

# **Sleep architecture and homeostasis in children with epilepsy – a neurodevelopmental perspective**

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## **Abstract**

Though the influence of sleep upon epilepsy has long been recognised, this relationship has yet to be fully exploited to benefit patients. The past decade has seen significant advances in understanding paediatric sleep, providing a framework by which to properly evaluate the sleep of children with epilepsy, which itself has been subject to increasing scrutiny. The role of sleep in learning and the potential for interictal discharges to disrupt sleep-related memory consolidation provide a novel perspective for understanding the association of childhood epilepsy with a high rate of intellectual disability. In this review, I outline the evolution of sleep duration, architecture and homeostasis across childhood, relating this to the development of cognitive functions. I describe how these may be disrupted or preserved in children with epilepsy – in particular, collating data from polysomnography. Finally, I explore how sleep may in future be modulated to improve cognitive outcome in these patients. [150 words]

## **Short title:**

Sleep architecture and homeostasis in epilepsy

## **What this paper adds:**

- Children with epilepsy tend to have less REM sleep than age-matched controls, but this improves with seizure cessation.
- Deep, or slow wave sleep is highly conserved in children with epilepsy, though sleep homeostasis may be disrupted either at a local or global level by the presence of interictal epileptiform discharges.

## **Introduction**

The influence of sleep upon epilepsy has been recognised since antiquity<sup>1</sup>, yet beyond the use of sleep or sleep deprivation as an activating procedure for electroencephalography, this relationship still remains to be exploited to improve the lives of patients. Humans, in common with many mammalian species<sup>2</sup>, spend most of their infancy asleep<sup>3</sup>. The subsequent evolution of sleep structure and function throughout childhood closely mirrors that of normal neurodevelopment<sup>4</sup>, whereas epilepsy with onset in early childhood is associated with a high rate of intellectual disability<sup>5</sup>.

## **Sleep – structure and regulation**

Sleep is not one but several distinct states, which occur in roughly 90-minute cycles through the night<sup>6</sup>. The major division is between REM (rapid eye movement) and non-REM sleep, their contrasting EEG appearances underpinned by vastly different neurochemical milieux<sup>7</sup>. NREM sleep can be further divided into stages (N1 to N3), numbered in order of increasing arousal threshold<sup>6</sup>. Deep NREM sleep (stage N3) is also termed slow wave sleep (SWS) – so named for the high amplitude, low frequency (0.6 – 4Hz) oscillations that dominate the EEG in this state.

The timing and duration of sleep are determined by the interaction of extrinsic and intrinsic factors. A “two-process model” to describe this was first proposed by Borbely in 1982, and has since been substantiated by extensive experimental data<sup>8</sup>. This comprises a circadian drive (Process C) which is independent of prior sleep, and a homeostatic process (Process S) whereby the need to sleep builds up with increasing time spent awake, and dissipates during sleep<sup>8</sup>. A further process – the mechanisms of which remain to be elucidated – determines the alternation between NREM and REM sleep<sup>9</sup>.

Sunlight captured by retinal ganglion cells entrains the suprachiasmatic nucleus (SCN) – a group of hypothalamic neurons located adjacent to the optic chiasm which behaves as the body’s master circadian clock<sup>10</sup> – to Earth’s 24-hour day/night cycle. The practical

consequence of this is that sleep is easiest to initiate and maintain when one's habitual bedtime coincides with the nadir of the circadian drive for arousal. Inter-individual variation in the relationship of this nadir with clock time has a strong genetic basis<sup>11</sup>.

Slow wave activity (SWA) – the power of the EEG in the 0.6 – 4Hz band – is greatest in the first sleep cycle, and declines in subsequent cycles across the night<sup>8</sup>. Additionally, SWA increases after a period spent awake, increases further with sleep deprivation and decreases with sleep<sup>8,12</sup>, thus serving as a useful quantitative marker of sleep homeostasis.

## **Sleep – evolution over childhood and correlation with neurodevelopment**

### Sleep duration

The profound changes in sleep schedule that characterise childhood have recently been quantified in two prospective, population-based studies which employed parental questionnaires<sup>3</sup> and detailed sleep diaries<sup>13</sup> respectively. Mean total sleep duration per 24 hours fell from 13-14 hours at 6 months to around 10 hours by 9 years, with both studies finding large variation – in the order of hours – at all ages. In adolescence, the most notable change is a delay in sleep phase: bedtimes and wake-up times become progressively later<sup>14,15</sup>. Sleep duration on weekdays but not weekends shortens, suggesting an increasing impact of social factors such as early school start times<sup>15</sup>.

Shorter sleep time in schoolchildren is associated with poorer cognitive and academic performance<sup>16,17</sup>. Urrila et al<sup>17</sup> also demonstrated correlations between shorter weekday sleep and later weekend sleeping hours in adolescents with decreased grey matter volumes in frontal, anterior cingulate, and precuneus cortex, suggesting that unsuitable sleeping schedules may have lasting effects on brain structure.

### Sleep architecture

Sleeping newborn infants cycle rapidly between episodes of quiescence (“quiet sleep”; QS) and REM-like “active sleep” (AS) characterised by saccadic eye movements and movements of the body and limbs. The quiescent periods last about 20 minutes and occur every hour<sup>18</sup>. During the first year of life, the length of the sleep cycle remains stable at around 60 minutes, though periods of AS shorten and QS lengthens<sup>19</sup>. Subsequently, the length of sleep cycles increases, reaching the mature length of approximately 90 minutes during adolescence<sup>20</sup>. The typical EEG features of sleep evolve over the course of infancy<sup>21</sup>, with sleep spindles first appearing at 3 to 8 weeks post-term, K complexes at about 5 months, vertex sharp waves recognisable by 16 months, and true slow wave sleep emerging by 2 to 9 months post-term<sup>19</sup>.

### *REM*

The proportion of sleep time occupied by REM sleep decreases from 50% to 25% over the first two years of life<sup>22</sup>, then remains virtually unchanged for the rest of childhood. The endogenous neuronal activation which characterises REM sleep likely contributes to early brain development. Precocial mammals – such as guinea-pigs, which are born well-developed – have much lower proportions of REM sleep<sup>2</sup> than altricial mammals (such as rats, which are born blind and dependent). REM deprivation in infant altricial mammals during the critical developmental period produces lasting plastic changes to central visual pathways<sup>23</sup>. The role of REM sleep in later childhood and in adulthood is less clear – it is likely important for the consolidation of procedural (skill-related) and emotional memory<sup>24</sup> though the underlying mechanisms remain poorly understood<sup>25</sup>.

### *SWS*

The proportion of sleep time spent in slow wave sleep peaks at 25-30% around the age of 3 years<sup>26</sup>. Between the ages of 5 and 15, SWS decreases by 5-7% per 5-year period<sup>20,27</sup>. This is the most prominent change in sleep architecture over the course of middle childhood. Despite this, SWA increases markedly over the same period, reaching a plateau around puberty<sup>4</sup> before declining in subsequent decades<sup>28</sup>.

There is now robust evidence for the role of SWS in declarative memory<sup>24</sup> - that for consciously recalled facts and events. These are respectively termed 'semantic' and 'episodic' memory<sup>29</sup>. The widespread slow oscillations seen on surface EEG during SWS reflect the synchronous on/off firing of large numbers cortical neurons<sup>30</sup>. It is thought that this alternation between sustained firing and neuronal silence serves the dual purposes of downscaling global synaptic strength (Figure 1, left) – thus freeing capacity for the encoding of new memories upon awakening – while at the same time driving the active consolidation of hippocampus-dependent episodic memory<sup>29</sup>. (Figure 1, right).

In the latter process, known as 'active system consolidation', cortical slow oscillations drive thalamocortical spindles, which in turn organise the replay of neuronal sequences in the hippocampus<sup>29</sup>. These can be seen on invasive EEG as sharp-wave ripples<sup>31</sup>. There is replay also of the corresponding trace in the cortex<sup>32</sup>. These sequences represent a transient memory store, and reactivation leads to long-term potentiation, writing these memories into long-term cortical storage.

Developmentally, the ability to form episodic memories emerges around pre-school age, and increases across childhood, in parallel with the rise in SWA, which peaks in adolescence. There is experimental evidence to suggest that this ability may decline after adolescence in tandem with the fall in SWA, with children outperforming adults in a task of sequential order – a key aspect of episodic memory<sup>29</sup>.

### *SWA topology*

The distribution of SWA across the scalp is termed its topology. The evolution of EEG spectral power and topology parallels the development of specific abilities over the course of infancy and childhood, with both processes likely underpinned by the maturation of cortical grey matter through synaptic pruning<sup>4</sup> (Figure 2). Visual acuity develops in the early years, when SWA is greatest in the occipital regions, while executive function is immature until late adolescence – when SWA has a frontal dominance, resembling the adult pattern<sup>4</sup>. There is great variability in the detail of SWA topology between individuals, but findings from night to night in the same individual are remarkably consistent and highly heritable<sup>33</sup>.

### *Sleep homeostasis*

The upregulation of SWA after nap deprivation can be seen from about 30 months of age<sup>34</sup>; prior to this, compensation is achieved by increasing the SWS duration. This development likely facilitates the dropping of naps seen in the majority of children around that age<sup>3</sup>. Further changes are seen in late adolescence. The build-up of homeostatic pressure over wakefulness is slower in Tanner 5 compared to Tanner 1 adolescents but decline remains similar<sup>12</sup>. This change in dynamics likely facilitates the observed sleep phase delay<sup>14,15</sup>.

### *Primary sleep disorders*

Parent-reported sleep disturbance is extremely common, with large population-based studies putting the prevalence at >30% in infants and 14-30% in pre-school children<sup>35</sup>. Nightwakings and bedtime resistance (behavioural insomnia) were the most frequent concerns. In a meta-analysis of 41 survey studies, daytime sleepiness was reported in 15-40% of children aged 8 to 15 years<sup>15</sup>. Studies utilising polysomnography to detect specific sleep disorders in community-based samples are rare, and give far more conservative figures<sup>36,37</sup>.

## **Sleep in children with epilepsy – disrupted and intact aspects**

### Duration and schedule

There are few objective data on sleep duration in children with epilepsy. Using actigraphy, Holley et al<sup>16</sup> compared children aged 6 to 13 years with idiopathic epilepsies attending mainstream school to age-matched controls, finding no difference in sleep time or efficiency. In a recent population-based study, adolescents with epilepsy reported no difference from their healthy peers in weekday sleep duration, but significantly longer sleep duration at weekends<sup>38</sup>. These data suggest that in those with relatively unimpaired cognitive function, sleep patterns are not grossly different from the norm, though sleep need may be increased in adolescents with epilepsy.

The situation is likely different in children with epilepsy and intellectual disability, which is associated with a higher rate of sleep disruption from all causes even at the onset of epilepsy<sup>39</sup>. Such children are also more likely to have medication-resistant seizures<sup>40</sup>.

Developmental delay will likely include a delay in achieving (or failure to achieve) age-appropriate adaptive sleep behaviours, leading to the persistence of the sleep-onset difficulties and nightwakings which are commonplace in healthy infants and preschoolers. Non-epileptic limb jerks and other movements which may lead to sleep fragmentation are seen more often in children with epilepsy, particularly those with co-morbid ADHD<sup>41</sup>. Finally, a high seizure burden – whether nocturnal or diurnal – would disrupt circadian regulation.

## Architecture

### *Data from polysomnography*

The single consistent finding across polysomnographic studies in children with epilepsy when compared to age-matched controls is reduced REM sleep (Table 1). This has been shown in children with childhood epilepsy with centrotemporal spikes (CECTS)<sup>42,43</sup>, ‘partial refractory’ epilepsies<sup>44,45</sup>, idiopathic generalised epilepsies<sup>46</sup> and epileptic encephalopathies<sup>47,48</sup>, and has been demonstrated even in a drug-naive<sup>43</sup> cohort. Additionally, children with focal lesional epilepsies may have increased SWS compared to controls<sup>34</sup>. Despite the heterogeneity of these data, they provide evidence firstly that most children with epilepsy will be relatively REM-deprived compared to their peers, and secondly that both epileptic activity and anti-epileptic therapy likely contribute to this derangement. SWS on the other hand, is likely to be found in normal or higher amounts.

### *Influence of seizures*

In adults with temporal lobe epilepsy, seizures are associated with decreased REM in the subsequent night’s sleep<sup>49,50</sup>, while SWS remains unchanged<sup>49,50</sup>. Gutter et al<sup>50</sup> studied 425 recordings from 339 patients on a seizure-free night, comparing those with and without a history of seizures during the past 24 hours. Bazil et al<sup>49</sup> made within-subject comparisons on 87 recordings from 21 patients; crucially, post-ictal slowing was excluded from sleep time. Taken together, these studies suggest a genuine decrease in REM, rather than

a relative decrease in the proportion of sleep time in REM due to any change in SWS. In children, data from polysomnography on the same subjects before and after treatment show that the cessation of infantile spasms with hormonal treatment<sup>47</sup> or near-cessation of seizures with the ketogenic diet<sup>51</sup> may lead to the normalisation of REM sleep time. These findings suggest that ongoing seizures may suppress REM sleep, with possible adverse effects on the plastic and cognitive functions that depend upon this state. They also suggest that to better understand the cognitive deficits seen in epilepsy, we require a greater understanding of the mechanisms underlying REM-related learning<sup>25</sup>.

#### *Influence of nocturnal interictal epileptiform discharges (IEDs)*

It is well established that sleep, particularly NREM sleep, activates IEDs. In the awake state, there is evidence from invasive EEG studies that IEDs can impair memory encoding<sup>52,53</sup>. During NREM sleep, the release of the thalamocortical system from cholinergic inhibition facilitates both physiological and pathological burst-firing<sup>54</sup>, whereupon the generation of IEDs may interfere directly with the hippocampo-cortical communication required for memory consolidation<sup>55</sup>. Neuropsychological regression emerges in tandem with the appearance of continuous spike-waves in slow wave sleep (CSWS) in the syndrome of encephalopathy with status epilepticus during slow sleep (ESES)<sup>56</sup>, and may improve with its resolution. In CECTS, a higher rate of centro-temporal spikes during sleep may be associated with poorer cognitive and behavioural outcomes<sup>57, 58</sup>. The enhancement of IEDs in sleep has also been associated with deficits in academic attainment and language skills in children with focal lesional epilepsies<sup>59</sup>, though outside of ESES the strength of the evidence remains at present insufficient to prescribe a threshold for intervention.

#### *Influence of treatment*

The influence of antiepileptic treatment on sleep architecture has been reviewed<sup>60</sup>, though most of the data derive from healthy adults. SWS is decreased by benzodiazepines and ethosuxamide. Carbamazepine, gabapentin, pregabalin and tiagabine consistently increase SWS, though carbamazepine may also reduce REM and increase sleep fragmentation. Lamotrigine and gabapentin increase REM sleep in patients while levetiracetam, phenytoin and phenobarbitone decrease it. Data on valproate are conflicting<sup>60</sup>.

Non-pharmacological treatment also impacts on sleep architecture. The ketogenic diet may increase REM, particularly in association with improved seizure control<sup>47</sup>; vagal nerve stimulation (VNS) produces an increase in SWS as well as REM<sup>61</sup>, though it may exacerbate or even cause obstructive sleep apnoea<sup>62</sup>. Deep brain stimulation (DBS) targetted at the centromedian or anterior thalamic nuclei is an emerging treatment modality in refractory childhood epilepsies<sup>63</sup>. However the stimulation of these nuclei – which are closely associated with the ascending arousal system – may lead directly to electroclinical arousals in a voltage-dependent manner<sup>64</sup>.

### Homeostasis

Sleep homeostasis in epilepsy has not been widely studied. Utilising the slope of individual slow waves as a measure of cortical synchrony<sup>30</sup>, Bolsterli et al<sup>65</sup> compared slow wave slopes early in the night with those in the latter part, finding a decrease in slow wave slope across the night in healthy controls, but none in patients with CSWS, suggesting impaired – or absent – homeostasis.

In patients with a low interictal discharge load, there is evidence that sleep homeostasis remains grossly intact<sup>66-68</sup>. Both adults<sup>66</sup> and children (Eriksson et al, in prep) with epilepsy due to various focal structural lesions showed a decline in SWA between early and late sleep – but of smaller magnitude than that seen in age-matched controls.

Patients with focal structural epilepsies also appear to be able to upregulate SWA in response to increased synaptic strength. We found an increase in SWA after sleep deprivation in a paediatric sample (Chan et al, in prep), while Boly et al<sup>66</sup> found a positive correlation between SWA and the number of seizures in the period preceding the sleep recording in adults. The question that remains is of whether this response is sufficient, given the supraphysiological need for neuronal recovery in the face of ongoing epileptic activity.

### SWA topology

SWA topology in focal lesional epilepsies may be influenced by both ictal<sup>66</sup> and interictal<sup>68</sup> (Eriksson et al, in prep) epileptiform discharges, with the majority of patients showing SWA peaks coinciding with these foci. Boly et al<sup>66</sup> showed that these slow waves during recovery sleep resembled physiological rather than pathological slow waves, supporting the idea that SWA is upregulated in response to increased synaptic strength at a local level also.

### Sleep-related memory consolidation

Enhanced memory task performance following a period of sleep has been demonstrated in patients with focal lesional epilepsies<sup>69,70</sup>, but not in patients with idiopathic focal epilepsies<sup>71,72</sup>. A higher interictal discharge load in SWS was associated with poorer memory performance in both groups<sup>70,71</sup>, suggesting that the results at group level may not be conflicting, but may in fact represent two ends of a continuum – whereby patients with very few, localised discharges in sleep show no deficit in sleep-related memory consolidation, but those with very frequent and widespread discharges activated by sleep show marked impairment.

### Co-morbid primary sleep disorders

A recent systematic review found that excessive daytime sleepiness was reported in 10-47% of children with epilepsy<sup>73</sup>. Although a high proportion, this is not so different from the rates reported in otherwise healthy children<sup>15,35</sup>. In common with healthy children, behavioural insomnia is likely the most frequent problem<sup>39</sup>. Polysomnographic data are limited (Table 1), but show that children with well-controlled seizures do not differ significantly from healthy controls in indices of obstructive sleep apnoea<sup>42</sup>. Gogou et al<sup>42</sup> studied children with CECTS, finding an increase in the obstructive apnoea-hypopnoea index (OAHI; apnoeas per hour from obstructive causes) compared to healthy controls, but the mean apnoea-hypopnoea index (AHI; apnoeas per hour from all causes) did not reach the clinical threshold. Carotenuto et al<sup>48</sup> examined children with epileptic encephalopathies and found AHI markedly increased compared to controls, falling within the range of obstructive sleep apnoea. The OAHI was not reported. Thus there remains no objective evidence that children with well-controlled seizures have a higher rate of obstructive sleep apnoea, whereas those with complex epilepsy may experience a clinically significant quantity of apnoeas in sleep, however it is not clear if these are predominantly obstructive or central.

## **Summary**

Objective measures show that sleep duration and schedule in children with epilepsy are similar to those in healthy children, with adolescents choosing to sleep longer when given the opportunity. SWS is highly conserved, but REM is reduced and its integrity related to the degree of daytime seizure control. Sleep homeostasis and sleep-related memory consolidation are grossly intact, but may be disrupted by frequent or widespread IEDs. Co-morbid behavioural sleep disorders are common, as in the general child population.

## **Modulating sleep to enhance neurodevelopmental outcome**

### Optimising sleep schedules and managing co-morbid sleep disorders

The similarities between children with epilepsy and their peers suggest that similar approaches – whether behavioural<sup>75</sup> or pharmacological<sup>76</sup> – are likely to be both relevant and effective. Public interest in later school start times for adolescents has grown in recent years, however the evidence for this intervention at a population level remains weak<sup>77</sup>. It is interesting that the ‘social jetlag’ reported by adolescents with epilepsy is even greater than that in their peers<sup>38</sup>, however the physiological reasons behind this remain open to speculation. Possibilities include a greater propensity to delayed sleep phase or dysmaturity in sleep homeostasis leading to greater sleep duration in lieu of increased SWA.

### SWS – enhancing sleep homeostasis

Although the idea of enhancing slow oscillations through phase-locked external stimulation is not new<sup>78,79</sup>, recent studies have demonstrated success in achieving this with auditory<sup>80,81</sup> rather than electromagnetic<sup>78,79</sup> stimulation. All of these authors also showed that memory task performance improved with the enhancement of SWA. The greater safety and tolerability of auditory stimulation raises

the possibility of long-term use in the home setting<sup>82</sup>. Though this has not yet been tried in patients with epilepsy, patients could stand to derive the further benefit of a raised seizure threshold, due to a decrease in cortical excitability<sup>79</sup>.

The available data on the nature of sleep homeostasis in patients with epilepsy – particularly those with focal lesional epilepsies – suggest that this group may stand to benefit both in terms of cognitive performance and better seizure control. Current knowledge on the developmental course of SWA dynamics<sup>4</sup> and the trait-like quality of SWA topology<sup>33</sup> will help to inform study design. A great advantage of enhancing SWA by physical rather than pharmacological means is the possibility to leave sleep architecture undisturbed<sup>80</sup>, particularly REM.

#### REM – preservation

The wake-like, desynchronised neuronal activity of REM sleep seems more difficult to achieve in the presence of epileptiform activity, and it is less obvious how REM sleep may be specifically enhanced. Seizure cessation consistently improves REM. Lamotrigine and gabapentin are unusual amongst antiepileptic medications for increasing REM sleep, and neither drug appears to impair cognition<sup>83</sup>. Interestingly, reducing IEDs by treatment with lamotrigine has been shown to improve behaviour<sup>84</sup> though not cognition<sup>85</sup> in children with various focal epilepsies.

#### **Conclusion**

The past decade has seen significant advances in our understanding of paediatric sleep; we now have normative data on the sleep schedules<sup>3,13</sup> and sleep architecture<sup>20</sup> of healthy children, and the evolution of SWA homeostasis and topology over the course of childhood and adolescence has been described<sup>4</sup>. This context is crucial in the interpretation of data from children with epilepsy, in whom we find many of the same behavioural sleep problems<sup>39</sup>, on top of REM suppression, as well as some subtle yet crucial differences in homeostasis<sup>66,68</sup> (Eriksson et al., in preparation).

At the same time, advances in technology mean that it is now possible to enhance SWA without impacting negatively on REM sleep<sup>80</sup>, and to do so in the home setting. It is perhaps time to move beyond utilising sleep merely for diagnostic purposes, toward optimising and harnessing the preserved functions to improve cognition and seizure control.

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<b>Study</b>	<b>Participants</b>	<b>Medication</b>	<b>Last seizure</b>	<b>Polysomnography parameters</b>	<b>Results</b>
Gogou et al., 2017	15 children with BECTS (mean age 10.5+/-2.31 years); and 27 healthy controls (mean age 11+/-2 years)	11 on monotherapy, 2 on 2 AEDs, 2 on none (AEDs not specified)	No seizures on the day before PSG	EEG, EOG, chin and leg EMG, ECG, chest and abdomen plethysmography, pulse oximetry, end tidal CO <sub>2</sub> , nasal/oral thermistor	REM% lower in patients (17.32+/- 4.61%) vs controls (21.24+/- 4.65%); p<0.01. No significant difference in other sleep architecture parameters.  Increased OAH1 (2.38 +/- 1.17 per hour vs 1.21 +/- 0.83 per hour) p<0.01
Bruni et al., 2010	10 children with BECTS (mean age 8.1, range 6-10); retrospective data from 10 controls (mean age 7.6, range 6-10)	none	Not recorded	EEG, EOG, chin and leg EMG, ECG	REM% lower in patients (15.5+/-4.6%) vs controls (21.2+/-4.34%); p<0.01. No significant difference in other sleep architecture parameters.
Pereira et al., 2012	31 consecutive admissions to epilepsy unit with “drug resistant partial epilepsy” (mean age 8.7, range 1.5-16.4); retrospective data from 23 controls (mean age 8.3, range 3-15.4)	14/31 were on carbamazepine; 20/31 on 2 or more drugs	Not recorded, however 11 of the patients had daily seizures	EEG, EOG, chin and leg EMG, ECG, nasal airflow, abdominal respiratory movement	REM% markedly lower in patients with lesional refractory epilepsy (5.52 +/- 5.38%) vs non-lesional (9.14+/- 9.94%) vs controls (22.9+/-5.04%); p<0.001.  SWS% decreased in the patients with refractory partial epilepsies (7.16+/- 7.47%) vs controls (23.7+/-5.31%); p<0.001  (cardiorespiratory data are not reported)
Nunes et al., 2003	17 patients under evaluation for epilepsy surgery (age range 4.7 –	3 on carbamazepine as monotherapy, the rest on 2 to 3	9 patients had seizures during the overnight recording	EEG, EOG, chin and leg EMG, ECG, nasal airflow, abdominal respiratory movement	REM% lower in patients with (16.23+/- 9.5%) and without (16.93 +/-4.5%) seizures than in controls (22.15 +/- 1.7%) but not reaching statistical significance

	16.2 years); retrospective data from 11 controls (age range 7.17-18.8 years)	AEDs			p=0.154  SWS% highest in patients with seizures overnight (36.7 +/-13.8%), followed by those without seizures (24.68 +/-7.4%) and healthy controls (16.55+/-5.6%). p=0.001  (cardiorespiratory data are not reported)
Magnanti et al., 2005	11 children with primary generalised epilepsies (mean age 13.36 years, range 9 to 17); 8 healthy controls (mean age 14.25 years, range 13-17)	10/11 on valproate either as monotherapy or with another drug	Patients were "seizure-free"	EEG, EOG, chin and leg EMG, ECG, nasal airflow, thoracic respiratory movement, oximetry	REM% lower in patients (17.91 ± 3.84%) than controls (22.03 ± 7.93%) but not reaching statistical significance p=0.1  SWS% nearly the same in patients (17.33 ± 5.45%) and controls (17.31 ± 5.77)  average oxygen saturations were similar in both groups
Carotenuto et al., 2014	23 children with epileptic encephalopathies (mean age: 8.7± 1.4 years); 40 healthy children (mean age: 8.9 ± 1.1 years)	All on 3 or more AEDs	Not reported	EEG, EOG, chin and leg EMG, ECG, chest and abdomen plethysmography, pulse oximetry, end tidal CO <sub>2</sub> , nasal/oral thermistor	REM% similar in patients and controls, but REM duration shorter in patients (98.2478 ± 2.94mins in patients vs 123.06 ± 35.15mins in controls; p = 0.026) TST and N2 also decreased SWS% higher in patients (38.279 ± 7.928 vs 28.98 ± 10.027 in controls; p = 0.006)  AHI higher in patients (11.539 ± 2.729 per hour vs 0.994 ± 0.205 per hour in controls) p<0.0001

**Table 1.** Findings on polysomnography in children with epilepsy – prospective samples compared with age-matched controls. BECTS= benign epilepsy with centro-temporal spikes; AED=antiepileptic drug; PSG=polysomnography; EOG= electro-oculography; EMG=electromyography; ECG=electrocardiography; OAHI=obstructive apnoea-hypopnoea index (number of obstructive and mixed apneas and hypopneas per hour of sleep); AHI=apnoea-hypopnoea index (total number of apnoeas per hour of sleep) ODI=oxygen desaturation index (number of dips in oxygen saturation below threshold per hour – however the authors here do not state the threshold); TST=total sleep time; N2=NREM sleep stage 2. All polysomnographic values and ages are expressed as mean +/- SD unless stated otherwise.

**Figure 1.** Proposed mechanisms of sleep-related memory consolidation.

Left: Synaptic Homeostasis. Global synaptic strength is high at the beginning of the night, following synaptic potentiation in response to daytime stimuli. Slow waves on the surface EEG represent the repeated on/off firing of widespread cortical neurons. This leads to a global decrease in synaptic strength, eliminating the weakest circuits (representing the least salient information). Toward the end of the night, slow oscillations are more localised and less powerful, reflecting a decrease in cortical synchrony.

Right: Active System Consolidation. Cortical slow oscillations drive thalamocortical spindles, which in turn organise the replay of neuronal sequences in the hippocampus (seen on invasive EEG as sharp-wave ripples). There is replay also of the corresponding trace in the cortex. These sequences represent a transient memory store, and reactivation leads to long-term potentiation, writing these memories into long-term storage in the cortex.

**Figure 2.** Linking brain maturation, SWA topography, and behaviour at an early and a late state of development. (Adapted from Ringli and Huber 2011)

Left column: synaptic pruning - reflected in the fall in synaptic density - takes place in the visual cortex (top) predominantly in early childhood, but not in the prefrontal cortex (bottom) until later on, most notably over the course of adolescence.

Middle column: Topographical distribution of NREM sleep SWA for age groups 2–5 years (top) and 17–20 years (bottom). Peak activity is seen over the occipital cortex and prefrontal cortices respectively.

Right column: Development of visual acuity in human infants plotted against age (top). Exponential decline in percent error in an executive function task across age (bottom).