The relationship between sleep and epilepsy: the effect on cognitive functioning in children

PASQUALE PARISI[1] | OLIVIERO BRUNI[2] | MARIA PIA VILLA[1] | ALBERTO VERROTTI[3] | SILVIA MIANO[1] | ANNA LUCHETTI[1] | PAOLO CURATOLO[4]

1 Child Neurology and Sleep Paediatric Disorders Centre, II Faculty of Medicine, Sapienza University, Sant'Andrea Hospital, Rome, Italy. **2** Department of Developmental Neurology and Psychiatry, Sapienza University, Rome, Italy. **3** Chair of Paediatrics, Paediatric Department, University of Chieti, Italy. **4** Paediatric Neurosciences, Tor Vergata University, Rome, Italy

Correspondence to Professor Pasquale Parisi at Child Neurology & Sleep Disorders Centre, Chair of Paediatrics, II Faculty of Medicine, Sapienza University, Sant'Andrea Hospital, Via di Grottarossa 1035–1039, 00189, Rome, Italy. E-mail: pasquale.parisi@uniroma1.it

PUBLICATION DATA
Accepted for publication 29th January 2010.
Published online 29th March 2010.

LIST OF ABBREVIATIONS

AED	Antiepileptic drug
CAP	Cyclic alternating pattern
ESES	Electrical status epilepticus during sleep
IED	Interictal epileptic discharge
NREM	Non-rapid eye movement
REM	Rapid eye movement
SWS	Slow-wave sleep

AIM The purpose of this review was to examine the possible pathophysiological links between epilepsy, cognition, sleep macro- and microstructure, and sleep disorders to highlight the contributions and interactions of sleep and epilepsy on cognitive functioning in children with epilepsy.
METHOD PubMed was used as the medical database source. No language restriction was placed on the literature searches, and citations of relevant studies in the paediatric age range (0–18y) were checked. Studies including a mixed population but with a high percentage of children were also considered.
RESULTS The searches identified 223 studies. One reviewer scanned these to eliminate obviously irrelevant studies. Three reviewers scanned the remaining 128 studies and their relevant citations. The review showed that several factors could account for the learning impairment in children with epilepsy: aetiology, electroencephalographic (EEG) discharges, and persistence and circadian distribution of seizures, etc. EEG discharges may affect cognition and sleep, even in the absence of clinical or subclinical seizures. The sleep deprivation and/or sleep disruption affect the neurophysiological and neurochemical mechanisms important for the memory–learning process, but also influence the expression of EEG discharges and seizures. Learning and memory consolidation can take place over extended periods, and sleep has been demonstrated to play a fundamental role in these processes through neuroplastic remodelling of neural networks. Epilepsy and EEG paroxysms may affect sleep structure, interfering with these physiological functions.
INTERPRETATION Improvement in the long-term cognitive–behavioural prognosis of children with epilepsy requires both good sleep quality and good seizure control. The antiepileptic drug of choice should be the one that interferes least with sleep structure and has the best effect on sleep architecture – thus normalizing sleep instability, especially during non-rapid eye movement sleep.

The spectrum of epilepsy in children is different from that in adults in terms of clinical presentation, pathogenetic aspects, and prognostic implications. Pathogenic and prognostic aspects are closely related to 'developmental status', which is intrinsically linked to the child's age. In the developmental period, in addition to socioeconomic status and parental education, all possible comorbid conditions associated with epilepsy (such as sleep disorders, headache, behavioural disorders, mood disorders, autism, attention-deficit–hyperactivity disorder, etc.) have a huge potential impact on cognitive, educational, and sociobehavioural skills.[1]

Academic, cognitive, and behavioural complications in paediatric epilepsy are often assumed to be the consequences of recurrent seizures or anticonvulsant treatments or primary fundamental characteristics of the disorder. However, in the last decade, relevant published papers are accumulating data on the role of 'sleep disruption' in individuals with epilepsy as a cause of cognitive impairment and the data are mainly related to nocturnal electroencephalographic (EEG) discharges or to nocturnal subclinical seizures.[2]

The purpose of this review is to examine the possible pathophysiological links between epilepsy, cognition, sleep macro- and microstructure, and sleep disorders to determine the contribution of sleep and epilepsy to cognitive functioning in children with epilepsy and their interaction, if any.

METHOD

Literature search strategy

In October 2009, a comprehensive search was undertaken to identify all kinds of articles (randomized controlled trials,

clinical controlled trials, open-label studies, meta-analysis, reviews, expert opinion, and series and case reports), existing and 'in press', particularly (but not only) in the last decade (from 2000–2009), using the following terms: 'epilepsy and cognition' (824 papers), 'epilepsy and sleep' (441 papers), 'cognition and sleep' (402 papers), and 'sleep and memory and learning' (56 papers) as key words. More relevant papers out of the considered range were also taken into account. PubMed was used as the source of literature; no language restriction was placed on the literature searches, and citations of relevant studies were checked. In addition, the search was limited to all paediatric (0–18) age groups. Articles were also considered if the study group was mixed population but included a high percentage of individuals less than 18 years old. As exclusion criteria, trials recruiting only individuals with a single seizure, status epilepticus, seizures after surgery, or febrile convulsions were not considered. After searching and selecting the literature, two reviewers independently abstracted the data and a third reviewer resolved discrepancies. The searches identified 223 studies. One reviewer scanned these to eliminate obviously irrelevant studies. Three reviewers scanned the remaining 128 studies and their relevant citations (46).

What this paper adds

- Improvement in the long-term cognitive–behavioural prognosis in children with epilepsy depends on both good sleep quality and good seizure control.
- Sleep disruption linked to the epileptic condition influences the expression of electroencephalographic discharges and seizures and affect the neurophysiological and neurochemical mechanisms underlying the memory–learning processes.
- The antiepileptic drug chosen should be one that interferes least with sleep structure.

RESULTS

The relationship between sleep and epilepsy in children

To evaluate the relationship between epilepsy and sleep, it is necessary to consider several factors: (1) the presence of generically defined sleep disturbances (changes in sleep habits, such as co-sleeping or parental presence at sleep onset, etc.); (2) the presence of specific sleep disorders with codified clinical and polysomnographic diagnostic criteria, such as rapid eye movement (REM) behaviour disorders, sleepwalking, sleep terrors, and confusional arousals; (3) 'interference' of epileptiform activity and seizures with sleep macro- and/or microstructure (cyclic alternating pattern; CAP); and (4) positive or negative effects on both sleep and coexisting sleep disorders of antiepileptic drugs (AEDs). All these factors can coexist and interact (in a positive or negative way) with each other, complicating the clinical picture.

Sleep activates both focal and generalized spikes in about one-third of all individuals with epilepsy. Some types of epilepsy are closely sleep-related with clinical onset exclusively or mainly during sleep (i.e. Rolandic epilepsy), whereas other epileptic syndromes are associated with a pathognomonic sleep-related EEG pattern (e.g. electrical status epilepticus during sleep [ESES] as in Landau–Kleffner syndrome or rhythmic fast EEG activity during nocturnal tonic seizures as in Lennox–Gastaut syndrome).[2]

Sleep problems in children with epilepsy

Several studies of sleep problems in children with epilepsy have been conducted.[3–9] The parents of children with epilepsy commonly report a higher rate of sleep problems, disturbed daytime behaviour, poor-quality or non-restorative sleep, and anxieties about sleeping.[7–9] In a study of sleep disturbances in 79 schoolchildren with epilepsy by means of parental questionnaires, a higher than normal rate of sleep disorders was documented, particularly in children aged 5 to 11 years; disturbed daytime behaviour, poor-quality sleep, and anxieties about sleeping showed a significant association with poor seizure control.[7] In another study of 89 children with partial and generalized idiopathic epilepsy, a higher incidence of parasomnia and night-waking, longer sleep latency, increased daytime drowsiness, and changes in sleeping habits (co-sleeping or parental presence at sleep onset) compared with healthy comparison individuals was documented.[8] In addition, a higher paroxysmal activity density and a short seizure-free period were significantly associated with an increased rate of sleep disturbances.[8] In another study in children with epilepsy, using a validated sleep questionnaire, neurobehavioural problems were also suggested to be, in part, due to an underlying sleep disturbance.[9]

Nocturnal seizures, polytherapy, developmental delay, refractory epilepsy, and epileptic syndromes with unfavourable outcomes are associated with poor sleep habits, sleep disorders such as recurrent nightmares, and disorders of arousal.[10,11]

The few polysomnographic studies available have shown sleep structure alterations in individuals with epilepsy. In children with epilepsy of different aetiologies, the main sleep macrostructure abnormalities are a reduction in total sleep time, sleep efficiency, and REM sleep and an increase in stage shifts, number of arousals, and waking after sleep onset. In children with refractory epilepsy, a decrease in stage 2 sleep and an increase in slow-wave sleep (SWS) have also been reported.[12,13] Further, in malignant epileptic syndromes such as West and Lennox–Gastaut syndromes, a loss of normal non-rapid eye movement (NREM) sleep patterns is common; as in refractory epilepsy, there is a decrease in stage 2 NREM and REM.[14] Moreover, specific sleep disorders such as obstructive sleep apnoea syndrome,[15–18] restless leg syndrome, and periodic limb movements[19] are reportedly common in children with epilepsy. More recently, an occasional association with REM behaviour disorder has been reported.[4]

Treatment of sleep disorders to improve epilepsy

From a therapeutic point of view, evidence is accumulating that treatment of obstructive sleep apnoea may improve seizure control, at least in adults,[17,18] and may reduce interictal epileptogenic activity.[18] In contrast, one study suggests that obstructive sleep apnoea may play a role in increasing epileptogenicity in children.[15]

Melatonin, a hormone secreted by the pineal gland, is thought to play an important role in many behavioural processes, and to have sedative, anxiolytic, and anticonvulsant

properties. There are both older[20] and more recent[21,22] data showing that in individuals with intractable epilepsy baseline melatonin levels are low (but increase dramatically after the seizure period).[20]

Corroborating these data, it has been shown that, in a model of chronic epilepsy, ramelteon, a selective melatonin receptor agonist, has anticonvulsant properties.[20] In addition, melatonin therapy may help control seizures in children and adolescents with epilepsy, improving sleep efficiency and reducing sleep disruption.[21] The mechanism whereby treatment of a sleep disorder improves a seizure disorder is unknown, but is probably linked to stabilization of sleep as a result of preventing the unsteadiness of EEG oscillations (which facilitate the occurrence of epileptic discharges and seizures). In individuals with obstructive sleep apnoea syndrome, this process could also be linked to the resolution of chronic sleep deprivation, to the improvement in cerebral hypoxaemia, and to the reduction in arousals from sleep.[23]

AED effects on sleep

AEDs may have beneficial or detrimental effects on sleep structure.[24,25] Individuals with epilepsy taking anticonvulsants known to disrupt sleep (i.e. phenobarbital, phenytoin, carbamazepine, or valproic acid) have increased drowsiness compared with individuals with epilepsy who are not taking anticonvulsants.[26] Studies on newer AEDs, although often discordant, in general suggest fewer detrimental effects on sleep. Lamotrigine was found in one study to have no effect on sleep,[27] but another study found a decrease in SWS.[28] Gabapentin, pregabalin, and tiagabine enhance SWS and sleep continuity in individuals with epilepsy.[24,27] A study of levetiracetam in individuals with epilepsy found little effect on sleep structure.[29] The effects of topiramate, oxcarbazepine, zonisamide, and rufinamide on sleep and sleep disorders have not yet been reported. A recent actigraphic study[30] monitoring 46 children (age range 1y 8–17y 5mo) before and after discontinuation of valproic acid monotherapy documented a decrease in sleep duration after discontinuation.

Cognitive impairment in paediatric epilepsy

Cognitive impairments are frequently reported in children with epilepsy, but their timing and pathogenesis is still a matter of debate. Examination of the rate of provision of diverse special school services for children with academic difficulties shows that about 25% of children with epilepsy received these services before their first recognized seizure.[31,32]

The presence of neurobehavioural comorbidities at the time of epilepsy onset would be a significant marker of abnormal cognitive development both before and after the onset of epilepsy.[31] Subnormal global cognitive function is recognizable in approximately one in four children with epilepsy. Young age at onset, symptomatic cause, epileptic encephalopathy, and continued treatment, despite their strong intercorrelations, are independently associated with this outcome.[32] It is less difficult to explain cognitive deficits associated with symptomatic epilepsies when they are the result of recognizable cerebral lesions (related or not to well-known diseases) rather than of epilepsy per se. More difficult to explain is why several, so-called, 'idiopathic benign epilepsies' are associated with cognitive impairment occurring at the onset of or during the natural course of epilepsy.

Among idiopathic 'benign' epileptic syndromes of infancy and childhood, the so-called 'benign epilepsy with centrotemporal spikes' is without doubt the one for which the outcome is still 'under judgement' for residual, transitory, or persistent[32] cognitive impairment. In fact, from a clinical and EEG point of view, benign epilepsy with centrotemporal spikes shows a continuum of clinical features from typical, apparently benign forms at one end of the spectrum to non-benign entities, such as pseudo-Lennox and Landau–Kleffner syndromes, at the other.[33–37]

Even in typical benign epilepsy with centrotemporal spikes, subtle deficits in reading, writing, or calculation may be detected by specific neuropsychological testing alone[38,39] (e.g. by means of tasks of visual discrimination between words and pseudo-words).[40] Further, in children with idiopathic syndromes, a Full-scale IQ of 80 or more does not seem to guarantee that the individual is cognitively 'normal', as subtle and/or specific cognitive disturbances could be masked by a global score.[33] Recently,[41] supporting the findings of previous studies on smaller samples, a broad range of untreated cognitive, linguistic, and behavioural–emotional comorbidities, even in childhood absence epilepsy, has been reported.

Children with frontal lobe epilepsy have been shown to be impaired in memory strategies and complex motor planning, with higher severity in those with an early age at epilepsy onset. Compared with those with temporal lobe epilepsy, children with frontal lobe epilepsy manifest more problems in planning, impulse control, verbal fluency, motor coordination, and executive functions, but they have better memory performances.[42]

Role of sleep in cognitive functioning

There is growing evidence that sleep in general and specific sleep stages such as REM and/or SWS are involved in memory formation and cognitive performances.

Recent studies on non-sleep-deprived typically developing individuals have shown that sleep after learning enhances consolidation of declarative, procedural, and emotional memories. SWS particularly enhances declarative memories,[43] whereas REM sleep preferentially supports procedural and emotional memory aspects. Declarative memory profits from rather short sleep periods (1–2h), whereas procedural memory benefits seem to depend on the amount of sleep the day after learning. Children's sleep, with large amounts of SWS, distinctly enhances declarative memories, whereas, in elderly and psychiatric individuals with disturbed sleep, sleep-associated consolidation of declarative memories is impaired.[44] A critical role for SWS in the off-line consolidation of episodic facts is suggested by investigation demonstrating that, on inducing sleep, slow oscillations (by transcranial application of slowly oscillating potentials) intensifies SWS and enhances consolidation of declarative memory.[45] Also, other studies have found that daytime-learning-dependent activation of the

hippocampal region re-emerges during SWS,[46] and that the amount of SWS reactivation in the hippocampus is correlated with the next-day task improvement.[47] Consolidation during subsequent sleep probably relies on the cortico-hippocampal dialogue; the slow oscillations of SWS originating primarily from the prefrontal cortex stimulate the reactivation of hippocampal memories, and these memories, in a system consolidation process, become redistributed to neocortical and other networks.[47]

The EEG slow oscillations that appear during SWS are also a component of the A1 subtypes of the so-called CAP and map over the frontal and prefrontal regions of the scalp.[48] CAP is an endogenous rhythm present in NREM sleep and is characterized by periodic EEG activity with sequences of transient electrocortical activation (phase A of the cycle) that are distinct from the background EEG activity (phase B of the cycle). These sequences are repeated several times during the night and organized in a cyclic pattern interrupted by the presence of a stable sleep lasting longer than 60 seconds, without oscillations, called non-CAP. Sequences of CAP are orderly distributed in NREM sleep, and the ratio of CAP time to NREM sleep time (CAP rate) is considered to be a physiological marker of NREM sleep instability.[49]

Overall, the different studies reveal a direct involvement of CAP in sleep-related learning and memory; in particular, during the A1 phase of CAP (characterized by EEG slow oscillations and mainly represented during SWS), EEG synchronization shows quasi-optimal network organization for information processing.[50,51] This correlation has also been reported in individuals with Asperger syndrome[52] and in hypermnesic individuals.[53] Further, a correlation between CAP rate and A1 index in SWS with Verbal IQ, Full-scale IQ, and the Memory and Learning Transfer Reading test (which is a measure of dyslexic impairment) has been found in a group of children with dyslexia;[54] also, a reduction in NREM sleep instability in terms of CAP rate, mainly during SWS, has been found in children with learning disability.* In addition to the suggested role for SWS, increases in spindle activity, numbers and density of spindles and in the duration of stage 2 NREM sleep are prominent after learning of verbal memory tasks,[55,56] as well as after visuospatial learning and learning of complex procedural motor skills.[55,57]

It is, therefore, probable that both SWS and spindles are involved in memory and learning. Learning before sleep modulates the regional expression of slow-wave activity, and spindle density during subsequent NREM sleep is important for plastic modifications underlying memory formation.[43,55,56]

Considerations on the cognitive consequences of sleep disruption in children with epilepsy

Given that brain lesions could affect bioelectrical activity either by modifying the EEG patterns that contribute to build a 'normal' sleep structure and/or by triggering a spike activity, it is virtually impossible to keep separate the contribution of central nerve system lesions to sleep and epilepsy.

Common polysomnogram findings in individuals with epilepsy are represented by enhanced sleep fragmentation and higher proportions of wakefulness and light sleep, with a decrease in stages 3 and 4 and REM.[58] On the other hand, CAP analysis shows that individuals with epilepsy exhibit marked sleep instability, even in the absence of nocturnal seizures.[59,60] Brief bursts of spikes, polyspikes, and spike–wave-like discharges are frequently associated with phase A1 of the CAP, which has an activating effect on epileptiform discharges[61,62] (whereas phase B exerts a powerful and prolonged inhibitory action).[59]

EEG synchronizing activity, either during SWS[63–65] or in stage 2 NREM,[63,66] facilitates the occurrence of epileptic discharges in both symptomatic and idiopathic tonic–clonic generalized epilepsy, whereas, in other idiopathic epilepsies, such as benign epilepsy with centrotemporal spikes or childhood absence epilepsy, discharges are mainly modulated by sigma and spindling activity.[67]

This interaction between EEG synchronizing events during sleep and EEG discharges could explain the relationships between cognitive deficit and epilepsy in children. The influence of epileptiform discharges on EEG sleep phasic events, e.g. slow-wave activity and spindles (whose orderly representation serves as building blocks for memory consolidation), could be responsible for the cognitive impairment in epilepsy,[2] even in the absence of associated seizures.[68]

Based on this assumption, even apparently subclinical epileptic discharges (not only 'subtle' seizures) during sleep may disrupt cognitive functions because of sleep structure disruption. It has also been postulated that many developmental or acquired defects of language (such as acquired epileptic aphasia or Landau–Kleffner syndrome) and behaviour (such as autism) in children are a consequence of apparently subclinical spikes during sleep.[2]

It has been suggested that the cognitive functions of a specific cortical area might be affected by the concomitant presence of epileptic focal discharges during sleep in the same area.[2] This disruption has been demonstrated even in a benign form of epilepsy, when abundant spike–wave activity persists during sleep and in ESES.[2,69] We hypothesize, therefore, that epileptiform activity may interfere with neuroplasticity processes when it occurs in a specific area involved in learning activity during sleep, thus disturbing the natural occurrence of learning-dependent slow wave activity or spindle activity.

Specific models supporting this hypothesis are the temporary cognitive deficits reported in children with ESES (in which the prolonged focal epileptic activity during sleep interferes with local slow-wave activity),[2] the linguistic skills impairment observed in children with Landau–Kleffner syndrome showing a persistent left frontotemporal epileptic focus,[2] and the cognitive impairment observed in nocturnal frontal lobe epilepsy.[42]

Unfortunately, interictal epileptic discharges (IEDs) continue to be unaffected by most currently used AEDs at a therapeutic level.[70] Thus, there is a need to assess the effects of IEDs on typical cerebral activity, to determine the blood levels of AED that prevent or reduce IED, and to arrange a

*North American usage: mental retardation.

standardized battery to evaluate the detection of IED-associated cognitive impairment.[71] In this regard, benzodiazepines, such as clobazam[72] and nitrazepam,[73] have been suggested to be useful in preventing the spread of IEDs during sleep, both in children with refractory frontal lobe epilepsy[73] and those with ESES clinical spectrum,[72] but these preliminary results need to be confirmed in a larger cohort of children with epilepsy.

CONCLUSIONS

Prolonged focal epileptic activity during sleep would, per se, interfere with NREM and REM sleep physiology, thus impairing, at multiple levels, the neural-related learning processes and, possibly, the local plastic changes associated with learning and other cognitive functions. The 'timing exposure concept' (age at onset) clearly makes the condition at developmental age markedly different from what occurs in adults. An early recognition and therapeutic intervention devoted to seizures and epileptiform discharges reduction, with a careful choice of AEDs and with the stabilization of sleep structure, should represent the main goals to prevent the negative effects of epilepsy on cognitive functioning in children. Unfortunately, to our knowledge strong evidence is not available in the literature, and there is great need for randomized controlled studies in this popular topic.

REFERENCES

1. Austin JK, Harezlak J, Dunn DW, Huster GA, Rose DF, Ambrosius WT. Behavior problems in children before first recognized seizures. *Pediatrics* 2001; **107:** 115–22.
2. Tassinari CA, Cantalupo G, Rios-Pohl L, Giustina ED, Rubboli G. Encephalopathy with status epilepticus during slow sleep: 'the Penelope syndrome'. *Epilepsia* 2009; **50** (Suppl. 7): 4–8.
3. Zucconi M, Ferini-Strambi L. NREM parasomnias: arousal disorders and differentiation from nocturnal frontal lobe epilepsy. *Clin Neurophysiol* 2000; **111** (Suppl. 2): S129–35.
4. Stores G. Rapid eye movement sleep behaviour disorder in children and adolescents. *Dev Med Child Neurol* 2008; **50:** 728–32.
5. Macleod S, Ferrie C, Zuberi SM. Symptoms of narcolepsy in children misinterpreted as epilepsy. *Epileptic Disord* 2005; **7:** 13–7.
6. Manni R, Terzaghi M, Repetto A. The FLEP scale in diagnosing nocturnal frontal lobe epilepsy, NREM and REM parasomnias: data from a tertiary sleep and epilepsy unit. *Epilepsia* 2008; **49:** 1581–5.
7. Stores G, Wiggs L, Campling G. Sleep disorders and their relationship to psychological disturbance in children with epilepsy. *Child Care Health Dev* 1998; **24:** 5–19.
8. Cortesi F, Giannotti F, Ottaviano S. Sleep problems and daytime behaviour in childhood idiopathic epilepsy. *Epilepsia* 1999; **40:** 1557–65.
9. Becker DA, Fennell EB, Carney PR. Sleep disturbance in children with epilepsy. *Epilepsy Behav* 2003; **4:** 651–8.
10. Wirrel E, Blackman M, Barlow K, Mah J, Hamiwka L. Sleep disturbances in children with epilepsy compared with their nearest-aged siblings. *Dev Med Child Neurol* 2005; **47:** 754–9.
11. Batista BH, Nunes ML. Evaluation of sleep habits in children with epilepsy. *Epilepsy Behav* 2007; **11:** 60–4.
12. Bazil CW, Walczak TS. Effects of sleep and sleep stage on epileptic and non-epileptic seizures. *Epilepsia* 1997; **38:** 56–62.
13. Nunes ML, Ferri R, Arzimanoglou A, Curzi L, Appel CC, Costa da Costa J. Sleep organization in children with partial refractory epilepsy. *J Child Neurol* 2003; **18:** 763–6.
14. Baxter P. Epilepsy and sleep. *Dev Med Child Neurol* 2005; **47:** 723 (Editorial).
15. Miano S, Paolino MC, Peraita-Adrados R, Montesano M, Barberi S, Villa MP. Prevalence of EEG paroxysmal activity in a population of children with obstructive sleep apnoea syndrome. *Sleep* 2009; **32:** 522–9.
16. Tezer FI, Rémi J, Noachtar S. Ictal apnoea of epileptic origin. *Neurology* 2009; **72:** 855–7.
17. Foldvary-Schaefer N. Obstructive sleep apnoea in patients with epilepsy: does treatment affect seizure control? *Sleep Med* 2004; **4:** 483–4.
18. Oliveira AJ, Zamagni M, Dolso P, Bassetti MA, Gigli GL. Respiratory disorders during sleep in patients with epilepsy: effect of ventilatory therapy on EEG interictal epileptiform discharges. *Clin Neurophysiol* 2000; **111** (Suppl. 2): S141–5.
19. Kaleyias J, Cruz M, Goraya JS, et al. Spectrum of polysomnographic abnormalities in children with epilepsy. *Pediatr Neurol* 2008; **39:** 170–6.
20. Bazil CW, Short D, Crispin D, Zheng W. Patients with intractable epilepsy have low melatonin, which increases following seizures. *Neurology* 2000; **55:** 1746–8.
21. Fenoglio-Simeone K, Mazarati A, Sefidvash-Hockley S, et al. Anticonvulsant effects of the selective melatonin receptor agonist ramelteon. *Epilepsy & Behav* 2009; **16:** 52–7.
22. Coppola G, Iervolino G, Mastrosimone M, La Torre G, Ruiu F, Pascotto A. Melatonin in wake-sleep disorders in children, adolescents and young adults with mental retardation with or without epilepsy: a double-blind, cross-over, placebo-controlled trial. *Brain Dev* 2004; **26:** 373–6.
23. Foldvary-Schaefer N, Grigg-Damberger M. Sleep and epilepsy: what we know, don't know, and need to know. *J Clin Neurophysiol* 2006; **23:** 4–20.
24. Legros B, Bazil CW. Effects of antiepileptic drugs on sleep architecture: a pilot study. *Sleep Med* 2003; **4:** 51–5.
25. Bazil CW. Nocturnal seizures and the effects of anticonvulsants on sleep. *Curr Neurol Neurosci Rep* 2008; **8:** 149–54.
26. Salinsky MC, Oken BS, Binder LM. Assessment of drowsiness in epilepsy patients receiving chronic antiepileptic drug therapy. *Epilepsia* 1996; **37:** 181–7.
27. Placidi F, Diomedi M, Scalise A. Effect of anticonvulsants on nocturnal sleep in epilepsy. *Neurology* 2000; **54:** S25–32.
28. Foldvary N, Perry M, Lee J, et al. The effects of lamotrigine on sleep in patients with epilepsy. *Epilepsia* 2001; **42:** 1569–73.
29. Bell C, Vanderlinden H, Hiersemenzel R. The effects of levetiracetam on objective and subjective sleep parameters in healthy volunteers and patients with partial epilepsy. *J Sleep Res* 2002; **11:** 255–63.
30. Schmitt B, Martin F, Critelli H, Molinari L, Jenni OG. Effects of valproic acid on sleep in children with epilepsy. *Epilepsia* 2009; **50:** 1860–7.
31. Hermann BP, Jones JE, Sheth R, et al. Growing up with epilepsy: a two-year investigation of cognitive development in children with new onset epilepsy. *Epilepsia* 2008; **49:** 1847–58.
32. Berg AT, Langfitt JT, Testa FM, et al. Global cognitive function in children with epilepsy: a community-based study. *Epilepsia* 2008; **49:** 608–14.
33. Staden U, Isaacs E, Boyd SG, Brandl U, Neville BG. Language dysfunction in children with Rolandic epilepsy. *Neuropediatrics* 1998; **29:** 242–8.
34. Deonna T, Zesiger P, Davidoff V, Maeder M, Mayor C, Roulet E. Benign partial epilepsy of childhood: a longitudinal neuropsychological and EEG study of cognitive function. *Dev Med Child Neurol* 2000; **42:** 595–603.
35. Stephani U, Carlsson G. The spectrum from BCECTS to LKS: the Rolandic EEG trait-impact on cognition. *Epilepsia* 2006; **47** (Suppl. 2): 67–70.
36. Baglietto MG, Battaglia FM, Nobili L. Neuropsychological disorders related to interictal epileptic discharges during sleep in benign epilepsy of childhood with centrotemporal or Rolandic spikes. *Dev Med Child Neurol* 2001; **43:** 407–12.
37. Kavros PM, Clarke T, Strug LJ, Halperin JM, Dorta NJ, Pal DK. Attention impairment in rolandic epilepsy: systematic review. *Epilepsia* 2008; **49:** 1570–80.
38. Piccinelli P, Borgatti R, Aldini A, et al. Academic performance in children with rolandic epilepsy. *Dev Med Child Neurol* 2008; **50:** 353–6.
39. Lillywhite LM, Saling MM, Harvey AS, et al. Neuropsychological and functional MRI studies provide converging evidence of anterior language dysfunction in BECTS. *Epilepsia* 2009; **50:** 2276–84.
40. Fonseca LC, Tedrus GM, Pacheco EM. Epileptiform EEG discharges in benign childhood epilepsy with centrotemporal spikes: reactivity and transitory cognitive impairment. *Epilepsy Behav* 2007; **11:** 65–70.
41. Caplan R, Siddarth P, Stahl L, et al. Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities. *Epilepsia* 2008; **49:** 1838–46.
42. Patrikelis P, Angelakis E, Gatzonis S. Neurocognitive and behavioral functioning in frontal lobe epilepsy: a review. *Epilepsy Behav* 2009; **14:** 19–26.

43. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. *Nature* 2004; **430:** 78–81.

44. Diekelmann S, Wilhelm I, Born J. The whats and whens of sleep-dependent memory consolidation. *Sleep Med Rev* 2009; **13:** 309–21.

45. Marshall L, Helgadóttir H, Mölle M, Born J. Boosting slow oscillations during sleep potentiates memory. *Nature* 2006; **444:** 610–3.

46. Eschenko O, Ramadan W, Mölle M, Born J, Sara SJ. Sustained increase in hippocampal sharp-wave ripple activity during slow-wave sleep after learning. *Learn Mem* 2008; **15:** 222–8.

47. Rasch B, Buchel C, Gais S, Born J. Odor cues during slow-wave sleep prompt declarative memory consolidation. *Science* 2007; **315:** 1426–9.

48. Ferri R, Bruni O, Miano S, Terzano MG. Topographic mapping of the spectral components of the cyclic alternating pattern (CAP). *Sleep Med* 2005; **6:** 29–36.

49. Terzano MG, Parrino L. Origin and significance of the cyclic alternating pattern (CAP). *Sleep Med Rev* 2000; **4:** 101–23.

50. Ferri R, Rundo F, Bruni O, Terzano MG, Stam CJ. The functional connectivity of different EEG bands moves towards small-world network organization during sleep. *Clin Neurophysiol* 2008; **119:** 2026–36.

51. Ferri R, Huber R, Aricò D, et al. The slow-wave components of the cyclic alternating pattern (CAP) have a role in sleep-related learning processes. *Neurosci Lett* 2008; **432:** 228–31.

52. Bruni O, Ferri R, Vittori E, et al. Sleep architecture and NREM alterations in children and adolescents with Asperger syndrome. *Sleep* 2007; **30:** 1577–85.

53. Ferini-Strambi L, Ortelli P, Castronovo V, Cappa S. Increased periodic arousal fluctuations during non-REM sleep are associated to superior memory. *Brain Res Bull* 2004; **63:** 439–42.

54. Bruni O, Ferri R, Novelli L, et al. Sleep spindle activity is correlated with reading abilities in developmental dyslexia. *Sleep* 2009; **32:** 1333–40.

55. Gais S, Molle M, Helms K, Born J. Learning-dependent increases in sleep spindle density. *J Neurosci* 2002; **22:** 6830–4.

56. Schabus M, Hoedlmoser K, Pecherstorfer T, et al. Interindividual sleep spindle differences and their relation to learning-related enhancements. *Brain Res* 2008; **1191:** 127–35.

57. Fogel SM, Smith CT. Learning-dependent changes in sleep spindles and Stage 2 sleep. *J Sleep Res* 2006; **15:** 250–5.

58. Touchon J, Baldy-Moulinier M, Billiard M, Besset A, Cadilhac J. Sleep organization and epilepsy. *Epilepsy Res* 1991; **2** (Suppl.): 73–81.

59. Parrino L, Halasz P, Tassinari CA, Terzano MG. CAP, epilepsy and motor events during sleep: the unifying role of arousal. *Sleep Med Rev* 2006; **10:** 267–85.

60. Terzaghi M, Sartori I, Mai R, et al. Coupling of minor motor events and epileptiform discharges with arousal fluctuations in NFLE. *Epilepsia* 2008; **49:** 670–6.

61. Ulbert I, Heit G, Madsen J, Karmos G, Halgren E. Laminar analysis of human neocortical interictal spike generation and propagation: current source density and multiunit analysis in vivo. *Epilepsia* 2004; **45** (Suppl. 4): 48–56.

62. Salih F, Khatami R, Steinheimer S, Kretz R, Schmitz B, Grosse P. A hypothesis for how non-REM sleep might promote seizures in partial epilepsies: a transcranial magnetic stimulation study. *Epilepsia* 2007; **48:** 1538–42.

63. Steriade M, Amzica F. Slow sleep oscillation, rhythmic K-complexes, and their paroxysmal developments. *J Sleep Res* 1998; **7** (Suppl. 1): 30–5.

64. Timofeev I, Bazhenov M, Sejnowski T, Steriade M. Cortical hyperpolarization-activated depolarizing current takes part in the generation of focal paroxysmal activities. *Proc Natl Acad Sci USA* 2002; **99:** 9533–7.

65. Steriade M. Sleep, epilepsy and thalamic reticular inhibitory neurons. *Trends Neurosci* 2005; **28:** 317–24.

66. Amzica F, Steriade M. The functional significance of K-complexes. *Sleep Med Rev* 2002; **6:** 139–49.

67. Nobili L, Ferrillo F, Baglietto MG, et al. Relationship of sleep interictal epileptiform discharges to sigma activity (12–16 Hz) in benign epilepsy of childhood with rolandic spikes. *Clin Neurophysiol* 1999; **110:** 39–46.

68. Laporte N, Sébire G, Gillerot Y, Guerrini R, Ghariani S. Cognitive epilepsy: ADHD related to focal EEG discharges. *Pediatr Neurol* 2002; **27:** 307–11.

69. Wolff M, Weiskopf N, Serra E, Preissl H, Birbaumer N, Kraegeloh-Mann I. Benign partial epilepsy in childhood: selective cognitive deficits are related to the location of focal spikes determined by combined EEG/MEG. *Epilepsia* 2005; **46:** 1661–7.

70. D'Antuono M, Köhling R, Ricalzone S, Gotman J, Biagini G, Avoli M. Antiepileptic drugs abolish ictal but not interictal epileptiform discharges in vitro. *Epilepsia* 2009; (Epub ahead of print) DOI: 10.1111/j.1528–1167.2009.02273.x.

71. Parisi P. News on the horizon is not good: interictal epileptic discharges continue to be unaffected by the therapeutic level of AEDs. *Epilepsia* (Forthcoming).

72. Kramer U, Sagi L, Goldberg-Stern H, Zelnik N, Nissenkorn A, Ben-Zeev B. Clinical spectrum and medical treatment of children with electrical status epilepticus in sleep (ESES). *Epilepsia* 2009; **50:** 1517–24.

73. Parisi P, Pelliccia A, Luchetti A, Miano S, Franci S, Villa MP. Nitrazepam in pediatric refractory frontal lobe epilepsy. 7th European Congress on Epileptology, International League against Epilepsy', Helsinki, 2–6 July 2006: Book Abstracts: 195–6.