Review article

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Quantitative EEG analysis in Encephalopathy related to Status Epilepticus during slow Sleep

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ABSTRACT – Since its first description, quantifying the burden of epileptiform abnormalities in sleep EEG has played a fundamental role in the diagnosis of Encephalopathy related to Status Epilepticus during slow Sleep (ESES). In fact, in the 1971 seminal paper by Tassinari's group and in the following studies on this syndrome, the amount of epileptiform discharges (EDs) was calculated as the percentage of slow sleep occupied by spike-and-waves and referred to as "spike and wave index" (SWI). However, nowadays it is becoming increasingly clear that the SWI alone does not explain the whole clinical course of patients affected by ESES. In this paper, we aim to provide a *state-of-the-art* summary of the quantitative EEG methods currently used in the ESES/CSWS literature, highlighting the possible pitfalls and discrepancies explaining the unsatisfactory correlation between SWI and clinical course. Furthermore; we illustrate a number of methodological refinements - taking into account inter-individual, intra-individual, and temporal variability of EDs - alongside "new" quantitative variables -including ED-related and sleep-related features - potentially useful to reach a reliable electro-clinical correlation in patients with ESES.

Key words: encephalopathy related to status epilepticus during slow sleep, ESES, quantitative analysis, EEG, spike index, CSWS, LKS, HFOs, independent component analysis, sleep downscaling

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The quantitative analysis of EEG plays a fundamental role in the diagnosis of Encephalopathy related to Status Epilepticus during slow Sleep (ESES). In fact, since its first description (Patry *et al.*, 1971), a computable measure of epileptiform discharge (ED) abundance during sleep was

used as a diagnostic criterion. Along the lines of Tassinari's hypothesis - that the severity of encephalopathy is proportional to the amount of sleep substituted by spike-and-wave complexes - the description of the EEG pattern of ESES has been based almost exclusively on the abundance of EDs, while other quantitative and qualitative measures have been usually neglected (Scheltens-de Boer, 2009; Tassinari *et al*., 2012; Peltola *et al*., 2014). However, nowadays it is becoming increasingly clear that this variable alone does not explain the whole clinical course of the patients. The aim of this paper was not to merely illustrate the best quantitative measure, but rather to provide the reader with a number of quantitative variables potentially useful to reach a reliable electro-clinical correlation. These quantitative measures can be related to the amount and quality of epileptiform paroxysmal activities but also to physiological components of sleep. Furthermore, we will examine the possible pitfalls and discrepancies in the methods currently used in the ESES/CSWS literature.

Epileptiform activities

Amount

Spike-and-wave index(es)

In the 70s, at the Centre Saint-Paul in Marseille, the quantification of EDs in ESES was inspired by the recently adopted (at that time) Rechtschaffen and Kales (1968) sleep scoring method (Tassinari personal communication), in which, for each epoch, the time occupied by an activity (*e.g.* delta waves) is expressed as percentage and serves as a scoring criterion. Accordingly, the amount of EDs was expressed as the percentage of the total duration of slow sleep occupied by a spike and the following slow wave or by sequences of rhythmic spike-and-wave complexes. This percentage was referred as "spike and wave index" (SWI) in the seminal paper by Patry *et al*. (1971), in which six patients were selected based on the "spectacular increase" of the spike-and-waves observed as soon as they fell asleep. In this selected population, the SI ranged from 85 to 100% and these values were used as a reference for the typical feature of overnight EEG in patients with ESES. The method of determining SI was not described in the paper, and as a consequence, a number of different methods were crafted and used to determine the SWI.

The great majority of the subsequent studies continued to rely on visual estimation, without further clarifying the computational rules to determine the percentage of time occupied by the pathologic pattern, with the exception of the study by Aeby *et al*. (2005), in which it is specified that the SWI was obtained by calculating the percentage of 1-second bins containing at least one spike-and-wave complex (Aeby *et al*., 2005). This method is similar to the "original" since even a one-second interval between two spike-and-wave complexes is computed as discharge-free. However, only 60 minutes of EEG were analyzed instead of the full night. The introduction of digital EEG systems offered an opportunity to reduce the workload needed for SWI assessment of the entire nocturnal recording. In fact, a number of computer-aided spike detection methods have been developed and some of these successfully applied to ESES/CSWS (Larsson *et al*., 2009; Nonclerq *et al*., 2009; Nonclerq *et al*., 2012; Peltola *et al*., 2012; Scherg *et al*., 2012; Chavakula *et al*., 2013; Joshi *et al*., 2018). A spike-detection algorithm is used to find each spike (with or without an aftercoming slow-wave) within the EEG (with different sensitivity and specificity based on the method used). These time points can be used to calculate the discharge-free interval, based on the assumption that a minimum interval between consecutive spikes (Inter-Spike Interval - ISI) is required to consider it as discharge-free. The first to use this approach to determine SWI in ESES were Larsson and coworkers (2009), documenting that ISI equal to 3 seconds yields reliable SWI in the majority of patients. Based on other studies with a similar approach, if this interval is as long as 10 seconds (Peltola *et al*., 2014), it will probably lead to overestimation and an enhanced ceiling effect.

Besides the SWI, the same spike-detection algorithms can be used to calculate the number of spikes per unit of time. Even if in a certain range a linear relation exists between the two measures (Larsson *et al*., 2009), there is a substantial and conceptual difference between computing the "time occupied by epileptiform activities" (or "spike and wave index" [SWI]) *vs* the "number of spikes/unit of time" (or "Spike Frequency" [SF]). The SF has the advantage of avoiding the ceiling effect intrinsic to SWI calculation, particularly with paroxysmal discharges >60/min (Larsson *et al*., 2009; Sánchez-Fernández et al., 2012). The use of SF might only preclude comparison with the "classical" percentage thresholds used in the past (Cantalupo *et al*., 2013), and studies aiming to compare SF and SWI - in terms of their ability to correlate with the clinical condition - are lacking. In other words, it is unclear whether the linear SF measures or the SWI better reflects the clinical features of ESES.

Overall, the methods employing the automatic counting of individual spikes may lead to some important features being overlooked, such as fundamental intermittent focal pseudo-slowing, corresponding to a sequence of prominent slow waves following low-amplitude spikes (Massa *et al*., 2001).

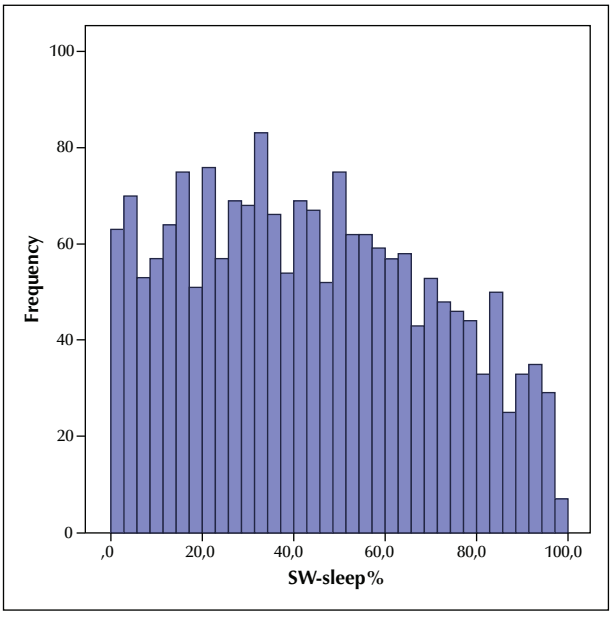

Figure 1. Frequency distribution of SWI - computed according to Larsson *et al*., 2009 with max ISI=3 - based on 1913 consecutive recordings. The x-axis corresponds to SWI during sleep and the y-axis to the number of recordings within a given SWI interval. (Data from PGL).

SWI variability

SWI varies within and between patients. Within patients there are dynamic changes during the night (see below), but there are also variations from night to night (see also Gardella *et al*., p. S22-S30). These variations are not well described and hence, not well understood. Reported between-patient variability ranges from 0 to 100%. *Figure 1* provides reported SWI values from 1913 recordings analyzed with a semi-automated method (Larsson *et al*., 2009). Cognitive impairment could be seen with SWI as low as 40. Probably, these low values are sufficient to produce negative influence in the brain. Anyway, in some cases, an underestimation of the SWI due to day-to-day variations cannot be excluded.

SWI also varies according to age of the subjects (*figure 2*). There is a tendency for a bell-shaped distribution with the highest values and the highest number of patients of around 10-11 years of age tapering off towards 18. This tapering is generally acknowledged to be due to puberty.

Caution should be taken interpreting this plot. At the left side, there is a time lag from symptoms until a full night EEG is recorded. There was no routine follow-up, and hence there are a set of reasons for recording in the middle of the age span. Also, the few recordings at the right side are probably influenced by the lack of new indications for a repeated recording.

Time course

When referring to SWI, usually a single value is given, usually the mean. This can be sufficient when a uniform distribution of discharges across the entire recording is present. This is in agreement with the term "continuous spike-and-wave during slow sleep" (CSWS), implying that the pattern of diffuse spike-and-waves should be continuously present. However, this is true only in a subset of children, while a more fragmented or skewed pattern is the most common (*figures 3, 4*). In these latter cases, a single mean SWI value for each recording does not illustrate accurately the differences in temporal distribution of EEG abnormalities throughout the recording. This is particularly important in evaluating studies in which SWI is computed only based on a relatively brief EEG recording. In fact, even if it is clear that the "original" SWI is computed considering the entire nocturnal sleep EEG, the principal difference in subsequent studies reflects the proportion of the EEG recording analyzed. *Figure 4* provides an overview of 40 consecutive, full night recordings showing a wide range of patterns. In

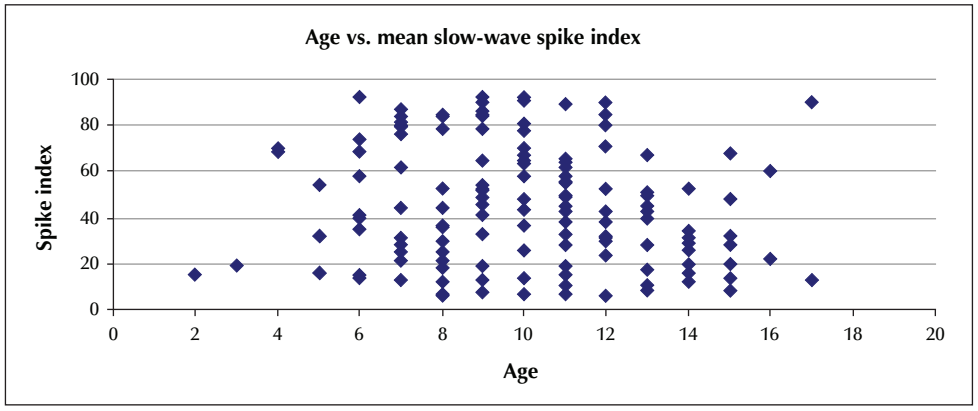

Figure 2. Relation between age and spike index (computed according to Larsson *et al*. [2009] with max ISI=3) based on 132 full night recordings. (Data from PGL).

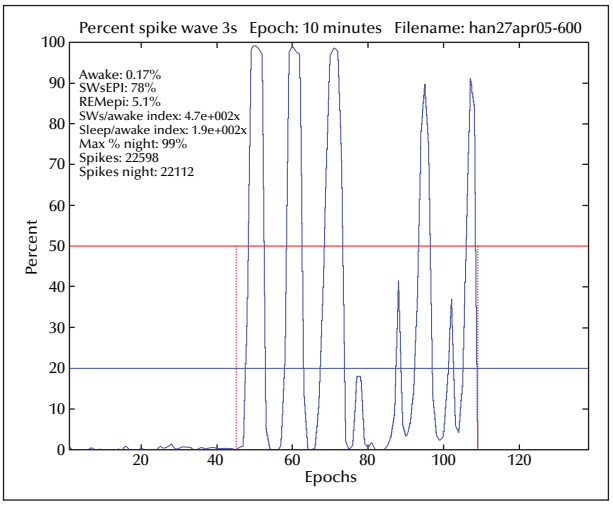

Figure 3. SI (computed according to Larsson *et al*. [2009] with max ISI=3) plotted in 10-minute epochs over 21 hours. The night sleep starts at about epoch 45. The dips in the plot reflect REM-sleep periods. SWI was reported as 78% for this patient. (Data from PGL).

almost all recordings, a rhythm with a cycle time (close to 90 minutes) is seen, corresponding to sleep cycles. Before the introduction of computer-aided techniques, the quantitative analysis of the entire overnight EEG was considered highly time-consuming and the majority of authors calculated the SWI based on a shorter EEG recording or a subsampling of the overnight EEG (see Scheltens-de Boer, 2009 for details). However, using a computer-aided semi-automated method like the one applied by Larsson *et al*. (2009) usually requires less than 30 minutes, mostly computer time, for the analysis of a full night recording.

During the era of analog EEG recording, the sleep EEG of a patient with ESES can be recognized just by looking at the very beginning of the EEG (*figure 5*). Although seemingly implausible or an over-simplification, this judgment is a statistical estimation based on scientific grounds: (1) the initial part represents a subsampling of the entire recording (one sample of about 10-20 ms for each 40-s folded page); (2) only high-amplitude spikes or steep transients can be observed in such

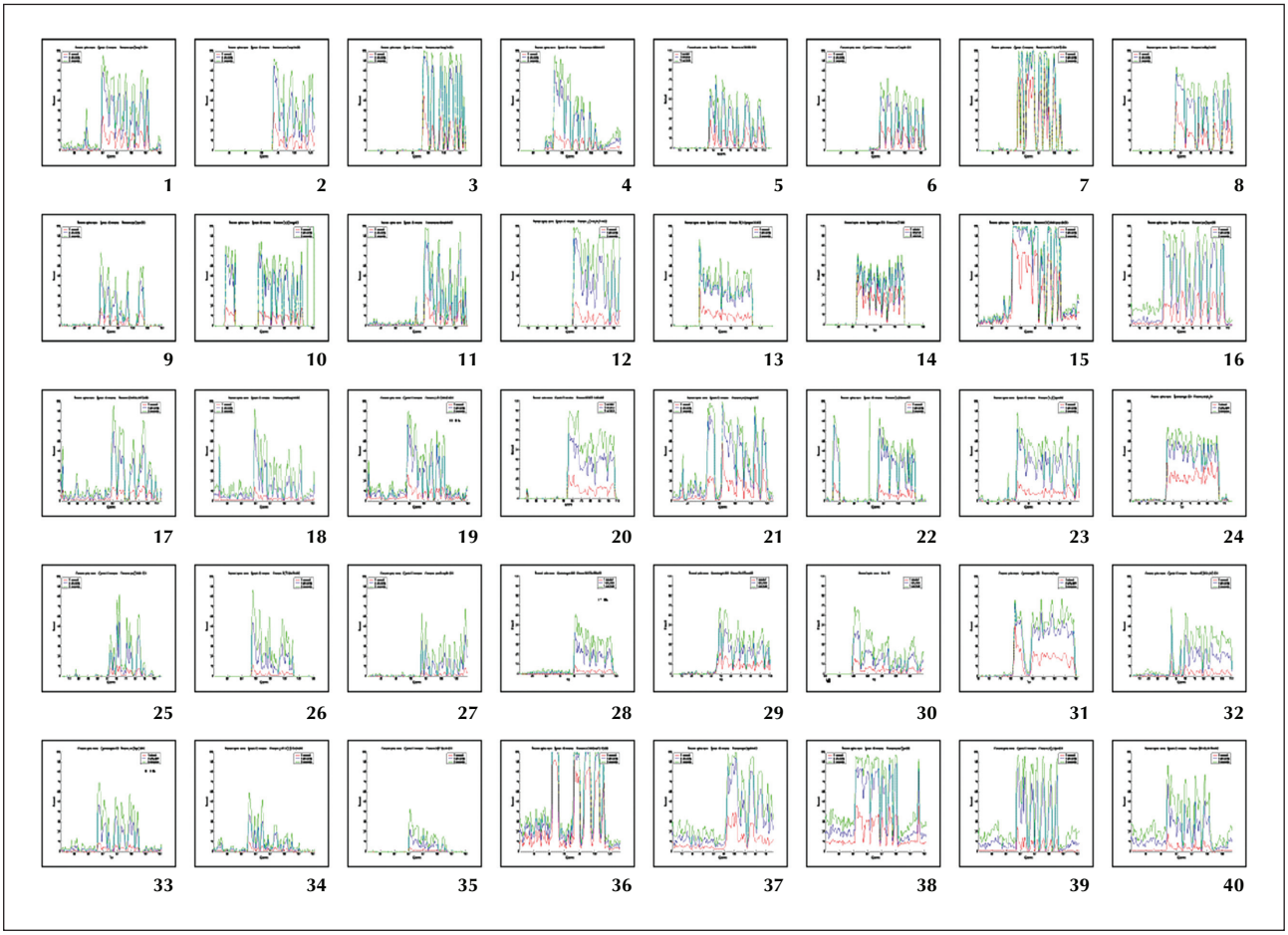

Figure 4. SWI from 40 full night recording. The x-axis gives time in epochs (number for each 10th 10 minutes epoch). Y-axis gives SWI computed accordingly to Larsson *et al*. (2009). In the plot red, blue and green represents max ISI of 1, 3 and 5 seconds respectively. (Data from PGL).

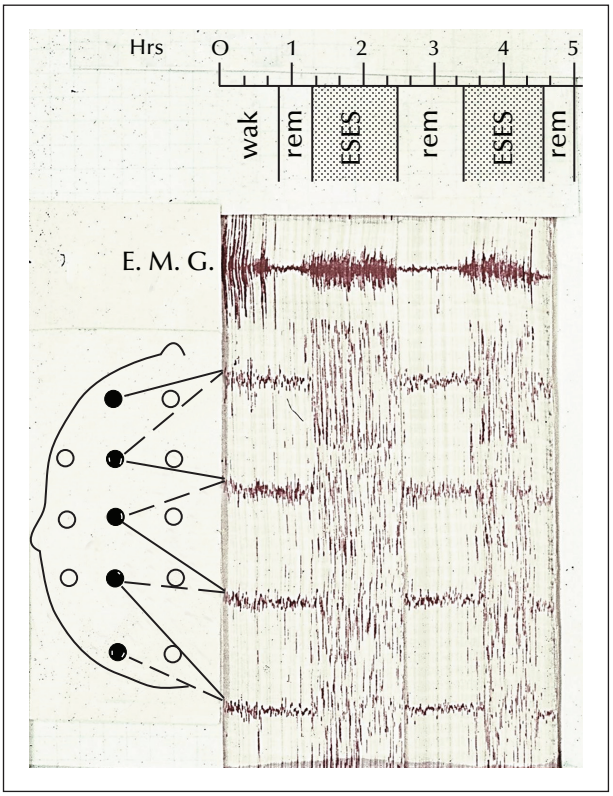

Figure 5. In this archival image, the very beginning of a paper EEG tome is mounted beside an EEG montage scheme (left) and an ad-hoc time scale (upper) and different sleep stages are identified based on the corresponding pattern visible on the paper trace. During NREM sleep, the trace reflects the occurrence of almost continuous high-amplitude spike-and-waves of ESES. (Courtesy of prof. C.A. Tassinari - personal iconography).

a limited time fraction; (3) the chance to view a high number of sequential high-amplitude spikes increases as the SI approximates to 100%, particularly when the time distribution is homogeneous. This was the case for the "classical" cases, however since the Venice Colloquium it was evident that these cases represented "the tip of the iceberg", in which the bulk is constituted by patients with similar clinical features but less EEG abnormalities (Beaumanoir, 1995). Particularly in those cases, a preferential occurrence of discharges in certain sleep stages can be observed. Nobili and coworkers (2001) demonstrated a higher number of discharges in the early stage of NREM sleep, but it should be noted that a prevalence in slow sleep can also be found (Cortinovis *et al*., 1995), revealing that different distributions are possible (*figure 6*).

Looking at the variability of SWI across the night and in different sleep stages (*figure 6*), it is clear that the choice of the subsample will affect the results in a way that varies from one patient to another. In particular, analyzing only the onset of sleep or a nap EEG will give

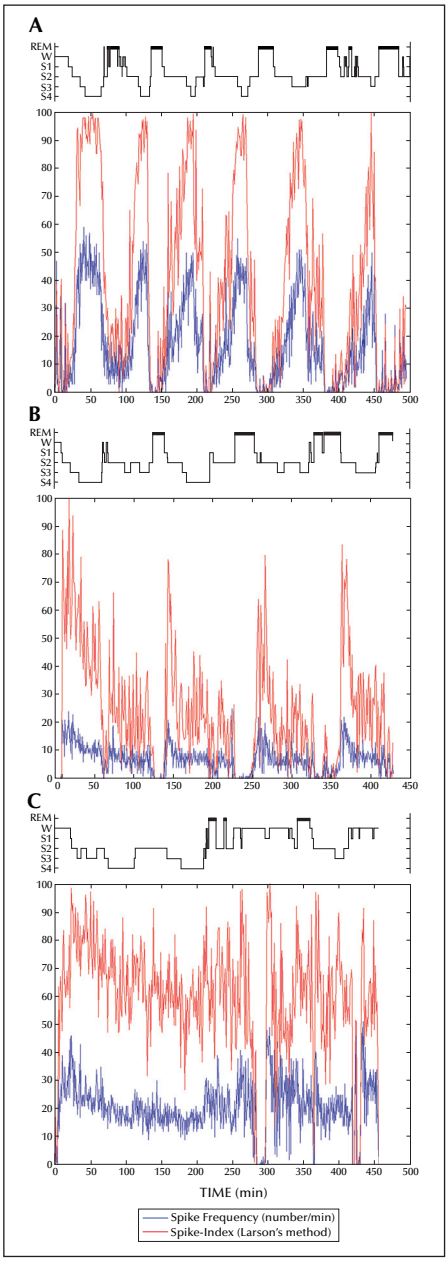

Figure 6. Overnight variation of the level of EDs in three patients with ESES. Different patterns can be observed: (A) the "slow-sleep pattern", with few discharges during wakefulness and REM sleep and increasing EDs from sleep stage I-II to sleep stage III-IV; (B) the "light-sleep pattern" with maximal EDs during sleep stage II, paralleling the sigma power as described by Nobili *et al*. (2001); (C) the "continuous pattern" with almost no difference between REM and NREM sleep. In each panel, the upper line represents a hypnogram based on visual scoring (accordingly to Rechtschaffen and Kales, 1968). In the lower part of each panel, the graph is generated by means of homemade MATLAB scripts (The Mathworks, Natick, MA) using EEG spike recognition trough BrainVision Analyzer 2.0 software (Brain Products, Munich, Germany). Blue lines represent the Spike frequency (number of spike/minute) and red lines the SI calculated using Larsson's method (Larsson *et al*., 2009) - using max ISI=3; one value/min. (Data from GC and PA).

a reliable result in patients with a homogeneous distribution, but will probably overestimate the SWI in patients with a high number of abnormalities in the first cycle and few discharges in the latter cycles. The same is true regarding the sleep stages. Sampling the first 30 minutes of NREM sleep of the first and last sleep cycles (Aeby *et al*., 2005) will mitigate the error due to the difference between sleep cycles but will not avoid the bias introduced by overestimating patients with high SWI in stages I-II (*figure 6B*) versus patients with the highest SWI in stage III-IV (*figure 6A*). This would also give erroneous results based on analysis of only one sleep-wake cycle (Saltik *et al*., 2005), a 15-min slow wave sleep (Lewine *et al*., 1999) or the first 5 minutes of NREM stage 2 during the first sleep cycle (Sánchez-Fernández et al., 2012) or 100 seconds of sleep (Weber *et al*., 2017). In fact, in patients with a large number of EDs (*i.e.* "classic" SWI >85%), there is good concordance between the traditional full-night method and "shortcut" methods used to analyse a small fraction of the night (Azcona *et al*., 2017), however, we do not know the reliability of those "shortcut" methods in patients with an intermediate amount or inhomogeneous distribution of EDs. Similarly, although a correlation has been demonstrated between nap and overnight SWI (Larsson *et al*., 2010), data from Dianalund Epilepsy Centre suggested that the two values can be discordant based on a non-negligible number of subjects (Gardella *et al*., 2016). To overcome the drawback of a unique SWI value, Scheltens-de Boer (2009) proposed to express the SWI as mean, range and most encountered value. Other possible adjunctive measures are the standard deviation of SWI, the percentage of time spent over a certain threshold, the SWI for each sleep stage, and - probably the most informative - Area Under the Curve (AUC) for both SWI and SF.

Quality

Topography

It is now recognized that spike-and-waves characterizing ESES are actually focal or multifocal discharges with a more or less prominent phenomenon of propagations and projection (ranging from focal ESES to the classic one - see Gardella *et al*., p. S22-S30). A time course of amplitude mapping has been used to demonstrate that the generalized aspect of spike-and-waves is the result of the extreme propagation of focal abnormalities (Farnarier *et al.,* 1995), through the mechanism of secondary bilateral synchrony (Kobayashi *et al*., 1994). Propagation of interictal EDs can be an indirect measure of the extent of the "epileptic network". However, up to now only few studies extracted some quantitative objective and reproducible measures for this feature. One of the most interesting approaches used Electric Source Imaging with a distributed model to calculate the amplitude of primary source and the number of propagation regions (Larsson *et al*., 2010). Another fascinating methodology has been proposed recently by Peltola and coworkers (2014) to extract the "spike-strength" (SS), an amplitude-derived value expressing both the spatial extent and the density of synchronously acting neuronal networks. The latter measure has the great advantage of being possibly plotted over time, allowing a combined use with the time-course of SWI and/or SF. A limitation of SS with respect to Larsson's propagation measure is the reduced information about propagation at distant sites. A promising method can be the use of Independent Component Analysis to better extract the primary and propagated sources. In fact, by analyzing the temporal evolution of the averaged EDs projected onto the Independent Component space (for details see Abreu *et al*., 2015), we can observe the different components of the spike-and-wave complex as virtually separated EDs with millisecond delays (*figure 7A*). It would then be possible to compute SWI, SF, and SS for each component, providing more detailed topographic information of the most involved region in ESES.

High Frequency Oscillations

High frequency oscillations (HFOs) ranging from 80 to 500 Hz have been identified as possible biomarkers for epileptogenic tissue based on intracerebral recordings, but recently HFOs were described also on scalp EEG of patients with symptomatic and idiopathic ESES, including LKS (Kobayashi *et al*., 2010; Gong *et al*., 2018). The possibility to record HFOs from scalp indicates the presence of hypersynchronous pathological high-frequency activity that involves a relatively large cortical area (Kobayashi *et al*., 2010). These HFOs can be observed, with the appropriate filtering, in strict association with spikes, however, not all the spikes are associated with HFOs, even in the same patient and in the same recording (*figure 7B, C*). Based on clinical data, HFOs associated with spikes have been proposed as a potential negative prognostic marker in Idiopathic Focal Epilepsies of Childhood, indicating a possible evolution to ESES/CSWS (Kobayashi *et al*., 2011). Further studies confirmed that HFOs in patients with ESES might reflect disease activity and treatment response (Qian *et al*., 2016; Gong *et al*., 2018). Thus, in our opinion, the presence (and abundance) of spike-related HFOs could be another quantitative variable to be integrated into the evaluation of ESES.

Sleep

Sleep structure

Apart from epileptiform activities, the overnight EEG recordings allow the extraction of a number of

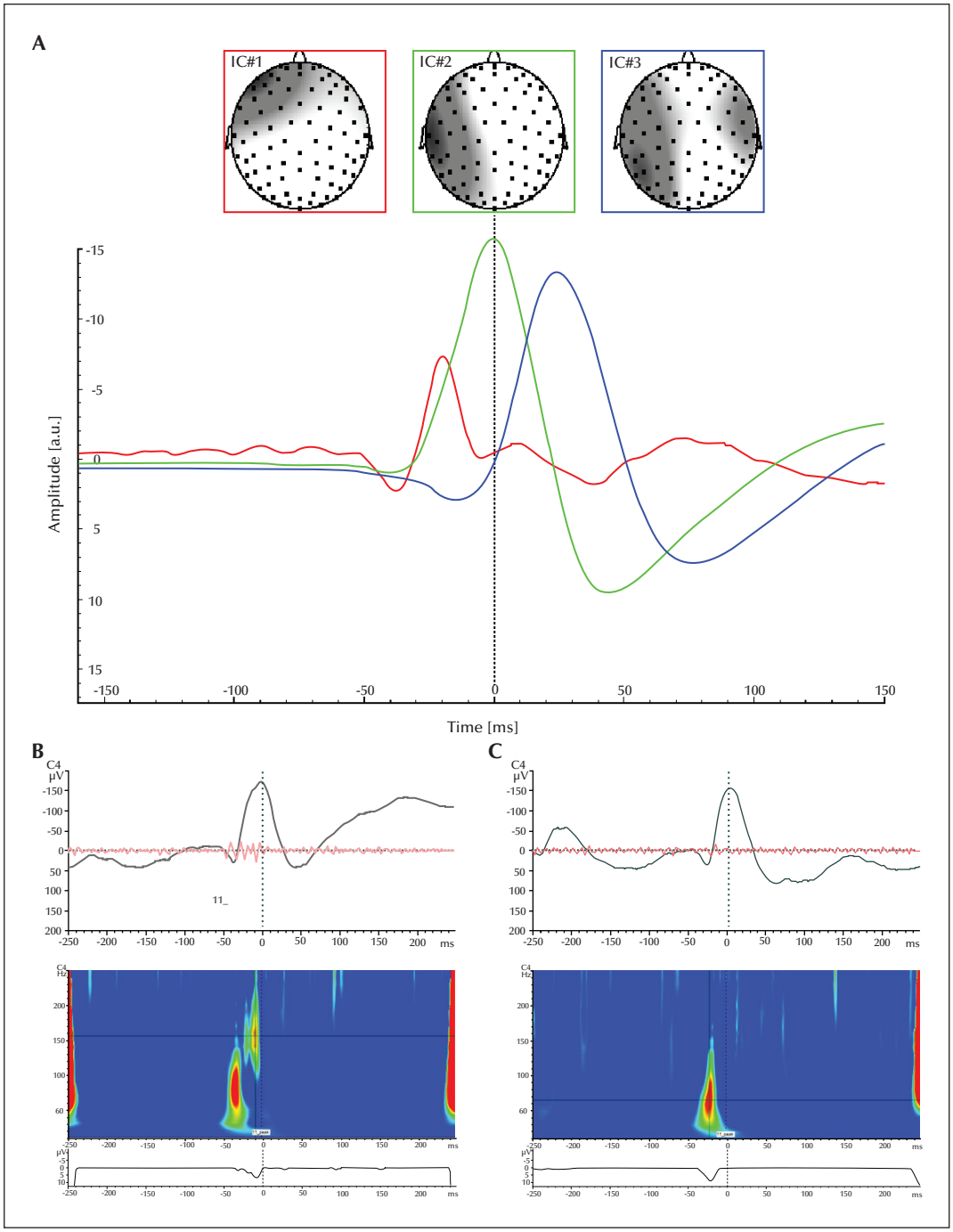

Figure 7. (A) Example of Independent Component (IC) Analysis applied to decompose raw 128-channels EEG, containing bilateral spikes, apparently synchronous on right and left centro-temporal regions. Amplitude time course of the average spike projected onto the IC space allows the recognition of an early component (IC#1 - red) with left frontal field, followed by the left centro-parietal component (IC#2 - green; peaking 30 ms after IC#1) and the bilateral component (IC#3 - blue; delayed by 30 ms from previous IC). Lower panels illustrate individual spikes from one subject - same topography and shape - with (B) or without (C) associated HFOs. In both panels a 500-ms time window centered on spike peak is represented. The upper part shows the unfiltered monopolar EEG (C4 channel) in black and the same EEG trace high-pass filtered above 100 Hz superimposed in red. The lower part represents the time-frequency wavelet analysis of the same unfiltered EEG trace, showing that in B the HFOs associated with the spike are visible as power increase at around 150 Hz. All transformations in this figure were performed using BrainVision Analyzer 2.0 software (Brain Products, Munich, Germany). (Data from GC and PA).

sleep-related features, potentially useful for the evaluation of patients affected by ESES. Since the first descriptions of the syndrome, attention was payed to the presence or absence of sleep graphoelements (namely sleep spindles) and a recognizable sleep macrostructure, with alternating NREM/REM stages and succeeding sleep cycles (Patry *et al*., 1971; Beaumanoir, 1995).

Sleep researchers have developed different, reliable quantitative measures based on visual inspection or computer-aided analysis of EEG signal (Ferri *et al*., 2005; Iber *et al*., 2007; Achermann, 2009). These analyses may indicate the quality of sleep macrostructure and provide markers of fragmentation/instability in sleep microstructure. However, these quantitative analyses have been rarely applied to ESES and related conditions (Nobili *et al*., 2001; Bruni *et al*., 2010; Gibbs *et al*., p. S54-S61).

Slow waves downscaling

One particular sleep-related EEG phenomenon deserves particular attention in the context of ESES (Tassinari *et al*., 2009). In fact, according to the synaptic homeostasis hypothesis (see also Rubboli *et al*., p. S62-S70), the beneficial effects of sleep on brain function and performance is due to the progressive renormalization (downscaling) of synaptic strength occurring during sleep. A higher synaptic strength at sleep onset is reflected by a higher synchronization of large cortical areas that in turn are responsible for the generation of EEG Slow Wave Activity (SWA). An overnight decrease of the slope of individual Slow Wave from the first to the last hour of sleep, which parallels the decline in SWA in the course of sleep, is an indirect testimonial of the occurrence of the physiologic sleep-related synaptic downscaling (Vyazovskiy *et al*., 2009). Using this indirect quantitative measure, an alteration of the physiologic overnight decrease of the Slow Wave slope has been demonstrated in ESES (Bölsterli *et al*., 2011). This lack of SWA downscaling was evident only on the affected hemisphere in focal cases, and interestingly the degree of the impairment of the overnight slope decrease correlated with spike frequency (Bölsterli *et al*., 2014). Furthermore, recent evidence demonstrates that these alterations of overnight dynamic SWA during active ESES are reversible when ESES resolves (Bölsterli *et al*., 2017).

Conclusions

In conclusion, the diagnosis of Encephalopathy cannot be done based on EEG without clinical information and does not rely only on EEG (*i.e*. ESES is not solely an EEG pattern; see Cantalupo *et al*., 2013). A semiquantitative visual inspection, yielding an approximated amount of epileptiform abnormalities in overnight sleep EEG can be sufficient for diagnosis when a full-blown clinical picture is present (appearance or worsening of neurological, cognitive and/or behavioral disturbances). However, the challenge for clinicians is to recognize also very selective or subtle deficit possibly due to impairment of local SWA homeostasis induced by Status Epilepticus during Sleep (Tassinari *et al*., 2015). Up to now, there has been a lack of accurate and adequately powered studies on correlation between amount of epileptiform activity and neurocognitive regression. Moreover, the amount of EDs is only one of the potential and somewhat independent features that can be quantified in EEG recordings of ESES (see also Gardella *et al*., p. S22-S30). Probably this is why currently there is no clear-cut lower boundary beyond which an EEG pattern is suggestive of evolution into ESES before the clinical diagnosis.

Possibly, an improved combination of clinical data and computer-aided EEG analysis will offer us the opportunity to recognize "dangerous" EEG features early in the course of the syndrome, thus to foresee (and possibly prevent) the evolution into ESES in patients at risk, but without an overt encephalopathy (Cantalupo *et al*., 2011; Tassinari *et al*., 2012). Thus, it is desirable that in future studies different EEG measures would be calculated in the same population (including ED amount, quality, and sleep-related features - such as macro-/micro-structure and SWA downscaling) in order to find out which (alone or in combination) is the best EEG correlate of clinical evolution. □

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None of the authors have any conflict of interest to declare.

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