

# The contribution of sleep to cognitive function in children with epilepsy

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I, Samantha Yuen-Sum Chan, confirm the work presented in this thesis is my own. Where information has been derived from other sources, I confirm this has been indicated in the thesis.

Signed: ..... Date: .....

## Abstract

Cognitive impairment is the major co-morbidity in childhood epilepsy, and in many cases will have a larger long-term impact than the seizures themselves. However, the mechanisms contributing to this are poorly understood, precluding targeted intervention. Sleep is crucial for intellectual functioning. Yet sleep in children with epilepsy, and its impact on intellectual function has scarcely been studied. This thesis aims to examine the structure and regulation of sleep in children with epilepsy, and to provide direct evidence of the impact of sleep on cognitive function by correlating neurophysiological characteristics with performance on sleep-dependent neuropsychological tasks administered over the same interval as the sleep recorded.

To examine sleep architecture in children with epilepsy, I developed a modified system for visual sleep scoring, taking into account nocturnal seizures and interictal activity. This was validated in a pilot sample, then applied to the scoring of 52 recordings from children with epilepsy. Based on established memory consolidation tasks and open-source psycholinguistic data, I developed and piloted a memory consolidation task battery suitable for testing school-aged English-speaking children, comprising parallel versions of a visuospatial and a verbal task.

With these tools, I performed a prospective, within-subject comparison of memory retention across similar length intervals with or without sleep, in order to determine the contribution of sleep to memory consolidation. I compared results from patient (n=22) and healthy control (n=21) samples, finding – contrary to expectations – that sleep benefits memory consolidation in children with epilepsy to the same degree as controls. However, the benefit of sleep showed an inverse relationship to the nocturnal interictal discharge load. I also employed quantitative EEG analysis of slow wave activity to examine sleep homeostasis in patients with epilepsy, studying a retrospective sample (n=16) who had undergone partial sleep deprivation. Sleep homeostasis was fundamentally intact in these patients, who had similar clinical characteristics to the prospective sample.

Findings from this thesis provide the first direct evidence that sleep benefits intellectual functioning in children with epilepsy, particularly where its structure and regulation is intact. Sleep-related memory consolidation may represent a compensatory mechanism, perhaps accounting for the relative cognitive preservation in this cohort of children with epilepsy with a structural aetiology, despite the early onset of seizures.

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# **Own contributions**

## **Study design**

The study design for Chapter 11 was conceived by Prof Cross and Prof Baldeweg. With their guidance I worked out the details of the study protocol and was entirely responsible for its practical implementation. The study design for Chapter 10 was conceived and developed by me, with guidance from Prof Baldeweg.

## **Participant recruitment**

Patient recruitment was carried out entirely by me; I produced and distributed publicity posters and contacted the relevant clinicians. After families had agreed to speak to a researcher, I approached all 40 families myself, and obtained consent from all 28 who agreed to take part. Control participants were recruited with help from Angela Mensah, who circulated an internal email to all staff at Young Epilepsy on my behalf. She also helped co-ordinate the testing schedule and assisted with email correspondence. I met with and obtained consent from all 22 participating families.

## **Memory task and sleep scoring system design**

The creation of the memory task battery is detailed in Chapter 8; this was entirely my own work. I received some useful comments from Dr Susanne Diekelmann, who tried out the app on her Android phone. The development of the sleep scoring system is detailed in Chapter 7; I received much valuable feedback throughout the process from Dr Ronit Pressler.

## **Patient testing**

Administration of the memory task battery to the patient cohort was performed mainly by me, with some assistance from my Neuroscience BSc placement year student, Cleo Chevalier-Riffard. For the administration of the memory task battery to the control group, I was assisted by Hannah Scrivener and Holly Sayer, Psychology Assistants at Young Epilepsy. EEG recordings in the control group were performed by me; I was trained in the placement of electrodes and the setting up of the recording system by physiologists at Great Ormond Street Hospital (GOSH) and Young Epilepsy. I set up the first two ambulatory studies under the supervision of Fiona Chivers, Clinical Neurophysiologist. I set up the remainder of the studies independently. I administered the Wechsler Abbreviated Scales of Intelligence (WASI) to all the control subjects myself, after observing fellow PhD student Louise Croft and receiving advice from Colin Reilly, Educational Psychologist at Young Epilepsy. EEG studies and neuropsychological testing on the patient cohort were performed as part of the clinical evaluation by physiologists and psychologists at GOSH.

## **Data processing and primary analysis**

Clinical data retrieval was performed entirely by me. I had assistance with questionnaire scoring and with EEG data retrieval for the retrospective sample from Cleo Chevalier-Riffard.

## **Statistical analysis and data interpretation**

I performed the statistical analysis on all the data for Chapters 7, 8 and 11 myself, with advice and some practical help from Prof Baldeweg. For Chapter 10, I advised and assisted Ms Chevalier-Riffard, who performed the initial analysis as part of her BSc placement year project. I repeated some of the analyses and performed new analyses on the existing processed data for the writing of Chapter 10.

# Publications arising from this thesis

## Chapter 11

- Chan S, Pressler R, Boyd SG, Baldeweg T, Cross JH. Does sleep benefit memory consolidation in children with focal epilepsy? *Epilepsia*. 2017 Mar;58(3):456-466. doi: 10.1111/epi.13668
- Chan S, Chevalier-Riffard C, Sayer H, Scrivener H, Pressler R, Boyd S, Baldeweg T, Cross JH. Sleep architecture and memory consolidation in children with focal epilepsy. *The Lancet* 2016. 387(1): S24 Abstract

## Chapter 10

- Chan S, Chevalier-Riffard C, Baldeweg T et al. Sleep homeostasis in children with focal epilepsy following sleep deprivation: relationship to seizure propensity. *Epilepsy Curr* 2015; 15: 86. Abstract.

## Chapter 8

- Chan S, Chevalier-Riffard C, Pressler R, Baldeweg T, Cross H. Examining sleep-related memory consolidation in children with epilepsy – design of verbal and visuospatial memory tasks and preliminary results. *Dev Med Child Neurol* 2014. 56(S3):12 Abstract

## Chapter 7

- Chan S, Chevalier-Riffard C, Pressler R, Baldeweg T, Cross H. An approach to staging sleep in polysomnographic studies in children with focal epilepsy. *Epilepsia* 2014. 55 (Suppl. 2):67 Abstract

**Literature review**

- Chan S, Baldeweg T, Cross JH. A role for sleep disruption in cognitive impairment in children with epilepsy. *Epilepsy Behav* 2011 Mar;20(3):435-40



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## **Part I**

# **Literature review**



# Chapter 1

## Seizures and epilepsy

“Men think epilepsy divine, merely because they do not understand it.” - Hippocrates c.460-377BC

### 1.1 Classification of epileptic seizures and syndromes

Epilepsy is not a single disease, but a collection of disorders characterised predominantly by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition (Fisher et al. 2005). An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al. 2005).

The current International League Against Epilepsy (ILAE) classification of seizures remains an operational one based on semiology (Scheffer et al. 2017). Seizures can be classified according to their onset – “focal” or “generalised”, or “unknown” if there is insufficient information to determine this. While a generalised onset implies altered awareness from the start, focal onset seizures may be further divided according to the presence or absence of impaired awareness. This is a clinically relevant distinction because it has practical implications for the patient. The precise symptoms present at onset – for example, automatisms or sensory symptoms – may be used to classify the seizure further (Figure ??). A focal onset seizure may evolve into a bilateral tonic-clonic seizure.

Epilepsies can similarly be divided into “focal”, “generalised” and “combined focal and generalised” types (Fisher et al. 2017), with some remaining of unknown type. Here, the typical interictal EEG (electroencephalography) findings aid (but are not essential for) classification: generalised spike and wave activity tends to be found in generalised epilepsy, focal discharges in focal epilepsies, and both tend to be present in the combined group.

It may be possible to further classify a patient's epilepsy by aetiology, the current recognised aetiologic groups being structural, genetic, infectious, metabolic, immune and unknown (Fisher et al. 2017). More than one category may be applied to any given epilepsy, depending on the investigations available. The patients studied in this thesis had focal epilepsies with a structural or presumed structural aetiology. In a population-based study, this group accounted for 103/468 (22%) of all cases of new childhood-onset epilepsy (Wirrell et al. 2014). They are likely to be medication-resistant and have high rates of co-morbid psychopathology (Nabbout et al. 2017).

An epilepsy syndrome is a cluster of features, including seizure types and EEG features, that tend to occur together. There may be distinctive findings on neuroimaging, biochemistry, immune serology or other aetiological investigations. Age of onset, seizure triggers, circadian patterns (see Section 4.4) and associated co-morbidities (see Section 2.2) may also be important defining features. Though there is no formal ILAE classification of specific epilepsy syndromes (Berg et al. 2010), many - such as childhood absence epilepsy and autosomal dominant nocturnal frontal lobe epilepsy - are well-recognised clinical entities.

It is important to mention here the 1989 ILAE classification (ILAE commission 1989), because it is these categories that are used in much of the literature cited in this thesis. Epilepsies were classified then, as now, into those with generalised seizures, those with focal ("partial") seizures, and those with both. A second major classifier was whether the epilepsy was attributable to a known ("symptomatic") or unknown ("idiopathic") cause, with the category of "cryptogenic" for those thought to be symptomatic but for which the precise aetiology could not be discerned (ILAE commission 1989). This tier of the classification was often used to segregate patients into groups for studies of outcome, particularly seizure remission and cognitive outcome (Berg et al. 2005, Aldenkamp et al. 2005). A few examples of epilepsy syndromes which fall under each category - taken from the classification paper (ILAE commission 1989) - are presented in the Table 1.1.1 below for illustration. It was recognised that some syndromes - such as West syndrome and Lennox-Gastaut syndrome- could be either symptomatic or cryptogenic. The idiopathic generalised epilepsies are still known as such for historical reasons. It is notable that the epileptic encephalopathies (see Section 2.2) fall under the symptomatic/cryptogenic category. The patients studied in this thesis would also have fallen into the symptomatic (or symptomatic/cryptogenic) category.

Idiopathic	Symptomatic	Cryptogenic
Childhood absence epilepsy	West syndrome	West syndrome
Juvenile myoclonic epilepsy	Rasmussen syndrome	Lennox-Gastaut syndrome
Benign childhood epilepsy with centrotemporal spikes	Aicardi syndrome	Epilepsy with myoclonic-astatic seizures
Childhood epilepsy with occipital paroxysms	Lafora disease	Epilepsy with myoclonic absences

Table 1.1.1: Examples of epilepsy syndromes, categorised under the 1989 ILAE classification

## 1.2 Pathophysiology of seizure activity

### 1.2.1 Generation of interictal discharges

In vitro and at the level of a single neuron, the basis of an interictal epileptiform discharge (IED) is the paroxysmal depolarisation shift (PDS): a depolarisation about ten times as long as a physiological excitatory postsynaptic potential (EPSP), generating a train of action potentials (Browne and Holmes 2008). In experimental animals, the application of an excitatory agent such as penicillin over a focal area of cortex produces high voltage sharp waves on the EEG corresponding to intracellularly recorded PDSs. The sustained neuronal depolarisation is mediated by an influx of calcium ions, while the action potentials are associated with sodium influx. Repolarisation and hyperpolarisation usually follow, mediated by potassium.

In vivo, an epileptogenic focus consists of numerous abnormal neurons that discharge in an abnormally synchronous fashion. PDSs may occur because of intrinsic abnormalities in the membrane ion channels, the receipt of excessive excitatory or deficient inhibitory neurotransmission (Bromfield et al. 2006). Impaired neurotransmitter reuptake may also contribute (Bromfield et al. 2006). Such a "focus", though sometimes manifest as a well-defined structural area of cortex, may be better conceptualised as an abnormal network, sometimes involving thalamic as well as cortical neurons; this is particularly true for spike-wave complexes (Blumenfeld 2005).

The major excitatory neurotransmitter is glutamate. There are several subclasses of glutamate receptor, and amongst these, the ionotropic alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA) receptors are most important in generating PDS (Bromfield et al. 2006). The activation of AMPA and kainate receptors is rapid and relatively transient, while that of NMDA receptors (NMDARs) is slower and voltage-dependent. At resting membrane potentials, magnesium ions enter and bind tightly to the NMDAR pore, preventing further ion permeation. A depolarisation of sufficient amplitude and duration to repel and dislodge the magnesium ions is required to allow the flow of permeant ions, including calcium, to which the NMDAR is highly permeant (Blanke and VanDongen 2009).

The major inhibitory neurotransmitter is GABA (gamma-aminobutyric acid); there are two types of GABA receptor, type A and type B. GABA-A receptors are found post-synaptically and are permeable to chloride ions, which hyperpolarise the membrane and inhibit action potentials. Inhibitory networks and GABAergic cells in particular may also contribute to the generation and sustenance of interictal discharges (de Curtis et al. 2012, Muldoon et al. 2015).

### 1.2.2 Generation of seizures

It is not known precisely what tips the epileptic brain from an interictal to an ictal state (Pavlov et al. 2013). It would seem to follow from the mechanisms of IED generation that given a sufficient temporal and spatial density of IEDs, a seizure should result. However, there is limited human data to support this assertion. In a recent study utilising long-term intracranial EEG recording, Karoly et al (2016) found that the spike rate prior to seizures was significantly increased in just 3 out of 15 human subjects. Depending on recording techniques and individual patient characteristics, seizure onset may variously be associated with increased or decreased synchrony on EEG (Jiruska et al. 2013). It thus follows that in a given patient, the IED rate and the seizure frequency may have differing and independent effects on general brain function, including cognition. Additionally, it is notable that 2-4% of apparently healthy children (Cavazzuti et al. 1980, Grant et al. 2016) and a far higher proportion of those with manifest neurodevelopmental problems (Spence and Schneider 2009, Sánchez Fernández et al. 2015) may have IEDs without ever having seizures.

### 1.2.3 Epileptogenesis and sleep circuitry

“Neurons wire together if they fire together” Siegrid Löwel, 1992 (paraphrasing Hebb, 1949)

“Epileptogenesis” refers to the cellular processes that transform a normal (or potentially normal) brain into one with a tendency to generate recurrent seizures (Blumenfeld 2011, Sloviter and Bumanglag 2013). In vitro (Ziobro et al. 2011) and in vivo (Lévesque et al. 2016, Kandravicius et al. 2014) models of epilepsy demonstrate a “latent period” following the initial brain insult before the first seizure occurs. This period may last days to months (Kandravicius et al. 2014) and is thought to correlate with the years which may elapse before various human epilepsies manifest (Mathern et al. 1995, Nabbut et al. 2017). During this time, plastic changes occur (Koyama 2016) and interictal discharges are seen (Lévesque et al. 2016). It would seem that neural networks need to “learn” in order to generate seizures.

It has been suggested that normal sleep circuitry - such as the spindle rhythm generator, consisting of inhibitory neurons in the reticular thalamic nucleus and excitatory thalamocortical neurons in the dorsal thalamic nuclei - may be “hijacked” to produce epileptiform activity, in this case spike-wave discharges (Beenhakker and Huguenard 2009). The transformation of spindle-like activity into 3Hz spike waves has been demonstrated both in vitro and in vivo, by applying GABA-A receptor antagonists to thalamic slice preparations and the thalami of behaving rats

respectively (Beenhakker and Huguenard 2009).

In turn, ripples and fast ripples are both generated in pyramidal neurons of the hippocampus. The latter, thought to be pathological, are more often recorded in the hippocampus ipsilateral to the seizure onset zone (Andrillon et al. 2011), and are thought to represent the co-ordinated firing of pathologically connected clusters of neurons (Beenhakker and Huguenard 2009). It has been hypothesised that recurrent IEDs may contribute to epileptogenesis by strengthening the synaptic connections between neurons in the epileptogenic focus (Staley and Dudek 2006). Using simultaneous scalp and intracranial EEG recordings, Bower et al (2017) showed that pre-seizure changes in neuronal activity may be reactivated in subsequent slow wave sleep, suggesting that these patterns of firing could be consolidated in a similar way to sequences which represent learned behaviours or memories (see Section 5.2).

Thus it would seem that sleep and epilepsy are intertwined at the most fundamental level. I argue later in this literature review that a primary function of sleep is to enable learning (Section 5.1). Therefore it is perhaps unsurprising that cognitive difficulties are common in patients with epilepsy. Additionally, the mechanisms underlying deranged learning at the neuronal level may ultimately account for both epileptogenesis and cognitive impairment in these patients.



## Chapter 2

# Cognitive impairment in children with epilepsy

### 2.1 Epidemiology and importance

Cognitive impairment is a frequent co-morbidity in childhood epilepsy, and is the most important predictor of poor social outcome in adulthood (Camfield and Camfield 2007b). Population-based registers of children with epilepsy put the prevalence of mental retardation at 21-26% (Camfield and Camfield 2007a, Berg et al. 2008), while a recent community-based study of those with “active epilepsy” – defined as being on antiepileptic medication or having had a seizure in the past year – found that 40% of these children had an IQ below 70 (Reilly et al. 2015). Major independent risk factors for cognitive impairment in epilepsy include an early age of seizure onset (Aldenkamp et al. 2005, Berg et al. 2008, Cormack et al. 2007, O’Callaghan et al. 2011) and continuing seizures/pharmacoresistance (Karrasch et al. 2017, Berg et al. 2012).

Several groups have attempted to segregate the effects of aetiology from the effects of continued illness and medical intervention by examining children at or soon after initial presentation. Fastenau et al (2009) compared 282 children presenting with a first unprovoked seizure to 147 sibling controls. Even within three months of presentation, relative deficits could be detected in attention/concentration and executive function. Symptomatic/cryptogenic aetiology and AED use emerged as the factors associated with the greatest odds for neuropsychological impairment, though a history of multiple seizures and epileptiform activity on the initial EEG were also predictive of deficits. Berg et al (2005) examined the use of special educational services in 613 children at the time of first diagnosis with epilepsy, finding that 54% of those with a remote symptomatic aetiology had been in receipt of services before their first seizure, compared with 15% of those with an idiopathic/cryptogenic

aetiology, and 13-14% of the local general child population.

These data show that a significant proportion of the intellectual deficits seen in childhood epilepsy are pre-existing, and depending on the precise aetiological basis, may not be modifiable by the time of presentation with the first seizure. However, evidence from the same sources suggests that the subsequent course of epilepsy may influence cognitive outcomes - encouragingly, none of the children in the cohort of Fastenau (2009) showed deficits in academic achievement, while some of those in the cohort of Cormack later showed gains in intellectual function following seizure cessation (Skirrow et al. 2011). This suggests that there is a window for intervention, and that a better understanding of how ongoing seizures and epileptiform activity influence neuropsychological development could lead to significant improvements in the care of children with epilepsy. Here I outline several paradigms which summarise the current state of knowledge.

## 2.2 Epileptic encephalopathies

The term epileptic encephalopathy relates to the concept that cognitive and behavior disturbances in the context of epilepsy are, at least in part, caused by ongoing epileptic activity, whether clinical or subclinical. Specifically, there are a group of childhood epilepsy syndromes characterized by developmental arrest or regression associated with frequent or severe seizures or subcontinuous paroxysmal interictal activity, where this concept particularly applies (Nabbout and Dulac 2003, Berg et al. 2010). Examples include Otahara, West, Dravet, Lennox–Gastaut and Landau-Kleffner syndromes. The electrographic and clinical manifestations of these syndromes are strongly age-related, often independent of the underlying cause. In the last few years, specific ion channel, neurotransmission and synaptic function genes have been implicated, particularly in the neonatal and infant-onset epileptic encephalopathies (Auvin et al. 2016), but findings so far do not alter the basic concept.

In encephalopathy with status epilepticus during slow sleep (ESES; Tassinari et al. 2009), which could be regarded as the archetypal epileptic encephalopathy, neuropsychological regression occurs in tandem with the appearance of continuous spike waves in slow wave sleep (CSWS). EEG resolution with treatment is associated with cognitive recovery. Conversely, when treatment fails to abolish CSWS, there may be severe residual impairments (Sánchez Fernández et al. 2012). In Landau-Kleffner syndrome, there is CSWS with predominant language regression; the duration of CSWS may be correlated with severity of language outcome (Robinson et al. 2001). In West syndrome, several studies have shown that a longer lead time to treatment adversely influences cognitive outcome, even across aetiologic

groups (Koo et al. 1993, Primec et al. 2006, O'Callaghan et al. 2011).

Lennox-Gastaut syndrome is defined by the association of multiple seizure types (particularly tonic seizures), cognitive impairment, and an interictal EEG pattern of diffuse, slow spike-wave complexes (Arzimanoglou et al. 2009) - however these features appear over time, and none of them is pathognomonic. Despite the wide variety of aetiologies - including brain injury, developmental anomalies, genetic causes (e.g. tuberous sclerosis) - the presentation and course of the illness is remarkably consistent. Early age of onset and poor seizure control are associated with worse cognitive outcome (Arzimanoglou et al. 2009).

The genetic basis of Dravet syndrome (DS) has been subject to intense study in the past decade (Depienne et al. 2009, Gataullina and Dulac 2017); mutations in the voltage-gated sodium channel gene *SCN1A* are found in 60–80% of patients (Depienne et al. 2009). Cognitive impairment - manifest as developmental slowing or arrest from the time of presentation rather than regression - is universal in DS, yet the cognitive outcome appears unrelated to age of seizure onset (Villeneuve et al. 2014, Nabbout et al. 2013). However, the electroclinical characteristics of Dravet syndrome are polymorphic (Scheffer 2012), and there is evidence that certain electroclinical features - myoclonic seizures (Bureau and Bernardina 2011;Nabbout et al. 2013), photo- or pattern sensitivity, frequent interictal discharges (Bureau and Bernardina 2011) and generalised spike-wave discharges (Bureau and Bernardina 2011;Kim et al. 2014) - may be associated with worse cognitive outcome. Additionally, the early period of continued developmental progress is associated with a striking lack of epileptiform activity on the EEG despite frequent episodes of status epilepticus (Scheffer 2012).

### **2.3 Long-term effects of seizure elimination**

At present, antiepileptic drugs - which essentially lower seizure threshold without altering the underlying cause of the epilepsy - are still the mainstay of epilepsy treatment. All antiepileptic drugs have some effect on cognitive function, mostly adverse (Ijff and Aldenkamp 2013). However, non-pharmacological treatments which directly address the cause of seizures - such as epilepsy surgery for those with a structural aetiology, and the ketogenic diet for glucose transporter type 1 (GLUT1) deficiency syndrome may also benefit cognition. Children who undergo surgery for drug-resistant focal epilepsy have been shown to maintain their IQ postoperatively, with improvements seen in the longer term (Freitag and Tuxhorn 2005;Skirrow et al. 2011). Freitag and Tuxhorn (2005) found that cognitive improvements were associated with seizure freedom in their surgical cohort with mixed lesional aetiologies. Skirrow et al (2011) studied patients with temporal lobe epilepsy, comparing a co-

hort who underwent surgery in childhood to a similar group who did not undergo surgery. Greater gains in IQ over time (beyond 6 years' follow-up) were seen in the surgical group, 86% of whom were seizure-free at follow-up, compared to 36% of the control group. Drug withdrawal was associated with greater gains in IQ, a finding recently replicated in a large multicentre study (Boshuisen et al. 2015). As with the epileptic encephalopathies, there is some evidence that a shorter lead time to surgery may be associated with better cognitive outcome (Freitag and Tuxhorn 2005, Shurtleff et al. 2015).

Ramm-Petersen et al (2013) described cognitive improvement at long term follow-up in a Norwegian cohort with GLUT1 deficiency (n=10) treated with the ketogenic diet. In particular, two patients diagnosed in infancy who became seizure-free after commencing the ketogenic diet showed normal neurodevelopment at 3 and 6 years respectively.

## 2.4 Animal models

Early life seizures may be modelled by inducing seizures in normally developing young animals, allowing the researcher to control the age of seizure onset, and to separate the effect of seizures from the effect of underlying aetiology (Holmes 2016). Rat pups subjected to experimental febrile status epilepticus (FES; Dubé et al. 2006) or seizures induced by flurothyl administration (Pitkänen et al. 2005) show deficits in spatial memory, auditory discrimination and behavioural flexibility when tested in adolescence and adulthood (Holmes 2016). In vitro recording using brain slices from flurothyl rats showed impairment of inhibitory GABAergic synaptic transmission in the juvenile period (Isaeva 2006), and alterations in both short-term (Hernan et al. 2013) and long-term (Isaeva et al. 2013) potentiation in the pre-frontal cortex at adolescence and maturity. In vivo recordings from the hippocampi of behaving FES and flurothyl animals showed deficits in the firing characteristics of place cells (see Section 5.2) in association with impaired spatial cognition (Holmes 2016). These studies provide evidence that seizures themselves may contribute to cognitive impairment, and suggest possible underlying mechanisms.

Interictal spikes may be induced in animals by the application of excitatory agents directly to the cortex (see Section 1.2.1). This allows researchers to time the occurrence of these with respect to critical windows in neurodevelopment, such as the neonatal period for the development of visual pathways in altricial mammals (Wiesel and Hubel 1963). Sensory deprivation during this time in this case, by suturing one of the animal's eyelids shut results in a lasting monocular visual deficit (Hubel and Wiesel 1970). In a rabbit model, IEDs generated by the application of penicillin (Baumbach and Chow 1981) or bicuculline (Ostrach et al. 1984) to the stri-

ate cortex disrupt the development of the receptive visual field properties of neurons in the lateral geniculate nucleus (LGN) of neonatal but not adult animals, reproducing the effect of sensory deprivation. This evidence suggests that IEDs occurring in the relevant cortical areas during critical periods of early human development may result in enduring deficits, and is a strong argument for intervention.

Recent advances in epilepsy genetics have led to the creation of various animal models carrying mutations in the implicated genes (Holmes 2016, Galanopoulou and Moshé 2015). Models of Dravet syndrome (see Section 2.2 above) appear to have spatial and social cognitive problems as well as thermally-induced and spontaneous seizures (Holmes 2016). While such models may not necessarily help to discern the mechanisms of cognitive impairment, the exercise of rescuing the phenotype (Galanopoulou and Moshé 2015) may lead to aetiology-based interventions that also improve cognition (Ohmori et al. 2014).

Animal models may also be used to illustrate the contribution of sleep to neural plasticity (Dang-Vu et al. 2006). Rapid eye movement (REM) sleep is at its most plentiful during the neonatal period, coinciding with the critical period for visual development. Adding REM sleep deprivation to the monocular deprivation model of Hubel resulted in an even greater difference in the size of LGN cells activated by the open and deprived eyes than monocular deprivation alone (Oksenberg et al. 1996). It is notable that children - including infants - with epilepsy tend to have less REM sleep than age-matched controls (see Section 4.2) and perhaps exist in a state of relative REM deprivation.

## 2.5 Transitory cognitive impairment

The concept of transitory cognitive impairment (TCI) was first proposed by Aarts in 1984, and refers to momentary cognitive deficits which occur during interictal epileptiform discharges (Aarts et al. 1984). It is demonstrated by continuous neuropsychological testing while attached to EEG monitoring, each stimulus presentation and response time-locked to the EEG (Binnie 2003). An excess of errors (Binnie 2003) or delayed reaction times (Aldenkamp and Arends 2004) during epochs containing IEDs over those without indicates impairment. Tasks involving working memory seem most sensitive to TCI, while IED laterality appears to correspond with the domain (verbal or visuospatial) affected (Binnie 2003). While an elegant approach in theory because the within-patient comparison controls for aetiological and therapeutic confounding factors, the demonstration of TCI is necessarily limited by the available technology. Early studies required patients with frequent IEDs in the alert state (Aarts et al. 1984) - and even then could only show TCI in 50% of subjects; or else risked conflating the effects of IEDs with those of subtle seizures

(reviewed in Binnie 2003, Aldenkamp and Arends 2004). Findings from the best-performed studies of the 1980s suggest that IEDs occurring during stimulus presentation had the largest effect (Aarts et al. 1984, Shewmon and Erwin 1988). In more recent years, Nicolai et al. (2012) and Pressler et al. (2006) have used the TCI task batteries of Aarts and Binnie to examine the effect of IEDs on neuropsychological performance at a group level. The former found an adverse effect of more frequent discharges on neuropsychological performance in a prospective cross-sectional study (Nicolai et al. 2012), while the latter found - in a randomised, double-blind crossover trial - that reducing the interictal discharge load with lamotrigine had no impact on performance (Pressler et al. 2006). These conflicting results suggest that scalp EEG likely lacks the spatial resolution to detect the actual abnormal neuronal activity which may disrupt the learning process (Holmes 2013, Krauss et al. 1997). EEG-fMRI may provide a non-invasive means of surmounting this limitation (Van Bogaert et al. 2012); this has been attempted - but was not successfully demonstrated - in a single patient (Moeller et al. 2010). Two groups have now utilised intracranial EEG in the examination of TCI: Kleen et al (2013) examined ten temporal lobe epilepsy patients implanted with hippocampal depth electrodes over 2070 trials of a working memory task, while Ung et al (2017) studied 67 patients undergoing invasive EEG monitoring with mostly cortical electrodes using a word recall task with a short (45 second) delay. Both groups found that IEDs during the seconds (2 to 6 seconds for Kleen et al; 0 to 2.4 seconds for Ung et al) following stimulus presentation resulted in errors at recall; additionally, IEDs occurring outside of the seizure onset zone had the greatest impact on task performance.

## **2.6 Sleep-related memory consolidation**

TCI by definition can only be demonstrated in the awake patient. The same IEDs occurring in the distinct neurochemical milieu of sleep (see Table 3.2.1) may have entirely different consequences at a cellular level. Retrospective studies show that a propensity for sleep-activated discharges is associated with worse cognitive function in children with epilepsy, even outwith the epileptic encephalopathies (Nicolai et al. 2007, Ebus et al. 2011, Glennon et al. 2016). Memory research in the past decade and a half has cast sleep in a central role, suggesting that disruption to the processes underlying sleep-related memory consolidation may lead directly to difficulties with learning. I discuss this paradigm in detail in Chapter 5.

## Chapter 3

# Sleep

"With regard to sleep and waking, we must consider what they are: whether they are peculiar to soul or to body, or common to both..." - Aristotle, *On Sleep and Sleeplessness*, 350BC

Sleep can be defined as a reversible state of disengagement from the environment, and is associated with specific postures and behaviours - quiescence, recumbance and closed eyes. Polysomnography - the combination of overnight electroencephalography (EEG), cardiorespiratory monitoring and electromyography (EMG) - reveals sleep to consist of not one but several distinct states (Kryger et al. 2015), occurring in roughly 90-minute cycles through the course of the night. This structural organisation of sleep is known as sleep architecture. The principal division of sleep is between rapid eye movement (REM) and non-rapid eye movement (NREM) sleep, with the latter further divided into stages N1 to N3 (Iber et al. 2007), numbered in order of increasing arousal threshold. Plotting the progression of these stages over the whole night produces an outline of the structure of sleep on a timescale of hours, known as a hypnogram.

### **3.1 Sleep architecture and the neurophysiological basis of key EEG features**

#### **3.1.1 Wake**

The normal waking EEG appears as low amplitude, mixed frequency activity, representing the asynchronous firing of neurons in response to ongoing environmental stimuli. The quiescence and eye closure which precedes sleep onset is associated in most individuals with the posterior dominant rhythm (PDR) - an 8 to 13 Hz (or "alpha") rhythm with maximal amplitude in the posterior EEG channels. In infants, the PDR is usually in the theta (5-7Hz) band, reaching alpha frequency by

around 8 years. The posterior dominant rhythm is generated at the level of large pyramidal cells in the visual cortex, and is associated on EEG-fMRI with metabolic deactivation (Moosmann et al. 2003).

### 3.1.2 N1

With increasing drowsiness and the onset of light sleep (N1), there is attenuation of the posterior dominant rhythm, general slowing of the EEG background, and the appearance of large surface-negative discharges maximal at the apex of the head, known as vertex sharp transients. Though their function remains unknown, EEG-fMRI data (Stern et al. 2011) show an association with metabolic activation in regions of primary sensorimotor cortex, suggesting a role in sensory processing during sleep. This is supported by the observation that sudden stimulation - regardless of sensory modality - may provoke vertex sharp waves.

### 3.1.3 N2

As sleep deepens (N2), the same provocation produces a K complex - a short surface positive wave followed by a large surface-negative wave, then a positive wave. Though occurring spontaneously in sleep, the K complex has been studied most extensively as an evoked potential (Halász 2005). Its peak is biphasic: the P200–N300 component, which is identical to the vertex sharp wave, is more dependent on received stimuli, while the N550–P800 wave, maximal in the frontal regions, is largely influenced by underlying sleep processes (Halász 2005). Overall, the K complex is generalised, with a frontal predominance. The K complex is thus believed to represent both information processing and microarousal (see later). In individuals with epilepsy, K complexes may be associated with the generation of spike wave discharges (Steriade and Amzica 1998). Spindles - spontaneous waxing and waning bursts typically between 12-15 Hz and lasting 0.5 to 1 second - are the other cardinal feature of N2 sleep. They are maximal over central scalp regions, and may occur independently, or in association with a K complex. Human EEG-fMRI data (Caporro et al. 2012) show increased metabolism in the thalami during spindles suggesting that the oscillation has a thalamic origin, consistent with earlier evidence from intracerebral recordings in cats (Steriade et al. 1987). Spindles are thought to have a role in memory consolidation (see later), having been observed to increase in density following memory tasks learned prior to going to sleep (Gais et al. 2002).



### 3.1.4 N3

Deep sleep (N3) is characterised on EEG by widespread high amplitude slow wave (0.5-2Hz) activity, representing the highly synchronised firing of large numbers of cortical neurons. Thus it is also termed "slow wave sleep". Intracellular recordings show a slow (<1 Hz) oscillation between "up" and "down" states at the neuronal level, the former associated with depolarisation and vigorous firing, the latter with hyperpolarisation and quiescence (Contreras and Steriade 1995). More recently, using simultaneous unit activity, intracranial EEG and surface EEG recording in humans, Nir et al (2011) demonstrated that most sleep slow waves - particularly in the latter part of the night - are regional rather than global phenomena. Additionally, they showed sequential time lags in peak slow wave activity between brain regions, indicating a clear direction of propagation, from the medial prefrontal cortex to the medial temporal lobe and hippocampus (Nir et al. 2011). There is evidence that sleep slow waves drive and group other key brain oscillations, in particular spindles (Möller et al. 2002) and ripples (Clemens et al. 2007). EEG slow wave activity is a robust indicator of sleep need (Borbély and Achermann 1999) suggesting that slow waves serve a homeostatic function (see later). Slow wave enhancement appears to improve memory consolidation (Marshall et al. 2006), while slow wave suppression interferes with it (Landsness et al. 2009), indicating a possible role for sleep slow waves in learning.

### 3.1.5 REM

Rapid eye movement sleep (REM) is also known as paradoxical sleep, due to the strong resemblance of the EEG to the waking trace (Jouvet, M. et al. 1959). Subjects woken from REM sleep can often recall vivid dreams (Aserinsky and Kleitman 1953). Intracranial EEG in rodents reveals that while the cortical EEG is low in voltage, hippocampal recordings show continuous high voltage theta activity, known as the hippocampal rhythmic slow activity (RSA). The human correlate of hippocampal RSA is still debated (Clemens et al. 2009), limiting the generalisability of findings from animal models to humans. Behaviourally, REM sleep is characterised by the eponymous rapid eye movements, which resemble saccades during wakefulness, as well as the suppression of muscle tone. These can be detected on electrooculogram (EOG) and electromyogram (EMG) respectively. Additionally, there is increased variability in the heart and respiratory rates, reflecting increased fluctuation between sympathetic and parasympathetic influences. Despite being the earliest sleep stage to be described, the function of REM sleep remains essentially unknown.

Stage	Description
W	Alpha activity, low amplitude mixed frequency EEG
N1	Low amplitude predominantly 4-7Hz activity, vertex sharp waves
N2	Presence of K complexes and sleep spindles
N3	Prominent slow wave activity (0.5-2Hz)
REM	Low voltage mixed frequency, low EMG, intermittent presence of rapid eye movements
N	NREM sleep without recognisable spindles, K complexes or slow waves

Table 3.1.1: Description of sleep stages as defined in the AASM manual (Iber 2007)

### 3.1.6 The microarchitecture of NREM sleep

The structure of sleep on a timescale of hours - as plotted on a hypnogram - is also known as its macroarchitecture. The examination of NREM sleep on a timescale of minutes - that is, at a microarchitectural level - reveals its underlying periodicity. A relatively stable and rhythmic background is repeatedly interrupted by sudden, transient changes in amplitude or frequency [Figure 3.1.1]. This periodicity underlies Cyclic Alternating Pattern (CAP) analysis (Terzano et al. 2001), a complementary description of sleep structure which focuses on shifts in cortical state during NREM. The EEG patterns used to distinguish "background" from "interruption" are similar to those used for conventional sleep staging - for example, vertex sharp waves, K complexes and intermittent alpha. However, other hallmarks of NREM which are ignored in the AASM (Iber et al. 2007) classification, such as delta bursts, polyphasic bursts and EEG arousals - are included. Movements and autonomic changes are also taken into consideration.

Under the CAP scoring system, the disruptive element is termed "phase A". The intervening background between two phase As separated by 60 seconds or less is termed "phase B". A "CAP sequence" comprises a series of shifts between phases A and B, and the more CAP sequences are present in NREM sleep, the more "unstable" sleep is deemed to be. Periods of sleep that do not contain CAP sequences are termed "non-CAP". Phase As are further divided into subtypes A1 to A3; broadly speaking, A1s consist mainly of delta bursts while A2s and A3s contain arousals (Terzano et al. 2001). Hence within the framework of conventional sleep cycles, the descent from N1 to N3 contains CAP sequences rich in phase A1s, while the ascent toward Wake or REM contains CAP sequences rich in A2s and A3s (Bruni et al. 2010b) [Figure 3.1.2]. Though an intuitive system given the fundamental oscillatory nature of brain rhythms (Buzsaki 2011), and particularly insight-provoking in the study of sleep in epilepsy (Halász 2013), the utility of CAP analysis is limited by its lack of widespread adoption by the neurological and sleep

medicine communities.

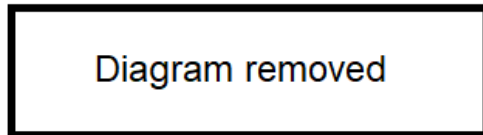


Figure 3.1.1: Several consecutive minutes' polysomnography shown in three sections, the middle section containing a CAP sequence (labelled), while the top and bottom sections represent non-CAP. For each section, EEG channels appear at the top; the unlabelled EEG channels are: Fp2-F4, F4-C4, C4-P4 and P4-O2. C4-A1 is labelled. EOG: electro-oculogram; EMG: electromyogram, EKG: electrocardiogram; PNG: plethysmography; TIB ANT: tibialis anterior. Adapted from Terzano (2001).

### 3.2 Anatomical and neuroendocrine basis of sleep generation

An anatomical centre for sleep generation was first proposed in the early 20th century by von Economo, based on clinical and post-mortem findings from patients with epidemic encephalitis lethargica (von Economo 1930). The majority of von Economo's patients presented with marked hypersomnolence and ophthalmoplegia, particularly ptosis. Others presented instead with insomnia and chorea. Based on the accompanying motor symptoms, he deduced that a wake-promoting region could be localised to the posterior wall of the third ventricle, near the oculomotor nuclei in the rostral midbrain, while a sleep-promoting region was located in the region of the lateral wall of the third ventricle, near the corpus striatum [Figure 3.2.1]. Autopsy findings confirmed this. Lesion, electrical and pharmacological manipulation studies over the last century have led to the elaboration of wake- and sleep-promoting pathways (reviewed in Brown et al. 2012). In particular, immunocytochemistry techniques have facilitated the discovery and localisation of key groups of monoaminergic neurons (Sherin et al. 1996, Gong et al. 2004) while the optogenetic manipulation of activity at a neuronal level now allows direct hypothesis testing on behaving animals (Jego et al. 2013, Apergis-Schoute et al. 2015). Despite these

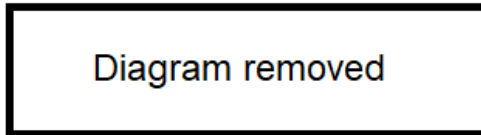


Figure 3.1.2: CAP and non-CAP (NCAP) periods in relation to sleep macroarchitecture. Small vertical lines superimposed on the hypnogram indicate each phase A event. The vertical axis of the hypnogram is marked with sleep stages from the Rechtschaffen and Kales scoring system (W: wake; MT: movement; REM: rapid eye movement sleep; S1-4: non-REM stages 1 to 4, ordered by increasing sleep depth). Adapted from Bruni (2010).

advances, a coherent model of sleep generation still remains to be formulated. The major pathways are described below, while the main neurotransmitters involved are summarised in Table 3.2.1.

### 3.2.1 Posterior hypothalamic wake-promoting pathways

Two major ascending pathways maintain arousal: the first originates in cholinergic cell groups of the upper pons, pedunclopontine and laterodorsal tegmental nuclei, and activates the relay and reticular nuclei of the thalamus, facilitating thalamocortical transmission (reviewed in Saper et al. 2005). The second pathway originates from neurons in monoaminergic cell groups, including the tuberomammillary nucleus (TMN) containing histamine, the A10 cell group containing dopamine, dorsal and median raphe nuclei containing serotonin and locus coeruleus containing noradrenaline, and activates neurons in the lateral hypothalamic area, basal forebrain and cerebral cortex (Saper 2005). These pathways form the basis of what is termed the "ascending reticular activating system" [Figure 3.2.2], first proposed by Moruzzi and Magoun (1949) based on experiments in cats.

Interactions between these wake-promoting neurotransmitter systems are complex, characterised by mutual excitation and redundancy (Brown et al. 2012). Additionally, the ongoing discovery and characterisation of more neurotransmitters, such as neuropeptide S (Adori et al. 2015), and roles in arousal pathways for what were traditionally regarded as sleep-promoting neurotransmitters (Venner et al. 2016) mean that the full picture is still evolving.

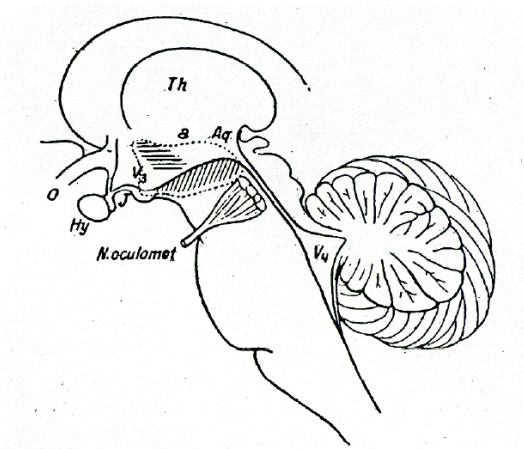


Figure 3.2.1: Illustration of the human brainstem, reproduced from von Economo (1930). Diagonal hatching indicates the wake-promoting region adjacent to the oculomotor nuclei, while horizontal hatching marks the sleep-promoting region, near the head of the caudate nucleus. Based on pathological-anatomical examination, von Economo proposed the borders of the "centre for sleep regulation" as indicated by the dotted lines.

### 3.2.2 Anterior hypothalamic sleep-promoting pathways

Monoaminergic cell groups in the ventrolateral preoptic area (VLPO) send inhibitory outputs to all of the major cell groups that mediate arousal, including those in the TMN (Sherin et al. 1996), locus coeruleus, pedunculopontine and laterodorsal tegmental nuclei (Saper et al. 2005). These neurons - containing GABA (gamma-aminobutyric acid) or galanin - are active primarily in sleep, their firing rates peaking in slow wave sleep (Szymusiak et al. 1998). Conversely, the VLPO also receives inhibitory afferents from each of these areas (Chou et al. 2002). In rodents, neurons in the median pre-optic nucleus have also been implicated in sleep promotion (Gong et al. 2004), particularly under conditions of sleep deprivation.

### 3.2.3 Lateral hypothalamic cell groups

von Economo further postulated that the then newly-described condition of narcolepsy was also caused by pathology in the anatomical regions he described (von Economo 1930). Patients with narcolepsy suffer attacks of irresistible sleepiness - with REM at sleep onset, and many also have cataplexy - the sudden loss of muscle tone in response to emotional stimuli. In 1998, two groups of researchers independently described a new family of neuropeptides found only in the posterior lateral hypothalamus. One group named these "orexins" (Sakurai et al. 1998) and

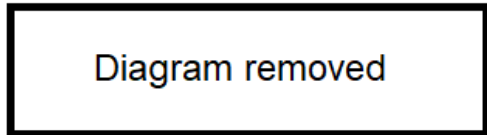


Figure 3.2.2: Ascending arousal systems of the brainstem and posterior hypothalamus. Nuclei producing wake-promoting monoaminergic neuromodulators are shown in green. These include noradrenaline (NA)-producing neurons of the locus coeruleus (LC), serotonin (5-HT)-producing neurons of the dorsal raphe (Raphe), and histamine (HIST)-producing neurons of the tuberomammillary nucleus (TMN). Nuclei shown in blue produce acetylcholine (ACh), which promotes forebrain activation in both waking and REM sleep. Cholinergic nuclei include the pedunculopontine (PPT) and laterodorsal (LDT). The ventrolateral preoptic area (VLPO) - a sleep-promoting region - is shown in red. VLPO neurons produce the inhibitory neuromodulator gamma-aminobutyric acid (GABA) and the inhibitory neuropeptide galanin (Gal). Adapted from Pace-Schott and Hobson (2013).

the other "hypocretins" (de Lecea et al. 1998). The loss of these neurons underlies narcolepsy (Thannickal et al. 2000, Peyron et al. 2000). Orexin/hypocretin (OH) neurons have ascending projections to the thalamus and cortex and descending projections to all of the monoaminergic and cholinergic cell groups of the arousal systems (Saper 2005), as well as direct projections to spinal motor neurons (Brown et al. 2012). Inhibitory afferents come from the VLPO (Saito et al. 2013).

Located in the same area - but unaffected by the processes which cause OH cell loss in narcolepsy - are neurons containing melanin-concentrating hormone (MCH). These reach their peak firing rate in REM sleep (Jego et al. 2013). They have similar projections to the OH neurons, and receive inhibitory inputs from the noradrenergic, serotonergic and cholinergic arousal systems (McGinty and Alam 2013). Additionally, OH and MCH neurons may be mutually inhibitory (Rao et al. 2008, Apergis-Schoute et al. 2015), and both populations also secrete GABA (McGinty and Alam 2013).

#### 3.2.4 REM sleep generation

The proposed anatomical origin of REM sleep is located at the mesopontine junction, ventral to the locus coeruleus and medial to the trigeminal motor nucleus

(Fraigne et al. 2015, Luppi et al. 2011). Cells in this subcoeruleus (also known as sublaterodorsal tegmental) nucleus mostly contain glutamine, though some contain GABA. Descending pathways through the ventromedial medulla of the spinal cord are thought to mediate motor atonia, while ascending pathways to the thalamus mediate cortical activation (Luppi et al. 2011). Afferents from cholinergic REM-active neurons maintain REM sleep but are not necessary for its generation (Grace 2014). MCH neuron firing does not precede the onset of REM, suggesting that these neurons too, maintain rather than initiate REM sleep.

### 3.2.5 A synthesis of current knowledge

In the mid-2000s, a model based on the concept of a flip-flop switch, with wake and sleep as the stable, binary states was proposed (Saper et al. 2005). The mutual inhibition of the ascending and descending pathways drove the switching between states, while orexin neurons acted as a stabilising "finger on the switch". Apart from difficulties with resolving more recent discoveries about the timings of state changes in the various populations of neurons involved (Brown et al. 2012), a particular weakness of this model was its failure to address REM sleep entirely - though the same authors later proposed a separate switch for REM (Lu et al. 2006). A comprehensive model would need to include pathways for the initiation and maintenance of each of the distinct states of NREM, REM and wake (Fort et al. 2009), as well as mechanisms for cycling between them.

## 3.3 The regulation of sleep

"The demand for recovery must depend on prior activity, whereas the opportunity for recovery depends mainly on the time of day."

- Daan 1984

The timing and quantity of sleep are determined by intrinsic as well as extrinsic factors. A "two-process model" to describe this was first proposed by Borbély in 1982: Process C is a sleep-independent circadian process, while Process S is a homeostatic process reflecting sleep need. Mathematical modelling using empirical and simulated data led to Process C being described by skewed sine waves representing the sleep-onset and -offset thresholds in relation to clock time (Daan et al. 1984, Borbély and Achermann 1999) while Process S is described by exponential functions representing the accumulation and dissipation of sleep need (Achermann et al. 1993, Borbély and Achermann 1999). Additionally, there is an ultradian process which leads to the alternation of NREM and REM states during a sleep episode, but this is currently not well described.

Neurotransmitter	Location and main projections	Wake				REM				Atypical sleep-modulating drug(s)
		Wake	REM	NREM	NREM	Wake	REM	NREM	NREM	
Acetylcholine	basal forebrain to cortex, laterodorsal and pedunculopontine nuclei to thalamus	high	high	low	low	atropine (muscarinic receptor antagonist), trihexyphenidyl				
Serotonin	raphe nuclei to VLPO for NREM suppression, to brainstem ACh nuclei for REM suppression	high	none	low	low	serotonin reuptake inhibitors e.g. fluoxetine				
Dopamine	ventral tegmental area, periaqueductal gray matter (not REM active) to basal forebrain, thalamus	high	high	low	low	modafinil (agonist)				
Norepinephrine	chiefly locus coeruleus (LC), but also throughout brainstem, targets as for serotonin	high	none	low	low	serotonin and norepinephrine reuptake inhibitors e.g. venlafaxine				
Histamine	tuberomammillary nucleus (TMN); inhibits VLPO, stimulates ascending reticular arousal system	high	none	low	low	first-generation antihistamines e.g. chlorphenamine				
Orexin	LH to all aminergic nuclei, strongest to LC; thalamus and cortex, spinal motoneurons	high	none	none	none	suvorexant (dual receptor antagonist)				
MCH	LH to all aminergic nuclei	low	high	low	low	none; though receptor antagonists are in development for obesity (Machell 2013)				
GABA	VLPO to TMN and dorsal raphe nuclei; median pre-optic nucleus to LC; LH to VLPO (Vemner 2016)	none*	low	high	high	benzodiazepines, barbiturates (GABA-A agonists), sodium oxybate (GABA-B agonist)				

**Table 3.2.1: Major neurotransmitters involved in the generation of sleep and wake, and their levels in wake, REM and NREM. ACh: acetylcholine; MCH: melanin-concentrating hormone; VLPO: ventrolateral pre-optic area; LH: lateral hypothalamus. \* A subpopulation of GABA-containing neurons in the basal forebrain project to the thalamus and cortex promoting wake (Brown 2015)**



### 3.3.1 Process C

The circadian rhythm is usually entrained to Earth's 24-hour solar cycle, but even in the absence of entraining stimuli (termed 'zeitgebers') demonstrates a period differing only slightly from 24 hours (Czeisler et al. 1999). The suprachiasmatic nucleus (SCN) - a group of hypothalamic neurons located adjacent to the optic chiasm - behaves as the master circadian clock, regulating the timing not only of sleep, but also - via projections to the dorsomedial nucleus of the hypothalamus - of body temperature, appetite and other essential functions (Saper et al. 2005). Its main input is from the retinohypothalamic tract; sunlight - the chief zeitgeber - is captured by the photopigment melanopsin contained in retinal ganglion cells, which project to the SCN (Moore 2007). Melatonin secretion by the pineal gland is controlled by SCN projections via the paraventricular nucleus of the hypothalamus. The feedback loop is completed by melatonin receptors on the SCN; melatonin inhibits the firing of SCN neurons, reducing the circadian drive for arousal (Moore 2007). The time at which salivary melatonin rises when measured under conditions of dim light (the dim light melatonin onset, or DMLO) may be utilised as an endogenous circadian marker (Martin and Eastman 2002). Since the 1990s, "clock" genes have been discovered which are expressed in nearly all mammalian cells (Takahashi 2017). They comprise a series of negative feedback loops: in the primary loop, transcription factors *CLOCK* and *NPAS2* interact with *BMAL1* in the daytime to activate transcription of the *PER* and *CRY* genes, resulting in high levels of these transcripts. During the night, the *PER-CRY* repressor complex is degraded; this allows *CLOCK:BMAL1* to activate a new cycle of transcription (Takahashi et al. 2008). Further players and secondary loops have since been elucidated (Takahashi 2017).

### 3.3.2 Process S

Spectral analysis of the human sleep EEG reveals that slow wave activity (power in the 0.75-4.5Hz frequency band; SWA) is greatest in the first sleep cycle, and declines in subsequent cycles across the night. Ample human experimental data employing various paradigms (reviewed in Borbély and Achermann 1999) show that SWA increases after a period spent awake, increases further with sleep deprivation and decreases with sleep [Figure 3.3.1]. Therefore slow wave activity serves in the two-process model as a measure of sleep need or sleep intensity. This has been expressed as exponential functions describing the accumulation and decay of sleep pressure during wake and sleep respectively:

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**Algorithm 3.1**  $t$  = time,  $\tau_d$  = time constant of the decreasing exponential function,  $\tau_i$  = time constant of the saturating exponential function,  $UA$  = upper asymptote,  $LA$  = lower asymptote,  $SSO$  = level of slow wave activity (S) at sleep onset, and  $SWU$  = level of S at wake up. Adapted from Jenni and Carskadon (2005).

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$$S(t) = UA - (UA - SWU) * \exp^{-t/\tau_i}$$

during wake

$$S(t) = (SSO - LA) * \exp^{-t/\tau_d} + LA$$

during sleep

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Extracellular adenosine (Porkka-Heiskanen et al. 1997, Bjorness et al. 2016) and nitric oxide (Kalinchuk et al. 2015) acting on cholinergic neurons of the basal forebrain (Kalinchuk et al. 2015) have been proposed as "sleep homeostatic factors" which accumulate and dissipate with the dynamics described in the model.

In healthy adults, there is great interindividual variation both in the absolute values of SWA and in the dynamics of sleep homeostasis (Rusterholz et al. 2010), the latter mainly reflected in the time constants for the build up ( $\tau_i$ ) and decline ( $\tau_d$ ) of SWA. A longer  $\tau_i$  - that is, a slower SWA build-up - may indicate a better capacity to stay awake longer. A shorter  $\tau_d$  indicates faster dissipation of sleep pressure - or more efficient restoration to baseline. The topographical distribution of SWA also varies between healthy subjects (Finelli et al. 2001), and is similarly trait-like, remaining remarkably similar in repeated recordings at baseline and under sleep deprivation.

Diagram removed

Figure 3.3.1: Schematic diagram of normalised slow wave activity across several nights. x-axis: time in hours, y-axis: percentage of mean slow wave activity. Adapted from Rusterholz et al. (2010)

### 3.3.3 REM/NREM cycling

Data from selective REM sleep deprivation studies show that REM sleep is also homeostatically regulated (Dement 1960, Endo et al. 1998). Across a single night's

sleep, an increasing number of interventions (the experimenter awakening the subject) was required to prevent REM sleep, though between subsequent nights the increase was less marked, and REM rebound during recovery sleep was modest - less than the amount lost (Endo et al. 1998). These complex dynamics, in addition to the lack of a measure for REM sleep intensity have hampered the formulation of a coherent model of REM sleep homeostasis.

### 3.3.4 Genetic basis of sleep traits

There are large, heritable interindividual variations in sleep traits such as a propensity for "morningness" or "eveningness", vulnerability and response to sleep deprivation (Dijk and Archer 2010) and even the frequency composition of the sleep EEG (Landolt 2011). Mutations and polymorphisms in the period genes *PER2* and *PER3* have been associated with advanced and delayed sleep phase respectively (Takahashi et al. 2008). Differences in sleep homeostasis in both rodents and humans have also been associated with polymorphisms in various clock genes (Takahashi et al. 2008) - this suggests that circadian and homeostatic regulation may be intrinsically linked. In particular, a variable number tandem repeat *PER3* polymorphism in humans has been shown to affect sleep structure, slow wave activity and cognitive performance in the face of sleep loss (Viola et al. 2007, Dijk and Archer 2010, Viola 2007, Dijk 2010). Those with the *PER3*<sup>5/5</sup> genotype - which is thought to be present in about 10% of the general population (Dijk and Archer 2010) - showed more slow-wave sleep and EEG low-frequency activity but were also more impaired by sleep deprivation than *PER3*<sup>4/4</sup> homozygotes (Viola et al. 2007). Similarly, a single nucleotide polymorphism in the adenosine deaminase gene (*ADA* G22A) has been associated with a greater duration of slow wave sleep and higher delta spectral power at baseline (Bachmann et al. 2012), in conjunction with greater fatigue and poorer cognitive performance after sleep deprivation (Bachmann et al. 2012). The dynamics of the sleep homeostatic response were however unaffected (Bachmann et al. 2012).

## 3.4 The normal maturation of sleep

"Sleep is the predominant state in developing animals" - Brown 2012

### 3.4.1 Sleep schedule and duration

Human sleep patterns evolve profoundly between infancy and adulthood. Recent population-based studies (Blair et al. 2012, Price et al. 2014) have quantified -

based on parental report - the decline in total sleep time between the ages of 0 and 11 years [Figure 3.4.1]. The large decline in early childhood is accounted for by the cessation of daytime naps. Both studies (total  $n=16309$ ) also demonstrated wide variation in all the measured parameters, though this variability possibly decreased with age (Blair et al. 2012). Even so, at age 11 years ( $n=7157$ ), total sleep time ranged from 8.5 to 11h per night (Blair et al. 2012). Studies utilising polysomnography (Scholle et al. 2011, Montgomery-Downs et al. 2006, Louis et al. 1997) tend to give slightly lower values for the total sleep time at any given age. There are changes too over the course of adolescence, most notably a delay in sleep phase - bedtimes and wake-up times both become progressively later (Sadeh et al. 2009, Gradisar et al. 2011). Social and cultural factors have a large impact on adolescent sleep schedules, with school start times dictating wake-up times during the week, leading to a shortened total sleep time (Gradisar et al. 2011). Two large meta-analyses showed that the age-related decline in TST across adolescence was only present on school nights (Gradisar et al. 2011; Ohayon et al. 2004). Actigraphic data support the finding from pooled questionnaire data that TST at the weekend is around 1.5h longer than at weekdays (Sadeh et al. 2009; Crowley et al. 2014). A recent longitudinal study which included dim-light melatonin onset (DLMO) as a measure of circadian phase (see section 1.3.3) demonstrated a shift toward sleep phase delay with age, though the mean DLMO moved forward by just an hour (Crowley et al. 2014). Phase angle - the interval between DLMO and sleep onset - was approximately 2 hours in the older adolescents (age 16-18 years), the same as that in adults (Crowley et al. 2014).



Figure 3.4.1: Left: Mean total sleep duration over 24 hours (including daytime naps) by parental report at 8 different ages; dotted lines represent the centiles as labelled. Adapted from Blair (2012). Right: Overnight polysomnography findings by age and pubertal stage. SL: sleep latency; WASO: wake after sleep onset; MT: movement; N1-N3: NREM sleep stages in order of depth; REM rapid eye movement sleep. Adapted from Scholle (2011).

### 3.4.2 Macroarchitecture

The rapid cycling of sleep in newborn infants - with a quiescent period of 20 minutes occurring every hour - was first noted by Aserinsky in 1951 (Aserinsky 1996). Between the episodes of quiescence ("quiet sleep"; QS) was "active sleep" (AS), characterised by saccadic eye movements and movements of the body and limbs. 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 (Jenni et al. 2004). Subsequently, the length of sleep cycles increases, reaching the mature length of approximately 90 minutes during adolescence (Scholle et al. 2011). Active sleep is basically REM without muscle atonia - the percentage of REM time without atonia decreases with age, comprising just 10-15% of REM time by adulthood. The proportion of sleep time spent in REM decreases from about 50% to 25% over the first two years of life (Grigg-Damberger et al. 2007), due mainly to the fall in the number of REM episodes - particularly episodes with REM at sleep onset - throughout the entire 24-hour period (Louis et al. 1997). The proportion of sleep occupied by REM subsequently remains little changed throughout the rest of childhood (Montgomery-Downs et al. 2006, Scholle et al. 2011). Sleep spindles first appear at 3 to 8 weeks post-term, and K complexes at about 5 months (Grigg-Damberger et al. 2007). Vertex sharp waves are recognisable by 16 months, though broader versions may appear by 5 months. At term, infants have high voltage slow waves on EEG, but it is uncertain if these evolve into slow wave sleep. Recognisable slow wave sleep emerges by 2 to 9 months post-term (Jenni et al. 2004). The proportion of sleep time spent in slow wave sleep begins to decline from around the age of 3 years (Montgomery-Downs et al. 2006) when it comprises about 25-30% of sleep. Between the ages of 5 and 15, SWS decreases by 5-7% per 5-year period (Scholle et al. 2011; Ohayon et al. 2004) [Figure 3.4.1]. This is the most prominent change in sleep architecture over the course of middle childhood. There is a converse increase in N2 (Scholle et al. 2011, Ohayon et al. 2004, Jenni and Carskadon 2004). The proportion of sleep spent in N1 does not appear to change significantly with age across childhood (Ohayon et al. 2004, Scholle et al. 2011).

### 3.4.3 Microarchitecture

The EEG correlate of quiet sleep in term neonates (conceptual age 37 to 44 weeks) is trace alternant, so called because 1-10 sec bursts of activity alternate with relatively "flat" periods lasting 6-10 secs (Niedermeyer and da Silva 2005). The bursts consist of moderate to high voltage mixed slow, medium and fast activity - often with spiky discharges, while the "flat" periods actually show mixed frequencies, though the voltage is depressed. This periodicity led initially to the belief that trace alternant

might be a precursor of CAP (Bruni et al. 2010b). However the current consensus is that CAP emerges with the appearance of sleep spindles, which alternate with high voltage slow waves to produce CAP sequences, in a rudimentary form of NREM sleep (Bruni et al. 2010b). The evolution of CAP throughout the human lifespan has now been examined in a number of cross-sectional studies (Bruni et al. 2010b; Miano et al. 2011). The CAP rate is low in infants, around 12% in those in whom NREM sleep can be reliably scored (about 10 weeks post-term). There is a gradual increase in CAP across infancy and the preschool years, then a steeper increase, reaching a peak of 62% just prior to adolescence (Bruni et al. 2010b). It is notable that most CAP sequences in children contain the highly synchronous phase A1s, which are not associated with EEG arousal - in fact, these could conceivably represent "anti-arousals" - transient shifts in cortical state leading to the preservation of sleep. The proportion of all phase As classed as A1s also increases between infancy and pre-adolescence, declining with age thereafter. Phase A2/3s follow the converse pattern (Bruni et al. 2010b).

#### **3.4.4 Spectral content, topology and homeostasis**

Cross-sectional (Kurth et al. 2010) and longitudinal (Jenni and Carskadon 2004, Feinberg et al. 2006) studies show changes in the spectral power and content of the sleep EEG which confirm and quantify the evolution seen on visual EEG analysis. The sigma band first appears at 2 months (Jenni et al. 2004, a), theta power is highest in the pre-school years, and slow wave activity peaks in middle childhood. Overall, the power of the sleep EEG declines gradually with age throughout childhood, reaching adult levels only at the end of the second decade of life (Kurth et al. 2010, Tarokh et al. 2011). By utilising high density EEG recordings, Kurth et al (2010) also demonstrated age-related changes in topological distribution of the various frequency bands, of which the postero-anterior shift in slow wave activity was the most striking. It has been observed that the evolution of EEG spectral power and topology parallels the development of specific abilities over the course of infancy and childhood [Figure 3.4.2], with both processes likely underpinned by the maturation of cortical grey matter through synaptic pruning (Ringli and Huber 2011). Sleep homeostasis is thought to develop over the first months of life, with theta activity reflecting the dissipation of sleep propensity in infancy (Jenni et al. 2004), though by 30 months of age, an increase in slow wave activity in response to sleep (nap) deprivation has been demonstrated (Lassonde et al. 2016). The strength of the homeostatic response to sleep deprivation increases through to late puberty (Jenni et al. 2005). The slower build-up of sleep pressure may facilitate the natural sleep phase delay that occurs in adolescence (Jenni et al. 2005).

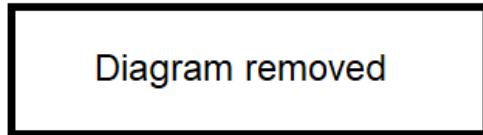


Figure 3.4.2: Relating cortical maturation, slow wave activity (SWA) and behaviour. Left column: Mean synaptic density (synapses/100 mm<sup>3</sup>) in visual cortex (area 17; top) and prefrontal cortex (bottom) at various ages. Middle column: Maps of EEG power during NREM sleep for ages 2–5 years (top) and 17–20 years (bottom). Right column: Top: Development of visual acuity in human infants plotted against age. Y-axis shows the number of minutes subtended by each black or white stripe of the acuity grating and x-axis age in years. Bottom: Direction error in percentage versus age in the antisaccade task (a test of executive function) with the target located on the right side and the correct saccades generated to the left side. Reproduced from Ringli and Huber (2011).

### 3.4.5 Primary sleep disorders of childhood

Sleep disturbance in childhood - as measured by parental report - is extremely common. Large population-based studies ( $n > 4000$  each) put the prevalence at  $> 30\%$  in infants (Martin et al. 2007), and between 14-30% for pre-school aged children (Hiscock et al. 2007, Mindell and Owens 2010). Nightwakings and bedtime resistance (behavioural insomnia) were the commonest concerns. In a meta-analysis of 41 survey studies, daytime sleepiness was reported in 15-40% of children aged 8 to 15 years (Gradisar et al. 2011).

There is a strong association between sleep disruption and behavioural problems (Hiscock et al. 2007, Mindell and Owens 2010), particularly ADHD (Hiscock et al. 2007). Studies utilising polysomnography to detect specific sleep disorders in community-based samples are rare, and give more conservative figures. The apnoea-hypopnoea index (AHI) is the total number of apnoeas and hypopnoeas that occur per hour of sleep as detected on polysomnography and scored using standardised criteria (Iber et al. 2007). Sleep-disordered breathing - defined as an AHI of  $>$  or  $= 5$  - occurs in 1.2-2.2% of school-aged children (Bixler et al. 2009, Rosen et al. 2003). The quality of studies in pre-schoolers is poorer, but these indicate the prevalence is likely higher, up to 13% (Castronovo et al. 2003). The prevalence of sleepwalking is estimated at about 5% in childhood (Stallman and

Kohler 2016), while that of restless legs syndrome is approximately 2% (Mindell and Owens 2010).

### **3.4.6 Summary**

Sleep evolves profoundly in quality and quantity over the course of childhood, and is intimately - perhaps causally - linked to neurodevelopment. It is the primary occupation of infancy and the early years, which represent a critical period for the acquisition of essential cortical functions (see Section 2.4). A large proportion of sleep "disorders" in children may be accounted for by a conflict between parental or societal expectations and normal developmental neurophysiology.



## Chapter 4

# Sleep disruption in children with epilepsy

### 4.1 Sleep behaviour and prevalence of problems by parental report

Parents report more sleep disturbances in children with epilepsy than in their nearest aged siblings (Cortesi et al. 1999, Wirrell et al. 2005, Byars et al. 2008). All three studies utilised the Sleep Behaviour Questionnaire (SBQ; Cortesi et al. 1999), though the largest (Byars et al. 2008; n=332 patients) did not have sibling SBQ scores and used historical controls from Cortesi (1999) instead. The SBQ consists of 6 questions regarding the timing and duration of sleep, followed by a 29-item Likert-type rating scale with questions designed to address 5 domains: Bedtime Difficulties, Parent/Child Interaction During the Night, Sleep Fragmentation, Parasomnias, and Daytime Drowsiness. There is a single item which alludes to sleep-disordered breathing (“snores while sleeping”). Higher scores indicate greater sleep disturbance. In their epilepsy sample (n=89) with normal intellect (FSIQ $\geq$ 85), normal neurological examination and on monotherapy at least a year after diagnosis, Cortesi et al. (1999) found higher total scores  $p<0.001$ , and higher rates of bedtime difficulties ( $p<0.001$ ) and daytime drowsiness ( $p<0.0001$ ) compared to controls. Byars et al (2008) examined a prospective sample of children within 3 months of their first recognised unprovoked seizure; these children had higher total SBQ scores than the historical controls ( $p<0.001$ ), with 45% of the sample scoring two standard deviations over the control group mean. Earlier age at seizure onset and lower intellectual function (as estimated on the Kaufman Brief Intelligence Test) were associated with higher SBQ scores. Bedtime difficulties and daytime drowsiness were the most markedly affected domains. In their epilepsy clinic sample (n=55 patients; n=55 siblings), Wirrell et al. (2005) found significantly higher total

SBQ scores in children with epilepsy; interestingly, the Bedtime Difficulties domain was the only one in which patients and controls did not differ. Refractory epilepsy and mental retardation were associated with higher SBQ scores. Thus children with epilepsy appear to have a higher rate of sleep disturbance than healthy children from the outset, and this is associated with lower intellectual function. The higher Bedtime Difficulties subscale scores suggest that behavioural insomnia may be the commonest problem in these children, just as it is in healthy children.

## 4.2 Alterations in macro and micro architecture

Polysomnographic studies in children with epilepsy are scarce, and mostly small ( $n < 20$  patients). Additionally, nights containing seizures are generally excluded (see Section 7.2), with some studies going so far as to exclude patients with active seizures altogether (Maganti et al. 2005). The single consistent finding is a reduced percentage of total sleep time spent in REM when compared to age-matched controls; this has been described in children with BECTS (Bruni et al. 2010a), 'partial refractory epilepsy' (Nunes et al. 2003, Pereira et al. 2012), idiopathic generalised epilepsies (Byars et al. 2008) and infantile spasms (Hrachovy et al. 1981). Hrachovy also demonstrated an increase in REM after successful hormonal treatment. It is notable that some of these samples were drug-naive (Bruni et al. 2010a; Pereira et al. 2012). Within-subject comparisons in adults with temporal lobe epilepsy show that seizures during the day are associated with decreased REM in the subsequent night's sleep (Bazil et al. 2000, Gutter and de Weerd 2012). Seizures during the night may also be associated with decreased REM (Bazil et al. 2000).

The influence of epilepsy on sleep microarchitecture appears to depend on the type of epilepsy. Children with BECTS showed a lower overall CAP rate than age-matched healthy controls (Bruni et al. 2010a). There was a lower percentage of phase A1s and a higher percentage of phase A3s. In contrast, adults with nocturnal frontal lobe epilepsy showed a much higher CAP rate than healthy controls (Parrino et al. 2012), and seizures tended to arise in association with phase As. Another possible interpretation is that both groups of patients show dysmaturity, given that CAP rate increases between infancy and adolescence and declines thereafter (Bruni et al. 2010a).

## 4.3 Alterations in homeostasis

Sleep homeostasis in epilepsy has not been widely studied. Drug-naive adults with nocturnal frontal lobe epilepsy exhibit slow wave sleep rebound in later sleep

cycles following the fragmentation of the early cycles by seizures (Parrino et al. 2012). This appears to be at the expense of REM sleep. There is evidence that sleep homeostasis in children with continuous spike waves during slow wave sleep (CSWS) is impaired (Bölsterli et al. 2011, Bölsterli Heinzle et al. 2014). The authors utilised the slope of slow waves as a measure of the degree of synchrony of cortical firing (Vyazovskiy et al. 2009), with a decrease in slope over the course of the night indicating intact homeostasis. This was demonstrated in healthy controls, while patients showed no significant change. The same analysis was applied to a sample with infantile spasms (Fattinger et al. 2015), who showed impaired slow wave downscaling at diagnosis, resolving with successful steroid treatment. The use of this method allowed for the aftercoming slow waves of the frequent generalised spike-wave complexes to be excluded from the analysis. In patients with mainly focal discharges, it may be possible to study sleep homeostasis using more conventional methods, such as power spectral analysis (Jenni et al. 2005), or by within-patient comparison of slow wave sleep duration with and without sleep deprivation (see Chapter 10).

#### **4.4 Circadian and ultradian trends in interictal discharges and seizures**

“In many cases, epilepsy sets in during sleep” - Aristotle c.400BC

The association between the timing of seizures and the sleep/wake cycle has been recognised since antiquity. In certain electroclinical syndromes, this relationship may be almost pathognomic (Foldvary-Schaefer and Grigg-Damberger 2006) [Table 4.4.1]. In adults, the circadian distribution of seizures has been studied in patients on long-term video EEG monitoring; temporal lobe seizures appear to peak in the mid-morning and early afternoon, while frontal and parietal seizures peak in the early hours of the morning (Durazzo et al. 2008, Kaleyias et al. 2011). One study combined this with dim light melatonin onset (DLMO) measurement, finding that temporal seizures occurred most frequently in the 6 hours before DLMO while frontal seizures occurred 6-12 hours after (Hofstra et al. 2009). Interestingly, in a rat model of mesial temporal lobe epilepsy (MTLE), the animals showed the same clock time peaks in seizure incidence as humans (i.e. during their inactive daylight hours) (Quigg 1998). This suggests it is possible that the activation of the suprachiasmatic nucleus (SCN) - which is stimulated by light in both diurnal and nocturnal animals (Saper et al. 2005) - may alter the seizure threshold for MTLE independently of changes in sleep/wake state. Where the distribution of seizures between sleep stages has been examined using polysomnography, stage 2 sleep

contained the greatest number of seizures per hour (Nunes et al. [2003]; Minecan 2002, Nunes 2003), and REM the least. Both these studies contained a mixture of patients undergoing prolonged EEG telemetry for various clinical indications and included children with focal epilepsies with structural etiologies.

It is also well established that sleep can activate interictal epileptiform discharges (IEDs) (Foldvary-Schaefer and Grigg-Damberger 2006), leading to its widespread use as an aid to increase the diagnostic utility of the EEG. At the cellular level, the highly synchronised thalamocortical oscillations of sleep enhance the responsiveness of cortical neurons, provoking some to self-sustaining oscillations or paroxysms (Steriade 2006). A recent study utilising continuous ambulatory electrocorticography found that both IEDs and seizures followed a circadian distribution, and within an individual, IEDs and seizures were liable to occur at similar times (Karoly et al. 2016).

#### **Sleep-activated Epilepsies**

Benign epilepsy of childhood with centro-temporal spikes (BECTS)

Frontal lobe epilepsies. e.g. autosomal dominant nocturnal FLE

Epilepsy with continuous spike-waves in slow wave sleep (CSWS)

#### **Awakening Epilepsies**

Juvenile myoclonic epilepsy

Epilepsy with grand mal seizures on awakening

Absence epilepsy

Table 4.4.1: Examples of epilepsy syndromes characterised by seizures occurring exclusively or predominantly from sleep or on awakening. Adapted from Foldvary-Schaefer and Grigg-Damberger (2006).

## **4.5 Effect of treatment**

Most antiepileptic drugs have an impact on sleep architecture - these are summarised in Table 4.5.1. The available data indicate that REM sleep is reduced by phenobarbitone, phenytoin and levetiracetam, and enhanced by ethosuxamide (Jain and Glauser 2014). Slow wave sleep is reduced by clobazam and ethosuxamide and increased by carbamazepine, gabapentin and tiagabine (Jain and Glauser 2014). Some drugs, such as topiramate and vigabatrin appear to have no effect on sleep structure, while the data on lamotrigine are equivocal, and data on valproic acid are conflicting (Jain and Glauser 2014). However, much of this evidence derives from healthy adults, with studies in epilepsy patients being insufficiently powered to separate the effect of seizures from the effects of medication. Additionally, a lack of effect on sleep architecture does not preclude a significant effect on

subjective sleep quality.

Non-pharmacological interventions may also impact on sleep: a small study (n=7) found decreased respiratory effort and end tidal volumes after vagal nerve stimulator (VNS) activation, while a study in children (n=15) showed that VNS activation produced an increase in slow wave sleep. One study (n=18) showed an increase in REM sleep in children with drug-resistant epilepsy at 3 months after starting the ketogenic diet (Hallböök et al. 2007), with a further increase in those followed up for 12 months (n=11). This was correlated with improved quality of life scores and with seizure reduction (though not reaching statistical significance in the latter). There was no change in the amount of slow wave sleep.

Antiepileptic drug	N1	N2	N3/SWS	REM	WASO/arousals
Levetiracetam	no change	increase	conflicting data	decrease	decrease
Pregabalin	decrease	no change	increase	no change	decrease
Clobazam	decrease	increase	decrease	no change	decrease
Gabapentin	decrease	no change	increase	conflicting data	decrease
Tiagabine	no change	no change	increase	decrease	decrease
Phenobarbitone	no change	increase	no change	decrease	decrease
Carbamazepine	no change	no change	increase	decrease	decrease
Ethosuxamide	increase	no change	decrease	increase	no change
Phenytoin	increase	increase	conflicting data	decrease	no change

Table 4.5.1: Impact of individual antiepileptic drugs on sleep macroarchitecture. Drugs are ordered by level of evidence. Valproate is excluded from the table as data are conflicting. Adapted from Jain and Glauser (2014).

## 4.6 Co-morbid primary sleep disorders

The prevalence of excessive daytime sleepiness in children with epilepsy is estimated at 10 to 47% (Giorelli et al. 2013), with the majority thought due to undiagnosed primary sleep disorders rather than seizures. Poorly controlled epilepsy may be associated with sleep apnoea (Jain et al. 2013). Conversely, there are case reports of seizure control improving with the treatment of obstructive sleep apnoea (Malow et al. 2003; Foldvary-Schaefer et al. 2008).

## 4.7 Summary

Sleep disruption is commonly reported in children with epilepsy, as it is in healthy children, and the distribution of underlying causes would appear to follow a similar pattern, with behavioural insomnia the commonest, followed by sleep disordered breathing and other primary sleep disorders. Those with poorly controlled epilepsy

appear most at risk of co-morbid sleep disorders. Objective polysomnographic data are, however, limited.

## Chapter 5

# Sleep and memory consolidation

### 5.1 Postulated functions of sleep

“The quest for a fundamental theory of sleep is one of the most important, unsolved problems in science.” - Savage and West (2007)

Sleep - which is ubiquitous in the animal kingdom (Roth et al. 2010) - occupies a significant portion of the day which could ostensibly be spent on more productive tasks to enhance survival. Additionally, the forgoing of vigilance for extended periods of time leaves an animal vulnerable to predation. Thus, in order to contribute to evolutionary fitness, sleep must serve essential functions that are conserved across species. It is postulated that sleep may be necessary for energy conservation (Berger and Phillips 1995; Roth et al. 2010), immune function (Bollinger et al. 2010, Majde and Krueger 2005), cellular repair (Siegel 2005) and neural plasticity (Tononi and Cirelli 2014, Dang-Vu et al. 2006, Ringli and Huber 2011). Evidence from sleep deprivation studies in humans show suppressed prolactin secretion (Bollinger et al. 2010), increased appetite with decreased glucose tolerance (Van Cauter et al. 2007), reduced T cell proliferation (Bollinger et al. 2010) and impaired response to vaccination (Majde and Krueger 2005). In 1989, a seminal study of prolonged total sleep deprivation in rats demonstrated a syndrome of debilitated appearance, skin lesions, increased food intake, weight loss, increased energy expenditure, decreased body temperature during the late stages of deprivation, increased plasma norepinephrine, decreased plasma thyroxine and sometimes death (Rechtschaffen et al. 2002). More recently, knock-out mouse models lacking genes that control sleep timing and duration - including *Clock*, *Bmal1* and *Per2* (see Subsection 3.3.4) - have been found to have altered immune function (Kurien et al. 2013). It can, however be argued that the effects of sleep deprivation cannot be entirely separated from those of stress, and that the clock genes represent a common mechanism regulating the circadian patterns of both sleep

and immunity. The early development of central visual pathways in young altricial mammals appears to require the endogenous neuronal activation of REM sleep (Dang-Vu et al. 2006). Learning too, evidently benefits from sleep (Marshall and Born 2007). Significantly, the same neuronal networks are used for both the immediate processing and the long-term storage of information, so these functions cannot occur simultaneously (Marshall and Born 2007, Tononi and Cirelli 2014). It can be argued therefore that the disengagement from the environment and loss of consciousness afforded by sleep is actually necessary for neural plasticity.

## 5.2 Proposed mechanisms of sleep-dependent memory consolidation

Memory may be principally divided into that for consciously recalled facts and events (declarative, or explicit memory) and non-conscious learning capacities that are expressed solely through performance (non-declarative, or implicit memory) (Squire and Zola 1996) [Figure 5.2.1]. Procedural memory refers to memory for perceptual and motor skills, which falls within the category of implicit memory. However it should be noted that the real-life experience of learning a task often engages more than one memory system at a time. Declarative memory appears to benefit most from slow wave sleep (SWS), while procedural memory benefits from REM; however the dichotomy is not absolute (Marshall and Born 2007).

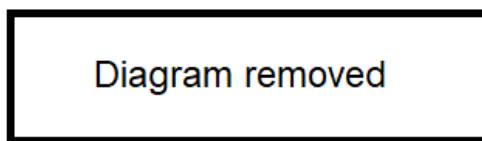


Figure 5.2.1: A taxonomy of long term memory systems, showing the chief anatomical structures involved in each. Adapted from Squire and Zola (1996).

The neuroanatomical seat of declarative memory is the medial temporal lobe, particularly the hippocampus (Squire and Zola 1996, Marshall and Born 2007). In the rodent hippocampus, many individual pyramidal cells of CA1 and CA3 act as "place cells", discharging only when the animal's head is in a specific part of its environment, termed the cell's "firing field" (Holmes and Lenck-Santini 2006). After spatial tasks such as maze learning, place cells which were active during learning



show reactivation in the same temporal sequence during sleep, particularly slow wave sleep (SWS) (Marshall and Born 2007); this has been shown to co-ordinate with replay in the visual cortex (Ji and Wilson 2007). In humans, regional cerebral blood flow patterns observed in the hippocampus while learning to navigate a virtual town showed reactivation during subsequent SWS, correlating with task performance (Peigneux et al. 2004).

### 5.2.1 Active system consolidation

This replay underpins one of the two major theories of sleep-dependent memory consolidation: Active System Consolidation (Born and Wilhelm 2012). Briefly, this theory states that the reactivation of hippocampal neuronal assemblies, representing transient storage of the day's learning, occurs in a temporal framework driven by cortical slow oscillations [Figure 5.2.2]. This timed replay ensures that neuronal firing occurs when conditions for long-term potentiation are favourable, so that new memories can be written into long term storage in the cortex (Diekelmann and Born 2010). The temporal relationship of slow oscillations and spindles has been demonstrated in healthy adults [Mölle et al., 2002, 2009], while that of ripples with slow oscillations and spindles has been shown in patients with refractory epilepsy undergoing intracranial EEG (Clemens et al. 2007, 2011); those with structural damage to the mesiotemporal regions showed less consistent associations (Clemens et al. 2007). Additionally, intense learning may lead to an increase in spindle density during the subsequent night's sleep (Gais et al. 2002, Fogel et al. 2007).

### 5.2.2 Synaptic homeostasis hypothesis

The latter putative mechanism arises from the concept of sleep homeostasis (Borbély and Achermann 1999), and has been termed the Synaptic Homeostasis Hypothesis (Tononi and Cirelli 2014). Environmental stimulation during the day leads to an overall increase in synaptic strength. During sleep, the repeated "on"/"off" firing which comprises the slow oscillations leads to global synaptic downregulation over the course of the night, until only the strongest connections - those potentiated the most during wake or best integrated with existing memories - survive (Tononi and Cirelli 2014). In other words, the contribution of sleep to memory consolidation is a reduction in the signal-to-noise ratio, allowing the most salient material to be retained. Dendritic spine density in the visual neuron VS1 in flies (Bushey et al. 2011) and cortical pyramidal cells in mice (Maret et al. 2011) has been shown to increase after wake or sleep deprivation and decrease after sleep. In humans, the cortical evoked response to transcranial magnetic stimulation - a surrogate measure of

synaptic strength - was enhanced by sleep deprivation and diminished following sleep (Huber et al. 2013).

The two mechanisms may not be mutually exclusive (Huber and Born 2014); it may be that local synaptic strength increases during sleep even as global synaptic strength declines - however this remains to be substantiated by experimental data.

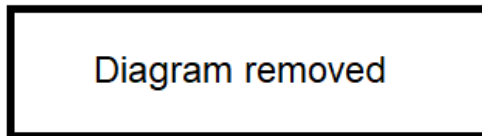


Figure 5.2.2: Active system consolidation. The depolarising "up" phases of the slow oscillation drive both the reactivation of hippocampal memory representations (which correlate with sharp-wave ripples), and thalamocortical spindles, creating "spindle-ripple events" (inset). During these events, it is postulated that calcium enters neocortical pyramidal cells, enhancing the synaptic expression of AMPA receptors and ultimately leading to long-term potentiation - in other words, the storage of information in the neocortical circuitry (Adapted from Born and Wilhelm 2012).

### 5.3 Studies in healthy individuals

Paired-associate learning is a well-established paradigm of hippocampus-dependent declarative memory, in which pairs of items are presented during a series of learning trials (Karantzoulis et al. 2011). At testing, the first item is presented as a cue for recall of the second item. A classic real-life example of such a task is learning people's names - one must learn not only the name and face, but also to relate the two. Many standardised psychometric instruments utilise paired associate tasks that are either purely verbal or visual in their content (Karantzoulis et al. 2011). Studies utilising verbal paired associate learning tasks consisting of semantically related (e.g. artist-painting) or unrelated (e.g. potato-trousers) words have shown that sleep benefits memory consolidation, both in adults (Plihal and Born 1997, Payne et al. 2012) and children (Backhaus et al. 2008, Wilhelm et al. 2008). Payne et al (2012) utilised a between-subjects design, allowing them to compare the effect of delayed and immediate sleep on memory consolidation - sleep was found to benefit memory consolidation even when preceded by a 12-hour interval of wake (i.e. a 24-hour interval between learning and retrieval). The other studies cited above

all utilised within-subject designs, comparing performance over an interval of sleep with that over a similar length interval awake. Performance on a visual paired associate task where subjects have to memorise the locations of pairs of cards showing the same picture (i.e. identical to the card game known as “pairs” or “concentration”) has also been shown to benefit from sleep in both adults (Rasch et al. 2007) and children (Wilhelm et al. 2008). Using this paradigm, it has been demonstrated that raising acetylcholine levels during slow wave sleep (Gais and Born 2004) can impair sleep-related declarative memory consolidation while boosting slow oscillations enhances it (Marshall et al. 2006). Procedural memory too has been shown to benefit from sleep, with REM sleep the main putative contributor (Plihal and Born 1997). This has also been demonstrated in children (Wilhelm et al. 2008, 2013).

#### **5.4 Studies in children with neurodevelopmental disorders other than epilepsy**

The effect of sleep on memory has been examined in children with autism spectrum disorder (ASD; Maski et al. 2015) and in those with attention-deficit/hyperactivity disorder (ADHD) (Prehn-Kristensen et al. 2011, 2014). Both conditions are associated with high rates of sleep disturbance (Goldman et al. 2012, Cortese et al. 2009). Additionally, children with ADHD show reduced activity in the prefrontal cortex – where slow oscillations originate – on functional MRI (Zang et al. 2005). Using a paired picture location task, Maski et al (2015) showed that children with ASD remembered better over an interval of night time sleep than a day spent awake. Prehn-Kristensen et al (2014) showed that performance in this task improved in children with ADHD to the level of controls if they received transcranial oscillatory direct current stimulation (rather than a sham procedure) during NREM sleep. In their earlier study (Prehn-Kristensen et al. 2011), the group had shown that children with ADHD had better picture recognition accuracy after a night’s sleep compared to a day awake, though the effect of sleep was less than that seen in controls. Thus it would appear that sleep also benefits memory consolidation in children with neurodevelopmental disorders, though perhaps to a lesser extent than in healthy controls. Boosting sleep slow oscillations also appears to have the same effect in those with ADHD (Prehn-Kristensen et al. 2014) as it does in healthy individuals (Marshall et al. 2006). It is notable that both ASD and ADHD are common co-morbidities of children with epilepsy (Russ et al. 2012, Reilly et al. 2014).

## 5.5 Studies in patients with epilepsy

Memory deficits are common in epilepsy and have been well documented in both adult and paediatric patients (Butler and Zeman 2008, Nolan et al. 2004). However, the effect of sleep on memory in epilepsy has only recently been examined; the literature is limited and studies have been small. A few studies comparing adults with temporal lobe epilepsy (TLE) to healthy controls have employed a within-subject design. Deak et al (2011) found poorer recall for a word list in patients ( $n=7$ ) than controls ( $n=9$ ) at a 30-minute interval, but similar recall in both groups after a 12-hour interval including overnight sleep. A 12-hour daytime interval spent awake saw the patients forget significantly more items than controls. A pilot study (Urbain et al. 2011) examining four children with epilepsy (one with benign epilepsy with centro-temporal spikes, one with benign childhood epilepsy with occipital paroxysms and two with continuous spike waves in slow wave sleep, CSWS) found that recall performance decreased in these patients following an interval of overnight sleep. Using separate healthy control groups for the "Sleep" (interval of overnight sleep) and "Wake" (day spent awake) conditions, the authors demonstrated that their verbal paired-associates task could detect a contribution of sleep to declarative memory consolidation in this age group. Interestingly, one of the CSWS patients who underwent successful corticosteroid treatment showed improved recall, suggesting that interictal epileptiform discharges may impair memory consolidation (Urbain et al. 2011). In a further study of similar design examining 15 patients with various idiopathic focal epilepsies (Galer et al. 2015), patients showed a decline in recall overnight on both the verbal paired-associates task and a paired object-location task, while controls showed a gain of performance overnight on the verbal task and similar performance on the object location task. There is a single study ( $n=10$ ) examining the contribution of sleep to memory consolidation in children with epilepsy using a within-subject design (Sud et al. 2014). 8 out of 10 subjects showed better recall (free recall of a word list) under the Sleep than the Wake condition. Therefore the contribution of sleep to memory consolidation in patients with epilepsy is unclear; the evidence is preliminary and conflicting.

## **Chapter 6**

# **Aims of the study**

### **6.1 Summary and conclusions from reviewing the literature**

The literature reviewed in the introduction to this thesis highlights the intimate relationship between sleep and epilepsy, down to the fundamental neuronal physiology underlying each phenomenon. I have summarised arguments for the active contribution of sleep to neurodevelopment and continued learning, and various paradigms to explain the development of cognitive impairment in epilepsy. Sleep disruption, though a common co-morbidity in children with epilepsy, remains poorly characterised. Despite various lines of circumstantial evidence linking sleep disruption to cognitive impairment in childhood epilepsy, the adverse cognitive impact of sleep disruption in the long term is basically assumed, and direct evidence of a plausible mechanism lacking.

### **6.2 Aims of the thesis**

#### **6.2.1 Investigate the structure and regulation of sleep in children with epilepsy**

I aimed to devise a system of scoring polysomnographic recordings containing epileptiform activity, including seizures. Visual sleep scoring would provide data on the sleep architecture of children with epilepsy, and facilitate subsequent quantitative and correlational analyses. I aimed to describe the dynamics of sleep homeostasis in children with focal epilepsy with a structural etiology, to determine if this is disrupted.

### **6.2.2 Provide direct evidence linking neurophysiological findings during sleep with concurrent neuropsychological performance measures**

I aimed to isolate the contribution of sleep to memory consolidation by comparing performance with and without sleep in the retention interval. I aimed to correlate the measure of “sleep benefit” thus derived with neurophysiological data captured over the course of the same night, in order to examine the relationship between sleep disruption and cognitive impairment. I also aimed to correlate measures of sleep homeostasis with general intellectual functioning.

## **6.3 How these aims are addressed in this thesis**

The original work for this thesis is described in Parts II and IV, with the main methods described in Part III:

### **6.3.1 Development (Part II)**

The development and validation of techniques to examine sleep architecture in children with epilepsy (Chapter 7) and to apply the paired-associates learning paradigm to English-speaking schoolchildren (Chapter 8).

### **6.3.2 Principal methods (Part III)**

These are detailed in Chapter 9.

### **6.3.3 Results (Part IV)**

A retrospective, quantitative EEG study of sleep homeostasis in children with focal epilepsy (Chapter 10), and a prospective, controlled experimental study to test the hypothesis that children with epilepsy show impaired memory consolidation with sleep (Chapter 11).

**Part II**

**Development**





## Chapter 7

# An approach to scoring sleep in polysomnographic studies in children with focal epilepsy

### 7.1 Abstract

**Purpose** The American Academy of Sleep Medicine (AASM) Manual is now widely used in clinical practice for scoring sleep in children. However, polysomnographic records from children with epilepsy often contain interictal EEG abnormalities which may obfuscate features of sleep. Additionally, the AASM Manual does not allow for the scoring of epochs containing ictal events other than as “wake” or “sleep”. We aimed to devise an optimised strategy for the scoring of sleep in children with focal epilepsy.

**Method** Patients with focal epilepsy who underwent long-term videoEEG monitoring with concurrent polysomnography were included. Sleep was scored using the AASM Manual. EEG features that interfere most with scoring were identified and quantified, exploring the effect of using different EEG derivations, as well as assigning epochs to seizure time.

**Results** A total of 20 studies in 9 patients with focal epilepsy were analysed. EEG features identified included interictal discharges and seizure-related abnormalities (pre-ictal build-up, ictal discharges, and post-ictal slowing). One study contained continuous discharges, 5/20 frequent discharges, 13/20 infrequent discharges and 1 study no discharges. Eleven seizures were recorded across 4/20 studies. Pre-ictal build-up began a median of 1 epoch (range 0–2) before a seizure, while post-ictal changes lasted a median of 6 epochs (range 5–40). Using a longitudinal bipo-

lar montage including the maximally affected channels, assigning ictal and peri-ictal epochs to “seizure” time, and utilising stage N where necessary - without age restriction - made all 20 studies scorable. In 4 studies scored by two independent raters, the overall level of epoch-by-epoch agreement was 85.1% ( $\kappa = 0.78$ ).

**Conclusion** The scoring of sleep in children with focal epilepsy – even those with nightly seizures – is facilitated by applying simple modifications to the AASM guidelines.

## 7.2 Introduction

The American Academy of Sleep Medicine (AASM) “Manual for the Scoring of Sleep and Associated Events” (Iber et al. 2007) (from hereon called “the AASM Manual”) provides technical specifications for polysomnography recordings, as well as criteria for determining sleep stages by visual scoring. Increasingly, it is replacing “A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects” (Kales et al. 1968) as the standard criteria for the visual scoring of sleep, and is now widely used for scoring sleep in children (Grigg-Damberger et al. 2007).

However neither manual makes any provision for the scoring of time spent having a seizure. Additionally, polysomnographic records from children with epilepsy often contain interictal EEG abnormalities which may mimic or obscure the features of sleep. Under Rechtschaffen and Kales’ criteria, it was possible to mark out an epoch filled with seizure time as “movement”, although this would imply a motor component to the seizure. The AASM Manual abolishes “movement” as a label altogether, in favour of scoring the epoch as “wake” if it contains any alpha rhythm or is preceded by “wake”, otherwise assigning it the stage of the subsequent scorable epoch (Iber et al. 2007). This makes it even more difficult to mark out seizure time, particularly where the seizure lasts for more than 30 seconds (the length of one scoring epoch), or is associated with pre-ictal build-up or prolonged postictal slowing.

As a result, even studies focussing primarily on the sleep structure of children with epilepsy have avoided examining nights on which the children had seizures (Pereira et al. 2012, Kaleyias et al. 2008, Racaru et al. 2013, Carotenuto et al. 2014) or recruited only patients who were seizure-free at the time (Maganti et al. 2005). A further strategy has been to mark the seizures independently from sleep scoring (Nunes et al. 2003), with the result that seizures do not result in stage shifts, an important quantitative measure of sleep disruption. Some authors have addressed these issues by modifying the criteria for the identification of the sleep

stages (Carotenuto et al. 2014; Miano et al. 2010), or utilising cyclic alternating pattern (CAP) parameters (see Section 3.1.6) to describe sleep structure, in place of conventional sleep stages. Though effective in their context, these approaches make it difficult to relate findings to the wider literature. We therefore aimed to devise an optimised strategy for the scoring of sleep in children with focal epilepsy, in which the occurrence of seizures would be reflected in quantitative parameters of sleep disruption, while the overall polysomnographic findings remain comparable with those reported in the general sleep literature.

## 7.3 Methods

### 7.3.1 Participants

Data were collected from nine patients with focal epilepsy who underwent video EEG telemetry as part of their clinical evaluation at Great Ormond Street Hospital for Children. These were consecutive inpatients who had been recruited to take part in our study on sleep and memory consolidation (see Section 11.3.1). A total of 20 polysomnographies were analysed.

### 7.3.2 EEG polysomnography recording

Recordings were performed on XLTEK EMU40 systems (Natus, USA). EEG was recorded with a full complement of 10-10 system electrodes. Additionally, we recorded ECG, chin EMG, respiratory effort and oxyhaemoglobin saturation. Electrodes F9 and F10 were utilised as left EOG and right EOG respectively. Full technical details are covered in Section 9.5.1.

### 7.3.3 Sleep scoring

Sleep was scored manually in 30-second epochs using standard criteria defined in the AASM Manual (see Section 3.1), unless epileptic activity interfered with this. In these cases, the EEG features in question were identified and collated, and the approaches described later in this chapter were used to enable the study to be scored. Seizures - including electrographic seizures - were defined as an abnormal, paroxysmal change from the background EEG activity, evolving in frequency, morphology and amplitude, and with a plausible electrographic field (Marzec 2003, Abend et al. 2013). Following convention, electrographic seizures had to last at least 10 seconds (Abend et al. 2011). Interictal epileptiform discharges included sharp waves, spikes, spike-and-slow wave and polyspike-and-wave complexes (Noachtar et al. 1999).

### 7.3.4 Montage

The recommended EEG derivations for sleep scoring in the AASM manual are: F4-A1, C4-A1, O2-A1, with F3-A2, C3-A2 and O1-A2 as backups.

### 7.3.5 Interobserver agreement

Four out of the twenty recordings were scored by two independent observers. One night's recording from each of the first three consecutive patients was scored prospectively by two independent raters. A further recording was selected at random from amongst those containing seizures to be scored retrospectively by a second independent rater, blind to the original scoring. Interobserver agreement was assessed based on the correlation of quantitative sleep parameters (intraclass correlations) as well as epoch-by-epoch comparison. The overall epoch-by-epoch percentage agreement was calculated using native functions in the spreadsheet software, Libreoffice Calc (version: 5.1.4.2, LibreOffice contributors 2016). Cohen's kappa and intraclass correlation coefficients (ICC) were calculated using the "psych" package (Revelle 2016) in R (version 3.2.2, R core R Core Team, 2015).

## 7.4 Results

### 7.4.1 Patient characteristics

These are summarised in Table [7.4.1](#).

### 7.4.2 Montages

In general, we appended eight to ten antero-posterior bipolar derivations to the recommended mastoid-referenced derivations. The bipolar derivations were selected to highlight the most frequent interictal discharges for each patient, as identified beforehand on a common reference montage that included all 27 scalp electrodes. We added the transverse bipolar derivations C3-Cz and Cz-C4 to highlight sleep features such as vertex sharp transients, K complexes and spindles [Figure [7.4.1](#)].

Electrodes T9 and T10 were used as A1 and A2 respectively. EOG derivations used were F9-T10 and F10-T9, with F9 and F10 approximating the outer canthi in order to avoid adding more wires to the headset. Chin EMG was performed as recommended in the AASM manual. During scoring, we referred to the common reference montage at a slower timescale (e.g. 10 seconds per page) if a sharp

Patient	Age (yrs)	Diagnosis	Nocturnal seizures	Nocturnal IEDs
1	6.9	L anterior temporal lesion	<1 per month	rare, mostly focal
2	9.8	L Parieto-occipital lesion; Beckwith-Wiedemann syndrome	None	frequent focal, rare generalised
3	15.5	R temporal FCD	1-3 per month	very rare, focal
4	15.3	R hippocampal lesion; low grade tumour or FCD	1-3 per month	moderate, mostly focal
5	12.9	L hemiplegia, likely R frontal lesion	1-3 per week	frequent, mostly focal
6	9.2	R frontal FCD	1-3 per week	rare, focal
7	10.4	Nocturnal frontal lobe seizures, MRI negative	Nightly	moderate, mostly focal
8	11.6	Nocturnal frontal lobe seizures, ?R temporal FCD	Nightly	frequent, mostly generalised
9	12.6	L temporal DNET (dysembryoplastic neuroepithelial tumour)	1-3 per week	infrequent, mostly focal

Table 7.4.1: Clinical characteristics. L=left; R=right; FCD=focal cortical dysplasia

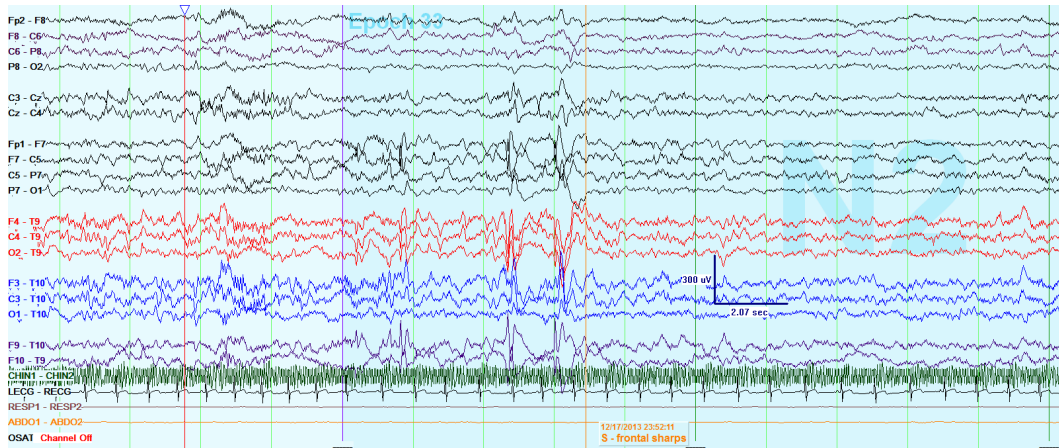


Figure 7.4.1: Bipolar derivations highlight frontal discharges maximal at F7. Transverse vertex derivations highlight spindles.

transient seemed ambiguous on the scoring montage, particularly if a stage shift depended on its identification [Figure 7.4.2].

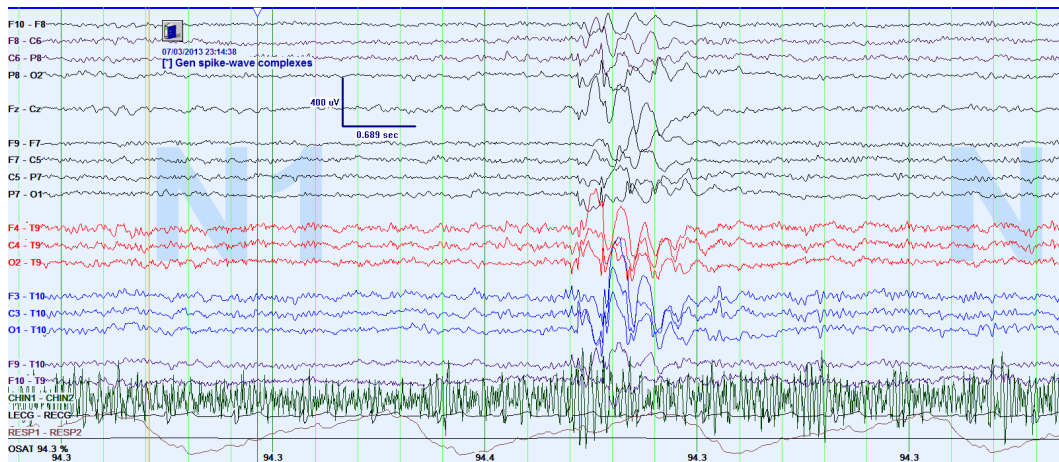


Figure 7.4.2: Generalised spike-wave complexes are better distinguished from K complexes when viewed at 10 seconds per page

### 7.4.3 Specific approaches to sleep scoring in children with epilepsy

The EEG features which presented challenges to sleep scoring were a) seizure-related abnormalities (pre-ictal build-up, ictal discharges, and post-ictal slowing) and b) interictal discharges. For each of these, we outline an approach to make accurate sleep staging possible, and the rationale for these modifications to the AASM scoring criteria.

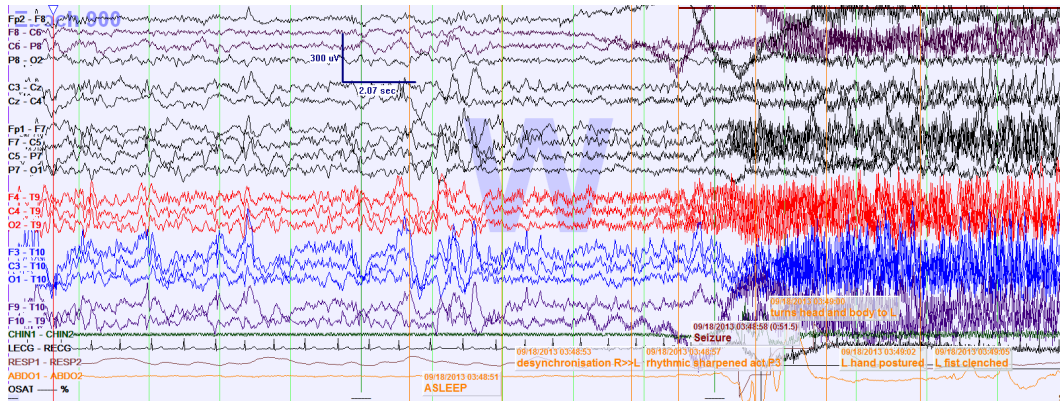
### 7.4.3.1 Seizure activity

**Problem** Pre-ictal build-up signals a change in state. While this would meet the criterion for an EEG arousal according to the AASM criteria, arousals do not always mandate a stage shift (Iber et al. 2007). Seizures with a motor component often obliterate the EEG trace completely. Post-ictal slowing contains delta waves, which if occupying 20% or more of the epoch, would meet the scoring criterion for N3.

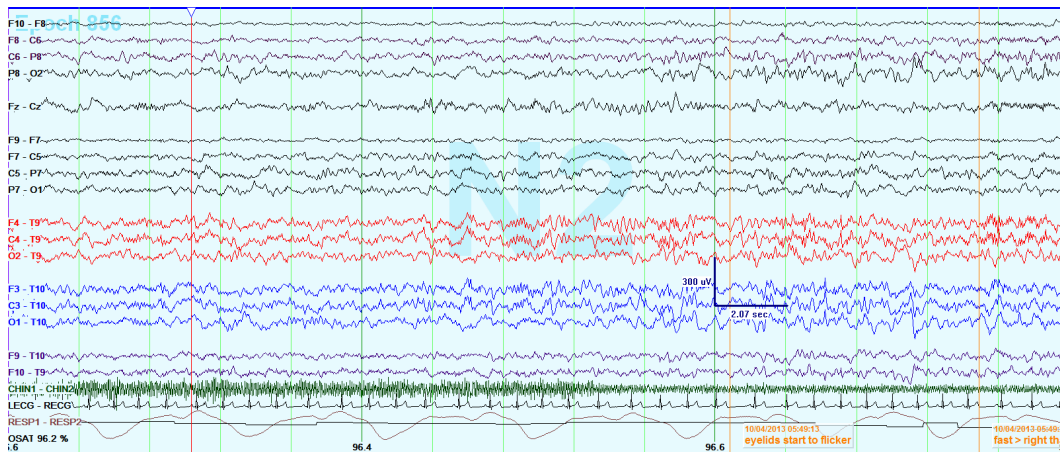
**Prevalence** Eleven seizures were recorded across 4/20 studies. Pre-ictal build-up began a median of 1 epoch (range 0-2) before a seizure, while post-ictal changes lasted a median of 6 epochs (range 5-40).

**Proposed scoring modification** When 50% or more of an epoch consists of pre-ictal build-up (Figure 7.4.3), seizure or post-ictal changes, the epoch should be scored as "seizure" and excluded from the total sleep time (TST) (Figure 7.4.5). Seizure time ends with transition to stage W, an arousal (change to N1 until a spindle occurs), or transition to N2 (when a spindle occurs in the first half of the epoch, or in the second half of the previous epoch). For transition to N3, only slow wave activity that appears subsequent to a sleep spindle may be taken into account.

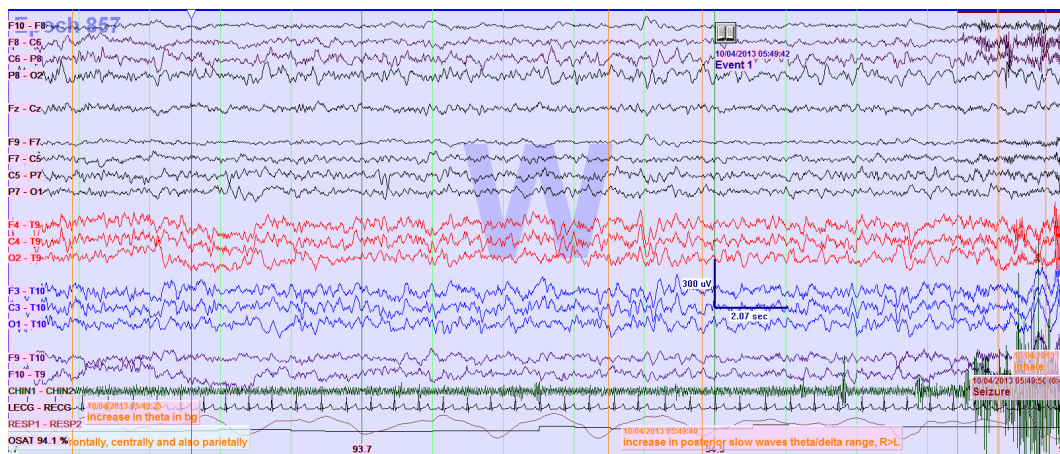
**Rationale** Seizure activity is by definition pathological, and should not be considered as sleep. Under this rule, an electrographic seizure would need to last at least 15 seconds (half of a 30-second epoch) to result in a stage shift, well within the common definition of >10 seconds (Abend et al. 2011). For transition to N2, we have excluded K complexes from the definition as it is difficult to discern K complexes from generalised discharges that may follow a seizure (Figure 7.4.4). While post-ictal slowing and the delta oscillations of slow wave sleep both reflect widespread neuronal synchrony, the latter arises as a consequence of a pathologic event and should not be regarded as equivalent to the physiological attainment of deep sleep. The requirement for the occurrence of a spindle - a physiological thalamocortical oscillation (Beenhakker and Huguenard 2009) indicating transition to N2 sleep - ensures that what is scored as N3 is in fact deep sleep.



(a) Desynchronisation begins just before the middle of this epoch, therefore it is scored as seizure time.



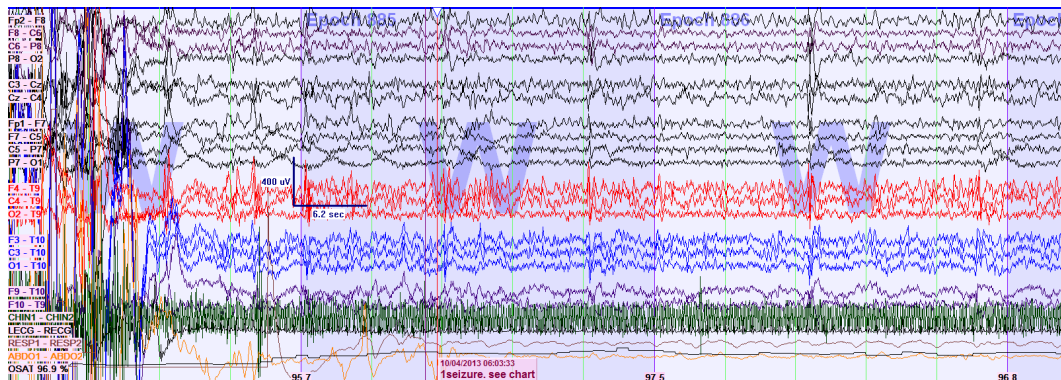
(b) Posterior slowing begins 19 seconds into Epoch 856, therefore this is still scored as N2.



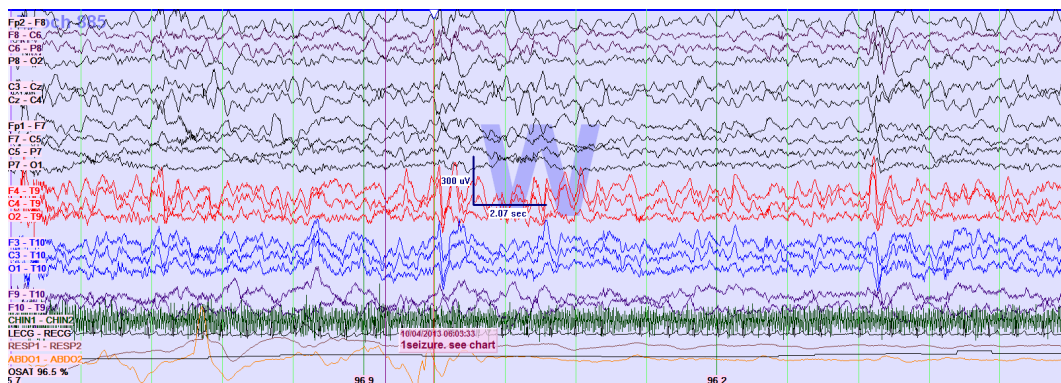
(c) The subsequent epoch is scored as seizure time. The clinical seizure onset is toward the end of this epoch.

Figure 7.4.3: Pre-ictal build-up. Subfigures b and c show consecutive epochs from the same recording.

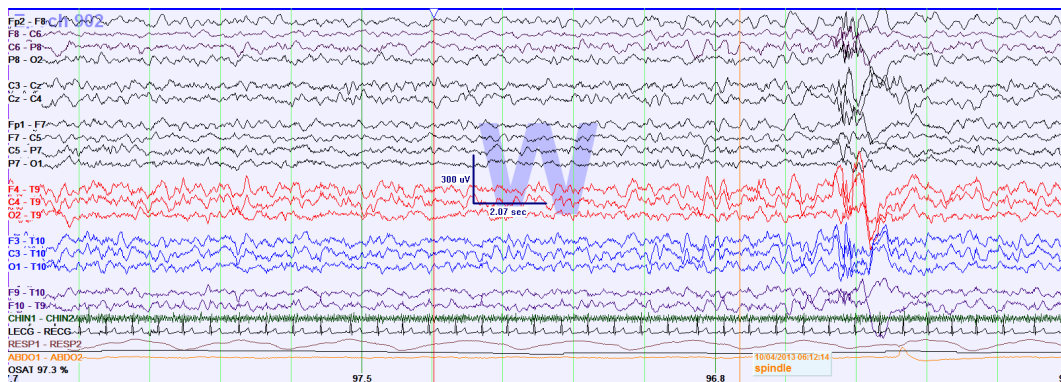




(a) Clinical seizure offset followed by post-ictal slowing with some generalised bursts.

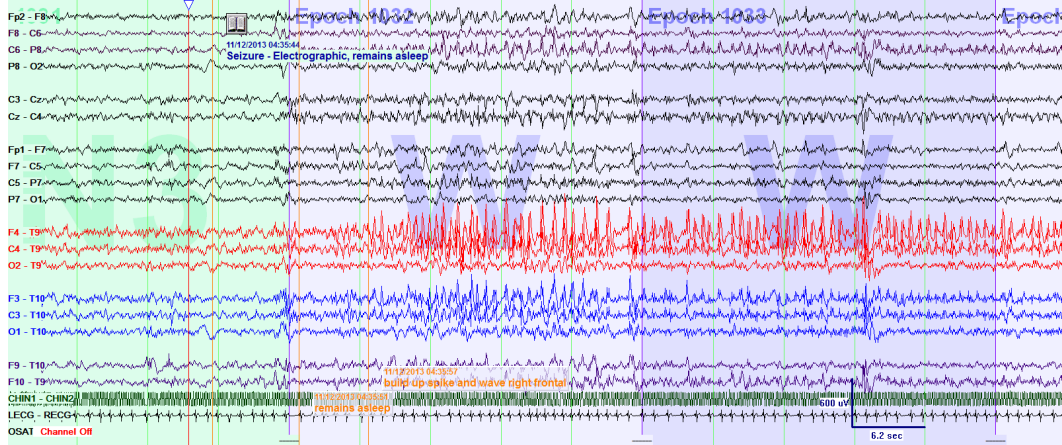


(b) Epoch 885 shown at 30 seconds per page; it is difficult to tell if these are K complexes or spike-wave discharges

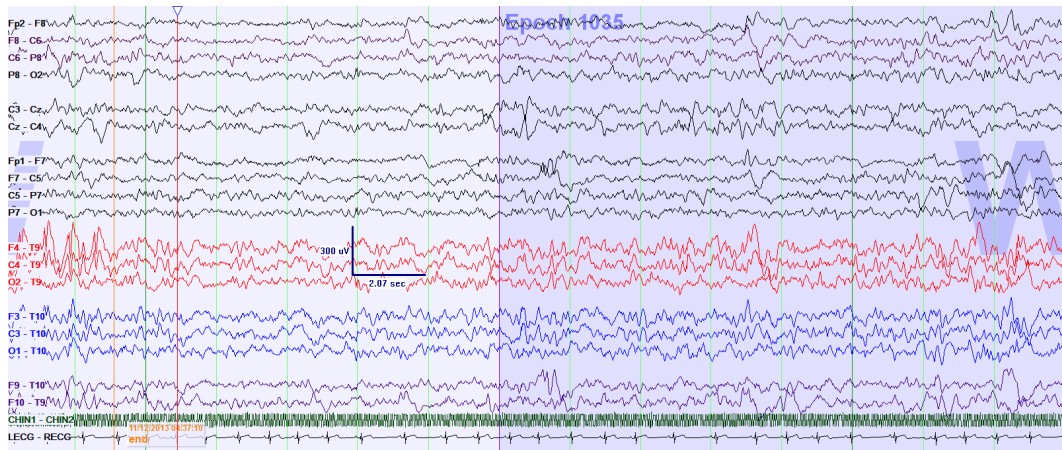


(c) A spindle occurs in the second half of this epoch; the subsequent epoch was scored as N2.

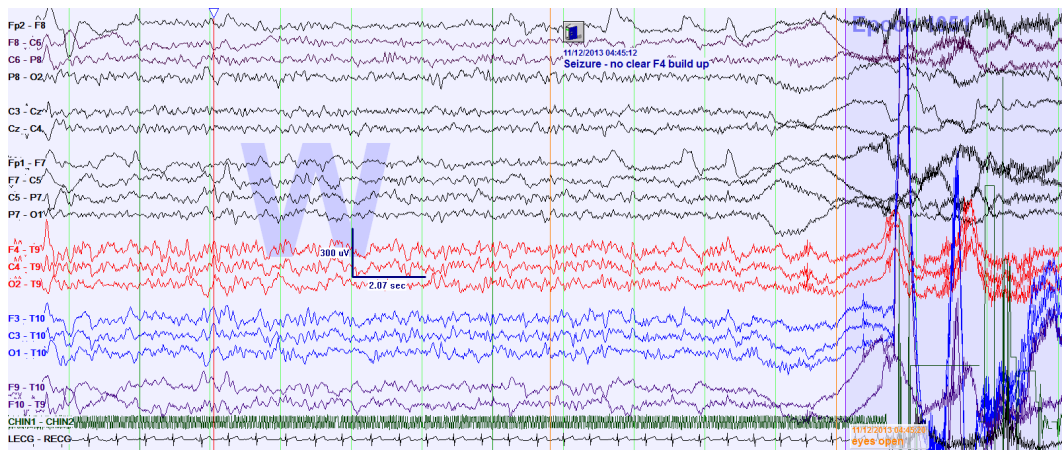
Figure 7.4.4: Transition from seizure time to N2



(a) Electrographic seizure arising from N3. Note amplitude is set at 30uV/mm.



(b) Offset of the seizure followed by post-ictal slowing



(c) Sixteen epochs later (all scored as seizure time due to lack of sleep spindles) there is a clinical seizure

Figure 7.4.5: Electrographic seizure followed by clinical seizure

### 7.4.3.2 Interictal epileptic discharges

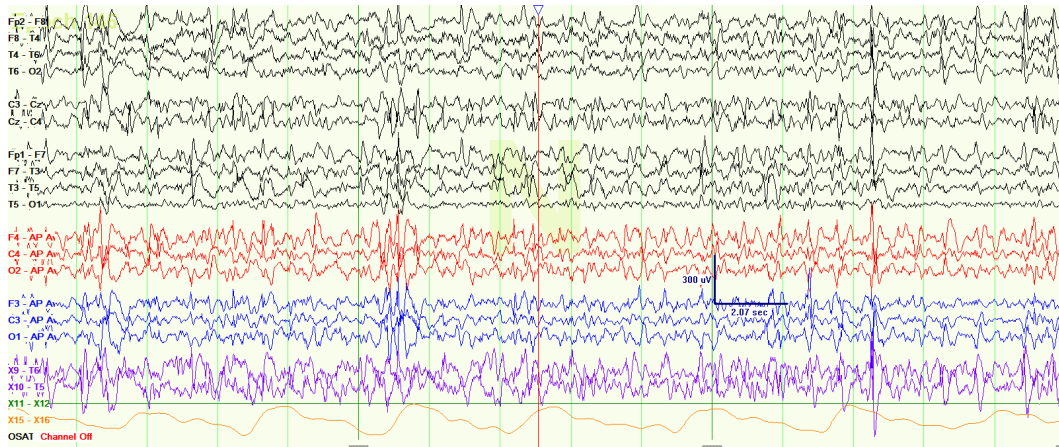
**Problem** Interictal epileptic discharges (IEDs) may resemble key sleep features - such as vertex sharp waves or K complexes - on which stage shifts may depend. Aftercoming slow waves may resemble the physiological delta waves of N3. Temporal discharges in particular may give the false impression of K complexes, due to contamination of the mastoid references. Continuous discharges, as in the syndrome of continuous spike waves in slow wave sleep (CSWS), may obscure or abolish normal sleep features altogether.

**Prevalence** I defined frequent discharges as greater than one per 10 seconds, and continuous discharges as greater than 8 per 10 seconds. One study contained continuous discharges, 5/20 frequent discharges, 13/20 infrequent discharges and one study no discharges.

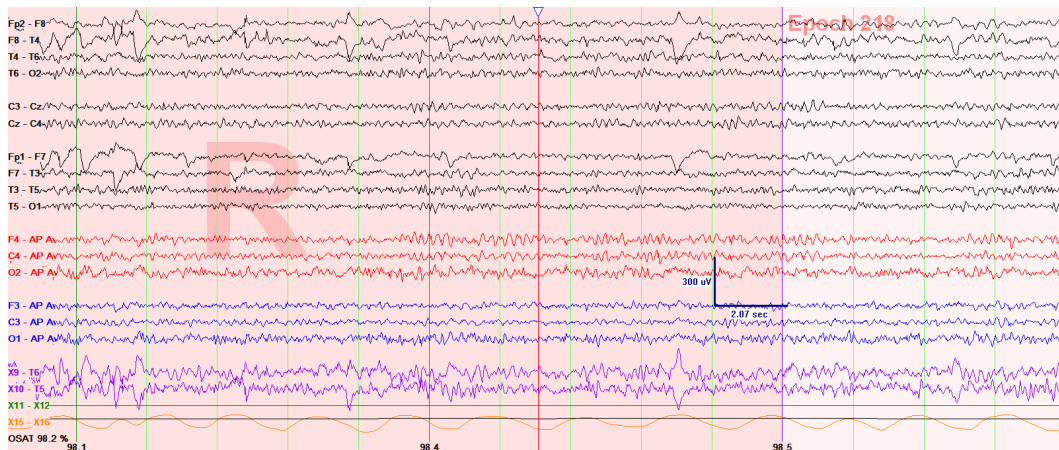
**Proposed scoring modification** Append antero-posterior bipolar derivations to the scoring montage to allow the identification of IEDs. Outside of "seizure" epochs (see above), complexes with features of both a K complex (see Section 3.1.3) and a spike or polyspike-and-wave complex should be considered as K complexes, particularly if followed by an identifiable spindle, and the AASM criteria regarding stage shifts should be applied. In patients with pathologic central sharp waves, vertex sharp waves should not be used to determine the onset of N1. Where interictal discharges are continuous such that normal NREM sleep features cannot be identified, epochs may be scored as "N" - as recommended in the AASM Paediatric sleep scoring criteria - regardless of the patient's age. Discharges usually abate sufficiently in REM for this to be identified and scored by standard criteria.

**Rationale** Antero-posterior bipolar derivations allow for focal interictal discharges to be detected and distinguished from sleep phenomena. Additionally, they can demonstrate the distribution of bilateral and generalised IEDs, and act as a check for contaminated mastoid references. IEDs by definition would not correlate to a clinically detectable change when awake and so should not lead to stage shifts during sleep. Their identification ensures they are not mistaken for physiological sleep features thereby resulting in spurious stage shifts. Physiological K complexes are indicative of paroxysmal cortical neuronal synchrony, which in the epileptic cortex may evoke IEDs or evolve to spike-wave seizures (Steriade and Amzica 1998). Therefore it is likely the epileptiform features are a consequence of the underlying physiological change in state, which ought to be reflected in the sleep scoring. Lastly, utilising the AASM Paediatric scoring criteria for epilepsy patients with

continuous discharges in NREM sleep of all ages enables standardised sleep architecture analysis, even where the stages N1-3 cannot be distinguished (Figure 7.4.6).



(a) Where discharges make stages N1-N3 indistinguishable, these may be scored as N



(b) REM sleep in the same patient

Figure 7.4.6: Use of AASM paediatric scoring criteria in an 11 year-old boy

## 7.4.4 Summary

The overall approach to the record containing IEDs and seizures can be summarised in Figure 7.4.7 below. First, we modified the recommended montage in order to highlight epileptiform discharges. IEDs were distinguished from physiological sleep features, so that where discernible, these could be used to determine stage shifts in the usual manner. Where sleep features could not be discerned due to a heavy load of IEDs, the EOG, EMG and cardiorespiratory parameters could still be used to distinguish REM from NREM sleep, the latter scored as stage 'N'.

Identified seizures were scored as “seizure”, according to the criteria detailed in Section [7.4.3.1](#) (referred to as “Chan & Chevalier criteria” in the figure).

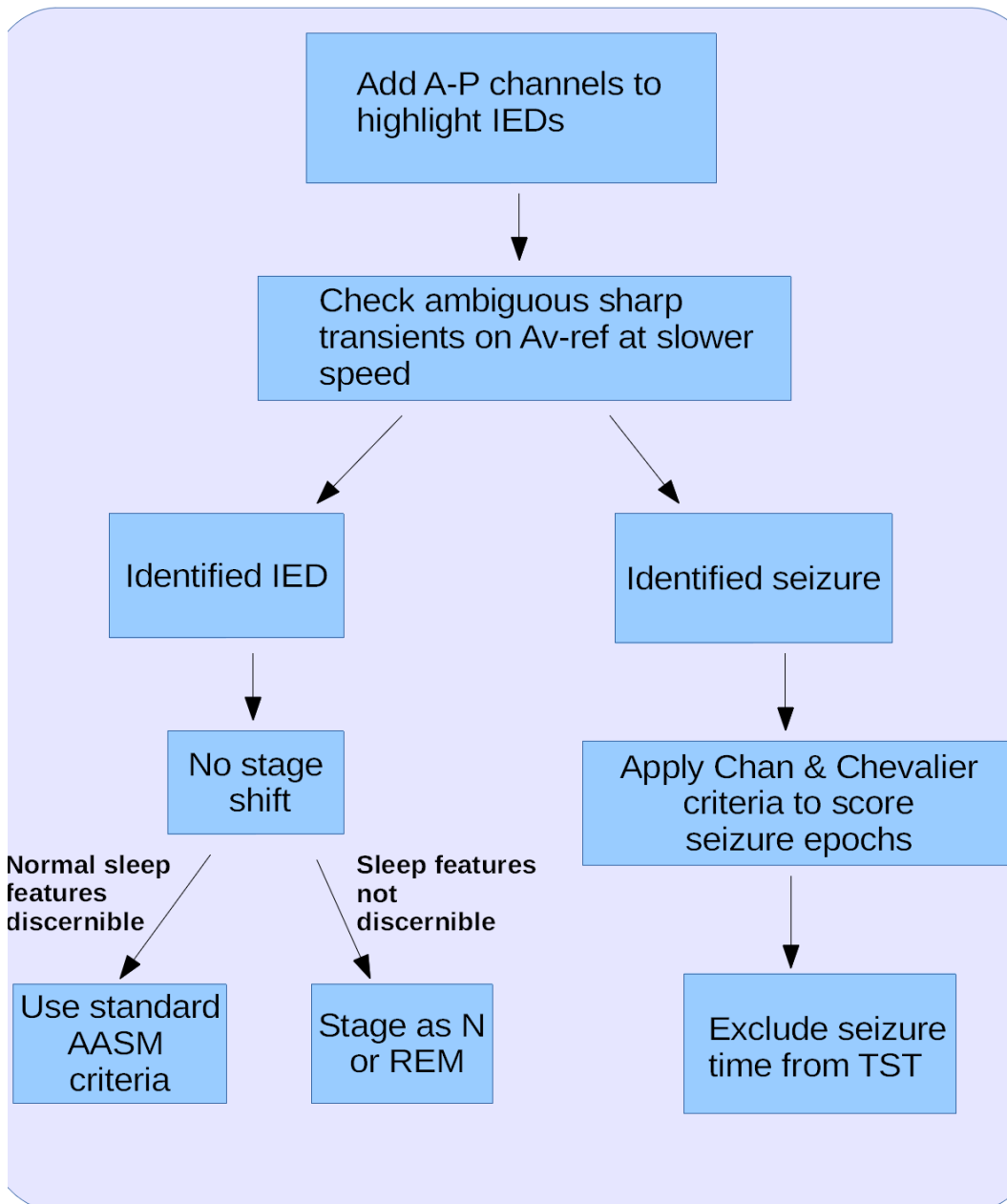


Figure 7.4.7: Approach to staging the sleep EEG record containing epileptiform discharges (see text for full description). *AP*=antero-posterior; *Av-ref*=average referenced; *WASO*=wake after sleep onset

### 7.4.5 Preliminary data on inter-rater reliability

Three studies contained no seizures, and the fourth (from patient number 6) contained three seizures. All four studies contained interictal discharges. The overall level of epoch-by-epoch agreement was 85.1% ( $\kappa = 0.78$ ). The level of agreement based on quantitative sleep parameters was very high; the intraclass correlation coefficient (ICC) was 1 for N2 and N3, 0.94 for REM and 0.91 for N1. Both observers scored 20 minutes of Seizure time for the single study that contained seizures.

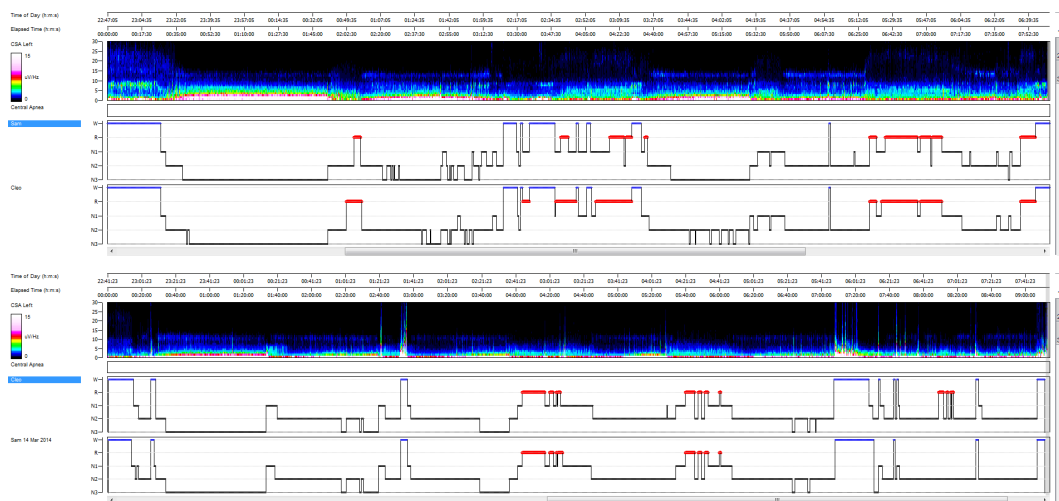


Figure 7.4.8: Hypnograms illustrating inter-observer agreement on records from patient 1 (above; with no seizures overnight) and patient 6 (below; with seizures at around 01:30, 06:50 and 07:10).

## 7.5 Discussion

We report adaptations to standard sleep scoring rules (Iber et al. 2007) which enable the analysis of EEG polysomnographic data from patients with epilepsy, including those with nightly seizures or continuous epileptiform discharges in NREM sleep.

In our sample of children with focal epilepsies of mainly structural etiology, seizures and interictal discharges presented the greatest challenges to sleep staging. However, our recommended modifications enabled all 20 studies to be scored, producing objective measures of sleep macroarchitecture.

Though the data are preliminary, an epoch-by-epoch agreement of 85.1% ( $\kappa = 0.78$ ) compares favourably with the inter-observer reliability of standard sleep scoring rules. In a study to determine the inter-rater reliability of the AASM stan-

dard, recordings from 72 subjects were scored by pairs of experts (Danker-Hopfe et al. 2009). Epoch by epoch agreement was 82% ( $\kappa=0.76$ ) for AASM and 80.6% ( $\kappa=0.74$ ) for R&K. Agreement by quantitative sleep parameters was even greater, but this analysis is affected to a greater degree by the limited sample size.

Marzec and colleagues (2003) described a similar approach based on the Rechtschaffen and Kales criteria (1968), utilising EEG polysomnography data from adults with epilepsy. However, there are no accounts in more recent literature, and none using the AASM criteria (Iber et al. 2007) as a basis. By adhering to the AASM manual definitions for the conventional sleep parameters yet excluding seizure time from total sleep time (TST), our method yields parameters that are optimised for comparison to those in the rest of the paediatric sleep literature.

### **7.5.1 Limitations**

We did not have available two independent trained scorers to analyse all 20 records, therefore the inter-rater reliability data for this scoring system is currently limited. However, this will be an aim of future work.

### **7.5.2 Conclusion**

This approach to sleep scoring enables the study of the natural history of sleep macroarchitecture in various epilepsies, and provides an objective outcome measure for interventional studies, even where the nocturnal seizure burden is not completely alleviated.



## Chapter 8

# Design, development and pilot of new memory consolidation tasks “The Lingfield Memory Consolidation Battery”

### 8.1 Abstract

**Purpose** Performance on paired-associate learning tasks – particularly the cued recall of semantically related word pairs – has been shown to benefit from sleep. This is best demonstrated using a within-subject experimental design. However, there is no verbal test material available for use in English-speaking children. In the visuospatial memory domain, a two-dimensional object location task has been used to demonstrate sleep-related memory consolidation in children, but is not currently available in an open-source format. I aimed to create and pilot a test battery suitable for the demonstration of sleep-related memory consolidation in school-aged, English-speaking children. Additionally, the tests had to be portable and practical for use both in the hospital and home settings.

**Methods** Adult (n=7) and adolescent (n=4) volunteers were recruited from amongst colleagues and work experience placement students at Young Epilepsy. Psycholinguistic variables were selected to control for task difficulty between age-group and parallel test versions. Test material was created using word pairs and pictures from freely available corpora. The resulting test battery was piloted for feasibility, acceptability, ease of administration and difficulty levels.

**Results** For the word pair task, there was no significant difference in the psycholinguistic properties of the parallel lists at all three difficulty levels ( $p \geq 0.6$  for word pair data,  $p \geq 0.1$  for individual word data). Using the hardest version (40 moderately related word pairs), I showed that both adults and adolescents could reach a criterion score of  $>60\%$  in a single attempt. It was possible to retain 95% of the material over a 20-hour interval containing overnight sleep. A 15-pair version of the two-dimensional object location task proved too difficult and time-consuming, however a 12-pair version produced criterion scores of 58-75% in 3-5 learning trials, conducted within 5 to 16 minutes. Material could be retained perfectly overnight as well as over a 5-hour daytime interval.

**Conclusion** The Lingfield Memory Consolidation Battery is a portable, open-source collection of test materials suitable for the assessment of memory consolidation in English-speaking children. Parallel versions facilitate a within-subject experimental design, while difficulty levels within the verbal task will make results comparable across age groups.

## 8.2 Introduction

Performance on paired-associate learning tasks has been shown to benefit from sleep in both adults and school-aged children (see Section 5.3). However, there are several caveats: the difficulty (Walker and Stickgold 2004) and emotional salience (Wagner et al. 2001) of the material can affect the sleep-dependency of a task. Different domains of memory (e.g. verbal, visuospatial) and modalities of presentation (e.g. visual, auditory) may also play a role (Walker and Stickgold 2004). Task dependency is a particular concern when studying patients with epilepsy, who may show dissociation between memory impairments even within a single domain (Salting 2009). Additionally, the effect of sleep on memory consolidation may be missed altogether if baseline delayed memory is not controlled for with an awake condition (Ackermann et al. 2015, Payne et al. 2012).

Therefore, I used a verbal and a visuospatial task, the former with an auditory presentation and the latter visual. Parallel versions of each task were needed in order to facilitate a within-subject experimental design (see Section 11.3.4). Additionally, because of the wide age range of my patient sample, I required more than one difficulty level to ensure the youngest or most impaired participants were able to complete the task, while avoiding ceiling effects (Wilhelm et al. 2013) in the oldest or most able.

For the verbal task, I chose the semantically associated word-pair task because it is the task for which there is the most evidence of sleep-related benefit to mem-

ory consolidation. However, there was no material available for testing English-speaking children. Existing lists in German or French could not simply be translated into English. This was partly for technical reasons; for example, *schaukelstuhl – oma* (rocking chair – grandmother; taken from the material used by Wilhelm and Diekelmann, courtesy of Dr. Diekelmann) when translated is no longer a pair of single words. Perhaps more significantly, cultural and linguistic differences may influence the psycholinguistic properties of words and their associations (Mitrushina 2005).

The picture pair (2D object location) task has been used successfully to demonstrate sleep-related memory consolidation in healthy children (Wilhelm et al. 2008) as well as those with neurodevelopmental disorders (Prehn-Kristensen et al. 2014; Maski et al. 2015) though some authors have found no benefit of sleep to task performance (Galer et al. 2015, Prehn-Kristensen et al. 2014). Most groups utilised a 15-pair array created using proprietary software and presented on a desktop or laptop computer (Rasch et al. 2007, Wilhelm et al. 2008, Maski et al. 2015, Prehn-Kristensen et al. 2014). Wilhelm and Diekelmann (2008) lowered the criterion score to enable healthy 6 to 8 year-old children to complete the task. I required a portable version of the task suitable for use both on the hospital ward and in participants' homes. The task needed to be interactive and engaging enough to encourage optimum performance, while maintaining standardised presentation of the stimuli. Two parallel versions of equal difficulty were required. I aimed to use open-source software so that the programme might be made freely available to other researchers.

## **8.3 Methods**

### **8.3.1 Participants**

Seven adult volunteers (aged 24-55 years) were recruited from amongst nursing and research colleagues at Young Epilepsy. Additionally, four adolescents (ages 15-16 years) who were attached to Young Epilepsy on work experience placements participated with the written consent of their parents.

### **8.3.2 Psycholinguistic variables**

#### **8.3.2.1 Individual stimuli**

Variables were selected to ensure recognition of the material, and to provide a measure of difficulty for comparison between parallel task versions.

**Age of acquisition** Age of acquisition (AoA) refers to the estimated age at which the word or the name of the object in question was learned. Usually generated from self-reported data (Kuperman et al. 2012, Adlington et al. 2009), it is an indication of cumulative exposure to the word or concept, in addition to how early in the course of language development it was acquired. AoA data for the words used in the verbal task were obtained from the database of Kuperman et al (2012); a collection of ratings for 30,000 words obtained by internet crowdsourcing (<https://www.mturk.com/mturk/welcome>; described in Mason and Suri 2012), but calibrated against data gathered by more traditional methods in the United Kingdom (Stadthagen-Gonzalez and Davis 2006). Pictures used in the visuospatial task were obtained from the Hatfield Image Test (Adlington et al. 2009) and had associated AoA values derived from the responses of 31 native English-speaking adults.

**Word frequency** Higher frequency words are more easily retrieved (Adlington et al. 2009). Word frequency data originated from the SUBTL database (Brysbaert and New 2009); a 51-million word collection of samples derived from American movie and television subtitles with an emphasis on those from 1990-2007, making this the most modern openly available database. This was accessed via the wordnorms website ([www.wordnorms.com](http://www.wordnorms.com)) (Buchanan et al. 2012); see Subsection 9.6.1.1), where the measurement is expressed as occurrences per million words.

**Concreteness** Concreteness refers to the ease with which a word can be visualised, or how tangible a noun is. Concreteness interacts with word frequency such that highly concrete words with high frequency are the easiest to access from memory (Paivio and Csapo 1969); the converse is also true. I obtained concreteness ratings from the wordnorms database (Buchanan et al. 2012). These were expressed on a seven-point Likert scale, with 1 being the most abstract and 7 the most concrete.

**Word length** This is simply the number of letters in each word. These data were extracted from [www.wordnorms.com](http://www.wordnorms.com) (Buchanan et al. 2012).

### 8.3.2.2 Word pairs

Variables were selected to indicate the semantic relatedness of word pairs.

**Forward strength** The forward strength of a word pair is the probability of the cue word eliciting the target word. Forward strength values were obtained from ([www.wordnorms.com](http://www.wordnorms.com)) (Buchanan et al. 2012)).

**Cosine** The cosine represents the degree of semantic overlap between words in a pair. It ranges from 0 to 1, with 0 representing no overlap and 1 complete overlap. It is calculated using the formula:

$$\frac{\sum_{i=1}^n A_i \times B_i}{\sqrt{\sum_{i=1}^n (A_i)^2} \times \sqrt{\sum_{i=1}^n (B_i)^2}}$$

Buchanan et al (2012) had experimental subjects list physical, functional and categorical features of words. The frequency (expressed as a percentage of all respondents) with which each feature occurred was recorded. To calculate the cosine of a word pair, only the frequencies of features common to both words in the pair were included. For a word pair A - B,  $A_i$  and  $B_i$  indicate the frequencies of the common feature “i” given in response to words A and B respectively, while  $n$  is the number of common features. Essentially, the list of frequencies for each word is treated as a vector, and the cosine derived from the dot product of the two vectors (each of length  $n$ ) divided by their magnitudes (Spiegel and Lipschutz 2009). Mathematically, this formula is equivalent to that for the sample Pearson correlation coefficient. Cosine values were obtained from [www.wordnorms.com](http://www.wordnorms.com) (Buchanan et al. 2012).

### 8.3.3 Task material construction

#### 8.3.3.1 Verbal task

The website [www.wordnorms.com](http://www.wordnorms.com) (Buchanan 2012; accessed 4 June 2013) is a searchable online lexical database containing psycholinguistic measures drawn from multiple sources, in addition to calculated word pair values. It was explicitly designed for experimental stimulus creation, including the generation of word-pair associates. I downloaded the full non-null database (Figure 8.3.1), and cross-referenced this with the full database of Kuperman et al (2012); both were available as Microsoft Excel (Microsoft, USA) files. I selected word pairs where both cue and target were highly concrete (rated  $>5$ ), then looked up and recorded the AoAs – all AoAs were less than 9.3 years. Word pairs without AoA data were excluded. I aimed to compile two lists ('A' and 'B') containing 40 word pairs each - the number used in previous studies on adults (Rasch et al. 2007, Gais et al. 2002). Based on data from healthy children, I chose 30-pair (Urbain et al. 2011) and 20-pair (Wilhelm et al. 2008) subsets out of each list to create easier versions targetted at 9-11 year-olds and 6-8 year-olds respectively. AoAs in the 30-pair lists were mostly less

than 7, and in the 20-pair lists were mostly less than 6. Where word pairs were available that matched those of Wilhelm and Diekelmann (e.g. hand – arm, doll – child) these were incorporated into the lists.

A18	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	
1	cue_word	target_word	cosine	jsn	isa	fsq	qss	tss	qcoo	tcoo	kf1	kf2	hal1	hal2	loghal1	loghal2	sub1	
2	spill	drip	0.20156439	3.450679	0.151078	0.014	0	16	10	4.49	4.98	1	1	1609	1348	7.38	7.21	8.4
3	faucet	drip	0.54233625	19.777308	0.24247	0.047	0.16	7	10	6.2	4.98	1	1	439	1348	6.08	7.21	1.4
4	caterpillar	moth	0.19378913	11.103339	0.658368	0.014	0	10	14	6.96	5.46	1	1	413	515	6.02	6.24	1.1
5	doe	fawn	0.21553098	10.459595	0.538243	0.027	0.089	8	6	5.75	5.47	1	1	4652	388	8.45	5.96	4.3
6	clarinet	flute	0.86036211	7.030865	0.511965	0.213	0.049	9	19	5.66	5.66	1	1	1634	3491	7.4	8.16	1.5
7	flute	clarinet	0.86036211	7.030865	0.511965	0.049	0.213	19	9	5.66	5.66	1	1	3491	1634	8.16	7.4	2.1
8	harp	flute	0.79190841	10.230807	0.457378	0.012	0	17	19	6.94	5.66	1	1	1667	3491	7.42	8.16	2.6
9	fawn	doe	0.21553098	10.459595	0.538243	0.089	0.027	6	8	5.47	5.75	1	1	388	4652	5.96	8.45	0.7
10	elk	doe	0.27216492	10.682733	0.280513	0.013	0	9	8	5.75	5.75	1	1	1184	4652	7.08	8.45	0.7
11	raccoon	squirrel	0.36806942	9.101086	0.458897	0.07	0	22	11	6.6	6.08	1	1	275	1989	5.62	7.6	1.4
12	prune	plum	0.62355317	10.229028	0.098891	0.053	0.039	14	13	6.26	6.18	1	1	739	825	6.61	6.72	1.4
13	drip	faucet	0.54233625	19.777308	0.24247	0.16	0.047	10	7	4.98	6.2	1	1	1348	439	7.21	6.08	5.1
14	pickle	prune	0.27901044	15.767151	0.071287	0.014	0	15	14	5.93	6.26	1	1	979	739	6.89	6.61	4.6
15	plum	prune	0.62355317	10.229028	0.098891	0.039	0.053	13	14	6.18	6.26	1	1	825	739	6.72	6.61	3.4
16	raisin	prune	0.39552053	1.832583	0.048201	0.121	0.106	12	14	6.96	6.26	1	1	314	739	5.75	6.61	1.6
17	camel	donkey	0.31789872	12.196907	0.173669	0.014	0	11	10	5.93	6.67	1	1	3375	2629	8.12	7.87	5.0
18	zebra	donkey	0.40752443	10.880801	0.061663	0.032	0	9	10	6.52	6.67	1	1	915	2629	6.82	7.87	2.5
19	prune	raisin	0.39552053	1.832583	0.048201	0.106	0.121	14	12	6.26	6.96	1	1	739	314	6.61	5.75	1.4
20	pumpkin	halloween	0	27.294066	0.496734	0.3	0.186	8	17	6.42	4.12	2	1	937	1826	6.84	7.51	10.8
21	butterfly	moth	0.53540008	1.564793	0.656286	0.109	0.267	20	14	5.91	5.46	2	1	1798	515	7.49	6.24	5.5
22	shrimp	lobster	0.52391158	3.423673	0.430478	0.084	0.038	15	23	6.25	5.84	2	1	1993	849	7.6	6.74	8.7
23	butterfly	caterpillar	0.2567991	10.254412	0.865306	0.097	0.358	20	10	5.91	6.96	2	1	1798	413	7.49	6.02	5.5
24	tumble	trampoline	0	23.333234	0.023238	0.011	0	13	9	4.66	5.18	3	1	568	114	6.34	4.74	1.5
25	necklace	bracelet	0.51363711	6.039304	0.303031	0.154	0.095	12	13	6.12	5.98	3	1	1149	443	7.05	6.09	9.7
26	tortoise	hare	0.08054951	14.265335	0.367347	0.075	0.046	7	6	5.98	6.03	3	1	2454	1946	7.81	7.57	1.1
27	peach	plum	0.62751213	4.191554	0.17076	0.031	0.055	10	13	6.05	6.18	3	1	1812	825	7.5	6.72	6.3
28	grape	prune	0.39516194	8.409863	0.033864	0.014	0.043	17	14	5.85	6.26	3	1	1637	739	7.4	6.61	0.7
29	grape	raisin	0.24871548	7.598957	0.096619	0.048	0.253	17	12	5.85	6.96	3	1	1637	314	7.4	5.75	0.7

Figure 8.3.1: Screenshot showing upper left corner of spreadsheet containing full non-null dataset from [www.wordnorms.com](http://www.wordnorms.com) (Buchanan 2012; accessed 4 June 2013). 'Zebra-donkey' is one of the pairs included in my test material.

### 8.3.3.2 Visuospatial task

This task was originally designed with 15 paired locations. For the two parallel versions, 30 pictures - two sets of 15 - were selected from the Hatfield Image Test (Adlington et al. [2009]), a corpus of photographic colour images with associated naming data. These were matched for age of acquisition and category of object. Three additional pictures were selected to create a demonstration version of the task. I programmed the application using MIT App Inventor Classic (<http://appinventor.mit.edu/explore/classic.html>), an online application-building tool with a graphical user interface and pre-fabricated 'blocks' of code to specify behaviours. These include the response of objects to being touched, and the length of time an image appears on the screen. The completed .apk file can be shared to any Android device. The demonstration, learning and testing phase material were created as separate .apk files.

To ensure similar difficulty levels between the parallel versions, I used the same template of picture-pair positions rotated by 90 degrees (Figure 8.3.2). Following initial trials in the adult subjects (see below), I removed 3 pairs from each version to create an easier task, with 12 paired locations.

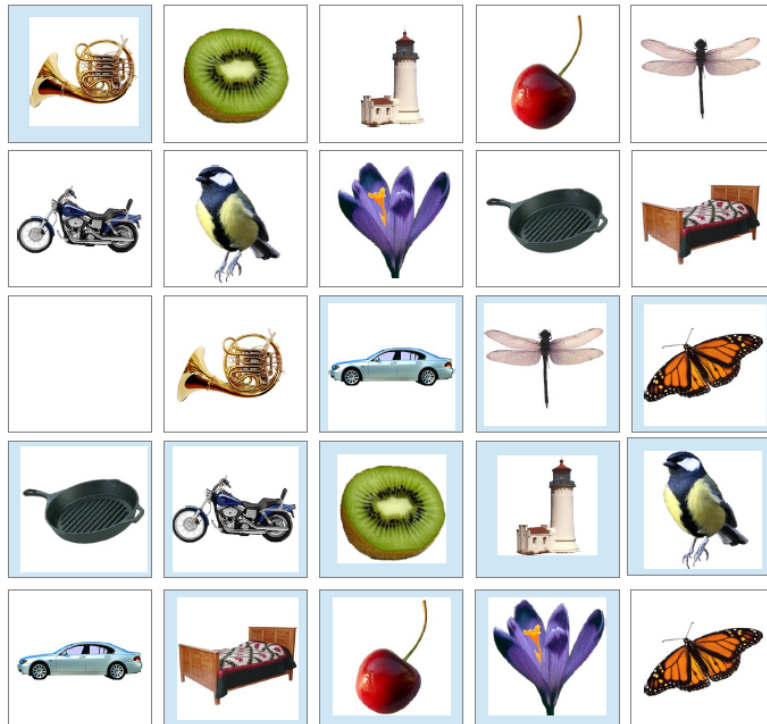


Figure 8.3.2: Template for version B of the visuospatial (2D object location) task. Positions with blue outline are the 'cue' positions.

### 8.3.4 Task material properties - statistical analysis

For each pair of word lists (e.g. 30A and 30B), I performed independent sample t-tests using SPSS version 21 (SPSS Inc, USA) to compare cosine and forward strength for word pairs, and age of acquisition, word frequency and word length for individual words.

### 8.3.5 Testing procedures

#### 8.3.5.1 Verbal task

In the learning phase of the task, all the word pairs were first read out, taking approximately 5 seconds for each pair. Learning trials took the form of cued recall with feedback. The subject was asked to respond with the associated target word on presentation of each cue word. Each correct response was affirmed before the next cue word was presented. For each incorrect response, the word pair was read out again. Learning trials were repeated until a criterion of at least 60% correct answers was reached. In the testing phase of the task, I read out the cue words in a fixed order, and the participant had a single attempt - with no time limit - to respond to each cue word with the target.

### 8.3.5.2 Visuospatial task

The task was presented on a Samsung Galaxy Note 10.1 tablet (Samsung, South Korea). In the learning phase of the task, each picture pair was presented for 4 seconds. The participant advanced to the next pair by touching the screen, though there was a lockout time of 0.5 seconds. All the pairs were presented twice, in a different order for each presentation. This was followed by a cued recall procedure - the cue picture was revealed, and the participant had to touch the array position of the matching picture (Figure 8.3.3). A correct response kept the pictures at the cue and target positions displayed for 0.5 seconds, while an incorrect response displayed the pictures at the correct cue and target positions for 2 seconds, without revealing the picture at the incorrect position. Learning trials were repeated until a criterion score of 7/12 pairs (approximately 60%) was reached, or the session was terminated after 35 minutes.



Figure 8.3.3: Screenshots from the visuospatial (2D object location) task, learning phase. The “Show Next” button is greyed out and will not respond during the lock-out time when the paired stimuli are presented (left), as well as pending a response from the subject during learning trials (right).

In the testing phase of the task, each cue picture was presented to the participant, who was given a single attempt - with no time limit - to respond to each cue by touching the target position. The cues were presented in a different order to that used for the learning trials. Touching the correct position revealed the matching picture, while touching the wrong position produced a buzzer sound without revealing



the picture at the chosen position.

### 8.3.6 Outcome measures

For each performance of each task, I recorded the number of trials to criterion (60% of items correctly recalled), the criterion score, immediate recall score (in some participants), delayed recall score, number of hours' delay, any sleep in that period, and the time taken for learning and for recall. Additionally, comments made by participants regarding how difficult or demanding they found the task were noted.

## 8.4 Results

### 8.4.1 Stimuli characteristics

Psycholinguistic properties of the parallel word-pair list versions are summarised in the tables below. The shorter lists also had greater mean cosines and forward strengths, indicating greater semantic association.

	Version A	Version B	p
Cosine	0.2 (+/- 0.2)	0.2 (+/- 0.2)	0.6
Forward strength	0.07 (+/- 0.06)	0.06 (+/- 0.06)	1
Age of acquisition (years)	5.1 (+/- 1.6)	5.2 (+/- 1.6)	0.7
Word frequency (per million words)	50.4 (+/- 68.2)	66.4 (+/- 103.9)	0.3
Word length (letters)	5.1 (+/- 1.4)	4.9 (+/- 1.3)	0.4

Table 8.4.1: Properties of the 40-pair lists. Version A and B values are mean (+/- standard deviation). P values are derived from independent sample t-tests.

	Version A	Version B	p
Cosine	0.2 (+/- 0.2)	0.2 (+/- 0.2)	0.7
Forward strength	0.07 (+/- 0.07)	0.07 (+/- 0.07)	0.9
Age of acquisition (years)	5.0 (+/- 1.6)	5.1 (+/- 1.6)	1
Word frequency (per million words)	46.7 (+/- 63.6)	64.6 (+/- 108.7)	0.3
Word length (letters)	5.2 (+/- 1.5)	4.9 (+/- 1.2)	0.2

Table 8.4.2: Properties of the 30-pair lists. Columns and units as above.

	Version A	Version B	p
Cosine	0.3 (+/- 0.2)	0.3 (+/- 0.2)	0.9
Forward strength	0.7 (+/- 0.4)	0.7 (+/- 0.4)	0.7
Age of acquisition (years)	5.4 (+/- 1.7)	5.5 (+/-1.6)	0.8
Word frequency (per million words)	38.0 (+/- 61.6)	51.3 (+/- 85.2)	0.5
Word length (letters)	5.6 (+/- 1.5)	5.0 (+/- 1.2)	0.1

Table 8.4.3: Properties of the 20-pair lists. Columns and units as above.

## 8.4.2 Performance data

Two of the adolescents performed both the verbal and the visuospatial tasks, while the other two performed the visuospatial task only. Three of the adults performed both tasks (two of these were tested on immediate but not delayed recall), while the other four performed only the visuospatial task. Four adults performed on both a 15-item and a 12-item version of the visuospatial task. Only one participant (an adult) completed both parallel versions of both tasks, though these were all performed with a memory retention interval of 5 hours awake.

### 8.4.2.1 Verbal task

It took 10-15 minutes to go through a single learning trial of the 40-pair verbal task. All subjects were able to reach criterion in a single attempt, the scores ranging from 30 to 39 (mean 34.2). There was only a single attempt - in an adolescent - containing sleep in the memory retention interval, resulting in a decrease of 5% of items recalled compared to baseline. However there was no within-subject performance for comparison.

### 8.4.2.2 Visuospatial task

This was tested more extensively due to the lack of psychometric data for assessing task difficulty. The 15-item version proved too difficult for the adult subjects, with 5 out of the 7 volunteers requiring 5 or more attempts, and 3 of these failing to reach criterion even after half an hour of learning trials. The 12-item version took between 5 and 16 minutes to administer in the learning phase, and 1 to 4 minutes in the testing phase. The adults required 3 attempts to reach criterion, while the adolescents required 3 to 5 attempts. Criterion scores ranged from 58 to 75%. Of the three adolescents who had a night's sleep between learning and testing, two maintained their scores while the third showed a 17% decrease in items recalled. The fourth adolescent was tested across a 5-hour daytime interval, and scored the same at testing as at criterion. No within-subject data were available for comparison.

## 8.5 Discussion

I describe here the creation and pilot testing of the “Lingfield Memory Consolidation Battery”, a new memory consolidation task battery suitable for use in English-speaking children. The battery contains parallel versions of both a verbal and a visuospatial task, allowing the examination of two declarative memory domains in a within-subject design. To my knowledge, there is no other such battery reported in the literature.

Due to time constraints, it was not possible to conduct a full validation study prior to applying the task battery to my experimental sample. However, both paradigms are well established (Marshall and Born 2007), and I had an age-matched control sample.

In Chapter 11, I administered the battery to 21 healthy school-aged children and 22 children with epilepsy, demonstrating that the verbal task can detect sleep-dependent memory consolidation (Chan et al. 2017). This is a larger total sample than all but one (Voderholzer et al. 2011) of the existing similar studies in children, whether healthy (Wilhelm et al. 2008, Backhaus et al. 2008, Urbain et al. 2011) or with neurodevelopmental problems (Galer et al. 2015, Prehn-Kristensen et al. 2014, Maski et al. 2015). The visuospatial task does not demonstrate a benefit of sleep to memory consolidation in the healthy children, but shows a benefit correlating to that in the verbal task in the patients. This is consistent with the findings of Galer et al (2015), who employed a similar task in children of the same age. It is not clear why this is, though the greater number of practice trials required by the patient sample may have ensured better encoding and perhaps allowed for the implicit motor aspects of the task to be consolidated in sleep as well. There was no ceiling effect in the healthy subjects.

The validation of this task battery in a larger sample of healthy children, and of the 40-pair version of the verbal task in healthy adults would enable it to be adopted by other researchers in the field of memory research.



## **Part III**

# **Principal methods**



## Chapter 9

# Principal methods

This chapter details methods common to the experimental studies described in subsequent chapters.

### 9.1 Participant recruitment

All subjects were aged between 6 and 16 years at the time of assessment, and had no prior diagnosis of primary sleep disorders. All patients had a firm diagnosis of medication resistant focal epilepsy with a structural or presumed structural etiology. The prospective cohort (see Chapter 11) were recruited from amongst those admitted for prolonged video EEG telemetry at Great Ormond Street Hospital for Children (GOSH) or at the medical facility at Young Epilepsy (YE). In addition to the diagnosis above, further criteria were 1) attendance at mainstream school (as a proxy for sufficient cognitive ability to complete the experimental tasks) and 2) planned hospital admission for at least 4 nights. The retrospective cohort (see Chapter 10) were taken from the GOSH video telemetry database. Patients were selected on the same diagnostic criterion, in addition to having been subjected to (and compliant with) sleep restriction during their admission. Healthy controls were recruited prospectively by advertisement directed at staff working at Young Epilepsy, a charity that supports children and young people with epilepsy in the United Kingdom. Additionally, healthy school-aged siblings of patient participants were invited to take part.

### 9.2 Clinical assessment

All patients underwent full clinical assessment as part of their presurgical evaluation. Demographic details, age of onset of epilepsy, clinical examination findings including handedness, seizure frequency, seizure semiology, MRI findings and

medication history were recorded. Additionally, clinical events (e.g. seizures) and diagnostic interventions (e.g. medication reduction, sleep restriction) and their timings with respect to the course of the admission were recorded.

## **9.3 Neuropsychological testing**

### **9.3.1 Intelligence**

Full scale IQ scores on the Wechsler Intelligence Scale for Children version 4 (WISC-IV; Pearson, USA) for all patients were extracted from recent neuropsychological reports, performed for presurgical evaluation. Control subjects underwent IQ testing using the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI; Pearson, USA) during their participation in the study. FSIQ scores derived from the two-subtest WASI are generally a few points higher than that measured using the WISC (Wolraich 2008). However there is a good correlation ( $r=0.86$ ), similar to that between versions III and IV of the WISC (Wolraich 2008).

### **9.3.2 Memory**

Patients whose parents reported memory problems were also administered the Children's Memory Scale (CMS; Pearson, USA) as part of their presurgical work-up. The CMS assesses declarative learning and memory functions across three domains: Auditory/ Verbal, Visual/ Nonverbal, and Attention/ Concentration (working memory). Administering the 6 subtests yields eight index scores: Attention/ Concentration, Verbal Immediate, Verbal Delayed, Delayed Recognition, Visual Immediate, Visual Delayed, Learning, and General Memory. Of note, the Verbal Delayed score is calculated using the 30-minute recall scores on stories as well as related and unrelated word pairs (Cohen 2011).

## **9.4 Questionnaires**

### **9.4.1 Sleep habits**

A parent completed the Children's Sleep Habits Questionnaire (CSHQ; Owens et al. 2000) in relation to each participant. The CSHQ is a retrospective parent-report sleep-screening instrument designed for and validated on children aged 4 to 10 years. It consists of 45 items, in which parents are asked to rate behaviours as occurring "usually", "sometimes" or "rarely" in a recent typical week. Some items are reversed, so that a higher score consistently indicates more disturbed sleep. Additionally, parents are asked to indicate if they consider each behaviour a problem



(yes/no). Parents are asked to state the child's typical sleep duration, bedtime, time of awakening in the morning and duration of nightwakings. 35 of the 45 items are used to calculate 8 subscales reflecting the following domains: 1) Bedtime Resistance, 2) Sleep Onset Delay, 3) Sleep Duration, 4) Sleep Anxiety, 5) Night Wakings, 6) Parasomnias, 7) Sleep- Disordered Breathing, 8) Daytime Sleepiness. The Total Sleep Disturbance score consists of 33 items, comprising the same items as those used for the subscales, but with duplicates removed - therefore the lowest possible score on the CSHQ is 33. A score of 41 is recommended as the threshold beyond which the child should be assessed at a sleep clinic (Owens et al. 2000). Of note, Cronenbach's alpha was only 0.36 for the Parasomnias subscale; the other subscales have alphas of 0.5-0.7. For the total score, alpha was 0.68 in controls and 0.78 in a sleep clinic sample.

#### **9.4.2 Behaviour**

The Strengths and Difficulties Questionnaire (SDQ; Goodman 1997) was completed by a parent in relation to each participant. The SDQ is a behavioural screening questionnaire validated for children aged 3-16 years, containing 25 items on psychological attributes. These are divided equally between 5 domains: 1) emotional symptoms, 2) conduct problems, 3) hyperactivity/inattention, 4) peer relationship problems and 5) prosocial behaviour. Each item can be marked "not true"(scored 0), "somewhat true"(scored 1) or "certainly true"(scored 2). Scoring is reversed on some items so that a higher score consistently indicates worse behaviour. The scores for domains 1-4 are added to give a Total Difficulties Score, which may range from 0 to 40. Scores of 0-13 are considered to be normal, and 14-16 as borderline (Goodman 1997).

#### **9.4.3 Memory**

The Everyday Memory Questionnaire (EMQ; Sunderland et al. 1983) was completed by a parent in relation to each participant recruited subsequent to February 2014. The EMQ was developed for adults with traumatic brain injury (TBI), and covers five categories in which this group of patients suffered memory failure: speech, reading and writing, faces and places, actions, and learning new things. Though correlation with neuropsychological tests is variable (Drysdale et al. 2004), the questionnaire has been validated on clinical samples with TBI, stroke and multiple sclerosis, showing significant differences between clinical and non-clinical groups. Importantly, it has been validated using both self- and carer reports. For validation in children, the questionnaire was modified to remove irrelevant items, such as "getting lost on journey travelled once or twice before", then administered to 226

schoolchildren aged 6-12 years, and 35 patients from a learning disorders clinic (Drysedale et al. 2004). Using an optimal cut-off score of 48, sensitivity was high at 89%, while specificity was low at 60%. The mean score for the school group was 72.89 (standard deviation 34.41).

## 9.5 EEG and polysomnography

### 9.5.1 Data acquisition

Sleep was recorded with the Xltek Trex (Natus, USA) system, using 8 EEG electrodes (F3, F4, C3, C4, O1, O2, A1, A2) positioned according to the international 10-20 system in control subjects, 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. Electrocardiogram, surface chin electromyogram, chest and abdominal movements and pulse oximetry were recorded in all participants. Eye movements were detected using standard electro-oculogram derivations (Iber et al. 2007) in controls, while electrodes F9 and F10 were utilised for this purpose in patients. The retrospective patient cohort had EEG (27 electrodes, as above) and ECG recorded only.

The equipment used on all subjects was similar: silver/silver chloride cup electrodes (Ambu Neuroline, Denmark) were used on the scalp and arms, and self-adhesive conductive gel electrodes (Ambu Neuroline, Denmark) for chin and EOG. The amplifiers used were Xltek Trex (Natus, USA) for controls and Xltek EMU40 (Natus, USA) for patients. Respiratory belts were piezo-electric belts (ProTech - Philips, Netherlands) for controls and respiratory inductance plethysmography (SleepSense, USA) for patients. Pulse oximeters were Masimo SET (USA). Natus NeuroWorks software (Natus, USA) was used for recording. Signals were sampled at 256Hz or 516Hz in controls and 516Hz or 1032Hz in patients.

### 9.5.2 Sleep scoring

Sleep recordings from healthy participants, and from patients who did not have seizures during the recording were scored visually according to standard criteria (Iber et al. 2007) using Sleepworks software (Natus, USA). Sleep scored as "N3" is equivalent to slow wave sleep (Iber et al. 2007). For recordings containing seizures (n=5), conventional sleep stages were scored by standard criteria, but epochs were scored as "seizure" if they contained ictal discharges, >50% pre-ictal build-up or >50% post-ictal slowing. "Seizure" epochs were not included in the Total Sleep Time. For all patient recordings, I added custom bipolar channels to the standard

sleep scoring montage, in order to highlight focal epileptiform activity and distinguish this from sleep phenomena. Full details of the rationale behind the modifications to standard criteria and results of a pilot validation study are described in Chapter 7.

### 9.5.3 Quantification of interictal discharges

Interictal epileptiform discharges (IEDs) included sharp waves, spikes, spike-and-slow wave complexes, and polyspike-and-slow wave complexes, as defined by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (Noachtar et al. 1999). I identified the IED morphologies for each patient, and verified these with a consultant neurophysiologist.

The count was recorded as the number of IEDs per minute, calculated by dividing the total number of IEDs by the duration of sleep time over which they were counted. I marked the discharges manually for the first two sleep cycles, to include at least one period of rapid eye movement (REM) sleep. There is evidence from paediatric patients with focal epilepsies that the IED rate does not differ significantly between sleep cycles across the night (Nobili et al. 1999). For the two patients with >10 discharges in most 10 s epochs, I counted 100 IEDs for each sleep stage in each sleep cycle, and divided the result by the duration of EEG reviewed for each stage. For all other patients, I parsed the record manually for the whole of the first two sleep cycles. For analysis, I expressed the discharge load for each patient as the number of discharges per 100 s, to facilitate comparison with existing studies in the literature.

### 9.5.4 Data pre-processing for quantitative analysis

The EEG record was pruned with lights on and lights off (as derived from visual sleep scoring, see 9.4.2) as the cut points, and then exported from Natus Neuroworks (Natus, USA) as an .edf file. The .edf file was downsampled to 128Hz in EDFbrowser, version 1.58 (van Beelen; <http://www.teuniz.net/edfbrowser/>). All further data processing and analysis was performed with Spike2, version 7 (Cambridge Electronic Design, Cambridge, UK). Analysis was carried out on EEG channels F3 and F4, each referenced to CpZ. Visual and semi-automatic artefact removal was performed. First, seizure time was cropped from the trace manually with cut points determined from visual sleep scoring (see Chapter 7). Next, movement artefact was removed using an amplitude threshold trigger, usually +/-500uV, though this was increased as necessary where visual inspection revealed the amplitude of true slow waves to be higher. A script was used to delete the trace 5

seconds before and 20 seconds after the amplitude trigger, joining the remaining data with a straight line.

## 9.6 Memory tasks

The memory tasks were adapted from Wilhelm and Diekelmann (2008). Verbal declarative memory was tested using a word-pair associate learning task, while visuospatial declarative memory was assessed using a two-dimensional (2D) object location task, similar in concept to the card game commonly known as “Pairs”. Full details on the creation and piloting of the test materials can be found in Chapter 8.

### 9.6.1 Verbal task

#### 9.6.1.1 Stimulus material

The generation of the word pairs is described in Section 8.3.3.1. I created three versions of the word pair lists, containing 20, 30 or 40 word pairs, for children aged 6 to 8 years, 9 to 11 years and 12 to 16 years respectively. Subjects with a full scale IQ of <80 were tested on the version for the age group just below their chronological age. Each age-group version consisted of two parallel lists of word pairs, allowing for two administrations of the task. This was necessary to facilitate within-subject comparison of performance under different conditions.

To allow for multiple learning trials, a random number sequence generator (Haahr; <https://www.random.org/>) was used to re-assort the word pairs for each learning trial beforehand. To avoid semantic priming effects, the resulting lists were checked and any consecutive pairs containing semantically related words (e.g. lobster-tail and coral-sea) rearranged in the list so that they were no longer consecutive.

#### 9.6.1.2 Testing protocol

The testing protocol was as described in Section 8.3.5.1.

### 9.6.2 Visuospatial task

#### 9.6.2.1 Stimulus material

The stimulus material is described in Section 8.3.3.2.

### 9.6.2.2 Testing protocol

The learning procedure was as described in Section 8.3.5.2. Learning trials were repeated until a criterion score of 7/12 pairs (approximately 60%) for children aged 9 to 16 years or 5/12 (approximately 40%) for children aged 6 to 8 years was reached, or the subject refused further trials.

The testing phase was as described in Section 8.3.5.2.

### 9.6.3 Scoring

For each administration of each task, the percentage of correct answers at the end of the learning trials was recorded as the “criterion score”. The percentage of correct answers in the testing phase was recorded as the “test score”. The criterion score was subtracted from the test score to obtain a “memory retention score”, representing the difference between delayed and immediate recall. Therefore for each subject, the administration of the full test battery produced a verbal memory retention score and a visuospatial memory retention score under each of the two testing conditions.

For the experimental protocol detailed in Subsection 11.3.4, the order of presentation of the parallel versions of each task was counterbalanced across subjects, and across conditions. In this study, the conditions in question were “wake” and “sleep”. The “wake” condition, an 8-hour daytime delay between immediate and delayed recall, served as the control condition, while the “sleep” condition - with a night’s sleep between immediate and delayed recall - was the experimental condition. For each subject, the difference between the sleep and wake condition memory retention scores for each task yielded a quantitative measure of the contribution of sleep to memory consolidation (“sleep benefit”) for that domain.



**Part IV**

**Results**





## Chapter 10

# Sleep homeostasis in children with focal epilepsy and correlation with cognitive measures

### 10.1 Abstract

**Objective** The global downregulation of synaptic strength by slow wave activity in sleep is thought to be essential in maintaining the ability to learn. I aimed to determine if sleep homeostasis is intact in children with focal epilepsy but without epileptic encephalopathy, and whether its integrity correlates with intellectual ability.

**Methods** Retrospective EEG recordings from 16 children (aged 7-16 years) who had undergone partial sleep deprivation during hospital admission were analysed. Sleep homeostasis parameters were determined by visual sleep scoring as well as the quantification of EEG slow wave activity (1-4Hz) using fast Fourier transform. These were correlated with full scale IQ scores obtained from contemporaneous neuropsychological test reports.

**Results** The proportion of time spent in slow wave sleep was significantly higher in the sleep deprived night ( $p=0.01$ ), and correlated with the degree of sleep deprivation ( $r=0.56$ ,  $p=0.03$ ). The average power density in the slow wave activity (SWA) band was also higher on the sleep deprived night, though this did not reach statistical significance ( $p=0.06$ ). Total SWA power ( $\mu V^2 \cdot s$ ) varied significantly across NREM cycles both on the baseline ( $F=13.3$ ,  $p<0.0001$ ) and sleep deprived ( $F= 4.6$ ,

$p=0.009$ ) nights. A repeated measures ANOVA with NREM cycle and night (baseline vs sleep deprived) as within-subject factors showed a significant main effect of NREM cycle ( $F=6.9$ ,  $p=0.01$ ) but no significant interaction of NREM cycle by night ( $F=0.3$ ,  $p=0.9$ ), and no significant main effect of night ( $F=0.8$ ,  $p=0.4$ ). The absolute SWA power showed great interindividual variability, but was highly conserved within individuals. I found no correlation of SWA power or dynamics with clinical factors or IQ. The majority of patients did not show a monotonic decline in SWA power density across the night; where seizures were recorded on the analysed EEG, their occurrence was associated with an increase in SWA power density later in the night.

**Conclusion** Sleep homeostasis is fundamentally intact in children with focal epilepsy with a structural or presumed structural etiology, with a clear fall in SWA power density across the night, and evidence of upregulation of both time spent in SWS and average SWA power density in response to acute sleep restriction. I did not show a correlation with global intellectual function. The synaptic downregulation afforded by sleep homeostasis may be utilised to address both the physiological and pathological causes of synaptic potentiation in this group of children.

## 10.2 Introduction

Sleep homeostasis (see Section 3.3.2) is thought to maintain normal daytime cognitive functioning through the global downregulation of synaptic strength over the course of a night's sleep (Tononi and Cirelli 2014). Apart from children with CSWS, in whom recent data suggest sleep homeostasis may be impaired (Bölsterli et al. 2011, Bölsterli Heinzle et al. 2014), the integrity of sleep homeostasis in children with epilepsy has not been examined, and its dynamics and relationship to cognitive functioning are essentially unknown.

Sleep deprivation is a well-known activator of ictal and interictal discharges (IEDs) in patients with epilepsy - yet the pathophysiological mechanisms remain poorly understood (Díaz-Negrillo 2013). The propensity to have seizures triggered by sleep deprivation varies greatly between individual patients, and between different epilepsy syndromes (Foldvary-Schaefer and Grigg-Damberger 2006). This variation in sensitivity to sleep manipulation suggests that patients with epilepsy likely have a wide range of sleep homeostasis dynamics, with impairment potentially contributing to both cognitive and seizure vulnerability. In healthy adults and adolescents, acute sleep deprivation does not alter the fundamental dynamics of homeostasis, but allows for enhanced observation of the build-up and decline of

sleep pressure as measured by slow wave activity (SWA) (Rusterholz et al. 2010, Jenni et al. 2005).

I aimed to investigate the integrity of sleep homeostasis and its relationship with cognitive ability in a group of children with epilepsy of focal structural (or presumed structural) etiology who underwent sleep deprivation. I hypothesised that sleep homeostasis would be fundamentally intact in this group without epileptic encephalopathy; that is, SWA would build up during prolonged wakefulness and decline during subsequent sleep. I hypothesised that there would be a positive correlation between favourable sleep homeostasis dynamics - that is, slower build-up and faster dissipation of SWA - and intellectual function.

## **10.3 Methods**

### **10.3.1 Participants**

I collected data retrospectively from 16 children with focal epilepsy. Two of these had participated in the main study (see Chapter 11). Data retrieval and inclusion criteria are described in Sections 9.1 and 9.2.

### **10.3.2 Sleep restriction**

Patients were instructed to remain awake for at least 2 hours after their habitual bedtime, and were awoken by a nurse the next morning at least 1 hour earlier than their habitual wake-up time. This was usually carried out on the second night of the admission, after medications had been reduced in the morning.

### **10.3.3 EEG records**

Video EEG recordings had been acquired between June 2012 and January 2014; these were parsed manually to exclude those containing daytime sleep episodes or evidence of non-compliance with sleep-restriction. Two nights' data were extracted for each participant: the sleep-restricted night (SD), and a baseline night (BN). The first night of admission was chosen as the baseline night, except in four patients in whom sleep restriction occurred on the first night of admission. In these patients, the third or fourth night was used as a baseline instead.

### **10.3.4 Intelligence scores**

I used the full scale IQ as a measure of cognitive ability (see Section 9.3.1). In all but one patient, neuropsychological testing was performed on the same admission

as video EEG telemetry.

### 10.3.5 EEG data acquisition and sleep scoring

These are detailed in Section 9.5. All but two patients had EEG and ECG electrodes only as this was a retrospective cohort. F9 and F10 were utilised as electro-oculogram for the purposes of sleep scoring.

### 10.3.6 EEG quantitative analysis

After pre-processing (detailed in Section 9.5.4), the EEG data were subject to spectral analysis offline using a fast Fourier transform (FFT) routine (Spike2, CED, UK). FFT configuration was 4-second Hanning windows, resulting in a frequency resolution of 0.25 Hz. The lowest four frequency bins (0.25 - 1 Hz) were not used for further analysis due to their sensitivity to low frequency EEG artefacts. Slow wave activity (SWA) was defined as power in the 1 - 4 Hz band. For further analysis, I selected the frontal channel (F3-CpZ or F4-CpZ) contralateral to the seizure focus as determined by semiology, imaging and video EEG (see Table 10.4.1).

To investigate SWA build-up, the mean power density (power/ 10 seconds) in the 1 - 4Hz frequency band for the whole night was calculated for each of the sleep deprived (SD) and baseline (BN) nights. Additionally, the mean power density up to a time point to match the length of the sleep restricted night was calculated for each baseline night - a truncated baseline night (BN-short) - in order to enable better comparison with the sleep deprived night, given that patients had been awoken early as part of the sleep deprivation protocol (Lassonde et al. 2016). The ratio of mean power density in SD to that in BN-short was calculated as a crude indicator of sleep need in lieu of the time constant of SWA build-up (Rusterholz et al. 2010; see Section 3.3.2).

To examine SWA decline, I calculated the total SWA power in each NREM cycle across the night for each recording. A median filter was applied with SWA averaged every 180 seconds. The start and end times for each NREM cycle were determined by a thresholding procedure as follows: for each patient, mean SWA power in the first REM period (as defined by visual sleep scoring) was calculated, and the threshold for NREM was set at 2 standard deviations above this value (Figure 10.3.1; see section 10.5.6). The area under the curve (delta power-time) was calculated for each NREM cycle (Figure 10.3.1). Normalised SWA power was calculated by dividing the SWA power in each NREM cycle by the average NREM SWA power on the baseline night for each subject (Malow et al. 1998). These were plotted for successive NREM cycles across each night to illustrate the variation in patterns of SWA dynamics across the patient group.

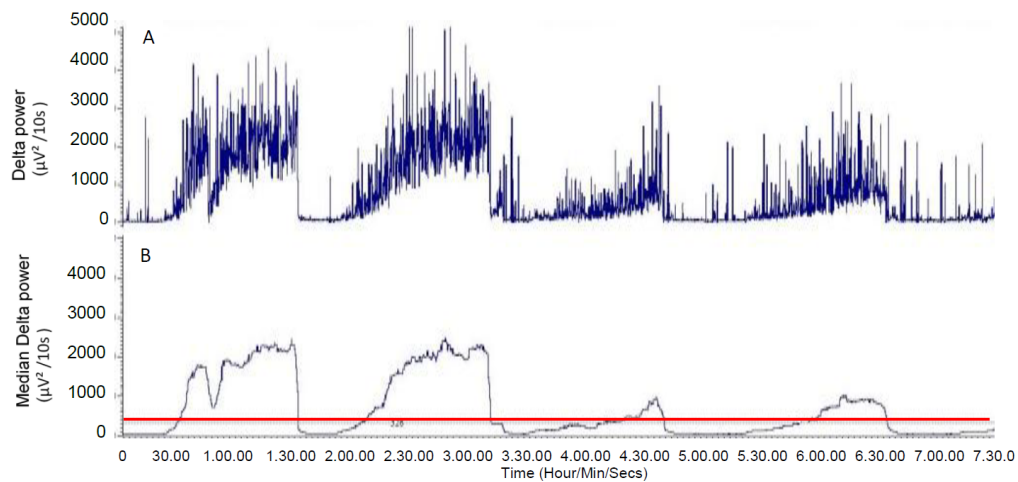


Figure 10.3.1: Calculation of SWA in each NREM cycle. A: Skyline plot of SWA in each 10-second epoch, for the whole night. B: A median filter was applied with SWA averaged every 180 seconds. NREM cycles were determined by applying a threshold (red line) set 2 standard deviations above the mean SWA in the first REM period for that patient (not shown). Four NREM cycles are identified in this recording.

### 10.3.7 Statistical analysis

Paired sample t-tests were used to compare the mean polysomnographic parameters and whole-night average power densities between the baseline and sleep restricted nights. Pearson's  $r$  correlation coefficient was used to investigate the association between whole-night average power densities on the baseline and sleep-deprived nights, and to investigate the relationship between the degree of sleep restriction (percentage reduction in total sleep time) and the percentage increase in SWA power density.

Trends in SWA power and power density across consecutive NREM periods were tested with repeated measures analysis of variance (ANOVA). Pearson's  $r$  correlation coefficient was used to test for a correlation of IQ with the percentage change in whole-night SWA power density.

## 10.4 Results

### 10.4.1 Participant characteristics

The clinical characteristics of the patient sample are summarised in Table 10.4.1. All patients had focal epilepsy with a structural or presumed structural cause and were admitted for pre-surgical evaluation.

Patient ID	Age (yrs)	Sex	Age at onset (yrs)	FSIQ	MRI findings	Seizure localisation	Seizure frequency	Antiepileptic medication
1	10.3	F	5.0	103	no lesion	L temporal	every 2 weeks	zonisamide
2	14.8	M	1.7	67	L corona radiata infarct	undetermined	5-6 per day	levetiracetam, sodium valproate
3	15.5	M	6.0	90	R temporal FCD	R temporal	every 2-3 weeks	lamotrigine
4	15.8	M	13.1	99	R temporal DNET	R temporal	every 1-2 weeks	sodium valproate, lamotrigine
5	12.3	F	8.0	95	L hippocampal sclerosis and FCD	L temporal	every 2-3 days	topiramate, levetiracetam, clobazam
6	15	M	10.0	83	no lesion	R frontal	3-4 per night	carbamazepine
7	11.8	M	1.6	78	no lesion	undetermined	daily	carbamazepine, topiramate, clobazam
8	12	F	0.75	97	R temporal/frontoparietal pial anglioma	R occipital	monthly	levetiracetam, lamotrigine, topiramate
9	16.9	F	7	56	no lesion	L temporal	3-4 per week	levetiracetam
10	16.4	F	8	106	no lesion	R temporal	weekly	topiramate, oxcarbazepine
11	8	F	1	89	L hippocampal sclerosis	L temporal	<1 per month	sodium valproate, levetiracetam
12	7	F	1	89	L temporal DNET	L temporal	Every 3-4 months in clusters	none
13	8.9	F	3	74	L perisylvian and parietal polymicrogyria	undetermined	<1 per month	lamotrigine
14	7.3	M	0.2	86	no lesion	L fronto-parietal	2 per night	levetiracetam, oxcarbazepine, clobazam, ketogenic diet
15	8.9	M	5	88	no lesion	R centro-temporal	<1 per month	sodium valproate, lamotrigine
16	16.1	F	7	83	no lesion	L fronto-temporal	daily	carbamazepine, sodium valproate

Table 10.4.1: Clinical characteristics of the sample. FSIQ = full scale intelligence quotient; FCD = focal cortical dysplasia; DNET = dysembryoplastic neuroepithelial tumour. Seizure localisation was determined by semiology, imaging and video EEG. Patients 3 and 4 participated in the main study (Chapter 10).

### 10.4.2 Diagnostic interventions and clinical events

Of those on medication, 14 (88%) had this reduced or stopped. All patients underwent sleep restriction, though compliance was variable. I recorded the degree of sleep restriction for each patient as the percentage reduction in sleep time using the baseline night as the reference. On average, the sleep restricted night was 36% (standard deviation +/- 13%) shorter than the baseline night. Eight patients (50%) had no seizures during their admission, five patients (31%) had seizures following sleep deprivation, three (19%) had seizures both before and after sleep deprivation and one (6%) had a seizure before sleep deprivation. Three records on the baseline night contained seizures while three records on the sleep restricted night contained seizures.

### 10.4.3 Sleep architecture

A comparison of sleep architecture on the baseline and sleep restricted nights is summarised in Table 10.4.2. At the group level, the proportion of time spent in N3 (equivalent to slow wave sleep) increased significantly ( $p=0.01$ ) with sleep deprivation, while that in N2 decreased ( $p=0.02$ ), suggesting that sleep was deeper on the sleep restricted night. There was a linear correlation between the percentage reduction in total sleep time and the percentage of total sleep time spent in N3 ( $R=0.56$ ,  $p=0.03$ ). The proportions of total sleep time spent in N1, N2, N3 and REM on the baseline night were consistent with normative values for age (Scholle et al. 2011).

	Baseline night	Sleep restricted night	p
TST (mins)	560 (+/- 65)	360 (+/- 87)	<0.001
N1 (% TST)	5.7 (+/- 3.5)	6.9 (+/- 3.5)	0.3
N2 (% TST)	33.8 (+/- 11.1)	26.2 (+/- 10.6)	0.02
N3 (% TST)	34.9 (+/- 13.6)	44.5 (+/- 12.9)	0.01
REM (% TST)	25.7 (+/- 7.6)	22.4 (+/- 8.5)	0.1

Table 10.4.2: Comparison of sleep architecture on the baseline and sleep restricted nights. All quantities are presented as mean (+/- standard deviation). TST = total sleep time. p values were derived from paired sample t-tests; non-parametric tests gave similar results.

### 10.4.4 SWA power density across the whole night

Mean SWA power density across the two nights was closely correlated within individuals ( $r=0.9$ ,  $p<0.001$ ), but showed a large variation between individuals (Figure

10.4.1). SWA power density was higher on the sleep restricted night compared to either the whole ( $p=0.055$ ) or the truncated ( $p=0.1$ ) baseline night, but this did not reach statistical significance. The ratio of SWA power density in the sleep restricted night to that in the truncated baseline night was  $>1$  in 10 patients, but  $<1$  in 6 patients. A higher percentage reduction in TST tended to correlate with a greater percentage increase in SWA ( $r=0.4$ ,  $p=0.1$ ).

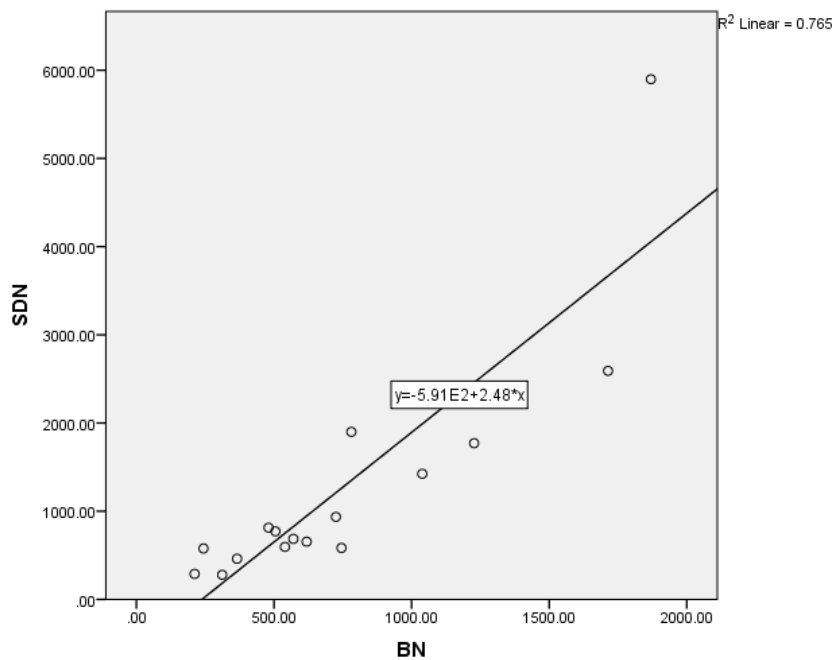


Figure 10.4.1: Mean SWA per 10-second epoch in NREM sleep across the whole night ( $\mu V^2 \cdot s/10$  sec). *BN* = baseline night; *SDN* = sleep restricted night

#### 10.4.5 Slow wave activity across NREM cycles

Total SWA power ( $\mu V^2 \cdot s$ ) varied significantly across NREM cycles both on the baseline ( $F=13.3$ ,  $p<0.0001$ ) and sleep deprived ( $F= 4.6$ ,  $p=0.009$ ) nights. A repeated measures ANOVA with NREM cycle and night (baseline vs sleep deprived) as within-subject factors showed a significant main effect of NREM cycle ( $F=6.9$ ,  $p=0.01$ ) but no significant interaction of NREM cycle by night ( $F=0.3$ ,  $p=0.9$ ), and no significant main effect of night ( $F=0.8$ ,  $p=0.4$ ). The normalised SWA power across the first four NREM cycles is plotted for each patient in Figure 10.4.3). Interestingly, most patients (11/16 on the baseline line and 9/16 on the sleep restricted night) did not show a monotonic decline - that is, the relative SWA power density increased between subsequent NREM cycles - even though there was an overall decrease from the first to the last cycle.



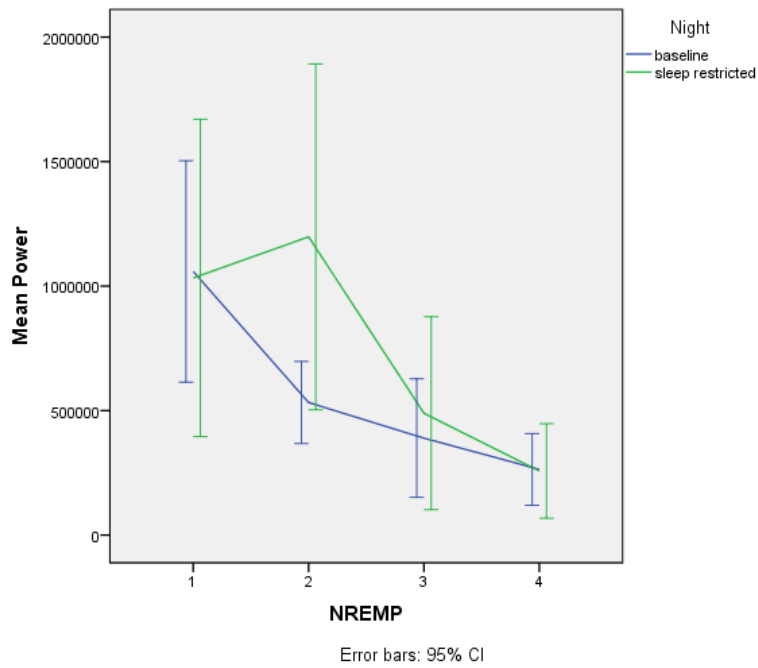


Figure 10.4.2: Mean SWA power (uV<sup>2</sup>.s) during successive NREM cycles (“NREMP”) for the first 4 cycles on the baseline and sleep restricted nights. Error bars show 95% confidence intervals.

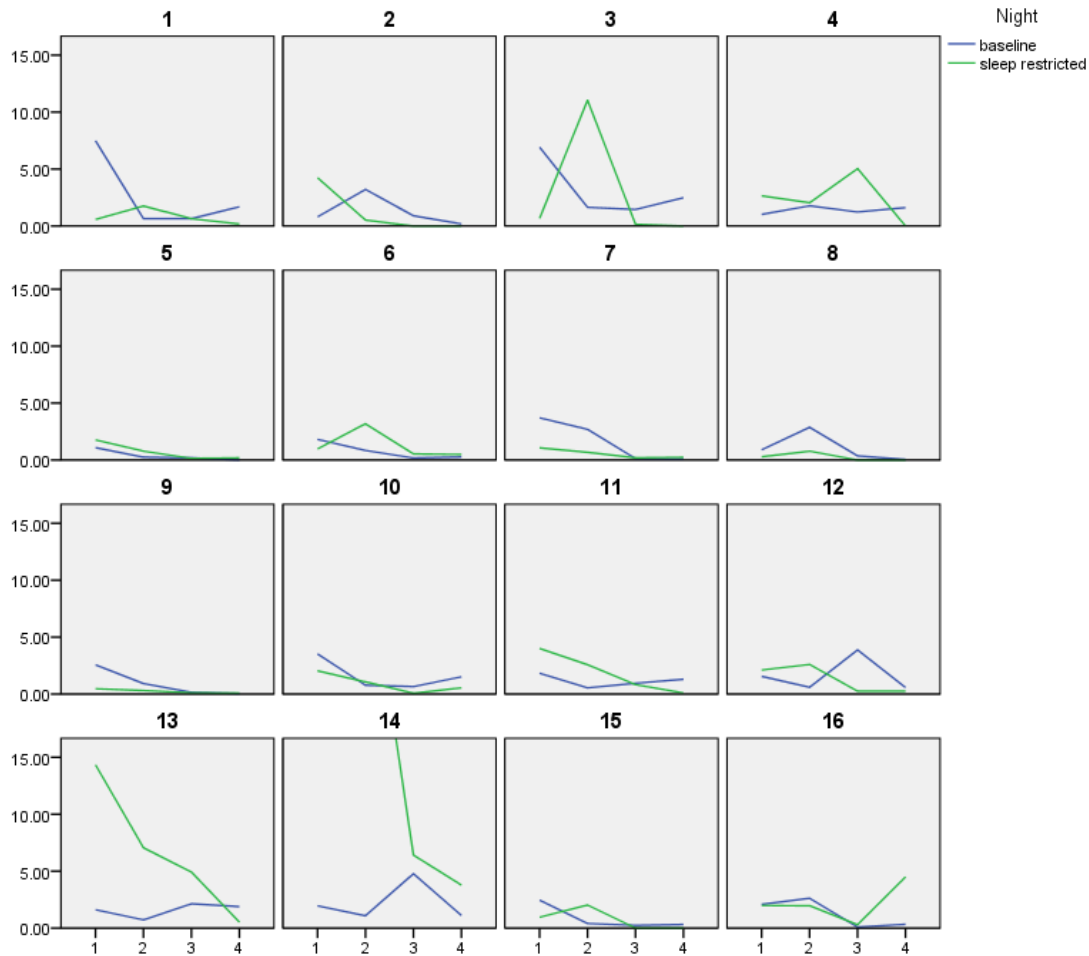


Figure 10.4.3: Normalised SWA power across the first four NREM cycles (x-axis: NREM cycle; y-axis: normalised SWA power) on the baseline and sleep restricted nights for each patient. Note that most patients did not show a monotonic decline in SWA power across successive NREM cycles, though the overall pattern was one of decline over the course of the whole night. Patient 14 had 30 times mean normalised SWA power in the first NREM cycle and 34.3 times in the second NREM cycle on the sleep restricted night. Patients 5 and 16 had seizures during the sleep restricted night while Patient 14 had a seizure during the baseline night.

Raw FFT and median filtered data are shown in Figure (10.4.4), illustrating the decline in SWA power across the night in all subjects for both nights, as well as the variation in dynamics.

#### 10.4.6 Relationship of sleep homeostasis to cognitive and clinical factors

The baseline whole-night SWA power density was not correlated with age ( $p=0.4$ ) or IQ ( $r=0.4$ ). There was no correlation between the increase in SWA power density

with sleep restriction and IQ ( $r=0.01$ ,  $p=1$ ). Controlling for the degree of sleep restriction (percentage change in TST) did not change this result ( $r=0.08$ ,  $p=0.8$ ). There was no correlation between age of onset of seizures and increase in SWA power density with sleep restriction ( $p=0.9$ ). In two of the three recordings which included seizures (Patient 14 on the baseline night and Patient 16 on the sleep deprived night), a late increase in SWA power density (in NREM cycles 3 and 4 respectively) was seen (Figure 10.4.3). However on the third recording (Patient 5 on the sleep deprived night) there was a monotonic decline in SWA power.

## 10.5 Discussion

In this study, I used paired baseline and sleep deprived overnight EEG recordings to examine the integrity of sleep homeostasis in children with focal epilepsy. I found that sleep homeostasis was fundamentally intact in these children: more prolonged wakefulness was associated with a greater increase in both the proportion of sleep time spent in slow wave sleep and the SWA power density. There was a clear decline in SWA across successive NREM cycles across the night, though this decline was not monotonic in the majority of patients. I did not find a correlation between SWA dynamics and IQ. The visual sleep scoring results provided further validation of our modified scoring criteria.

### 10.5.1 Changes in SWA between nights

The ability to compensate for sleep loss is present from the neonatal period, though this ability continues to develop throughout childhood (see Section 3.4.4). Newborns are able to respond to NREM sleep deprivation by increasing the time - both absolute and as a proportion of total sleep time - spent in quiet sleep (QS, or NREM) during the recovery period (Anders and Roffwarg 1973). While there are no published studies of sleep deprivation in children aged between 8 days and 30 months, data from the power spectral analysis of overnight EEG in infants aged between 2 weeks and 9 months suggest that SWA dissipation does not increase in response to sleep pressure in this age group (Jenni et al. 2004, a). By 30-36 months of age however, an increase in SWA power density in response to sleep deprivation can be demonstrated (Lassonde et al. 2016), occurring together with an increase in SWS, both absolute and as a proportion of TST (Lassonde et al. 2016). In my cohort, I found an increase in SWS duration with sleep deprivation, and were able to demonstrate a linear correlation with TST restriction, providing evidence that this aspect of sleep homeostasis is intact in children with focal epilepsy. However, the increase in SWA power density with sleep deprivation did not reach statistical sig-

nificance, nor did the correlation of this with TST. This dissociation could reflect a degree of impairment in sleep homeostasis in children with focal epilepsy, with the more primitive mechanism better conserved.

Another possible explanation is that SWA power density may be more sensitive than SWS duration to other clinical factors - such as acute medication changes, recent seizures (Boly et al. 2017), interictal discharges (Bölsterli et al. 2011) or a background of chronic sleep deprivation (Clasadonte et al. 2014) - than SWS duration. That is, the regulation of SWA power density in this group may be wholly intact, but may be responding here to factors other than acute sleep pressure.

### 10.5.2 Changes in SWA across the night

I showed that SWA power density declined across the night, suggesting fundamentally intact synaptic homeostasis. However, the majority of this cohort did not show a monotonic decline in SWA, as would be expected in both adults (Borbély and Achermann 1999) and adolescents (Campbell et al. 2011). Examining individual patients in whom seizures were apparent from the analysed EEG recordings suggests that there may be an association between seizures early in the night, and an increase in SWA power density in the latter part. This has been described in adult patients with nocturnal frontal lobe epilepsy (Parrino et al. 2012). Indeed, the two patients who demonstrated this phenomenon had lesion-negative epilepsy with a frontal lobe focus, whereas the patient who had a seizure overnight but still showed a monotonic decline in SWA power density had temporal lobe epilepsy.

### 10.5.3 Correlation with intellectual function

The purported role of slow oscillations in memory consolidation (see Section 5.2.1) suggests that there may be some cognitive impact of their dysregulation. However, I found no correlation between IQ and my measures of sleep homeostasis. The correlation of sleep homeostasis with intelligence has not been previously examined, however a positive correlation between sleep spindle density and IQ has been described in healthy individuals (Bódizs et al. 2005, Geiger et al. 2011). Boly et al (2017) recently described a negative correlation between spindle density and IQ in 14 adults with focal epilepsy. However, it is likely that the full scale IQ is not a sufficiently sensitive measure to detect the cognitive effects of impaired sleep homeostasis.

#### 10.5.4 Inter- and intra-individual variation in SWA

I found a large range of absolute SWA power density values in this sample, consistent with the findings of studies in healthy adults (Achermann et al. 1993, Rusterholz et al. 2010) and adolescents (Jenni et al. 2005, Jenni and Carskadon 2004, b). This large interindividual variation would have masked any trends in relation to age (Campbell et al. 2011) and likely IQ. However, within individuals, the absolute values were consistent from night to night, as in healthy adult subjects, in whom the quantitative and topological characteristics of overnight SWA power density have been described as trait-like (Finelli et al. 2001).

#### 10.5.5 Sleep architecture

Though delineating the sleep architecture of my patient cohort was not the primary aim of this study, the size and age range of my sample compares favourably with published studies of sleep architecture in children with epilepsy (Nunes et al. 2003, Maganti et al. 2005, Carotenuto et al. 2014). My findings suggest that this group of children with focal epilepsy with a structural aetiology have normal sleep architecture for age. Our scoring criteria (Chapter 7) allow this to be captured despite the occurrence of nocturnal seizures.

#### 10.5.6 Limitations

The major limitations of this study were its retrospective design and the lack of data from healthy controls. The retrospective nature of this study meant that I could not standardise the sleep restriction procedure. Perhaps more significantly, it was not possible to ascertain if the baseline night was a fair representation of the patient's usual sleep. In particular, acute sleep deprivation just prior to the hospital admission could not be ruled out. I could not control for effects of acute medication withdrawal, as this tended to occur at the same time as sleep restriction, that is, during the period of extended wakefulness. However, the majority (12/16) of the patients were not on medications known to have a large impact on sleep structure (see Section 4.5).

In lieu of control data, I compared my measurements to published data to gauge their validity. Jenni et al (Jenni et al. 2005, Jenni and Carskadon 2004) studied a total of 29 adolescents: 16 in a cross-sectional study comparing Tanner 1 with Tanner 5 adolescents at baseline, and 13 under conditions of sleep deprivation. A longitudinal study (Campbell et al. 2011) examined 67 children aged between 9 and 18, but used a linear model, with the aim of documenting age-related changes in SWA power rather than the dynamics of SWA build-up and decline. Sleep deprivation

was not applied. My measures of SWA power density and total SWA power in 12 of the 16 patients fell within the general range of values cited in these studies.

Control data would also have allowed for the validation of my method of NREM cycle definition. Ideally, the visual sleep scoring data would have been fully integrated into the thresholding procedure, and the established criteria of Feinberg (1979), with modifications by Jenni (2005) applied. I was however limited by a lack of technical expertise - this will be addressed in further work. With the present method, the accidental splitting of the first NREM cycle into two may have accounted for some of the non-monotonic declines in SWA power. However the whole night average SWA power densities would not have been affected by this methodological limitation.

Lastly, I did not model my data to the exponential functions of SWA build-up and decline (Jenni et al. 2005, Rusterholz et al. 2010). However, my chosen measures of sleep homeostasis are established in the sleep literature (Campbell et al. 2011, Lassonde et al. 2016, Malow et al. 1997).

### 10.5.7 Conclusion and further work

I have demonstrated that sleep homeostasis is fundamentally intact in children with focal epilepsies with a structural or presumed structural cause - there is a clear fall in SWA power density across the night, and evidence of upregulation of both time spent in SWS and average SWA power density in response to acute sleep restriction. I have shown that the SWA power density profile in these children shows a high interindividual variation that is conserved between nights, as it is in healthy individuals. The majority of my patients did not show a monotonic decline in SWA power across NREM cycles, and this may be related to the occurrence of seizures early in the night. I did not show a correlation with intellectual function.

Both learning (Ji and Wilson 2007; Whitlock et al. 2006) and epileptiform activity (Staley and Dudek 2006) cause an increase in synaptic strength in animal models. There is evidence from human data that slow wave sleep may facilitate the replay of both physiological (Peigneux et al. 2004) and epileptic (Bower et al. 2015) neuronal firing sequences. Taken together, these data suggest that in a system with intact sleep homeostasis, the physiological and pathological neuronal assemblies would compete for long-term potentiation, perhaps accounting for some of the cognitive impairments seen in patients with epilepsy. However, this hypothesis has not been tested directly.

Utilising the EEG and behavioural data collected for Chapter 11, future work will aim to correlate the magnitude of sleep-related benefit to memory consolidation with the time constants of SWA power build-up and decline. I would also aim to

characterise the topology of SWA power and relate this to the epileptogenic focus.

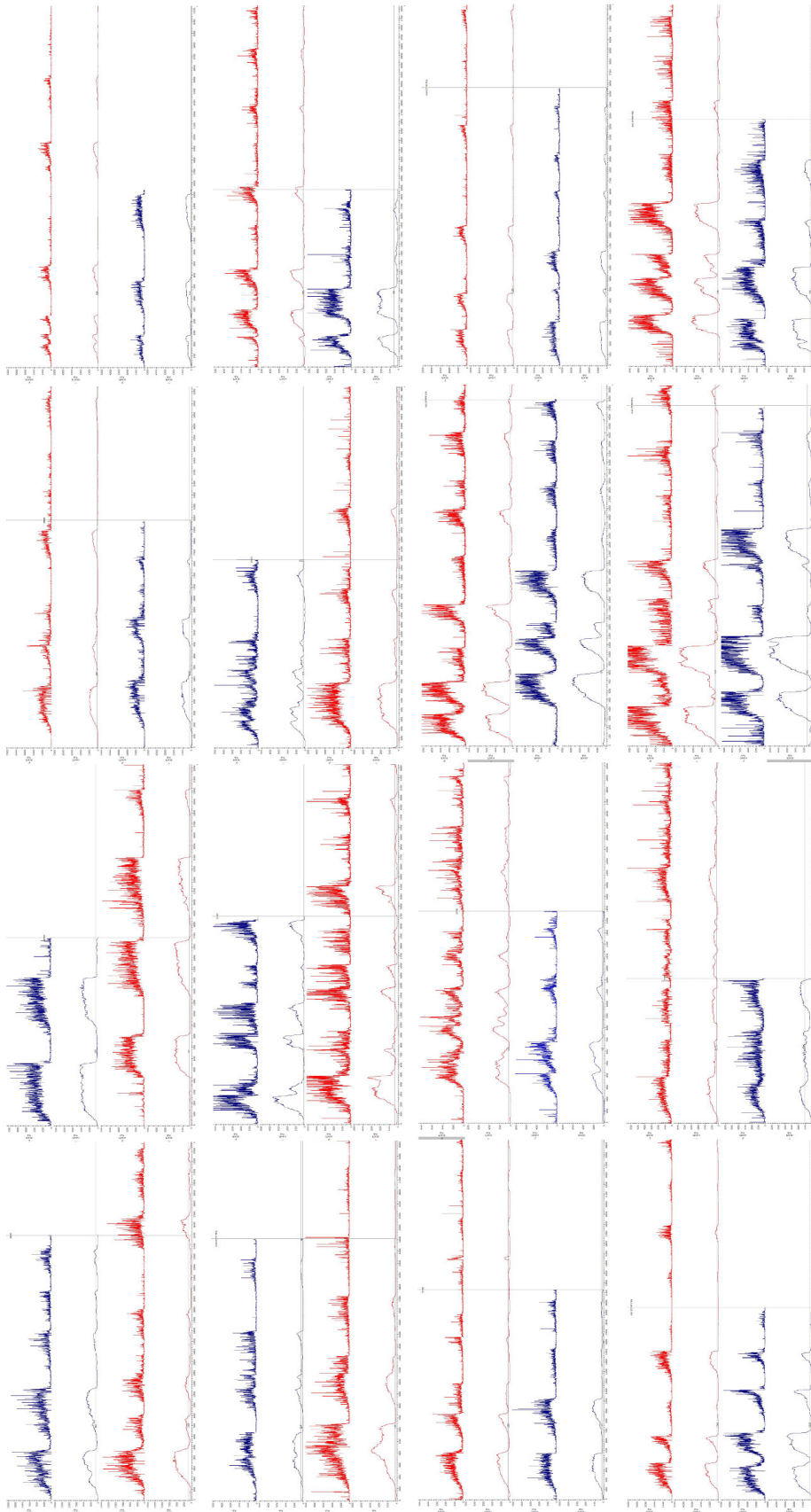


Figure 10.4.4: Juxtaposition of the SWA profiles for the baseline (red) and sleep restricted (blue) nights in each subject. *Top row, left to right: patients 1 to 4; second row: patients 5-8; third row: patients 9-12; fourth row: patients 13 - 16.* Axes are similar those in Figure 10.3.1, however the scales vary between patients.



## Chapter 11

# Sleep-related memory consolidation in children with focal epilepsy

### 11.1 Abstract

**Objective** Sleep benefits memory consolidation in healthy individuals, but it is uncertain if this is also true in patients with epilepsy. I aimed to determine the contribution of sleep to memory consolidation in children with focal epilepsy, comparing it to that in healthy controls, and correlating the magnitude of the sleep-associated benefit (or deficit) with clinical characteristics.

**Methods** I performed a within-subject comparison of memory retention across intervals of wake or overnight sleep. Healthy children ( $n=21$ , 6-16 years, 12 females) and children with focal epilepsy ( $n=22$ , 6-16 years, 9 females) performed verbal and visuospatial memory tasks under each condition. Sleep was assessed with EEG polysomnography during the overnight interval. Interictal discharges were quantified manually.

**Results** Memory retention was greater in the sleep condition in both the verbal [ $F(1,39)=10.8$ ,  $p=0.002$ , Cohen's  $d=0.67$ ] and the visuospatial [ $F(1,36)=4.23$ ,  $p=0.05$ , Cohen's  $d=0.40$ ] tasks, with no significant interaction of group by condition in either task. Across the total sample, gain in memory retention with sleep in the verbal task correlated with duration of slow wave sleep ( $r=0.4$ ,  $p=0.01$ ). In patients, sleep-dependent memory consolidation was negatively correlated with interictal discharge rate in both the verbal ( $Rho=-0.49$ ,  $p=0.04$ ) and visuospatial ( $Rho=-0.45$ ,  $p=0.08$ ) tasks. On post-hoc analysis, a longer history of epilepsy ( $r=0.53$ ,

$p=0.01$ ) and a temporal [ $t[10]=1.8$ ,  $p=0.1$ , Cohen's  $d=0.86$ ] rather than an extra-temporal seizure focus [ $t(10)=0.8$ ,  $p=0.4$ , Cohen's  $d=0.30$ ] were associated with greater contribution of sleep to verbal memory retention.

**Significance** I have demonstrated that memory consolidation in children with focal epilepsy benefits from sleep, showing the same correlation with slow wave sleep as in healthy children, but an inverse relationship with the interictal discharge load during sleep. This mechanism appears to be increasingly recruited with longer duration of illness, indicating a resilient homeostatic function which may be harnessed to aid learning.

## 11.2 Introduction

The mechanisms underlying the development of cognitive impairments in children with epilepsy are poorly understood, though it has been proposed that sleep disruption and epileptic activity during sleep may be significant contributors (see Section 2.6). Sleep benefits memory consolidation in healthy individuals (see Section 5.3), with slow wave sleep contributing particularly to the consolidation of declarative memory. Thus it might be expected that the disruption of this process by epileptiform activity may be one way in which cognitive deficits accrue.

In this chapter, I compared a group of children with focal epilepsies of structural or presumed structural etiology to an age-matched group of healthy children. I examined the gain in items recalled with sleep and the association of this with sleep parameters and clinical characteristics, using a within-subject comparison of memory retention over intervals with and without sleep. Specifically, I hypothesized that the children with epilepsy would show impaired memory consolidation with sleep, and that impairment would correlate i) inversely with the amount of slow wave sleep and ii) positively with the amount of interictal discharges in sleep.

## 11.3 Methods

### 11.3.1 Participants

I collected data on 22 children with focal epilepsy (6-16 years) and 21 healthy children (6-16 years) recruited prospectively to take part in this study. Inclusion criteria are detailed in Section 9.1.

Over a period of 18 months, I approached 40 consecutive inpatients at the EEG video-telemetry unit at Great Ormond Street Hospital (GOSH) or Young Epilepsy. Twelve declined to participate. Of the 28 who consented, three were discharged

home before they could complete the study protocol, one withdrew, and two were unavailable to perform the tasks during the time window for testing. Additionally, one participant was found not to have epilepsy, and was excluded from the analysis. No apnoeas or desaturations were detected in patients apart from those associated with seizures.

23 healthy children consented to take part in the study; one did not complete the study protocol. One child showed evidence of sleep disordered breathing on polysomnography and was excluded from the analysis. Only one control participant was the sibling of a patient.

### **11.3.2 Clinical assessment**

This is described in Section [9.2](#).

### **11.3.3 Intelligence scores and parental questionnaires**

For all but one patient, I obtained full scale IQ scores on the Wechsler Intelligence Scale for Children version 4 (Pearson, USA) from recent neuropsychological reports. The assessments had been performed as part of evaluation for epilepsy surgery. I administered the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (Pearson, USA) to all control subjects during their participation in the study. For each participant, the Children's Sleep Habits Questionnaire (CSHQ) and Strengths and Difficulties Questionnaire (SDQ) were completed by a parent. For those recruited after February 2014, parents also completed the Everyday Memory Questionnaire. For details on these assessments and questionnaires see Section [9.4](#).

### **11.3.4 Experimental design**

We performed a within-subject comparison of memory retention across similar length intervals with or without sleep (Figure [11.3.1](#)). Each participant was tested on two occasions - once under each of the 'sleep' and 'wake' conditions. For each condition, participants performed parallel versions of a verbal and a visuospatial memory task. The order of task versions and order of conditions were randomised separately, using a block design for each. For each participant, the sleep and wake conditions were separated by at least 24 hours.

For the overnight ("sleep") condition, material was learned in the early evening (between 5:00 and 6:00pm), after preparation for polysomnographic recording. Participants went to bed at their habitual time, apart from patients who underwent sleep restriction for diagnostic purposes ( $n=6$ ), who stayed up 2 to 3 hours later than

usual. The next morning, participants were awakened at their usual time. Testing took place an hour later. The interval between learning and testing was approximately 15 hours ( $15.3 \pm 1.2$ ). For the daytime ("wake") condition, learning took place in the morning an hour after awakening, and testing in the evening, at an approximately 8 hour ( $8.4 \pm 1.1$ ) interval. Parents kept a record of the child's activities through the day.

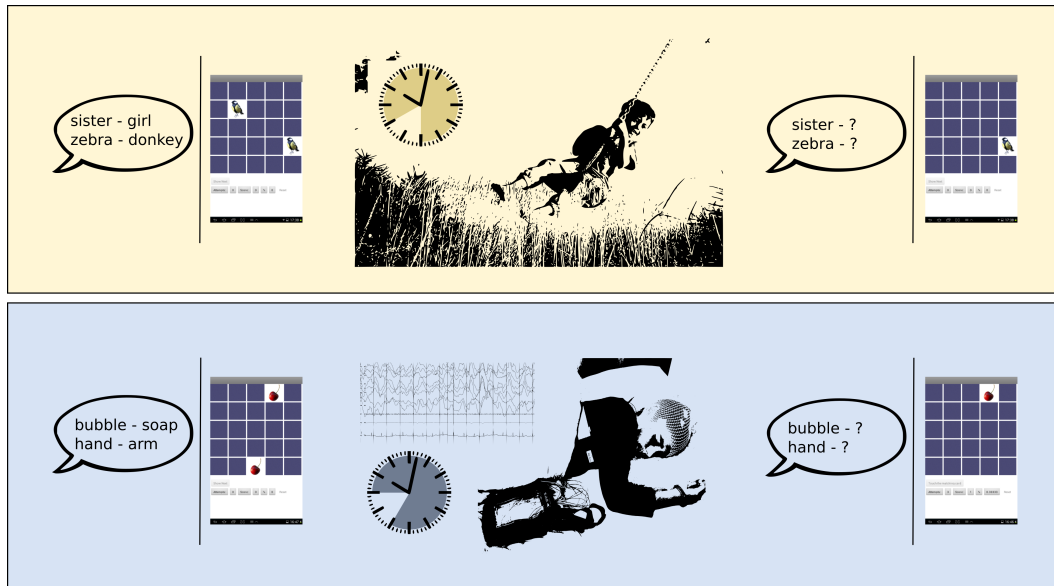


Figure 11.3.1: Study design. Each participant performed a verbal and a visuospatial task under both "wake" (top) and "sleep" (bottom) conditions, with the order of conditions balanced across participants.

### 11.3.5 Memory tasks

The stimulus material, testing procedures and scoring for the memory tasks were as detailed in Section 9.6.

### 11.3.6 EEG and polysomnography, sleep scoring and quantification of interictal discharges

These are detailed in Section 9.5.

### 11.3.7 Statistical analyses

Independent sample t-tests were used to compare descriptive data between patients and controls. Pearson's  $r$  correlation coefficient was used to investigate the relationship between FSIQ, and parent-rated measures of sleep, behaviour and memory.

A repeated measures ANOVA was used to investigate the effect of sleep on memory retention for each task, with Condition (sleep or wake) as the within-subject factor and Group (patient or control) as the between-subjects factor. Paired sample t-tests were used for post-hoc comparisons between the sleep and wake conditions for controls and patients respectively. The same statistical tests were employed for patient subgroup analyses.

Pearson's  $r$  correlation coefficient was used to investigate the association of gain in performance with sleep between the two memory tasks, and the relation between sleep architecture parameters and gain in memory performance with sleep. Independent two-group t-tests (Welch) were used to compare sleep architecture parameters.

The association between memory scores and clinical factors in the patient group was examined with Pearson's  $r$  correlation coefficient. The relationship between memory consolidation and interictal discharge count was investigated with Spearman's Rho, because the distribution of counts remained positively skewed after log transformation. Log transformation was performed using the formula  $y = \log_{10}(x+1)$ , due to the number of patients ( $n=4$ ) with zero discharges.

### 11.3.8 Power calculation

I anticipated an effect size of group and condition on memory score at least equal to the standard deviation, as had been found in studies of sleep-dependent memory consolidation in healthy school-aged children (Wilhelm et al. 2008, Voderholzer et al. 2011). With a two-sided significance of 0.05 and a power of 0.8, this required a minimum sample size of 16 for each group.

## 11.4 Results

### 11.4.1 Participant characteristics

Demographic, neuropsychological and questionnaire data for the patients and controls are summarised in Table 11.4.1. Patients had significantly lower intelligence, and worse parent-rated sleep, behaviour and everyday memory than controls. Twenty (20/22) patients met the recommended cut-off on the CSHQ for a sleep clinic referral, while 12/22 had borderline or high scores on the SDQ, indicating behavioural concerns. CSHQ and SDQ scores were highly correlated in patients ( $p < 0.001$ ) but not controls ( $p = 0.6$ ). CSHQ and EMQ scores were also correlated in patients ( $p = 0.009$ ) but not controls ( $p = 0.3$ ). EMQ and SDQ scores were correlated in both patients and controls ( $p < 0.03$ ), with a stronger correlation in the latter. None of the questionnaire scores was significantly correlated to FSIQ.

	Patients (n=22)	Controls (n=21)	p
Age (years; mean +/-SD)	11.5 (+/-3.0)	10.6(+/-2.8)	0.3
Sex (females, males)	8,14	12,9	0.2
FSIQ (mean +/-SD)	88.4(+/-11.3)	115.3(+/-12.9)	<0.001
Years maternal education	14 (+/- 1.9)	16.7 (+/- 2.6)	0.004
CSHQ (mean +/-SD)	49.6 (+/-9.6)	37.4(+/-3.8)	<0.001
SDQ (mean +/-SD)	18.4 (+/-8.4)	5.3 (+/-4.1)	<0.001
EMQ (mean +/-SD)	129.1 (+/-43.9) [n=14]	54.4 (+/-23.3) [n=16]	<0.001
Right handed	19 (86%)	19 (90%)	1

Table 11.4.1: Participant characteristics. *SD* = standard deviation; *FSIQ* = full scale intelligence quotient; *CSHQ* = Children's Sleep Habits Questionnaire total score; *SDQ* = Strengths and Difficulties Questionnaire Difficulties score; *EMQ* = Everyday Memory Questionnaire total score. *p* values are derived from independent sample *t*-tests.

Clinical characteristics of the patients are summarised in Table 11.4.2. Locations of the predominant focal interictal discharges for each patient are summarised in Table 11.4.3. Twenty patients (20/22) were admitted for pre-surgical evaluation. One of these underwent invasive EEG monitoring. The remaining two patients (2/22) were admitted to guide the management of their seizures. Demographics and epilepsy characteristics of those who declined to take part were similar to those of the participants.

Epilepsy characteristics		
Age of epilepsy onset (mean +/- SD)	5.3 years (+/-4.1)	
Duration of epilepsy (mean +/- SD)	6.1 years (+/-2.8)	
MRI findings	no lesion	7 (32%)
	Focal cortical dysplasia	7 (32%)
	Mesial temporal sclerosis	2 (9%)
	Low grade tumour	2 (9%)
	Other lesion	4 (18%)
Seizure frequency	Daily	5 (22%)
	Weekly	9 (41%)
	Monthly	3 (14%)
	<1 per month	5 (23%)
Seizure localisation	Frontal	3 (13%)
	Temporal	6 (27%)
	Fronto-temporal	5 (23%)
	Central	1 (5%)
	Parietal	1 (5%)
	Undetermined	6 (27%)
Number of anti-epileptic drugs	0	2 (9%)
	1	10 (45%)
	2	7 (32%)
	3	3 (14%)
Type of anti-epileptic drug	Levetiracetam	8 (36%)
	Sodium valproate	7 (32%)
	Carbamazepine	6 (27%)
	Lamotrigine	4 (18%)
	Clobazam	3 (14%)
	Oxcarbazepine	2 (9%)
	Topiramate	2 (9%)
	Lacosamide	1 (5%)

Table 11.4.2: Clinical characteristics of the patient sample. *Seizures were lateralised and localised by semiology, imaging and video EEG. Figures for anti-epileptic drugs used do not add up to 100% due to polypharmacy.*

#### 11.4.2 Diagnostic interventions and clinical events

Of those on medication, 16(72%) had this reduced or stopped. Twelve (54%) patients underwent sleep restriction at some point during the study period, half of these during the overnight study condition. Five patients (23%) had seizures during the overnight memory retention interval, and 2 (9%) during the daytime interval. Nine patients (41%) had no seizures during the study period. Four patients (18%) did not contribute data to the sleep architecture or interictal discharge rate analyses; three of these had their EEG electrodes removed (2 for MRI, one for early

discharge) before testing could be completed, while one underwent invasive EEG monitoring and did not have adequate surface electrode data for analysis. One control (5%) did not contribute data to the sleep architecture analysis due to technical problems with the EEG data acquisition.

### 11.4.3 Testing schedule

Due to dropouts subsequent to randomisation, of those who completed the study, nine patients were tested under the Wake condition first, while 13 were tested under the Sleep condition first. The day of testing under each condition for each patient relative to admission is detailed in Table 11.4.3. One patient (Patient 10) was discharged home early and returned to the hospital on a separate occasion 3 weeks later for testing under the Wake condition. The patient who underwent invasive EEG monitoring (Patient 16) was tested 4 days (Sleep condition) and 6 days (Wake condition) after implantation respectively. Neither of these patients underwent medication reduction or sleep deprivation. For the remaining 20 patients, the average time from admission to be tested under each condition was night 2(+/-1) for the Sleep condition and day 3(+/-1) for the Wake condition.

### 11.4.4 Sleep architecture

Sleep architecture during the sleep condition memory retention interval is summarised in Table 11.4.4. Patients slept less than controls ( $t[30]=3.4$ ,  $p=0.002$ ), but spent similar amounts of time in light sleep (N1 and N2;  $p>0.6$ ), with the deficit occurring instead in N3 ( $t[37]=2.1$ ,  $p=0.04$ ) and REM ( $t[37]=4.2$ ,  $p<0.001$ ). In the control sample, there was a strong inverse correlation between age and amount of time spent in N3 ( $r=-0.60$ ,  $p=0.007$ ), but this was not observed in the patient sample ( $r=-0.18$ ,  $p=0.43$ ). Therefore the analysis of sleep macroarchitecture suggests patients experienced more disrupted sleep during the sleep condition memory retention interval than controls.



Patient no.	IED location	Sleep	Wake
1*	F7, F3	4	3
2	O1	3	2
3	F4	2	4
4	P8	2	4
5	C6, P8	4	3
6*	F4, F3	1	3
7	F4, F8	3	2
8	F7, F9, T7	1	3
9	F4, F8	1	2
10	C5, C6	2	23
11	F9, F7, T9	3	2
12	P8, P4	1	3
13	F4, C4	2	4
14	T7, T9	1	3
15	F8, F10	2	4
16*	RAD1, LHD1	5	7
17	F4	1	3
18	T7, F9	3	2
19	F4	1	3
20	Fz, F3	4	2
21*	C3	4	2
22	F3, C3	4	2

Table 11.4.3: Locations of the predominant focal interictal discharges for each patient, and time of testing (number of days after admission) for the Sleep and Wake conditions. *Patients who did not contribute data to the interictal discharge rate analysis are marked with an asterisk ‘\*’. RAD = right amygdala depth electrode, LHD = left hippocampal depth electrode.*

	Patients (n=18)	Controls (n=20)	p
TST	477 (+/-104)	566 (+/-51)	0.002
WASO	24 (+/- 19)	28 (+/-34)	0.7
N1	34 (+/- 17)	36 (+/-19)	0.6
N2	192 (+/-80)	178 (+/-47)	0.6
N3	162 (+/-56)	205 (+/-60)	0.04
REM	88(+/-45)	147 (+/-34)	<0.001

Table 11.4.4: Sleep architecture during overnight memory retention interval. *All quantities are in minutes and presented as mean (+/- standard deviation). TST = total sleep time; WASO = wake after sleep onset; N1, N2, N3 = deepening stages of NREM sleep; N3 is equivalent to slow wave sleep. REM= rapid eye movement sleep. WASO includes nocturnal seizures (n=5 Patients). Independent sample t-tests (Welch) were used to compare parameters between patients and controls.*

### 11.4.5 Learning performance and raw test scores

Patients achieved similar criterion scores to controls ( $p > 0.2$ ) where they had undergone a greater number of learning trials ( $p < 0.001$ ), but lower criterion scores than controls ( $p$  ranging from 0.007 to 0.06) if the number of trials had been similar ( $p > 0.2$ ). The raw test scores were significantly lower in patients than in controls ( $p \leq 0.04$ ) for both conditions in the verbal task, and for the wake condition in the visuospatial task, but was similar to that in controls for the sleep condition in the visuospatial task ( $p = 0.3$ ) (Table 11.4.5). These findings indicate that patients found the tasks more difficult than controls, and emphasise the need for a within-subject design in order to detect the contribution of sleep to memory consolidation.

			Control (n=21)	Patient (n=22)	p
Verbal task	Sleep condition	Criterion score	75 (+/- 11)	72 (+/- 9)	0.2
		Raw test score	83 (+/-10)	74 (+/-16)	0.04
		Trials	1(1-2)	2(1-3)	<0.001
	Wake condition	Criterion score	79(+/-10)	66(+/-18)	0.007
		Raw test score	78(+/-12)	62(+/-21)	0.003
		Trials	2(1-2)	2(1-3)	0.2
Visuospatial task	Sleep condition	Criterion score	55(+/-14)	46(+/-17)	0.06
		Raw test score	46(+/-20)	40(+/-18)	0.3
		Trials	3(1-5)	3(1-5)	0.2
	Wake condition	Criterion score	57(+/-14)	46(+/-19)	0.03
		Raw test score	45(+/-14)	30(+/-19)	0.007
		Trials	3(1-5)	3(1-5)	0.8

Table 11.4.5: Learning performance in controls and patients. Scores are expressed as mean % items correctly recalled (+/- standard deviation). Trials are expressed as median (range). P values are from independent sample t-tests (Welch) comparing the two groups.

### 11.4.6 Memory task performance

#### Verbal task

Memory retention was greater in the sleep condition [ $F(1,39)=10.8$ ,  $p=0.002$ ; Cohen's  $d=0.67$ ], with no significant interaction of condition by group [ $F=0.03$ ,  $p=0.9$ ], and no significant main effect of group [ $F=2.1$ ,  $p=0.1$ ] (Figure 11.4.1). Co-varying for differences in baseline task performance did not alter the result. In separate pairwise comparisons between the sleep and wake conditions for each group, both controls ( $t[20]=3.0$ ,  $p=0.008$ ; Cohen's  $d=0.76$ ) and patients ( $t[21]=2.0$ ,  $p=0.06$ ; Cohen's  $d=0.61$ ) remembered more word pairs in the sleep condition. The mean gain in recall with sleep was 8.3% in controls and 7.5% in patients; on an independent samples T-test, this did not differ between the groups ( $p > 0.8$ , Cohen's  $d=0.05$ ). The patient with the largest decrease in memory retention with sleep (Figure 11.4.1)

(Patient 8 in Table 11.4.3) had a high overnight interictal discharge count, consistent with later findings in the correlation analysis.

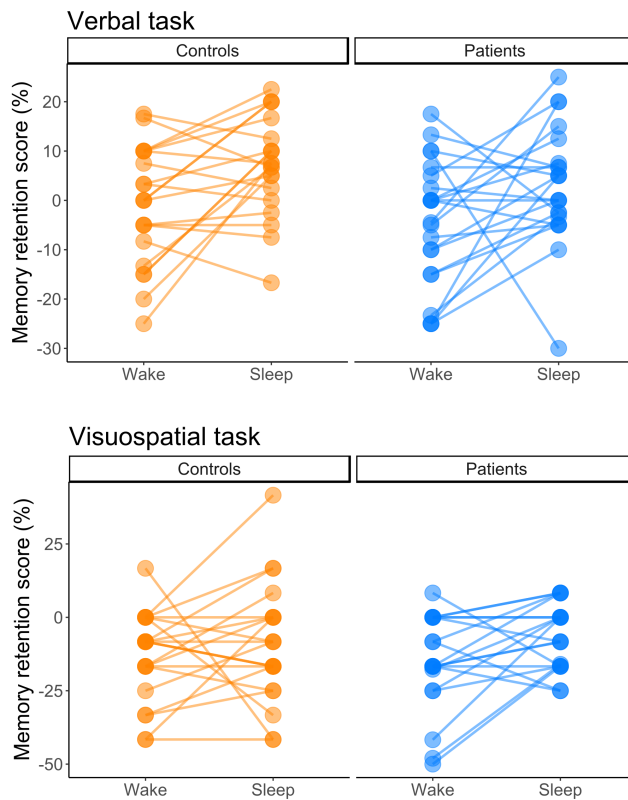


Figure 11.4.1: Memory task performance. *Memory retention scores, calculated as the percentage difference in items recalled at testing compared to criterion. The Wake and Sleep condition scores for individual participants on each task are connected to show the change in recall with sleep. In the verbal task (top), memory retention was greater in the sleep condition [ $F(1,39)=10.8$ ,  $p=0.002$ ; Cohen's  $d=0.67$ ], with no significant interaction of condition by group [ $F=0.03$ ,  $p=0.9$ ], and no significant main effect of group [ $F=2.1$ ,  $p=0.1$ ]. In the visuospatial task (bottom), memory retention was greater in the sleep condition [ $F(1,36)=4.23$ ,  $p=0.05$ , Cohen's  $d=0.40$ ], with no significant interaction of condition by group [ $F=0.6$ ,  $p=0.4$ ].*

### Visuospatial task

Two patients were unable to co-operate on the visuospatial task due to inattention. One patient completed testing on the verbal task over the telephone following hos-

pital discharge, but this was not possible for the visuospatial task. Memory retention was greater in the sleep condition [ $F(1,36)=4.23$ ,  $p=0.05$ , Cohen's  $d=0.40$ ]. There was no significant interaction of condition by group [ $F=0.6$ ,  $p=0.4$ ] (Fig 11.4.1). In separate pairwise comparisons between the sleep and wake conditions for each group, patients remembered significantly more object locations in the sleep condition ( $t[18]=2.3$ ,  $p=0.03$ ; Cohen's  $d=0.65$ ) but controls did not ( $t[20]=0.79$ ,  $p=0.4$ ; Cohen's  $d = 0.22$ ). The mean gain in recall with sleep was 9.2% in patients and 4.0% in controls, and this was not different between the groups ( $p>0.4$ , Cohen's  $d=0.25$ ).

### **General findings and interim conclusion**

The gain in memory retention with sleep was correlated for the two tasks in the patient group ( $R=0.53$ ,  $p=0.02$ ) but not the control group.

Thus we found that patients did not show impaired memory consolidation with sleep compared to controls. The magnitude of benefit from sleep was similar to that in controls for the verbal task and greater than that in controls for the visuospatial task.

#### **11.4.7 Relationship of memory consolidation to slow wave sleep duration**

Across the total sample, the gain in memory retention with sleep in the verbal task correlated with time spent in slow wave sleep ( $r=0.40$ ,  $p=0.01$ )(Figure 11.4.2). This correlation remained after controlling for age ( $r=0.4$ ,  $p=0.03$ ). Analysing the control and patient groups separately yielded the same correlation, but not reaching statistical significance ( $r=0.4$ ,  $p=0.07$  in controls;  $r=0.4$ ,  $p=0.1$  in patients).

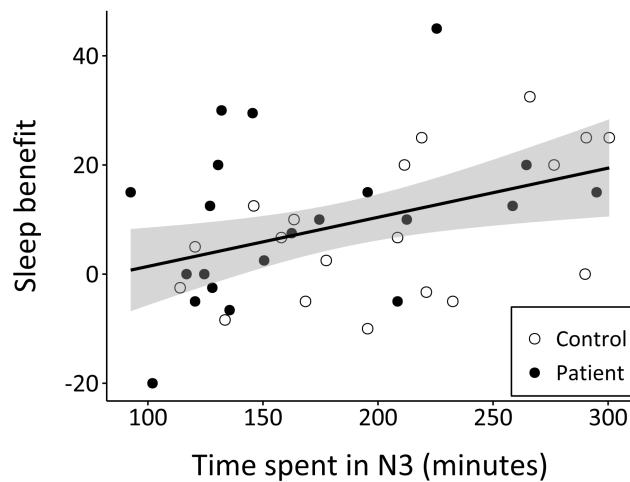


Figure 11.4.2: Sleep benefit and time spent in N3. *Across the total sample, the gain in memory retention with sleep (i.e. sleep condition memory score - wake condition memory score) for the verbal task correlated with time spent in N3 ( $p=0.01$ ). This correlation remained after controlling for age ( $p=0.03$ ).*

### 11.4.8 Effect of epilepsy

#### Interictal epileptiform discharges in sleep

Four patients had no interictal discharges overnight during the sleep condition memory retention interval, six had only focal or unilateral discharges (3 left; 3 right), and eight had bilaterally independent or generalised discharges. Specific locations of IEDs for each patient are detailed in Table 2. Those with bilateral discharges tended to have higher IED loads than those with unilateral discharges only ( $t[9]=1.5$ ,  $p=0.2$ , Cohen's  $d=0.76$ ) (Figure 11.4.3). The log transformed interictal discharge rate in sleep was negatively correlated to sleep-related memory consolidation in the verbal task ( $Rho=-0.49$ ,  $p=0.037$ ) (Figure 11.4.3A), but this correlation did not reach significance in the visuospatial task ( $Rho=-0.45$ ,  $p=0.08$ ) (Figure 11.4.3B).

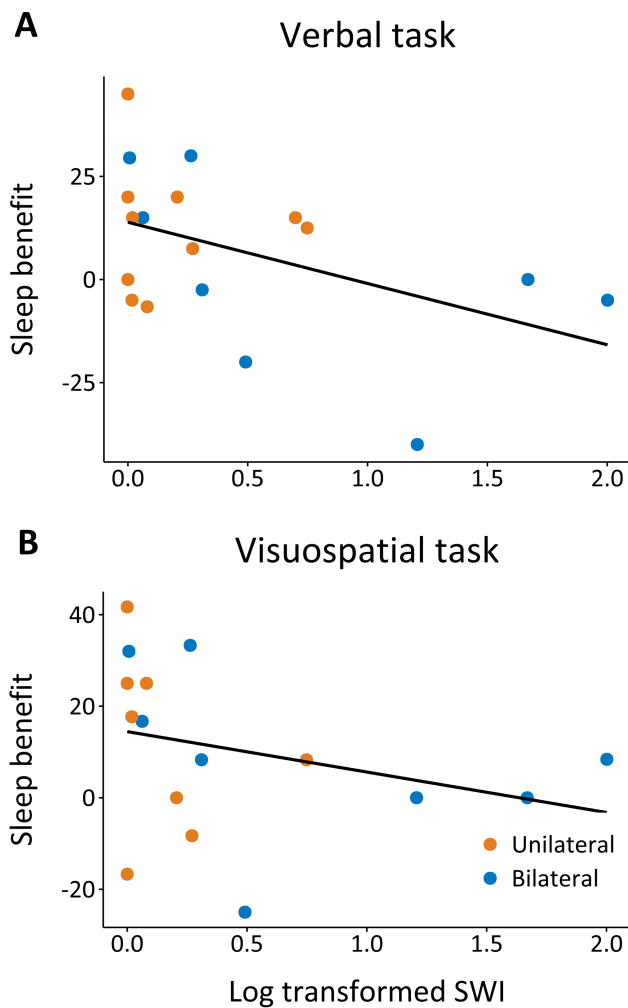


Figure 11.4.3: Effect of interictal discharges on sleep benefit. *In the verbal task (A), a higher rate of interictal discharges was associated with lesser gain in memory retention with sleep ( $p=0.04$ ). In the visuospatial task (B) this correlation did not reach significance ( $p=0.08$ ). Sleep benefit was calculated as the difference between the sleep and wake condition memory retention scores – this was positive if the patient remembered more items in the sleep condition. SWI= spike wake index; transformation used =  $\log_{10}(1+x)$ .*

### Length of illness

In the verbal task, a longer duration of epilepsy was associated with poorer memory retention in the wake condition ( $r=-0.61$ ,  $p=0.003$ ), but not the sleep condition ( $r=0.13$ ,  $p=0.5$ ) (Figure 11.4.4A). Therefore, for the verbal task, the contribution of sleep to memory consolidation increased with duration of epilepsy ( $r=0.53$ ,  $p=0.01$ ). In the visuospatial task, longer duration of epilepsy was associated with poorer memory retention under the wake condition ( $r=-0.58$ ,  $p=0.009$ ), with a trend toward

poorer memory retention in the sleep condition ( $r=-0.43$ ,  $p=0.07$ ) (Figure 11.4.4B). Thus the contribution of sleep to memory consolidation in the visuospatial task also increased with duration of epilepsy, but this did not reach statistical significance ( $r=0.28$ ,  $p=0.2$ , corrected  $p=0.8$ ).

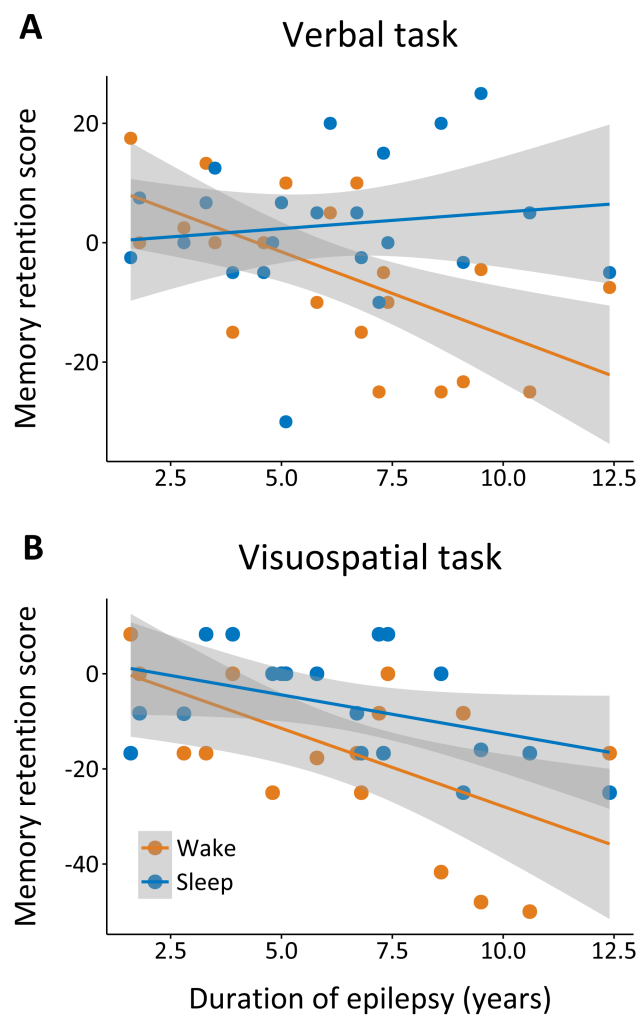


Figure 11.4.4: Effect of duration of epilepsy on memory retention. *In the verbal task (A), a longer duration of illness was associated with poorer memory retention in the wake condition ( $p=0.003$ ), but no change in memory retention in the sleep condition ( $p=0.5$ ). In the visuospatial task (B), a longer duration of illness was associated with poorer memory retention in both conditions (wake condition:  $p=0.009$ , sleep condition:  $p=0.07$ ).*

#### 11.4.9 Subgroup analysis by seizure focus

According to the seizure semiology, imaging and video EEG telemetry findings, 11 patients had a temporal or fronto-temporal seizure focus while 11 had frontal,

central, parietal, occipital or undetermined foci (see Table 11.4.2). We termed the former group "temporal" and the latter "extra-temporal".

In the verbal task, a repeated measures ANOVA with condition (wake or sleep) as the within-subjects factor and subgroup (control, temporal, extratemporal) as the between-subjects factor showed that memory retention was greater in the sleep condition ( $F[1, 39]= 11.2$ ,  $p=0.002$ , Cohen's  $d=0.67$ ), with no significant interaction of condition by subgroup ( $F=0.9$ ,  $p=0.4$ ) (Figure 11.4.5, top). In pairwise comparisons between the sleep and wake conditions for each subgroup, the temporal group remembered more word pairs in the sleep condition, though this did not reach statistical significance ( $t[10]=1.8$ ,  $p=0.1$ , Cohen's  $d=0.86$ ). The extratemporal group had similar scores in both conditions ( $t[10]=0.8$ ,  $p=0.4$ , Cohen's  $d=0.30$ ).

In the visuospatial task, memory retention was also greater in the sleep condition ( $F[1,36]=3.8$ ,  $p=0.05$ , Cohen's  $d=0.40$ ), with no significant interaction of condition by group ( $F=0.3$ ,  $p=0.7$ ) (Figure 11.4.5, bottom). All of the patients ( $n=3$ ) who did not complete the visuospatial task were from the extratemporal subgroup. In pairwise comparisons between the sleep and wake conditions for each subgroup, neither group showed a significant difference between the wake and sleep condition scores ( $p>0.1$ ).



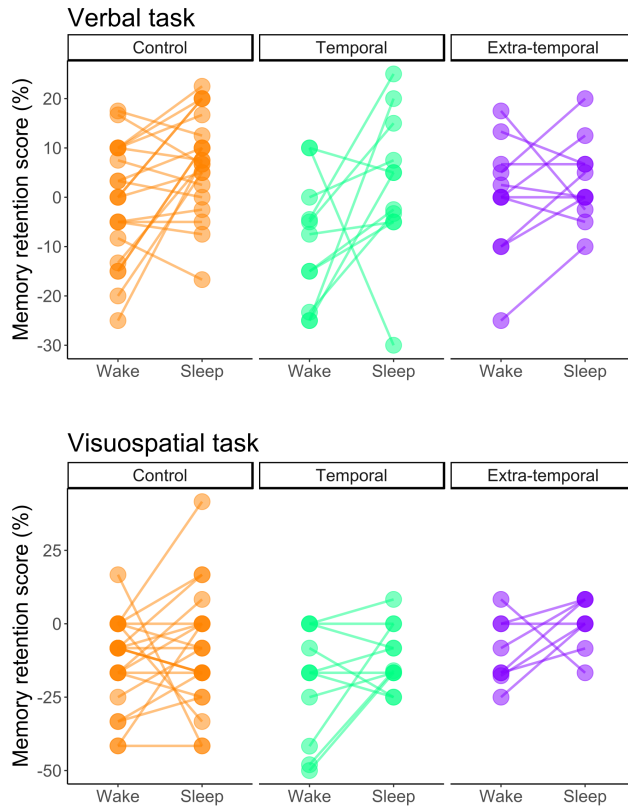


Figure 11.4.5: Memory task performance by temporal/ extra-temporal seizure focus. *Memory retention scores, calculated as the percentage difference in items recalled at testing compared to criterion. The Wake and Sleep condition scores for individual participants on each task are connected to show the change in recall with sleep. In the verbal task (top), Memory retention was greater in the sleep condition ( $p=0.002$ ), with no significant interaction of condition by group. Post-hoc pairwise comparisons of performance in the Sleep and Wake conditions show a large effect of sleep on memory consolidation in the 'temporal' subgroup ( $t[10]=1.8$ ,  $p=0.1$ , Cohen's  $d=0.86$ ) but not the 'extra-temporal' subgroup ( $t[10]=0.8$ ,  $p=0.4$ , Cohen's  $d=0.30$ ). In the visuospatial task (bottom), memory retention was greater in the sleep condition ( $p=0.05$ ), with no significant interaction of condition by group.*

## 11.5 Discussion

Contrary to my primary hypothesis, I found that sleep contributes to memory consolidation in children who have focal epilepsy with a structural or presumed structural

etiology, to the same degree as it does in healthy children. The correlation between the duration of slow wave sleep across the night and the gain in memory with sleep was the same in both groups, suggesting an intact, common underlying mechanism. The data demonstrate this phenomenon to be robust despite a long history of illness, increasingly recruited where delayed verbal memory during waking is more impaired. Taken together, these findings suggest that sleep-related memory consolidation may serve as a compensatory mechanism to maintain cognitive function in this group of patients. Lastly, in agreement with predictions, a higher interictal discharge load during sleep was associated with lesser contribution of sleep to memory consolidation.

### 11.5.1 Sleep-related memory consolidation

My findings appear to contradict those of smaller studies (Urbain et al. 2011, Galer et al. 2015, Sud et al. 2014) examining sleep-related memory consolidation in children with various focal epilepsies (see Section 5.5). However, there are important differences in both the patient samples and study designs that could account for this. Urbain et al.(2011) and Galer et al.(2015) studied patients (total  $n = 19$ ) with primary genetic epilepsies and higher interictal discharge loads (median spike wave indices of 65 and 34, respectively) than those in my study (median spike wave index = 0.7). In addition, the lack of a delayed recall condition without sleep in these studies did not allow for the effect of sleep to be separated from the effect of delay, which is likely significant in a sample with childhood epilepsy (Cormack et al. 2012, Danielsson and Petermann 2009). Sud et al. (2014) performed their study in a similar setting, on patients similar to mine (median spike wave index = 5). Seven of 10 subjects remembered better in the sleep condition; however, the analyzed sample ( $n = 9$ ) was too small to show an effect of sleep. Therefore, despite differences in study design, these results, taken together with my findings, all support the idea that sleep-related memory consolidation occurs in children with epilepsy, but may be vulnerable to high interictal discharge loads in sleep.

It is also possible that sleep-related memory consolidation may be impaired in the primary genetic epilepsies but not in focal epilepsies with a structural etiology, an idea supported by data from adult patients with temporal lobe epilepsy (Deak et al. 2011). Additionally, my results are concordant with those of other studies in children with neurodevelopmental conditions (see Section 5.4)

### 11.5.2 Relationship with slow wave sleep

I found a correlation between duration of slow wave sleep (equivalent to time in N3), and the magnitude of sleep-related benefit to memory consolidation in both

the control and patient samples, which was statistically significant over the total sample even when corrected for age. A correlation between sleep-related memory consolidation and N3 time has been demonstrated in adults (Backhaus et al. 2007) - including those with epilepsy (Deak et al. 2011), though not to our knowledge in children. Maski (2015) and Prehn-Kristensen (2011) examined slow wave activity (expressed as delta power in NREM); the former found no linear correlation with sleep-related memory consolidation in either healthy children or those with autism, while the latter demonstrated a correlation in controls but not patients with ADHD. Both slow wave sleep duration and slow wave activity are markers of sleep homeostasis, but I chose to analyse the former due to its lower intra-individual variability in the face of sleep deprivation (Voderholzer et al. 2011, Bersagliere and Achermann 2010), and lesser developmental decrease over the age range of my subjects (Feinberg et al. 2006).

It may be even more pertinent to quantify sleep homeostasis directly, using a measure independent of both absolute delta power and N3 time, such as that employed by Bölsterli et al (2014). They showed that sleep homeostasis is impaired in children with continuous spike waves in slow-wave sleep (CSWS), the syndrome affecting two of the four children in whom Urbain et al (2011) found impaired memory consolidation over an interval of sleep. In Chapter 10, I demonstrate that sleep homeostasis is fundamentally intact in a retrospective sample with similar clinical characteristics to the sample here.

### 11.5.3 Relationship with nocturnal interictal discharges

I found an inverse correlation between nocturnal IED load and sleep-related memory consolidation. Galer et al. (2015) showed a negative correlation between spike wave index and memory performance, although only in the visuospatial domain. They also showed that the spike wave index correlated highly with the diffuseness of interictal discharges. Similarly, those cases in our sample with the greatest IED loads tended to have bilateral discharges. It is notable that all but two of our patients showed sleep benefit within the range seen in healthy controls, even though just four were free of IEDs. This suggests it may be possible to elucidate a threshold below which interictal discharges in sleep have no significant impact on cognition and hence would not warrant treatment. There is evidence that this threshold may lie between spike wave indices of 1 and 10 (Ebus et al. 2011, Glennon et al. 2016) regardless of underlying etiology, and my findings are consistent with this.

#### **11.5.4 Relationship with duration of epilepsy**

Early age of onset (Berg et al. 2012) and long duration (Nolan et al. 2004) of epilepsy are known to be associated with a high risk of cognitive impairment in general, particularly where there is drug resistance (Berg et al. 2012), as in my sample. Although the wake condition memory retention scores showed a strong correlation with duration of epilepsy, the sleep condition scores did not, suggesting some protective or compensatory effect of sleep on memory retention. This was more marked (reaching statistical significance) in the verbal task, consistent with this task benefiting strongly from sleep in both patients and controls.

#### **11.5.5 Effect of seizure focus**

When assessed with standard psychometric tests, children with temporal lobe epilepsy show greater memory impairment—particularly in the verbal domain—than children with frontal seizure foci (Nolan et al. 2004). In our sample, memory retention in the Wake condition—which is similar to standard tests of delayed verbal recall—was poorer in the “temporal” subgroup, yet the benefit of sleep to memory consolidation was greater, thus supporting the idea of a robust compensatory mechanism.

#### **11.5.6 Limitations**

The main weakness of my study was the lack of patients with moderate to high interictal discharge loads in sleep, limiting my examination of the relationship between sleep-related memory consolidation and interictal epileptiform discharges. However, this is typical for a group of children with focal epilepsies with a structural etiology, and I was still able to demonstrate a linear relationship. The heterogeneity of my patient sample meant that once it was broken into subgroups by underlying pathology, medication or seizure burden, numbers became too small for meaningful analysis. Conversely, this clinical diversity increases the generalizability of my results to children with such focal epilepsies. The hospital setting and clinical interventions may have disrupted patients’ sleep, although one would have expected an adverse effect on sleep-related memory consolidation. There is in fact evidence that neither setting (Galer et al. 2015) nor acute sleep disruption (Voderholzer et al. 2011) significantly influence performance on delayed memory tasks. Patients undergoing long-term video-EEG telemetry for presurgical evaluation tend to accumulate clinical interventions and ictal events over the course of their admission. To minimize the influence of this on memory task performance, I counterbalanced the order of the sleep and wake conditions across participants. The first testing was performed as soon as possible after consent was obtained, and the second testing

as soon as possible with at least a 24-hour interval from the first.

### **11.5.7 Conclusions and further work**

I have demonstrated that sleep-related memory consolidation is intact in children with focal epilepsies with a structural or presumed structural cause. It appears resilient to ongoing seizures, poor sleep habits, and acute sleep disruption perhaps accounting for the relatively preserved cognition in this sample. This finding may be exploited by children with epilepsy and their families, who should be encouraged to recap each day's learning before retiring to bed. The efficacy of such an educational strategy could be quantified on neuropsychological testing and academic outcome measures in a randomised trial.

Our data also suggest that high rates of nocturnal interictal epileptiform discharges may disrupt sleep-related memory consolidation. A prospective study including patients with a full range of nocturnal interictal discharge loads would allow for a "cognitively significant" threshold beyond which sleep no longer benefits memory to be discerned, particularly if the focality of discharges were to be consistent between patients. Patients in the BECTS to Landau-Kleffner spectrum might provide such a sample, though it would be important to use a within-subject design.



## **Part V**

# **Discussion and conclusion**





# Chapter 12

## Conclusion

### 12.1 Addressing the aims of this thesis, and main findings

The main aims of this thesis were firstly, to examine the structure and regulation of sleep in children with epilepsy and secondly, to provide direct evidence of the impact of sleep on cognitive function by correlating neurophysiological characteristics with performance on sleep-dependent neuropsychological tasks administered over the same interval as the sleep recorded. How well this thesis addresses each of these aims, and the main findings are outlined below:

#### 12.1.1 Examining the structure of sleep in children with epilepsy

Based on the current standard visual sleep scoring criteria (Iber 2007), I developed a systematic approach to scoring polysomnographic records containing interictal discharges and seizures.

- Preliminary data showed good inter-rater agreement (Section [7.4.5](#))
- Using my scoring criteria, I found that sleep architecture in children with focal epilepsy with a structural or presumed structural etiology is generally appropriate for age (Section [10.4.3](#))
- The output from visual sleep scoring facilitated the quantitative EEG analysis (Section [10.4.5](#)), and correlational analyses (Sections [11.4.7](#); [10.4.4](#); [10.4.5](#))

#### 12.1.2 Examining the regulation of sleep in children with focal epilepsy

I demonstrated that sleep homeostasis is fundamentally intact in children with focal epilepsies with a structural or presumed structural cause (Chapter [10](#)). As in healthy individuals, the children showed:

- A clear fall in SWA power density across the night
- Upregulation of both time spent in SWS and average SWA power density in response to acute sleep restriction
- High interindividual variation in the SWA power density that is conserved between nights

However, the decline in SWA power across NREM cycles in most patients was not monotonic.

### **12.1.3 Neuropsychological tasks to examine sleep-dependent memory consolidation**

Based on the paired-associates paradigm, I designed and developed memory consolidation tasks suitable for use in English-speaking children.

- The “Lingfield Memory Consolidation Battery” is a new memory consolidation task battery, created using open-source psycholinguistic data, images and software, and running on an Android platform
- It comprises a verbal and a visuospatial task presented in two different modalities (auditory and visual respectively), allowing the examination of two declarative memory domains
- The battery contains parallel versions of both tasks, allowing for a within-subject experimental design.
- Age-group versions allow the testing of children as young as 6 years old; older children with cognitive impairment may also use the simpler versions
- I was able to demonstrate sleep-related memory consolidation in healthy children and children with epilepsy, particularly in the verbal domain (Chapter 11)

### **12.1.4 Sleep-related memory consolidation and its relationship to neurophysiological and clinical features**

Finally, I demonstrated that memory consolidation in children with focal epilepsy benefits from sleep, showing the same correlation with slow wave sleep as in healthy children (Chapter 11)

- High rates of interictal discharges – particularly bilateral discharges – during sleep may disrupt sleep-related memory consolidation

- The contribution of sleep to memory consolidation increased with duration of epilepsy, and was greater in those with temporal lobe epilepsy

## 12.2 Discussion and conclusions

My examination of sleep structure and homeostasis in children with focal epilepsy with a structural or presumed structural etiology reveals that sleep as a biological function is not objectively disrupted in this group, despite refractory seizures and high rates of medication use. The picture on parental survey data (Section 11.4.1) is somewhat different, but this needs to be interpreted in the light of data from healthy children, in whom parent-rated “sleep problems” afflict up to 40%, yet the prevalence of polysomnographic abnormalities is low (Section 3.4.5).

Taken together with evidence that the brain oscillations thought to underlie sleep-related memory consolidation are unaffected in many patients with focal epilepsy (section 5.2.1), the finding that sleep benefits memory consolidation – and therefore may be a contributor to cognitive function rather than dysfunction in this group – is therefore not wholly surprising. But how does this help explain the general cognitive impairment seen in refractory focal epilepsy?

In a rat model of temporal lobe epilepsy, Titiz et al (2014) showed that the reactivation of behaviour-driven patterns in CA1 place cells during SWS was intact, even though task performance was impaired. These rats also showed normal sleep macroarchitecture. While there are no studies of the reactivation of physiological neuronal assemblies in humans, data from adult patients with TLE undergoing intracranial EEG monitoring revealed the reactivation of seizure-related neuronal activity during subsequent SWS (Bower et al. 2015). My data support these in providing evidence that sleep-related consolidation is intact in patients with focal epilepsy. However, in a Hebbian model of learning by long-term potentiation, the greater synchrony of epileptic activation would give these pathological traces an edge over useful memories in the competition for consolidation.

Recent data from adult TLE patients show a global increase in SWA associated with generalised seizures in the 3 to 5 days previously, and focal increases in SWA in areas of seizure foci (Boly et al. 2017). This focal increase parallels that seen after intensive training on a motor task activating a specific cortical area (Huber et al. 2004), suggesting that the synaptic homeostasis afforded by SWS may also be utilised in epilepsy patients to downregulate synaptic strength postictally. This may account for the lack of a monotonic decline in SWA seen in most of my patient cohort (Section 10.4.5). Thus, epileptic activity may increase the burden of synaptic homeostasis, and at some point, there may be decompensation.

### 12.2.1 Future directions

The finding that sleep benefits memory consolidation in children with focal epilepsy could be applied to an educational psychology intervention for this group of children, which could be tested in a randomised controlled trial with academic performance and neuropsychological test scores as outcome measures. Teenagers and those with a natural tendency to eveningness may particularly stand to benefit.

My findings suggest that those with focal epilepsy and parent-rated sleep disturbance would likely benefit from simple sleep hygiene interventions, or screening and treatment for primary sleep disorders, because the underlying sleep structure and regulation is likely to be intact in spite of refractory epilepsy and polypharmacy. These interventions could also be tested in randomised controlled trials, with subjective sleep quality and seizure control as the primary outcome measures.

Caution should probably be advised on the boosting of slow oscillations either by pharmacological or physical means, because this would likely increase the consolidation of epileptic neuronal assemblies more than physiological ones. However, the “tagging” of salient memories would appear a tantalising option; this has been attempted in healthy individuals by targetting memory reactivation with olfactory or auditory cues (Rasch et al. 2007; Oudiette and Paller 2013).

To further investigate the contribution of interictal discharges to cognitive impairment, the experimental paradigm employed in Chapter 11 could be applied to a sample with a full range of interictal discharge loads – though perhaps including only those with bilateral discharges – in order to determine a “cognitively significant” threshold, beyond which it may perhaps be justifiable to medicate with the primary aim of reducing interictal discharges.

The study of sleep homeostasis in children with epilepsy may reveal more about the processes of ictogenesis and epileptogenesis, and the further ongoing work described in Section 10.5.7 will help to facilitate this.

Lastly, the validation of my sleep scoring system on recordings from patients with other epilepsies both paediatric and adult will provide a tool for examining sleep macroarchitecture in patients with epilepsy, helping to advance the field. The validation of the memory task battery will facilitate the examination of sleep-related memory consolidation in English-speaking cohorts.

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