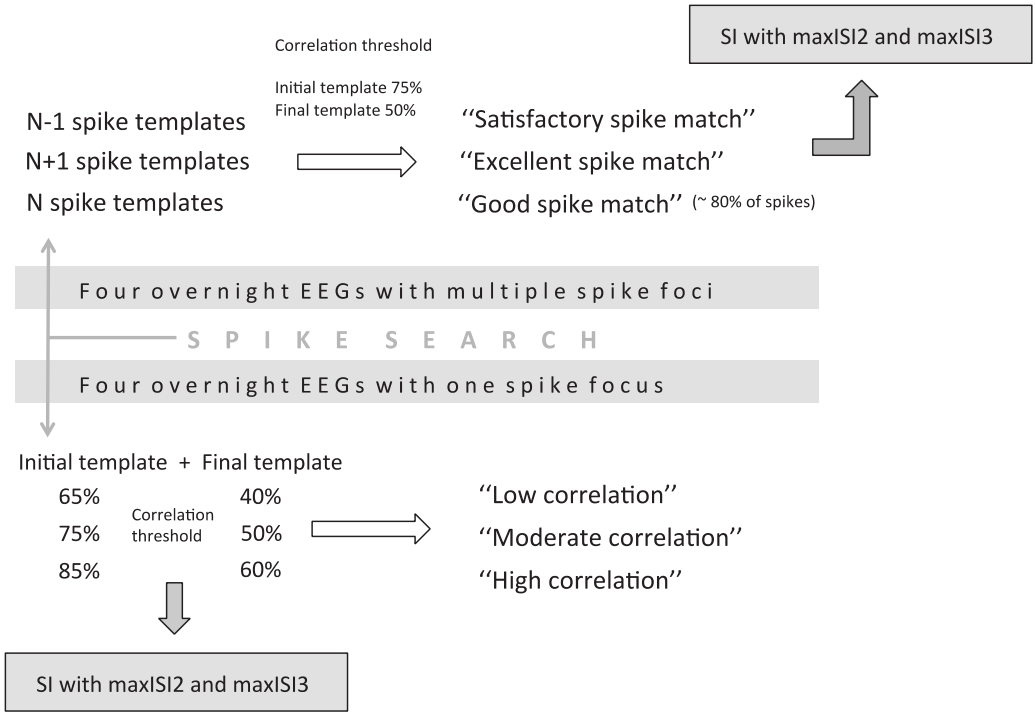

Figure 6. The study design to analyze the sensitivity of SI on variations in the spike search protocol in Study II.

4.5.3 Study III

The spike-to-spike variability of amplitude and RMS was studied by comparing measures from the averages of even and odd spikes during ten minutes of sleep EEG to ascertain the repeatability of spike averaging. Further analysis was done from the average of all spikes in each epoch studied.

The temporally longer time scale stability of amplitude, RMS, Ampl-Q, and RMS-Q was studied by comparing the measures from two, ten minute epochs during the first hour of NREM sleep (in data set 1), as well as by analyzing overnight variation (in data set 2).

In addition to ±150 ms analysis window over the spike, the RMS-Q of the ten minute epoch was calculated over the duration of spike to study the effect of varying baseline on the stability of RMS-Q. Finally, the Ampl-Q and the RMS-Q over ±150 ms window were analyzed, from the postoperative data, to compare the ability of Ampl-Q and RMS-Q in order to detect a change (either positive or negative) in spike strength between pre- and postoperative recordings (data set 1).

The statistical analysis was performed with the IBM SPSS® software version 20.0 (IBM Corp., Armonk, NY, USA). Differences between the groups were evaluated with Wilcoxon Signed Rank test, and considered significant if $p<0.05$. The pair-wise correlations between parameters were analyzed with a Spearman rank correlation test, and considered significant at $p<0.01$ level (2-tailed). To improve comparability between subjects, the interquartile range measures were divided with the median.

4.6 Ethical considerations

The Ethics Committee for Pediatrics, Adolescent Medicine, and Psychiatry, at the Hospital District of Helsinki and Uusimaa, approved the study protocol of retrospective Studies I-III that were all based on EEG recordings made on the clinical grounds.

5 RESULTS

5.1 Outcome of callosotomy and resective surgery in pharmacoresistant ESES with symptomatic etiology (Study I)

5.1.1 Clinical outcome

Six patients underwent anterior callosotomy, three total callosotomy, two hemispherotomy, and two lobar resections at the age of 3.6 to 9.0 years. Postoperative complications included mild worsening of preoperatively manifested unilateral fine motor deficit after anterior callosotomy in two patients and a predicted visual field deficit after parieto-occipital resection or hemispherotomy, in three patients.

The postoperative outcome at two years after surgery is shown in Figure 7. The total cessation of seizures occurred after focal resection or hemispherotomy in two of the three patients with preoperative seizures. After callosotomy, atypical absences terminated in one patient with anterior callosotomy and one patient with total callosotomy who both still continued to have rare focal seizures (Engel Class II outcome). However, in total, six out of eight patients, who had frequent daily atypical absences obtained postoperatively greater than 90% reduction in seizure frequency compared to presurgical levels. Two anterior callosotomy patients with unfavorable seizure outcome were implanted with a vagal nerve stimulator six and 13 months after surgery, and one of them obtained greater than 90% reduction in atypical absences.

The patients' cognitive trajectory from the first measured IQ/DQ to the last postoperative follow-up at two years after surgery is seen in Figure 8. All patients with the first measured IQ/DQ greater than 30 points showed a cognitive decline until surgery. Cognitive deterioration was stopped after surgery in all except one patient. Catch-up improvement occurred in three patients whose first measured IQ/DQ was at least 75. One of them had no preoperative documented seizures. The mean age at surgery in the patients with cognitive catch-up development was 8.9 years and the duration of ESES was 3.7 years compared to 5.8 years and 2.5 years, respectively, in patients without catch-up. The distribution of IQ was skew. Binomial probabilities for

the cessation of cognitive deterioration or catch-up development after 13 surgeries are presented in Table 4.

Table 4. Binomial probability for success (cognitive catch-up or cessation of deterioration) in 7-13 out of 13 epilepsy surgeries when the probability of success on a single trial (x) is 0.5 or 0.7 (unpublished data).

Number of patients with cognitive catch-up or cessation of deterioration	**Binomial probability**	
	P(x)=0.5	**P(x)=0.7**
13	0.0001	0.01
12	0.002	0.05
11	0.010	0.14
10	0.035	0.22
9	0.087	0.23
8	0.157	0.18
7	0.209	0.10

Behavioral improvement was reported by the parents of all four patients with resective surgery, two out three patients with total callosotomy and four out of six with anterior callosotomy. In seven out of ten patients, a favorable response was associated with a greater than 90% reduction in daily multiple atypical absences.

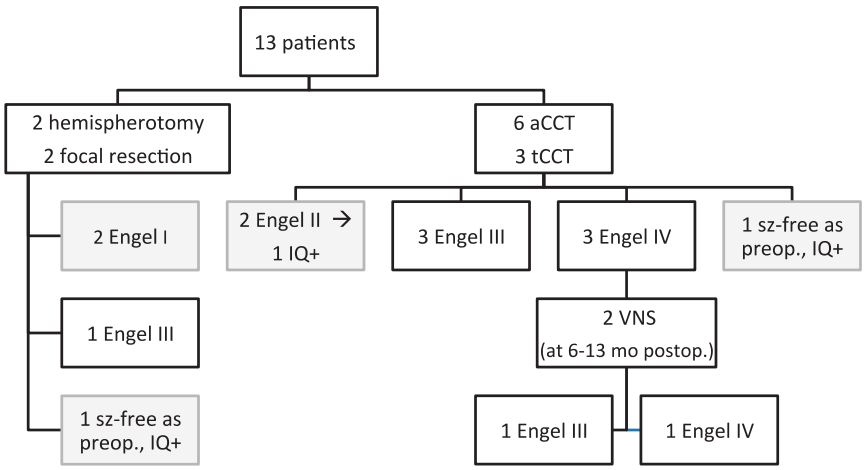

Figure 7. Postoperative outcome. Shaded boxes, favorable seizure outcome; IQ+, increase of IQ ≥10 points; aCCT, anterior callosotomy; tCCT, total callosotomy; sz, seizure; VNS, vagal nerve stimulator; preop., preoperatively; Engel, Engel Epilepsy Surgery Outcome Scale (Engel, 1987).

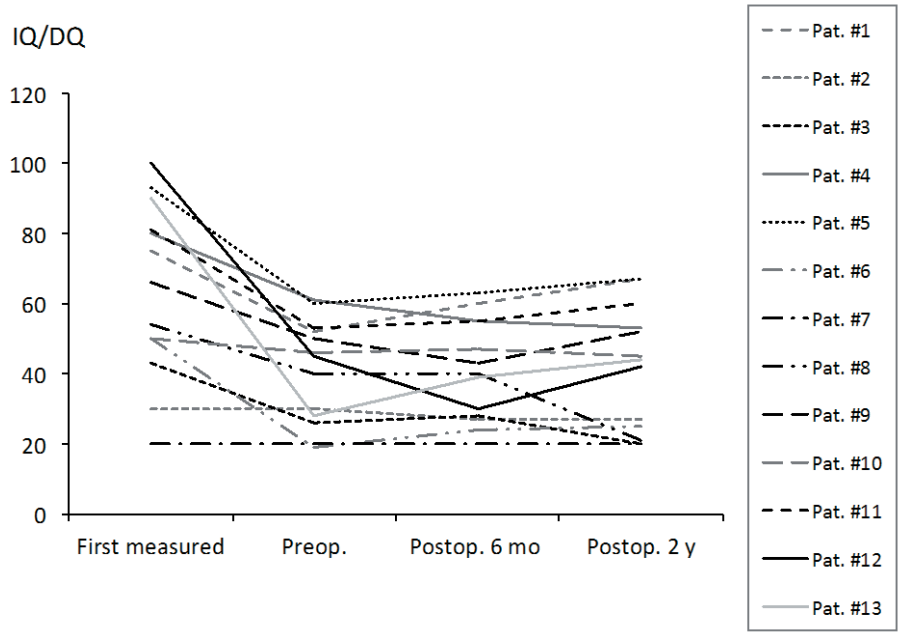

Figure 8. IQ/DQ measurements before and after the surgery. Preop., preoperative; postop., postoperative; mo, month; y, year.

5.1.2 Pre- and postoperative EEG findings

Seven of 13 patients had more than one focus participating in ESES in preoperative EEG. The onset area of ESES was frontal in eight patients, occipito-parietal in eight, and centrotemporal in two. Three different propagation patterns of ESES were recognized in the preoperative EEGs (Figure 9). Nine patients had ESES, which propagated from one hemisphere to another. Six of them had classical ESES; i.e., bilateral "synchronous" discharge (one-way interhemispheric propagation, ESES type 1). Three patients had multifocal asynchronous ESES, where spikes propagated from only one focus to the contralateral hemisphere (one-way interhemispheric propagation, ESES type 2). The leading side of interhemispheric propagation was always consistent with clinical and MRI findings suggesting unilateral or asymmetrical pathology. Four patients had multifocal asynchronous bilateral ESES, which propagated equally from both hemispheres to the contralateral side (two-way interhemispheric propagation, ESES type 3).

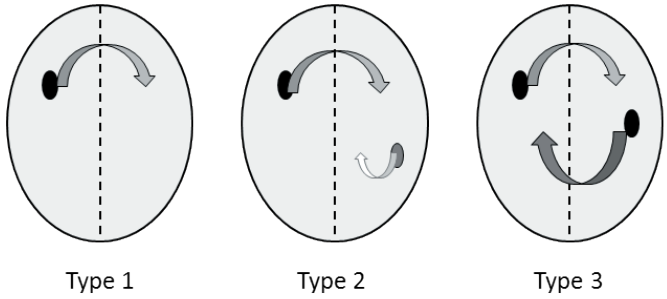

Figure 9. Three propagation patterns of bilaterally distributed ESES were found in preoperative EEGs. Type 1: bilateral synchronous SES. Type 2: bilateral asynchronous SES with one-way interhemispheric propagation. Type 3: bilateral asynchronous SES with two-way interhemispheric.

Focal resection led to prominent EEG changes. The source strength decreased markedly, bilateral propagation was stopped, and ESES was limited into focal (two adjacent electrodes/one brain region) or regional discharge in the proximity of the epileptogenic lesion. Hemispherotomy isolated ESES to the disconnected side. EEG response after the callosotomy was less consistent. Interhemispheric propagation was inhibited and propagation area diminished in two of eight patients with postoperative EEG. Both of them had undergone anterior callosotomy. An EEG example of restricted propagation is seen in Figure 10. Source strength was decreased in two additional patients. None of the preoperative foci was totally suppressed after surgery and the remaining spiking or spike-and-wave discharge was still continuous.

All four patients with Engel class I-II seizure outcome and all three patients with cognitive catch-up (two of them with no documented preoperative seizures) had either type 1 or type 2 preoperative ESES pattern. Four out of seven patients with Engel class III-IV seizure outcomes had type 3 preoperative ESES.

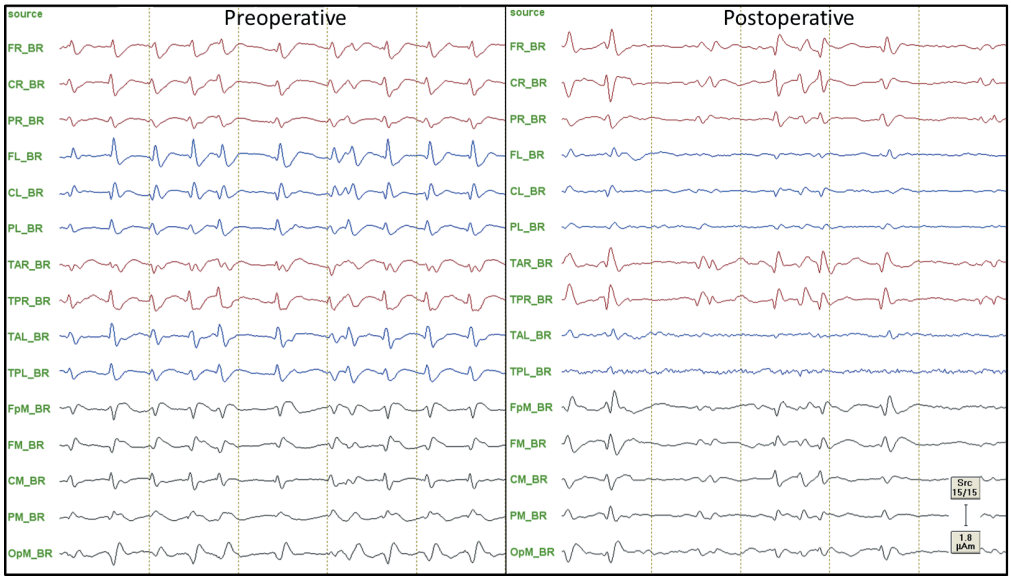

Figure 10. Preoperative EEG shows bilateral synchronous ESES, type 1 (Pat. #1). Source of ESES is in the right frontal area. After anterior callosotomy, the propagation area is restricted mainly on the right hemisphere with a small amplitude propagation to the left frontal area. The montage shown is regional brain source montage, one second between lines. TA=temporal anterior, TP=temporal posterior, F=frontal, C=central, P=parietal, Fp=fronto-polar, Op= occipito-polar, L=left hemisphere, R=right hemisphere, M=midline, BR=brain region.

5.1.3 Semiautomatic quantification of SI –the search for the optimal paradigm (Study II)

5.1.3.1 Temporal characteristics of ISI and SI

The natural distribution of ISI in ten EEGs with ESES showed that from 77 to 100 % (mean 96%) of ISIs were shorter than 3.0 s. Thus, calculating SI with a maxISI of 3 s (maxISI3) would comprise nearly all spiking. SI showed instability by increasing strongly with the duration of maxISI, but reached a plateau at around maxISI of 3 s.

The stability of SI, over a whole night sleep was assessed using maxISI3. The SI analyzed in epochs of 20 and 60 min overnight showed a random variation with a slight tendency for a higher SI at the beginning of sleep (Figure 10). However, the SI of the first hour of sleep did not differ significantly from the SI of the whole night

sleep (p=0.097). Further analysis from the first hour of sleep showed that the stability of SI increased along the length of analysis epoch (2-60 min) but reached a good stability with a 30 min long epoch of NREM sleep in eight of ten EEGs.

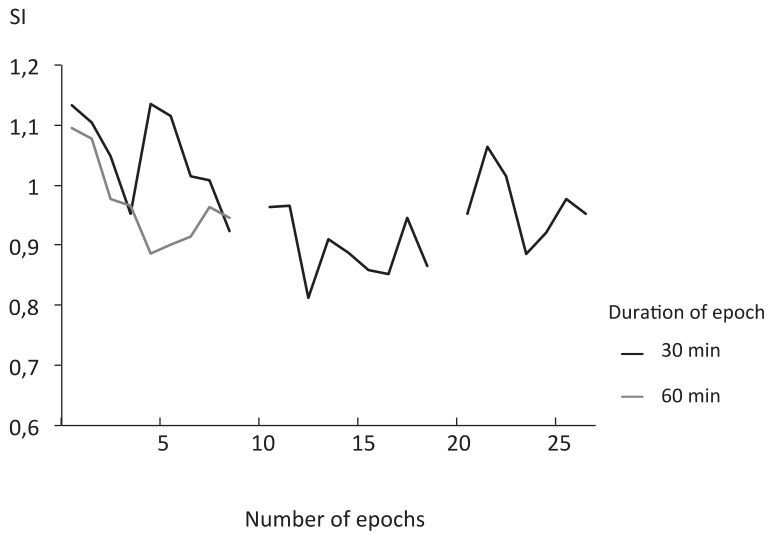

Figure 10. Overnight variation of normalized SI calculated in 20 and 60 min epochs overnight. Example from the Patient #9 (Refer to original publication Peltola et al. 2012.).

5.1.3.2 Stability of SI for variations in the spike search

SI stability was first examined by varying the correlation percentages in spike search in four EEGs with unifocal ESES. Moderate correlation percentages resulted in lower SI values than low or high correlation percentages. The difference was reduced when maxISI was increased from 2 to 3 s. The relative mean differences were 9.2% (range: 3.0-19.9%) for the SI calculated with maxISI2 and 4.2% (range: 0.07-9.7%) for the SI with maxISI3. Thus, maxISI3 was considerably less sensitive to the variation in the stringency of spike template matching.

The robustness of quantification of SI was tested with a satisfactory, good, and or excellent result of the spike search in four EEGs with multifocal ESES. The SI calculated with both maxISI2 and maxISI3 was comparable between the excellent and good searches, but the satisfactory spike search resulted in higher variation in SI values with maxISI2 than maxISI3. (Refer to Figure 4 in the original publication II Peltola et al. 2012.)

5.1.3.3 Validation

The semiautomatic SI and the gold standard generated by expert markings differed by only 7.0 (range: 0.4 - 19.6) SI percentage units ($p=0.05$) corresponding to a relative error of 0.5-23.2% (mean 7.6%). The semiautomatic SI estimate was slightly but not significantly lower than the gold standard in eight out of ten patients.

5.1.4 Comparison of methods to measure spike strength in CSWS (Study II)

Spike averaging was successful in 19 out of 20 EEGs, but resulted in unstable search in one EEG with multifocal spiking, which was excluded from the further analysis. The amplitude and RMS calculated from the separate averages of odd and even spikes was highly correlated in 19 EEGs. Further analysis was done from all spikes averaged together.

5.1.4.1 Short time scale stability of spike strength measures

Amplitude, RMS, Ampl-Q, and RMS-Q over ± 150 ms analysis window were analyzed from two epochs of ten min EEG, during the first hour of sleep. At a group level, the median relative difference (absolute value) between the epochs was highest for RMS (10%) and significant ($Z= -2.67$, $p=0.008$). Amplitude, Ampl-Q, and RMS-Q showed a median variability of 3-4%. Despite the good stability in the group level, the individual variability was marked in two of nine EEGs, particularly for the amplitude. The single channel spike amplitude varied up to 71% compared to 43% variation of Ampl-Q and 34% of RMS-Q. The overall correlation between all measures was expectedly strong ($rS\ (16) \geq 0.96$, $p<0.001$). In addition, RMS-Q was computed over the duration of the whole spike instead of the fixed ±150 ms in order to minimize the effect of varying baseline, but this did not improve the stability of RMS-Q. The raw EEG data implied that the high variability of RMS-Q seen in two patients (No's. 5 and 7, refer to original publication III Peltola et al. 2014) was probably caused by multiple short arousals and the difference of sleep quality between the successive ten minutes epochs. Arousals were clearly related to a transient increase in the frequency and decrease in the amplitude of spikes.

5.1.4.2 Overnight stability of spike strength measures

The overnight variation of amplitude, RMS, RMS-Q, and Ampl-Q was greatest for the single spikes, and diminished with averaging consecutive spikes, but overnight variation was marked, nevertheless (Figure 11).

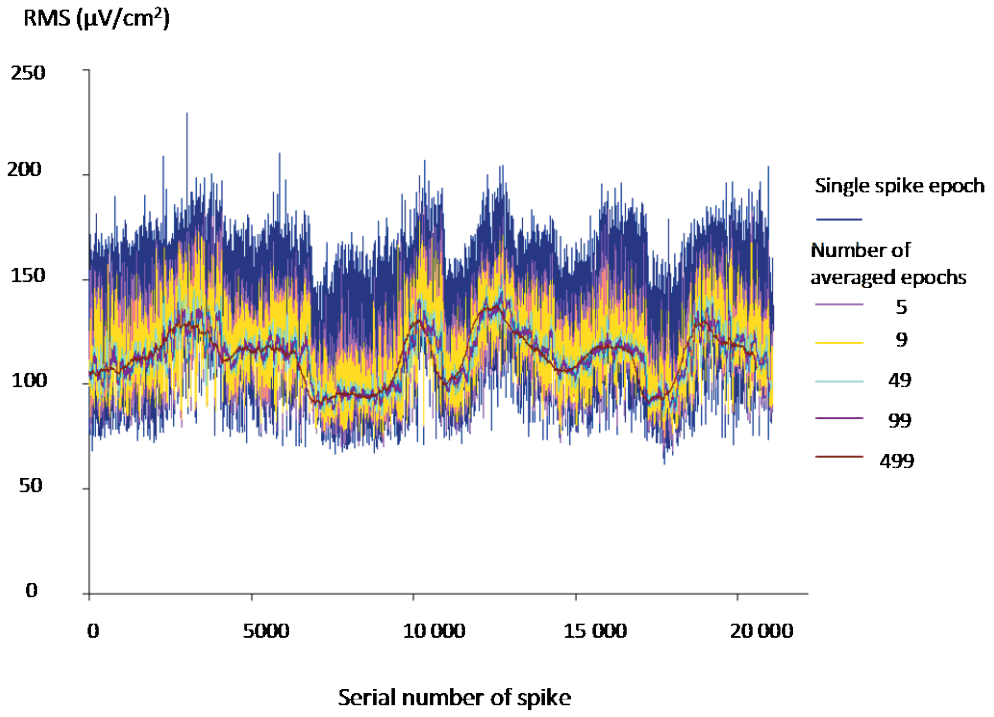

Figure 11. Overnight stability of RMS-Q increased with the number of spike epochs averages. This example was taken from the patient #4 (Refer to original publication III Peltola et al. 2014.).

Raw EEG data indicated that arousals and REM-sleep were associated with momentary decreases in spike strength parameters whereas increases occurred upon transition to NREM sleep. Ampl-Q and RMS-Q stabilized during NREM sleep when it was uninterrupted by arousals. No particular NREM period showed constantly better stability than others. The higher likelihood of NREM sleep in the beginning of the night, however, resulted in generally more stable measures during the first hour of sleep as compared to the whole night averages (Refer to Figure 5 in the original publication III Peltola et al. 2014.).

Finally, the comparison of the Ampl-Q and the RMS-Q calculated from the preoperative and postoperative EEGs showed an equal ability of the parameters to show a change. In Study I, the source strength was measured by spectral analysis from same pre- and postoperative EEGs than in Study III. The relative postoperative change of RMS-Q in Study III was well correlated with that of spectral amplitude in Study I (unpublished data, Figure 12).

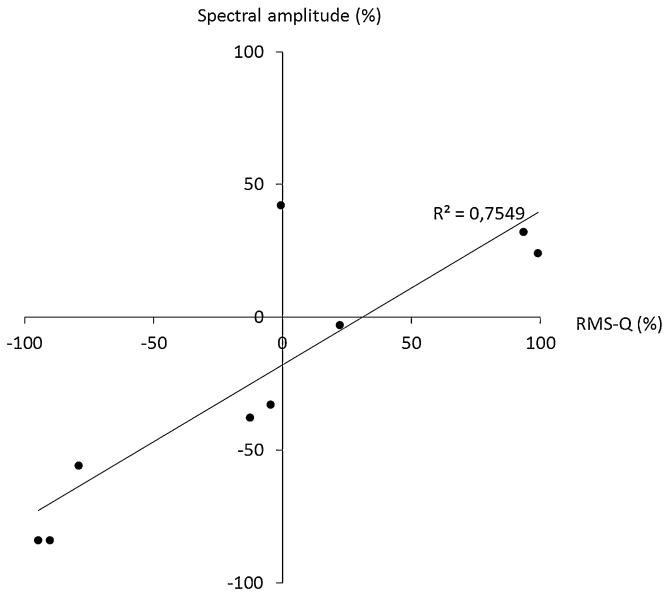

Figure 12. Relative postoperative change of RMS-Q and spectral amplitude were highly correlated in eight of the nine patients with postoperative EEG.

6 DISCUSSION

6.1 Epilepsy surgery may be beneficial in selected patients of pharmacoresistant CSWS with symptomatic etiology

6.1.1 Clinical outcome

This thesis presents original data supporting the use of callosotomy in patients with CSWS with bilaterally propagating ESES and structural etiology. Over a 90% reductions in seizures were obtained in six out of eight patients with preoperative atypical absences. These had a significant effect on the life quality of patients. The results are in line with previous studies in other types of epilepsies (Cendes et al., 1993; Maehara & Shimizu, 2001; Rathore et al., 2007; Tanriverdi et al., 2009; Stigsdotter-Broman et al., 2014).

VNS is successfully used against generalized seizures in pharmocoresistant pediatric epilepsy for an option to callosotomy and after unsuccessful callosotomy (Hallböök et al., 2005; Amar et al., 2008; Kabir et al., 2009; Cukiert et al., 2013). We observed over 90% reduction in seizures in one out of two patients in whom a vagal nerve stimulator was implanted after ineffective anterior callosotomy. Previous experiences of VNS in patients with CSWS have not been reported.

A few case studies and one small series have suggested beneficial effect of resective surgery against seizures in patients with CSWS and unilateral structural abnormalities (Kallay et al., 2008; Battaglia et al., 2009; Loddenkemper et al., 2009; Roulet-Perez et al., 2010) and our results showing seizure termination in two of three patients after resective surgery are in line with these previous observations.

In addition to favorable seizure outcome, patients with CSWS may improve, cognitively and behaviorally, after surgery (Kallay 2008, Loddenkemper et al. 2009, Battaglia 2009, Roulez-Perez 2010). We observed an improved behavior in ten out of 13 patients that was associated with a markedly reduced seizure frequency as observed in other types of epilepsy (Cendes et al., 1993; Rathore et al., 2007).

A termination of cognitive deterioration was found in all except one patient with a preoperative IQ/DQ greater than 30. In line, in other types of epilepsies, the majority of children show preserved cognitive level from preoperative to postoperative follow-up assessment (Pulsifer et al., 2004; Dunkley et al., 2011; Villarejo-Ortega et al., 2013). Postoperative catch-up improvement was seen only in three of our patients whose first measured IQ/DQ was at least 75 that may indicate those patients having had more regenerative capacity.

The strength in this thesis was that we used a serial standardized pre- and postoperative assessment of IQ/DQ to show a cognitive trajectory from the beginning of CSWS to the last postoperative control at two years after the surgery (Liukkonen et al., 2010) instead of using only one preoperative value obtained close to the surgery. However, in children with very low preoperative cognitive level, formal neuropsychological tests scores may not sensitive enough to show improvement although patients have gained important skills. One out of our four patients with preoperative DQ less than 30 lost her ability to walk after the beginning of ESES and regained it three months after callosotomy.

Because of the young age of our patients, it is unlikely that termination of cognitive deterioration would be a consequence of CSWS's natural course. Decreased frequency of seizures may have had an impact on cognitive abilities in patients with very frequent, multiple daily preoperative seizures.

The small size of our patient group does not allow us to draw firm conclusions regarding all patients with CSWS and structural etiology. Ideally, we should have conducted a randomized trial, but as in most studies of epilepsy surgery this has not been done because of ethical and practical problems in designing a feasible study. However, based on binomial probabilities, we think that it is unlikely that cessation of cognitive decline or cognitive catch-up would be a mere chance or in our group of selected patients or would strongly overestimate the good cognitive outcome. Moreover, our results are in line with favorable cognitive outcome reported in earlier studies (Kallay 2008, Loddenkemper et al. 2009, Battaglia 2009, Roulez-Perez 2010).

6.1.2 EEG outcome

As expected by earlier studies, hemispherotomy terminated the ESES on the side contralateral to operation (Kallay 2009, Loddenkemper et al. 2009, Battaglia 2009, Roulez-Perez 2010). After focal resection, we observed focal continuous spiking or

regional ESES on the proximity and side of the resection instead of total resolution ESES reported in earlier studies. This indicates that the onset area of ESES was not totally resected in our patients.

EEG outcome, after callosotomy, although more complex and variable, was in line with earlier studies, which have shown decreased propagation of discharges after callosotomy in at least half of the patients with epilepsies other than CSWS. Bilateral propagation of predominantly interictal discharges is not infrequent after callosotomy despite favorable seizure outcome and may be a consequence of subcortical propagation (Spencer & Spencer, 1985; Oguni et al., 1994; Matsuo et al., 2003).

The limitation of EEG analysis in Study I was a lack of an objective semiautomated/automated method to quantitate ESES, which we have addressed in Studies II to III. However, Study I clearly showed the need to combine different EEG parameters aside of SI in EEG diagnostics of CSWS. Also, because of the retrospective nature of the study, postoperative EEG was available only in patients in whom it was needed on clinical grounds. Postoperative EEGs from the patients with excellent outcome were missing, which may have weakened the association between the postoperative EEG findings and outcome. Furthermore, because of the small number of patients with cognitive catch-up and postoperative EEG, we cannot relate the cognitive improvement with reduction of ESES (Aeby et al., 2005; Van Hirtum-Das et al., 2006).

6.1.3 Factors associated with the outcome

Our study offered new insights into EEG diagnostics of CSWS by analyzing the type of propagation pattern in ESES and its relation to surgical outcome. We found that the preoperative propagation pattern of ESES may predict outcome after callosotomy. Two-way interhemispheric propagation (ESES type 3) was seen after callosotomy only in patients with unfavorable seizure outcome and may indicate more extensive bilateral epileptogenic lesions. This was supported by the convergence of the leading side in EEG and lateralized findings in MRI in patients with one-way interhemispheric propagation.

Earlier studies have reported that the IQ level may or may not be a predictor of outcome after epilepsy surgery in children (Spencer et al., 1988; Bjornaes et al., 2004; Gleissner et al., 2006). In our series, normal or nearly normal early development increased possibility of favorable outcome after surgery. This is in line with our earlier

observation showing that the medically treated patients with higher IQ at ESES diagnosis had a tendency for a better cognitive outcome (Liukkonen et al. 2009).

6.2 Semiautomatic quantification of SI is a promising tool

6.2.1 General aspects on quantification of SI

The SI has been traditionally quantified visually by variable methods (Hommet et al., 2000; Aeby et al., 2005; Fernández, Loddenkemper et al., 2012). Our study showed, that the visual scoring of spike free time and SI was concordant between two experienced clinical neurophysiologists. However, the visual analysis of whole night EEG is extremely time-consuming. Recent studies have addressed the problem by introducing semiautomated or wholly automated methods for the spike search and quantification of SI in CSWS (Larsson et al., 2009; Nonclercq et al., 2009, 2012; Martín Miguel et al., 2011; V Chavakula et al., 2013). Before introducing new tools in clinical practice they need to be optimized and validated. There is no commercial tool for quantification of SI. We chose to use BESA® Research for spike search and an open algorithm published by Larsson et al. (2009), both being available for a larger community as well.

6.2.2 User defined parameters affecting the semiautomated quantitation SI

We studied the properties of Larsson´s algorithm in relation to "open parameters" i.e. parameters of script that are adjustable by the user and affect the output. The most important was the ISI that comprise the definition of 'continuous' discharge and influenced strongly the SI. Based on earlier studies Larsson and colleagues suggested that the time each spike might interfere on cognitive processing would approximately be three seconds. However, we felt that the choice of maxISI needed more argumentation. Our objective was to choose the maxISI that could i) catch the natural spiking behavior in the EEG, ii) be sufficiently stable across patients and over time, and iii) be sensitive to changes associated with treatment and recovery. In semiautomated spike search, choice of strategies implemented in spike search varies by different users and EEGs. Fixed search strategies do not allow the most efficient search and may not yield in acceptable output depending on the amplitude and amount of spatiotemporal variation of spikes.

The maxISI3 fulfilled best all the criteria. Shorter maxISIs rendered the SI unstable and sensitive to small random variation in spiking and spike search, and longer ones resulted in unnecessary stable SI liable to lose its sensitivity.

Our findings are fully compatible with the earlier work of Larsson and colleagues (Larsson et al., 2009; Larsson, Evsiukova, et al., 2010), and we extend the existing literature by demonstrating the effects of user-defined settings in SI quantification, as well as the natural characteristics of spiking in patients with CSWS and showing the comparability of semiautomated and visually scored SI.

6.2.3 Temporal variability of SI

CSWS diagnosis is conventionally based on a whole night sleep (Morikawa et al., 1985; Tassinari et al., 2000; Inutsuka et al., 2006; Liukkonen et al., 2010). However, because of the extremely time-consuming visual method to quantitate the SI, most estimates of SI are based on several short samples of EEG during NREM, not on the calculation over the contiguous whole night EEG. We found that the SI of the first hour was not significantly different from the whole night SI and an epoch of from 30 to 60 min of NREM was sufficiently repeatable to calculate the SI. This is in accordance with the earlier finding that the frequency of spikes per min peaks during the first ten minutes of each sleep cycle, but the mean spike frequency of each NREM-REM-sleep cycle remains stable over night (Nobili et al., 1999, 2001).

Limitation in the thesis was that our results are from the patients with overnight SI over 50%. If overnight recordings are not available, risk for overestimation of SI from a nap compared to overnight SI need to be considered (Larsson, Evsiukova, et al., 2010). However, the clinical meaning of SI is always interpreted in a context of cognitive impairments and other clinical symptoms. Shorter recordings may have both practical and technical advantages. The short recording permits of the use of electrode caps instead of fixed electrodes and allows better control on the quality of recording and spike search.

Nevertheless, our results showed that semiautomatic quantification of spike index (SI) with appropriate parameter settings is a robust and promising tool for the quantification of ESES.

6.3 Spike strength – a good candidate for a complementary quantitative EEG measure in CSWS

6.3.1 New EEG measures needed for ESES

ESES is the hallmark of CSWS, but the SI seldom explains the severity of clinical course in CSWS (Morikawa et al., 1985; Hommet et al., 2000; Sánchez Fernández, Loddenkemper, et al., 2012; Caraballo et al., 2013). Hence, the spike amplitude reflecting different mechanisms than SI might be a good candidate for a new parameter needed for monitoring treatment in CSWS. In Study I, we found the decrease in spike propagation and/or strength after surgery that is in accordance with earlier results obtained after levetiracetam treatment in patients with enhanced focal nocturnal epileptiform activity (Larsson, Eeg-Olofsson, et al., 2010).

6.3.2 Challenges of measuring the spike amplitude

Spike amplitude is used in clinical EEG diagnostics, but methodological studies on the stability and sensitivity of measure are lacking. Spatiotemporal variation in spike morphology potentially renders the amplitude unstable and we were prompted to study different spike amplitude-related parameters, in detail.

Our results confirmed that conventional measures like single channel amplitude may not be stable enough for quantitating purposes and reminded the caveat of intuitive choices of parameters for clinical diagnostics (Aeby et al., 2005; Larsson, Eeg-Olofsson, et al., 2010). Maximum intra-individual variability of single channel amplitude between two epochs of ten min was as high as 71%, which made it an unusable parameter for clinical diagnostics. The spatial integration of amplitude and RMS offered the stability of the paradigm that is necessary for clinical purposes, i.e. estimating therapy response.

An overnight variation of spike strength parameters clearly showed that the measures were sensitive to short arousals and transitions to REM sleep. Hence, the stability of NREM sleep is essential for a repeatable quantitative assessment of spike strength and needs to be carefully considered in clinical use when choosing the analysis epoch.

A fluctuating baseline increases the variability in the measurement of EEG transients. An averaging of spikes improved the signal to noise ratio, but was unable to completely stabilize the baseline. An analysis over the spike duration instead of longer

fixed analysis window did not significantly improve the stability suggesting that spatiotemporal variation of spikes is the main source of instability.

The Ampl-Q and RMS-Q were both robust and promising parameters for clinical trials. However, we preferred RMS-Q, which is calculated over time and theoretically less sensitive to spatiotemporal variation of spikes, although not proved in our limited dataset. Wholly automated spike detection algorithms could further our methodological workup. By reducing user dependent variability in the spike search, they may offer both higher objectivity and reduced analysis times.

6.4 Future considerations

Recent genetic and functional imaging studies have offered new insights on possible molecular and pathophysiological mechanisms of ESES and CSWS (Siniatchkin et al., 2010; De Tiège et al., 2013; Lemke et al., 2013; Lesca et al., 2013; Carvill et al., 2014). While genetic studies may help us to recognize at least some patients with increased risk for encephalopathy, we are still lacking additional predictors of epileptic encephalopathy with ESES, and measures to monitor the clinical course and treatment response in CSWS. Further studies are needed to validate the role of SI, RMS-Q, and propagation patterns of ESES in clinical monitoring of CSWS. There is increasing evidence that the SI alone is not a sufficiently sensitive measure for clinical monitoring suggesting that the pathophysiological mechanisms of ESES are not related only to the activity of epileptic focus. Future studies targeting pathophysiological mechanisms of ESES should take account on the effect of ESES on dynamics and functional organization of brain networks by measuring cortico-cortical connectivity of brain rhythms, which are related to neuronal oscillations (Lopes da Silva, 2013). Neural oscillations are fundamental elements in coding information, modulating attention, and organizing cognitive networks.

Published data on epilepsy surgery in CSWS are scarce. Considering the rarity of syndrome, multicenter data are needed to better recognize the patients who most benefit from resective surgery. The role that callosotomy and VNS plays in treatment of CSWS remains ambiguous and needs to be clarified by further studies with detailed attention on cognitive outcome.

7 SUMMARY AND CONCLUSIONS

The clinical and EEG outcome of epilepsy surgery in patients with CSWS was explored here. In addition, two quantitative EEG parameters, based on different neural mechanisms, the SI and the spike strength, were evaluated to obtain a more comprehensive objective measure for ESES.

This thesis presents original results that callosotomy may be beneficial in patients with pharmacoresistant CSWS and bilateral ESES who are not candidates for resective surgery. In line with other studies, we also found positive outcomes after the resective surgery. Good clinical response after callosotomy was observed as decreased atypical absences, improved behavior, cessation of cognitive deterioration, and less often as catch-up development. The patients who were most likely to benefit from surgery had a pre-ESES IQ greater than or equal to 75 and a one-way interhemispheric propagation pattern of ESES on the preoperative EEG. Postoperative EEG showed a decreased source strength and/or restricted propagation of ESES in patients with favorable outcome. Our results accumulated evidence for cognitive and seizure-related benefits of epilepsy surgery in patients with CSWS with structural etiology and offer new insights on possible preoperative EEG markers predictive of outcome.

The semiautomated quantification of SI proved to be a robust tool for clinical and scientific use. SI was highly dependent on maxISI defining the continuous discharge, as expected. Regarding the natural spiking behavior in the EEG, a maxISI of 3 s was an optimal setting for a stable measure across and within patients over time and treatment. In our EEG samples with overnight SI greater than 50%, the SI of the first hour of sleep was representative of the whole night SI. Furthermore, the semiautomated quantification of SI compared well with human scoring that was taken as a gold standard. As a result, this study yielded recommendations for the use of semiautomatic quantification of SI (Larsson et al., 2009).

SI alone may not be sensitive enough for clinical monitoring of CSWS. The strength of spikes during sleep offered a complementary method that is based theoretically on different neural mechanisms than SI. The spatial integration over multiple electrodes rendered the spike strength measures stable enough for clinical use when short (e.g. 10

min) epochs of NREM sleep were chosen for analysis. Spatially integrated RMS (RMS-Q) is a robust and promising tool for quantifying ESES.

Careful choice of epochs with uninterrupted NREM will further improve the repeatability and reliability of the measure. However, determining of the clinical significance of RMS-Q remains a challenge for future studies. The significances of this thesis's results are that they offer the prospect to combine several EEG measures, such as SI, RMS-Q, and propagation pattern of ESES. These will offer us a better understanding of the relationship between ESES and clinical course of CSWS.

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