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ORIGINAL ARTICLE

Sleep homeostasis, seizures, and cognition in children with focal epilepsy

Maria H. Eriksson[1,2] | **Torsten Baldeweg**[1,2] | **Ronit Pressler**[3] | **Stewart G. Boyd**[3] | **Reto Huber**[4,5,6,7] | **J. Helen Cross**[1,8,9] | **Bigna K. Bölsterli**[4,10,†] | **Samantha Y. S. Chan**[1,11,†]

[1]Developmental Neurosciences Research & Teaching Department, UCL Great Ormond Street Institute of Child Health, London, UK

[2]Neuropsychology, Great Ormond Street Hospital NHS Trust, London, UK

[3]Neurophysiology, Great Ormond Street Hospital NHS Trust, London, UK

[4]Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland

[5]Child Development Center, University Children's Hospital Zurich, Zurich, Switzerland

[6]Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zurich, Zurich, Switzerland

[7]Pediatric Sleep Disorders Center, University Children's Hospital Zurich, Zurich, Switzerland

[8]Neurology, Great Ormond Street Hospital NHS Trust, London, UK

[9]Young Epilepsy, Lingfield, UK

[10]Department of Pediatric Neurology, University Children's Hospital Zurich, Zurich, Switzerland

[11]Department of Paediatric Neurology, St George's Hospital, London, UK

Correspondence
Maria H Eriksson, Developmental Neurosciences Research & Teaching Department, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London, UK, WC1N 1EH.
Email: m.eriksson.16@ucl.ac.uk

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Aim: To investigate the link between sleep disruption and cognitive impairment in childhood epilepsy by studying the effect of epilepsy on sleep homeostasis, as reflected in slow-wave activity (SWA).

Method: We examined SWA from overnight EEG-polysomnography in 19 children with focal epilepsy (mean [SD] age 11 years 6 months [3 years], range 6 years 6 months–15 years 6 months; 6 females, 13 males) and 18 age- and sex-matched typically developing controls, correlating this with contemporaneous memory consolidation task scores, full-scale IQ, seizures, and focal interictal discharges.

Results: Children with epilepsy did not differ significantly from controls in overnight SWA decline ($p = 0.12$) or gain in memory performance with sleep ($p = 0.27$). SWA was lower in patients compared to controls in the first hour of non-rapid eye movement sleep ($p = 0.021$), although not in those who remained seizure-free ($p = 0.26$). Full-scale IQ did not correlate with measures of SWA in patients or controls. There was no significant difference in SWA measures between focal and non-focal electrodes.

Interpretation: Overnight SWA decline is conserved in children with focal epilepsy and may underpin the preservation of sleep-related memory consolidation in this patient group. Reduced early-night SWA may reflect impaired or immature sleep homeostasis in those with a higher seizure burden.

Abbreviations: IED, interictal epileptiform discharge; NREM, non-rapid eye movement; REM, rapid eye movement; SWA, slow-wave activity.

[†]Joint first authors.

Children with epilepsy display high rates of impairment across neuropsychological domains.[1] The origins of these impairments are disputed and a range of factors have been implicated, including underlying aetiology, ongoing seizures, and use of antiseizure medication.[2,3] More recently, it has been hypothesized that the disruption of recovery during sleep by epileptic activity could play a key mechanistic role.[4–6]

Electroencephalography (EEG) in deep sleep is dominated by slow waves of high amplitude, generated by widespread cortical neurons alternating in synchrony between depolarized and hyperpolarized states.[7] Slow-wave activity (SWA) (power in the 0.6–4.4 Hz band) correlates closely with sleep need, building up with time spent awake and dissipating with sleep,[7] thereby providing a quantitative measure of sleep homeostasis.

It has been proposed that the decrease in global SWA across the night reflects the process of synaptic renormalization,[8] which restores cellular functioning and promotes memory consolidation—the synaptic homeostasis hypothesis.[9] A causal role for the slow waves themselves has also been proposed—the active system consolidation hypothesis—in which cortical slow oscillations drive and synchronize the replay of neuronal sequences associated with learning during wakefulness, leading to the reactivation and redistribution of temporary, hippocampus-dependent memories to longer-term cortical representation.[10]

Over the course of infancy and childhood, there is evolution of both spectral power and topography in the sleep EEG.[11] This is particularly marked in the SWA band, in which we see a 10-fold decrease in power and an occipital-to-frontal shift in the location of maximal power between preschool age and late adolescence.[11] This occurs in parallel with the acquisition of visual acuity and executive functioning at those respective ages.[11]

Children with epilepsy, particularly those with comorbid intellectual difficulties, have very high rates of parent-reported sleep disturbance.[12,13] However, apart from retrospective studies in cohorts with continuous spike waves in slow-wave sleep,[14–16] the influence of epileptic activity on sleep homeostasis in the developing brain and its relationship to cognitive measures have not been investigated. Data from adult patients with focal epilepsy suggest that in the mature brain, whole-night SWA may be upregulated both globally and locally in response to the burden of epileptic activity.[17]

We have previously investigated sleep-related memory consolidation in children with focal lesional epilepsies,[18] demonstrating that memory consolidation benefits from sleep in this group to the same degree as in typically developing controls.

In this study, we extended those findings by examining sleep homeostasis, as reflected in SWA dynamics, in the same patient cohort. We explored the relationship between SWA, seizures, and cognition, and the influence of focal epileptic activity on the topographical distribution of SWA. We hypothesized that this group of patients would show age-appropriate overnight SWA decline, corresponding to the observed benefit from sleep-related memory consolidation.

What this paper adds

- The decline in slow-wave activity (SWA) across the night, reflecting global synaptic downscaling, was preserved in children with focal lesional epilepsies.
- Sleep benefited memory consolidation in this group of patients, as in typically developing children.
- Reduced early-night SWA was associated with increased likelihood of a subsequent seizure.

METHOD

Participants

Participants were 19 children with drug-resistant focal epilepsy of structural (or presumed structural) aetiology and 18 age- and sex-matched typically developing controls. Patients were recruited prospectively from the EEG video telemetry unit at Great Ormond Street Hospital for Children, as described previously.[18] Inclusion criteria were attendance at a mainstream school (as a proxy for sufficient cognitive ability to complete the experimental tasks) and planned hospital admission lasting a minimum of 4 days. Patients were instructed to not sleep during the day and this was confirmed by reviewing nursing observations. Those with a previous diagnosis of primary sleep disorders were excluded. Control participants were recruited by advertisements directed at staff working at the UK charity Young Epilepsy. Controls attended the EEG department of Young Epilepsy to be set up for a single-night ambulatory sleep study. Compared to the previously reported cohort,[18] six participants (three patients and three controls) were excluded due to EEG data being unavailable for SWA analysis.

The study was approved by the National Research Ethics Service. Written informed consent was obtained from a parent of each participant.

EEG acquisition and processing

EEG-polysomnography acquisition, visual sleep scoring, and the visual quantification and marking of seizures and interictal discharges have been described in previous work.[18] EEG data were recorded with the Xltek Trex (Natus Medical Incorporated, Pleasanton, CA, USA) system, using eight EEG electrodes (F3, F4, C3, C4, O1, O2, A1, A2) positioned

according to the International 10–20 system in controls, and 27 EEG electrodes (Fz, Cz, Pz, Fp1, Fp2, F3, F4, F7, F8, F9, F10, C3, C4, C5, C6, T5, T6, T7, T8, T9, T10, P3, P4, P9, P10, O1, O2) positioned according to the International 10–10 system in patients, with the reference electrode at CPz. EEG signal sampling occurred at 512 Hz or 1024 Hz in patients and 256 Hz or 512 Hz in controls.

EEG data were exported to MATLAB (MathWorks, Natick, MA, USA) for bandpass filtering between 0.3 Hz and 40 Hz and downsampling to 128 Hz. We performed spectral analysis using a fast Fourier transform. Power spectra of consecutive 30-second epochs (Hanning window, averages of six 5-second epochs) of non-rapid eye movement (NREM) sleep were computed, resulting in a frequency resolution of 0.2 Hz. The lowest two frequency bins (0.2 Hz and 0.4 Hz) were not used for further analysis due to their sensitivity to low frequency artefacts.[19] SWA was defined as power in the 0.6 Hz to 4.4 Hz range. For each channel, epochs containing artefacts were rejected by visual inspection and semi-automatically, whenever power in the SWA and 20 Hz to 30 Hz bands exceeded a threshold based on a moving average determined over fifteen 30-second epochs.[20]

All analyses were performed on average-referenced EEG.[17,21] To describe overnight changes in SWA, we performed analyses on artefact-free epochs from the first hour versus the last hour of NREM sleep.[22] SWA decline was defined as the difference between SWA in epochs from the first hour and epochs from the last hour. Normalized SWA decline was defined as the SWA decline divided by SWA in the first hour of NREM sleep. For group-level comparisons between patients and controls, mean SWA was calculated using the eight-electrode average-referenced montage common to both groups. To examine the influence of interictal epileptiform discharges (IEDs) during sleep on the topographical distribution of SWA, we compared SWA at channels containing IEDs (focal) with those in which IEDs were not seen (non-focal). Analyses were performed on both absolute and relative (z-scored) SWA values.

Neuropsychological testing

Full-scale IQ

Control participants underwent IQ assessment using the Wechsler Abbreviated Scale of Intelligence, Second Edition. IQ scores on the Wechsler Intelligence Scale for Children, Fourth Edition were available for 16 out of 19 patients from recent neuropsychological testing.

Memory consolidation

Participants completed memory tasks designed to assess the contribution of sleep to verbal and visuospatial memory consolidation.[18] Briefly, the verbal task required children to learn a list of semantically related word pairs, with memory tested using a cued recall procedure. The visuospatial task was a two-dimensional object location task using paired

TABLE 1 Participant demographics and patient clinical characteristics

Demographics	Patients (n = 19)	Controls (n = 18)	p
Age, mean (SD), years:months	11:6 (3:0)	10:4 (2:10)	0.229
Sex (females, males)	6, 13	10, 8	0.141
Full-scale IQ, mean (SD)	87.5 (11.6)	114.1 (12.7)	<0.001
Maternal education, mean (SD), years:months	13:11 (2:0)	16:7 (2:8)	0.005
CSHQ, mean (SD)	48.9 (8.0)	37.7 (3.7)	<0.001
Epilepsy characteristics			
Age at epilepsy onset, mean (SD), years:months	5:1 (4:2)		
Duration of epilepsy, mean (SD), years:months	6:5 (2:11)		
Aetiology, n (%)			
MRI negative	5 (26)		
Malformation of cortical development	7 (37)		
Mesial temporal sclerosis	2 (11)		
Low-grade tumour	3 (16)		
Other	2 (11)		
Seizure side, n (%)			
Right	8 (42)		
Left	5 (26)		
Bilateral	3 (16)		
Undetermined	3 (16)		
Seizure focus, n (%)			
Frontal	3 (16)		
Temporal	5 (26)		
Fronto-temporal	5 (26)		
Parietal	3 (16)		
Undetermined	3 (16)		
Seizure frequency, n (%)			
Daily	3 (16)		
Weekly	9 (47)		
Monthly	3 (16)		
<1 per month	4 (21)		
Number of antiseizure medications, n (%)			
None	1 (5)		
One	9 (47)		
Two	7 (37)		
Three	2 (11)		

Abbreviations: CSHQ, Children's Sleep Habits Questionnaire; MRI, magnetic resonance imaging. Significance was determined by an independent samples t-test and χ^2 test, as appropriate.

TABLE 2 Patient information

Patient ID	Age, years:months	Sex	Age at epilepsy onset, years:months	Duration of epilepsy, years:months	Aetiology	Seizure side	Seizure focus	Seizure frequency	Seizure(s) during admission	Antiseizure medications
1	6:7	Female	2:0	4:7	Focal cortical dysplasia	Right	Fronto-temporal	Monthly	No	Carbamazepine
2	7:0	Male	0:11	6:1	Focal cortical dysplasia[a]	Left	Frontal	<1 per month	No	Levetiracetam, sodium valproate
3	7:10	Male	2:0	5:10	Angioma	Undetermined	Undetermined	<1 per month	No	Clobazam, levetiracetam, topiramate
4	8:2	Male	1:6	6:8	Malformation of cortical development	Bilateral	Fronto-temporal	<1 per month	No	Carbamazepine, sodium valproate
5	8:10	Female	1:6	7:4	Hippocampal sclerosis[a]	Left	Temporal	Weekly	Yes	Levetiracetam, sodium valproate
6	9:2	Female	2:0	7:2	MRI negative	Right	Undetermined	Weekly	Yes	Clobazam
7	9:10	Female	4:10	5:0	Focal cortical dysplasia[a]	Left	Parietal	Weekly	No	Levetiracetam
8	10:5	Male	3:0	7:5	MRI negative	Undetermined	Frontal	Daily	Yes	Carbamazepine
9	11:1	Male	2:0	9:1	MRI negative	Undetermined	Fronto-temporal	Weekly	Yes	Carbamazepine, topiramate
10	11:4	Male	8:0	3:4	MRI negative	Right	Undetermined	<1 per month	No	Levetiracetam, sodium valproate
11	12:7	Male	2:0	10:7	Ganglioglioma[a]	Left	Temporal	Weekly	Yes	Levetiracetam
12	12:7	Male	4:0	8:7	Focal cortical dysplasia[a]	Right	Fronto-temporal	Daily	Yes	Lamotrigine
13	12:10	Male	8:0	4:10	MRI negative	Left	Frontal	Daily	Yes	Lacosamide
14	14:7	Female	13:0	1:7	DNET[a]	Right	Parietal	Weekly	Yes	Lamotrigine, levetiracetam
15	14:10	Female	12:0	2:10	Meningoencephalitis	Right	Parietal	Weekly	No	No medications
16	14:10	Male	8:0	6:10	Focal cortical dysplasia[a]	Bilateral	Fronto-temporal	Weekly	Yes	Levetiracetam, oxcarbazepine, sodium valproate
17	14:11	Male	2:6	12:5	Hippocampal sclerosis[a]	Bilateral	Temporal	Weekly	Yes	Oxcarbazepine
18	15:4	Male	13:6	1:10	Glioneuronal tumour[a]	Right	Temporal	Monthly	No	Lamotrigine, sodium valproate
19	15:6	Male	6:0	9:6	Focal cortical dysplasia	Right	Temporal	Monthly	No	Lamotrigine

Abbreviation: DNET, dysembryoplastic neuroepithelial tumour.

[a]Denotes patients who had surgery and therefore also histopathology.

pictures. Recall was tested after similar length delays either overnight or in the daytime using parallel versions of the tasks, allowing for within-participant comparison to determine the contribution of sleep to memory consolidation (sleep benefit) in each domain. The order of conditions was balanced across participants.

Parent-rated sleep disturbance

Parents were asked to rate the frequency of various sleep behaviours as they would occur in a typical week using the Children's Sleep Habits Questionnaire.[23]

Statistical analysis

Group differences in demographic data, full-scale IQ, Children's Sleep Habits Questionnaire scores, and sleep parameters were examined using independent samples *t*-tests for continuous variables and χ^2 tests for categorical variables.

Two-way mixed analyses of variance with group (patient or control) were used to investigate (1) the overnight change in SWA and (2) the effect of sleep on memory retention. Normality checks and Levene's test were carried out and assumptions were met. We report Bonferroni-adjusted *p*-values. Independent samples *t*-tests were used to compare memory retention and SWA decline in the patient and control groups. Paired *t*-tests were used to compare SWA z-scores between the first and last hours of NREM sleep in the focal and non-focal channels, respectively. Relationships between SWA, age, clinical characteristics, memory performance, and full-scale IQ were examined with the Pearson's *r* correlation coefficient.

Statistical analyses were performed in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).[24] Figures were produced using MATLAB and the R package ggplot2.[25]

RESULTS

Participant demographics and clinical characteristics are summarized in Tables 1 and 2

Sleep parameters

Sleep parameters for patients and controls are reported in Table 3. Compared to controls, patients had a shorter total sleep time ($p = 0.002$), a lower percentage of time spent in rapid eye movement (REM) sleep ($p < 0.001$), and a higher percentage of time spent in N2 sleep ($p = 0.03$). Visual inspection of the EEG record revealed normal morphology of sleep features, including slow waves and spindles, in both groups.

TABLE 3 Sleep parameters

	Patients ($n = 19$)	Controls ($n = 18$)	*t*	*p*
Sleep parameters				
Total sleep time, mean (SD), minutes	477 (104)	567 (52)	3.37	0.002
Sleep efficiency, mean (SD), %	91.0 (5.9)	93.1 (7.1)	0.96	0.350
REM latency, mean (SD), minutes	176 (85.4)	145 (62.4)	−1.27	0.210
Time in NREM sleep, mean (SD), minutes	353 (76.0)	385 (34.8)	1.64	0.100
REM sleep, mean (SD), %	18.1 (7.1)	25.7 (4.9)	3.77	<0.001
N1 sleep, mean (SD), %	7.2 (3.3)	6.4 (3.2)	0.83	0.400
N2 sleep, mean (SD), %	39.2 (11.8)	31.6 (8.7)	−2.26	0.030
N3 sleep, mean (SD), %	35.3 (13.5)	36.4 (9.8)	0.26	0.800

Abbreviations: NREM, non-rapid eye movement; REM, rapid eye movement.

Memory performance

Verbal task

Verbal memory retention was greater in the sleep condition ($F[1,35] = 15.6$, $p < 0.001$), with no interaction of condition by group ($F[1,35] = 0.019$, $p = 0.89$), and no main effect of group ($F[1,35] = 1.25$, $p = 0.27$). In post-hoc pairwise comparisons, the main effect of condition was significant in both controls ($p = 0.02$) and patients ($p = 0.01$), with both groups recalling more word pairs in the sleep condition.

Visuospatial task

Two patients were unable to complete the visuospatial task due to difficulties with sustaining attention. There was no difference in memory retention between the sleep and wake conditions ($F[1,33] = 2.96$, $p = 0.1$), no interaction of condition by group ($F[1,33] = 1.13$, $p = 0.72$), and no significant main effect of group ($F[1,33] = 0.13$, $p = 0.3$).

Overnight changes in SWA

SWA was lower in the last hour of NREM sleep ($F[1,35] = 88.1$, $p < 0.001$), with an interaction between time and group ($F[1,35] = 6.95$, $p < 0.001$). The simple main effect of group was significant in the first ($p = 0.04$) but not the last ($p = 1$) hour of NREM sleep. Post-hoc comparisons showed that SWA was significantly higher in controls than patients in the first hour of NREM sleep ($p = 0.021$) but similar in the two groups in the last hour ($p = 0.76$; Figure 1a). There was no difference in

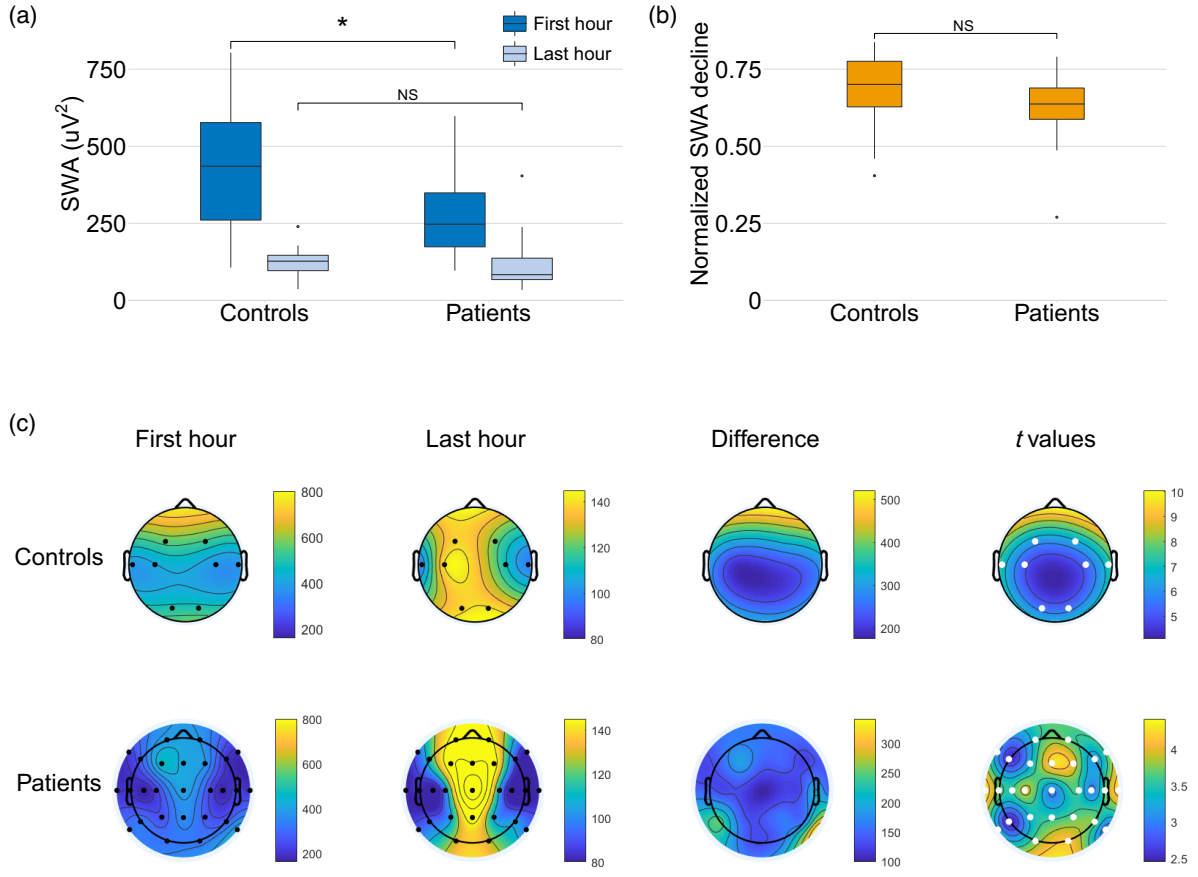

FIGURE 1 Slow-wave activity (SWA) across the night. (a) Mean SWA across electrodes in the eight-electrode montage. Controls showed higher SWA early in the night ($p = 0.021$) but SWA was similar between the two groups by the last hour ($p = 0.76$). (b) Normalized SWA decline (calculated as the difference between early- and late-night SWA divided by early-night SWA) was not different between patients and controls ($p = 0.12$). (c) Group-level SWA topographies in controls (top) and patients (bottom) during the first and last hour of non-rapid eye movement sleep. Across the night, there was a significant fall in SWA at all electrodes and an anteroposterior shift in the SWA peak in both groups. NS, not significant. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

normalized SWA decline between patients and controls ($p = 0.12$; Figure 1b).

Topography of SWA at the group level

SWA in the first hour of NREM sleep was highest in the frontal region in both controls and patients (Figure 1c). By the last hour of NREM sleep, the peak had shifted to the central region. A significant decline in SWA across the night was seen at all electrodes (Figure 1c).

Relationship between SWA and age

In the control group, we found a decline in SWA with age. This was true of both the first ($r[16] = -0.68$, $p = 0.002$; Figure 2) and last ($r[16] = -0.61$, $p = 0.007$) hours of NREM sleep. The magnitude of the decline in SWA across the night also showed an inverse correlation with age ($r[16] = -0.62$, $p = 0.02$). We found no significant correlation between SWA and age in the patient group (Figure 2).

Effect of epileptic activity on SWA

Seizures and SWA

Patients who had seizures during their hospital admission showed less SWA in the first hour of NREM sleep than controls ($p = 0.004$), while those who did not have seizures during their admission showed similar SWA to controls ($p = 0.26$; Figure 3). All seizures were recorded after the night for which SWA was analysed. Patients who experienced seizures earlier in their admission were discharged home before the study night and thus were not included in this study.

Post-hoc analyses revealed no differences in time spent in slow-wave sleep, number of antiseizure medications, or duration of epilepsy between patients with and without seizures during the study period. Those who had seizures during admission usually experienced more frequent seizures (modal category: weekly seizures) than those in whom seizures were not recorded during admission (modal category: monthly seizures).

We found no correlation between epilepsy duration and absolute SWA decline ($p = 0.97$) or normalized SWA decline ($p = 0.48$).

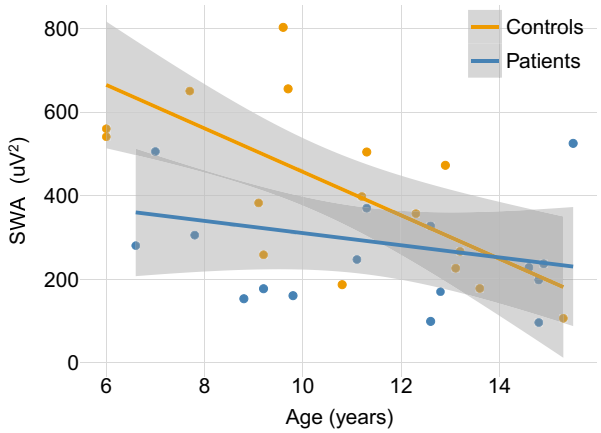

FIGURE 2 Decline in slow-wave activity (SWA) with age. Early-night SWA decreased with age in typically developing controls ($r[16] = -0.68$, $p = 0.002$) but this correlation did not reach significance in patients ($r[17] = -0.26$, $p = 0.29$)

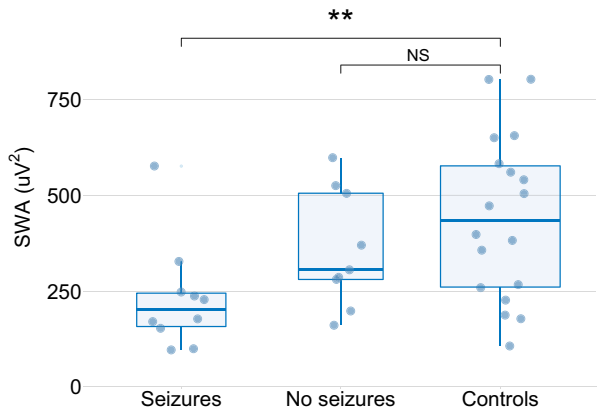

FIGURE 3 Slow-wave activity (SWA) and seizure propensity. Patients who had seizures during their hospital admission showed less SWA in the first hour of non-rapid eye movement sleep than controls ($p = 0.004$), while those who did not have seizures during their admission showed SWA not different from controls ($p = 0.26$). Box widths are proportional to group size and the jitter plots show data for individual participants. NS, not significant. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Interictal discharges and SWA topography

There was no difference in SWA between focal and non-focal channels in the first hour of NREM sleep (mean = 368, SD = 287 μV^2 vs mean = 287, SD = 154 μV^2, $t[17] = 1.86$, $p = 0.08$) or the last hour of NREM sleep (mean = 144, SD = 140 μV^2 vs mean = 112, SD = 90 μV^2, $t[17] = 2.1$, $p = 0.054$), although there was a tendency towards higher SWA in focal electrodes at both time points (Figure 4). Normalized SWA decline was similar in focal and non-focal channels (mean = −0.56, SD = 0.31 vs mean = −0.57, SD = 0.29, $t[17] = 1.22$, $p = 0.24$). Using z-scores to control for interindividual differences in global SWA yielded similar results. Across the night, there was no change in z-scores between the first and last hours of NREM sleep at focal or non-focal channels (all $p > 0.3$).

Relationship between SWA and cognition

We found no correlation between SWA and sleep benefit in either memory task across the total sample or within each group (all $p > 0.1$). There was also no correlation of full-scale IQ with SWA characteristics (all $p > 0.1$).

DISCUSSION

We demonstrated that children with focal lesional epilepsies show similar SWA decline across the night to their typically developing peers and similar gains in memory consolidation with sleep. Reduced early-night SWA was associated with seizures on subsequent nights. In this cohort of children with epilepsy with few IEDs, SWA topography was not significantly influenced by focal IEDs in sleep.

SWA build-up and decline

SWA at the start of the night reflects sleep need[7] and has been shown to build up with prolonged wakefulness, both in adults[26] and school-age children.[27] While SWA in the control group was consistent with published data from typically developing children,[22,27,28] the patient group showed lower early-night SWA across all scalp regions.

Similar findings have been reported in children with attention-deficit/hyperactivity disorder[29] and autism spectrum disorder,[30] who showed a reduction in early-night SWA compared to controls. This suggests that the ability to generate slow waves may be impaired or immature in these neurodevelopmental cohorts. Of note, attention-deficit/hyperactivity disorder and autism spectrum disorder both occur more commonly in children with epilepsy than in the general population.[31,32]

We found that children with focal epilepsy showed similar normalized SWA decline to controls over the course of the night, reaching similar SWA levels by the last hour of NREM sleep. This suggests that synaptic downscaling is successfully achieved,[10] which may facilitate both memory consolidation[9] and the normalization of cortical excitability[33] in these patients.

Effect of epilepsy on SWA

We demonstrated a striking decrease in early-night SWA with age across our cohort of typically developing controls, replicating the findings of Kurth et al.[34] and Feinberg et al.[35] However, this relationship was attenuated in patients.

Those in whom we recorded no seizures during their admission showed similar early-night SWA to controls, while those experiencing seizures during admission had lower early-night SWA. All recorded seizures occurred after the analysed overnight EEG. Having seizures during a short hospital stay may indicate a higher seizure burden.

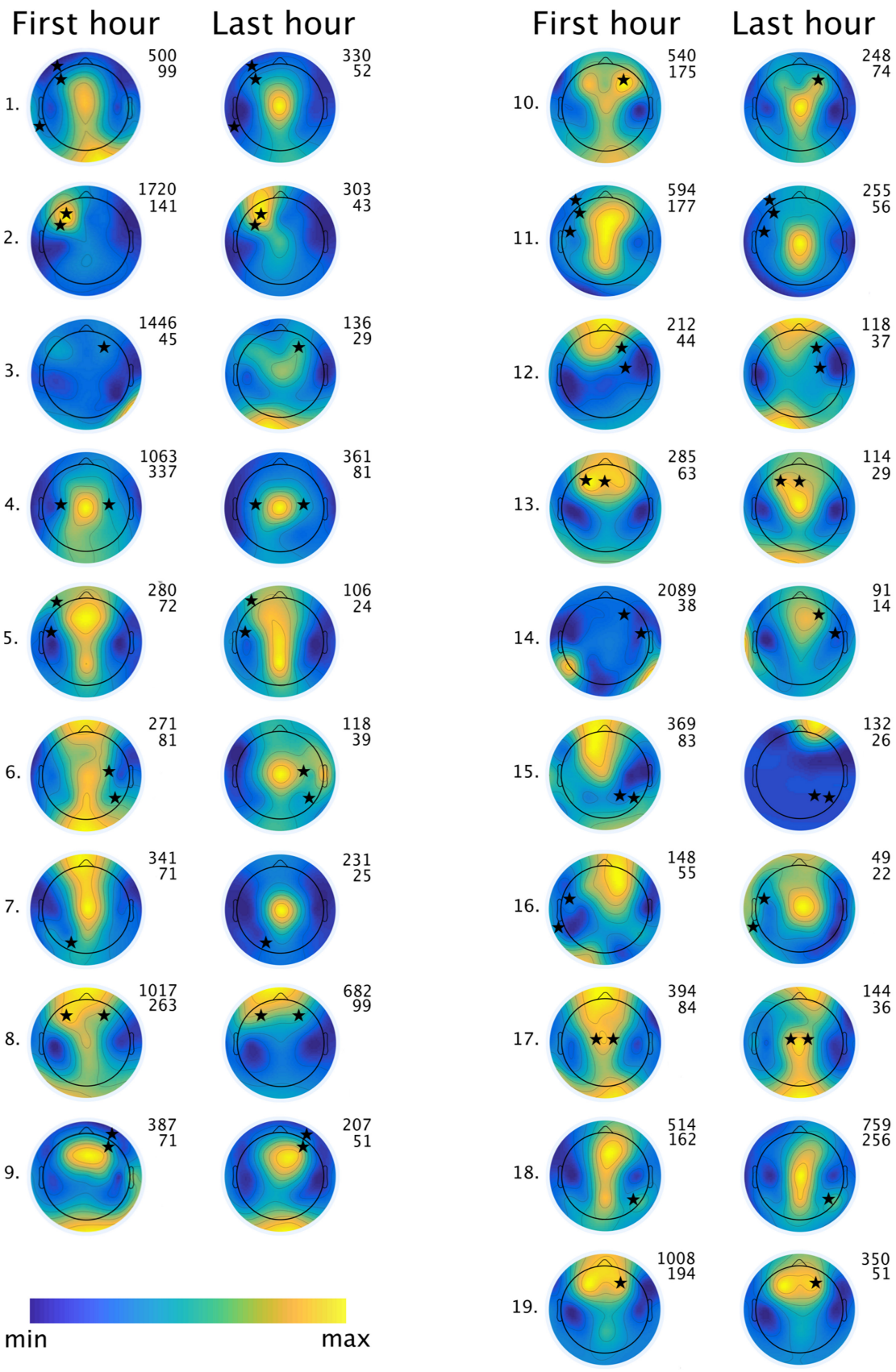

FIGURE 4 Changes in local slow-wave activity (SWA) overnight. Individual topographies for all patients arranged in order of increasing age. The black stars indicate foci of interictal discharges as stated on the clinical electroencephalogram report. In most patients (15 out of 19), peak SWA persisted at or moved towards the interictal foci in the last hour of non-rapid eye movement sleep

Indeed, the parents of these patients reported a higher habitual seizure frequency. Thus, we propose that more active epilepsy may correlate with an impairment of sleep homeostasis.

In a single study[17] comparing adults with focal lesional epilepsies to typically developing controls, SWA in NREM sleep across the night showed a positive correlation with the frequency of secondarily generalized seizures in the 3 to 5 days preceding the study night. Seizure frequency subsequent to the study night was not examined.

We did not show an influence of IEDs in sleep on SWA topography, in line with findings in the published adult cohort.[17] However, Boly et al.[17] reported a correlation between the frequency of IEDs in the last hour of wakefulness preceding sleep and higher local SWA, a relationship that we did not examine. Since patients were recruited to our study during their hospital admission, we did not have an EEG record for the 5 days before the study night, precluding a direct comparison to this previous study.

In patients with continuous spike waves in slow-wave sleep, the decline in the slow-wave slope across the night—a proxy measure of synaptic downscaling[21]—is impaired, particularly at focal electrodes.[14] This is presumed to be due to the prolific epileptiform discharges that fill most of slow-wave sleep in this condition. By contrast, patients with focal lesional epilepsies tend to have low IED counts, with a median of 0.33 per minute in our cohort[18] and 0.38 per minute in Boly et al.'s [17] cohort, perhaps accounting for the preserved SWA decline across the night. This suggests that there may be a threshold IED rate above which synaptic homeostasis may be disrupted.

Cognitive correlates

We found no correlation between early-night SWA or normalized SWA decline and performance in the memory tasks, although we previously reported the correlation between sleep benefit on the verbal task and slow-wave sleep duration.[18] Wilhelm et al.[36] demonstrated a correlation between SWA across NREM sleep over the whole night and performance on a motor sequence task the following day in population norm adults. Both slow-wave sleep duration and whole-night SWA are dependent on the amount of sleep time occupied with cortical slow oscillations; thus, their positive correlation with memory task performance is consistent with the active system consolidation hypothesis.[10] We did not find a correlation between early-night SWA and full-scale IQ.

Behavioural correlates

There was no correlation between SWA and the score on the Children's Sleep Habits Questionnaire, although parents of patients reported more behavioural and sleep difficulties in their children than the parents of controls.[18] This suggests that behaviour does not have a simple relationship with SWA dynamics.

Study limitations

The patient group was heterogeneous in their baseline clinical characteristics; having been admitted to hospital to capture ictal EEG, they underwent interventions including reduction of antiseizure medication and sleep restriction. It is thus difficult to comment on the differences in sleep architecture compared to controls, although it is notable that sleep efficiency and REM latency were similar in the two groups. Pathological slowing or the effects of partial sleep deprivation[19,27] are possible confounding factors; however, these would have caused an increase in SWA in the patient group compared with controls, rather than the reduction in SWA we demonstrated. It is also unlikely that medication effects would have led to a systematic bias of the results since patients were on different medications with an even spread between those that increase and those that decrease slow-wave sleep.[37] Our analysis of SWA topography in controls was limited due to the eight-electrode montage; however, we replicated the findings of others in terms of SWA and age-related trends in typically developing children. More accurate results regarding focal changes in SWA topography could be sought using high-density EEG.

Conclusions

Our findings provide new insight into the relationship between sleep, seizures, and cognition in children with epilepsy. Early-night SWA was reduced in patients, interestingly more so in the ones with higher seizure propensity. This suggests that an adequate response to sleep need may be required to maintain the seizure threshold or that a high seizure burden may interfere with the maturation of sleep homeostasis. Indeed, this may represent a vicious cycle, which would decrease opportunities for learning. On the other hand, overnight SWA decline, reflecting global synaptic downscaling, was preserved in this patient group, who showed few IEDs in sleep. This may underlie the conservation of sleep-related memory consolidation and the relative preservation of intellect in this cohort. The modulation of sleep homeostasis, for example, by closed loop auditory stimulation during slow-wave sleep,[38,39] may provide a new therapeutic approach to childhood epilepsy.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

ORCID

Maria H. Eriksson https://orcid.org/0000-0001-6869-5804
Samantha Y. S. Chan https://orcid.org/0000-0003-0488-1207

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