Sleep slow-wave homeostasis and cognitive functioning in children with electrical status epilepticus in sleep

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Abstract: Study objectives: Encephalopathy with electrical status epilepticus in sleep (ESES) is characterized by non-rapid eye movement (non-REM)-sleep-induced epileptiform activity and acquired cognitive deficits. The synaptic homeostasis hypothesis describes the process of daytime synaptic potentiation balanced by synaptic downscaling in non-REM-sleep and is considered crucial to retain an efficient cortical network. We aimed to study the overnight decline of slow waves, an indirect marker of synaptic downscaling, in patients with ESES and explore whether altered downscaling relates to neurodevelopmental and behavioral problems. Methods: Retrospective study of patients with ESES with at least one whole-night electroencephalogram (EEG) and neuropsychological assessment (NPA) within 4 months. Slow waves in the first and last hour of non-REM-sleep were analyzed. Differences in slow-wave slope (SWS) and overnight slope course between the epileptic focus and non-focus electrodes and relations to neurodevelopment and behavior were analyzed. Results: A total of 29 patients with 44 EEG NPA combinations were included. Mean SWS decreased from 357 to 327 μV/s (-8%, $p < 0.001$) across the night and the overnight decrease was less pronounced in epileptic focus than in non-focus electrodes (-5.6% vs. -8.7%, $p = 0.003$). We found no relation between SWS and neurodevelopmental test results in cross-sectional and longitudinal analyses. Patients with behavioral problems showed less SWS decline than patients without and the difference was most striking in the epileptic focus (-0.9% vs. -8.8%, $p = 0.006$). Conclusions: Slow-wave homeostasis-a marker of synaptic homeostasis-is disturbed by epileptiform activity in ESES. Behavioral problems, but not neurodevelopmental test results, were related to severity of this disturbance.

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ORIGINAL ARTICLE

Sleep slow-wave homeostasis and cognitive functioning in children with electrical status epilepticus in sleep

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Abstract

Study Objectives: Encephalopathy with electrical status epilepticus in sleep (ESES) is characterized by non-rapid eye movement (non-REM)-sleep-induced epileptiform activity and acquired cognitive deficits. The synaptic homeostasis hypothesis describes the process of daytime synaptic potentiation balanced by synaptic downscaling in non-REM-sleep and is considered crucial to retain an efficient cortical network. We aimed to study the overnight decline of slow waves, an indirect marker of synaptic downscaling, in patients with ESES and explore whether altered downscaling relates to neurodevelopmental and behavioral problems.

Methods: Retrospective study of patients with ESES with at least one whole-night electroencephalogram (EEG) and neuropsychological assessment (NPA) within 4 months. Slow waves in the first and last hour of non-REM-sleep were analyzed. Differences in slow-wave slope (SWS) and overnight slope course between the epileptic focus and non-focus electrodes and relations to neurodevelopment and behavior were analyzed.

Results: A total of 29 patients with 44 EEG ~ NPA combinations were included. Mean SWS decreased from 357 to 327 μV/s (–8%, $p < 0.001$) across the night and the overnight decrease was less pronounced in epileptic focus than in non-focus electrodes (–5.6% vs. –8.7%, $p = 0.003$). We found no relation between SWS and neurodevelopmental test results in cross-sectional and longitudinal analyses. Patients with behavioral problems showed less SWS decline than patients without and the difference was most striking in the epileptic focus (–0.9% vs. –8.8%, $p = 0.006$).

Conclusions: Slow-wave homeostasis—a marker of synaptic homeostasis—is disturbed by epileptiform activity in ESES. Behavioral problems, but not neurodevelopmental test results, were related to severity of this disturbance.

Statement of Significance

The hallmark of encephalopathy with electrical status epilepticus in sleep (ESES) is near-continuous epileptiform activity in slow-wave sleep, accompanied by neuropsychological disturbances. Slow-wave sleep is of known importance for cognitive functioning. The synaptic homeostasis hypothesis proposes a framework for the role of slow-wave sleep in cognitive functioning. With this study, we analyzed whether slow waves are related to neurodevelopmental and behavioral functioning in children with ESES. We found that an impaired overnight decline in slow-wave slope is related to behavioral problems. Disrupted slow-wave homeostasis might link epileptiform activity in non-REM sleep to neuropsychological problems. Unraveling the mechanisms behind neuropsychological deficits, may lead to a better understanding of this epileptic encephalopathy and how disturbances of sleep physiology impact cognition.

Key words: synaptic downscaling; slow waves; ESES; CSWS; sleep; cognition

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Introduction

Epileptic encephalopathy with electrical status epilepticus in sleep (ESES) is a rare childhood epilepsy syndrome characterized by near-continuous epileptiform activity during non-rapid eye movement (REM)-sleep associated with neuropsychological deficits. Patients usually present with a global cognitive, language, or behavioral regression between 2 and 12 years of age. A majority of patients has (occasional) seizures, often with onset before the occurrence of developmental deficits [1–3]. ESES can be diagnosed in the context of structural (especially when involving the thalamus or perisylvian region) or genetic abnormalities (e.g. a *GRIN2A* mutation), but in about one-third of cases the etiology is unknown [4–8]. Seizures generally respond well to anti-epileptic drug (AED) treatment, while the treatment of cognitive symptoms is challenging. That ESES leads to cognitive decline is accepted, but how is incompletely understood. The spike-wave index (SWI), reflecting the proportion of non-REM-sleep affected by epileptiform discharges, is often used as an electroencephalogram (EEG) marker of ESES severity [9], with EEG abnormalities in typical ESES often defined as bilateral and with an SWI above 85%, while atypical cases with an SWI of 50%–85% are also considered part of the spectrum. The SWI is also used to evaluate of treatment efficacy. However, previous studies have shown that it does not always correlate to the severity of neurodevelopmental deficits and that in a substantial part of the patients, there is a discrepancy between SWI and cognitive response to treatment [10–13].

The crucial role of sleep—in particular slow-wave sleep—for cognitive functioning is well known and illustrated by the *synaptic homeostasis hypothesis* [14]. This hypothesis states that during wakefulness, through active thinking and exposure to novel experiences and sensory stimuli, people learn. On a cellular level, this is reflected by *synaptic potentiation:* an increase in number and strength of connections between neurons. During sleep, the brain is functionally detached from external stimuli and a recuperative process named *synaptic downscaling* is suggested to take place. The (partially selective) reduction in the number and strength of synaptic connections during sleep is essential because it restores net synaptic strength to an efficient baseline level. The overnight reduction in synaptic connections thus provides space and saves energy for another increase in synaptic connections during the following day [15–17]. The process of synaptic homeostasis is, based on both animal and human studies, thought to be reflected, and possibly induced, by slow-wave activity (SWA) [17–19]. Slow waves are delta (0.5–4 Hz) waves seen in the EEG during non-REM sleep, caused at the cellular level by near-synchronous oscillations of large groups of neurons [20, 21]. The slow-wave amplitude and slope are closely related to the firing synchronicity or efficacy of neuronal interaction and thus provide markers of synaptic strength [18, 19, 22, 23]. In healthy people, SWA decreases with sleep; while slow waves in non-REM sleep have a relatively high amplitude and slope at sleep onset, they are much lower toward the end of the night [19].

The hypothesis that slow waves are related to cognitive functioning has been explored by several studies. In healthy subjects, performance of a specific motor learning task just before sleep was associated with local increases in SWA in the region used in this task in the following period of sleep and a subsequent improvement in task performance after sleep [24]. In addition, boosting slow waves by auditory closed-loop stimulation, enhanced performance on an overnight memory task [25]. In a study in patients with epilepsy, seizures and interictal spikes increased SWA in the epileptic focus and reduced the homeostatic overnight slow-wave decline as well as visual learning abilities during wakefulness [26].

Several studies have suggested that the near-continuous epileptiform activity during non-REM sleep in patients with ESES interferes with learning and memory consolidation by disturbing physiological SWA [27–29]. Evidence for impaired slow-wave homeostasis was found in a study comparing the overnight course of slow-wave characteristics between nine ESES patients and nine healthy controls. While the controls showed a significant reduction in slow-wave amplitude and slope across the night, this was not seen in the ESES patients [30]. In a subsequent study, the slow-wave slope (SWS) change across the night was found to be correlated to the SWI [31]. Furthermore, the SWS at the end of the night was steeper in the electrodes at the epileptic focus as compared with the "non-focal" electrodes. After remission of ESES, the slow-wave homeostasis normalized and in an exploratory analysis, the cognitive sequelae seemed larger in children with the most impaired slow-wave homeostasis during their active ESES phase [32].

To our knowledge, the possible relation between slow-wave parameters and neuropsychological functioning has not been assessed in the population of ESES patients.

With the current study we explored: (1) whether there is a difference in overnight slow-wave course (slow-wave homeostasis) between the electrodes in the epileptic focus and the non-focus electrodes. Based on previous studies [31, 32], we hypothesized that the SWS decline in the epileptic focus would be less marked or absent as compared with the non-focus electrodes; (2) the relation between slow-wave homeostasis and neurodevelopment and behavior across patients with ESES. We hypothesized that patients with a (more pronounced) decline of SWS across the night have relatively preserved neuropsychological functioning and normal behavior as compared with those with severely impaired slow-wave homeostasis; and (3) the relation between a change in the slow-wave homeostasis and a change in neuropsychological functioning in an exploratory longitudinal comparison within ESES patients. We expected that an improvement in slow-wave decline across the night over time would be associated with an improvement in cognitive functioning and behavior.

Methods

Patient selection

We retrospectively included all patients with at least one whole night sleep EEG and a neuropsychological assessment (NPA) performed between January 2009 and July 2017 at the University Medical Center Utrecht, if they fulfilled the following criteria:

- at least one whole night sleep EEG showing an ESES pattern, defined as a SWI in sleep of at least 50% and at least 25% aggravation in comparison to wakefulness.
- acquired cognitive or behavioral deficits; either new deficits or alteration of the expected developmental trajectories.
- at least one EEG/NPA combination fulfilling the selection criteria below.

Combinations of EEG and NPA were included if:

- interval between EEG and NPA <4 months.
- age below 12 years at the time of these investigations.
- no more than one (clinical or electrophysiological) seizure during the whole night registration.

The study was approved by the medical ethics committee who judged that the Dutch Medical Research Involving Human Subjects Act did not apply.

Patient characteristics

Baseline patient characteristics (gender; age at ESES diagnosis; etiology, categorized as structural, genetic/syndromal, post-infectious or unknown; MRI findings; seizure frequency; and development before ESES diagnosis) were collected. For continuous variables that follow a normal distribution, means and standard deviations are reported, whereas for not normally distributed variables, median and range are reported.

Neuropsychological findings

For each NPA, the type of test and test results were collected. A type of test was chosen and adapted to the age and abilities of the child. Depending on the tests performed, we extracted total intelligence quotient (TIQ), developmental quotient (DQ), verbal IQ (VIQ), performance IQ (PIQ), processing speed, Beery test of visuomotor integration (VMI), digit span (memory), and Peabody Picture Vocabulary Test from the reports and test forms. For patients with severe cognitive impairment, in whom full intelligence testing was not possible, mental age and DQ were calculated. Development before ESES onset and behavioral problems (e.g. mood regulation problems and anxiety) were categorized as absent, mild, moderate, or severe in concordance with criteria used by Massa *et al.* [33]. Patients with a pre-existing developmental delay could only be included if they had a clear regression or arrest of development on top of this. This deviation from expected developmental trajectories was preferably shown by a repeat NPA (if they already had an NPA before) or otherwise based on parental history as taken by the pediatric neurologist and neuropsychologist. Behavior was assessed by the neuropsychologist using a structured parental interview, often supplemented by a behavioral questionnaire (the Child Behavior Checklist). Behavioral abnormalities were first categorized as absent, mild, moderate, or severe in concordance with criteria used by Massa *et al*. Considering the relatively small number of measurements, we subsequently categorized this as normal/abnormal (mild, moderate, or severe behavioral abnormalities were thus all recoded as abnormal). This allowed statistically comparing SWS course between two groups of reasonable size.

EEG acquisition and preprocessing

Scalp EEGs with 21 electrodes according to the international 10–20/10–10 system and electrooculograms were recorded. In most cases, chin electromyography was also available and in some cases measurements of respiratory effort. For each included EEG, a SWI was calculated in an epoch of 10 min (600 s), starting 5 min after alpha attenuation or, in absence of alpha rhythm, after sleep had commenced based on video and EEG features suggestive of sleep onset. The number of seconds containing epileptiform discharges at any of the electrodes was divided by the total number of seconds in the epoch (600) and multiplied by 100 to reflect the SWI as a percentage. In addition, the background pattern, presence or absence of physiological sleep phenomena and localization (focus) of epileptiform abnormalities were assessed. EEG epochs were scored as wake, non-REM, REM or movement/artifacts according to the *American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events*, version 2.3 (2016), if possible. If this was not possible because of a lack of recognizable sleep architecture, the modified criteria used in previous studies with ESES patients were used [30–32]. EEG channels for which the signal consisted of mainly artifacts (e.g. channels that were lost during the night), were removed from the analysis.

Calculation of slow-wave characteristics

We used data processing algorithms for the detection of sleep slow waves (0.5–2 Hz), spikes and artifacts, based on previously published methods [19, 30]. First, sleep slow waves of the first hour (FH) and last hour (LH) of artifact-free non-REM sleep were automatically detected in each electrode. Subsequently, spikes were detected. Then, slow waves that occurred within a time window of 0.5 s after a spike were considered part of a spike-wave complex and thus excluded from the analysis. The *amplitudes* of the included slow waves were assessed. The *absolute slopes* of the included slow waves were calculated as the amplitude of the negative peak divided by the time interval between the negative peak and the next zero-crossing, that is, the ascending slope. To account for variability in amplitude of individual slow waves (also influenced by age and technical aspects)—which inherently would influence the calculated slope—the slope was also calculated at a set amplitude of 75 μV, as in previous studies [30–32]. The amplitudes and absolute slope characteristics are described only, while the *normalized slope* is used as the primary slow-wave characteristic in the analyses and further referred to as *slope*. It was calculated for each electrode for the FH and LH of non-REM sleep (FH slope and LH slope). Relative slope change (FH slope subtracted from LH slope, divided by the FH slope) was calculated for each EEG electrode to reflect the overnight course of slope.

We predefined regions of interest for the analysis of slow-wave characteristics: analyses were performed for the mean slow-wave characteristics of *all electrodes*, for the *focus electrodes*, *non-focus electrodes,* and for *default-mode network (DMN) electrodes*. The focus was defined as up to four electrodes with epileptiform activity and if more than four electrodes showed epileptiform activity, the four with the highest amplitude spikes were selected. The remaining electrodes were designated as non-focus electrodes. Based on previous studies, the DMN was chosen as a region of interest for the relation of slow-wave characteristics with neuropsychological functioning [34, 35]. In accordance with a recent study, the DMN included the electrodes recording over the prefrontal cortex (Fp1 and Fp2 electrodes), precuneus (Pz electrode), and bilateral parietal areas (P7/P8 electrodes) [36].

Outcome definition

In the first analysis, comparing the SWS characteristics of the focus versus non-focus electrodes, the outcome was defined as the relative SWS change across the night (normalized at 75 μV). For the cross-sectional and longitudinal analyses of possible relations between SWS characteristics and neuropsychological functioning, we used the test results of the NPA (TIQ, VIQ, PIQ, PS, VMI, and digit span) as quantitative outcome measures. Behavior was included as a qualitative outcome measure (normal/abnormal) at the time of the EEG recording/NPA. We also analyzed whether treatment with conventional AEDs, benzodiazepines, or steroids at the time of the EEG/NPA was related to behavior, as this might be a confounding factor in assessing the relation between overnight SWS course and behavior. Lastly, for the longitudinal analysis, we also used SWI improvement (at least 25% decrease in SWI) and subjective improvement (improved/not improved) in daily functioning as reported by the parents and the treating physician, as qualitative outcomes.

Statistical analysis

For *all patients*, we described SWS course in the predefined regions and analyzed possible correlation of the relative SWS difference in these regions with neuropsychological outcome measures in their first EEG ~ NPA combination. Thus, for patients with multiple EEG ~ NPA combinations, only the first combination was used for this analysis. To assess differences in FH and LH SWS and to compare overnight slope course between focus and non-focus electrodes, paired samples *t*-tests were reported. For continuous outcomes, linear regression analysis was performed; for correlation of slow-wave characteristics and SWI (not normally distributed), Spearman's Rho was assessed and for dichotomous outcome (behavioral abnormalities), an independent samples *t*-test or Mann–Whitney U-test was used (depending on the distribution of the data). Fisher's exact test was used to assess whether there was an association between the presence or absence of treatment with AED, benzodiazepines and steroids, and behavioral abnormalities.

For the *patients with multiple EEG ~ NPA combinations,* we assessed whether improvement in SWI (decrease of at least 25%) and subjective improvement in daily functioning was associated with a change in SWS course at 75 μV. Subsequently, a linear mixed model was fitted, incorporating all repeated measurements in the patients with multiple EEG ~ NPA combinations. With this mixed model, we analyzed possible correlation of overnight SWS course at 75 μV with TIQ, VIQ, PIQ, processing speed, Beery test of visual-motor integration, and digit span. The neuropsychological outcome measures were defined as the dependent variable, a random intercept per patient was used, and the relative mean SWS difference for the prespecified regions was included as a fixed variable.

For statistically significant findings from linear regression analyses/linear mixed model analyses, we calculated Cohen's f^2 as an effect size measure as defined by using the formula Cohen's $f^2 = R^2/(1 - R^2)$. A Cohen's $f^2 \geq 0.02$ is considered a small effect, ≥ 0.15 a medium effect and ≥ 0.35 a large effect.

The analyses were performed with MATLAB version 2018a and SPSS version 25. *p*-Values <0.05 were considered significant. GraphPad Prism 8 was used for graphical illustration.

Results

Patient characteristics and EEG/neuropsychological findings

We included 29 patients. In total, 44 EEG ~ NPA combinations were performed; 12 patients had 2 and 3 patients had 3 EEG ~ NPA combinations that fulfilled the selection criteria. Patient characteristics are shown in Table 1. The mean(±*SD*) time between the EEG and NPA was 1.1 ± 1.2 months for the first, 0.5 ± 1.3 months for the second, and 0.0 ± 0.0 months for the third EEG ~ NPA combination, respectively. The median SWI was 90% for the first EEG, 91% for the second EEG, and 70% for the third EEG. Concurrent treatment with conventional AEDs and corticosteroids was much more prevalent at the time of the second and third EEG as compared with the time of first EEG. EEG and neuropsychological findings are shown in Table 2.

Slow-wave characteristics, overnight course, and regional differences

The mean (±*SD*) *amplitude* of slow waves across all electrodes was 67 ± 19 μV in the FH and decreased to 41 ± 14 μV in the LH of non-REM sleep (–38%). The mean *absolute slope* of slow waves decreased from 322 ± 94 in the FH to 187 ± 67 μV/s in the LH (–41%). The mean *normalized slope* (at 75 μV, referred to as SWS in the following analyses) over all electrodes decreased from 357 ± 19 to 327 ± 22 μV/s (–8%, $p < 0.001$). The SWS in the LH of non-REM sleep was significantly lower than during the FH of non-REM sleep for all electrode regions ($p < 0.001$ for all electrodes, focus electrodes, non-focus electrodes as well as DMN electrodes). The SWS was higher in the focus than in the non-focus electrodes, both in the

Table 1. Patient characteristics (*n* = 29)

Male (%)	16 (55%)
Age at ESES diagnosis: mean (±*SD*)	75 ± 26 months/ 6.3 ± 2.2 years
Presumed (main) etiology	
Structural	10 (35%)
Genetic/syndromal	4 (14%)
Post-infectious	1 (3%)
Unknown	14 (48%)
MRI abnormalities (incl. non-epileptogenic)	19 (66%)
Lateralization of MRI abnormalities	
Left	3 (10%)
Right	3 (10%)
Bilateral	13 (45%)
None	10 (35%)
Frequency of seizures at time of diagnosis	
Daily	4 (14%)
Monthly	10 (35%)
Yearly	5 (17%)
Sporadic	8 (28%)
None	2 (7%)
Development before ESES onset	
Normal	10 (35%)
Mild delay	11 (38%)
Moderate delay	4 (14%)
Severe delay	4 (14%)

FH and the LH (both $p < 0.001$). The relative change in SWS from FH to LH of non-REM sleep was different between the focus and the non-focus electrodes (–5.6% for focus electrodes and –8.7% for non-focus electrodes; $p = 0.003$). The overnight SWS course is shown in Figure 1. A detailed overview of overnight slow-wave course for all regions of interest is provided in Table S1.

Relation between SWS and SWI

The mean SWS at 75 μV across all electrodes in the LH of non-REM sleep was significantly correlated to SWI (rho 0.37; $p = 0.049$), while SWS in the FH and SWS change were not significantly correlated to SWI (rho 0.26; $p = 0.17$ and rho 0.12; $p = 0.53$). The SWS of the LH in focus electrodes showed a non-significant trend toward positive correlation with SWI (rho 0.36; $p = 0.054$), while the other slow-wave characteristics for focus and non-focus electrodes were not significantly correlated to SWI (Table S2).

Cross-sectional relation between overnight slope change, baseline patient characteristics, EEG findings, and neuropsychological functioning at first combined investigation.

Among the clinical variables, the severity of developmental abnormalities before ESES onset was strongly associated with TIQ and VIQ (β=–15.7, $p = 0.001$, Cohen's f^2=0.71 and β=–12.7, $p = 0.01$, Cohen's f^2=0.47) over the course of the disease (Table 3). The percentage of time occupied by epileptiform discharges was also correlated to neuropsychological functioning: the higher the SWI, the lower TIQ and PIQ (β=–0.7, $p = 0.04$, Cohen's f^2=0.24 and β=–0.8, $p = 0.01$, Cohen's f^2=0.44). The mean relative slope change (at 75 μV) across all electrodes, focus, non-focus, and DMN electrodes was not related to the neuropsychological outcomes in this analysis (Table 3).

Cross-sectional relation between slow-wave characteristics, SWI, neuropsychological test results, and treatment with behavior at first investigation.

Patients with behavioral problems showed a smaller decrease in SWS (at 75 μV) than those without, across all electrodes (–5.2% vs. –10.2%; $p = 0.02$), focus electrodes (–0.9% vs. –8.8%; $p = 0.006$, Figure 2), non-focus electrodes (–6.1% vs. –10.6%, $p = 0.04$), and DMN electrodes (–5.9% vs. –11.3%; $p = 0.02$) (Table 4). The SWI

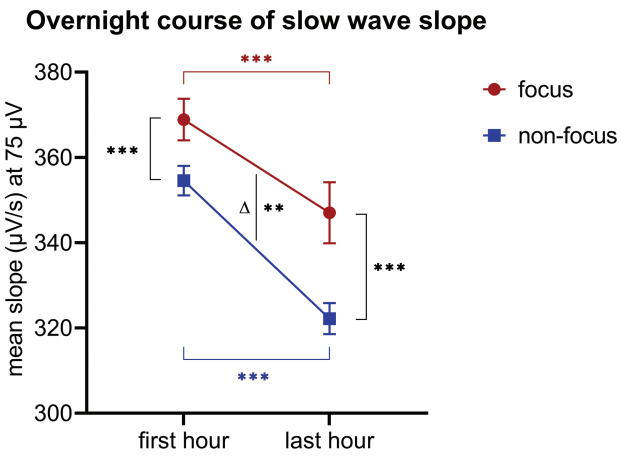

Figure 1. Overnight course of SWS. Differences were tested with dependent *t*-tests; $^{**}p < 0.01$, $^{***}p < 0.001$.

Table 2. EEG and NPA findings ($n = 44$)

Combination of EEG ~ NPA	First ($n = 29$)	Second ($n = 12$)	Third ($n = 3$)
Time between EEG and NPA (months): mean ± *SD*	1.1 ± 1.2	0.5 ± 1.3	0.0 ± 0.0
EEG findings whole night EEG			
Age at EEG recording (years): mean ± *SD*	6.7 ± 2.2	7.5 ± 1.7	8.9 ± 1.4
Time between diagnosis and EEG (months): mean ± *SD*	6 ± 11	12 ± 12	20 ± 0.6
SWI (%): median (range)	90 (62–100)	91 (0–100)	70 (46–95)
Normal background pattern (%)	22 (76)	10 (83)	3 (100)
Sleep phenomena present (%)	24 (83)	11 (92)	3 (100)
Distribution of epileptiform activity in sleep			
Generalized	9 (31%)	4 (33%)	1 (33%)
Multifocal bilateral	8 (28%)	2 (17%)	1 (33%)
Multifocal unilateral	5 (17%)	0 (0%)	0 (0%)
Focal unilateral	7 (24%)	4 (33%)	1 (33%)
No epileptiform abnormalities	0 (0%)	2 (17%)	0 (0%)
Concurrent AED treatment	19 (66%)	10 (83%)	2 (67%)
Concurrent benzodiazepine treatment	5 (17%)	6 (50%)	1 (33%)
Concurrent corticosteroid treatment	5 (17%)	7 (58%)	0 (0%)
Neuropsychological findings			
Total IQ: mean ± *SD*	78 ± 17 ($n = 22$)	84 ± 17 ($n = 9$)	84 ± 5 ($n = 3$)
Verbal IQ: mean ± *SD*	84 ± 15 ($n = 18$)	87 ± 15 ($n = 8$)	88 ± 8 ($n = 3$)
Performance IQ: mean ± *SD*	84 ± 18 ($n = 19$)	84 ± 19 ($n = 9$)	83 ± 5 ($n = 3$)
DQ (if no IQ available): mean ± *SD*	43 ± 37 ($n = 4$)	29 ± 10 ($n = 2$)	
Processing speed: mean ± *SD*	75 ± 15 ($n = 13$)	80 ± 21 ($n = 9$)	90 ± 6 ($n = 2$)
Beery VMI: mean ± *SD*	89 ± 11 ($n = 19$)	85 ± 10 ($n = 9$)	87 ± 6 ($n = 3$)
Memory: Digit Span (WISC III): mean ± *SD*	7 ± 3 ($n = 12$)	8 ± 4 ($n = 8$)	8 ± 2 ($n = 3$)
Peabody Picture Vocabulary Test: mean ± *SD*	105 ± 18 ($n = 10$)	95 ± 22 ($n = 7$)	91 ± 6 ($n = 3$)
Presence of behavioral problems (%)	12 (41)	6 (50)	0 (0)

EEG, electroencephalogram; NPA, neuropsychological assessment; SWI, spike-wave index; IQ, intelligence quotient; DQ, developmental quotient; Beery VMI, Beery developmental test of visual-motor integration; WISC III, Wechsler Intelligence Scale for Children-III

Table 3. Univariate Linear regression analysis of clinical, EEG and NPA findings of first WN EEG ~ NPA combination

	TIQ β (*P*-value)	VIQ β (*P*-value)	PIQ β (*P*-value)	PS β (*P*-value)	VMI β (*P*-value)	DS β (*P*-value)
MRI abnormalities	1.8 (0.81)	−9.0 (0.22)	1.4 (0.87)	7.3 (0.41)	−7.9 (0.11)	**−3.8 (0.04), f^2 = 0.55**
Seizure frequency	−0.5 (0.88)	−0.1 (0.97)	−1.0 (0.77)	1.8 (0.63)	−1.4 (0.51)	1.0 (0.22)
Presence/severity of developmental deficit before ESES	**−15.7 (0.001), f^2 = 0.71**	**−12.7 (0.01), f^2 = 0.47**	−11.1 (0.07)	−11.6 (0.18)	−5.5 (0.19)	−1.4 (0.39)
SWI	**−0.7 (0.04), f^2 = 0.24**	−0.5 (0.12)	**−0.8 (0.01), f^2 = 0.44**	−0.34 (0.39)	−0.37 (0.09)	0.06 (0.57)
Sleep phenomena	7.0 (0.51)	5.1 (0.60)	18.7 (0.09)	10.4 (0.40)	10.1 (0.14)	1.18 (0.75)
All electrodes relative slope change (at 75 µV)	−14.1 (0.84)	51.4 (0.81)	−21.5 (0.76)	0.3 (1.00)	52.6 (0.21)	−0.02 (0.99)
Focus relative slope change (at 75 µV)	10.5 (0.83)	30.4 (0.51)	−29.2 (0.55)	−33.8 (0.50)	33.8 (0.25)	−0.01 (0.99)
Non-focus relative slope change (at 75 µV)	−19.3 (0.78)	55.0 (0.42)	−3.4 (0.96)	29.5 (0.71)	55.1 (0.20)	0.4 (0.98)
DMN relative slope change (at 75 µV)	−19.1 (0.80)	48.9 (0.52)	−18.7 (0.81)	0.9 (0.99)	45.1 (0.33)	2.0 (0.91)

NPA, neuropsychological assessment; TIQ, total intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performal intelligence quotient; PS, processing speed; VMI, Beery developmental test of visual-motor integration; DS, digit span; SWI, spike-wave index; DMN, default-mode network; f^2, Cohen's f^2. Bold numbers represent significant findings.

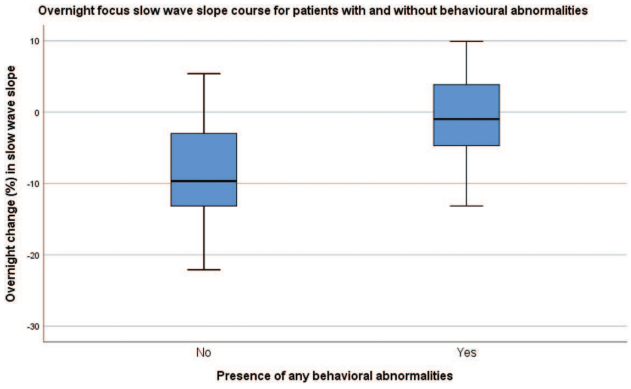

Figure 2. Overnight focus SWS course for patients with and without behavioral abnormalities.

was 84% for patients with and 90% for patients without behavioral abnormalities and this difference was not significant (p = 0.20). Neuropsychological test results did not differ significantly between the patients with and those without behavioral problems (Table S3). The presence or absence of treatment with AED, benzodiazepines, or steroids at the time of the investigation was not associated with the presence or absence of behavioral problems (Table S4).

Longitudinal changes of SWS characteristics versus changes in SWI and subjective daily functioning

Of the 12 patients with at least two EEG ~ NPA combinations, 3 showed SWI improvement and 9 showed subjective improvement in daily functioning between the first and the second time point. The difference in the overnight SWS course (at 75 µV) between their first and second EEG ~ NPA combination did not differ significantly for patients with SWI improvement versus those without SWI improvement; neither was subjective cognitive improvement associated with difference in overnight SWS course (at 75 µV; Table 5).

The mixed model analysis of patients with multiple EEG ~ NPA combinations showed no significant correlation of overnight SWS course (at 75 µV) with TIQ, VIQ, PIQ, PS, VMI, or digit span (Table S5).

Discussion

With this study of patients with epileptic encephalopathy with ESES, we found that: (1) the overnight SWS decline is less pronounced in electrodes representing the epileptic focus as compared with the non-focus electrodes, hence slow-wave homeostasis is more altered in the epileptic focus; (2) in a cross-sectional comparison between patients, neurodevelopment, as measured with a NPA, does not relate to overnight SWS course across patients. Patients with behavioral problems have a more impaired SWS decline as compared with patients without reported or diagnosed behavioral problems, with the largest difference seen in the focus electrodes. (3) Longitudinal changes in SWS course across the night were not associated with longitudinal changes in SWI and neuropsychological test results, or subjective improvement in daily functioning.

The difference in overnight SWS course between focus electrodes and non-focus electrodes that we found is in line with previous observations. In a study of 14 patients with ESES, the SWS was not significantly different between focus and non-focus electrodes in the FH of sleep, while in the LH the non-focus electrodes showed a smaller SWS. The authors found that the relative decline of SWS was just not significantly different between the focus and non-focus electrodes [31]. Our study further assessed these parameters in a larger cohort of 29 patients and found that both FH and LH SWS is higher in focus electrodes compared with non-focus electrodes and that the SWS decline across the focus electrodes is less prominent as compared with the non-focus electrodes. These findings provide additional evidence that slow-wave downscaling is locally impaired by epileptiform activity in children with epileptic encephalopathy

Table 4. Slow-wave characteristics for patients with and without behavioral problems (first EEG ~NPA combination)

	Behavioral problems (n = 17)	No behavioral problems (n = 12)	P-value
All electrodes relative slope change (at 75 μV)	−5.2%	−10.2%	0.02
Focus relative slope change (at 75 μV)	−0.9%	−8.8%	0.006
Non-focus relative slope change (at 75 μV)	−6.1%	−10.6%	0.04
DMN relative slope change (at 75 μV)	−5.9%	−11.3%	0.02

EEG, electroencephalogram; NPA, neuropsychological assessment; DMN, default-mode network.

Table 5. Slow-wave characteristics for patients with and without improvement in SWI and daily functioning between first and second EEG ~ NPA combination*

	SWI improvement			Improvement daily functioning		
	Yes (n = 3)†	No (n = 9)	P-value	Yes (n = 9)	No (n = 3)	P-value
All electrodes relative slope change (at 75 μV) ~difference	−1.2%	+0.4%	0.22	+2.2%	+0.7%	0.70
Focus relative slope change (at 75 μV) ~difference	+0.7%	+1.9%	0.79	+1.8%	+1.0%	0.86
Non-focus relative slope change (at 75 μV) ~difference	−2.6%	+3.5%	0.11	+2.0%	+0.7%	0.67
DMN relative slope change (at 75 μV) ~difference	−1.4%	+3.5%	0.29	+2.2%	+2.5%	0.95

*Mean ± *SD* interval between first and second EEG ~ NPA combination: 7 ± 3 (range: 5–17) months.
†Three patients with >25% decrease in SWI had an SWI decrease from 75% to 8%, from 68% to 0%, and from 84% to 0%, respectively.
NPA, neuropsychological assessment; SWI, spike-wave index; DMN, default-mode network.

with ESES and implicate that local synaptic homeostasis might be affected by spike waves.

In contrast to our expectations, we did not find a relation between overnight course of SWS and neuropsychological test results. Previous studies have linked slow-wave sleep to learning by showing that SWA is increased locally at sleep onset after a visual learning task [24] and that a reduced homeostatic decrease in SWS is correlated with poorer daytime visuomotor learning [26]. Another study found that the normal overnight improvement in performance on a memory task was absent in patients with predominant epileptic activity during sleep and at least in one task related to spike-wave density and suggested that this may reflect impaired sleep-related memory consolidation [37]. That we did not find a relation between overnight SWS course and neuropsychological test results in our cross-sectional (between patients) analysis may be attributed to several aspects:

1. the context of an enormous variability in patient characteristics. The presence of structural lesions, pre-existing developmental deficits, the location of epileptiform abnormalities, and treatment may explain most of the variability in test performance between the children with epileptic encephalopathy with ESES [11, 38–40]. This possible explanation is supported by the observation that in our linear regression analysis, developmental abnormalities before ESES are the strongest determinant of TIQ and VIQ over the course of ESES. Previous studies showed that age at ESES diagnosis and ESES duration are important determinants of cognitive functioning; earlier onset and longer ESES duration are associated with worse cognitive outcome [39, 40]. Also, previous studies have shown that SWA shows an age-dependent evolution [41, 42]. The variability of these factors may have complicated the assessment of the relation of overnight slow-wave course and neuropsychological test results.
2. We suggest that the neuropsychological tests we used were relatively insensitive to fluctuations occurring in the context of ESES. A substantial part of the included patients had EEGs showing focal ESES (24% of the first EEGs, 33% of the second and third EEGs). Previous publications have suggested that standard NPA may be relatively insensitive to specific cognitive deficits in children with focal ESES [43, 44]. Therefore, the conventional neuropsychological outcome measures that we analyzed, may have been insensitive to deficits in the context of these patients. The insensitivity of NPA to fluctuations in the context of ESES, was also suggested by a previous study. In this study, we found that subjective improvement in cognitive functioning after treatment was not significantly related to TIQ improvement and that SWI decrease was associated with subjective cognitive improvement, while it was not related to TIQ change [13]. In our current study, we also included subjective improvement in cognitive functioning, as assessed by the pediatric neurologist during the outpatient clinic visits. Their assessment was based on information provided by the parents/guardians of the child. Often the information of the teachers was reported by the parents during the visits. Although this is a subjective outcome measure, we thought it could be of interest because subjective improvement can take any form and may therefore be more sensitive to changes with regard to the specific deficits in the individual child, in comparison to the NPA. Also, the subjective improvement may be clinically highly relevant. However, in our current analysis of overnight SWS course versus subjective improvement in functioning in the subgroup of patients with multiple EEG ~ NPA combinations, we did not find a relation either. This analysis, however, was based on a relatively small number of patients (n = 12).

Most of the abovementioned factors of influence on neurodevelopment should be of less influence in the mixed linear model analysis (thus correcting for the correlation between measurements from the same patient). However, also in this analysis, we did not find a relation between SWS course and neuropsychological test results and subjective cognitive functioning. We speculate that the relatively small sample size of

patients with multiple EEG ~ NPA combinations (n = 12) may have been insufficient to detect a relation or that change in treatment (e.g. benzodiazepine and corticosteroids) between the time points blurred a possible relation. Also, within the group with combined longitudinal EEG – NPA assessment, most patients still had a high SWI during the second and third follow-up (9 of 12 patients and 2 of 3 patients, respectively). This suggests that these patients were still in the active phase of ESES and that overt neuropsychological disturbances could appear later.

Interestingly, we did find a relation between behavioral problems and SWS course across the night. For all combinations of electrodes (average of all electrodes, focus, non-focus, and DMN electrodes), the SWS showed a smaller decline for patients with behavioral problems compared with patients without reported or diagnosed behavioral problems and this difference was most pronounced for the focus electrodes. We hypothesize that behavior of patients with ESES, as suggested by a previous study [45], fluctuates easily and therefore is more closely related to the slow-wave homeostasis at a certain moment in time. A strong contribution of treatment to these fluctuations could be suggested, however we did not find any association of AED, benzodiazepine, or corticosteroid treatment with the presence or absence of behavioral problems. To our knowledge, this concept has not been investigated in previous studies.

Our results need to be interpreted carefully. Firstly, the heterogeneity of our study population, including patients with newly diagnosed as well as longstanding ESES, with and without structural etiology and with and without treatment, increases variability and hence confounding factors limit the generalizability of our findings. However, the heterogeneity of our cohort is representative for the broad spectrum of patients with ESES [1, 11]. Secondly, although we have used different approaches that all did not yield a clear relation between slow-wave characteristics and neuropsychological test results, our study was not designed (and underpowered) to prove that there is no relation. Furthermore, the design of our study, relating the overnight course of SWS to neuropsychological test results of one test session might have been insufficient to analyze the effect of ESES on synaptic homeostasis. Testing overnight *performance improvement* (i.e. comparison of test results before and after a night's sleep) may be a better method to answer this research question.

In conclusion, we add evidence that, in children with ESES, sleep slow-wave homeostasis is altered by epileptic activity as it is most affected in the epileptic focus. The presence of behavioral problems is associated with reduced slow-wave downscaling, while we did not find a relation between overnight SWS decline and neuropsychological test results. Based on the previously reported relationship between slow waves and network synchrony and indirectly synaptic strength, we might conclude that synaptic homeostasis is disturbed by epileptiform activity in children with ESES, at most in the epileptic focus; future studies with overnight EEG recordings and overnight neuropsychological testing with appropriate tests (i.e. testing before a night's sleep and repeat testing afterwards), may elucidate whether this disturbance of synaptic homeostasis explains the occurrence of cognitive deficits.

Supplementary material

Supplementary material is available at *SLEEP* online.

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