Sleep Dependent Learning

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Abstract

Research evidence has indicated an important role for sleep in processes of learning and memory. Evidence has shown that a night of sleep in adults can lead to procedural task performance improvements that are not matched during similar periods awake. This thesis further examines the relationship between sleep and processes of learning and memory, and investigates sleep and cognitive function in various clinical disorders.

The first study established that in a group of 20 healthy adults, performance gains on a procedural task were significantly greater after a period containing sleep than after a similar period awake. In addition, greater recognition (but not recall) of declarative material was observed after a period of sleep than after a period of wake. A similar pattern of results was observed in a group of 20 healthy children, indicating mechanisms of sleep dependent learning exist in childhood.

Sleep dependent learning was then assessed in a case series of 4 children undergoing investigation for sleep disordered breathing, the anecdotal evidence suggested that sleep disordered breathing is associated with deficits in sleep dependent learning.

After having established the importance of sleep for learning, a large scale questionnaire study assessed sleep in 2968 healthy adults, the findings established that self-reported sleep problems were predictive of poor memory, disrupted cognitive functioning, and negative affect. In addition, sleep disturbances were shown to impair quality of life, memory, and mood in 99 adults with epilepsy.

A final study assessed sleep disturbances in 87 children with epilepsy compared with 117 healthy controls, and found children with epilepsy were significantly more likely to report sleep disturbances than controls. Following this, 20 children with epilepsy were also randomly selected to undergo seven nights of actigraphy. Correlations between parent report measures and actigraphy were reasonable, and descriptive analysis indicated actigraphy may have utility recording nocturnal seizures.

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Abbreviations

AED	Anti-Epileptic Drug
CA	Central Apnoea
EEG	Electroencephalography
EOG	Electro-oculography
EMG	Electromyography
fMRI	Functional Magnetic Resonance Imaging
NREM	Non-Rapid Eye Movement Sleep
OSA	Obstructive Sleep Apnoea
PSG	Polysomnography
QoL	Quality of Life
SD	Standard Deviation
SDB	Sleep Disordered Breathing
SWS	Slow Wave Sleep
REM	Rapid Eye Movement Sleep
TST	Total Sleep Time

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Chapter 1

A review of the current literature on sleep, learning and memory, and the clinical conditions obstructive sleep apnoea and epilepsy.

1.0 General introduction

This review of literature provides an introduction to the experimental body of the thesis, and attempts to provide some background to areas that are discussed in subsequent experimental chapters. A central theme of this thesis is the investigation of the relationship between sleep and processes of learning and memory. As such, an overview of normal human sleep is presented in order to provide a theoretical context to the empirical work. An understanding of the various physiological characteristics of sleep, and the presiding theories on functions of sleep, is important in generating background to the empirical studies. Likewise, a description of the characteristic features of sleep in children provides context for studies assessing sleep and learning in this group. Methods for recording information on sleep are also briefly described in order to provide an understanding of the ways in which sleep quality can be assessed. A detailed review of processes of learning and memory, and of the evidence associating sleep with these processes, provides the relevant background to chapters investigating the complex relationship between sleep and learning. Finally, a general overview of the clinical conditions obstructive sleep apnoea and epilepsy is presented. This is followed by a discussion of the relationships between these conditions and sleep, and also between these conditions and aspects of learning and cognitive function. These conditions are not discussed in painstaking detail, but rather the overview is intended to provide vital context to empirical studies specifically assessing sleep and its effects on learning in these clinical groups.

1.1 An overview of normal human sleep: Its architecture, timing and theories on function.

1.1.1 Normal Human Sleep

Normal human sleep is characterised by the cyclical alternation of REM (rapid-eye movement) and NREM (non rapid-eye movement) stages of sleep. Conventionally, standardized criteria (Rechtschaffen & Kales, 1968) are used to identify the different sleep stages by their characteristic physiological features, especially EEG (electroencephalogram – measurement of electrical activity of the brain by recording from electrodes placed on the scalp), EOG (electro-oculogram - measurement of the resting potential of the eye, in this case to record eye movements) and EMG (electro-myogram – measurement of the electrical potential generated by muscle cells). NREM sleep can be subdivided into 4 stages, REM sleep may be further subdivided into two stages: phasic and tonic (Stores, 2001[a]).

NREM Sleep

NREM sleep accounts for 75-80% of total sleep time and is characterised by a decrease in muscle tone, body temperature, ventilation, heart rate and blood pressure. It can be subdivided into four stages of increasing depth. Stage 1 NREM (fig. 1.1) occurs at sleep onset or following arousal from another stage of sleep and represents 3-8% of the main sleep period. It is characterised by a reduction of alpha activity (characteristic of wakefulness), and an emerging low voltage, mixed frequency EEG pattern. The EEG shows high amplitude activity, generally in the theta range (4-8Hz), with the presence of vertex sharp waves (50-2000ms) towards the end of stage 1. Slow rolling eye movements are seen on the EOG and EMG activity decreases (Rama et al., 2006).

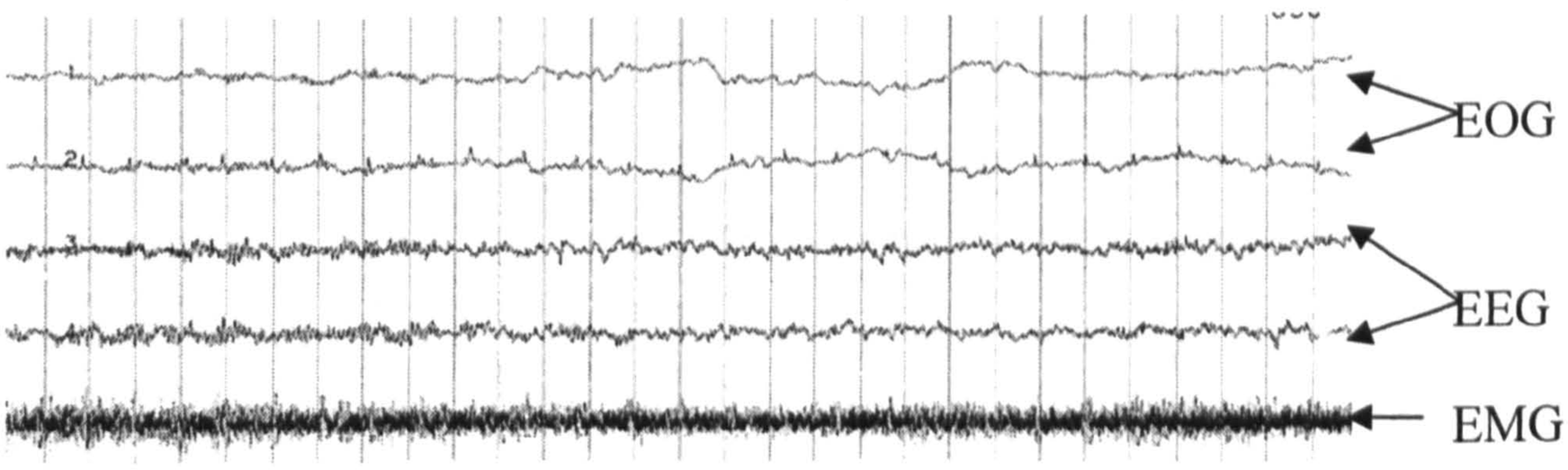


Fig. 1.1: Stage 1 NREM sleep, note the characteristic slow rolling eye movements on the EOG.

Stage 2 NREM accounts for 45-55% of total sleep time and usually begins after approximately 10-12 minutes of stage 1. The characteristic EEG features of stage 2 NREM include sleep spindles and K-complexes (fig. 1.2), distinguishing features such as these allow for relatively easy identification of stage 2. Sleep spindles have a 12-14 Hz waveform lasting at least 0.5 seconds and have a 'spindle' shaped appearance. A K-complex is a waveform with two components, a negative wave followed by a positive wave, neither lasting more than 0.5 seconds. Delta waves (0.5-4.0 Hz) may also be seen on the EEG but are only present in small amounts. EMG activity is diminished compared to wakefulness.

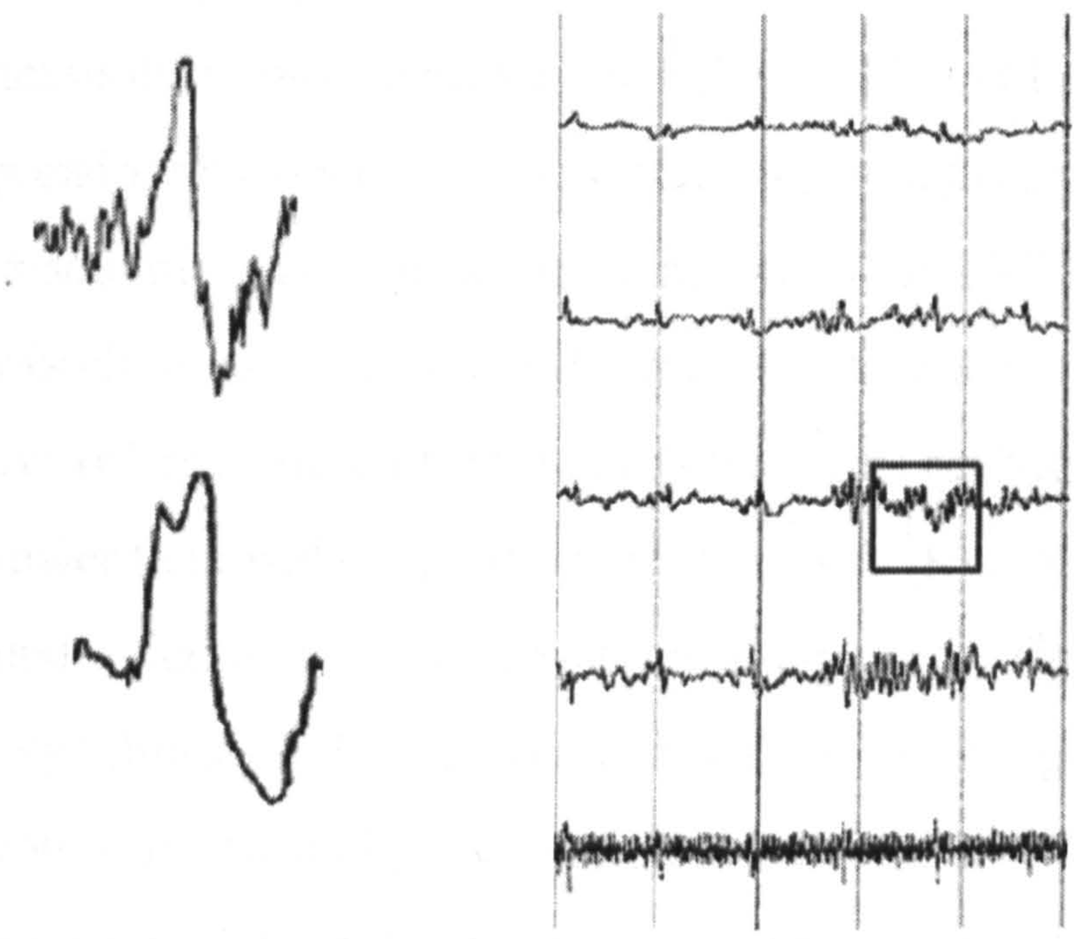
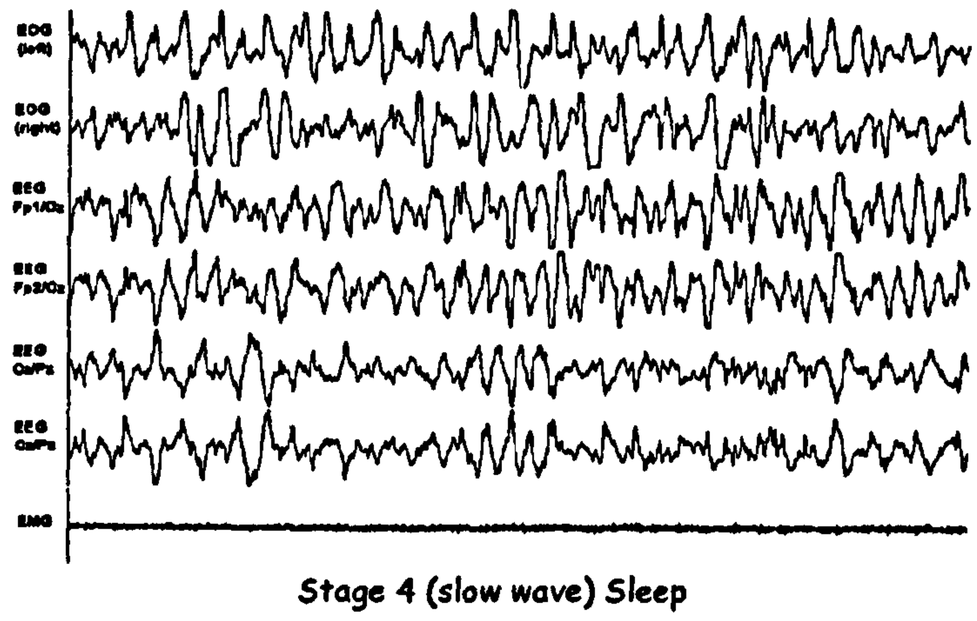


Fig. 1.2: Examples of K-complexes (left) and sleep spindles (right), characteristic EEG features of stage 2 NREM sleep.

Stages 3 and 4 NREM are known as slow wave sleep (SWS), these are the deepest levels of sleep during which awakening is particularly difficult, they are characterized by predominately slow EEG activity. Stage 3 accounts for 4-6% of total sleep time and is characterized by moderate amounts of high-amplitude, slow-wave EEG activity. The majority of SWS sleep is compromised of stage 4 which accounts for 12-15% of total sleep time. Stage 4 EEG is characterized by large amounts of high-amplitude, slow-wave activity (fig. 1.3). EOG does not register eye movements in stages 2-4 of NREM and muscle tone is decreased compared to wakefulness or stage 1 NREM sleep (Rama et al., 2006).



Stage 4 (slow wave) Sleep

Fig. 1.3: Slow wave sleep (stage 4 NREM).

REM Sleep

REM sleep is physiologically very different from NREM sleep due to greater brain metabolism and characteristic EEG, EMG and EOG activity. It is often known as 'paradoxical sleep' as in this state, individuals are both physiologically activated and muscularly inactivated. REM accounts for 20-25% of total sleep time and the first episode usually occurs 60-90 minutes after the onset of NREM sleep. EEG shows a low voltage, mixed frequency (saw tooth) activity with slow alpha (defined as 1-2 Hz slower than wake alpha) and theta waves (Rama et al., 2006). REM can be further subdivided into two stages, tonic and phasic. The tonic stage is characterised by a desynchronised EEG, atonia of skeletal muscle groups, and suppression of monosynaptic and polysynaptic reflexes. Phasic REM is characterised by rapid eye movements in all directions, transient swings in blood pressure, heart rate changes, irregular respiration, tongue movements and myoclonic twitching of chin and limb muscles (Orem, 1980; Oksenberg et al., 2001; Chokroverty, 1980).

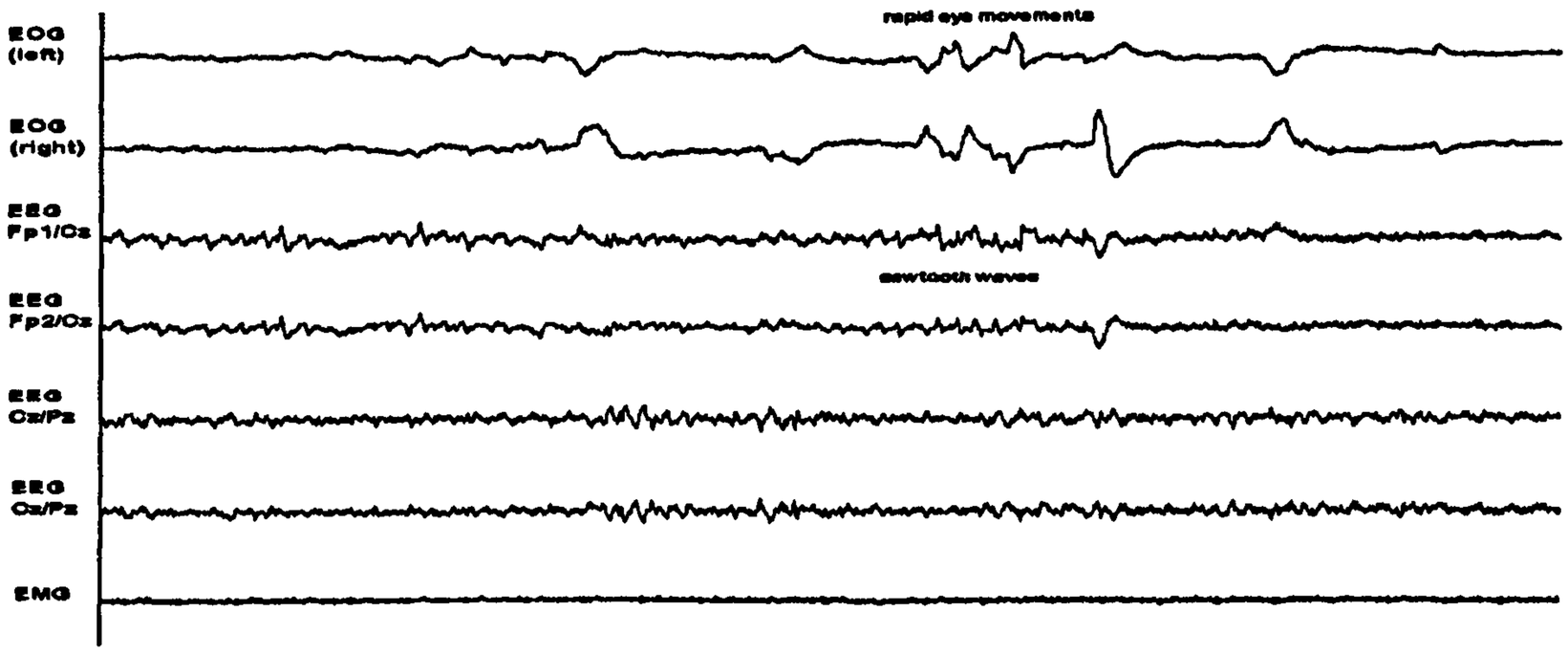


Fig. 1.4: REM sleep with characteristic saw tooth activity on the EEG and rapid eye movements on the EOG.

1.1.2 Sleep Architecture

NREM and REM sleep alternate in a cyclical manner throughout the night, starting with a period of NREM lasting about 80 minutes followed by a period of REM lasting about 10 minutes. This 'sleep cycle' is then repeated 3-6 times throughout the night, with the amount of NREM (SWS) sleep decreasing in each successive cycle and with each period of REM typically ending in a brief awakening or transition to light REM sleep. Typically, slow-wave sleep is prominent in the first third of the night and REM sleep is prominent in the last third of the night (Rama et al., 2006). In addition to the conventional sleep staging described above, there is increasing interest in the microstructure of sleep, particularly brief but frequent arousals, which are observed as changes in the EEG but are not accompanied by any clinical manifestation. Arousals such as these can occur without significant changes to sleep time or other conventional sleep parameters but may be associated with reduced daytime alertness (Roehrs et al., 1994). It is believed that these brief arousals are a normal physiological aspect of sleep, but the borderline between normal and abnormal rates of arousals is not well defined. However, high rates of arousals are noted in certain sleep disorders such as obstructive sleep apnoea and periodic leg movements. The term sleep fragmentation refers to the frequent occurrence of brief arousals such as these and/or other frequent interruptions to sleep including those involving awakenings (Stores, 1991)

1.1.3 Sleep Timing

Timing of sleep is controlled by a circadian clock in the suprachiasmatic nucleus of the hypothalamus, light perception is the main cue for appropriate sleep timing although social cues (such as mealtimes and social activities) and internal cues (such as hunger or hormonal changes) are also important (Stores, 1991). The tendency to sleep displays an ultradian pattern in which sleepiness is greater in the early hours of the morning and again in the early afternoon (sometimes known as the 'post-lunch' dip). Fluctuations in performance may reflect this pattern. Level of alertness is generally at its highest in the early evening, during which sleep is particularly difficult to attain. Sleep duration decreases steadily from birth (16–18 hours) throughout childhood to reach an average of 7-8 hours a night in young adults. SWS and REM sleep patterns also change throughout life. SWS declines after adolescence and continues to decline as a function of age. REM sleep decreases

from more than 50% of total sleep time at birth to 20-25% during adolescence and middle age (Stores, 2001[a]).

1.1.4 Theories on Functions of Sleep

The functions of sleep are thought to be multiple, although the precise role of sleep remains unclear is it known that persistent disturbance of sleep can lead to psychological and sometimes physical impairment. Humans will also try relentlessly to make up for lost sleep, and will crave sleep when it is restricted, much in the way that food is craved when hungry. Although humans can overcome sleepiness for short periods, they cannot perform at high levels for sustained periods without sleep (Siegal, 2005). Animal experiments have shown that total sleep deprivation in rats results in death after 2-3 weeks following loss of temperature regulation and multiple system failure. REM deprived rats survive for longer periods but will also ultimately end up dying (Stores, 2001[a]). The fact that sleep is so fundamental to physical survival, and that lost sleep requires making up, suggests that it serves vital functions. Theories of sleep function can be broadly subdivided into those that propose sleep is needed for the body (somatic), and those that propose sleep is needed for the brain (neural).

Somatic theories: The fatal effects of prolonged sleep deprivation, and the knowledge that sleep appears to have beneficial effects on general health support a general 'life-sustaining' function for sleep. Sleep amounts may influence mortality and morbidity and there are important interactions between sleep and the endocrine and immune systems. (Frank, 2006). Sleep may also be required to conserve energy and suppress behaviour across portions of the 24 hour day. This energy conservation may be particularly important in newborns, in whom the high ratio of surface area to body mass makes the energy conservation theory highly adaptive (Siegal, 2005). However, a purely somatic function for sleep does not adequately explain the extensive neural changes that occur during sleep. In addition, there is no evidence to show that the facilitation of anabolic processes, or endocrine or immune functions, would require the loss of consciousness or the physiological characteristics of REM and NREM sleep.

Neural theories (detoxification and regeneration): Neural metabolic theories propose that sleep function is related to brain processes, perhaps by removing a toxic by-product of wakefulness or by having some neurorestorative function. However, there is little support for theories of detoxification as even in animals sleep-deprived until death, there does not appear to be any significant brain damage or toxin build up. Detoxification theories also fail to address the respective roles of REM and NREM stages, given that REM is characterised by heightened EEG activity, it is hard to imagine how it could counteract the effects of intense brain metabolism. There is stronger evidence in support of neurorestorative theories. Cerebral protein synthesis in the brain is increased during slow wave sleep, and there is evidence to suggest sleep may have a general role in allowing or facilitating neurogenesis (Siegal, 2005). However, a neurorestorative theory for sleep has generated some debate and it has been argued that REM sleep does not appear to have a role in the synthesis of molecules needed for neuronal structure or function (Frank, 2006). Despite this, the association between NREM slow wave sleep and protein synthesis has led to proposals that sleep in general may be involved in the upregulation of genes that are important for neuronal membranes and other structural components. What is not clear is the functional consequence of these sleep related changes in structure. Another problem for neurorestorative theories is the abundance of sleep in infancy, if the primary function of sleep were to replace something depleted in wake, you would expect infants to sleep less than adults not more (Frank, 2006).

Neural Theories (learning and brain development): In contrast to the mixed evidence offered in support of metabolic theories, there now appears to be a convergence of findings supporting a role for sleep in learning, neural plasticity and brain development (Walker et al., 2002; Stickgold et al., 2000; Benington & Frank, 2003). However, there are issues that need to be resolved in order to accept a purely cognitive theory for sleep. Firstly, the underlying mechanisms responsible for sleep-dependent consolidation have not been identified. A second issue concerns the fact that there is no obvious communication between learning or plasticity mechanisms and sleep homeostasis. Finally, sleep is different in developing and adult brains and a parsimonious theory needs to propose mechanisms common to both (Frank, 2006). An in depth analysis of the role of sleep in learning and consolidation can be found in section 1.3.

1.1.5 Characteristic features of sleep in children

Sleep changes across the whole life span, with the greatest change taking place during childhood. Sleep in early childhood generally progresses towards differentiation and organization of conventionally defined sleep states, shorter total sleep time, less SWS and longer sleep cycles (Stores, 2001[a]). In the newborn, sleep can be divided into three distinct sleep states: active sleep (REM), quiet sleep (NREM), and indeterminate sleep (a mixture of the other two). During the first 6 months of life total sleep time decreases from around 16-17 hours a day to 13-14 hours a day, consolidation of sleep during nocturnal hours also occurs, with daytime sleep being consolidated into discrete naps. There is also a marked reduction in REM sleep seen during the first 6 months, this represents a redistribution of sleep stages, which may be an important indicator of central nervous system maturation (Sheldon, 2006). After the first year of life, sleep changes become more gradual. Between 3-5 years REM percentage gradually decreases, this is accompanied by a gradual change to a single nocturnal sleep period, with daytime naps gradually being phased out (Stores, 2001[a]). Growth and development continue through middle childhood with sleep patterns beginning to resemble those of older people, total sleep time in middle childhood is still approximately 2.5 hours longer than adults but sleep architecture appears to be stable. Body movements in sleep also decrease in frequency, and daytime napping becomes uncommon (Sheldon, 2006). Most young adults sleep 7-8 hours a night (slightly longer at weekends) but there is considerable variation between individuals (Stores, 2001[a]).

1.1.6 Methods of recording information on sleep: polysomnography

In order to provide detailed information on aspects of sleep, various methodologies have been developed to record data on quality and quantity of sleep. The gold standard for the measurement of sleep quality in the laboratory setting is polysomnography (PSG), this multi-channel recording method is designed to document a variety of physiological activities during sleep. The EEG is the core measurement of PSG, the four stages of NREM sleep are distinguished from one another principally along this dimension. The most common placements for recording the EEG during sleep are C3 (central left), C4 (central right), O1, (occipital left) and O2 (occipital right) (Carskadon & Rechtshcaffen, 1989). The standard manual (Rechtschaffen & Kales, 1968) recommends the reference of one EEG lead

to an indifferent auricularly placed electrode on the contralateral mastoid or ear lobe, hence C3/A1 or C4/A2. Sleep staging does not require the measurement of focal EEG activity or regional comparisons such as might be required for the EEG assessment of other conditions (e.g. epilepsy). All the EEG waveforms required to stage sleep are well visualised at C3 or C4, particularly with the relatively large interelectrode distance afforded by a contralateral reference (Carskadon & Rechtschaffen, 1989). Scoring of sleep stages can be achieved with as little as two recording EEG electrodes, this is not generally recommended as it leaves the system with no back-up, but it can be a useful option in patients who are anxious or uncooperative, or in children.

Recording of EOG has two important purposes in PSG, firstly to record the phasic bursts of rapid eye movement characteristic of REM sleep, and secondly to record the slow rolling eye movements that are associated with sleep onset and transitions to stage 1 occurring throughout the night. In addition, EOG can also be useful in the detection of waking eye movements. Eye movement activity is measured by placing surface EOG electrodes near the outer canthus of each eye (Keenan, 1992). The recordings are based on the small electro-potential difference from the front to the back of the eye. The cornea is positive with respect to the retina so the eyeball exists as a potential field within a volume conductor, as such the placement of electrodes next to the eyes allows the measurement of eye movements.

In a standard PSG recording, the EMG from muscles beneath the chin (mentalis and submentalis) is used as a criterion for staging REM sleep. EMG electrodes are placed under the chin (the chin muscles are used for reasons of convenience and accessibility) and are recorded bipolarly (Carskaddon & Rechtschaffen, 1989). EMG can also be recorded from a number of other sites to give information on other aspects of sleep. These include the masseter muscle to record EMG associated with bruxism, the tibialis muscles to assess the presence of periodic limb movements in sleep, the digitorum muscle to assess REM sleep behaviour disorders, and the intercostal muscles to measure respiratory effort (Keenan, 1992).

ECG recordings in PSG provide an important assessment of cardiac rhythms during sleep. Although a single ECG channel cannot be expected to yield a complete

diagnostic evaluation, any significant rhythm irregularities can be detected and correlated to other sleep variables (Murcia & Butkov, 1993). Two electrodes are usually placed below the right clavicle and in the region of the lower left thorax.

There are a variety of approaches to monitoring respiration during sleep, and many devices lend a qualitative approach to assessment. It is important to record both respiratory effort and airflow to be able to categorise certain breathing abnormalities. Information about oxygen saturation and carbon dioxide levels are also important in order to be able to determine the severity of sleep disordered breathing. Effort of breathing is generally measured by strain gauges in the thoracic and abdominal regions, both need to be recorded in order to provide an accurate trace and to detect paradoxical breathing. Airflow is most conveniently recorded by the use of thermistors and thermocouples, these are heat sensitive devices that respond to changes in temperature associated with inspiration and expiration. Oxygen saturation is most commonly recorded with an oximeter, a device that measures the amount of oxygen in the haemoglobin by means of light transmission. Oximeters are most commonly positioned on the ear or finger. Carbon dioxide is measured in addition to oxygen saturation in order to provide accurate assessments of gas exchange. CO_2 is commonly measured using both transcutaneous electrodes and a nasal canula to measure expired gas. Body position is often recorded as position related apneas are well documented, position monitors are generally attached to the chest of the patient and generate signals reflecting movement. Some patients (such as those complaining of reflux) may also require endoesophageal pH monitoring, an assessment of pH occurs via an oesophageal pH sensitive electrode (Keenan, 1992).

Video and microphone are also useful adjuncts to PSG, and provide information on aspects of sleep such as snoring, sleepwalking, and REM sleep behaviour disorder. Scoring of sleep from a polysomnogram is accomplished by trained sleep physiologists and is based on the Rechtschaffen and Kales manual, a robust tool describing the criteria for stages of normal sleep (Rechtschaffen & Kales, 1969). Although PSG remains the gold standard for recording information on sleep, it is expensive, time consuming, and requires a skilled technician. Other means of recording information on sleep can include aspects of PSG, for example oximetry can be used alone to assess gas exchange problems symptomatic of sleep apnea.

1.1.7 Methods of recording information on sleep: Actigraphy and subjective measures

Actigraphy is another useful and relatively new tool in the assessment of sleep. The term actigraphy refers to methods using miniaturised computerised wristwatch-like devices (called actiwatches) to monitor and collect data generated by movements (Sadeh & Acebo, 2002). A sensor in the actiwatch produces a signal that is proportional to the *g* force to which it is subjected, making the signal proportional to the movement intensity. Detected movements are translated to digital counts accumulated across pre-determined epoch intervals (e.g. one minute), and are stored in an internal memory. The actiwatch can collect data continuously over extended periods (e.g. one week or longer). Data is downloaded onto a computer and the sleep analysis software uses algorithms to allow the automatic scoring of actigraphy records, in order to infer periods of sleep and wakefulness (Sadeh & Acebo, 2002). Determination of sleep and wakefulness by the algorithm uses the activity data recorded by the actiwatch in a series of linked calculations. The algorithm looks at each data point from each epoch and those surrounding it and makes a total score based on these activity counts (Cambridge Neurotechnology Ltd, 2005). Various studies have assessed the validity of actigraphy and the general conclusion is that the epoch by epoch agreement between actigraphy and PSG is excellent for normal adult individuals (greater than 90% agreement), and reasonably good for sleep disordered individuals (75-85% agreement) (Sadeh et al., 1995).

In addition to the objective measures described, sleep diaries and questionnaires can also provide useful subjective information on sleep. Various validated questionnaires exist for the assessment of sleep, and include self-rated, partner-rated, and parent-rated scales. Questionnaires and sleep diaries are often used alongside more objective measures in order to provide an accurate picture of overall sleep function, whilst also giving some insight into how sleep affects the individual.

1.2 An overview of learning and memory processes

1.2.1 What is memory?

The process of acquiring information (such as facts, experiences, actions, skills, etc.), and modifying that knowledge over time can be considered the process of memory

formation, expressed behaviourally as learning. Once developed the size of the mammalian cerebral cortex is largely fixed, placing anatomical and functional limitations on information storage (Walker, 2005). Therefore, in order for memory to retain the ability for continued formation, the cortex must be capable of some modifications of its central representations, ensuring salient information is prioritised and retained. Brain plasticity is a term coined to describe the ability of the brain to make lasting changes in neuronal properties (such as structure or function) in response to certain stimuli. This plasticity may be evident in a number of ways such as changes in structural organizations of cortical networks, disinhibition of circuitry, modifications to synaptic connections, and structural remodelling of synaptic connections (Buonomano & Merzenich, 1998).

1.2.2 Memory classifications

Human memory, and the processes that create and sustain memory cannot be classified as a single entity. The spectrum of memory categories that exist in the human brain is believed to be wide and diverse. Human memory has been subject to many different classification systems, the most accepted is based on the distinction between declarative and non-declarative memory.

Declarative memory can be broadly classified as consciously available fact based memories, and can be subdivided into categories such as episodic memory (memory of one's past events) and semantic memory (memory for general knowledge, not connected to an event) (Walker & Stickgold, 2006). Declarative memories are usually acquired with relatively little exposure to the information, for example one or two readings of a text or a single exposure to an event.

Nondeclarative memory is regarded as non-conscious and can be broadly subdivided into associative and non-associative categories. Nondeclarative memory includes procedural memory (knowing "how", learning skills, actions etc.) and priming or implicit learning (a passive process involving the acquisition of knowledge simply through exposure, and normally without conscious awareness). Other types of nondeclarative memory include classical conditioning, habituation, and sensitisation. The basic organisation of nondeclarative memory is shown in figure 1.5. Nondeclarative learning often requires longer periods of acquisition than declarative

memory, and can involve repetitions of performance or repeated exposure to stimuli (Walker, 2005).

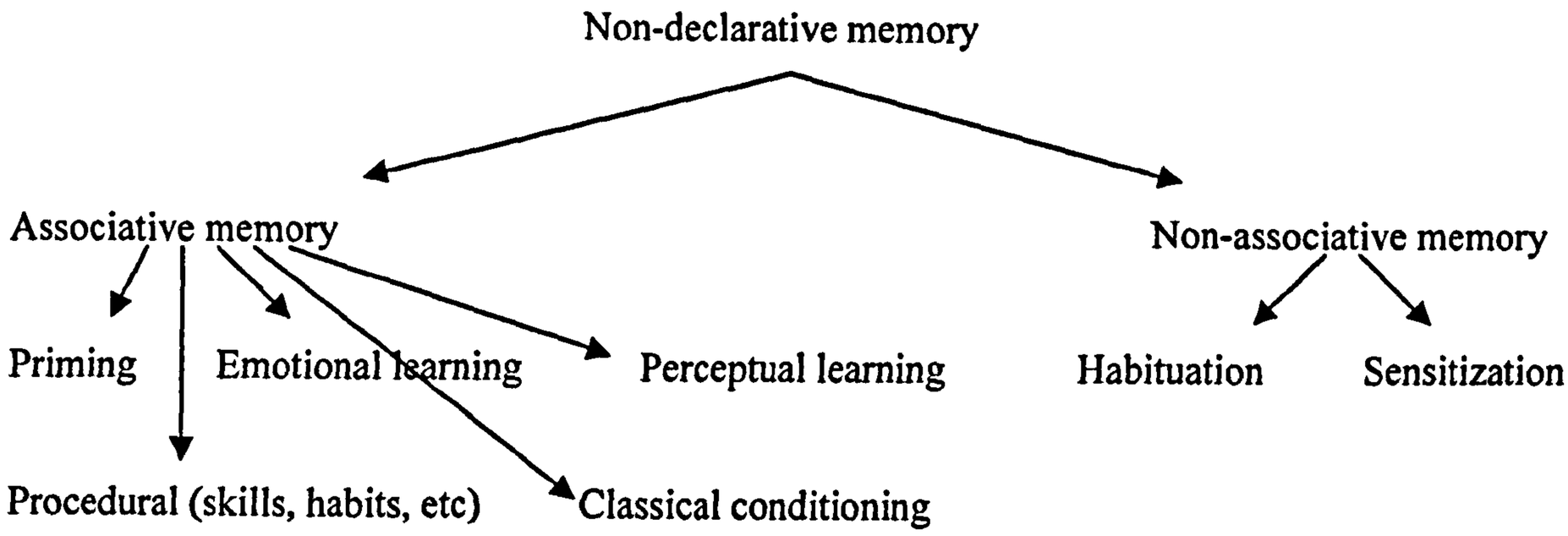


Fig. 1.5: Basic organisation of nondeclarative memory

Memory systems can be distinguished not only in terms of memory type, but also in terms of operating characteristics. Studies have suggested that declarative memory is more flexible than non-declarative memory (Reber et al., 1996), and has access to multiple response systems. Non-declarative memory is more encapsulated and has reduced access to systems not involved in the initial learning (Squire & Zola, 1996). Another distinction between declarative and non-declarative memory is that declarative memory generally offers a greater awareness of what has been learned. Reber & Squire (1994) showed that despite having no awareness of what has been learnt, subjects suffering amnesia could still perform as well as healthy controls on a non-declarative serial reaction time task. This indicates a role for declarative memory in supporting conscious recollections, whilst non-declarative memory does not afford any awareness of memory content.

In addition to a functional classification of memory systems, the categories of memory can also be distinguished by the differing contribution of different brain systems and neural processes. Some of the best evidence for distinguishing between different kinds of memory has come from the study of amnesic patients who have sustained bilateral damage to the medial temporal lobes or midline diencephalic structures (e.g. Scoville & Milner, 1957; Rempel-Clower et al., 1996). These patients are severely impaired on tests of declarative memory such as recall or recognition of places, words, faces, and other material. However, these patients perform as well as normal subjects on many other tests of a non-declarative nature

i.e. skill or habit learning, priming. Evidence of this kind implies that the types of learning and memory that are intact in amnesia, depend on different brain systems than those damaged in amnesia (Squire & Zola, 1996).

Declarative Memory

Research investigating declarative memory in both animals and humans has established a robust link between declarative memory and a system of structures in the medial temporal lobes, including the hipppocampal formation and the adjacent perirhinal and parahippocampal cortices (e.g. Remper-Clower et al., 1996). A wealth of animal research has shown that ischemia or lesions to the hippocampal regions result in significant and long lasting memory impairment (e.g. Zolamorgan & Squire, 1986; Zolamorgan et al., 1989; Bolhuis et al., 1994; Wincour et al., 2005). Case studies of human amnesia have also demonstrated that bilateral damage to the hippocampus results in moderately severe anterograde memory impairment. Early case studies involving neuropsychological and neuropathological analysis were able to show that damage limited to even a small area of the hippocampus (CA1) was sufficient to produce moderate declarative memory impairment (Squire & Zola, 1996). As a general rule, it seems the extent of hippocampal damage is related to the severity of the amnesia. More extensive damage involving more of the hippocampal region and entorhinal or perirhinal cortices, leads to a greater degree of memory impairment. Current opinion is that the medial temporal lobes are required at the time of learning and for a lengthy period afterwards. It is proposed that during this lengthy period, the medial temporal lobes direct consolidation in the neocortex by binding together the multiple cortical regions that together store memory for a whole event. As a result of gradual changes, storage of declarative memory and its retrieval eventually become independent of the medial temporal lobe system (Squire & Zola, 1996). A detailed discussion of declarative consolidation can be found in section 1.2.4.

Non-Declarative Memory

The brain processes and neural circuitry involved in non-declarative memory are generally less well defined. However, a wide range of tasks have been developed to assess the various forms of non-declarative memory, and to provide information on the brain systems involved in non-declarative learning. For example, probabilistic

classification tasks have been developed to promote a type of learning analogous to habit learning. Research has shown that patients with Parkinson's disease perform poorly on these tasks, whilst patients with amnesia perform normally. This evidence suggests that the neostriatum (caudate nucleus and putamen), damaged in Parkinson's patients, are important for the gradual, incremental learning of associations that is characteristic of habit learning (Knowlton et al., 1996). Other forms of non-declarative memory have also been linked to specific brain areas, e.g. the neocortex is known to be involved in priming, the amygdala and cerebellum are important structures for classical conditioning, and reflex pathways have been linked to non-associative learning (Squire & Zola, 1996). Although evidence suggests that declarative and non-declarative systems are largely independent from each other, the demonstration of numerous double dissociations has shown that they interact in a number of ways. In sum, together the systems form a dynamically interacting network which yields both cooperative and competitive learning and processing, such that memory function may be optimised (Ullman, 2004). Although there appear to be striking separations of function among the different brain areas involved in the two memory systems, it does not appear to be the case that all parts of each lobe subserve only one or the other system, for example aspects of the temporal lobe have been shown to play some role in the procedural system (Ullman, 2004). The complex relationship between declarative and non-declarative memories, and the wide ranging anatomical structures involved in their processing, indicates the complexity of the combined memory systems.

1.2.3 Memory processes

Memory formation does not transpire as a single solitary event, but instead evolves in several discrete stages. The classical theory is that memory develops over time, eventually resulting in a more robust and permanent memory representation. The time course of behavioural modification can also be diverse, rapid changes in seconds or minutes can take place during or soon after an experience, while more delayed gains can be experienced hours or days after the event (Walker, 2005; Karni et al., 1998). The most common classification of memory process is the division of memory into temporal processes, usually initial acquisition, followed by a consolidation phase, and a later ability to retrieve memories. In terms of the scope of the present research, the phases of acquisition and consolidation are most significant

and will be discussed in detail, a brief discussion of the retrieval phase will also be given in order to provide some useful context.

Acquisition

Acquisition can be defined as the initial formation or encoding of memory, usually attained by engaging with an object or performing an action, leading to the formation of a representation of the object or action within the brain (Walker & Stickgold, 2006). Acquisition generally involves some degree of learning, in the procedural domain behavioural performance will often improve across an acquisition or training session, and successful acquisition corresponds to a certain level of task proficiency. The mechanisms involved in acquisition, and the neural changes that may be associated, have been investigated in both animal and human models. It is presumed that the rapid learning associated with brief training sessions or exposure to objects, is too fast to be associated with any extensive structural changes. Instead, it is proposed that the disinhibition of existing cortical networks may underlie the process of acquisition. Studies in animals and humans have demonstrated early learning involves the rapid alteration of synaptic connections. Butefisch et al. (2000) showed that practice dependent improvements on a motor task could be mediated by drugs that influence synaptic plasticity in the motor cortex. They suggested that the alteration of synaptic connections, and the disinhibition of cortical networks, might be a mechanism underlying use-dependent plasticity and early acquisition. Similar mechanisms have also been proposed in the visual, auditory, and somatosensory cortices (Walker, 2005). Rapid disinhibition of networks would also allow an explanation of the functional and electrophysiological changes that are seen at acquisition (Muller et al., 2002).

Studies have also investigated the role of brain state in the process of initial acquisition. The majority of evidence indicates that wake is the most preferable time for the initial encoding and performance improvement associated with acquisition. In the procedural domain, wake provides the ability for conscious and attentive motor output (e.g. Karni et al., 1998; Muellbacher et al., 2002; Shadmehr & Brashers-Krug, 1997). In other domains, attentive wake allows for focused perceptive attention to the task in hand (Joseph et al., 1997) and the ability to perform mental repetitions of a task. It may be that this wake preference for

acquisition has an evolutionary basis. A system where rapid gains in performance are seen during a brief period of training would make sense, especially for a beneficial procedure where immediate improvement may be essential for survival (Walker, 2005).

However, there is also evidence to suggest that information provided by external stimuli does reach the brain during sleep, although the amount of information is reduced during sleep compared to wakefulness (Coenen & Drinkenburg, 2002). Cheour et al. (2002) showed that newborn infants had the capacity to discriminate between similar vowel sounds when they were asleep. Electrophysiological data showed that they were able to detect a change in speech sounds throughout all stages of sleep. Portas et al. (2000) used combined EEG and fMRI recordings to assess the response of the adult brain to auditory stimuli across the sleep-wake cycle. They found that auditory stimulation produced bi-lateral activation in several areas (auditory cortex, thalamus, caudate) during both wake and non rapid eye movement sleep (NREM) sleep. Areas that showed decreased activation during sleep compared to wake (left parietal, bilateral prefrontal and cingulate cortices, and thalamus) are believed to be involved in the further processing of sensory information that is required for conscious perception. Coenen & Drinkenburg (2002) proposed two factors played a crucial role in causing changes in the sleeping brain, these were identified as the intensity and the relevance of the stimulus. Intensive stimuli, and stimuli that are arousing or salient, appear to have a lower threshold for brain activation when compared to neutral stimuli. In addition to the actual acquisition of information during sleep, there is also the possibility that continued processing of information acquired during wake, can occur during sleep. Auditory learning during wake can be modified by presentation of similar auditory cues during sleep, and can lead to improvement during subsequent wake (Walker, 2005).

Despite this evidence, the role of the sleep state in acquisition of information is unlikely to be the main function of sleep. There would be few advantages to a vital role for sleep in acquisition, apart from perhaps a reduction in interfering and competing stimuli. In addition, sleep locations are usually chosen for, among other things, the relative scarcity of sensory information. This implies that even though

acquisition of information occurs during sleep, it is not the primary role of sleep (Walker, 2005).

Consolidation

Consolidation is the process by which memory traces stabilise and become invulnerable to interference. Processes of consolidation and theories surrounding functions of consolidation are a major component feature of this thesis and as such an in depth discussion of consolidation is provided in section 1.2.4.

Retrieval

Memory retrieval is the cognitive operation of accessing information stored in memory. Retrieval takes various forms in the different memory domains, in declarative memory retrieval may be the free recall of a list or the recognition of pictures. In the domain of non-declarative memory, retrieval may take the form of performance of a motor skill or action. Although memory is achieved through multiple phases, memory retrieval is the most effective means we have of measuring memory and can be used to assess both acquisition and consolidation. In addition, memory retrieval is not a passive phenomenon but a dynamic process that triggers further processing. It triggers a number of processes that can either reinforce or alter stored information. Processing that occurs as a result of retrieval, is believed to be a crucial prerequisite of memory extinction (Garelick & Storm, 2005). Memory retrieval can also trigger a second memory consolidation phase (reconsolidation), modulated by factors such as age and strength of stored memories (Suzuki et al., 2004). Although this chapter has concentrated primarily on the processes of acquisition and consolidation (those believed to be most affected by sleep), it is also important to remember that post-consolidation stages of memory processing can occur and may be mediated by retrieval.

1.2.4 Consolidation theories

The term consolidation was first coined over one hundred years ago to describe the reduction in fragility of a declarative memory after it's encoding (Robertson et al., 2004[b]). Through consolidation, a new, initially fragile memory is transformed into a robust and stable memory. Experimental findings have now extended the concept of consolidation to apply to other memory systems. For example in procedural

memory, consolidation can describe two different behavioural phenomena, the off-line improvement of skills that occurs between practice sessions (enhancement), and the reduction in fragility of a memory after the acquisition of a novel skill (stabilization) (Robertson et al., 2004[b]).

Declarative Memory

Consolidation of memory in the declarative domain refers to the process by which memories become invulnerable to interference (Walker, 2005). Structures situated in the medial temporal lobes are known to be central to the formation of declarative memory. However, studies of amnesic patients with damage to the medial temporal lobes show that though recent memories are impaired, remote memories remain intact (e.g. Rempel-Clower et al., 1996; Takashima et al., 2006). This demonstrates that the role of the medial temporal structures is temporary, and once consolidation has occurred the hippocampal neurons are no longer required to retain or retrieve the memory. The medial temporal lobes are involved in the initial stages of memory formation and are also involved in the process of consolidation, after which memories become established in other areas of the brain and become independent of the medial temporal lobes (Alvarez & Squire, 1994; Paller, 1997). The hippocampus is able to encode the sequences of traces that constitute declarative memory, they are linked together in an organisation that underlies the ability to make inferential associations across different experiences. Interactions between the various components of this system are critical and may underlie the associations leading to the eventual permanent storage of declarative memories in the neocortical areas of the brain (Eichenbaum, 2000). This pattern of associations has been conceptualised as a system-level or cross-cortical consolidation, a process resulting in a shift from the hippocampus towards distributed neocortical traces (Takashima et al., 2006; Paller & Voss, 2004). The time course of this cross-cortical consolidation is poorly defined, retrospective lesions and functional neuroimaging studies have estimated upper limits of up to several decades, whilst other studies suggest upper estimates of a few weeks. It remains to be determined whether these findings are related to a similar set of processes supporting memory consolidation or whether they are related to separate operations acting on greatly differing time scales (Takashima et al., 2006).

Paller & Voss (2004) have suggested that the time frame of cross-cortical consolidation may depend on the extent to which a memory is retrieved and associated with other stored information. They proposed the nature and frequency of memory access during the time period from acquisition to retrieval was an important determinant of consolidation, and that connections to related information could enrich the memory trace and provide additional routes for retrieval. Behavioural studies in humans have also shown that consolidation can be observed on a short time scale such as a night of sleep (e.g. Gais & Born, 2004), this suggests that cross-cortical reorganization can occur across a range of time periods.

Despite several studies demonstrating the existence of cross-cortical consolidation in declarative memory, little is known about systems and cellular level processes mediating this consolidation (McGaugh, 2000). However, recent studies have begun to investigate the mechanisms involved in the shift from hippocampal storage to a more permanent location, and have begun to provide glimpses of the molecular and cellular processes underlying cortical memory consolidation (e.g. Wiltgen et al., 2004). This provides the first suggestion that the mechanisms of cross-cortical consolidation may soon be uncovered, and our understanding of declarative memory consolidation can be further advanced.

Procedural memory

For procedural memories, consolidation can describe at least two behavioural stages. The first is the stabilization of memory associated with a reduction in the fragility of an acquired memory. The second is the off-line improvement or enhancement that occurs in the absence of further training. These types of consolidation are not mutually exclusive, and may even be complementary. However, the behavioural properties and the criteria that must be satisfied to demonstrate their existence differ (Robertson et al., 2004[b]).

Consolidation based stabilisation is the conversion of a memory representation from an initially labile state to a more stable form, allowing information to be retained after a set period of time. Representations become more resistant to disrupting or competing factors, but the process is one of maintenance only, and does not result in any increase in performance over and above that accomplished during acquisition

(Walker, 2005). Several studies have indicated that procedural learning is preserved, without decrement, across time periods with no interfering stimuli (Stickgold et al., 2000, Walker et al., 2002). However, a more reliable way to assess stabilisation is to investigate the effect of interference, that is the exposure to a second task between testing and recall on an original task. Muellbacher et al. (2002) used transcranial magnetic stimulation applied to the primary motor cortex to promote interference after acquisition of a motor skill task. They showed that interference reduced performance back to pre-training values, while controls without interference showed maintenance of performance over the same time period. Shadmehr & Brashers-Krug (1997) went on to show that stabilisation on a motor task was disrupted by subsequent interference from a second task. They also showed that stabilisation was associated with significant patterns of regional brain activation, suggesting that the passage of time after skill acquisition is associated with a change in the neural representation of the skill. A previous study demonstrated that it was the first 4 hours that represented a crucial period during which interference could occur from similar motor skills, and that after this motor memory was relatively impervious to interference (Brashers-Krug et al., 1996). Interference between tasks appears to be a key behavioural feature of consolidation based stabilisation, however it should be pointed out that different forms of procedural skill may differ in the extent to which they demonstrate stabilisation, and that some components of a skill may require stabilisation and some might not.

Consolidation based enhancement implies that additional learning on a procedural task occurs in the absence of further rehearsal or experience. This process is believed to involve both a replay of past events, and a reorganization of the representation in the brain. As discussed above, Shadmehr & Brashers-Krug (1997) showed that consolidation based stabilisation was susceptible to initial interference after first acquisition, and that a temporal distance of over 4 hours was required to prevent impairment caused by interference. They also demonstrated that human brains had the ability to retain the consolidated memory for up to 5 months post-training. A separate group of participants were not subjected to interference tasks, and were simply retested 24 hours after initial acquisition. Following this intervening time period, participants now displayed additional learning relative to initial training, rather than simply maintaining performance levels.

Many procedural skills have now been shown to demonstrate a degree of off-line learning or enhancement, these include finger skills (Karni et al., 1998; Fischer et al., 2002; Walker et al., 2002), visual discrimination skills (Stickgold et al., 2000) and serial reaction times (Robertson et al., 2004[a]). However, there are two categories of procedural skill that have failed to show off-line learning: kinematic adaptation and dynamic adaptation. Although these types of skill appear to show a degree of consolidation based stabilisation, there is no evidence that performance shows any degree of off-line improvement over time (Krakauer et al., 1999; Donchin et al., 2002).

The combined evidence demonstrates that the improvement of skill without practice, termed *off-line learning*, is a robust finding across many procedural tasks. Whether off-line learning should be regarded as a general feature of procedural learning is less certain. Some procedural tasks have failed to demonstrate a capacity for off-line learning, and others have yet to be tested for an off-line learning capacity (Robertson et al., 2004[b]). Nevertheless, the rules that guide off-line learning and the potential involvement of different brain states such as sleep and wake have generated much research interest, and have lead to a large body of evidence linking the sleep state to consolidation based enhancement and off-line learning.

1.3 Processes of learning and memory: The role of sleep

1.3.1 Procedural learning and sleep

Improvement on a motor skill task is known to continue for some time after initial training and has been identified as consolidation based enhancement (Korman et al., 2003; Karni et al., 1998). Gains in both speed and accuracy have been recorded up to 3 weeks after initial training on a motor sequence. Participants trained on a finger to thumb opposition sequence showed that improvement was specific to the trained hand, with no significant transfer to the untrained hand. In addition, the effects of training on a sequence did not generalise to the performance of a similar (but untrained) control sequence (Karni et al., 1998). Improvements in performance are greatest after the first 24 hours post-training, it is important to note that whilst practice during an initial training session leads to improvements in speed and

accuracy, significant additional gains are also apparent after an intervening 24 hour session where no training has occurred. These time-dependent performance gains, that continue is the absence of further training, can be assumed to represent ongoing changes in the brain. However, the time course of this improvement is insufficient to confirm whether the speed and accuracy gains are simply a factor of passing time, or whether they are dependent on a specific brain state, that of either wake or sleep, or on a particular stage of sleep (Walker et al., 2002).

In an attempt to investigate the hypothesis that sleep is the crucial factor in skill improvement, Walker et al. (2002) designed a study that trained and subsequently retested subjects on a keyboard finger tapping motor skill task. Subjects were trained and then re-tested after a 12 hour period containing normal sleep, and after a 12 hour period awake. Testing schedule was counterbalanced between subjects so half were tested after sleep first, and half after wake first. They found a night of sleep resulted in a 20% increase in motor speed, without loss of accuracy, whilst an equivalent period of time awake provided no benefit. Sleep dependent improvement was independent of testing schedule (i.e. whether they were tested after sleep or wake first) and did not generalise to similar sequences performed in a different order. Subjects also spent the night in a sleep laboratory so that overnight motor skill improvement could be correlated with sleep stage recordings. A significant positive correlation was found between percentage of overnight motor skill improvement and the percentage of stage 2 NREM sleep, particularly late in the night (Walker et al., 2002).

Fischer et al. (2002) used a similar paradigm and also found that improvements in finger motor skills were distinctly greater and more consistent over retention periods of sleep than of wakefulness. They adopted a finger thumb opposition task and showed a 33.5% increase in speed of performance dependent on sleep after practice. They also found that overnight improvements correlated with amount of time in REM sleep, this is at odds with the Walker et al. (2002) finding which showed sleep dependent improvement to be correlated with stage 2 NREM sleep. This discrepancy is essentially unresolved but may indicate that novel tasks (i.e. finger-thumb oppositions) require more REM sleep than tasks which are essentially

variations on well learned skills (i.e. keyboard finger tapping), which in turn require NREM sleep (Walker et al., 2006).

Other forms of procedural based learning have also been found to benefit from sleep dependent improvements. Stickgold et al., (2000) found that improvement on a computer based visual discrimination task was only observed when subjects obtained at least 6 hours of post-training sleep prior to retesting, and improvement was proportional to the amount of sleep in excess of 6 hours. For subjects averaging 8 hours of post-training sleep, improvement was proportional to the amount of slow wave sleep in the first quarter of the night, as well as the amount of REM in the last quarter (Stickgold et al., 2000). These findings provide further conflicting evidence regarding the stages of sleep that are required for overnight improvements on a procedural task. It may be the case that in addition to the effects of novel vs. well learned tasks, the nature of the task performed (i.e. visual discrimination vs. motor skill) is also important in terms of sleep stage requirements.

Smith and MacNeill (1994) have shown that selective sleep deprivation can impair retention of a rotary pursuit motor task, this memory decrement has been shown to result specifically from the loss of stage 2 NREM sleep, again providing support for the role of NREM sleep in procedural learning. They also suggested that the mechanisms of sleep-dependent learning are dissociable from those governing the initial practice dependent learning during acquisition, as well as from the subsequent stabilisation of the memory during initial waking episodes. Cohen et al. (2005) offered further evidence that different aspects of the procedural task are processed separately during consolidation. They used a serial reaction time task that was designed to dissociate goal and movement based skill improvements. They showed that only the movement sequence was enhanced during the day, whereas the goal intention was enhanced over sleep. Further attempts to disentangle the various components of sleep-dependent procedural learning have investigated the time course of motor skill learning. It has been shown that increasing the amount of initial practice on a motor skill does not lead to increased overnight gains, and the degree of practice dependent learning achieved during training does not correlate with the degree of sleep-dependent learning. It has also been shown that practice-dependent improvement will only occur before, but not following, the larger sleep-

dependent improvements that develop across a night asleep (Walker et al., 2003). This provides further evidence that consolidation cannot be considered as a single process, and may be composed of a number of discrete stages, possibly involving unique contributions of different brain states.

The way in which memories are acquired may also be an important consideration when investigating the role of sleep in consolidation. There is evidence to suggest that whilst skills that are acquired intentionally (explicit learning) are sleep-dependent, skills that are acquired unintentionally (implicit learning) may not require sleep for consolidation. Robertson et al. (2004[a]) found that sleep dependent improvement was limited to explicit encoding of a sequence learning task. In the implicit task, consolidation occurred regardless of whether the intervening time period contained sleep or wake. They showed that these improvements were not attributable to practice available within each session, and therefore that sufficient time post training was necessary for off-line learning to occur.

However, a study by Huber et al. (2004) found a sleep dependent increase in performance on an implicit motor task involving rotation adaptation, they found that delayed learning was observed exclusively across a night of sleep, and not across equivalent periods awake. In addition, through the use of high density EEG recordings early in the night, they were able to show that performance gains were correlated with an increase in NREM slow wave activity over the parietal cortex (Huber at al., 2004). The apparent discrepancies between studies investigating effects of sleep on implicit and explicit tasks have yet to be resolved but it may be the case that the distinction between implicit and explicit procedural learning needs to be further clarified in order to correctly assign tasks and to understand their relationship to sleep. Terms such as implicit and explicit are useful in their simplicity but may not satisfactorily reflect task characteristics and may not represent the most appropriate classification in this instance.

Kuriyama et al. (2004) investigated whether procedural task characteristics (particularly task difficulty) were important for predicting sleep dependent improvement. Subjects were trained and subsequently tested on finger tapping sequences that varied in difficulty, namely sequence length, and unimanual or

bimanual performance. They reported that the subjects showing the greatest overnight improvement were those performing the more difficult sequences, indicating that the sleep dependent learning process selectively provides maximum benefit to the most difficult motor skill procedures (Kuriyama et al., 2004). It may be the case that task difficulty, rather than the implicit or explicit nature of the task, is the crucial factor for predicting overnight improvement in performance of a motor skill.

This combined evidence supports the notion that sleep dependent learning occurs across a range of procedural learning tasks. The studies outlined indicate that a night of sleep triggers delayed learning, without the need for further training. The contribution of different sleep states to sleep-dependent learning is less clear, there are suggestions of a contribution of both REM and stage 2 NREM to the process of overnight consolidation. This may suggest different brain states contribute differentially to the consolidation of subtly different memory types, and may suggest that different and distinct mechanisms are involved in the offline learning of procedural skills. Whatever the subtleties, it is now a robust finding that sleep is vital for the consolidation of procedural skill.

1.3.2 Declarative memory and sleep

Evidence for the involvement of sleep in declarative memory has until now been inconclusive. Although sleep has long been known to sustain declarative memories more effectively than daytime wake, this effect has usually been attributed to the absence of destructive interference that weakens memories whilst awake, rather than to active processes driven by sleep (Stickgold, 2005). Methodological difficulties also arise when investigating declarative memory, as such memories do not usually show an improvement over time. Studies have been forced to measure a balance between stabilisation and enhancement, and interference and passive loss. Some studies have also attempted to correlate sleep stages with declarative memory and to isolate neurophysiological characteristics that may be involved in declarative memory processing.

Early studies offer mixed conclusions. Human studies cited no relationship between sleep and memory when a simple memorization task was used, but did find a sleep-

memory effect when utilizing more complex cognitive tasks. Animal studies indicated that post-training REM sleep may be important for learning and memory (Smith, 2001). Research now shows that the type of memory task used in these studies is very important, and more sophisticated experimental paradigms have been designed to investigate the role of sleep in declarative memory. One of the most popular declarative learning tasks now used is verbal paired associates, this appears to be sensitive to the effects of sleep and its specific stages. Benson & Fienberg (1977) showed that subjects who had a night of sleep after learning a verbal paired associates task, performed better the next day than participants who had been awake for an equal amount of time. Gais & Born (2004) also showed performance on a paired associates task improved after sleep when using related word pairs such as dog-bone, rather than unrelated word pairs such as dog-flower. It seems that the role of sleep in declarative memory is not absolute, and depends on more subtle aspects of the task.

The emotional impact of declarative memories has also been shown to have an impact on level of consolidation. Hu et al. (2006) have recently demonstrated that memories with higher emotional impact lead to a greater overnight enhancement of memory accuracy than neutral memories. Subjects were trained and subsequently retested on the recognition of emotional arousing and neutral pictures. They showed a sleep dependent enhancement of recognition accuracy, and an enhancement of memory bias, but only related to the emotional pictures. Whilst studies such as this provide evidence for the role of sleep in declarative memory, they cannot establish which state of sleep is most beneficial. Plihal & Born (1999) used an early/late night design to determine which sleep states were important for spatial memory. They trained subjects on a spatial rotation task (a form declarative memory task) and tested recall after either early sleep (dominated by NREM slow wave sleep), or late sleep (dominated by REM). Recall of spatial memory was greater after early sleep than late sleep, and also after equivalent periods awake. Similarly, Drosopoulos et al. (2005) were able to show early sleep is important for recognition memory. They trained subjects on a task used to assess both explicit (recollection) and implicit (familiarity) recognition memories. They found sleep enhanced explicit memory, but not implicit memory, when compared with wakefulness. Explicit memory was particularly enhanced by early sleep, dominated by slow wave NREM sleep. These

findings concur with earlier work investigating the role of specific sleep stages and declarative learning (Yaroush et al., 1971; Fowler et al., 1973; Barrett & Ekstrand, 1972), and suggest that NREM sleep is particularly important for the consolidation of declarative learning.

Schabus et al. (2004) went on to further investigate the role of slow wave NREM sleep in declarative memory. They trained subjects on a word pair associates task and recorded sleep spindles (electrophysiological characteristic of stage 2 NREM sleep) during subsequent sleep. They found that the number of words recalled was correlated with increased sleep spindle activity. This finding has been replicated and extended to include other verbal declarative tasks such as face-name association, and visual recognition (Gais et al., 2002; Clemens et al., 2005). A recent study by Marshall et al. (2006) has also shown that artificial induction of slow oscillations, leading to increased slow wave sleep and sleep spindle activity in the frontal cortex, enhances hippocampus-dependent declarative memories. The combined evidence seems to suggest a robust link between NREM sleep, particularly sleep spindle activity, and verbal declarative memory consolidation.

Conversely, other studies have proposed a role for REM sleep in certain types of declarative memory. Wagner et al. (2001) compared memory retention of emotional versus neutral text material, over a night of sleep. They found that late sleep dominated by REM particularly enhanced emotional memory when compared with early sleep (dominated by NREM). They proposed the role of REM was specific to memory with emotional context as REM sleep is known to lead to a selective activation of the amygdala, known to play a decisive role in the processing of emotional memory.

Other studies have attempted to investigate the role of specific brain areas and neurochemicals in sleep dependent declarative learning. Peigneux et al. (2004) trained subjects on a spatial learning task and used cerebral blood flow measures to assess related hippocampal activity. They found that hippocampal areas activated during spatial learning (route learning in a virtual town) were re-activated during subsequent SWS. Hippocampal activity during SWS also correlated with improvement of performance in route retrieval the next day. Animal studies have

also shown a reactivation of rat hippocampal cells in slow wave sleep following spatial behavioural tasks (Wilson & McNaughton, 1994). Gais & Born (2004) suggested that low hippocampal levels of the neurotransmitter acetylcholine, are required for the replay of new memories during SWS, and subsequent memory consolidation. They showed that declarative memory consolidation could be blocked by increasing acetylcholine levels during slow wave sleep, proposing low cholinergic tone during SWS is essential for declarative memory consolidation. This combined evidence indicates that hippocampal activity during SWS is essential for the offline processing of recent memory traces, and may lead to the plastic changes underlying the subsequent improvement in performance.

1.3.3 Sleep related neural changes/brain plasticity and memory

Whilst the behavioural characteristics of sleep dependent learning have become increasingly well defined, the underlying neural changes that accompany this learning remain less clear. Memory formation depends on brain plasticity, lasting structural and/or functional neural changes in response to stimuli (Walker & Stickgold, 2006). Sleep has been implicated in the plastic cerebral changes that underlie learning and memory in the adult brain, and are behaviourally expressed as the consolidation of learning. The conventional view is that sleep is primarily involved in the processing of memory traces, leading to a consolidation where traces may be "reactivated, analysed and gradually incorporated into long term memory" (Maquet, 2001). There is to date a mounting wealth of evidence describing sleep dependent brain plasticity at a variety of levels in both animals and humans, complementing evidence of sleep dependent changes in behaviour (Walker & Stickgold, 2004). Animal studies have shown that hippocampal neuronal assemblies are reactivated during post-training sleep, reflecting behavioural experience and indicating a role in memory processing (Louie et al., 2001; Nadasdy et al., 1999; Hennevin et al., 1995). In humans Maquet et al. (2000) demonstrated that waking experiences can influence regional brain activity during subsequent sleep. They demonstrated that subjects trained on a serial reaction task had significantly greater levels of activity in several brain areas during REM sleep than non-trained subjects. Amounts of REM sleep have also been shown to increase in a night of sleep following training in several experimental paradigms (Maquet, 2001). It has also

been shown that sleep deprivation can damage post-training performance of a learned task in animals (Hennevin et al., 1995) and humans (Maquet, 2001).

Electrophysiological data have also provided evidence that sleep is fundamentally linked to the learning process. Theta waves, seen in the hippocampus during sleep, have been shown to facilitate the induction of hippocampal long term potentiation (LTP) (Cantero et al., 2003), believed to be a mediator of memory formation (Walker & Stickgold, 2004). There is also evidence to suggest that sleep spindles, commonly seen during stage 2 NREM sleep, can provide brief trains of depolarizing inputs to targets in the neocortex that are similar to inputs often used experimentally to induce long term synaptic potentiation (Walker & Stickgold, 2004). Phasic events during REM sleep, particularly ponto-geniculo-occipital (PGO) waves, have also been associated with learning. It has been suggested that this REM-PGO stimulation may serve as an endogenous mediator of synaptic plasticity (Walker & Stickgold, 2004).

Whilst important, these results do not provide definitive evidence for the involvement of sleep in learning processes. Several studies have attempted to correlate plastic brain changes in humans to sleep dependent learning. Maquet et al., (2003) trained subjects on a procedural visuomotor pursuit task, three days later they were retested with functional magnetic resonance imaging (fMRI). Half of the subjects were sleep deprived the night following training, and half were allowed to sleep normally. The subjects who slept normally showed enhanced behavioural performance after three days, they also showed a selective increase in activation in the superior temporal sulcus that was not seen in the sleep deprived subjects. Peigneux et al. (2003) trained subjects on a serial reaction time task (SRT), manipulated to include either random sequences or implicitly learnable probabilistic sequences. They showed the level of acquisition of probabilistic rules in the SRT attained prior to sleep was correlated with an increase in regional cerebral blood flow during REM. This suggests the post-training cerebral reactivation is modulated by the strength of the memory traces developed during the learning episode. This evidence provides support for a link between behavioural performance and cerebral changes during sleep.

Walker et al. (2005) investigated plastic brain changes associated with sleep dependent learning by means of fMRI following sequence learning. They trained subjects on a finger tapping task and retested them during fMRI scanning either after a day awake of after a night asleep. Imaging showed that following sleep relative to wake, regions of increased activity were seen in the right primary motor cortex, medial prefrontal lobe, hippocampus, and left cerebellum. These changes can be interpreted as supporting faster motor output and more precise mapping of the finger tapping sequence. Regions of decreased activation were expressed in the parietal cortices, the left insular cortex, temporal pole and fronto-polar region, perhaps reflecting a decreased need for conscious spatial monitoring and a reduced emotional task burden (Walker et al., 2005). These findings show that sleep-dependent motor learning is associated with systems level changes in neural representations, offering further support to the idea that sleep presents a unique brain state, crucial for the changes in representation required for motor learning.

In the field of declarative learning, Molle et al. (2004) were able to show that learning is linked to increased encephalographic (EEG) coherence in subsequent sleep. EEG coherence was measured during performance on a declarative learning task (word-pair associates) and subsequent sleep. When compared with a non-learning control condition, learning performance was associated with an increase in coherence in several slow oscillation EEG frequency bands. This evidence suggests that slow oscillations in humans are particularly relevant for a reprocessing of declarative memories during sleep (Molle et al., 2004). This evidence of sleep-dependent plasticity complements evidence of sleep-dependent changes in behaviour. This provides support for the idea that sleep is a critical mediator of memory consolidation.

1.4 Clinical aspects; An overview of sleep disorders and sleep disordered breathing

A brief overview of the main aspects of sleep in healthy humans has been presented, alongside evidence for a vital role for sleep in processes of learning and memory. Although the majority of the population is able to maintain a healthy quality and quantity of sleep throughout life, alterations to sleep resulting in disturbed sleep

patterns, disrupted sleep architecture, and problems with aspects of attaining or maintaining sleep are not uncommon. Problems with maintaining appropriate sleep patterns can also be related to problems in other areas of functioning and may lead to associated clinical complications. The study of clinical sleep disorders is therefore vital in the field of sleep research, and may help provide clues as to the functions of sleep.

1.4.1 Classification of sleep disorders

The sleep disorders are a group of conditions characterized by difficulties related to sleep, including difficulty falling asleep or maintaining sleep, falling asleep at inappropriate times, excessive total sleep time, or abnormal behaviours associated with sleep. Sleep disorders can be classified into four main categories defined by the International Classification of Sleep Disorders (ICSD). The first category, dysomnias, concerns disorders resulting in difficulty initiating or maintaining sleep, or excessive sleepiness. Dysomnias can be further sub-divided into three groups, intrinsic sleep disorders (e.g. obstructive sleep apnoea – see below), extrinsic sleep disorders, and circadian rhythm disorders. The second category constitutes parasomnias, these are disorders that intrude into the sleep process and are not primarily disorders of sleep and wake states per se. These disorders are manifestations of central nervous system activation. They are divided into four groups; arousal disorders, sleep-wake transition disorders, REM related parasomnias, and other parasomnias. The third category is sleep disorders associated with mental, neurologic, or other medical disorders. Disorders in this category are not primary sleep disorders but rather are other mental, neurological, or medical disorders in which either sleep disturbance or excessive sleepiness are a major feature. The final category is proposed sleep disorders, these are disorders for which there is insufficient information available to confirm the existence of the disorder (AASM, 2001). The primary sleep disorder featuring in this thesis (chapter 3) is sleep disordered breathing and as such is the only primary disorder described in detail.

1.4.2 Childhood sleep disordered breathing (SDB) and obstructive sleep apnoea (OSA)

Sleep disordered breathing (SDB) describes a sub-group of intrinsic sleep disorders characterised by abnormalities of respiratory pattern or quality of ventilation during

sleep. In children, SDB ranges from relatively benign primary snoring, through upper airway resistance syndrome, to obstructive sleep apnoea (OSA). In all these categories the primary symptom is habitual snoring (i.e. snoring on most nights) (Urschitz, 2003). Questionnaire studies have revealed that snoring is relatively common in childhood, with approximately 10% of primary school children being affected. (Ali et al., 1993; Ali et al., 1994; Anuntaseree et al., 2001; Urschitz, 2003). OSA is less common, the prevalence is estimated at about 2% of children and although it occurs in all age groups it is commonest in preschoolers. (Gislason & Benediktsdottir, 1995; Brunetti et al., 2001; Bandla & Marcus, 2006). The distribution of OSA is approximately equal between the sexes, in contrast to adults where males are more commonly affected (Bandla & Marcus, 2006).

OSA results from recurrent episodes of partial or complete collapse of the pharyngeal airway during sleep, and results in the disruption of normal ventilation and sleep patterns. The cause and mechanisms are multifactorial but commonly result from the combination of a structurally vulnerable upper airway combined with a sleep related loss of muscle tone (Woodson, 2006). Most children with OSA have some degree of upper airway narrowing as a result of either one or a combination of adenotonsillar hypertrophy (enlargement of the tonsils or adenoids), craniofacial abnormalities, or excess adipose tissue due to obesity (Bandla & Marcus, 2006). In otherwise healthy children, adenotonsillectomy (a surgical intervention involving removal of the adenoids and tonsils) usually leads to a resolution of symptoms, suggesting that adenotonsillar hypertrophy is a major factor in childhood OSA (Suen et al., 1995). The clinical features of childhood OSA include nocturnal symptoms such as snoring, laboured breathing, paradoxical respiratory effort, observed apnoea, restlessness, sweating, unusual sleep positions, and secondary enuresis. The daytime symptoms include mouth breathing, frequent upper respiratory tract infections, excessive daytime somnolence, morning headaches, fatigue, hyperactivity, aggression, and social withdrawal. Children with OSA are usually of normal height and weight but obesity has been increasingly recognised as a risk factor. Adenotonsillar hypertrophy is a common physical finding in children with OSA although its absence does not exclude the diagnosis (Bandla & Marcus, 2006). Chronic untreated OSA can result in serious comorbidities as a result of hypoxia, acidosis and sleep disturbance. Complications include growth impairment,

pulmonary hypertension, cor pulmonale, and heart failure, treatment of OSA is often effective in reversing the effects of complications such as these (Bandla & Marcus 2006). Neurocognitive deficits, learning problems, and behavioural problems have also been noted in children with untreated OSA and are discussed in detail in section 1.4.3.

The gold standard for diagnosing OSA is full polysomnography. Without the appropriate respiratory measurements used in PSG it may be impossible to differentiate between primary snoring and OSA. Although there are no set diagnostic criteria for the polysomnographic diagnosis of OSA, there is a general agreement amongst clinicians as to what is considered normal in terms of the various sleep and respiratory parameters. Obstructive events are uncommon in the normal population and would be expected to occur < 0.3 – 0.7 per hour slept. A mean oxygen saturation of 97.5% has been recorded in healthy children, with a nadir of > 94% with obstructions. Normal CO_2 levels are < 45mmHg, with a CO_2 peak at around 51mmHg, in most children the time spent with CO_2 > 50mmHg is 0.03%. A normal arousal index would show up to 10 arousals per hour slept, although respiratory arousals are usually < 1 per hour slept. These guidelines are used by polysomnographists to help identify children with significant obstructive problems or fragmented sleep.

Although full-blown OSA only occurs in around 2% of children, the spectrum of sleep related breathing disorders is broad and many children not fulfilling the criteria for full OSA still suffer clinically relevant upper airway obstruction. Lesser symptoms and milder respiratory disturbance may not lead to the gas exchange problems associated with OSA, but may still have a significant effect on sleep quality, arousals, and daytime sleepiness.

1.4.3 Sleep disordered breathing and cognitive impairment

The consequences of OSA are multiple, in adults OSA has been associated with systemic and pulmonary hypertension, cardiovascular and cerebrovascular disease, arrhythmias, and hormonal abnormalities. In children cardiovascular alterations, hormonal abnormalities, and growth impairment have been noted (Beebe et al., 2004). However, many of the most functionally disruptive effects are

neuropsychological rather than medical. In adults, OSA has long been associated with excessive daytime sleepiness, this in itself has been shown to have a marked impact upon executive functioning and has been linked to decreased attention and vigilance. A meta-analysis investigating the effects of sleep-related breathing disorders (SRBD) in adults found impairments in many areas of functioning including memory, vigilance, attention, and driving simulation performance (Fulda & Schultz, 2001).

Amongst children, snoring, a common but non-specific symptom of OSA has been linked to a range of cognitive difficulties including hyperactivity, attentional difficulties, poor academic performance and aggressiveness (Ali et al., 1993, Chervin et al., 2003, Gottlieb et al., 2003, Urschitz, 2003). Associations have also been found between snoring and daytime sleepiness, Gozal et al. (2001) found shortened sleep latencies in association with OSA, and evidence of excessive daytime sleepiness among more severe and/or obese patients. Theories have suggested daytime sleepiness is an important predictor of daytime behaviour problems and cognitive impairments (Chervin et al., 2003). There is also increasing evidence that OSA in children is associated with reduced neurocognitive performance and increased problematic behaviour. A review by Blunden et al. (2001) summarized the literature available and found deficits in many areas, particularly the interrelated domains of attentional capacity, memory and intelligence (including learning and school performance). In terms of attention, it was found that children with OSA are less reflective, more impulsive, and show poorer sustained and selective attention (e.g. Blunden et al., 2000; Owens-Stively et al., 1997; Ali et al., 1996). Memory studies in this area are more limited but have reported that children with OSA show significantly reduced memory capacity when compared to controls, it has also been found that the severity of OSA is associated with the degree of impairment (Blunden et al., 2000; Rhodes et al., 1995). Due to the relatively small number of studies, findings are suggestive but not conclusive of reduced memory performance.

Studies of intelligence are again relatively few, but have shown significantly reduced IQ scores in school age children with OSA (Blunden et al., 2000; Rhodes et al., 1995). Conversely, other studies have indicated that IQ is not impaired in OSA (Owens-Stively et al., 1997), it may be the case that the negative effects related to

OSA are more selective in nature and an assessment of specific areas (e.g. verbal IQ) may be required. Several studies have shown that children with OSA show reduced academic performance and learning, it has also been reported that children who are poor academic achievers show a higher prevalence of sleep related breathing problems. Data has also suggested that OSA and sleep disordered breathing in early childhood may continue to adversely affect learning in later years (e.g. Richards et al., 2000; Guilleminault et al., 1976; Stradling et al., 1990; Gozal & Pope, 2001).

In addition to the wealth of evidence demonstrating extensive cognitive deficits related to OSA, there have also been many studies linking OSA to behavioural problems including hyperactivity, aggression, impulsivity, anxiety, shyness and withdrawn behaviour (Blunden et al., 2001). However, a significant finding that is perhaps not fully appreciated is that treatment for childhood OSA can significantly improve both cognitive performance and behaviour. Guilleminault et al. (1982) found that 8 out of 10 children requiring special educational assistance were able to return to mainstream schooling after treatment for OSA (adenoidectomy and/or tonsillectomy). A study by Glaze et al. (2002) found that the severity of a child's OSA was correlated with measures of intelligence, memory, academic performance, attention/impulsivity, and adaptive behaviour. After treatment with tonsillectomy or adenoidectomy, improvements were seen in behaviour, quality of life, and cognitive function. However, cognitive improvements were only partial in contrast to the larger improvements seen in behaviour. Gozal (1998) found that a sample of children with poor academic achievement showed improved grades after treatment with adenotonsillectomy. A similar study by Montgomery-Downs (2005) showed improved cognitive scores after treatment for OSA. These findings have been replicated across a number of studies, providing robust evidence that OSA treatment leads to an improvement in cognitive function (e.g. Stradling et al., 1990; Ali et al., 1996; Goldstein et al., 2000).

These findings confirm that OSA and sleep related breathing difficulties in children are linked to a significant cognitive impairment, apparent across multiple domains. This cognitive impairment appears to have some degree of reversibility, and treatment of the OSA usually results in some improvement in cognitive function. However, it remains unclear which underlying patho-physiological mechanisms of

OSA are responsible for this reversible impairment. In adults, the most commonly proposed model suggests that hypoxaemia and sleep fragmentation are the most important factors (Blunden et al., 2001). However, in children these factors are usually less severe and evidence for the relative impact of each is not as conclusive. Adenotonsillectomy in children typically results in decreased sleep arousals, normalisation of sleep and marked improvements in respiratory indices. Evidence suggests that sleep fragmentation and abnormal blood-gas exchange associated with OSA may induce substantial alterations in brain function, and more specifically may affect the prefrontal cortex. It is suggested that this may lead to the impairment in cognitive functioning associated with childhood OSA (Montgomery-Downs et al., 2005).

The specific relationship between the severity of hypoxaemia and subsequent neurocognitive deficits has only been explored indirectly. Studies have shown that reduced nocturnal oxygen levels are linked to cognitive impairment, however none of these studies report correlational data and it is not known what level of desaturation is damaging (Blunden et al., 2001). Similarly, sleep fragmentation and disturbed sleep architecture have been associated with impaired cognitive function in both anecdotal and objective studies (Blunden et al., 2001). Rhodes et al. (1995) demonstrated significant correlations between total numbers of arousals and neurocognitive measures in children with OSA. In addition, adult sleep fragmentation is moderately correlated with daytime cognitive deficits.

The emerging evidence suggests that the neurocognitive effects of OSA may be linked to both hypoxaemia and sleep fragmentation caused by increased arousals. Given the robust line of evidence now established that links sleep to the consolidation of learning, it can be postulated that sleep fragmentation and increased arousals during sleep are having a large impact on cognitive function through the effects of reduced consolidation. As previously discussed, consolidation is an important component of learning and any reduction in consolidation caused by impaired sleep will presumably have some negative effect on cognitive function in general. We theorise that a reduced level of consolidation in children with OSA, caused by a marked disruption to sleep architecture, is an important factor to consider when assessing the causality of cognitive impairment.

1.4.4 Sleep disturbances and disorders of mood and affect

In addition to the effects disturbed sleep appears to have on aspects of cognitive function, it is also important to consider the effect of sleep on psychological and emotional wellbeing. Sleep disturbances have been a common complaint in psychiatric disorders for centuries, and self reported sleep disturbances are present in over 80% of patients with depression (Armitage, 2007). Data from more objective studies has suggested that EEG defined sleep appears to be abnormal in those at risk of depression, and there is a general consensus of opinion that sleep is different in individuals at high risk of depression (Kupfer, 1995). There is also evidence that regulation of mood in affective illness is related to the regulation of sleep, and although there is a certain level of dissociation between sleep and depressed mood, the two domains are important and interactive in terms of our understanding of mood disorders (Kupfer, 1995). Several abnormalities characterise the sleep of people with depression. Sleep onset latency, number of awakenings, wake after sleep onset, and rapid eye movement density are increased. Conversely, total sleep time, sleep efficiency, slow wave sleep and REM latency are reduced (Benca et al., 1992; Kupfer, 1995; Hubain et al., 2006). A recent review by Armitage (2007) reported that sleep microarchitecture, based on sleep EEG frequency analysis, is more likely to differentiate depressed patients from controls, than are standard measures. They also found gender and age to be important moderators of sleep disturbance.

In addition to the interactions between sleep and clinical affective disorders, further evidence for the association between sleep and mood comes from studies of sleep deprivation. Chronic sleep deprivation has been shown to result in fatigue, poor mood, and daytime sleepiness (Stepanski et al., 2000; Surani et al., 2007). 30 hours of sleep deprivation has also been shown to result in significant negative disturbances to subjective vigour, fatigue, and depression (Scott et al., 2006). The combined evidence suggests that sleep and mood states have important interactions, both in depressed patients and in healthy subjects.

1.5 Clinical aspects: Associations between epilepsy and sleep

An overview of sleep disordered breathing has been presented above. In addition to primary sleep disorders such as this, there are a range of other medical disorders that, while not classed as sleep disorders, have important and well documented

interactions with sleep. In an attempt to provide an insight into the interactions between one such disorder and sleep, an overview of epilepsy is presented. This neurological disorder is not generally classified as a sleep disorder (exceptions being ESES and sleep related epilepsy), but provides an ideal example of a medical condition in which interactions with sleep appear to be a major feature.

1.5.1 Epilepsy

Epilepsy is a chronic disorder of the brain characterised by an enduring disposition towards unprovoked recurrent seizures. It is the most common serious neurological disorder, the prevalence is around 50 -70 people per 100,000 of the population. Incidence varies greatly with age, with high rates in early childhood, low levels in early adult life, and a second peak in people aged over 65 years old. Seizures represent the clinical manifestation of an abnormal and excessive synchronised discharge of cortical neurons in the brain, seizures can be broadly classified as partial or generalised. Partial seizures originate in a focal region of the cortex and can be further subdivided into simple partial (consciousness not impaired) and complex partial (consciousness impaired). Both types of seizure can spread to other cortical areas, resulting in what is known as secondary generalisation. Generalised seizures are characterised by widespread involvement of bilateral cortical regions at the outset and are usually accompanied by impairment of consciousness. In addition to the classification of seizures, there is a separate system for classifying epilepsies and epileptic syndromes, these are defined by groups of clinical, neurological and neurophysiological characteristics. Epilepsies can be divided into localisation related (or focal), or generalised epilepsies, further subdivisions include idiopathic (presumed genetic origin), symptomatic (of known cause) and cryptogenic (presumed to be symptomatic but with an unidentified underlying abnormality) (Brodie et al., 2005).

1.5.2 Associations between epilepsy and sleep

Epilepsy has a complex association with sleep, this relationship has been recognised since antiquity, when both Hippocrates and Aristotle observed the occurrence of epileptic seizures during sleep (Passount, 1984). Not surprisingly, this relationship varies from one type of epilepsy to another, and can also vary according to factors such as age, medication, epilepsy severity etc. In addition to the direct effects of

epilepsy on sleep and vice versa, it is also important to consider the impact that disturbed sleep may have on daytime functioning, and on quality of life. Early studies based on clinical observations noted that in many patients, epileptic seizures occurred during the night, or shortly after waking (Gowers, 1885). Since the discovery of the EEG in 1929, it has become possible to define more clearly the complex relations between epilepsy and sleep.

In the early studies based on clinical observation alone, it was found that between 42-45% of patients experienced seizures that occurred predominantly during the daytime, 19-24% of patients experienced seizures that occurred only during nocturnal sleep, and 33-37% of patients experienced seizures that occurred both during the day and during sleep (Dinner, 2002). Although these studies demonstrate close conformity between the 3 sub-groups, it has since become clear that various types of epilepsy and seizure are affected differently by the sleep-wake cycle. Epileptiform discharges and seizures in primary generalised epilepsies are both commonly promoted by sleep deprivation. In addition, primary generalised seizures often occur within a couple of hours of waking, whether from overnight sleep or daytime naps. Partial seizures appear to have a greater propensity to spread during sleep, frontal lobe seizures occur often predominantly (sometimes exclusively) during sleep, however other partial seizures such as temporal lobe seizures are relatively uncommon during sleep (Walker & Sisodiya, 2005). Sleep loss or disruption has a well documented effect on the likelihood of clinical seizure occurrence, especially in association with emotional or physical stress. Sleep deprivation can activate the EEG and can also induce seizures, especially in generalised epilepsies (Walker & Sisodiya, 2005). Sleep deprivation may be used alongside a sleep EEG in order to provoke seizure activity or epileptiform discharges.

In children, various epilepsies and epilepsy syndromes have important associations with sleep. A classic example is benign rolandic epilepsy, a relatively common childhood epilepsy syndrome characterised by partial rolandic seizures that occur during the night or shortly after awakening (Stores, 2001[b]). Other epilepsies commonly presenting with nocturnal seizures include mesial frontal seizures, Lennox-Gestaut Syndrome (Amir et al., 1986), and Landau-Kleffner Syndrome

(Massa et al., 2000). Other epilepsy types may be linked to the sleep-wake cycle and seizures may be associated with the transition from sleep to wake, a striking example is juvenile myoclonic epilepsy. This is a common epilepsy syndrome in which myoclonic and generalised tonic-clonic seizures occur characteristically in the morning during the first 1-2 hours after awakening but are rare at other times of the day (Dinner, 2002; Timmings & Richens, 1992). An example of an epilepsy syndrome differentially affected by different sleep stages is Electrical Status Epilepticus During Slow Wave Sleep (ESES), this is a generalised epilepsy characterised by continuous spike and wave activity during slow wave NREM sleep. These discharges are usually substantially less frequent during REM sleep and wake, and are thought to be suppressed by the state of REM sleep (Scholtes et al., 2005).

In addition to the presence of clinically relevant seizures during sleep, there is also a close association between EEG activation and sleep. Both focal and generalised epileptic discharges are common during NREM sleep, even if clinical seizures do not occur. During REM sleep, either generalised epileptiform discharges are infrequent, or the spread is restricted. Focal discharges occur during REM sleep but are highly localised. Clinically evident seizures rarely occur during REM sleep (Shouse, 2006). In general, EEG activation and seizures in epilepsy are most frequent during NREM sleep. The longest trains of spike and wave complexes occur in stage 1 NREM sleep, the next most prominent time for discharges is stage 2 NREM sleep. Deep NREM stages (stages 3 and 4) are usually considered less likely to activate discharges, however the evidence is less than conclusive and there are some suggestions that SWS is equally conducive to discharges (for example in syndromes such as ESES) (Shouse, 2006). This evidence illustrates the ability of sleep to activate the EEG, the finding is common across many kinds of epilepsy but may often go unnoticed due to the subclinical nature of the epileptiform discharges. Examples in childhood again include benign rolandic epilepsy, this presents with frequent centro-temporal spikes at night, this is in addition to the clinically relevant nocturnal partial seizures that are also present (Baglietto et al., 2001).

In addition to the effects of sleep on epilepsy, it may also be important to consider the effect of epilepsy on sleep. Although there is no consistent or typical pattern of sleep disruption, alterations involving the amount and the architecture of sleep are

more common in patients with epilepsy (Bourgeois, 1996). Evidence suggests that the very presence of epilepsy can disrupt sleep, seizures themselves can cause sleep disruption and even seizures during wakefulness can disrupt subsequent sleep (Bazil, 2003). Studies have found that epilepsy can produce an increase in sleep latency, wake time after sleep onset and stage shifts, an increase in stage 1 and 2 NREM sleep, and a decrease in sleep spindle density and REM sleep (Foldvary, 2002). Many studies have also shown improvement in sleep with the improvement of seizures, in particular most have shown improvement of sleep efficiency, decreased arousals, and an increase in REM sleep (Bazil, 2003).

Treatment with anti-epileptic medications (AED's) may also have a potent effect on sleep, studies suggest that AED's alter sleep architecture both acutely and chronically. The most consistently observed short-term effects appear to be those that are associated with the older classes of AED's (e.g. phenobarbitol, phenytoin, benzodiazepines) and include a decrease in wake after sleep onset, an increase or decrease in light sleep, and increase or decrease in SWS, and a decrease in REM sleep (Foldvary, 2002). In recent years, several newer AED's have been developed with comparatively minor side-effects when compared to the older drugs. However, the effects of most of the newer AED's on sleep are less well defined. In general, it seems that the newer AED's have less of a detrimental effect on sleep than the older AED's, and some studies even suggest that newer AED's may have a stabilising effect on sleep (Placidi et al., 2000). However, it remains to be seen whether the improvement in sleep patterns is a direct result of the AED therapy or is a consequence of improved seizure control.

Seizures (especially those that may appear particularly dramatic) may well be confused with other recurrent episodes of disturbed behaviour associated with sleep, or with a clinical sleep disorder (Stores, 2001[b]). The possible confusions between epilepsy and sleep disorders, and the misdiagnoses that may occur can have important implications in terms of appropriate treatment and management. Sleep disorders that may be misdiagnosed as epilepsy can include arousal disorders, REM sleep behaviour disorders, head banging, enuresis, OSA, and automatic behaviour disorder (Stores, 1991). Conversely, epilepsy may be misdiagnosed as a sleep disorder, examples include complex partial seizures of temporal lobe or frontal lobe

origin, nocturnal/hypnogenic paroxysmal dystonia, episodic nocturnal wanderings and non-convulsive status epilepticus (Stores, 1991). In addition to the possible confusions between epilepsy and sleep disorders, research has also shown that primary sleep disorders are more common in epilepsy. For example, OSA type symptoms are more common in epilepsy (Becker et al., 2003), and sleep apnoea can exacerbate seizures. Studies treating OSA in children with epilepsy have also shown an increase in seizure control (Koh et al., 2000). Other sleep disorders, including insomnia, may be more common in epilepsy and may potentially worsen seizures (Malow, 2004). For various reasons, patients with epilepsy are more likely to be predisposed to clinical sleep disorders. In addition to the presence of clinically relevant disorders, there is also an association between epilepsy and more low level, diffuse sleep disturbances. As they are often not serious enough to warrant a clinical diagnosis, these disturbances may go unnoticed by clinicians but can still have a large impact on issues such as daytime functioning and quality of life.

A range of studies has now shown that children with epilepsy are more vulnerable to sleep disturbances and inappropriate bedtime behaviour, than children in the general population. A study by Stores et al. (1998) used a parental report questionnaire to assess sleep disturbances in 79 children with epilepsy. They found that children with epilepsy showed much higher rates of sleep disturbances than controls, particularly poor quality sleep and anxieties about sleep. Cortesi et al. (1999) replicated these findings and also showed increased levels of reported sleep disturbance in children with idiopathic generalised epilepsy, sleep problems were greater in those children with current seizures than those without. Research comparing sleep problems in children with epilepsy and their non-epileptic siblings has also shown that disturbed sleep is more common in epilepsy (Cortesi et al., 1999; Wirrell et al., 2005). A further study specifically assessing daytime sleepiness in epilepsy found that, when compared to controls, children with epilepsy were much more likely to suffer from excessive daytime sleepiness (Maganti et al., 2005).

In adults, studies assessing the subjective report and clinical relevance of sleep disturbances in epilepsy patients are surprisingly few. De Weed et al. (2004) found that patients with partial epilepsy had a highly significant twofold higher prevalence of sleep disturbance compared with controls. The presence of sleep disturbance in

patients with epilepsy was also found to be associated with impairments to quality of life. Xu et al. (2006) also found that patients with partial epilepsy reported more sleep problems than controls, and patients with sleep disturbance also reported poorer quality of life. Studies have also suggested that clinical sleep disorders are more common in people with epilepsy, with a higher prevalence of symptoms of insomnia, restless legs/periodic leg movements syndrome, and sleep apnoea (Bazil et al., 2003). In general, the evidence suggests that adults with epilepsy have a high prevalence of sleep disturbance than controls, they report a range of problems with sleep, and associated problems with issues such as quality of life are commonly reported.

1.5.3 Epilepsy and cognitive impairment: memory

In addition to their vulnerability to sleep problems, people with epilepsy as a group are at a greater risk of developing cognitive impairment and learning problems than people in the general population. It is estimated that learning problems occur in between 5-50% of people with epilepsy (Thompson, 1987). Cognitive impairment refers to deficits in cognitive functions, these are the mental processes by which we take in, make sense of and act upon information from the outside world (Thompson, 1987). Complex learning skills such as reading, writing and arithmetic involve many aspects of cognitive functioning, therefore cognitive impairment can lead to a wide range of problems and deficits in may areas. Cognitive impairment may be particularly damaging in children, in whom it can lead to unsatisfactory educational progress and poor scholastic performance. Aspects of cognitive functioning that may be impaired in epilepsy include memory, attention, perception and motor skills, reading, and arithmetic.

Disturbances of memory and related functions have often been noted in association with epilepsy, indeed early this century such difficulties were felt to be an inevitable consequence of the disorder (Thompson, 1987). Adults with epilepsy frequently complain of memory problems and perform poorly on subjective measures of memory function. They also report that memory difficulties have a significant negative impact on their everyday lives (Thompson & Corcoran, 1992). However, patients with epilepsy who complain of high levels of subjective memory difficulties often achieve average or high-average scores in standard laboratory memory tests.

This discrepancy may be due to a number of factors, for example there may be a poor correspondence between the parameters assessed by laboratory memory tests and the type of everyday memory difficulties reported by people with epilepsy. It has also been suggested that people with epilepsy may be prone to an exaggerated perception of memory failure due to anxiety or depression, or other cognitive impairments (Giovagnoli et al., 1997). However, studies have shown that, far from exaggerating their memory difficulties due to neuroses, people with epilepsy actually underestimate the frequency of their everyday memory failures (Thompson & Corcoran, 1992). It has also been suggested that everyday memory may be affected by clinical, pathological, and antiepileptic drug related factors (Giovagnoli et al., 1997). Another suggestion is that the memory difficulties so often experienced by people with epilepsy are due to an impairment of very long term memory consolidation processes, beyond those normally assessed by standard laboratory memory tests. A study by Blake et al. (2000) showed that people with temporal lobe epilepsy performed disproportionately poorly on tests of long term forgetting, and suggest this is indicative of consolidation impairment. Although the paradox remains essentially unresolved, the established link between sleep and processes of consolidation (Walker et al., 2002; Stickgold et al., 2000), may lead to speculation that disruptions to sleep are in part responsible for the memory difficulties experienced by people with epilepsy.

Disturbances of memory and related functions are also often reported by the parents and teachers of children with epilepsy. Such problems may well interfere significantly with the child's educational and social progress, and it is important that they are recognised wherever possible. However, the precise nature of these problems can be difficult to identify, and may represent a diverse range of impairments. Studies specifically assessing learning and memory problems have shown that children with epilepsy are inordinately vulnerable when processing memory tasks, especially when placed under conditions of increased demand (Schouten et al., 2002). Bailet & Turk (2000) used a battery of neuropsychological tasks and found that children with epilepsy scored significantly lower on measures of memory, presenting a long-term risk of learning problems. A neurophysiological study by Koop et al. (2005) also showed memory impairment in children with epilepsy, and found correlations with slow wave EEG activity. Findings such as

these are consistent with results from several other studies (Nolan et al., 2004; Jambaque et al., 1993) and confirm the negative impact of epilepsy on learning and memory in children.

1.5.4 Epilepsy and cognitive impairment: other difficulties

In addition to the deficits in learning and memory, a number of other cognitive difficulties have been identified in association with epilepsy. Transient interruption of attention characterises certain classes of seizure e.g. absence seizures. More prolonged alterations of attention may be seen in the post-ictal or confusional state following other types of seizure. Attentional deficits may also be associated with epilepsy in more subtle ways, and may be observed in the absence of any overt seizures (Stores et al., 1973). Studies of attention patterns in epileptic patients have found that people with epilepsy present with inferior cognitive performance in relation to concentrated attention, compared with controls (Stella & Maciel, 2003). Attentional decline and psychomotor speed decline has also been shown in patients with temporal lobe epilepsy (Piazzini et al., 2006). In children, an early study by Whitmore & Holdsworth (1971) demonstrated that 42% of children with epilepsy attending mainstream school were reported by their teachers to be "markedly inattentive". Further studies have also shown that children with epilepsy (irrespective of epilepsy type) suffer deficits in alertness and attention (Bennet-Levi & Stores, 1984). Perceptual difficulties and motor problems have also been reported in association with childhood epilepsy. Bailet & Turk (2000) found psychomotor speed was significantly slower in children with epilepsy than in controls. Motor skill deficits have also been demonstrated in various types of childhood epilepsy including benign focal epilepsy (Maalouf et al., 2006), frontal lobe epilepsy (Hernandez et al., 2002), and severe and intractable epilepsy (Beckung & Uvebrant, 1993; Beckung et al., 1997).

In children, it is particularly important to understand the effect of epilepsy on more global aspects of cognitive function, and education in particular. Many studies have concentrated on these more generic aspects of cognitive function, including concepts such as academic achievement, learning skills and performance in school. The majority of research evidence has confirmed that children with epilepsy are more likely to underachieve at school (e.g. Seidenberg et al., 1986; Fowler et al., 1984;

Mitchell et al., 1991) and have broad-spectrum problems with learning (e.g. Stores, 1978; Cornaggia & Gobbi, 2001; Bailet & Turk, 2000). Other research has assessed complex learning skills requiring many aspects of cognitive function, spanning many domains. Studies have shown that children with epilepsy have particular problems with reading skills (Rutter et al., 1970; Stores & Hart, 1976; Long & Moore, 1979) and mathematical or arithmetic skills (Bagley, 1970; Green & Hartlage, 1971; Ross & West, 1978; Aldenkamp, 1983).

1.5.5 Epilepsy and depression

In addition to the cognitive impairment often associated with epilepsy, psychiatric comorbidities are also common. Nearly 1 in 3 people with epilepsy report significant concern about their mood states, depression is the most common psychiatric condition in patients with epilepsy and is reported in some studies to exist in up to 55% of patients (Brodie et al., 2005). A large body of evidence exists associating epilepsy with depression and mood disorders, and studies have shown that negative affect, anxiety and depressive symptoms are common across all types of epilepsy (e.g. Mendez et al., 1986; Robertson et al., 1987; Piazzini et al., 2001). Depression most often occurs interictally and presents as a chronic waxing and waning disorder, often in association with variable levels of irritability and emotionality (Brodie et al., 2005). Studies assessing psychiatric disorders in children with epilepsy have drawn similar conclusions, anxiety and depression are common in childhood epilepsy and appear particularly prevalent amongst males compared to females (Bilgic et al., 2006). Depression in children with epilepsy may also contribute to poor psychosocial outcome, and may be a risk factor for suicide (Plioplys, 2003).

1.5.6 Causes of cognitive impairment in epilepsy

The causes of cognitive impairment in epilepsy are not fully understood, and many methodological issues surround the empirical research of a disorder as heterogenous as epilepsy. Despite this, many studies have investigated potential factors involved and have identified a number of contributing variables.

Daytime seizures can have direct effects on several aspects of the information processing system. Deficits in alertness, short-term learning, abstraction, and more stable aspects such as educational achievement have all been shown in connection

with seizures (Aldenkamp, 1990; Aldenkamp & Arends, 2004). Prolonged post-ictal effects may also exist, but can be more difficult to identify. Nocturnal seizures are thought to have detrimental effects on language functions, on memory, and on alertness (Aldenkamp, 1990). Age of onset of seizures can also have an effect; early onset seizures can interfere with brain development and are associated with a higher degree of cognitive impairment (Binnie, 1990). Interictal epileptiform EEG discharges can also produce subtle transient cognitive impairment (TCI) in the absence of any clinical phenomena (Binnie, 1992).

Some epilepsies may be associated with structural brain abnormalities, these individuals tend to show greater impairments than those without demonstrable pathology. In addition, deficits in patients with localization related epilepsy are more specific to different types of test material (Binnie 1990). In general, a demonstrable organic aetiology for epilepsy is a poor prognostic indicator for intellectual ability and scholastic performance (Dam, 1990). In addition, structural abnormalities are often associated with poor seizure control, which in itself can lead to problems with cognition and academic attainment.

The negative effect of AED's on cognitive function has been documented, but it is still largely unclear what the relative contributions of the different AED's are. Several studies have examined the established old AED's but no certain conclusions have been reached as to what degree individual drugs have an effect on cognition. Data regarding the cognitive effects of the new drugs are sparse (Brunbech & Sabers, 2002). In general, however, there seems to be an agreement that polytherapy and high-dose treatment can produce adverse cognitive effects. Of course, one possibility to be considered is that patients on polytherapy or receiving high dose treatment are those with the most severe and resistant forms of epilepsy. As such, it should be considered that the association between polytherapy/high dose treatment and cognitive impairment may be a factor of epilepsy severity rather than a direct consequence of drug therapy.

The associations between sleep and epilepsy are complex and multiple, despite this surprisingly little research has investigated the extent or consequence of sleep disturbance in either children or adults with epilepsy. In addition, relatively little of

the research into cognitive impairment in epilepsy has concentrated on sleep, this seems surprising given the growing body of evidence connecting sleep with learning (see section 1.3). Neither has any significant research concentrated on the effect of sleep on psychiatric comorbidities such as depression, again surprising given the associations between sleep and depression.

1.6 Summary

The topics discussed in this literature review have attempted to provide a general introduction to the experimental work of this thesis. The overview of sleep physiology, and the evidence supporting the theory that sleep is an important mediator of processes of learning and memory provides the theoretical basis for studies described in chapter two. Although there is a robust body of evidence associating sleep with the consolidation of non-declarative procedural memory, the role of sleep in other memory domains (particularly declarative) is less well known. An investigation of the role of sleep in processes of declarative memory would help elucidate the mechanisms behind sleep dependent learning, and may provide additional evidence to help clarify the inter-relationships between different types of memory. Another crucial point to consider is the lack of any empirical research assessing the role of sleep on learning and memory in children, a population in whom the consequences of learning and educational performance are considerable. These concerns will be addressed in chapter two, where empirical research attempts to assess the role of sleep in the declarative memory domain, and investigates sleep dependent learning in children.

An overview of clinical sleep disorders, in particular OSA and sleep disordered breathing, provides evidence that disturbed sleep can be associated with a degree of cognitive impairment. However, the cause of this associated cognitive impairment has not been fully established, and no research to date has investigated the specific impact of the sleep disturbance on sleep dependent learning. The question remains as to whether chronic but relatively subtle disturbances to sleep can impact on processes of sleep dependent learning, once again this question is particularly pertinent in children, a group in which cognitive impairment has such great consequences. This hypothesis is addressed in chapter three, with an assessment of cognitive function and sleep quality in children undergoing investigation for OSA.

Finally, an overview of aspects of epilepsy was presented, a clinical condition that has associations with sleep but is not classified as a sleep disorder. Relatively little research has concentrated on the assessment of sleep disturbance in epilepsy, despite known interactions between the disorder and sleep. In addition epilepsy has long been associated with cognitive impairment and psychiatric comorbidities, however researchers have yet to investigate the specific interactions between sleep and these variables in epilepsy. Chapter four attempts to provide some insight into the interactions between self-reported sleep quality, memory, cognitive function, and mood. Predictive relationships are initially assessed in a population of healthy controls, and subsequently in a group of adults with epilepsy. The final experimental chapter addresses some of the clinical concerns that apply in the treatment of children with epilepsy. Initially, the prevalence of sleep disturbances in a group of children with epilepsy are assessed, in comparison with a group of healthy control children. Although disturbed sleep in childhood epilepsy is frequently reported as a concern by parents, it often goes unreported and is not routinely assessed by clinicians. As such, objective and subjective methods of recording information on sleep are also assessed, in order to provide some research evidence that can have direct clinical relevance, and can hopefully be incorporated into clinical practice

In summary, this thesis attempts to confirm the vital role of sleep in adult procedural learning, and also investigates the role of sleep in declarative memory processes. The impact of sleep on these memory domains is also assessed for the first time in children. The thesis also investigates the role of sleep disturbance on procedural and declarative memory in a case series of children with sleep disordered breathing. In a large-scale prevalence study, subjective sleep disturbances are assessed in both people with epilepsy and controls, and associations between sleep and memory, mood, and quality of life are assessed. Finally, sleep disturbances are assessed in children with epilepsy and the various techniques available for collecting information on sleep are evaluated.

Chapter 2

The effects of sleep on procedural and declarative learning in adults and children

2.1.1 Introduction

Although the precise functions of sleep remain largely unknown, there is a substantial body of evidence pointing towards a role for sleep in memory processes and brain plasticity (see chapter 1). Evidence for sleep dependent improvements on procedural tasks are provided by many different authors, with research indicating that sleep plays an important role in the enhancement of procedural performance (e.g. Walker et al., 2002, Stickgold et al., 2000). Various forms of procedural learning have been found to benefit from sleep dependent improvements. Stickgold et al., (2000) found improvements on a computer based visual discrimination task were dependent on sleep, whilst Smith & Macneill (1994) demonstrated performance on a rotary pursuit motor task could be impaired by selective sleep deprivation. Serial reaction time tasks (Cohen et al., 2005), explicit sequence learning tasks (Robertson et al., 2004a), and rotation adaptation tasks have also all been shown to show selective improvements over sleep.

However, the majority of the research into sleep dependent procedural learning has concentrated on finger tapping tasks, which have been established by many authors as being sensitive to sleep. A 2002 study by Walker and colleagues was one of the first to show a sleep dependent improvement on a finger tapping task, the study trained and subsequently retested subjects on a keyboard finger tapping motor skill task. The task required subjects to press four numeric keys on a standard computer keyboard with the fingers of their non-dominant hand, repeating the five-element sequence, 4-1-3-2-4, as quickly and as accurately as possible, for a period of 30 seconds. The sequence was displayed at the top of the screen at all times to exclude any working memory component to the task. Subjects were trained and then re-tested after a 12 hour period containing normal sleep, and after a 12 hour period awake. They found a night of sleep resulted in a 20% increase in motor speed, without loss of accuracy, whilst an equivalent period of time awake provided no benefit. Sleep dependent improvement was independent of testing schedule (i.e.

whether they were tested after sleep or wake first) and did not generalise to similar sequences performed in a different order (Walker et al., 2002).

A study by Fischer et al. (2002) used a similar task and also found that improvements were distinctly greater and more consistent over retention periods of sleep than of wakefulness. The finger-to-thumb opposition task required the subject to tap (with their non-dominant hand) a finger-thumb sequence as rapidly and accurately as possible. They showed sleep after practice enhanced speed of sequence performance on average by 33.5% and reduced error rate by 30.1% as compared with corresponding intervals of wakefulness. The effect of sleep on learning proved to be stable when retesting was postponed for another night, and was independent of whether sleep occurred during the daytime or at night.

The current study aims to replicate findings that have shown a sleep dependent improvement on a finger tapping tasks in adults. A study of this kind will add to the existing literature, which although reasonably robust, represents a relatively small body of work. Further evidence that sleep is required for the consolidation of procedural learning will add weight to the existing literature. In addition, exploratory analyses assessing sleep dependent learning alongside IQ and subjective sleep quality may generate further interesting findings, perhaps providing a starting point for future research into sleep and its effects on learning.

Evidence for the involvement of sleep in declarative memory has to date been less convincing, with early studies offering mixed conclusions. Although sleep is known to sustain declarative memories more effectively than daytime wake, this effect has usually been attributed to the absence of destructive interference that weakens memories whilst awake, rather than to active processes driven by sleep (Stickgold, 2005). However, certain types of task have now been shown to shown to be sensitive to sleep. Benson & Fienberg (1977) showed that subjects who had a night of sleep after learning a verbal paired associates task, performed better the next day than participants who had been awake for an equal amount of time. Gais & Born (2004) also showed performance on a paired associates task improved after sleep when using related word pairs such as dog-bone, rather than unrelated word pairs such as dog-flower.

The emotional impact of declarative memories has been shown to be an important factor in determining level of consolidation. Hu et al. (2006) have recently demonstrated that memories with higher emotional impact lead to a greater overnight enhancement of memory accuracy than neutral memories. Subjects completed an initial study session involving arousing and neutral pictures, either in the evening or in the morning. Twelve hours later, after sleeping or staying awake, subjects performed a recognition test requiring them to discriminate between these original pictures and novel pictures by responding "remember," "know" (familiar), or "new". Selective sleep effects were observed for consolidation of emotional memory, recognition accuracy for *know* judgments of arousing stimuli improved by 42% after sleep relative to wake, and recognition bias for *remember* judgments of these stimuli increased by 58% after sleep relative to wake (resulting in more conservative responding). These findings suggest that the facilitation of memory for emotionally salient information may preferentially develop during sleep. The combined evidence seems to suggest that the role of sleep in declarative memory is not absolute, and depends on more subtle aspects of the task.

The current study, in addition to the assessment of procedural sleep dependent consolidation, will also attempt to assess the role of sleep on declarative memory. As discussed, the evidence for the involvement of sleep in the declarative domain is less conclusive that that in the procedural domain. In general it seems that declarative sleep dependent consolidation is reliant on subtle aspects of the task, and may occur optimally when emotionally salient information is included. Although word pairs have traditionally been used in tests of declarative memory dependence on sleep, this method has certain limitations. Although recall memory can easily be assessed using word pairs, it is more difficult to assess recognition memory, and assessments of recognition may be open to bias as they rely on honest responses from participants. In addition, it may be difficult to convey emotionally salient information using a single word, or pair of words. As such, the current study will assess short story recall and recognition rather than word pairs. The use of stories allows for an easy and reliable assessment of recognition as well as recall (via the use of a series of forced choice questions relating to the story). The use of stories also allows a more precise assessment of memory, as scores can be generated for rote recall as well as a more general thematic recall (unlike word pairs, where responses

can only be coded as correct or incorrect). Stories are also inherently more emotionally salient than word pairs, as they convey meaning and provide narrative within a recognisable context.

Although the current literature describes a number of studies investigating sleep dependent consolidation in adults, there is no research investigating sleep dependent learning in children. Whilst the development of learning through childhood has received a great deal of research attention, the relationship between sleep and learning in children is unknown. Sleep undergoes significant changes across the life span, with the greatest change taking place during childhood. Sleep in early childhood generally progresses towards differentiation and organization of conventionally defined sleep states, shorter total sleep time, less SWS and longer sleep cycles (Stores, 2001[a]). Growth and development through middle childhood are associated with changes in sleep, as sleep patterns alter to resemble that of older people. However, total sleep time in middle childhood is still approximately 2.5 hours longer than adults although sleep architecture appears to be stable. To date, there is no single definitive explanation as to why sleep undergoes such significant changes during childhood. The development of learning and memory in children has been researched extensively over the years. The development of learning in children obviously has great importance in term of education and general intellectual development, consequences that have led to a great deal of research in this area. The relatively new discovery that sleep promotes consolidation of memory in adults has obvious implications in children, despite this sleep dependent consolidation has not been investigated in any group other than healthy adults. The current study will attempt to investigate sleep dependent procedural and declarative consolidation in children, using similar methods to the research in adults, but making attempts to adapt tasks for children where necessary. It is hoped this study will demonstrate appropriate methods that can be used to assess procedural and declarative learning in children, but will also allow an assessment of sleep dependent learning in this group.

This chapter comprises four distinct research studies. The first and second studies assess sleep dependent procedural and declarative consolidation (respectively) in adults, the third and fourth studies assess sleep dependent procedural and declarative consolidation (respectively) in children. There is some degree of overlap between

the four studies, with similar methodologies, some overlap between participants etc. However each study is described separately, with an explanation of similarities between studies where appropriate. Separate discussions relate to the research in adults, and the research in children, no comparisons are made between the groups.

Sleep and Procedural Skill Learning in Adults

2.1.2 Aims and Hypotheses

Aims

The aim of this study is to replicate previous findings that have demonstrated that sleep is vital for the consolidation of procedural skill learning in adults (e.g. Walker et al., 2002; Stickgold et al., 2000). The study aims to investigate the specific effect that a period of sleep has on the performance of a previously learned finger thumb opposition task, and to compare this effect with that of a similar period of wake.

Hypothesis

The hypothesis is that a night of sleep leads to performance improvements on a procedural skill finger tapping learning task, improvements which are independent of any intervening training and which are not matched by similar periods of wake.

2.1.3 Methods

2.1.3.1 Consent

Before the experiment each of the adult participants gave written informed consent. Prior to the study participants were informed the study was investigating the effects of sleep on learning. Upon completion of the experimental tasks, participants were fully de-briefed as to the nature of the study and were invited to ask any further questions. The study was approved by the Department of Psychology Ethics Sub-Committee.

2.1.3.2 Participants

Participants consisted of twenty adults between the ages of 18 and 33 years (mean age = 22.50 years, SD = 4.33, 4 male and 16 female). Participants were staff and students recruited (via advertisements) from the University of Sheffield Psychology Department. Participants were offered a £10 incentive for participation. None of the

adults had any reported learning difficulties or special educational needs, and none had any reported sleep disorder or other medical disorder affecting sleep.

2.1.3.3 Apparatus

IQ and sleep measures

All participants completed the Matrix Reasoning sub-test of the Wechsler Abbreviated Scale of Intelligence (WASI) in order to provide an estimate of general intellectual ability (IQ). Matrix reasoning performance reflects an individual's ability to mentally manipulate abstract symbols and to perceive the relationships among them. It is regarded as a measure of non-verbal fluid reasoning and thus general intellectual ability (Wechsler, 1997). Participants also completed the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI provides a self-rated index of sleep quality and disturbance in adults over a one-month time interval. It has been shown to be a reliable and valid measure and has a high specificity for distinguishing 'good' and 'poor' sleepers (Buysse et al., 1989). It provides an estimate of mean sleep time per night, and provides scores for the following sleep factors: sleep latency, sleep disturbances, habitual sleep efficiency, subjective sleep quality, sleep medication, and daytime dysfunction. Higher scores on sleep factors indicate more problems, or a 'worse' sleeper. More detailed information on the PSQI can be found in chapter 4. Participants also completed a measure of sleep quality for the night they were involved in the study. Participants were asked to indicate on a scale how well they had slept the previous night. The scale ranged from 1 (*worse than usual*) to 5 (*better than usual*), this measure was termed 'sleep quality (study night)'. Any participants who reported that they did not sleep on the study night were excluded.

Procedural skill task

Participants wore a fabric glove specially adapted to record finger-thumb oppositions. The glove was fitted with copper pads on each of the fingers and the thumb, these were wired into a laptop computer's USB input via a Personal Measurement Device (PMD). Specially designed software on the laptop recorded oppositions between fingers and thumb, the software was programmed to record trials lasting thirty seconds, after the recording period of thirty seconds the software automatically saved the data file. Analysis programmes designed in Microsoft

Excel allowed conversion of the raw data file and produced scores for number of correct sequences performed in a thirty second block, and time (in milliseconds) per sequence i.e. the average time taken to perform a sequence within a thirty second block. Several gloves of different sizes were made in order to cover a range of hand sizes. The glove was designed to record finger-thumb oppositions in a similar way to that described in the task developed by Korman et al. (2003).

2.1.3.4 Design

As the study was designed to assess the differential effect of sleep and wake on consolidation, subjects participated in both a sleep and a wake condition. Participants were tested on three occasions spanning a day awake and a night asleep (fig. 2.1.3). Testing sessions were either a consecutive morning-evening-morning (termed wake-first), or a consecutive evening-morning-evening (termed sleep-first). In order to counteract any effects caused by testing order, participants were counterbalanced randomly across the two conditions (sleep-first condition = 9; wake-first condition = 11). Thus, wake-first participants attended their first session at either 8.00 or 8.30a.m (day 1), their second session at either 6.00 or 6.30p.m (day 1), and their third session at either 8.00 or 8.30a.m (day 2). Sleep-first participants attended their first session at either 6.00 or 6.30p.m (day 1), their second session at either 8.00 or 8.30a.m (day 2), and their third session at either 6.00 or 6.30p.m (day 2). Although an ideal design would have separated all sessions by exactly 12 hours, this was not possible due to practical constraints.

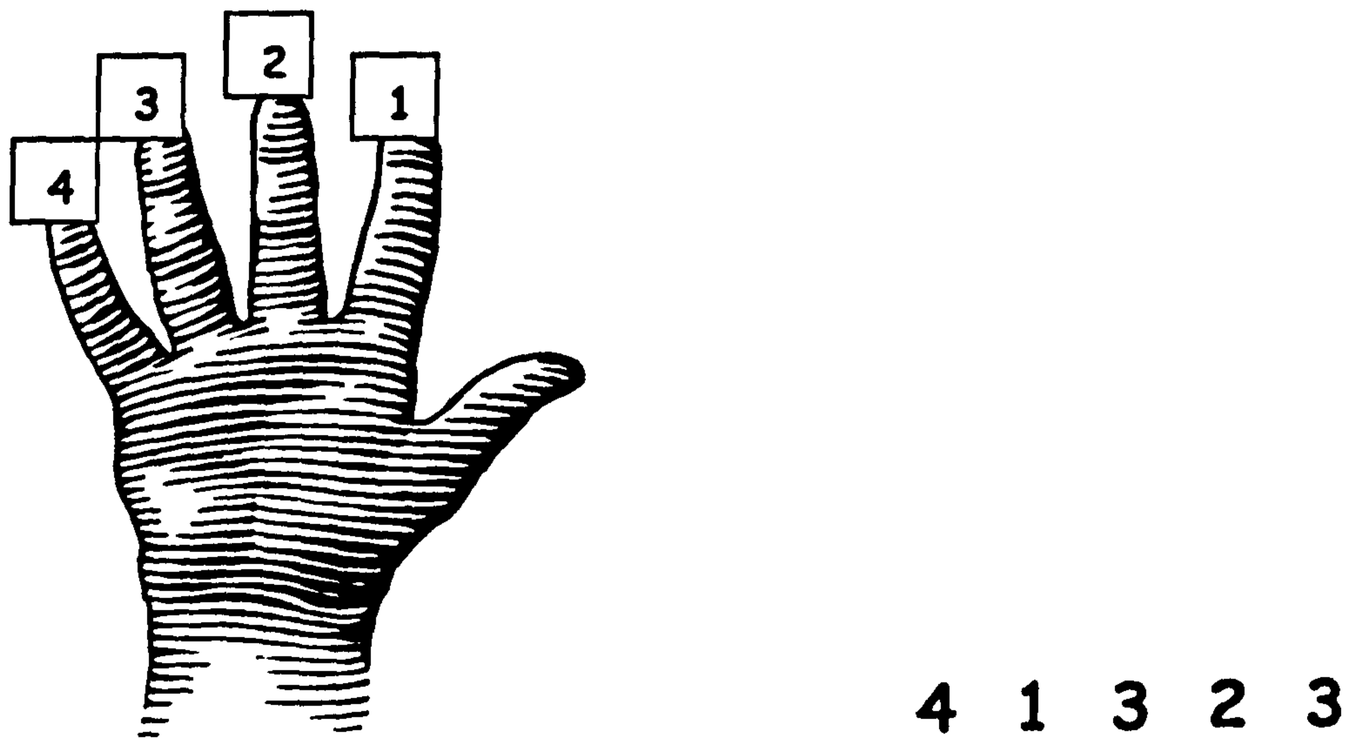
2.1.3.5 Procedure

All participants were tested in an office within the Psychology department, the office was in a quiet outbuilding and blinds were drawn to minimise external distraction. At the time of the first session, written consent was taken from all participants, and participants completed the matrix reasoning subtest of the WASI as per the standardised instructions provided. Participants were also given the PSQI to take away and complete in their own time. At the post-sleep session (either session 2 or 3 depending on counterbalancing) participants were asked to complete the 'sleep quality study night' measure, in order to assess sleep quality on that particular night. All participants were tested either by the author or by a similarly aged female clinical psychologist in training. In an attempt to standardise the administration of measures

between experimenters, written instructions were generated and piloted for each task or measure, and formed a standardised protocol for testing sessions.

Once participants had completed the questionnaire and IQ measures, they were seated comfortably and instructed to wear the motor glove on their non-dominant hand. Participants were instructed to oppose the fingers of their hand to their thumb, in a specific sequence. The sequence was composed of five component movements, and participants were required to repeat the sequence as many times as possible, with no visual feedback and as accurately as possible, for a period of 30 seconds. Training began with the presentation of a crib sheet with a 5 digit numerical sequence (fig. 2.1.1). Each digit of the sequence represented a finger, with fingers numbered upwards from the index finger. Participants were instructed to touch the tip of their thumb onto the appropriate finger in the given order, all participants were trained on the same five digit sequence 4-1-3-2-3. In order to exclude any working memory component, the crib sheet with the sequence was displayed at all times during training and subsequent testing. The procedure was based on the model developed by Korman et al. (2003).

Fig. 2.1.1: Example of crib sheet for sequence 4-1-3-2-3

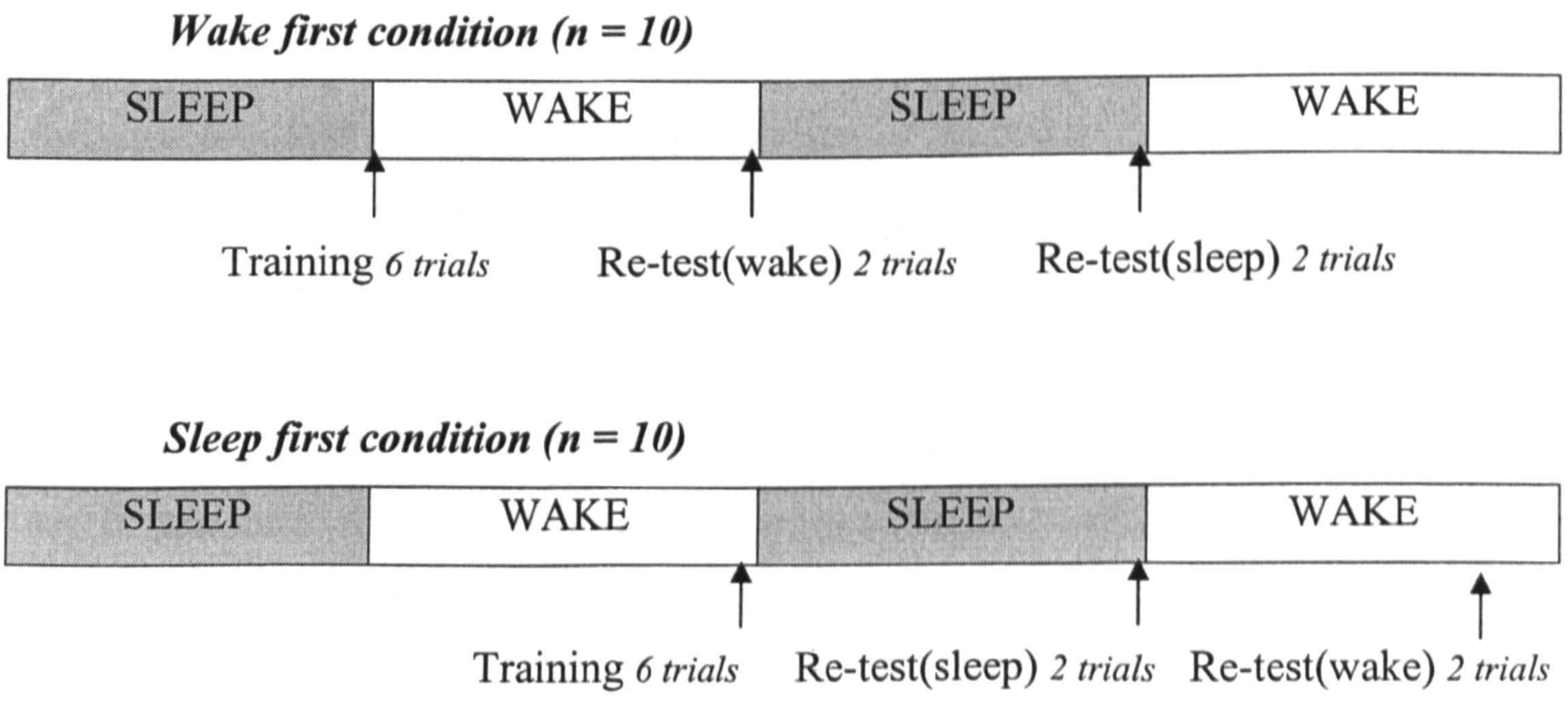


During training, participants performed six trials each lasting 30 seconds, with a 30 second rest period between each of the trials. Participants were instructed to complete the sequence as many times and as accurately as possible during each trial. The score from the first trial of the training session constituted the baseline measure, with the mean of the last two trials of the training session constituting the post-

training measure. At each re-test, participants performed two trials of 30 seconds each, separated by a 30 second rest period. Participants were re-tested on two occasions, once after a period of sleep and once after a period of wake. At each of the two re-test sessions, the mean average of performance on the two trials was calculated, this provided two final outcome measures: re-test(sleep) and re-test(wake) (fig. 2.1.2).

In addition to performing the procedural task, the majority of subjects also participated in three other cognitive tasks. The first was a declarative memory task, described in detail in section 2.1.6. The second task was a computerised visual discrimination task based loosely on the model developed by Stickgold in 2000, the third was a computerised motor pursuit task. The second and third tasks were developed by a colleague (clinical psychologist in training) and formed a part of her research thesis, they were developed in order to assess the effects of sleep on visual discrimination task performance, and motor pursuit task performance. In order to minimise effects of participant fatigue, subjects were encouraged to take breaks when needed between tasks. All participants also completed the set of four tasks in the same order in an attempt to control for interference effects. It is acknowledged that this experimental design, while practically necessary, offers limitations in terms of task competition and potential interference.

Fig. 2.1.2: Training and re-test schedule showing counterbalancing across sleep first and wake first conditions.



2.1.3.6 Variables and analyses

Each participant generated a baseline score, a post-training score, a re-test(sleep) score, and a re-test(wake) score. The initial 6 trial training period generated the baseline score (trial 1), and the post-training score (mean of trials 5 & 6). Each participant was re-tested after both sleep and wake, therefore generating scores for before and after a period of sleep, and before and after a period of wake. In order to generate a measure of change in performance observed after a period of sleep vs. change in performance observed after a period of wake, scores termed Δsleep and Δwake were calculated. Δsleep corresponds to the change in scores over the period of sleep, and Δwake the change in scores over the period of wake (this was either the difference between post-training and the first re-test, or the difference between the two re-test measures, depending on counterbalancing). This generated four final outcome measures for each participant: baseline, post-training, Δsleep, and Δwake. Each of the four outcome measures could be defined in terms of; number of correct sequences (number of correct sequences performed in thirty seconds), and time per sequence (mean time in seconds per sequence i.e. time between first correct finger press and final correct finger press within a sequence). For the variables Δsleep and Δwake, absolute values are quoted in order to ease analysis and interpretation of data. As such, Δsleep > Δwake indicates that greater performance improvements have been seen over sleep than over wake (as defined by both number of sequences and time per sequence).

Outcome variables were tested for normality, those displaying substantial skew were subject to a log transformation. All measures of time (baseline time, post-training time, Δsleep time, Δwake time) displayed positive skew and were log transformed. As some time variables measured a change in time, occasional scores were negative. In order to create a set of positive scores, a 0.5 constant was added to all values prior to log transformation. The log transformed time variables were found to show satisfactory normality and were used in all subsequent analyses, however actual time scores (absolute values) are reported in figures and tables. All other measures were found to show satisfactory normality.

Initial statistical analyses were performed using repeated measure *t*-tests to assess whether performance on the task improved from baseline to post-training. Repeated measure *t*-tests were then used to assess whether performance improved after a period of sleep, and also after a period of wake. Finally repeated measures *t*-tests were used to assess whether performance improvements observed after a period of sleep were significantly different from those observed after a period of wake. In exploratory analyses, correlations between questionnaire defined sleep variables, matrix reasoning, and changes on the various measures over sleep and wake, were examined using Pearson's coefficients.

2.1.4 Results

2.1.4.1 Improvement over initial training session.

In order to confirm that initial training had led to significant performance improvements, repeated measures *t*-tests were performed to assess changes in number of correct sequences and time per sequence, from baseline to post-training. The number of correct sequences was significantly greater at post-training (mean = 16.08, SD = 4.38) than it was at baseline (mean = 12.30, SD = 4.57), $t = -3.97$, df = 19, $p < 0.005$. Sequences were also performed significantly faster at post-training (mean time = 1.37, SD = 0.30) than they were at baseline (mean time = 1.96, SD = 0.55), $t = 7.17$, df = 19, $p < 0.001$ (table 2.1.3).

	Baseline	Post-Training
Mean number of correct sequences	12.30 (4.57)	16.08 (4.38)
Mean time per sequence (secs)	1.96 (0.55)	1.37 (0.30)

Table 2.1.3: Changes in scores from baseline to post-training (means and standard deviations).

2.1.4.2 Performance gains after sleep and wake

After showing that significant performance gains could be observed as a consequence of training, further analyses were undertaken to assess whether performance gains could be observed, independent of intervening practice, after a period spanning sleep or wake. A Bonferroni correction for multiple *t*-tests was applied (i.e. significance threshold set at $p < 0.01$). A repeated measures *t*-test

comparing pre-sleep with post-sleep number of correct sequences was significant t = -4.94, df = 19, $p < 0.001$, with significantly more correct sequences being performed after sleep than before sleep (pre-sleep correct sequences = 16.60, SD = 4.23; post-sleep correct sequences = 19.33, SD = 4.37). However, a t-test comparing pre-wake with post-wake number of correct sequences was not significant t = -0.372, df = 19, p = 0.714 (pre-wake correct sequences = 17.62, SD = 4.49; post-wake correct sequences = 17.95, SD = 4.75).

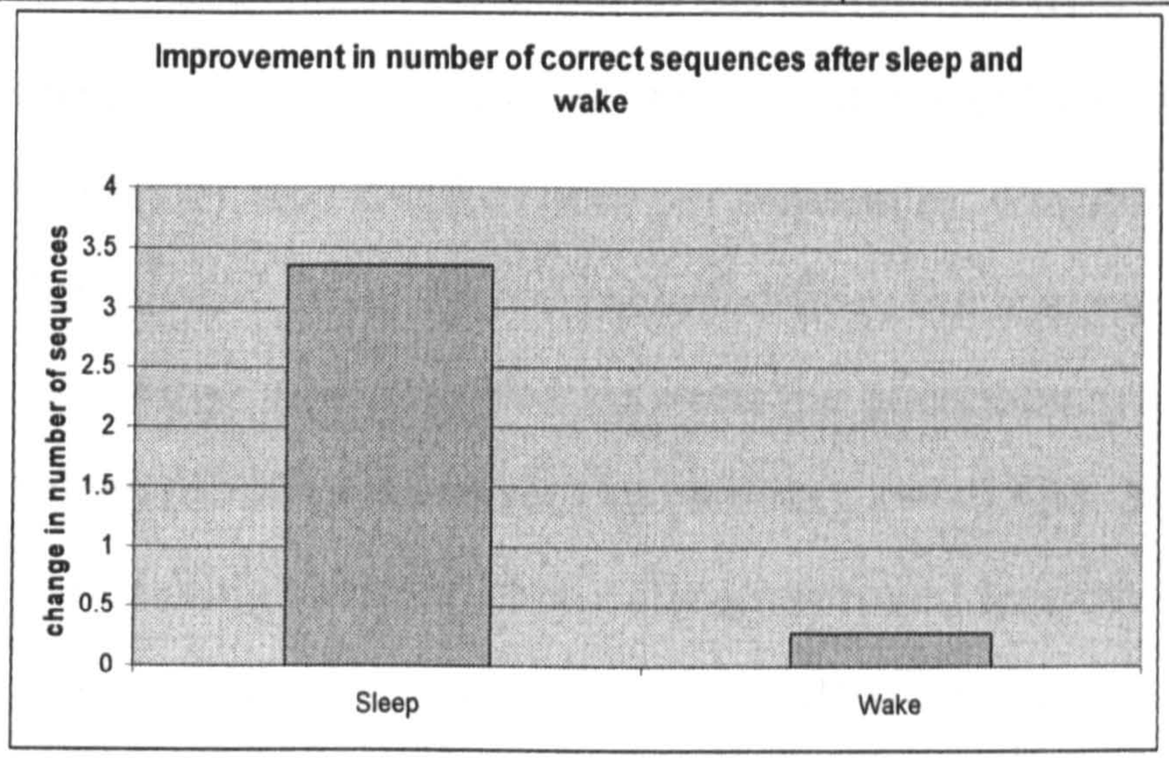
In order to assess performance gains in time taken to perform a sequence, further repeated measures t-tests compared pre-sleep time with post sleep time, and pre-wake time with post-wake time. There was a significant difference between pre-sleep and post-sleep time per sequence t = 5.37, df = 19, $p < 0.001$, with time per sequence showing a significant decrease after sleep (pre-sleep time (secs) = 1.34, SD = 0.35; post sleep time (secs) = 1.19, SD = 0.24). However, there was no significant difference between pre-wake and post-wake time per sequence t = 1.00, df = 19, p = 0.330 (pre-wake time (secs) = 1.31, SD = 0.32; post-wake time (secs) = 1.29, SD = 0.38).

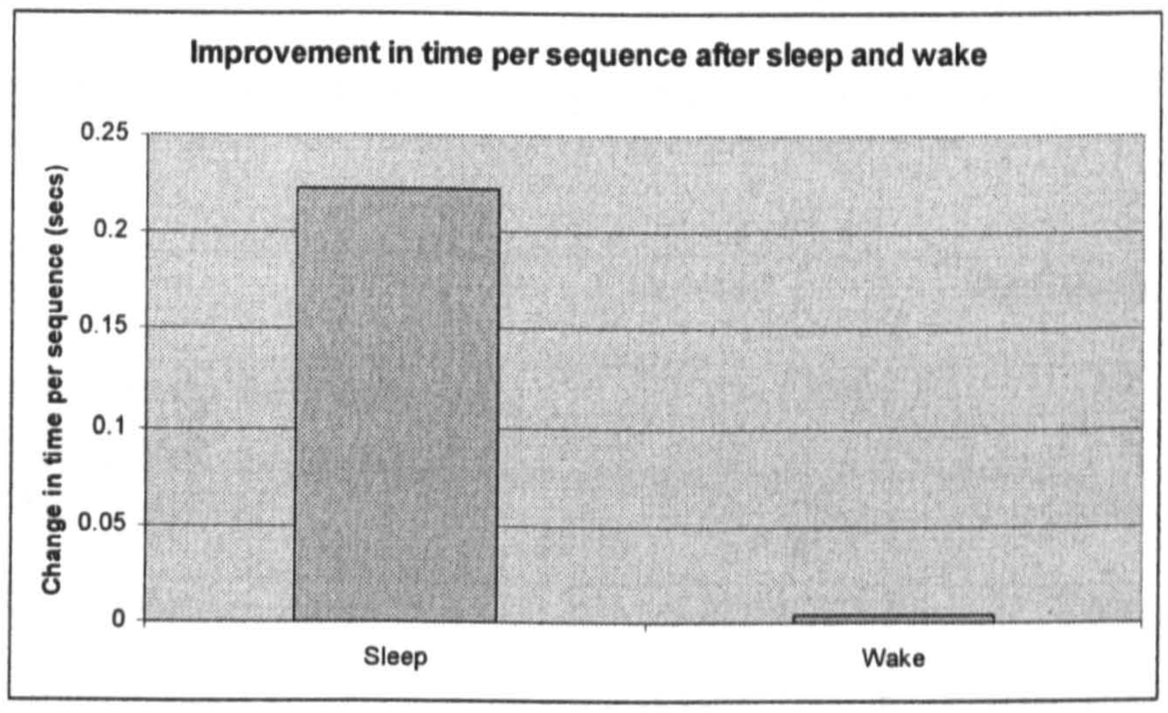
2.1.4.3 Differential improvements on procedural task after sleep and wake

Further analyses were conducted to assess the differential effects of sleep and wake on performance changes. A repeated measures t-test compared change in number of sequences after sleep with change in number of sequences after wake, and change in time per sequence after sleep with change in time per sequence after wake. There was a significant difference between change in number of sequences after sleep, and change in number of sequences after wake t = 3.15, df = 19, $p < 0.005$, with a greater improvement seen after sleep than seen after wake (mean improvement after sleep = 3.35, SD = 2.61; mean improvement after wake = 0.28, SD = 3.24). There was also a significant difference between the change in time per sequence after sleep, change in time per sequence after wake t = 2.76, df = 19, $p < 0.05$, with a greater improvement seen after sleep than seen after wake (mean improvement after sleep = 0.222, SD = 0.35; mean improvement after wake = 0.004, SD = 0.14) (table 2.1.4).

Table 2.1.4: Changes in scores over periods containing sleep and wake (absolute means and standard deviations).

	ΔSleep	**ΔWake**
Mean number of correct sequences	3.35 (2.61)	0.28 (3.24)
Mean time per sequence (secs)	0.222 (0.35)	0.004 (0.14)





2.1.4.4 Correlations between dependent variables and sleep measures

In order to investigate possible effects of sleep disturbances on overnight performance improvements, correlations between the dependent variables (correct number of sequences and time per sequence) and questionnaire defined sleep variables were assessed using Pearson's correlation coefficients

Sleep variables included in the correlation matrix consisted of the following variables derived from the Pittsburgh Sleep Quality Inventory (PSQI); mean sleep time per night, sleep latency, sleep disturbances, habitual sleep efficiency, subjective sleep quality, sleep medication, and daytime dysfunction. Table 2.1.5 shows means and standard deviations for all factors alongside norms generated from a group of

2968 healthy adult controls (mean age = 27.12, SD = 10.49, 35.3% male). A full breakdown of information for this control sample can be found in chapter 4. There were no significant differences between participants and controls on any questionnaire variables. The variable sleep quality (study night), was used alongside questionnaire variables, the mean score for sleep quality (study night) = 3.08 (SD = 0.90). Dependent variables in the correlation matrix consisted of; Δsleep (number of correct sequences), Δwake (number of correct sequences), Δsleep (time per sequence), and Δwake (time per sequence). Participants who did not complete a sleep questionnaire were excluded from the analyses. A significant negative correlation was observed between the questionnaire variable sleep medication and Δsleep (number of correct sequences), $r = -0.634$, $N = 14$, $p < 0.05$, indicating that those taking sleeping medication improved less overnight (as defined by number of sequences performed). There were no other significant correlations between any of the dependent variables and any sleep measures in adults. Table. 2.1.6 shows all correlations between dependent variables and questionnaire defined sleep variables.

	Controls	Participants
Mean sleep time per night (hrs)	7.11 (1.29)	7.68 (1.14)
Sleep Latency	2.22 (1.87)	2.60 (2.01)
Sleep Disturbances	6.27 (3.75)	5.64 (4.41)
Habitual Sleep Efficiency	84.99% (11.62)	88.84% (8.13)
Subjective Sleep Quality	1.39 (2.37)	0.90 (0.85)
Sleep Medication	0.20 (1.05)	0.21 (0.58)
Daytime Dysfunction	2.24 (3.27)	1.55 (1.28)

Table 2.1.5: Comparison of PSQI variables in participants and 2968 healthy controls (means and standard deviations). Full details of control group found in chapter 4.

	Δsleep (no. of correct sequences)	Δwake (no. of correct sequences)	Δsleep (time per sequence)	Δwake (time per sequence)
Mean sleep time per night	0.07	-0.09	0.06	-0.14
Sleep latency	-0.07	0.15	-0.20	0.11
Sleep Disturbances	-0.47	0.31	0.06	0.32
Habitual Sleep Efficiency	-0.03	-0.40	0.01	-0.05
Subjective Sleep Quality	-0.21	0.21	-0.08	0.20
Sleep Medication	*-0.63	0.32	-0.13	0.37
Daytime Dysfunction	-0.43	0.16	0.07	0.20
Sleep Quality (study night)	-0.02	-0.31	-0.26	0.07

*Table 2.1.6: Matrix showing correlations between dependent variables and questionnaire defined sleep variables. *$p < 0.05$.*

2.1.4.5 Correlations between dependent variables and matrix reasoning

In order to determine whether IQ is related to overnight performance improvements, correlations were assessed between matrix reasoning (Wechsler, 1997) and the various dependent variables using Pearson's correlation coefficients. The matrix reasoning subtest provides a T score for each participant, standardization sample distribution of T scores has a mean of 50 and standard deviation of 10. One participant was excluded from matrix reasoning analyses as they did not complete the measure. The remaining nineteen participants had a mean score of 54.7 (SD = 8.6), the range was 37.0 – 66.0. Variables included in the correlation matrix were; matrix reasoning score, Δsleep/Δwake (number of correct sequences), and Δsleep/Δwake (time per sequence). There were no significant correlations between any of the dependent variables and matrix reasoning scores (table 2.1.7).

	Δsleep (no. of correct sequences)	Δwake (no. of correct sequences)	Δsleep (time per sequence)	Δwake (time per sequence)
Matrix IQ	0.290	-0.126	-0.076	0.190

Table 2.1.7: Correlations between matrix reasoning scores and dependent variables.

2.1.5 Aims and Hypotheses

Aims

The aim of the study is to investigate the differential effect of periods of sleep and wake on retention of declarative memory in healthy adults. Specifically, to assess whether periods of sleep result in better retention (expressed as reduced decay) of declarative material than do similar periods of wake.

Hypothesis

The hypothesis is that after a period containing sleep, decay of declarative material (as measured by recall and recognition), will be significantly less than the decay observed after a similar period containing wake.

2.1.6 Methods

2.1.6.1 Consent

Consent was taken as for the previous study (section 2.1.3.1).

2.1.6.2 Participants

Participants consisted of twenty adults between the ages of 18 and 45 years (mean age = 22.55 years, SD = 6.11, five male and fifteen female). Participants were staff and students recruited (via advertisement) from the University of Sheffield Psychology Department. Participants were offered a £10 incentive for participation. None of the adults had any reported learning difficulties and none had any reported sleep disorder or other medical disorder affecting sleep.

2.1.6.3 Apparatus

IQ and Sleep measures

All participants completed the same IQ and sleep measures as adults described in the previous study (section 2.1.3.3).

Declarative Task

The declarative task comprised story telling and recall. Stories were taken from the stories sub-test of the Children's Memory Scale (CMS), a well-known and reliable

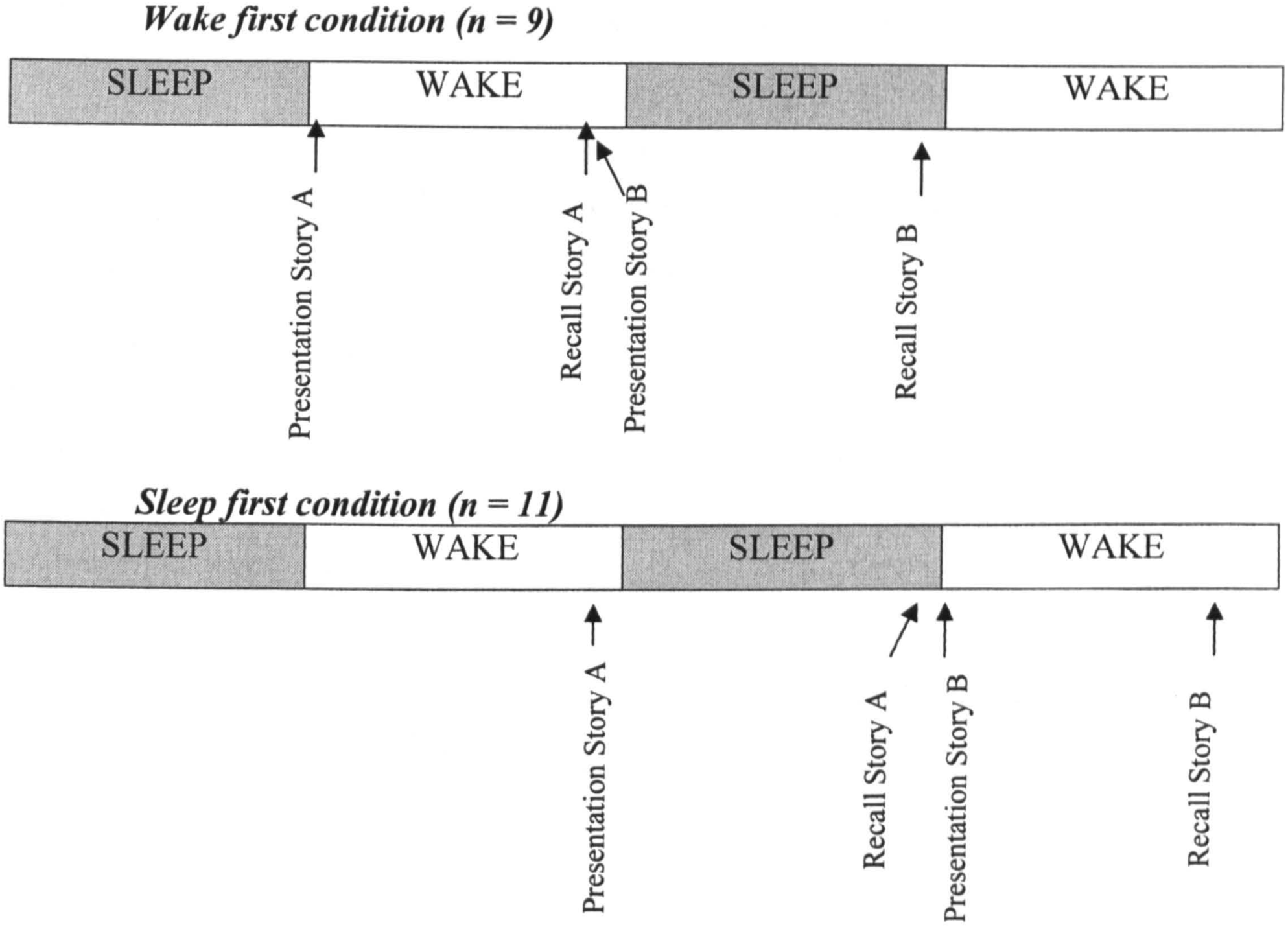
neuropsychological tool for assessing memory in children. The CMS provides six stories, two stories each for three age groups (5-8yrs, 9-11yrs and 12-16yrs). Participants were read stories for the 12-16yrs age group, previous piloting had shown the absence of a ceiling effect when using the 12-16yrs stories on adults, so it was assumed that this story would be appropriate for use with an adult sample. Stories were provided with standardised instructions and scoring, scoring generated three measures; rote recall, thematic recall, and recognition. Rote recall score provides a detailed measure of total recall based on remembering specific words and numbers from the story. Thematic recall score gives a more general measure of story recall and is defined by gist information and thematic units. Recognition score is the number of correctly answered questions, from fifteen yes/no forced choice questions about the story.

2.1.6.4 Design

As the study was designed to assess the differential effect of sleep and wake on consolidation, subjects participated in both a sleep and a wake condition.

Participants were tested on three occasions spanning a day awake and a night asleep (fig. 2.1.8). Testing sessions were either a consecutive morning-evening-morning (termed wake-first), or a consecutive evening-morning-evening (termed sleep-first). In order to counteract any effects caused by testing order, participants were counterbalanced randomly across the two conditions (sleep-first condition = 9; wake-first condition = 11). Thus, wake-first participants attended their first session at either 8.00 or 8.30a.m (day 1), their second session at either 6.00 or 6.30p.m (day 1), and their third session at either 8.00 or 8.30a.m (day 2). Sleep-first participants attended their first session at either 6.00 or 6.30p.m (day 1), their second session at either 8.00 or 8.30a.m (day 2), and their third session at either 6.00 or 6.30p.m (day 2) (fig. 2.1.8). Although an ideal design would have separated all sessions by exactly 12 hours, this was not possible due to practical constraints.

Fig. 2.1.8: Declarative task design and counterbalancing.



2.1.6.5 Procedure

Participants completed the WASI, the PSQI, and the 'sleep quality study night' measures as described in section 2.1.3.5, and within the same room in the Psychology Department. All participants were tested either by the author or by a similarly aged female clinical psychologist in training. In an attempt to standardise the administration of measures between experimenters, both experimenters adhered to the same set of standardised written instructions for each task or measure, which formed a standardised protocol for testing sessions. Both experimenters had also been involved in previous piloting work, intended to homogenise aspects of story delivery such as tone, pitch, and pace (story delivery typically took 40 -50 seconds).

Once participants had completed the questionnaire and IQ measures they were seated comfortably and were read one of the two CMS stories (from the12-16 yrs age group). Participants were asked to give an immediate recall of the story, and then a delayed recall after 30 minutes (the 30 minute recall was included in order to ensure some encoding of the story into the long term memory). After the subsequent interval of approximately 12 hours containing sleep or wake, participants were again

asked to recall the story, and were then asked 15 yes/no forced choice recognition questions. The procedure was identical over both the sleep and wake conditions, with a different story used for each condition. The stories were randomly counterbalanced across both participants and conditions. Participants were instructed using the standardised instructions for the stories as given in the CMS. Scores were recorded on a standardised form, giving scores for rote recall, thematic recall, and recognition.

In addition to participating in the declarative task, the majority of subjects also participated in three other cognitive tasks. The first was a procedural memory task, described in detail in section 2.1.3. The second task was a computerised visual discrimination task based loosely on the model developed by Stickgold in 2000, the third was a computerised motor pursuit task. Typically these three tasks were completed between the initial reading of the story, and the 30 minute delayed recall. In order to minimise effects of participant fatigue, subjects were encouraged to take breaks when needed between tasks. All participants also completed the set of four tasks in the same order in an attempt to control for interference effects. It is acknowledged that this experimental design, while practically necessary, offers limitations in terms of task competition and potential interference.

2.1.6.6 Variables and Analyses

Each participant generated scores for both a sleep and a wake condition. Scores consisted of immediate rote recall, immediate thematic recall, 30 minute rote recall, 30 minute thematic recall, post sleep/wake rote recall, post sleep/wake thematic recall, and post sleep/wake recognition. Rote and thematic recall scores for each condition were generated by subtracting the post sleep/wake score from the 30 minute score. This provided a measure of rote recall change and thematic recall change in each condition (Δsleep and Δwake respectively), a higher score indicating a greater degree of decay, or worse retention of the material. Recognition scores were simply composed of the post-sleep and post-wake recognition scores marked out of 15, a higher score indicating better recognition. This generated the following six final outcome measures for each participant; Δsleep (rote), Δwake (rote), Δsleep (thematic), Δwake (thematic), recognition after sleep, and recognition after wake.

Variables were tested for normality and found to be acceptable so no transformations were required. Repeated measures *t*-tests were used to assess whether memory recall was significantly different before and after a period containing sleep, and additionally before and after a period containing wake. Further statistical analyses were performed using repeated measures *t*-tests to assess whether recall changes after sleep were significantly different from recall changes after wake. A final repeated measures *t*-test compared recognition after a period of sleep with recognition after a similar period of wake. In exploratory analyses, questionnaire defined sleep variables and IQ were correlated with changes in recall and recognition using Pearson's correlation coefficients.

2.1.7 Results

2.1.7.1 Differences in recall after sleep and wake

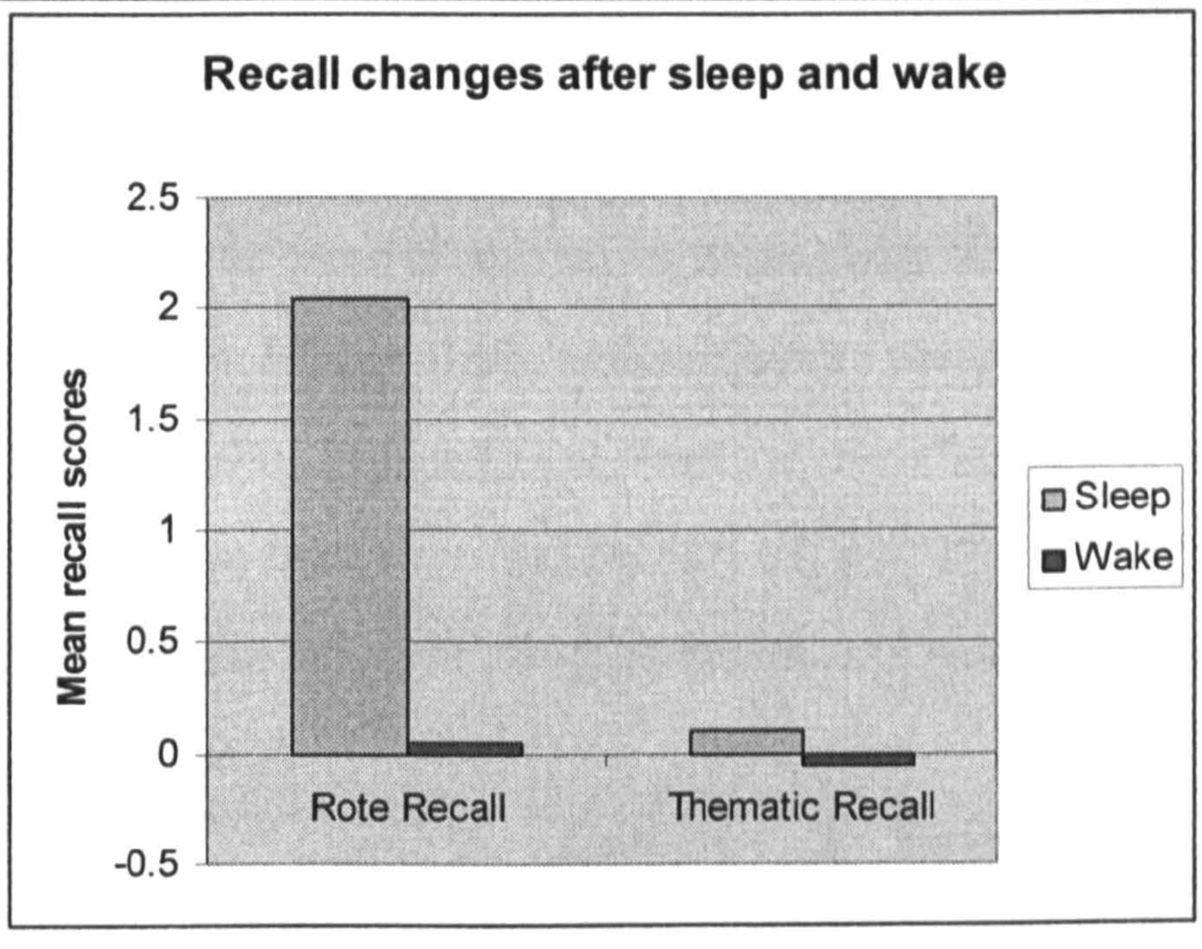
Repeated measures *t*-tests were performed to assess whether recall decreased significantly after a period of approximately twelve hours, spanning either sleep or wake. A Bonferroni correction for multiple *t*-tests was applied (i.e. a significance threshold set at $p < 0.01$). There was no significant difference observed between rote recall before sleep and rote recall after sleep $t = 2.72$, $df = 19$, $p = 0.014$, neither was there a significant difference between rote recall before and after wake $t = 0.21$, $df = 19$, $p = 0.838$. There was no significant difference between thematic recall before and after sleep $t = 0.809$, $df = 19$, $p = 0.428$, or thematic recall before and after wake $t = -0.438$, $df = 19$, $p = 0.666$.

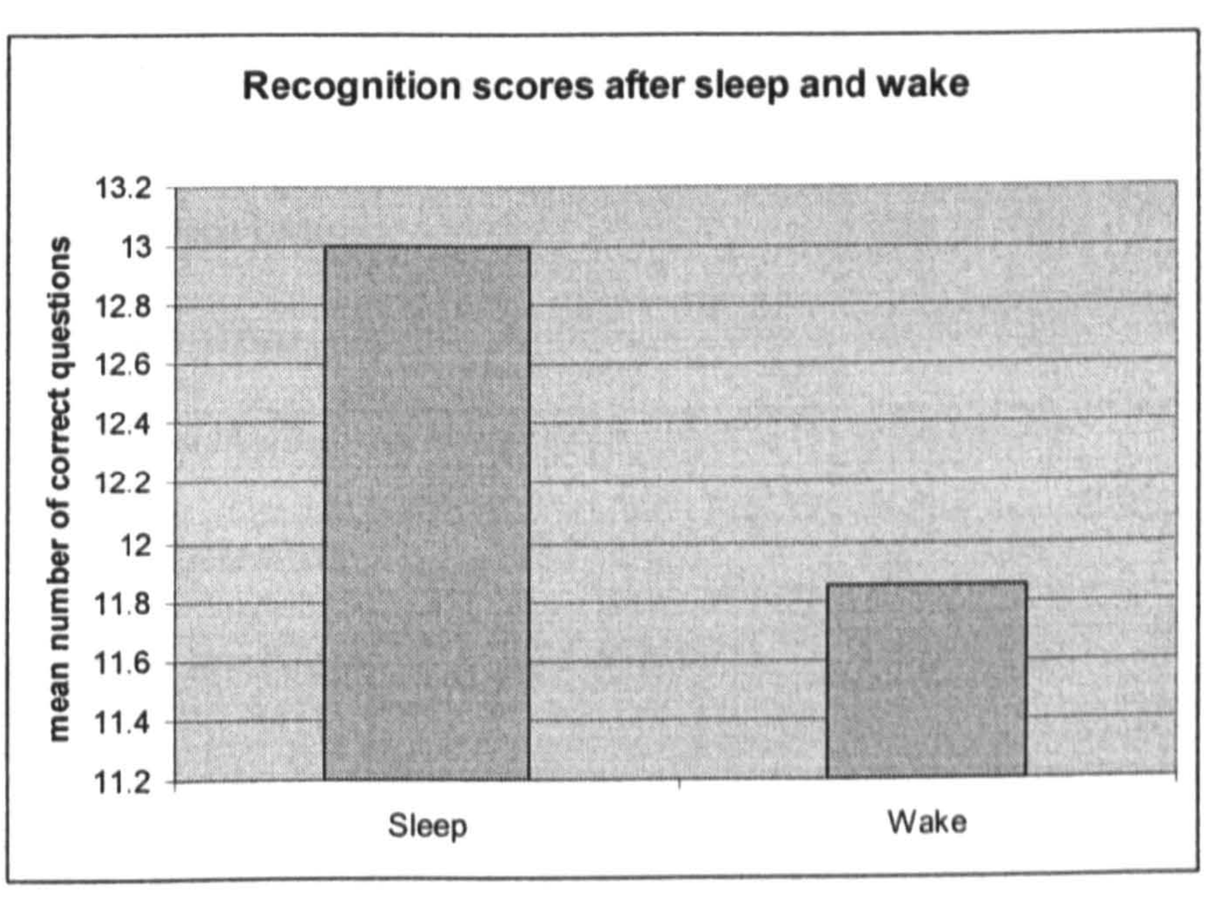
2.1.7.2 Comparison of declarative memory after sleep and wake

Further repeated measures *t*-tests were performed to compare performance changes over sleep with changes over wake. A Bonferroni correction was applied (i.e. a significance threshold set at $p < 0.02$). There was no significant difference between rote recall change after sleep and rote recall change after wake $t = 2.06$, $df = 19$, $p = 0.054$, neither was there a significant difference between thematic recall change after sleep and thematic recall change after wake $t = 1.000$, $df = 19$, $p = 0.330$. However, the number of recognition questions answered correctly after sleep was significantly greater than the number answered correctly after wake $t = 2.981$, $df = 19$, $p < 0.01$ (mean recognition after sleep = 13.00, mean recognition after wake = 11.85) (table 2.1.9).

*Table 2.1.9: Means and standard deviations of recall change and recognition scores over sleep and wake (means and standard deviations), *p < 0.01.*

	Sleep	Wake
Rote recall change	2.05 (3.14)	0.05 (3.24)
Thematic recall change	0.10 (0.55)	-0.05 (0.51)
Recognition	*13.0 (1.34)	*11.85 (2.11)





2.1.7.3 Correlations between dependent variables and sleep measures

In order to investigate possible effects of sleep problems on overnight changes in declarative memory, correlations between the recall/recognition variables and questionnaire defined sleep variables were assessed using Pearson's correlation coefficients. Sleep variables included in the correlation matrix consisted of the PSQI variables; mean sleep time per night, sleep latency, sleep disturbances, habitual sleep efficiency, subjective sleep quality, sleep medication, daytime dysfunction, and sleep

quality (study night). Table 2.2.0 shows means and standard deviations for all factors alongside norms generated from a group of 2968 healthy adult controls (mean age = 27.12, SD = 10.49, 35.3% male). A full breakdown of information on the control sample can be found in chapter 4. There were no significant differences between scores from the participant sample and scores from controls on any of the questionnaire variables. The variable sleep quality (study night), was used alongside questionnaire variables, the mean score for sleep quality (study night) = 3 (SD = 0.79). Recall and recognition variables are listed in table 2.2.1. Participants who did not return a questionnaire were excluded from the analyses. Significant positive correlations were observed between sleep disturbances and Δsleep (thematic) $r = 0.667$, $N = 13$, $p < 0.05$, and subjective sleep quality and Δwake (rote) $r = 0.485$, $N = 19$, $p < 0.05$. A significant negative correlation was observed between sleep latency and Δwake (rote) $r = -0.728$, $N = 19$, $p < 0.001$. There were no other significant correlations between sleep variables and recall/recognition measures (table 2.2.1).

	Controls	Participants
Mean sleep time per night (hrs)	7.11 (1.29)	7.92 (1.13)
Sleep Latency	2.22 (1.87)	2.20 (1.96)
Sleep Disturbances	6.27 (3.75)	1.85 (1.14)
Habitual Sleep Efficiency	84.99% (11.62)	90.79 (8.39)
Subjective Sleep Quality	1.39 (2.37)	1.00 (0.67)
Sleep Medication	0.20 (1.05)	0.11 (0.46)
Daytime Dysfunction	2.24 (3.27)	1.75 (1.64)

Table 2.2.0: Comparison of sleep questionnaire variables between participants and 2968 healthy controls (means and standard deviations). Information on control sample can be found in chapter 4.

	Δsleep (thematic)	Δwake (thematic)	Δsleep (rote)	Δwake (rote)	sleep recognition	wake recognition
Mean sleep time per night (hrs)	0.10	0.25	0.17	0.25	-0.24	-0.25
Sleep Latency	0.13	-0.01	0.08	**-0.73	-0.37	-0.07
Sleep Disturbances	*0.67	0.25	0.46	0.10	-0.32	-0.16
Habitual Sleep Efficiency	0.22	-0.32	0.06	-0.44	-0.32	-0.27
Subjective Sleep Quality	-0.31	0.28	-0.07	*0.49	0.38	0.21
Sleep Medication	-0.17	0.41	-0.33	0.24	-0.25	-0.47
Daytime Dysfunction	-0.19	0.19	-0.09	-0.30	-0.05	0.06
Sleep Quality (study night)	0.24	0.00	0.17	-0.12	0.50	0.38

*Table 2.2.1: Matrix showing correlations between dependent variables and questionnaire variables. **$p < 0.001$; *$p < 0.05$.*

2.1.7.4 Correlations between declarative memory and matrix reasoning

In order to determine whether IQ is related to overnight changes in declarative memory, correlations were assessed between matrix reasoning and the various dependent variables using Pearson's correlation coefficients. The matrix reasoning subtest provides a T score for each participant, standardization sample distribution of T scores has a mean of 50 and standard deviation of 10. All participants completed the matrix reasoning, the mean score was 54.95 (SD = 8.06), the range of scores was 37.0 – 65.0.

Correlations between matrix reasoning and the recall and recognition variables were assessed using Pearson's correlation coefficients. There was a significant negative correlation between matrix reasoning score and sleep recognition $r = -0.468$, $n = 20$, $p < 0.05$. There were no significant correlations between matrix reasoning and any of the other recall/recognition measures (table 2.2.2).

	Δsleep (thematic)	Δwake (thematic)	Δsleep (rote)	Δwake (rote)	sleep recognition	wake recognition
Matrix IQ Score	0.178	-0.154	0.242	-0.081	-0.468*	-0.412

*Table 2.2.2: Correlations between matrix reasoning IQ and dependent variables, *p < 0.05.*

2.1.8 Discussion

2.1.8.1 Sleep dependent motor skill improvement

Practice on the procedural task improved significantly with repeated performances over the initial training session, in addition participants also went on to demonstrate a subsequent time-delayed improvement, independent of any further intervening training. The extent of the subsequent improvement was specifically dependent on sleep, with participants showing a significantly greater improvement after a period of sleep, than after a similar period awake. This finding replicates earlier work by Walker et al. (2002) who showed that improvement on a similar motor skill task in adults was dependent on sleep, and who also coined the term *sleep dependent consolidation* to describe the specific improvement seen over sleep. Fischer et al. (2002) also reported similar findings, and the current study adds weight to the theory that sleep is important in the consolidation of procedural learning. Although participants in the current study showed a significantly greater improvement in the task after sleep than they did after wake, the relative difference between sleep and wake is not as great as that reported by Walker et al. in their 2002 study. The results reported in the current study may be less conclusive due to differences in methodologies (finger tapping vs keyboard sequence), or may be a result of differing sleep quality/quantity in the two studies. As the current study was unable to provide any information on sleep staging, we cannot conclusively confirm the sleep quality of participants. The only means of assessing sleep quality was via a subjective questionnaire, a method of assessment that does not allow the accurate measurement of sleep quality and quantity that is provided when using methods such as polysomnography. As such, the current study is limited by being unable to provide an objective assessment of sleep, such an assessment may have shown differences in

sleep dependent consolidation were related to sleep quality or quantity, and allowed for better comparisons with previous research.

2.1.8.2 Effects of sleep quality and IQ on overnight improvement on the task

Examination of sleep questionnaire responses indicates very little within group variability in questionnaire defined sleep problems. There were no significant differences between participant scores and score from a control group, indicating that the group as a whole were relatively good sleepers. No correlations were found between questionnaire defined sleep variables and dependent variables, this leads to one of two possibilities. The first possibility is that the quality of an adult's sleep does not have an effect on overnight improvement. The second possibility is that as our sample on the whole was composed of 'good sleepers', any effects of poor sleep on overnight improvement may have been missed. This possibility could be further explored by investigating overnight performance gains in poor sleepers, and comparing those who sleep well with a sample of participants diagnosed with a clinical sleep disorder. A further investigation of the effects of disturbed sleep on memory and cognitive function can be found in chapter 4.

Matrix reasoning scores were used as a general measure of IQ, analyses did not reveal any significant correlations between task improvement and IQ. The result implies that IQ is unrelated to sleep dependent consolidation, and IQ presumably develops independently of sleep based learning. Of course this study comprised a relatively small sample size, similar analyses in a larger sample of adults may generate different results and may warrant further investigation. In addition, the IQ measure used in the current study was a short-form assessment and did not generate a full scale IQ score. Assessments of correlations between full scale IQ and sleep dependent consolidation may be necessary to establish the true relationship between IQ and sleep dependent learning.

2.1.8.3 Declarative memory changes over sleep in adults

In order to investigate the relative effects of sleep and wake on declarative memory, *t*-tests were performed to allow a comparison of the change seen over sleep and wake in recall and recognition. These analyses revealed no significant differences between declarative rote or thematic recall change over sleep, and declarative rote or thematic

recall change over wake. The indication from this finding is that periods of sleep are no more beneficial for the recall of declarative material, than are periods of wake. However, analyses revealed that recognition of declarative material was significantly better after a period of sleep than after a period of wake. This result shows that adults were better at recognising story material after a period of sleep than after a period of wake, indicating that the sleep state has some positive influence over declarative memory retention, when assessed using recognition measures.

Robust research findings (e.g. Walker et al., 2002; Stickgold et al., 2000; Fischer et al., 2002) have confirmed that sleep dependent improvement occurs in the procedural domain, however evidence for the involvement of sleep in declarative memory has until now been less conclusive. Although studies using word-pair methods (e.g. Gais & Born, 2004) have shown sleep can sometimes prevent decay of declarative memory, short stories have never been used in the assessment of sleep dependent declarative memory consolidation. In the current study, the use of stories allowed us to generate a reliable measure for recognition, and also provided two measures of recall (rote and thematic), as opposed to the single measure of recall that is provided by word-pair methodologies. One of the most recent studies investigating the relationship between declarative memory and sleep found that the emotional nature of material was an important factor in predicting the amount of material retained (Hu et al., 2006). The current study employed a story telling paradigm, an obvious advantage of stories is their ability to convey meaning, provide narrative, and generate greater emotional salience than word pairs. Although the stories were not specifically selected with emotional content in mind, it is interesting to speculate that the use of a story may have inadvertently led to greater retention of material than might a standard word pair paradigm.

The current study provides evidence that sleep leads to a greater recognition of story material than wake. The most obvious explanation for this result is that sleep prevents the interference mechanisms that are often attributed to the destruction of memory traces and which are present throughout a normal period of wake. The decay or forgetting of memory over time is generally thought to be attributed to both interference and temporal decay, as the present study had an approximately equal temporal interval in both sleep and wake conditions, it is proposed that interference

is the main contributing factor to the increased decay seen after wake. Interference mechanisms at work during a period of wake may include competition, blocking, unlearning, response suppression, and storage load (Wickelgren, 1977). The present study may be particularly susceptible to the interference effects of competition, due to participants being tested on two stories. Although efforts were made to reduce effects of competitive interference (counterbalancing, using stories with different thematic material), a certain amount of interference would still be expected. The consequence of this interference whilst awake, is that sleep allows a greater relative opportunity for the stabilisation of memory traces required for the successful encoding of a memory, in essence the role of sleep is a passive one, simply facilitating memory storage by reducing interference. Previous studies have also attributed the beneficial effects of sleep to this absence of destructive interference whilst asleep (Stickgold, 2005).

However, we must also consider that although the sleep state effectively prevents interference, during a period of sleep we are also prevented from the conscious rehearsal of material learnt during the day. During periods of wake, the trace maintenance process provided by conscious rehearsal can lead to memory enhancements. Rehearsal is known to be particularly effective when items being remembered are relatively discrete, for example words or other verbal material such as that used in the current study. Participants in the current study were aware that after initial acquisition, they would be re-tested after approximately 12 hours and may have rehearsed the material in the intervening period, provided this was a period of wake.

The presumed trade-off between the negative effects of interference over wake, and the positive effects of rehearsal over wake, weaken the argument that the role of sleep in the enhancement of memory is entirely passive. This allows us to speculate that active processes taking place during sleep, may be effective for the enhancement of declarative learning, perhaps utilising similar underlying mechanisms to those promoting overnight improvements on procedural tasks.

An interesting finding from this study is that sleep dependent retention of a memory trace appears restricted to recognition, and the effect is not seen when assessing

recall. Examination of the data and the descriptive statistics reveals thematic recall shows very little change over periods of sleep or wake, whilst rote recall is better preserved (non-significantly, $p = 0.054$) after sleep than after wake. It appears that recall of thematic schema is relatively robust, and is comparatively unaffected relative to the ability to recall specific words. Thematic recall represents a relatively crude measure of declarative memory, measuring an ability to recall more global aspects of a story and not to assess specific components. As such, a thematic measure may be inappropriate in a study of this nature, where any differences in memory traces are expected to be relatively subtle, and so would not be revealed by this more global measure. In contrast, the measure of rote recall provides a more specific gauge of memory retrieval and would be expected to pick up subtle changes over sleep and wake, should they occur. One explanation for the different findings of recall and recognition is that the processes of recall and recognition may rely on different storage systems, or different retrieval mechanisms. If this is the case, it can be speculated that only recognition mechanisms are facilitated by sleep, and the alternative mechanisms required by recall are independent of changes in the sleep/wake state. However, it is widely accepted that recall and recognition tap the same basic storage system, and evidence supports a direct access retrieval hypothesis for both recall and recognition (Wickelgren, 1977).

An alternative explanation for the result is that differences in the decision process required for recall and recognition, and differences in associations tapped by recall and recognition, mean that in the current study the recall measure was not sensitive to sleep. In the decision stage, recall and recognition differ as recall is a comparative judgement of many possible responses and recognition is an absolute judgement with regard to a single response (Wickelgren, 1977). In addition, there are differences in the associations tapped by recall and recognition, because recognition has more retrieval cues than recall. This evidence leads us to suggest that the absence of sleep dependent retrieval in recall is due to differences in the nature of the recall and recognition measures, rather than reflecting a narrow spectrum for sleep, specific to recognition. Future research could seek to further explore this hypothesis by developing more refined measures of declarative recall.

2.1.8.4 Correlations between sleep variables and dependent variables

Results in section 2.1.7.3 show there is very little difference between participant sleep questionnaire scores and scores from a control sample of 2968 healthy control adults, indicating a sample of relatively good, or normal sleepers. A significant negative correlation was observed between sleep latency and rote recall change after wake, indicating that increased sleep latency reduces the ability to accurately recall information. One explanation for this finding is that greater sleep latencies result in a shorter total sleep time, and this may reduce the positive effects of sleep on memory enhancements. However, as the correlation is only significant with regard to wake recall change, and as there are no correlations between mean sleep time per night and recall variables, it seems unlikely that this is the case. Positive correlations were observed between sleep disturbances and thematic recall change over sleep, and sleep quality and rote recall change over wake, unexpectedly pointing to an association between problematic sleep and better recall. Once again the possibility arises that the correlations observed may not reflect the true nature of the associations between sleep and declarative memory retrieval, and may be attributable to other factors, either as a result of poor measures of sleep or memory, or as a consequence of external factors. These findings point to a need to further investigate the validity of subjective measures of sleep quality, and to further assess direct associations between sleep and declarative memory retrieval.

2.1.8.5 Correlations between IQ and dependent variables

A significant negative correlation was observed between recognition after sleep and matrix reasoning score (table 2.2.2), indicating a higher IQ is associated with a worse ability to recognise material after sleep. Whilst a positive correlation might be expected (i.e. a higher IQ linked to better recognition abilities), this result does not seem to be easily explained and does not provide support for the theory that sleep is an important mediator of learning and subsequent intellect. Although the main findings from this study seem to suggest that sleep is important for the enhancement of declarative memory recognition, the effect was small and did not transfer to the recall of declarative material. In addition, the finding that IQ is correlated with worse recognition after sleep perhaps points to a need for further research in this area. A clear limitation of the current study is the small size of the participant sample. The results generated here, whilst not conclusive, certainly warrant further

investigation with a larger sample of participants. The use of objective assessments of sleep would also provide accurate data for sleep quality and quantity, and would allow for more sophisticated analyses. In addition, a more comprehensive assessment of IQ such as a full scale IQ test may help disentangle the relationship between sleep dependent learning and IQ.

2.1.9 Conclusions and Implications

The two studies outlined above provide evidence that sleep plays an important role in procedural and declarative memory processes. The main findings suggest that sleep is preferable to wake for improving performance on a motor skill task, and for preserving recognition (but not recall) based memories. Performance enhancements over sleep are seen in both the procedural and declarative domains, but there is evidence to suggest that the relative contribution of sleep in the procedural domain is greater than in the declarative domain. It seems clear from the results outlined that sleep has a role mediating learning and memory processes, however the way in which sleep promotes these processes, and the differences between these mechanisms in the different memory domains is not known.

Although the results described above have provided some preliminary evidence that sleep is involved in memory enhancement, there are several limitations to these studies. The sample size in these studies is small, although the number of participants was sufficient to demonstrate the positive effect of sleep on procedural memory, the effect on declarative memory was less conclusive. Increasing the number of participants may reveal sleep dependent effects on declarative memory recall, and may help clarify the role of sleep in the declarative domain. The studies were also unable to provide objective data on sleep quality, and did not include a night of PSG like many earlier studies (e.g. Walker et al., 2002, Stickgold et al., 2000). Although our design has potential benefits (e.g. participants were able to sleep in their own beds on the night of the study and have a 'normal' nights sleep) it is also clearly limited by the lack of any objective data on sleep. The use of PSG would help disentangle the complex relationship between various sleep stages and sleep dependent learning. It would also provide a means of confirming that all participants slept on the night of the study, and would allow for the exclusion of any

participants who were unable to attain an adequate amount of sleep on the study night.

Sleep and Procedural Skill Learning in Children

2.2.1 Aims and Hypotheses

Aims

The aim of this study is to investigate the differential effects of sleep and wake on the performance of a procedural skill learning task in children. The study aims to establish whether sleep dependent improvements on procedural tasks exist in children as they have been shown to in adults (Walker et al., 2002; Stickgold et al., 2000).

Hypothesis

The hypothesis is that a night of sleep in children leads to performance improvements on a procedural skill learning task, improvements which are independent of any intervening training and which are not matched by similar periods of wake.

2.2.2 Methods

2.2.2.1 Consent

Before the experiment each of the child participants had a parent/guardian give informed consent on their behalf, and children gave informed assent. Prior to the study participants were informed the study was investigating the effects of sleep on learning. Upon completion of the experimental tasks, participants were fully de-briefed as to the nature of the study and were invited to ask any questions they wished. The study was approved by the Department of Psychology Ethics Sub-Committee.

2.2.2.2 Participants

Participants consisted of twenty children between the ages of 6 and 11 years (mean age = 8.85 years, SD = 1.46, 10 boys and 10 girls). Children were recruited from two local mainstream primary schools which run after-school clubs. Children who attended the after-school club were asked by school staff if they wished to participate

in the study. None of the children had any reported problems at school or any learning difficulties, none of the children had any reported sleep disorder or other medical disorder affecting sleep. None of the children were used to taking naps during the day.

2.2.2.3 Apparatus

IQ and sleep measures

All children completed the Matrix Reasoning sub-test of the Wechsler Abbreviated Scale of Intelligence (WASI) in order to provide an estimate of general intellectual ability (IQ). Matrix reasoning performance reflects an individual's ability to mentally manipulate abstract symbols and to perceive the relationships among them. It is regarded as a measure of non-verbal fluid reasoning and thus general intellectual ability (Wechsler, 1997). Parents of children completed the Paediatric Sleep Questionnaire (PSQ) (Gianotti et al., 1995) on behalf of their child. The questionnaire assesses general sleep disturbances in childhood, and has been shown in previous literature to be a valid and reliable tool in assessing childhood sleep disturbances (Gianotti et al., 1995; for a full review of the PSQ see chapter 5). The PSQ provides an estimate of mean sleep time per night, and also provides scores for the following five sleep factors: parent/child interactions during the night, parasomnias (intrusions into the sleep process), sleep fragmentation, daytime drowsiness, and bedtime difficulties. Higher scores on all sleep factors indicate more problems in that area, or a worse quality of sleep. Children also completed a measure of sleep quality for the night they were involved in the study. They were asked to indicate on a scale how well they had slept the previous night. The scale ranged from 1 (*worse than usual*) to 5 (*better than usual*), this measure was termed 'sleep quality (study night)'. Any participant who was believed not to have slept on the study night was excluded.

Procedural skill task

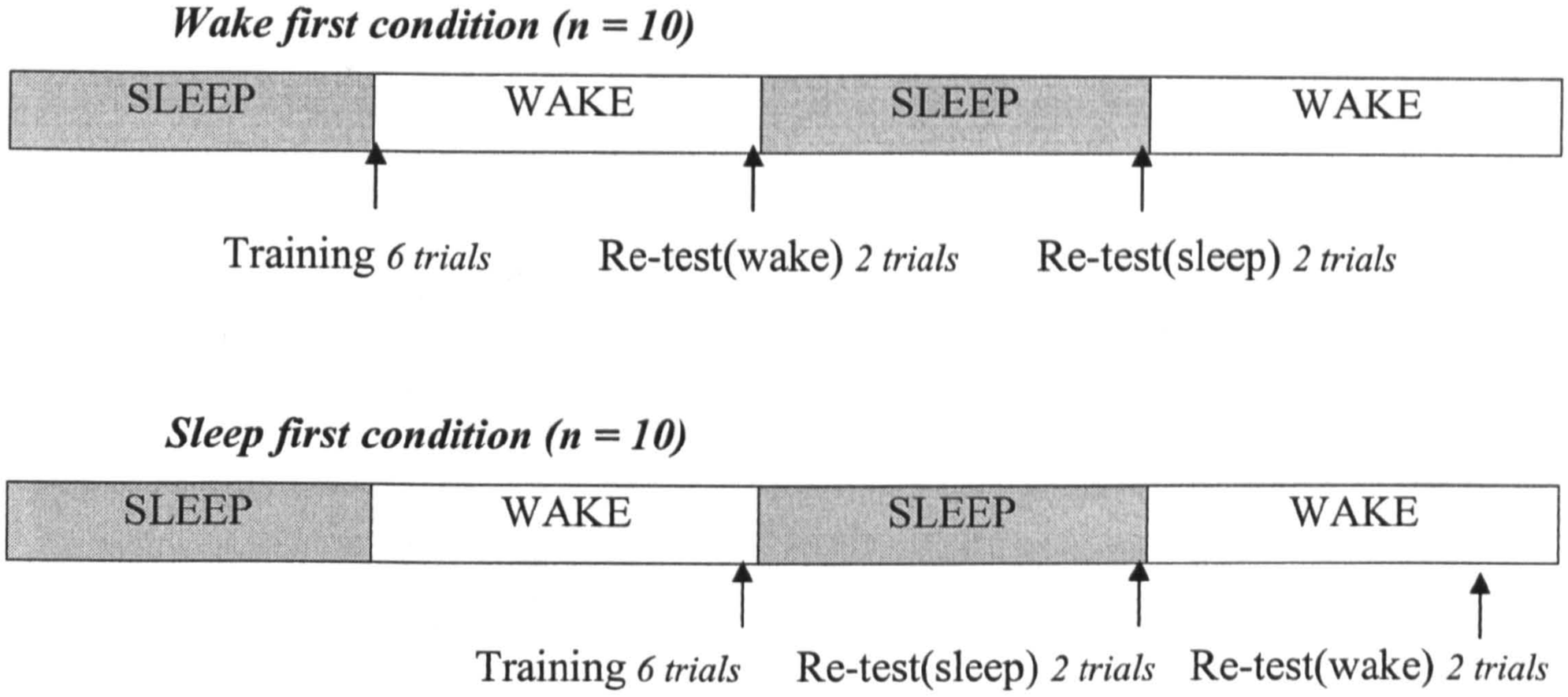
Participants wore a fabric glove specially adapted to record finger-thumb oppositions. The glove was fitted with copper pads on each of the fingers and the thumb, these were wired into a laptop computer's USB input via a Personal Measurement Device (PMD). Specially designed software on the laptop recorded oppositions between fingers and thumb, the software was programmed to record

trials lasting thirty seconds, after the recording period of thirty seconds the software automatically saved the data file. Analysis programmes designed in Microsoft Excel allowed conversion of the raw data file and produced scores for number of correct sequences performed in a thirty second block, and time (in milliseconds) per sequence i.e. the average time taken to perform a sequence within a thirty second block. Several gloves of different sizes were made in order to cover a range of hand sizes. The glove was designed to record finger-thumb oppositions in a similar way to that described in the task developed by Korman et al. (2003).

2.2.2.4 Design

As the study was designed to assess the differential effect of sleep and wake on consolidation, children participated in both a sleep and a wake condition. Participants were tested on three occasions spanning a day awake and a night asleep (fig. 2.2.3). Testing sessions were either a consecutive morning-evening-morning (termed wake-first), or a consecutive evening-morning-evening (termed sleep-first). In order to counteract any effects caused by testing order, participants were counterbalanced randomly across the two conditions (sleep-first condition = 9; wake-first condition = 11). Thus, wake-first participants attended their first session at 8.00 or 8.30a.m (day 1), their second session at 6.00 or 6.30p.m (day 1), and their third session at 8.00 or 8.30a.m (day 2). Sleep-first participants attended their first session at 6.00 or 6.30p.m (day 1), their second session at 8.00 or 8.30a.m (day 2), and their third session at 6.00 or 6.30p.m (day 2). Although an ideal design would have separated all sessions by exactly 12 hours, this was not possible due to practical constraints.

Fig. 2.2.3: Training and re-test schedule showing counterbalancing across sleep first and wake first conditions.



2.2.2.5 Procedure

Both schools that children were recruited from had after-school clubs in order to care for children before and after school time. Typically, they cared for children before school from 8.00a.m in the morning, and after school until 7.00p.m in the evening. Both clubs were based within the school premises. All participants were tested in a quiet empty classroom, or a cordoned off section of a larger room, on school premises. Prior to the first session written consent was taken from parents of all children, and parents were given the PSQ to take away and complete in their own time, on behalf of their child. At the time of the first session, written assent was taken from all children, and children completed the matrix reasoning subtest of the WASI as per the standardised instructions provided. At the post-sleep session (either session 2 or 3 depending on counterbalancing) children were asked to complete the 'sleep quality study night' measure, in order to assess sleep quality on that particular night. All participants were tested either by the author or by a similarly aged female clinical psychologist in training. In an attempt to standardise the administration of measures between experimenters, written instructions were generated and piloted for each task or measure, and formed a standardised protocol for testing sessions.

Participants were instructed to wear the glove on their non-dominant hand. Participants were instructed to oppose the fingers of their hand to their thumb, in a

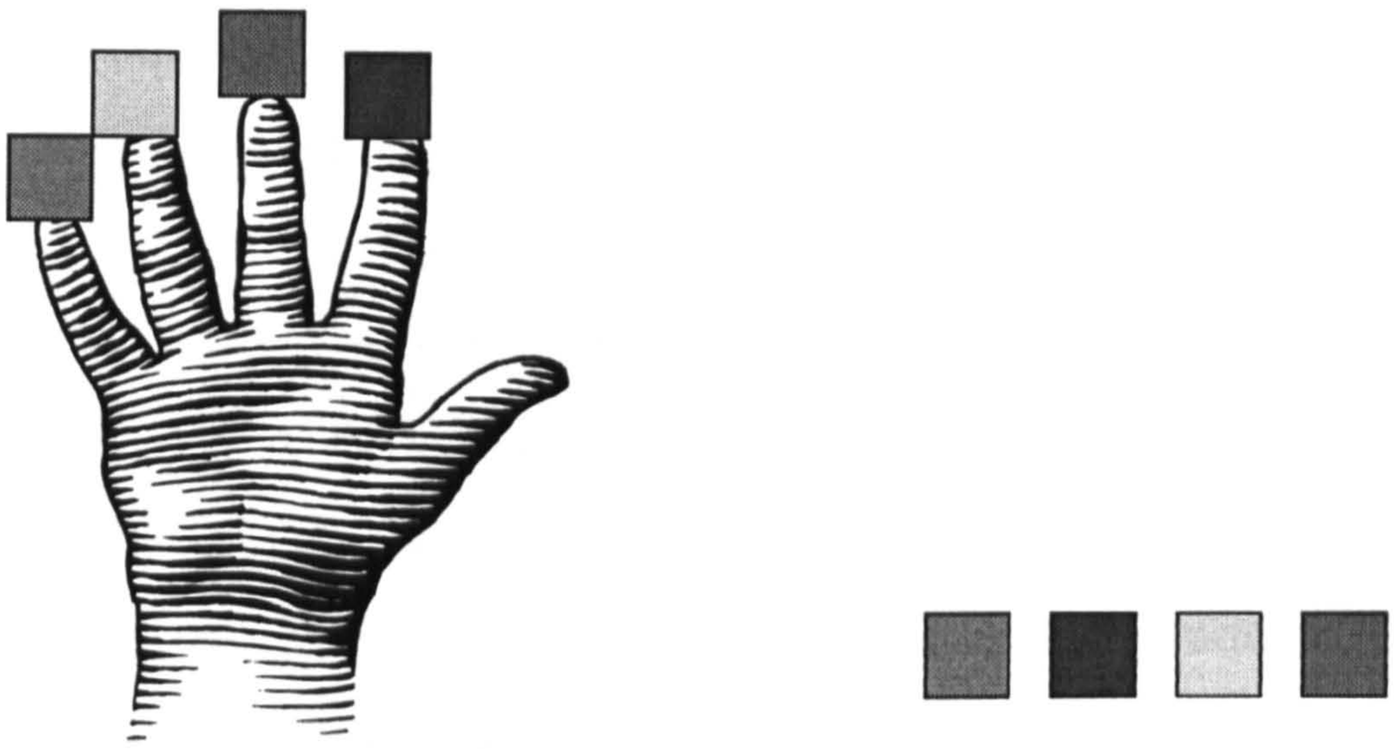
specific sequence. The sequence was composed of four component movements. Although the intention had been to use a five component sequence as in adults, previous piloting had indicated some children had problems performing a five digit sequence, the difficulty level of the task was such that they were unable to perform sufficient sequences within the test period to be able to gain any benefit from training. As such, it was decided to use a four digit sequence with children to reduce the difficulty of the task and to simplify training. A crib sheet available during training and testing showed the sequence represented as a series of coloured squares (fig. 2.2.4). Each coloured square corresponded to a different finger, coloured sticky dots on the fingers of the glove indicated the colour for each finger (index = green, middle = yellow, ring = blue, little = red). Previous piloting had shown that some children struggled with the numerical nature of a numbered crib sheet, and using a coloured crib sheet with the sequence represented as coloured dots eliminated this problem.

Participants were required to repeat the four digit sequence as many times as possible, with no visual feedback and as accurately as possible, for a period of 30 seconds. Participants were instructed to touch the tip of their thumb onto the appropriate finger in the given order *green-red-yellow-blue*. In order to exclude any working memory component, the crib sheet with the sequence was displayed at all times during training and subsequent testing. The procedure was loosely based on the model developed by Korman et al. (2003).

In addition to performing the procedural task, the majority of children also participated in three other cognitive tasks. The first was a declarative memory task, described in detail in section 2.2.5.3 The second task was a computerised visual discrimination task based loosely on the model developed by Stickgold in 2000, the third was a computerised motor pursuit task. The second and third tasks were developed by a colleague (clinical psychologist in training) and formed a part of her research thesis, they were developed in order to assess the effects of sleep on visual discrimination task performance, and motor pursuit task performance. In order to minimise effects of participant fatigue, children were encouraged to take breaks when needed between tasks. All children also completed the set of four tasks in the same order in an attempt to control for interference effects. It is acknowledged that

this experimental design, while practically necessary, offers limitations in terms of task competition and potential interference.

Fig. 2.2.4: Example of child crib sheet.



During training, participants performed six trials each lasting 30 seconds, with a 30 second rest period between each of the trials. Participants were instructed to complete the sequence as many times and as accurately as possible during each trial. The score from the first trial of the training session constituted the baseline measure, with the mean of the last two trials of the training session constituting the post-training measure. At each re-test, participants performed two trials of 30 seconds each, separated by a 30 second rest period. Participants were re-tested on two occasions, approximately 12 hours apart, and therefore once after a period of sleep and once after a period of wake. At each of the two re-test sessions, the mean average of performance on the two trials was calculated, this provided two final outcome measures: re-test(sleep) and re-test(wake).

2.2.2.6 Variables and analyses

Each participant generated a baseline score, a post-training score, a re-test(sleep) score, and a re-test(wake) score. The initial 6 trial training period generated the baseline score (trial 1), and the post-training score (mean of trials 5 & 6). Each participant was re-tested after both sleep and wake, therefore generating scores for before and after a period of sleep, and before and after a period of wake. In order to generate a measure of change in performance observed after a period of sleep vs.

change in performance observed after a period of wake, scores termed Δsleep and Δwake were calculated. Δsleep corresponds to the change in scores over the period of sleep, and Δwake the change in scores over the period of wake (this was either the difference between post-training and the first re-test, or the difference between the two re-test measures, depending on counterbalancing). This generated four final outcome measures for each participant: baseline, post-training, Δsleep, and Δwake. Each of the four outcome measures could be defined in terms of; number of correct sequences (number of correct sequences performed in thirty seconds), and time per sequence (mean time in seconds per sequence i.e. time between first correct finger press and final correct finger press within a sequence). For the variables Δsleep and Δwake, absolute values are quoted in order to ease analysis and interpretation of data. As such, Δsleep > Δwake indicates that greater performance improvements have been seen over sleep than over wake (as defined by both number of sequences and time per sequence).

Outcome variables were tested for normality, those displaying substantial skew were subject to a log transformation. All measures of time (baseline time, post-training time, Δsleep time, Δwake time) displayed positive skew and were log transformed. As some time variables measured a change in time, occasional scores were negative. In order to create a set of positive scores, a 0.5 constant was added to all values prior to log transformation. The log transformed time variables were found to show satisfactory normality and were used in all subsequent analyses, however actual time scores (absolute values) are reported in figures and tables. All other measures were found to show satisfactory normality.

Initial statistical analyses were performed using repeated measure *t*-tests to assess whether performance on the task improved from baseline to post-training. Repeated measure *t*-tests were then used to assess whether performance improved after a period of sleep, and also after a period of wake. Finally repeated measures *t*-tests were used to assess whether performance improvements observed after a period of sleep were significantly different from those observed after a period of wake.

In exploratory analyses, correlations between questionnaire defined sleep variables, matrix reasoning, and changes on the various measures over sleep and wake, were examined using Pearson's coefficients.

2.2.3 Results

2.2.3.1 Improvement over initial training session.

In order to confirm that initial training had led to significant performance improvements, repeated measures *t*-tests were performed to assess changes in number of correct sequences and time per sequence, from baseline to post-training. The number of correct sequences was significantly greater at post-training (mean = 8.2, SD = 2.93) than it was at baseline (mean = 5.2, SD = 2.40), $t = -6.18$, df = 19, $p < 0.001$. Sequences were also performed significantly faster at post-training (mean time = 2.17, SD = 0.48) than they were at baseline (mean time = 3.20, SD = 1.12), $t = 7.36$, df = 19, $p < 0.001$ (table 2.2.5).

	Baseline	Post-Training
Mean number of correct sequences	5.2 (2.40)	8.2 (2.93)
Mean time per sequence (secs)	3.20 (1.12)	2.17 (0.48)

Table 2.2.5: Changes in scores from baseline to post-training (means and standard deviations).

2.2.3.2 Performance gains after sleep and wake

After showing that significant performance gains could be observed as a consequence of training, further analyses were undertaken to assess whether performance gains could be observed, independent of intervening practice, after a period spanning sleep or wake. A Bonferroni correction for multiple *t*-tests was applied (i.e. significance threshold set at $p < 0.01$). A repeated measures *t*-test comparing pre-sleep with post-sleep number of correct sequences was significant $t = -6.74$, df = 19, $p < 0.001$, with significantly more correct sequences being performed after sleep than before sleep (pre-sleep correct sequences = 9.53, SD = 3.62; post-sleep correct sequences = 12.45, SD = 3.18). However, a *t*-test comparing pre-wake with post-wake number of correct sequences was not significant $t = -1.59$, df = 19, p

= 0.128 (pre-wake correct sequences = 10.48, SD = 2.88; post-wake correct sequences = 11.35, SD = 3.17).

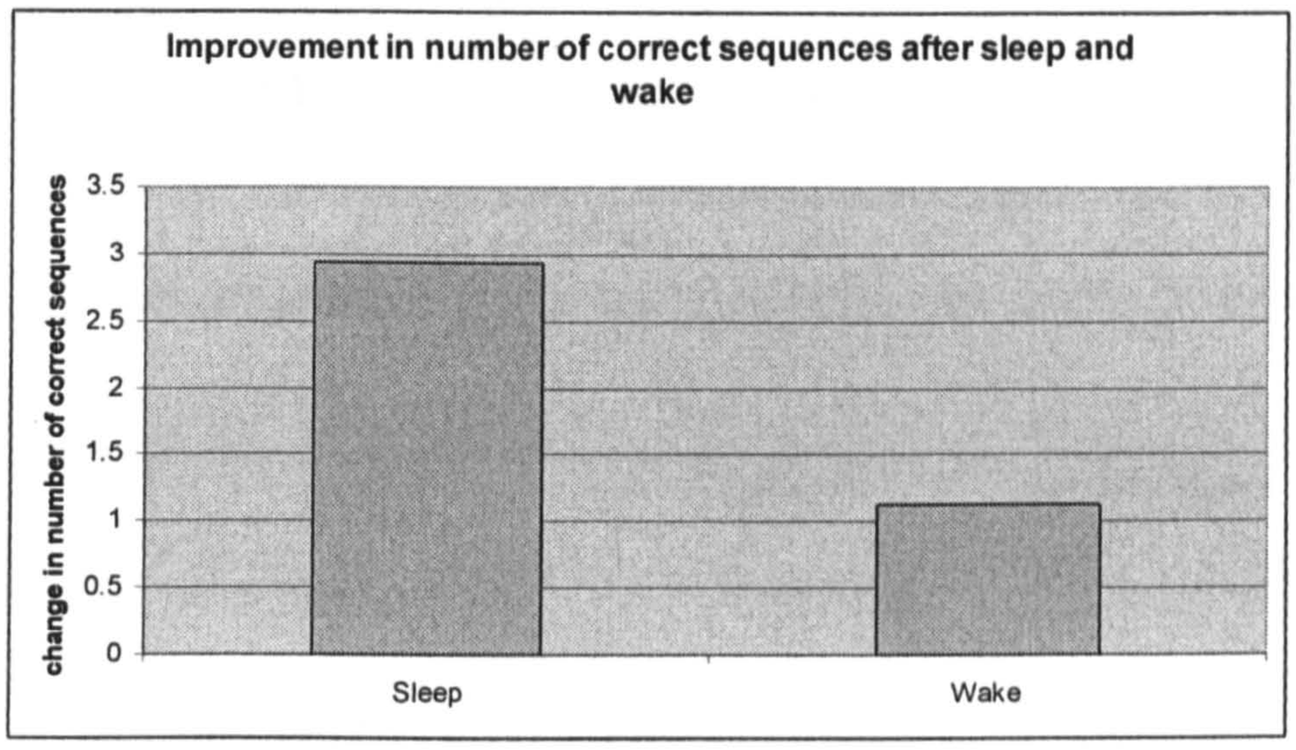
In order to assess performance gains in time taken to perform a sequence, further repeated measures *t*-tests compared pre-sleep time with post sleep time, and pre-wake time with post-wake time. There was a significant difference between pre-sleep and post-sleep time per sequence $t = 6.52$, df = 19, $p < 0.001$, with time per sequence showing a significant decrease after sleep (pre-sleep time (secs) = 2.01, SD = 0.51; post sleep time (secs) = 1.64, SD = 0.36). There was also a significant difference between pre-wake and post-wake time per sequence $t = 4.34$, df = 19, $p < 0.001$, with time per sequence showing a significant decrease after wake (pre-wake time (secs) = 1.87, SD = 0.44; post-wake time (secs) = 1.63, SD = 0.31).

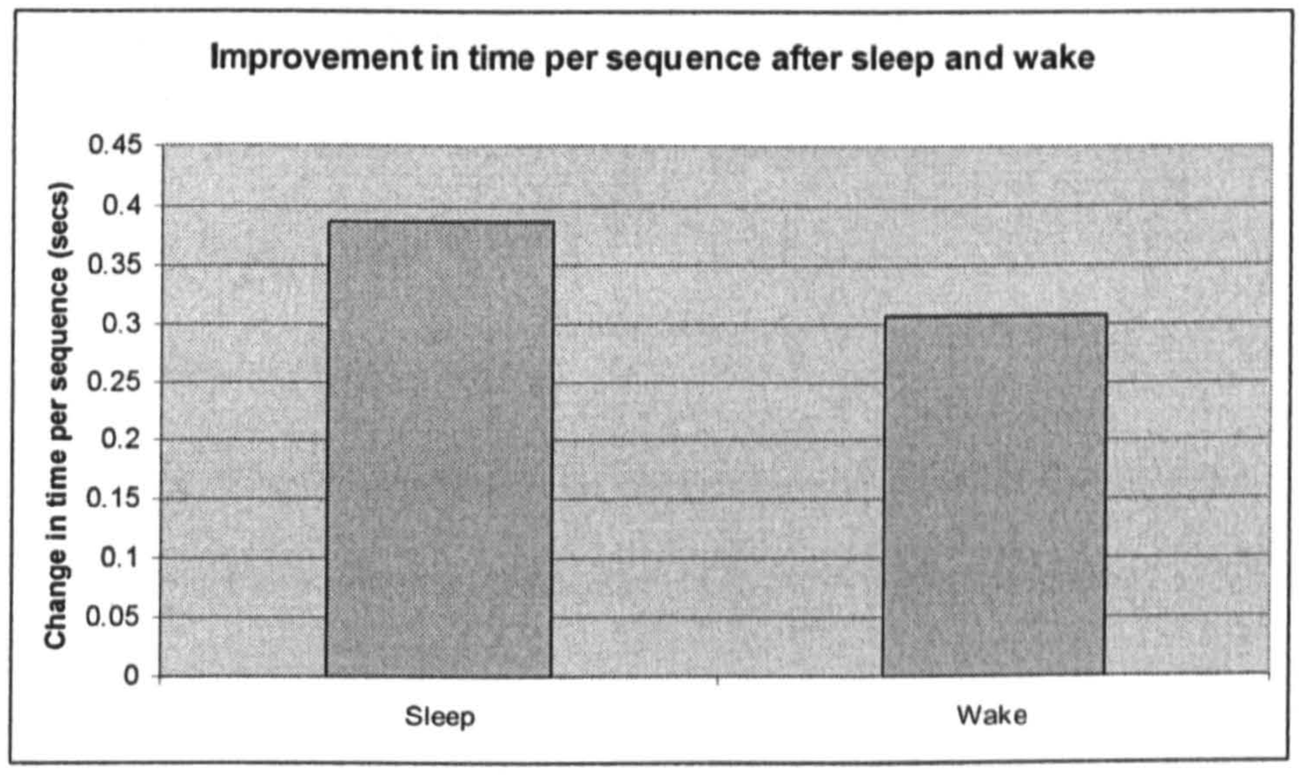
2.2.3.3 Differential improvements on procedural task after sleep and wake

Further analyses were conducted to assess the differential effects of sleep and wake on performance changes. A repeated measures *t*-test compared change in number of sequences after sleep with change in number of sequences after wake, and change in time per sequence after sleep with change in time per sequence after wake. There was a significant difference between change in number of sequences after sleep, and change in number of sequences after wake $t = 2.11$, df = 19, $p < 0.05$, with a greater improvement seen after sleep than seen after wake (mean improvement after sleep = 2.93, SD = 1.94; mean improvement after wake = 1.13, SD = 2.66). However, there was no significant difference between the change in time per sequence after sleep, and the change in time per sequence after wake $t = 1.07$, df = 19, $p = 0.300$, (mean improvement after sleep = 0.387, SD = 0.27; mean improvement after wake = 0.307, SD = 0.40) (table 2.2.6).

Table 2.2.6: Changes in scores over periods containing sleep and wake (absolute means and standard deviations).

	ΔSleep	**ΔWake**
Mean number of correct sequences	2.93 (1.94)	1.13 (2.66)
Mean time per sequence (secs)	0.387 (0.27)	0.307 (0.40)





2.2.3.4 Correlations between dependent variables and sleep measures

In order to investigate possible effects of sleep disturbances on overnight performance improvements, correlations between the dependent variables (correct number of sequences and time per sequence) and questionnaire defined sleep variables were assessed using Pearson's correlation coefficients. Questionnaire defined sleep variables comprised six factors: parent/child interactions at night, parasomnias, sleep fragmentation, daytime drowsiness, bedtime difficulties, and mean sleep time per night. Children whose parents did not return a PSQ questionnaire were excluded from these analyses. Table 2.2.7 shows means and

standard deviations for all factors alongside norms generated from a group of 117 healthy control children (mean age = 11.05, SD = 3.41). A full breakdown of information for the control group can be found in chapter 5. There were no significant differences between scores from controls and participants on any of the questionnaire variables. The single sleep variable generated from the night within the study; sleep quality (study night), was used alongside questionnaire defined variables within the correlation matrix. The mean score for sleep quality (study night) = 3.56 (SD = 0.53). Variables included in the correlation matrix consisted of all six sleep factors, sleep quality (study night) and the following dependent variables; Δsleep (number of correct sequences), Δwake (number of correct sequences), Δsleep (time per sequence) and Δwake (time per sequence).

	Controls	Participants
Parent/child Interactions	5.10 (2.10)	5.60 (3.00)
Sleep Fragmentation	8.36 (2.05)	9.00 (2.45)
Parasomnias (intrusions into sleep)	11.13 (5.08)	11.71 (2.87)
Daytime drowsiness	8.32 (2.65)	8.47 (2.92)
Bedtime Difficulties	7.29 (2.61)	8.92 (3.84)
Mean sleep time per night (hrs)	9.93 (1.12)	10.92 (0.67)

Fig. 2.2.7: Comparison of sleep questionnaire variables in participants and 117 healthy controls (means and standard deviations). Full details of control sample are given in chapter 5.

A significant positive correlation was observed between parasomnias and Δsleep (time) $r = 0.697$, $N = 14$, $p < 0.01$, indicating an increase in parasomnias is linked to an improved consolidation during sleep. A significant negative correlation was observed between parasomnias and Δwake (time) $r = -0.561$, $N = 14$, $p < 0.05$, indicating an increase in reported parasomnias is linked to a decrease in the consolidation seen over a period of wake. A significant negative correlation was observed between sleep fragmentation and Δwake (time) $r = -0.660$, $N = 14$, $p < 0.05$, indicating an increase in reported sleep fragmentation is linked to a decrease in the amount of consolidation occurring over a period of wake. No other significant

correlations were observed. Table 2.2.8 shows all correlations between dependent variables and questionnaire defined sleep variables.

	Δsleep (no. of correct sequences)	Δwake (no. of correct sequences)	Δsleep (time per sequence)	Δwake (time per sequence)
Mean Sleep Time per night	-0.07	-0.24	-0.21	-0.38
Parent/Child Interactions	-0.36	0.26	-0.30	0.28
Sleep Fragmentation	-0.04	-0.09	0.13	*-0.66
Parasomnias	0.44	-0.34	**0.70	*-0.56
Daytime Drowsiness	-0.42	0.11	-0.15	0.28
Bedtime Difficulties	-0.28	0.03	-0.09	0.12
Sleep quality (study night)	0.43	-0.49	0.53	-0.14

*Table 2.2.8: Matrix showing correlations between dependent variables and questionnaire defined sleep variables in children. *$p < 0.05$; **$p < 0.01$.*

2.2.3.5 Correlations between dependent variables and matrix reasoning

In order to determine whether IQ is related to overnight performance improvements, correlations were assessed between matrix reasoning (Wechsler, 1997) and the various dependent variables using Pearson's correlation coefficients. The matrix reasoning subtest provides a T score for each participant, standardization sample distribution of T scores has a mean of 50 and standard deviation of 10. Two children were excluded from matrix reasoning analyses, one did not complete the measure and one failed to achieve sufficient understanding of the rules. The remaining eighteen participants had a mean score of 52.6 (SD = 10.1), the range of scores was 33.5 – 68.0. Variables included in the correlation matrix were; matrix reasoning score, Δsleep/Δwake (number of correct sequences), and Δsleep/Δwake (time per sequence). There were no significant correlations between any of the dependent variables and matrix reasoning scores (table 2.2.9).

	Δsleep (no. of correct sequences)	Δwake (no. of correct sequences)	Δsleep (time per sequence)	Δwake (time per sequence)
Matrix IQ	0.382	0.231	-0.092	-0.240

Fig 2.2.9: Correlations between matrix reasoning scores and dependent variables.

2.2.4 Aims and Hypotheses

Aims

The aim of the study is to investigate the differential effect of periods of sleep and wake on retention of declarative memory traces in healthy children. Specifically, to assess whether periods of sleep result in better retention (expressed as reduced decay) of declarative material than do similar periods of wake.

Hypothesis

The hypothesis is that after a period containing sleep, decay of declarative material in children (as measured by recall and recognition), will be significantly less than the decay observed after a similar period containing wake.

2.2.5 Methods

2.2.5.1 Consent

Consent was taken as for the previous study (section 2.2.2).

2.2.5.2 Participants

Participants consisted of twenty-one children between the ages of 4 and 11 years (mean age = 8.57 years, SD = 1.99, ten boys and eleven girls). Children were recruited from two local mainstream primary schools which run after-school clubs. Children who attended the after-school club were asked by school staff if they wished to participate in the study. None of the children had any reported problems at school or any learning difficulties, none of the children had any reported sleep disorder or other medical disorder affecting sleep. None of the children were used to taking naps during the day.

2.2.5.3 Apparatus

IQ and Sleep measures

All participants completed the same IQ and sleep questionnaire measures as those children described in the previous study (section 2.2.2).

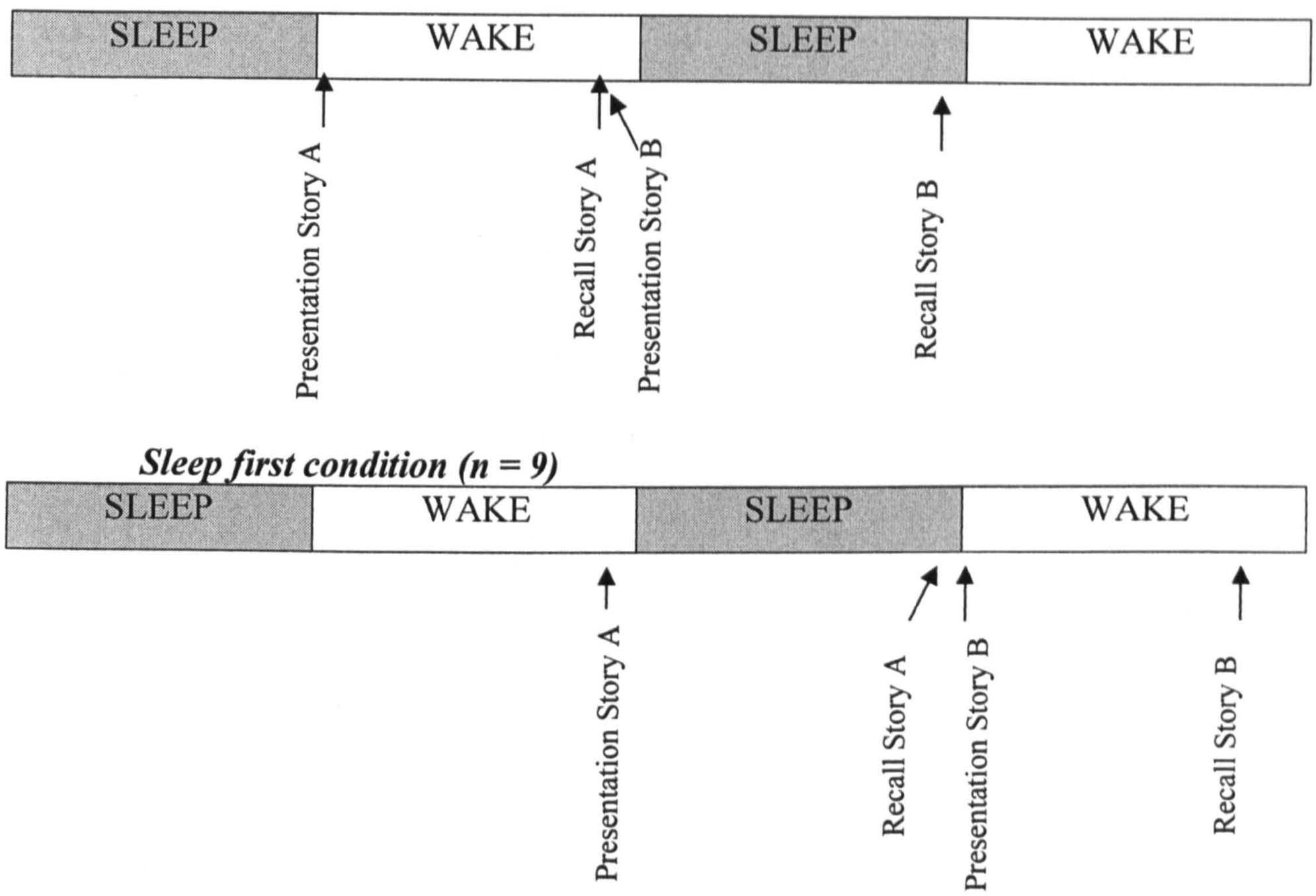
Declarative Task

The declarative task comprised story telling and recall. Stories were taken from the stories sub-test of the Children's Memory Scale (CMS), a well-known and reliable neuropsychological tool for assessing memory in children. The CMS provides six stories, two stories each for three age groups (5-8yrs, 9-11yrs and 12-16yrs). Participants were read stories appropriate to their age. Stories were provided with standardised instructions and scoring, scoring generated three measures; rote recall, thematic recall, and recognition. Rote recall score provides a detailed measure of total recall based on remembering specific words and numbers from the story. Thematic recall score gives a more general measure of story recall and is defined by gist information and thematic units. Recognition score is the number of correctly answered questions, from fifteen yes/no forced choice questions about the story.

2.2.5.4 Design

As the study was designed to assess the differential effect of sleep and wake on consolidation, subjects participated in both a sleep and a wake condition. Participants were tested on three occasions spanning a day awake and a night asleep (fig. 2.3.0). Testing sessions were either a consecutive morning-evening-morning (termed wake-first), or a consecutive evening-morning-evening (termed sleep-first). In order to counteract any effects caused by testing order, participants were counterbalanced randomly across the two conditions (sleep-first condition = 9; wake-first condition = 12). Thus, wake-first participants attended their first session at 8.00 or 8.30a.m (day 1), their second session at 6.00 or 6.30p.m (day 1), and their third session at 8.00 or 8.30a.m (day 2). Sleep-first participants attended their first session at 6.00 or 6.30p.m (day 1), their second session at 8.00 or 8.30a.m (day 2), and their third session at 6.00 or 6.30p.m (day 2) (fig. 2.3.0). Although an ideal design would have separated all sessions by exactly 12 hours, this was not possible due to practical constraints.

Fig. 2.3.0: Declarative task design and counterbalancing.



2.2.5.5 Procedure

Both schools that children were recruited from had after-school clubs in order to care for children before and after school time. Typically, they cared for children before school from 8.00a.m in the morning, and after school until 7.00p.m in the evening. Both clubs were based within the school premises. All participants were tested in a quiet empty classroom, or a cordoned off section of a larger room, on school premises.

Participants and parents completed the WASI, the PSQI, and the 'sleep quality study night' measures as described in section 2.2.2, All participants were tested either by the author or by a similarly aged female clinical psychologist in training. In an attempt to standardise the administration of measures between experimenters, both experimenters adhered to the same set of standardised written instructions for each task or measure, which formed a standardised protocol for testing sessions. Both experimenters had also been involved in previous piloting work, intended to homogenise aspects of story delivery such as tone, pitch, and pace (story delivery typically took 40 -50 seconds).

Once participants had completed questionnaire and IQ measures they were seated comfortably and were read one of the two CMS stories (from appropriate age band; 5-8yrs, 9-11yrs or 12-16yrs). Participants were asked to give an immediate recall of the story, and then a delayed recall after 30 minutes (the 30 minute recall was included in order to ensure some encoding of the story into the long term memory). After the subsequent interval of approximately 12 hours containing sleep or wake, participants were again asked to recall the story, and were then asked 15 yes/no forced choice recognition questions. The procedure was identical over both the sleep and wake conditions, with a different story used for each condition. The stories were randomly counterbalanced across both participants and conditions. Participants were instructed using the standardised instructions for the stories as given in the CMS. Scores were recorded on a standardised form, giving scores for rote recall, thematic recall, and recognition.

In addition to participating in the declarative task, the majority of subjects also participated in three other cognitive tasks. The first was a procedural memory task, described in detail in section 2.2.2. The second task was a computerised visual discrimination task based loosely on the model developed by Stickgold in 2000, the third was a computerised motor pursuit task. Typically these three tasks were completed between the initial reading of the story, and the 30 minute delayed recall. In order to minimise effects of participant fatigue, subjects were encouraged to take breaks when needed between tasks. All participants also completed the set of four tasks in the same order in an attempt to control for interference effects. It is acknowledged that this experimental design, while practically necessary, offers limitations in terms of task competition and potential interference.

2.2.5.6 Variables and Analyses

Each participant generated scores for both a sleep and a wake condition. Scores consisted of immediate rote recall, immediate thematic recall, 30 minute rote recall, 30 minute thematic recall, post sleep/wake rote recall, post sleep/wake thematic recall, and post sleep/wake recognition. Rote and thematic recall scores for each condition were generated by subtracting the post sleep/wake score from the 30 minute score. This provided a measure of rote recall change and thematic recall change in each condition (Δsleep and Δwake respectively), a higher score indicating

a greater degree of decay, or worse retention of the material. Recognition scores were simply composed of the post-sleep and post-wake recognition scores marked out of 15, a higher score indicating better recognition. This generated the following six final outcome measures for each participant; Δsleep (rote), Δwake (rote), Δsleep (thematic), Δwake (thematic), recognition after sleep, and recognition after wake.

Variables were tested for normality and found to be acceptable so no transformations were required. Repeated measures *t*-tests were used to assess whether memory recall was significantly different before and after a period containing sleep, and additionally before and after a period containing wake, in the group as a whole. Further statistical analyses were performed using repeated measures *t*-tests to assess whether recall changes after sleep were significantly different from recall changes after wake. A final repeated measures *t*-test compared recognition after a period of sleep with recognition after a similar period of wake. In exploratory analyses, questionnaire defined sleep variables and IQ were correlated with changes in recall and recognition using Pearson's correlation coefficients.

2.2.6 Results

2.2.6.1 Differences in recall after sleep and wake

Repeated measures *t*-tests were performed to assess whether recall decreased significantly after a period of approximately twelve hours, spanning either sleep or wake. A Bonferroni correction for multiple *t*-tests was applied (i.e. a significance threshold set at $p < 0.01$). There was no significant differences observed between rote recall before sleep and rote recall after sleep $t = 1.64$, $df = 20$, $p = 0.116$, neither was there a significant difference between rote recall before and after wake $t = 1.36$, $df = 20$, $p = 0.189$. There was no significant difference between thematic recall before and after sleep $t = 1.07$, $df = 209$, $p = 0.296$, or thematic recall before and after wake $t = 1.16$, $df = 20$, $p = 0.261$.

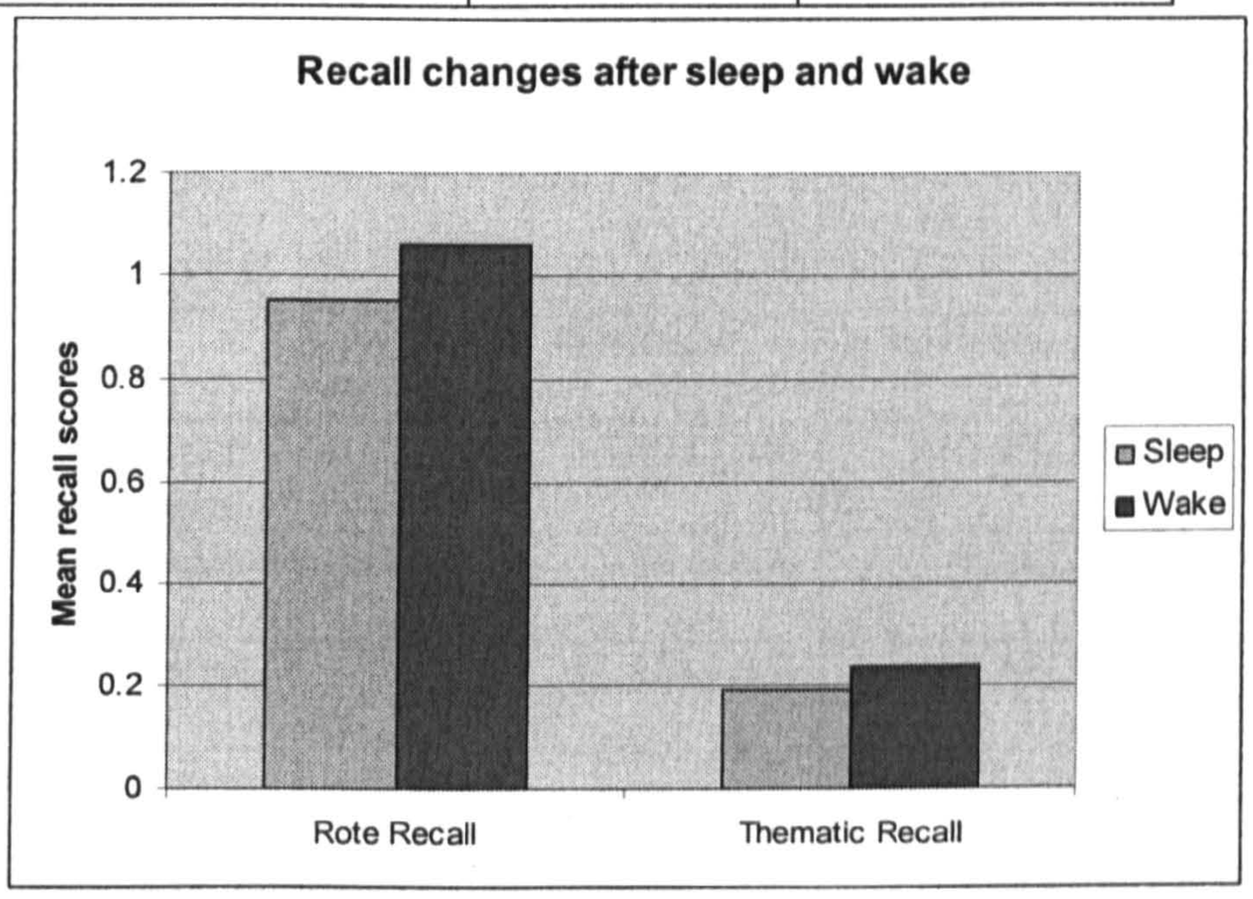
2.2.6.2 Comparison of declarative memory after sleep and wake

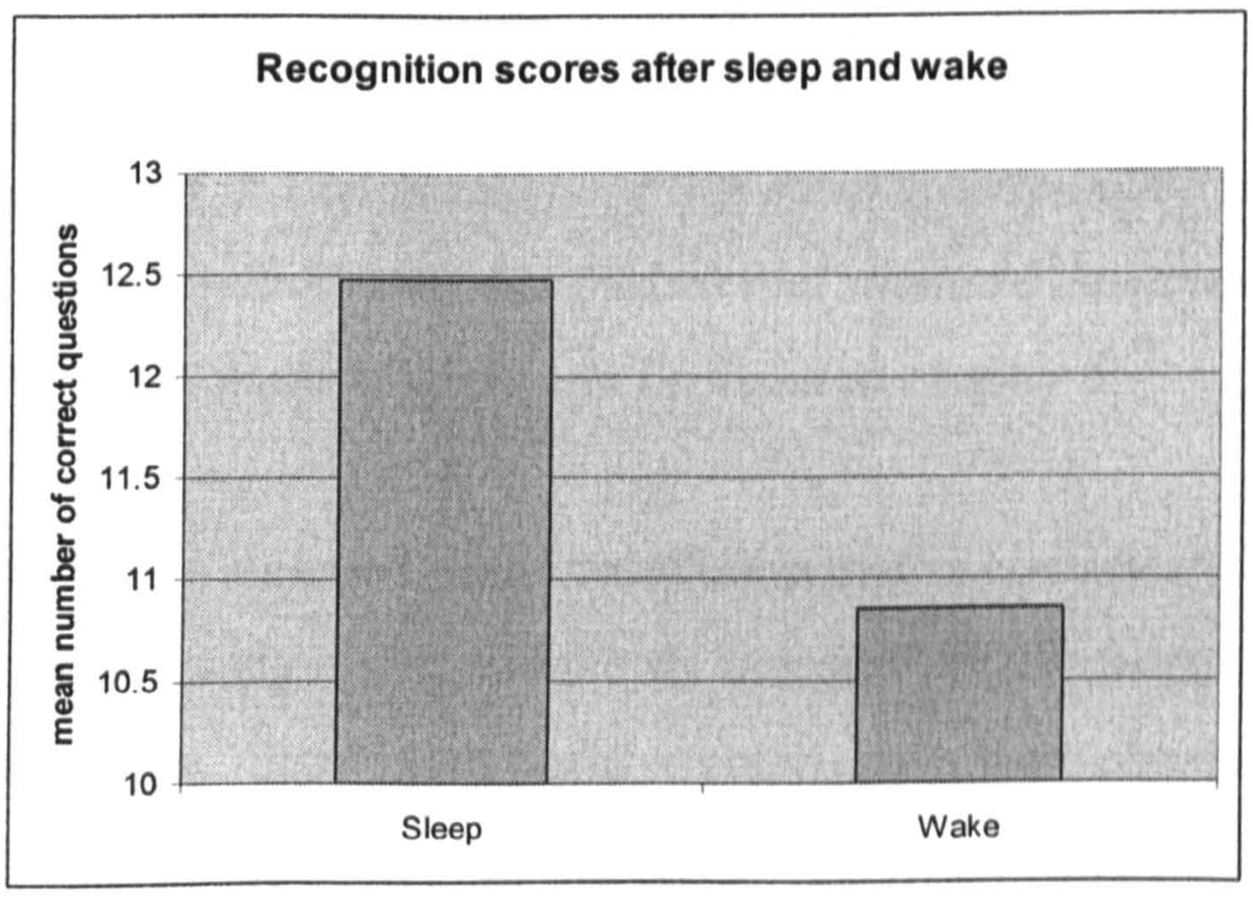
Further repeated measures *t*-tests were performed to compare performance changes over sleep with changes over wake. A Bonferroni correction was applied (i.e. a significance threshold set at $p < 0.02$). There was no significant difference between rote recall change after sleep and rote recall change after wake $t = -0.15$, $df = 20$, $p =$

0.888, neither was there a significant difference between thematic recall change after sleep and thematic recall change after wake $t = -0.33$, df = 20, p = 0.748. However, the number of recognition questions answered correctly after sleep was significantly greater than the number answered correctly after wake $t = 2.88$, df = 20, $p < 0.01$ (mean recognition after sleep = 12.48, mean recognition after wake = 10.86) (table 2.3.1).

*Table 2.3.1: Means and standard deviations of recall change and recognition scores over sleep and wake (means and standard deviations), *p < 0.01.*

	Sleep	**Wake**
Rote recall change	0.95 (2.65)	1.05 (3.53)
Thematic recall change	0.19 (0.81)	0.24 (0.94)
Recognition	12.48 (1.86)	10.86 (2.01)





2.2.6.3 Correlations between dependent variables and sleep measures

In order to investigate possible effects of sleep problems on overnight changes in declarative memory, correlations between the recall/recognition variables and questionnaire defined sleep variables were assessed using Pearson's correlation coefficients. PSQI questionnaire defined sleep variables comprised six factors: parent/child interactions at night, parasomnias, sleep fragmentation, daytime drowsiness, bedtime difficulties, and mean sleep time per night. Children whose parents did not return a PSQI questionnaire were excluded from these analyses. Table 2.3.2 shows means and standard deviations for all factors alongside norms generated from a group of 117 healthy control children (mean age = 11.05, SD = 3.41). A full breakdown of information for the control group can be found in chapter 5. There were no significant differences between scores from controls and participants on any of the sleep questionnaire variables. The single sleep variable generated from the night of the study; sleep quality (study night), was used alongside questionnaire defined variables within the correlation matrix. The mean score for sleep quality (study night) = 3.14 (SD = 0.48).

	Controls	Participants
Parent/child Interactions	5.10 (2.10)	5.93 (2.99)
Sleep Fragmentation	8.36 (2.05)	9.14 (2.14)
Parasomnias	11.13 (5.08)	11.79 (3.38)
Daytime drowsiness	8.32 (2.65)	8.80 (2.70)
Bedtime Difficulties	7.29 (2.61)	9.14 (3.86)
Mean sleep time per night (hrs)	9.93 (1.12)	10.84 (0.68)

Table 2.3.2: Comparison of PSQI sleep questionnaire variables between participants and 117 healthy controls (means and standard deviations). A full breakdown of information on controls can be found in chapter 5.

Variables included in the correlation matrix consisted of all six sleep factors, sleep quality (study night) and the six outcome recall/recognition variables previously described. Significant positive correlations were observed between parasomnias and Δsleep (thematic) $r = 0.566$, $N = 14$, $p < 0.05$, parasomnias and Δwake (thematic) $r = 0.674$, $N = 14$, $p < 0.01$, and parasomnias and Δwake (rote) $r = 0.668$, $N = 14$, $p <$

0.01. A small but non significant positive trend was also observed between parasomnias and Δsleep (rote) r = 0.513, N = 14, p = 0.061. The results appear to indicate that parasomnias are linked to a greater degree of declarative memory decay, not only over sleep but also over wake. There were no other significant correlations between sleep variables and recall/recognition measures (table 2.3.3).

	Δsleep (thematic)	Δwake (thematic)	Δsleep (rote)	Δwake (rote)	sleep recognition	wake recognition
Parent/Child Interactions	0.12	0.13	0.13	0.14	-0.05	-0.27
Sleep Fragmentation	0.11	0.10	0.07	0.12	0.03	0.01
Parasomnias	*0.57	*0.67	0.51	*0.67	-0.10	0.31
Daytime Drowsiness	-0.03	0.14	0.04	0.23	-0.16	-0.37
Bedtime Difficulties	0.07	0.18	0.30	0.15	-0.04	-0.01
Sleep quality (study night)	-0.07	-0.08	0.08	0.06	-0.04	-0.28
Mean sleep Time per night	0.14	0.05	0.21	0.12	0.02	0.09

*Table 2.3.3: Matrix showing correlations between dependent variables and questionnaire defined variables. *p < 0.05.*

2.2.6.4 Correlations between declarative memory and matrix reasoning

In order to determine whether IQ is related to overnight changes in declarative memory, correlations were assessed between matrix reasoning and the various dependent variables using Pearson's correlation coefficients. The matrix reasoning subtest provides a T score for each participant, standardization sample distribution of T scores has a mean of 50 and standard deviation of 10. Seven children were excluded from matrix reasoning analyses, 4 were unable to understand the rules and 3 either refused or did not complete. The remaining fourteen child participants had a mean score of 51.68 (SD = 9.99), the range of scores was 33.5 – 68.0.

Correlations between matrix reasoning and the recall and recognition variables were assessed using Pearson's correlation coefficients. There were no significant

correlations between matrix reasoning scores and any of the recall/recognition measures (table 2.3.4).

	Δsleep (thematic)	Δwake (thematic)	Δsleep (rote)	Δwake (rote)	sleep recognition	wake recognition
Matrix IQ Score	0.143	0.120	-0.231	0.052	0.360	0.305

Table 2.3.4: Correlations between matrix reasoning IQ and dependent variables.

2.2.7 Discussion

2.2.7.1 Sleep dependent motor skill improvement

Practice on the procedural task improved significantly with repeated performances over the initial training session, in addition participants also went on to demonstrate a subsequent time-delayed improvement, independent of any further intervening training. The improvement seemed to be dependent on sleep, with participants showing a significantly greater improvement in number of correct sequences after a period of sleep, than after a similar period awake. This improvement was limited to the number of correct sequences being performed, and did not transfer to the time per sequence. Although children were faster at performing sequences after sleep than they were after wake, this difference was not statistically significant ($p = 0.300$).

To date, research into the effects of sleep on procedural learning has been limited to studies involving adults. Although no data is available on sleep dependent learning in children, it is interesting to note that the findings reported here are comparable to those reported in section 2.1.3, a similar study with adults. The findings also appear to replicate earlier work by authors such as Walker et al. (2002) and Fischer et al. (2002), who showed improvements on motor skill tasks in adults were dependent on sleep. However, the results discussed in section 2.1.3, and those reported by Walker et al. (2002) and Fischer et al. (2002), seem to show a more robust dependence of procedural learning on sleep. In section 2.1.3, adult participants showed significant sleep dependent improvements in both number of correct sequences and time per sequence. Walker et al. (2002) also showed that sleep selectively improved both speed and accuracy of a procedural task. The findings from the current study show a

sleep dependent improvement in number of correct sequences, but no corresponding improvement in time per sequence, perhaps indicating that sleep in children is more effective at reducing the rate of errors, rather than increasing speed. The results reported here indicate that although sleep dependent consolidation appears to occur in children, it does not seem to be as robust as in adults.

Previous research has indicated that specific stages of sleep are particularly important for overnight improvement on a task, and correlations have been observed between various sleep stages and degree of overnight improvement. However, there appears to be some dispute about which stages are the most beneficial with claims that both stage 2 NREM (Walker et al., 2002), and REM and slow wave sleep (Stickgold et al., 2000) provide most benefit for overnight improvement on a task. It has been suggested that factors such as task complexity and learning domain specificities may lead to variations in sleep state dependence (Walker et al., 2002). Whilst no sleep staging information is available in the current study it is interesting to speculate that immature sleep architecture in children may lead to a different pattern of results than has been observed in studies with adults. Sleep undergoes considerable changes during infanthood and early childhood, with a gradual progression towards differentiation and organization of conventionally defined sleep states, shorter total sleep time, less SWS and longer sleep cycles (Stores, 2001). It can be speculated that the impact of sleep on learning changes considerably during development, and the mechanisms of sleep dependent consolidation may not become fully developed until sleep patterns have completely matured.

Clearly, further research is necessary to gain a fuller understanding of sleep dependent procedural learning in children. Although the current study provides us with preliminary evidence that sleep enhances motor skill learning in children, further work will help disentangle the relationship between sleep and learning in children. Research employing sleep staging techniques will allow a comparison of specific sleep parameters with learning, additionally a larger sample of participants may be required in order to increase the experimental power sufficiently to provide more meaningful results.

2.2.7.2 Effects of sleep quality and IQ on overnight improvement on the task

Comparison of the descriptive statistics reveals very little difference between the participant sample questionnaire scores and scores from a control sample of 117 healthy children (table 2.2.7). There were no significant differences between the participant sample and the control sample, indicating our participant sample is relatively normal in terms of their sleep quality. Correlational analyses revealed a positive correlation between parasomnias and change in time after sleep, and change in time after wake. This finding indicates that an increase in reported parasomnias is linked to an increase in overnight improvement on the task. This finding appears to be at odds with what might be expected, namely that sleep disturbance would presumably be expected to impair consolidation at night, rather than to facilitate it.

A possible explanation for this may be that parasomnias are a poor measure of general sleep quality, questionnaire items coding for parasomnias included questions concerning sleepwalking, sleeptalking, bruxism etc. These items do not necessarily reflect poor sleep as they may occur during normal sleep, rather than act as true intrusions into the various stages of sleep. There is much evidence to suggest that parsomnias in children lead to disrupted sleep (e.g. Mahowald & Rosen, 1990), however some have claimed that parasomnias do not necessarily impair sleep quality. The possibility that reported parasomnias represent an altered state of sleep rather than a disrupted state of sleep should be considered.

Another possibility is that parasomnias alter the sleep process in such a way, that either the stages of sleep responsible for overnight consolidation are increased relative to other stages, or sleep pattern alterations in general are somehow contributing to increased consolidation. Parasomnias are observed in both NREM and REM stages of sleep, however the specific effect of the parasomnia on duration and architecture of the various stages is less well known. Negative correlations were also observed between change in time after wake and both parasomnias and sleep fragmentation. This indicates improvement on the task over wake is linked to a decrease in reported parasomnias and fragmentation. Although reported sleep problems may not be expected to have a significant effect on subsequent changes in daytime performance, disruptions or alterations to the sleep process may have an impact on daytime functioning. In particular those children reported to suffer from

fragmented sleep may be susceptible to deficits in daytime functioning due to an insufficient amount of sleep at night.

A second possible explanation for the unexpected correlations seen here is that parent-report questionnaires are not a very accurate method of assessing sleep problems in children. Some researchers have questioned the validity of parental report data, and have commented on the susceptibility of parent-report to systematic distortions (Morsbach et al., 2006). This possibility needs to be further explored by investigating the reliability and particularly the validity of parent-report questionnaires, comparing them with other more objective measures of sleep (this is addressed in chapter 5).

Correlational analyses revealed there were no significant correlations between matrix reasoning and improvement on the task (table 2.2.9). Matrix reasoning scores were used as a general measure of IQ. The results imply that IQ is unrelated to sleep dependent consolidation. As discussed above, this study comprised a relatively small sample size, similar analyses in a larger sample of children may generate different results. In addition, the IQ measure used in the current study was a short-form assessment and did not generate a full scale IQ score. Assessments of correlations between full scale IQ and sleep dependent consolidation may be necessary to establish the true relationship between IQ and sleep dependent learning.

2.2.7.3 Declarative memory changes over sleep in children

Initial analyses showed there were no significant changes in the amount of story material recalled before and after a period of sleep, or before and after a period of wake. In order to further investigate the relative effects of sleep and wake on declarative memory, repeated measures *t*-tests were performed to allow a comparison of the change seen over sleep and wake, in recall and recognition. These analyses revealed there were no significant differences between declarative recall change over sleep and declarative recall change over wake. This indicates that, relatively speaking, sleep is no better than wake for preventing the decay of declarative material when assessed by rote or thematic recall. However, analyses did reveal that recognition of declarative material was significantly better after a period of sleep than after a period of wake. Children were better at recognising story material after a

period of sleep than after a period of wake, indicating that the sleep state has some positive influence over declarative memory retention.

Robust research findings (including those discussed in sections 2.1.1) have confirmed that sleep dependent improvement occurs in the procedural domain, however evidence for the involvement of sleep in declarative memory has until now been less conclusive (Walker et al., 2002; Stickgold et al., 2000; Gais & Born 2004). The current study provides preliminary evidence that sleep leads to a greater recognition of story material than wake, findings that were also observed in a similar study with adults, reported in section 2.1.6. As discussed in section 2.1.7, the most obvious explanation for a result of this kind is that sleep prevents interference mechanisms, which are thought to contribute to the destruction of memory traces and which are present throughout a normal period of wake. The decay of memory over time is generally thought to be attributed to both interference and temporal decay, as the present study had an approximately equal temporal interval in both sleep and wake conditions, it is proposed that interference is the main contributing factor to the increased decay seen after wake. The consequence of any interference that may occur whilst awake, is that sleep is allowed a greater relative opportunity to stabilise memory traces, in essence the role of sleep is a passive one, simply facilitating memory storage by reducing interference. The role of interference is discussed in more detail in section 2.1.7.

However, another possibility that must be considered is that although the sleep state effectively prevents interference, during a period of sleep we are also prevented from the conscious rehearsal of material learnt during the day. During periods of wake, conscious rehearsal can lead to memory enhancements. Rehearsal is known to be particularly effective when items being remembered are relatively discrete, for example words or other verbal material such as that used in the current study. Participants in the current study were aware that after initial acquisition, they would be re-tested after approximately 12 hours and may have rehearsed the material in the intervening period, provided this was a period of wake. Although efforts were made to reduce rehearsal (by expressly asking participants not to consciously rehearse), all participants were children and may not have fully complied with this request. The presumed trade-off between the negative effects of interference over wake, and the

positive effects of rehearsal over wake, weaken the argument that the role of sleep in the enhancement of memory is entirely passive. This allows us to speculate that active processes taking place during sleep, may be effective for the enhancement of declarative recognition, perhaps utilising similar underlying mechanisms to those promoting overnight improvements on procedural tasks.

An interesting finding from this study is that sleep dependent retention of a memory trace appears restricted to recognition, and the effect is not seen when assessing recall. This finding was also observed in the study with adults discussed in section 2.1.6. The fact that a study assessing declarative memory in adults found a similar result to a study assessing declarative memory in children provides support that the result represents a genuine enhancement due to sleep. Although the two studies cannot be compared directly due to slight differences in methodology, it is interesting to note the similarities. Various explanations for the differences observed between recall and recognition are discussed in detail in section 2.1.7, with reference to a sample of adults. The general conclusion drawn is that the absence of sleep dependent recall is due to differences in the nature of the recall and recognition measures, rather than reflecting a narrow spectrum for sleep, specific to recognition. Whilst there are presumed differences between the mechanisms involved in sleep dependent consolidation in adults and children, this explanation for the differences in recall and recognition would also seem the most fitting for a sample of children.

2.2.7.4 Correlations between sleep variables, dependent variables, and IQ

In children, comparison of the descriptive statistics reveals very little difference between the participant sample questionnaire scores and scores from a control sample of 117 healthy children (table 2.3.2). All of the participant sample scores lie within one standard deviation of the control group means, indicating our participant sample is relatively normal in terms of their sleep quality. Correlational analyses revealed a significant positive correlation between parasomnias and three of the four measures of recall, but a non-significant correlation with the fourth measure of recall (however despite being non-significant there is a suggestion of a trend). As in the previous study, we are faced with the unexpected result that seems to suggest children suffering from parasomnias have better recall abilities. As discussed in the previous study, this finding could be the result of a beneficial change in the sleep

state due to parasomnias, or could reflect poor accuracy and validity in the parent-report questionnaire used to assess sleep.

Correlational analyses revealed there were no significant correlations between matrix reasoning and changes in recall and recognition (table 2.3.4). A similar result was reported in section 2.2.3, where matrix reasoning and improvement on a procedural task were found to be uncorrelated. The results imply that matrix reasoning IQ scores are unrelated to sleep dependent changes in both the procedural and declarative domains.

Although this finding provides an interesting discussion point, it seems clear that further research utilising a more comprehensive measure of IQ is required before any firm conclusions can be drawn.

2.2.8 Conclusions and Implications

The two studies discussed above provide evidence that sleep plays an important role in procedural and declarative memory processes in children. The findings suggest that sleep is preferable to wake for improving performance on a motor skill task, and for preserving recognition based memories. Performance enhancements over sleep are seen in both the procedural and declarative domains, but the evidence suggests that procedural skills are more sensitive to the effects of sleep than are declarative memories. These results are similar to the findings from the studies assessing the effect of sleep on procedural and declarative memories in adults (see sections 2.1.3 and 2.1.6 for results). The findings are also supported by previous work from a range of authors, reporting sleep dependent consolidation in both procedural and declarative domains in adults (e.g. Walker et al., 2002; Stickgold et al., 2000; Gais & Born, 2004; Hu et al., 2006). However, despite the relative wealth of evidence investigating sleep dependent learning in adults, the studies reported here are the first to assess the effect of sleep on learning in children. The finding that sleep dependent consolidation appears to occur in children has great implications in terms of the development of learning, and the relationship between sleep and learning may also have important consequences when considering education and schooling.

Although the results described above have provided some evidence that sleep is involved in memory enhancement in children, there is an obvious need for further

research in this area, and there are a number of limitations to this study. The sample size in the study is small, the lack of any previous research in this area means accurate calculations employing appropriate power statistics were difficult to undertake. Although the number of participants was sufficient to demonstrate the positive effect of sleep on procedural memory, the effects were not as conclusive as they were in adults, and the effect on declarative memory was less conclusive still. Increasing the number of participants may help reveal sleep dependent effects where none are present is the current study. The studies described here also lack any objective information on sleep, a study employing a night of PSG would be an obvious step towards generating more accurate data. Whilst the studies described above provide indications that sleep promotes learning in children, the findings need to be replicated before any firm conclusions can be drawn. An assessment of sleep dependent learning in children of different ages would also help disentangle the relationship between development and sleep dependent learning. In addition, comparisons with adults may add to our understanding of the relationship between sleep and learning in children.

Chapter 3

Sleep dependent consolidation in children with sleep disordered breathing and obstructive sleep apnoea: a case series

3.1 Introduction

The studies described in chapter two have provided some preliminary evidence that sleep plays an important role in processes of learning and memory. The findings established that sleep is preferable to wake for consolidation on a procedural task in both adults and children. The results also demonstrated that declarative memory recognition is better after a period containing sleep than after a period awake, in both adults and children. However, declarative memory recall was unaffected by sleep (relative to wake), in both groups. Research findings by other authors have also demonstrated sleep dependent consolidation in adults, in both the procedural and declarative domains (Walker et al., 2002; Stickgold et al., 2000; Gais & Born, 2004; Hu et al., 2006). The concept of sleep dependent consolidation in healthy adults now appears to be a relatively robust finding. However, there is no research to date investigating the effects of chronically disturbed sleep on sleep dependent consolidation.

Clinical sleep disorders refer to a large group of conditions characterised by difficulties relating to sleep, including difficulty falling asleep or maintaining sleep, falling asleep at inappropriate times, excessive total sleep time, or abnormal behaviours associated with sleep. Sleep disordered breathing (SDB) describes a sub-group of disorders characterised by abnormalities of respiratory pattern or quality of ventilation during sleep. The group of disorders range from relatively benign upper airway obstructions to chronic obstructive sleep apnoea (OSA). OSA is a primary sleep disorder characterised by upper airway obstruction resulting in the disruption of normal ventilation, which in turn leads to disturbed sleep patterns. Upper airway occlusion leads to the disruption of normal respiratory flow, resulting in hypoxia followed by repeated arousal episodes in an attempt to restore normal airway function (for a full review see section 1.4). Patients complain of disturbed sleep, frequent night arousals and occasional daytime somnolence. Parents and bed partners report loud snoring, often accompanied by apnoeic episodes at night (Bandla & Marcus, 2006).

The idea that learning and memory processes are consolidated over sleep has important implications for patients with sleep disorders. If learning processes are consolidated during sleep, then patients with chronically disturbed sleep (such as OSA) may suffer some impairment to these processes. Chronic sleep disruption or disruption to sleep architecture, leading to insufficient or inadequate sleep, may be damaging to aspects of learning and memory. The potential implications of impaired sleep dependent learning are particularly pertinent in children with OSA, as the consequences of impairments to learning are so important in terms of education and scholastic performance.

There is emerging evidence that children with OSA show reduced neurocognitive functioning. Snoring alone has been linked to a range of cognitive difficulties, a 1993 study by Ali et al. found that habitual snoring amongst 4-5 year olds was significantly associated with daytime sleepiness, restless sleep, and hyperactivity. Urschitz et al. (2003) assessed academic performance in primary school children who snored. They reported that snoring "always" (as defined by parental report) was significantly associated with poor academic performance in mathematics, science, and spelling. Snoring "frequently" was also significantly associated with poor academic performance in mathematics and spelling. Other data suggest that children with sleep disordered breathing also show neurocognitive and behavioural deficits. Studies have shown that the attentional capacity of children with sleep disordered breathing is often impaired, children with SDB have been shown to exhibit reduced selective and sustained attention (Blunden et al., 2000). Interestingly, deficits in attention have been shown to be reversible in children treated for SDB and successful adenotonsillectomy can lead to significant improvements in attention (Ali et al., 1996). Studies specifically assessing memory in children with SDB are limited but are suggestive of a reduced memory capacity in children with SDB (Blunden et al., 2001).

Studies of intelligence in children with SDB are also relatively limited, and are restricted to three published reports. Two of these studies reported significantly reduced IQ in children with SDB, whilst the other found that IQ was not impaired in children with SDB (Blunden et al., 2001). Studies assessing the learning and school performance of children with SDB are more conclusive, with several authors

reporting anecdotal and questionnaire data indicating children with SDB show reduced academic performance and learning (e.g. Guilleminault, 1976; Stradling et al., 1990). Conversely, other studies have shown that children who are poor academic achievers have a higher prevalence of night time snoring and breathing difficulties when compared to controls. In another paper, Gozal & Pope (2001) present data suggesting that SDB in early childhood may continue to adversely affect learning in later years. A review by Blunden et al. (2001) summarises the available evidence and concludes that children with SDB show reduced neurocognitive functioning, especially in the inter-related areas of attentional capacity, memory, and cognitive function.

The findings outlined above provide evidence that children with sleep disordered breathing and OSA are vulnerable to cognitive deficits. In addition, we have outlined findings (including those discussed in chapter 2) that demonstrate the importance of sleep for memory consolidation. The present study will attempt to investigate the effects of sleep disordered breathing and OSA on learning and memory in children, and to assess the effects of chronic sleep disturbance on cognitive function. We predict that chronic sleep disruption caused by sleep disordered breathing and OSA may be associated with deficits in sleep dependent learning, and may impair processes of overnight memory consolidation and enhancement. This study will add to the current literature on sleep dependent consolidation as it will directly assess sleep dependent learning in children with OSA, and will utilise objective measures of sleep. The study will also generate data on neurocognitive function, and will hope to investigate the relationship between neurocognitive function and sleep dependent consolidation in children with OSA. A study of this kind has the potential to provide valuable and meaningful additions to the existing literature base. The study describes a case series of four children undergoing investigation for OSA, and attempts to investigate the relationship between sleep and cognitive function in these children.

Aims

The aim of this study is to investigate whether sleep dependent learning is impaired in children who suffer from sleep disturbances due to sleep disordered breathing.

Hypothesis

The hypothesis states that children who have disturbed sleep due to sleep disordered breathing will be impaired on tests on sleep dependent learning, when compared with healthy children who sleep well. Specifically, the hypothesis states that disruption to sleep quality and quantity in children leads to deficits in the ability to successfully consolidate procedural and declarative material over sleep.

3.2 Methods

3.2.1 Consent

Prior to the study, parents and children were provided with comprehensive information and were invited to a meeting with the research team to discuss the study and to have any questions answered. Parents gave written informed consent and children gave written informed assent. The study was approved by the NHS South Sheffield Research Ethics Committee.

3.2.2 Participants

Described here is a series of four patients who presented with clinical sleep disordered breathing features symptomatic of OSA. Each patient was referred by their GP to the ENT (Ear, Nose and Throat) or Medical clinic at the Sheffield Children's Hospital, for consideration of adenotosillectomy because of concerns about possible obstructive sleep apnoea. Children were referred for a full in-patient sleep study after assessment from ENT specialists.

Case 1-BD

A non-obese 10-year old boy was referred to ENT after his mother voiced concerns about his snoring and breathing problems at night. His mother reported frequent snoring, coughing and sneezing, and apnoeic episodes lasting up to five seconds, she also reported that he did not sleep comfortably and ate with his mouth open. The boy also suffered from occasional daytime somnolence but had no history of recurrent tonsillitis or allergies. Two years previous to the referral a post-nasal space x-ray showed enlarged adenoids, but at the time of referral his tonsils were not enlarged. The patient was otherwise healthy except for some speech problems as a young child (attended speech therapy). The patient attended a mainstream school and had no reported special educational needs or behavioural problems.

Case 2-LG

A non-obese 5-year old boy was referred for a sleep study after suffering significant problems with his tonsils and bouts of sore throat requiring repeated antibiotics. His father also reported frequent loud snoring, significantly disturbed sleep, and constant mouth breathing. Two years previously, the patient's older brother had reported similar symptoms and a subsequent adenotonsillectomy was successful in treating the problem. Examination revealed large, obstructive looking tonsils, and the patient was hyponasal with noisy breathing, however there was little evidence of daytime somnolence. His father also expressed concerns over his hearing, but an audiogram was normal. The patient was otherwise healthy, he attended a mainstream school and there were no reported special educational needs or behavioural problems.

Case 3-SS

A non-obese 7-year old girl was referred for a sleep study after her mother expressed concerns over her persistent loud snoring and occasional obstructed breathing at night. Her mother reported mouth breathing throughout the night. The patient reported that she repeatedly woke during the night and her mother confirmed significantly disturbed sleep. Examination revealed large tonsils that appeared obstructive, and the patient was hyponasal. The patient was otherwise healthy and did not report daytime somnolence. The patient attended a mainstream school and had no reported special educational needs or behavioural problems.

Case 4-JW

A non-obese 10-year old boy was referred for a sleep study after his mother expressed concerns over his constant and very loud snoring. The snoring had begun in early childhood but had recently become worse and was associated with significantly disturbed sleep, his mother reported that he had never had a good night's sleep. Examination revealed enlarged tonsils and there was evidence of daytime somnolence. The patient also suffered from asthma, but other than this he was healthy and had no problems at his mainstream school. There was no evidence of special educational needs and no reported behavioural problems.

For purposes of comparison we have also described data from a recent study designed to characterise normal polysomnographic values in healthy children and adolescents. The study assessed sleep and respiratory parameters in 70 healthy children, the mean age was 7.9 years (SD = 4.4), the age range was 1 to 15 years and 43% were male. Children with a clinical history of sleep disordered breathing were

excluded, as were those with the following; snoring, laboured breathing or chest retractions during sleep, sleep apnoeas, craniofacial anomalies, obesity, chronic illness, history of adenoidectomy or tonsillectomy, or other airway surgery (Uliel et al., 2004). No control data was available for the following variables; sleep onset latency, desaturation index, percentage of time spent snoring (snorers were excluded from control study).

Control data for the various cognitive tasks has also been presented, studies described in chapter two generated control data for both the procedural (n = 20, mean age = 8.85, SD = 1.46) and declarative tasks (n = 21, mean age = 8.57, SD = 1.99). Control data from chapter two is also presented for the subjective variable 'sleep quality-study night' (n = 21, mean age = 8.57, SD = 1.99). Studies described in chapter five generated control data for the Paediatric Sleep Questionnaire (PSQ) (n = 117, mean age = 11.05, SD = 3.41).

3.2.3 Apparatus

Sleep Studies

Each child underwent a night of full polysomnography (PSG) with video recording in the specialised sleep lab at the Sheffield Children's Hospital. For each child, a parent or guardian was also invited to stay in the sleep lab on the night of the sleep study, in order to provide reassurance during PSG set up and during the night. Sleep studies were conducted and scored (blind) by a qualified sleep physiologist. PSG comprised recordings on the following channels: EEG (C3-A2; C4-A1; O1-A2; O2-A1), EOG (left and right), EMG (sub mental chin left and right), ECG, nasal/pressure/airflow, SpO_2 and pulse waveform, CO_2 (end-tidal/transcutaneous), body position, actimetry, microphone, and video. After scoring, recordings from the sleep study provided information on both sleep architecture and respiratory function. Sleep variables consisted of the following; total sleep time (TST), sleep onset latency, sleep efficiency ([sleep after sleep onset divided by TST] x 100), percentage of TST in each sleep stage, and arousal index (number of arousals per hour of sleep). Respiratory data consisted of the following; respiratory disturbance index (number of events or breathing pauses per hour slept), minimum SpO_2 (minimum levels of blood oxygen), desaturation index (number of 4% desaturations per hour i.e. number of

times SpO_2 dips more than 4% below baseline for child per hour), and percentage of time asleep spent snoring.

Cognitive measures

Children underwent a battery of cognitive tests designed to assess sleep dependent learning in different memory domains. A declarative memory task involved story recall and recognition, and a procedural motor skill task involved training and testing on a finger-thumb opposition task, these tasks are described in detail in the methods section of chapter two.

Questionnaire measures

Parents were asked to complete a short questionnaire on behalf of their child. The Paediatric Sleep Questionnaire (PSQ) is a generic measure of sleep quality and is designed to assess sleep disturbances and sleep-related disorders in childhood. It is designed to assess general problems with sleep, not to provide an accurate diagnosis of sleep disorders (Cortesi et al., 1999). Items from the questionnaire were grouped to yield five sleep factors (parent/child interactions at night, sleep fragmentation, parasomnias, daytime drowsiness, bedtime difficulties). In addition, the sum of all questionnaire items generated a total score, on all factors a higher score indicated more sleep problems. The questionnaire is described in detail in chapter five. During the night of the sleep study parents were encouraged to note any significant night time events that occurred, and to comment on their child's sleep as compared to normal. After the night of the sleep study, children were also asked to mark on a five point scale how well they thought they had slept compared to a normal night of sleep (1 = worse than usual, 5 = much better than usual). This item was termed 'sleep quality (study night)'.

3.2.4 Design

As the study was designed to assess the effect of sleep on consolidation, patients were tested on three occasions spanning a day awake and a night asleep. In order to incorporate a day phase and a night phase, testing sessions were either a consecutive morning-evening-morning, or a consecutive evening-morning-evening. In an attempt to counterbalance testing order, patients BD, SS and LG were tested evening first, while patient JW was tested morning first. It was not possible to

counterbalance fully due to the constraints of patient travel to and from hospital. Thus, participant JW attended his first session at 8.30a.m (day 1), his second session at 7.00p.m (day 1), and his third session at 8.00a.m (day 2). Participants BD, SS, and SS attended their first session at 7.00p.m (day 1), their second session at 8.00a.m (day 2), and their third session at 6.30p.m (day 2). Although an ideal design would have separated all sessions by exactly 12 hours, this was not possible due to practical constraints, schooling etc. Training was given prior to the first testing session for all participants.

3.2.5 Procedure

Children and parents were asked to attend the sleep lab in the late afternoon so children could be familiarised with the surroundings. One to two hours before the child's usual bedtime, a paediatric sleep physiologist began the application of recording electrodes for the sleep study, after which the child was encouraged to follow their usual bedtime routine and to try and sleep as normal. Parents were able to provide reassurance throughout the set-up and were provided with a bed in the sleep lab for the duration of the study. During their stay in the sleep laboratory, children participated in both a procedural and a declarative task, the procedure for instructing and testing children was identical to that in chapter two, and was undertaken by the same two experimenters (see sections 2.2.2 & 2.2.5). A parent accompanying the child was asked to complete the PSQ on behalf of their child, as accurately and honestly as possible. The morning after the sleep study children were asked to record how well they thought they had slept on a scale of 1-5 (worse than usual to better than usual).

3.2.6 Variables and Analyses

The sleep study generated sleep and respiratory variables as listed in section 3.2.3, subjective questionnaire variables gave further information on sleep (section 3.2.3). Variables generated by the procedural and declarative cognitive tasks are as listed in chapter two. As the number of participants in this study is too small to justify the use of inferential statistics, descriptive statistics are given alongside normalised values or data from suitable control groups (Uliel et al., 2004; also see data from chapters 2 & 5). Speculative suggestions and inferences are made on the basis of trending relationships and non-statistical associations.

3.3 Results

3.3.1 Sleep quality (PSG)

All four children underwent full inpatient PSG in a sleep laboratory, data was scored blind by a qualified sleep physiologist. Sleep data is shown in table 3.1 and respiratory data is shown in table 3.2, normalised values from a group of 70 healthy control children are also included for purposes of comparison (Uliel et al., 2004). Those participants who deviated from the control mean by more than two standard deviations are flagged.

	Norms (mean & SD)	BD	LG	SS	JW
Total sleep time (TST) (mins)	387.6 (74.4)	422.0	*554.5	*624.0	464.5
Sleep onset latency (mins)	n/a	85.5	14.0	11.0	48.5
Sleep efficiency (%)	90.8% (6.5%)	87.1%	90.3%	95.3%	93.2%
% REM	17.4% (5.7%)	15.8%	19.9%	17.4%	22.0%
% Stage 1 NREM	4.1% (4.1%)	1.8%	6.6%	7.2%	5.5%
% Stage 2 NREM	48.9% (9.7%)	55.1%	49.3%	39.7%	44.3%
% Slow Wave Sleep	25.2% (9.1%)	27.4%	24.1%	35.7%	28.2%
Arousal Frequency (per hour of sleep)	5.29 (3.49)	7.8	*14.6	9.9	8.7

Table 3.1: PSG generated sleep data for participants and norms from a group of 70 healthy control children (Uliel et al., 2004) (>2 SD's from norm mean).*

	Norms (mean & SD)	BD	LG	SS	JW
Respiratory disturbance index	Apnoeas observed in 41% of norms, within these mean CA index = 0.4	0.0	0.9	0.0	2.6
Minimum SpO_2	94.6% (2.2%)	95.0%	95.0%	95.0%	92.0%
Desaturation index	n/a	0.2	0.0	0.0	0.8
% of time spent snoring	n/a	0.0%	22.4%	19.1%	1.0%

Table 3.2: PSG generated respiratory data for participants and norms (Uliel et al., 2004) (CA = central apnoea).

3.3.2 Sleep quality (subjective)

Parents of all participants completed the Paediatric Sleep Questionnaire (PSQ) on behalf of their child, the PSQ grouped items into factors relating to different areas of sleep disturbance, scores are shown in table 3.3. Scores are also shown for a control group of 117 healthy control children (mean age 11.05 yrs, SD = 3.41), characteristics of the control group are described in detail in chapter five.

	Controls (mean & SD)	BD	LG	SS	JW
Parent/Child Interactions	5.10 (2.10)	6	7	*10	8
Sleep Fragmentation	8.36 (2.10)	7	*13	5	*14
Parasomnias	11.13 (5.10)	14	14	8	17
Daytime Drowsiness	8.32 (2.65)	9	11	6	*16
Bedtime Difficulties	7.29 (2.61)	8	11	8	*14
Total Score	45.5 (8.90)	50	63	43	*79

Table 3.3: PSQ scores for participants and 117 controls (for more information see chapter 5) (>2 SD's from control mean).*

In addition to the parental report measures, children completed a measure of subjective sleep quality for the night of the sleep study. The healthy control mean generated from studies described in chapter two (n = 21) was 3.14 (SD = 0.48). Scores for participants are as follows: BD = 3, LG = 4, SS = 3, JW = 2, indicating that all four children felt they had a reasonable night's sleep during their stay in hospital.

3.3.3 Cognitive data – Procedural task

Table 3.4 shows a comparison of scores between controls and participants on the procedural task. Control data was generated from the studies described in chapter two. Scores for controls are mean averages whilst scores for participants are actual scores. Scores are shown for all control participants (n = 20, mean age = 8.85, SD = 1.46), and also for those controls that were in the sleep first condition (n = 11, mean age = 9.18, SD =1.25) in order to provide better comparisons with subjects BD, LG and SS who also participated in sleep first conditions. Scores are given for change in number of correct sequences over periods of sleep and wake, and the difference between sleep change and wake change. Similarly, scores are given for change in time per sequence over sleep and wake periods, and the difference between sleep

time change and wake time change. Arguably, the most meaningful parameters generated by the cognitive tasks are 'sleep change minus wake change' parameters, as these provide a single score providing information on the differential relative effects of the sleep and wake periods (a positive score indicates greater performance gains are seen over sleep, whilst a negative score indicates greater gains are seen over wake). Table 3.5 shows a comparison of scores between all controls (n = 20, mean age = 8.85, SD = 1.46), wake first controls (n = 9, mean age = 8.44, SD = 1.67), and subject JW who participated in the wake-first condition.

	All Controls (n=20)	Sleep-First Controls (n=11)	BD	LG	SS
Change in number of correct sequences (sleep)	2.92 (1.94)	3.59 (1.36)	4.0	6.0	2.0
Change in number of correct sequences (wake)	1.13 (2.66)	-0.27 (2.22)	0.5	2.0	0.0
Sleep change minus wake change	1.8	3.86	3.5	4.0	2.0
Sleep change in time (secs)	0.387 (0.26)	0.555 (0.23)	-0.08	0.17	0.14
Wake change in time (secs)	0.307 (0.40)	0.146 (0.2)	0.01	0.32	0.07
Sleep change minus wake change (secs)	0.080	0.409	-0.09	-0.15	0.07

Table 3.4: Comparison of scores between all controls (mean & SD), sleep first controls (mean & SD), and participants BD, LG and SS on the procedural task (for information on control sample see chapter 2).

	All Controls (n=20)	Wake-First Controls (n=11)	JW
Change in number of correct sequences (sleep)	2.92 (1.94)	2.11 (2.30)	0.5
Change in number of correct sequences (wake)	1.13 (2.66)	2.83 (2.18)	5.5
Sleep change minus wake change	1.8	-0.7	-5.0
Sleep change in time (secs)	0.387 (0.26)	0.182 (0.13)	0.44
Wake change in time (secs)	0.307 (0.40)	0.502 (0.49)	0.45
Sleep change minus wake change (secs)	0.080	-0.320	-0.01

Table 3.5: Comparison of scores between all controls (mean & SD), wake first controls (mean & SD), and subject JW on the procedural task (for information on control sample see chapter 2).

3.3.4 Cognitive data – Declarative task

Table 3.6 shows a comparison of scores between controls and OSA participants on the declarative task. Control data was generated from the studies described in chapter two. Scores for controls are mean averages from the group of 21 healthy children described in chapter two (mean age = 8.57, SD = 1.99), whilst scores for OSA participants are actual scores. Scores are given for rote and thematic recall over sleep and wake, and the difference between sleep change and wake change. Again, the most meaningful parameters are the 'sleep minus wake' parameters, as these generate a single score providing an indication of the relative effects of the sleep and wake phases. Scores are also given for recognition after sleep and wake, and the difference between sleep and wake on recognition. As results for the declarative task are not based on cumulative scores (as in the procedural task), no distinction was made between children in different conditions (i.e. sleep first vs. wake first).

	All Controls (n=21)	BD	LG	SS	JW
Rote recall change (sleep)	-0.95 (2.65)	0	0	0	1
Rote recall change (wake)	-1.04 (3.53)	1	0	2	0
Sleep recall minus wake recall (rote)	0.09	-1	0	-2	1
Them recall change (sleep)	-0.19 (0.81)	0	0	0	0
Them recall change (wake)	-0.24 (0.94)	0	0	1	0
Sleep recall minus wake recall (them)	0.05	0	0	-1	0
Recognition (sleep)	12.29 (2.1)	14	14	13	12
Recognition (wake)	11.05 (1.9)	12	12	12	14
Sleep minus wake (recognition)	1.24	2	2	1	-2

Table 3.6: Comparisons between healthy controls (mean & SD) and participants BD, LG, SS and JW on the declarative task (for information on control sample see chapter 2).

3.3.5 Comparison of *z*-scores

A clear weakness of the current study is the small sample size, the analysis of data from single participants does not allow us to draw any statistically significant conclusions regarding the data. However, comparison of standard scores (*z*-scores) provides a more meaningful way of presenting the data, and allows a better assessment of participants in comparison to controls. Table 3.7 shows *z*-scores for the four participants for the procedural task, and table 3.8 shows *z*-scores for the declarative task, *z*-scores are calculated from the distribution of the control sample

described in chapter two. Although the most meaningful parameters generated by the cognitive tasks are 'sleep change minus wake change' parameters, these derived scores cannot be converted into standard scores. As such, *z*-scores are only calculated for 'change over sleep' and 'change over wake' parameters for the various cognitive measures. Scores that are notably deviant from distribution means and may therefore represent an abnormal result are flagged (i.e. $z > 1.5$ or $z < -1.5$).

	BD	LG	SS	JW
Change in number of correct sequences (sleep)	0.56	*1.59	-0.42	-1.25
Change in number of correct sequences (wake)	-0.24	0.33	-0.42	*1.64
Sleep change in time (secs)	*-1.80	-0.83	0.95	0.20
Wake change in time (secs)	-0.74	0.03	0.59	0.36

Table 3.7: Comparison of z-scores for participants on procedural task ($z > |1.5|$).*

	BD	LG	SS	JW
Rote recall change (sleep)	0.36	0.36	0.36	0.74
Rote recall change (wake)	0.58	0.29	0.86	0.29
Thematic recall change (sleep)	0.23	0.23	0.23	0.23
Thematic recall change (wake)	0.26	0.26	1.32	0.26
Recognition (sleep)	0.81	0.81	0.34	-0.14
Recognition (wake)	0.87	0.87	0.87	*1.55

Table 3.8: Comparison of z-scores for all participants on declarative task ($z > |1.5|$).*

3.4 Discussion

3.4.1 Participant BD

Participant BD presented with a history of snoring and breathing problems at night, his mother had voiced concerns about his sleep and reported occasional daytime somnolence, despite this he had no reported educational problems and was doing well at school. PSG derived sleep data are shown beside data from healthy controls in table 3.1, comparison of the various sleep parameters confirms that BD is relatively normal in terms of sleep quality with all recorded sleep parameters falling within two standard deviations of the control mean. Although we have no control data for sleep onset latency, it would be predicted that most children of this age would take significantly less than 85.5 minutes to fall asleep. However, as the current study did not include an acclimatisation night at the sleep lab, it can be

speculated that this unexpectedly long sleep latency is a result of the presence of recording equipment and the unfamiliar surroundings. An assessment of respiratory data (table 3.2) also shows that BD's sleep appears relatively undisturbed in terms of respiratory events and desaturations. Although some desaturations were recorded (an average of 0.2 per hour slept), a minimum oxygen saturation (SpO_2) of 95% demonstrates that respiratory function and gas exchange are not compromised during sleep. There is a noted absence of respiratory events during the night (RDI = 0), this is perhaps surprising given that desaturations have been recorded as one would normally expect to observe respiratory events in association with oxygen desaturations. However, the low desaturation index and the healthy levels of blood oxygen indicate that either respiratory events were too subtle to be scored, or some external artefact has led to an over-reporting of oxygen desaturation (as occasionally happens when recording electrodes become loose, contacts are lost etc.).
Interestingly, despite the reported history of chronic snoring at night, the data reveals that there was no snoring on the night of the sleep study. In addition, assessment of subjective sleep quality as measured by the PSQ (table 3.3) confirms that BD scores within two standard deviations of the control means for all sleep factors.

In summary, despite the history of sleep difficulties and concerns over snoring, BD appears to fall well with the range of normal in terms of sleep quality and sleep respiratory function. Clinical assessment of the sleep study by a physiologist led to a conclusion of '*essentially normal sleep, no significant respiratory events and normal gas exchange throughout*'. The study did not support the need for surgical intervention or any further treatment for sleep disordered breathing.

Assessment of performance on the procedural task (table 3.4) shows that BD demonstrates a greater improvement in number of sequences performed after a period of sleep than after a period of wake. Examination of the *z*-scores indicates that BD's performance is not significantly deviant from controls (table 3.7). Numerically, there is very little difference in time taken to perform a sequence after sleep and wake, analysis of the *z*-scores indicates that when compared to control means, BD does not show a comparable improvement in speed over sleep (change in time (sleep), $z = -1.80$) (table 3.7), perhaps indicating performance gains are a result of decreased errors rather than increased speed. Findings discussed in chapter two

demonstrate that sleep is preferable to wake for the consolidation of a procedural skill in healthy children. This general pattern of results is reflected in the data described for BD, confirming a greater improvement is seen after sleep than wake. Assessment of performance on the declarative task (table 3.6) also shows a similar pattern of results to healthy controls, with little change in recall, but greater recognition of material after sleep than after wake. Examination of *z*-scores for the declarative task confirms that BD does not differ from the control group by any notable margin (i.e. $z < |1.5|$) (table 3.8).

The PSG derived sleep and respiratory data, combined with the subjective parental report PSQ provide a reasonable picture of the sleep quality of BD. It appears that despite concerns over snoring and breathing difficulties at night, his sleep is within the range of normal for a child. Although this assessment of 'normal' sleep is perhaps unexpected given the medical history, it is not uncommon for a child's sleep to improve spontaneously without the need for intervention. Although this study was predicting impaired cognitive skills in children with chronic sleep disturbances, given the relatively normal sleep observed in BD, it is not surprising that we do not see any obvious impairment to sleep dependent procedural and declarative learning.

3.4.2 Participant LG

Participant LG presented with a history of chronic tonsillitis and sore throats, frequent snoring was reported, along with constant mouth breathing and very disturbed sleep. There were no reported cognitive difficulties or educational problems and LG attended a mainstream school. Comparison of PSG derived sleep parameters (table 3.1) shows that LG's total sleep time (TST) is more than two standard deviations greater than the mean TST from a group of healthy controls. However, given that the mean age of the control sample is 7.9 years, and that LG is 5 years old, we might expect LG to have a longer total sleep time as younger children are known to sleep for longer, with sleep time typically decreasing throughout childhood (Sheldon, 2006; Stores, 2001). A sleep onset latency of 14 minutes demonstrates a healthy ability to attain asleep, and is not unduly long. Other sleep parameters (sleep efficiency, percentage of sleep stages) are comparable with values from controls, with the exception of arousal frequency. On the night of the sleep study LG's arousal frequency was nearly three times that of the control mean,

indicating a significant degree of disturbance to his sleep. This may also account for the higher than predicted total sleep time, with a longer sleep period needed in order to compensate for the frequent arousals. In terms of respiratory parameters, a respiratory disturbance index of 0.9 may explain the high arousal frequency, as respiratory events often lead to arousals. Although a respiratory disturbance index of 0.9 was observed, none of these events resulted in oxygen desaturations, and blood oxygen levels did not fall below 95%. The percentage of time spent snoring was also relatively high, with LG snoring for nearly a quarter of the time asleep. Assessment of subjective sleep quality as measured by the PSQ also confirms that sleep fragmentation is a problem area for LG, this being the only area in which he scores more than two standard deviations from control means.

In summary, although LG's sleep is not significantly compromised in terms of oxygen saturation, he still suffers from frequent arousals and fragmentation to his sleep most probably caused by respiratory events. Clinical assessment of the sleep study by a physiologist led to a conclusion of '*frequent snoring, restless sleep, occasional respiratory events consistent with upper airway resistance syndrome, despite no significant disturbance of gas exchange*'. The study supported the impression of a clinically relevant upper airway obstruction and at the time of writing LG was being discussed as a candidate for adenoteonsillectomy.

When we look at LG's performance on the procedural cognitive task, we see the number of correct sequences performed is greater after sleep than after wake, analysis of the *z*-scores indicates that LG's improvement in performance after sleep is considerably greater than in controls ($z = 1.59$) (table 3.7). However, the time taken to perform a sequence showed a marginally greater improvement after wake than after sleep. Despite this, examination of the *z*-scores indicates that LG falls within the range of what can considered normal with respect to change in time after sleep and wake (i.e. $z < |1.5|$ for both parameters). Although we would normally expect to see an improvement in performance accuracy accompanied by an improvement in speed, the results produced by LG are not so deviant from controls as to suggest any significant abnormality. Therefore, we can conclude that LG's performance on the task reflects the pattern of results observed in the control group,

and performance gains are greater over periods of sleep compared to periods of wake.

When we look at the performance of LG on the declarative task, we observe no differences in recall over sleep and wake, but recognition is better after a period of sleep than a period of wake, results that reflect findings in controls. Examination of *z*-scores confirms there is no notable deviation from control means ($z < |1.5|$). In summary, it appears that LG has some significant disturbance to his sleep, resulting in repeated arousals and fragmented sleep. Although LG's respiratory function does not appear to be hugely compromised, there is certainly some deviation from a normal sleep pattern. It can also be speculated that this sleep disturbance results in the need for a longer total sleep time, and is reflected in the considerably extended TST. In terms of cognitive performance, the results suggest that LG's performance on the declarative task is very similar to controls. In addition, although his performance on the procedural task does not show a great sleep dependent improvement in terms of speed, there is a considerable improvement in terms of the number of sequences performed. Although we cannot draw significant conclusions from this anecdotal evidence, it appears that LG's cognitive function is not significantly impaired by his sleep disordered breathing, although the results would certainly warrant further investigation into the effect of disturbed sleep on procedural learning.

3.4.3 Participant SS

Participant SS presented with a history of persistent loud snoring and occasional obstructed breathing at night, she reported repeated awakenings during the night and significantly disturbed sleep. No daytime or educational problems were reported, and she attended a mainstream school. Comparison of PSG derived sleep parameters (table 3.1) shows that SS falls within two standard deviations of the control means on all parameters except total sleep time (TST). The TST recorded for SS is almost twice that of the control mean, this is despite SS being of a similar age to the control group (7.0 years vs. 7.9 years). A sleep onset latency of 11 minutes appears normal and indicates there are no problems with attaining sleep. Although the arousal frequency recorded for SS is slightly higher than normal, it still lies within two standard deviations of the control mean. Inspection of the respiratory data (table 3.2)

reveals that the sleep of SS was not compromised by any respiratory events, did not suffer any significant oxygen desaturations during the night, and retained a healthy blood oxygen level above 95.0%. She did however, spend a significant portion of the night snoring (19.1%). Assessment of subjective sleep quality as measured by the PSQ reveals that 'parent/child interactions during the night' is the only area in which SS scores particularly highly. This indicates that SS requires more parental involvement at bedtime and during the night than control children, although this gives us useful information regarding the behavioural aspects of sleep, it does not necessarily reflect any specific disturbances to sleep architecture, and indeed it does not appear to predict any objectively defined sleep or respiratory disturbances.

It appears that despite parental concerns and persistent snoring, the sleep of SS is relatively normal when compared to healthy control children, in fact she sleeps for much longer than the majority of her peers and despite a slightly higher than average arousal frequency she does not appear to have any significant difficulties with sleep. Clinical assessment of the sleep study by a physiologist led to a similar conclusion and reported *'heavy snoring confirmed but no respiratory compromise observed'*. Post-study, parents also reported an improvement in snoring and breathing at night, and SS did not require surgical intervention or other treatment.

An inspection of the cognitive data reveals that on the procedural task, SS shows a greater improvement in performance over a period of sleep than over a period of wake, as defined by both number of sequences performed and time per sequence (table 3.4). Examination of the *z*-scores also indicates that on the procedural task, SS does not differ from control means by any significant margin (table 3.7). With respect to the declarative task, although SS was able to recall slightly less after a period of sleep than after a period of wake, her recognition was slightly better after sleep than after wake (table 3.6). An examination of the *z*-scores reveals that none of the recall parameters has a *z*-score of $z > |1.5|$, indicating that the pattern of recall observed in SS is not notably different from that observed in controls. Although it is interesting to note that SS recalls slightly more after wake than after sleep, it is difficult to interpret this finding without being able to analyse the statistical significance and without further investigation of the processes of declarative recall in a control sample. Inspection of the *z*-scores for recognition reveals that SS does not

differ notably from controls in terms of recognition, indicating her pattern of recognition after sleep and wake is similar to that of controls.

In summary, it appears that despite a referral for sleep disordered breathing, SS has a relatively normal sleep pattern and there are no particular concerns regarding either sleep patterns or respiratory function. Since the sleep study was performed, parents reported a significant and spontaneous improvement in the sleep of SS, and reported that snoring and awakenings have decreased. Given the relative normality of sleep patterns in SS, we would not predict any impairment in her ability to consolidate material overnight. Analysis of the cognitive data revealed a similar pattern of results to controls on the procedural task, with greater performance gains being observed over sleep than over wake. On the declarative task, the results are a little less clear cut, with SS recalling more after wake than after sleep, but conversely having better recognition after sleep than after wake. It should be noted however that the differences in recall and recognition were very small and would be unlikely to prove statistically significant. In addition, evidence for the role of sleep in processes of declarative memory is less conclusive, with research suggesting that sleep is only effective in promoting recognition. In this case, it is a possibility that the small differences observed in the declarative performance of SS are insignificant, nevertheless findings such as these prompt the need for further research into sleep and declarative memory.

3.4.4 Participant JW

Participant JW was referred for persistent and very loud snoring, his mother also reported very disturbed sleep and occasional daytime somnolence. He had no reported cognitive difficulties and attended a mainstream school. Inspection of the PSG derived sleep data (table 3.1) indicates that JW falls within two standard deviations of the control means on all sleep parameters. A sleep onset latency of 48.5 minutes is rather high for a child, however this particular participant suffered a degree of anxiety at the application of the recording electrodes and required some reassurance by his mother. I would speculate that the slightly long sleep latency is due to anxiety rather than a reflection of a true sleep disturbance. This indicates that in terms of sleep architecture, JW falls within the range of normal scores and does not appear to be suffering any significant sleep disturbance. The arousal frequency

reported for JW is slightly higher than that of the control group, it is not so high as to warrant concern regarding sleep quality, but it may indicate some level of respiratory disturbance. Inspection of the PSG respiratory data reveals that JW is indeed suffering some degree of respiratory disturbance during sleep, with an average of 2.6 respiratory events per hour slept. Respiratory events in JW are also associated with some oxygen desaturations, and a lower than desirable minimum SpO_2 of 92%. Although JW is only recorded as snoring for 1% of the time slept, it appears that respiratory events are contributing to a considerable disturbance to normal respiratory function during sleep, despite sleep architecture in general seemingly unaffected. Assessment of subjective sleep quality as measured by the PSQ reveals JW is reported as having considerable problems in the areas of sleep fragmentation, daytime drowsiness, and bedtime difficulties, with scores on all these factors exceeding the control mean plus two standard deviations. In addition, the total score for the PSQ is considerably greater than that of the mean from the healthy control sample. The high score for parent reported sleep fragmentation is reflected in the slightly elevated PSG arousal frequency index. However, problems with daytime drowsiness and bedtime difficulties are not easily correlated with PSG derived data as they are designed to assess more behavioural aspects of sleep such as the daytime consequences of sleep disturbance, and problems before sleep onset. PSG data provides information on objective sleep and respiratory parameters only, and as such it is useful to collect additional information regarding other aspects of sleep from parents.

In summary, JW appears to have a significant sleep disturbance, sleep architecture is preserved relatively intact except for indications of slightly elevated arousals and fragmented sleep. However, there is considerable respiratory disturbance and subsequent daytime somnolence confirmed by both objective and subjective measures. This conclusion was confirmed by the sleep physiologist's clinical assessment of the sleep study which concluded '*significant upper airway obstruction during sleep, RDI abnormally high but no severe gas exchange problems*'. As a result of the sleep study JW has undergone subsequent adenotonsillectomy.

Analysis of the cognitive data reveals that on the procedural task (table 3.5), JW showed greater performance gains after a period of wake than after a period of sleep.

An inspection of the *z*-scores provides further evidence that JW differs notably from the pattern of results observed in the control sample. The *z*-scores for 'change in number of correct sequences' for sleep and wake are $z = -1.25$ and $z = 1.64$ respectively (table 3.7), this indicates that JW is performing slightly worse than controls after a period of sleep, and considerably better than controls after a period of wake. This result is contradictory to the findings described in chapter two, which demonstrated that sleep is preferable to wake for the improvement and consolidation of a procedural skill. However, as was also discussed in chapter two, testing order is an important moderator of sleep dependent performance gains. To recap, children's performance improved more after sleep than after wake, but this effect was greatest in those who were first tested after the sleep phase, when compared to those first tested after the wake phase. As JW was the only participant in the current case series tested first after the wake phase, we would expect a different pattern of results to the other three children, hence the separate tabulation with comparisons with other children in the 'wake-first condition' (table 3.5). Inspection of the results provided by the control children in the 'wake-first condition' reveals that they too improved marginally more after wake than after sleep, although not to so great an extent as JW.

Inspection of results on the declarative task revealed that although recall varied very little after sleep or wake, recognition was better after a period of wake than after a period of sleep (table 2.6). This is substantiated by examination of the *z*-scores, the standard score for 'recognition (wake)' ($z = 1.55$) indicates JW is performing notably better than controls after a period of wake. This again contradicts the findings from the healthy group described in chapter two, who recognised significantly more after a period of sleep than after a period of wake. As the declarative task is not based on a cumulative performance, scores from control children are not separated into 'sleep-first and 'wake-first', and would not be expected to be influenced by order. The cognitive data from JW appears to show a preference for wake over sleep for improvement on procedural and declarative tasks, this is contrary to our earlier findings and those of other research groups which have shown periods of sleep lead to performance enhancements not matched by similar periods awake.

3.4.5 Effect of sleep disordered breathing on sleep dependent procedural and declarative learning

The aim of the current study was to make preliminary investigations into the effect of sleep disorders on sleep dependent procedural and declarative learning. Previous research has shown that children with OSA and sleep diosreded breathing are susceptible to neurocognitive deficits, Blunden et al. (2001) concluded that children with SDB show reduced neurocognitive functioning, especially in the inter-related areas of attentional capacity, memory, and cognitive function. The current study attempted to investigate whether impairments to sleep dependent learning might be responsible for the neurocognitive deficits often associated with OSA. Of the four children referred with features symptomatic of OSA, only two of the children (LG and JW) were found on the basis of the sleep study to have any clinically significant sleep disordered breathing. The other two children (BD and SS) were reported as having essentially normal sleep and despite snoring episodes there was no indication of significant disturbance to sleep architecture or respiratory function. Although the data presented is generated from an insufficient number of participants to allow the use of inferential statistics, analysis of the descriptive data and *z*-scores provides us with some interesting points to consider. As previously discussed, participants BD and SS were found to have essentially normal sleep, and despite referrals for obstructed breathing were found to fall within the range of normal for both sleep and respiratory parameters. As such we would not predict any significant deficits in the performance of the specific cognitive tasks designed to assess sleep dependent learning. Indeed, inspection of the cognitive data also revealed a similar pattern of results to that seen in controls (see chapter two), with both BD and SS revealing an enhanced level of performance after a period of sleep, when compared with a similar period of wake.

In contrast, participants LG and JW were found on the basis of the sleep study to have some considerable and clinically relevant disturbance to their sleep. Although both children demonstrated significant obstructive breathing patterns, and were observed as having high respiratory disturbance indices, neither child appeared to suffer severe gas exchange problems, with minimum SpO_2 of 95% and 92% respectively. As such, participants LG and JW fit the profile of children who have a significant and clinically relevant respiratory sleep disturbance, but who are not

compromised in terms of oxygen saturation. When we assess the cognitive performance of these two children, we see that LG's performance is within the range of normal when compared to controls, on both declarative and procedural tasks. This leads to one of two possibilities; either that chronic sleep disturbance is not damaging in terms of sleep dependent learning, or that LG is in some way compensating for the sleep disturbance and is able to reverse the damaging effects of disrupted sleep. As mentioned previously, the total sleep time recorded for LG was significantly longer than that of the control sample (Uliel et al., 2004) and may reflect an ability to sleep for longer in order to compensate for repeated arousals and fragmentation throughout the night. In this particular case, this explanation is probably unlikely as LG was the youngest participant, and at five years old would be expected to sleep for longer than the other participants and the control group (mean age 7.9 years). However, it raises interesting questions as to the ability of children to adapt sleeping patterns and sleep time in order to compensate for chronically disturbed sleep.

In contrast, when we assess the cognitive performance of JW we observe a quite considerable reversal of the expected result, with better performance after wake than after sleep, on both procedural and declarative tasks. As discussed above, it must be taken into account that JW is the only participant in this study to be tested first after the wake phase, and as such would not be expected to show the same striking preference for sleep over wake for procedural learning. However, even if this is taken into account, indications are that JW is compromised in terms of sleep dependent learning abilities, on both procedural and declarative tasks (the latter being unaffected by order effects and still showing a wake preference).

Of course the pertinent question to be answered is whether the sleep disturbance observed in JW is causative of the deficits in overnight procedural and declarative learning. Previous research has demonstrated that sleep is preferable to wake for improvement on a procedural task (Walker et al., 2002), and has also indicated that sleep deprivation can impair task retention (Smith & MacNeill, 1994). We predict that chronic but subtle sleep disruption such as that associated with sleep disordered breathing is likely to lead to similar outcomes, the results from participant JW provide some support (albeit anecdotal) for the theory that clinical sleep disorders

such as OSA are damaging in terms of learning. JW is an otherwise healthy child, with no other medical or health problems, no learning difficulties and no reported behavioural or emotional difficulties that might lead to differing patterns of sleep dependent learning. In addition, there were no significant gas exchange problems associated with the obstructed breathing, so deficits in sleep dependent learning cannot be attributed to hypoxia. As such the most plausible theory is that obstructed breathing leads to a subtle but chronic sleep disturbance, which in turn disrupts the mechanisms of memory enhancement and consolidation during sleep. Of course, anecdotal data such as this cannot be used as reliable evidence to support this theory, the need for further research with a larger number of participants is clear and will generate a clearer picture of the relationship between sleep disorders and learning. We also have to consider the case of LG, who appeared to have some significant disturbance to his sleep but whose sleep dependent learning was relatively preserved. As discussed above, it may be the case that children are able to utilise mechanisms to compensate for chronic sleep disturbance, in this case it was suggested that an increase in total sleep time may counteract the negative effects of arousals and sleep fragmentation, and provide mechanisms for preserving sleep dependent learning. In addition, although participant JW showed a notable deficit in learning over sleep when compared to controls, his improvement in procedural performance over periods of wake was considerably better than in controls. This indicates that although processes of sleep dependent learning may be impaired in sleep disordered children, compensatory mechanisms may allow for an increased level of consolidation over periods of wake in order to partly offset the deficits seen over sleep.

The mechanisms of sleep dependent learning and the specific brain states required for successful consolidation have not been conclusively established. Researchers have demonstrated correlations between various sleep stages and sleep dependent consolidation, with the prevailing theories seeming to favour stage 2 NREM (Walker et al., 2002) and REM sleep (Fischer et al., 2002). Although correlations have been shown between these sleep stages and successful consolidation, no research has established the means by which these sleep stages lead to enhanced or consolidated memory traces. Further research investigating the specific mechanisms that are involved in sleep dependent learning will not only improve our knowledge of the functions of sleep, but may also provide information that can be used to further

elucidate the relationship between obstructive breathing disorders such as OSA, and sleep dependent memory enhancement. Participant JW does not differ notably from controls in terms of sleep architecture, and appears to fall within the range of normal in terms of proportion of time spent in the different sleep stages. Despite this he shows clear deficits to aspects of sleep dependent learning, it may be the case that in addition to the effects of specific sleep stages, global aspects of sleep architecture such as arousal frequency, may have an important impact on the mechanisms of sleep dependent learning.

3.5 Conclusions and Implications

The case series outlined here provides anecdotal evidence that obstructive breathing disorders in children are associated with some deficits to the processes of sleep dependent memory enhancements. Previous studies described in this thesis (see chapter 2) demonstrated that sleep dependent learning occurs in healthy children, in both procedural and declarative domains. Sleep dependent learning was also observed in the current study in the two participants (BD and SS) who were found on the basis of a sleep study to have essentially normal sleep. In comparison, the two participants (LG and JW) who were found to have significant and clinically relevant obstructive breathing disorders, showed differing patterns of learning. Although LG's cognitive performance did not appear to be hugely impaired, JW performed poorly on tasks designed to assess sleep dependent learning, despite being otherwise healthy and uncompromised in terms of gas exchange. These results provide some preliminary evidence that chronically disturbed sleep in children can lead to deficits in the processes of sleep dependent memory enhancements. The possible implications of such a finding could be considerable given the importance of learning processes in childhood. To date, no research has investigated the long term consequences of deficits in sleep dependent learning, but we can speculate that difficulties with the enhancement and consolidation of memory can have negative consequences in terms of general learning abilities. Consolidation of memory is the process by which a memory trace becomes less fragile, and is transformed into a robust and stable memory (Robertson et al., 2004[b]). Processes of consolidation are required in order that successful retrieval of memory traces can occur, and can provide us with a reliable and robust means of storing material to be used in other cognitive processes. If processes of consolidation and enhancement are disrupted,

there is reason to predict that learning impairment may be an eventual consequence. Further support for the theory that sleep disruptions can eventually lead to general cognitive impairment comes from previous research investigating general cognitive functioning in children with sleep disordered breathing and OSA. There is increasing evidence that OSA in children is associated with reduced neurocognitive abilities and increased problematic behaviour, deficits have been found in attention, memory and intelligence (Blunden et al., 2001). An increased prevalence of excessive daytime somnolence has also been reported in children with OSA (Gozal et al., 2001). The findings outlined clearly point to a need for further research in this area, sleep disordered breathing is a relatively common occurrence in children and investigations into the consequences of this, and other sleep disorders, will lead to a greater understanding of both the functions of sleep and the complex mechanisms of learning.

Whilst the findings from the current study provide a useful starting point for future research, there are clear limitations to the study and we should be cautious when drawing conclusions from any results reported. The number of participants in the study was insufficient to be able to justify the use of any statistical techniques when analysing the data. Therefore, any conclusions that are drawn from the current study are based on single case data, and should be considered with a degree of caution. In addition, the study lacks a procedurally matched control group of healthy children. Although a group of healthy control children (see chapter 2) completed the same tasks as the children described in the case series, the experimental conditions under which they completed the tasks were different, and they did not undergo sleep staging. Therefore, comparisons between sleep disordered children and healthy children cannot be fully reliable.

Chapter 4

Subjective sleep disturbance in adults with epilepsy and healthy controls: A questionnaire based study on prevalence and impact on memory, mood, and quality of life.

4.1 Introduction

Results from the studies described in chapter two have shown that sleep is important for the consolidation and improvement of memories in the procedural and declarative domains. The findings provide evidence that sleep results in procedural performance gains that are not matched during similar periods awake, in both adults and children. In addition, the findings demonstrate that declarative memory retention (but not recall) is selectively enhanced over sleep, in both adults and children. Although the studies described in chapter two did not use sleep staging, and so are potentially limited by a lack of objective sleep data, the results suggest a role for sleep in the formation of memories and the subsequent learning that occurs as a result of successful memory consolidation and retrieval. These results support previous work by a number of authors who have demonstrated sleep dependent learning in the procedural and declarative domains (e.g. Walker et al., 2002; Stickgold et al., 2000; Gais & Born, 2004; Hu et al., 2006).

The study described in chapter three is less conclusive but provides some preliminary evidence that clinical sleep disorders such as obstructive sleep apnoea and sleep disordered breathing impair overnight consolidation and performance gains, suggesting that sleep disorders can be damaging in terms of both sleep disturbance, and in terms of learning and memory processes. Once again, limitations of the study design and the lack of any inferential statistics (due to the small number of participants), means conclusions have to be drawn with a degree of caution. However, the combined evidence would seem to suggest that sleep quality and quantity are necessary components of successful learning and memory.

In addition to the effects on learning and memory, sleep disturbances have also been shown to have important interactions with mood and affect. It is well established that sleep patterns are altered in psychiatric disorders and represent a very common presenting complaint. Sleep disturbance is a key feature of many psychiatric

conditions, however its most prominent role appears to be in mood disorders. Altered sleep patterns are common in depressive illness and up to 80% of patients with depression report disturbed sleep (Kupfer et al., 1995; Armitage, 2007). Several abnormalities characterise the sleep of patients with depression; sleep onset latency, number of awakenings, wake after sleep onset, and rapid eye movement density are increased. Other sleep parameters such as total sleep time, sleep efficiency, slow wave sleep, and REM latency are reduced (Benca et al., 1992; Kupfer et al., 1995; Hubain et al., 2006). Further evidence for the association between sleep and negative affect comes from studies of sleep deprivation. Chronic sleep deprivation has been shown to lead to fatigue, poor mood, daytime sleepiness, lack of vigour, and depression (Stepanski et al., 2000; Surani et al., 2007; Scottet al., 2006). The combined evidence suggests that sleep has important interactions with mood, it seems that disturbed sleep and depressive mood are often correlated. As has been previously discussed, sleep plays an important role in the consolidation of learning and memory processes, the above evidence suggests that sleep may also have a potential role in the mediation of affect.

Despite the established negative effects of sleep disturbance, and the known associations with mood disorders, the under-reporting of sleep problems is common in many clinical disorders. Epilepsy has long been known to have important associations with sleep, early studies found that between 19-24% of patients reported seizures that occurred exclusively during nocturnal sleep, whilst a further 33-37% of patients reported night time seizures in addition to daytime seizures. More recently it has become apparent that various types of seizure are affected differently by the sleep-wake cycle. Up to 45% of patients with generalised tonic-clonic seizures have reported that their seizures are restricted to sleep. Absence epilepsy has also been shown to have associations with sleep, with epileptiform activity noted particularly during NREM sleep. Seizures originating from the frontal lobes also show a tendency to occur preferentially during sleep, and temporal lobe epilepsy patients often report seizures during sleep, most commonly during NREM sleep but also during REM sleep (e.g. Foldvary, 2002; Dinner, 2002).

Despite the known associations between epilepsy and sleep, few studies have investigated the prevalence or consequence of subjective sleep disturbance in adults

with epilepsy. A study by DeWeerd et al. (2004) assessed sleep disturbance and impact on quality of life in patients with partial epilepsy. Questionnaires were completed by 486 patients with partial epilepsy, for comparison with 492 age and gender matched controls. Questionnaires comprised a number of recognised sleep measures, and a measure of general health and quality of life. Respondents with partial epilepsy had a highly significant, twofold higher prevalence of sleep disturbance when compared with controls. Most sleep-disorder subscales showed significant abnormalities in respondents with epilepsy, compared with controls. General health and quality of life scores were also significantly lower in respondents with epilepsy compared with controls, in both the respondents with notable sleep disturbance and in those without. The presence of a sleep disturbance in respondents with epilepsy was associated with the greatest impairment in quality of life (DeWeerd et al., 2004).

A more recent study by Xu et al. (2006) investigated the impact of sleep disturbance in partial epilepsy patients. They surveyed 201 adults with stable partial epilepsy, for sleep disturbances and for quality of life. Of the patients with epilepsy, 34% had diagnosed sleep disturbances, and 10% received prescription sleep medications. Patients with diagnosed sleep disturbance reported poorer mean quality of life scores relative to those without diagnosed sleep disturbances. The mean sleep problems index score was considerably worse than the general population mean. Patients with physician-reported anxiety or depression had more sleep problems than did those without. Higher levels of reported sleep problems were also significantly correlated with poorer quality of life. Patients experiencing a seizure within the past week reported worse sleep than did those with a less-recent seizure. They concluded that diagnosed and self-reported sleep disturbances in patients with partial-onset epilepsy are frequently overlooked, but are negatively associated with everyday functioning and well-being, and therefore contribute significantly to the burden of epilepsy (Xu et al., 2006).

The two studies described above (DeWeerd et al., 2004; Xu et al., 2006), provide some preliminary evidence that patients with epilepsy commonly report difficulties relating to sleep. In patients with partial epilepsy, sleep disturbances are more common than in the general population, and often have a negative impact on quality

of life. Both studies relate exclusively to patients with partial epilepsy, and the literature regarding patients with other types of epilepsy is lacking. In addition, there is no research to date which investigates the impact of self reported sleep problems in epilepsy on other aspects of functioning (such as mood or cognitive function). The current literature is clearly lacking in empirical research relating to the assessment of self reported sleep problems in patients with epilepsy, particularly those without partial epilepsy. In addition, the effects of sleep disturbances in patients with epilepsy, in terms of memory, cognitive function, and mood have not to date been investigated. The current study attempts to add to the current literature by investigating the prevalence of disturbed sleep in a sample of people with unselected epilepsy, for comparison with a large group of healthy controls. It will also further investigate the consequences of disturbed sleep by assessing memory/cognitive function, and mood, and investigating relationships between these variables and disturbed sleep, in both epilepsy and controls. Given the link between sleep and learning it is proposed that subtle, but chronic, sleep disturbances may be predictive of poor memory and cognitive function. The extensive literature relating sleep with mood disorders also leads us to propose that sleep disturbances may be predictive of negative mood. Both DeWeerd et al. (2004) and Xu et al. (2006) also reported that sleep problems in partial epilepsy were highly correlated with impaired quality of life, the current study will attempt to replicate this finding in the group of unselected epilepsy patients and may provide further support for these results.

Aims

The aim of this study is to investigate the prevalence of self-reported sleep disturbances in a large sample of healthy adults, and in a smaller sample of people with epilepsy, and to compare the incidence of sleep problems in these two groups. The study also aims to assess aspects of self-reported memory/cognitive function, mood, and quality of life in these groups, and to assess the relationship between sleep disturbances, mood, quality of life, and memory/cognitive function, in both people with epilepsy and healthy controls.

Hypotheses

The study has three main hypotheses, the first states that in healthy subjects, self-reported sleep and mood problems are predictive of memory and cognitive function

deficits. The second hypothesis states that people with epilepsy report significantly more sleep problems than healthy controls, when assessed using a subjective self-report measure. The third hypothesis states that in people with epilepsy, self-reported sleep problems, poor mood, and impaired quality of life are predictive of memory and cognitive function deficits.

4.2 Methods

4.2.1 Consent

Before participating in the study, all subjects were asked to read a brief introduction informing them of the nature of the research, all participants gave informed consent. The study was approved by the Department of Psychology Ethics Sub-Committee.

4.2.2 Participants

Participants recruited for the study consisted of 2968 healthy adults between the ages of 17 and 78 (mean age = 27.12 years, SD = 10.49), 35.6% of the sample were male. Participants were recruited from the staff and students at the University of Sheffield. An e-mail was sent to all students, and to all staff with computer access, inviting them to complete a short questionnaire for purposes of research. The questionnaire was circulated to approximately 24,000 people in this way. Participants included undergraduate and postgraduate students, academic staff, research staff, technicians, administrative staff, and support staff. In addition, 99 adults with epilepsy between the ages of 18 and 80 were also recruited for the study (mean age = 35.59 years, SD = 13.76). Members of the charity Epilepsy Action, and users of the Epilepsy Action website were invited to complete the questionnaire via a link on the website, or via a link sent to Epilepsy Action's on-line community. It is not possible to estimate the circulation and uptake of the questionnaire via the Epilepsy Action website, as the site is accessible to any internet user. Participants with a wide range of epilepsy types were included in the study, there were no exclusion criteria based on epilepsy type. Any participants with medical disorders (except epilepsy) predisposing to sleep problems, or conditions significantly affecting their sleep, were excluded from the study. Any participants with learning difficulties or mood disorders (e.g. depression) were also excluded due to the effects on memory/cognitive function and mood.

4.2.3 Apparatus

All participants completed an on-line questionnaire composed of seven subsections, the subsections comprised various standardised questionnaire measures, general demographic material, and specific epilepsy related items. The seven subsections are described in detail below, participants with epilepsy completed all sections of the questionnaire, whilst healthy controls only completed sections 1, 4, 5, 6 & 7. The questionnaire took between 10-15 minutes to complete and was designed and implemented using the on-line survey software Survey Monkey (www.surveymonkey.com).

1. General demographic information

This short section contained items relating to age, sex, presence of medical sleep disorders etc. This section also asked participants whether that had epilepsy, those who answered 'yes' continued onto the next section, those who answered 'no' were automatically redirected to section 4.

2. Epilepsy related items

This section contained items relating to a participant's epilepsy and included; epilepsy type (if diagnosed), seizure type, seizure frequency, duration of epilepsy, number of anti-epileptic drugs (AED's), and names of AED's.

3. Quality of Life in Epilepsy Scale (QOLIE-10)

The QOLIE-10 is a brief 10 item self-report questionnaire designed to screen aspects of health related quality of life in people with epilepsy. The questionnaire covers general and epilepsy specific domains, with items grouped into three factors: epilepsy effects (memory, physical and mental effects of medication), mental health effects (energy, depression, overall quality of life), and role functioning (seizure worry, work, driving, social limits). The questionnaire asks subjects to rate on a scale from one to five, how often each item occurs. (Cramer et al., 1996). The questionnaire has been shown to be brief to administer and the reliability and validity of responses has been reflected in test-retest data, and high correlations with other standardised measures. Correlations with systemic toxicity and neurotoxicity, as well as with seizure frequency, also demonstrate the validity of the scale (Cramer et al., 1996).

4. Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-rated questionnaire designed to assess sleep quality and sleep disturbances over a 1-month time interval. It is composed of nineteen individual items pertaining to sleep and sleep behaviours, participants are asked to rate the frequency of occurrence of each item on a scale from zero (not during the past month) to three (three or more times a week). The nineteen items generate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score. It also generates a partner derived component score for those subjects who share their bed with a partner (partner ratings did not contribute to the global score as subjects without a bed partner did not complete this section). Measures of internal homogeneity, consistency (test-retest reliability), and validity were found to be acceptable (Buysse et al., 1989). The various properties of the PSQI have suggested its utility both in clinical practice and in research activities.

5. Epworth Sleepiness Scale (ESS)

The ESS is a simple self-administered questionnaire, shown to provide a measurement of a subject's general level of daytime sleepiness. Participants are asked to rate from zero (would never doze) to three (high chance of dozing) the chances that they would doze off or fall asleep when in eight different situations commonly encountered in daily life. ESS scores have been shown to reliably distinguish normal sleepers from patients in various diagnostic groups, and ESS scores also correlate significantly with sleep latency (Johns, 1991).

6. Multiple Abilities Self-Report Questionnaire (MASQ)

The MASQ is a self-report measure designed to assess an individual's self-appraisal of memory and cognitive ability. It comprises items from five cognitive domains; language, visuo-perceptual memory, verbal memory, visual memory, and attention. Participants are asked to rate from one (never) to five (always) how frequently they experience items within each domain. The MASQ has been shown to have adequate levels of reliability (internal consistency and test-retest reliability). Discriminative and concurrent validity have also been established by comparisons with objective measures of performance (Seidenberg et al., 1994).

7. Positive and Negative Affect Schedule (PANAS)

The PANAS is a brief and easily administrable mood scale developed to assess both positive and negative dimensions of affect. It is composed of two 10-item scales, one contains 10 words associated with positive feelings and emotions, and the other contains 10 words associated with negative feeling and emotions. Participants are asked to rate from one (very slightly or not at all) to five (extremely), to what extent they have experienced items within the previous 1-month time period. The scales have been shown to be highly internally consistent, largely uncorrelated, and stable at appropriate levels over a 2-month time period. Normative data and factorial and external evidence of convergent and discriminant validity for the scales has also been established (Watson et al., 1988).

4.2.4 Design and Procedure

The questionnaire was administered at a single time point, participants were asked to complete the anonymous questionnaire as accurately and honestly as possible, no time restrictions were given. The healthy participant sample were sent an e-mail asking them to complete a short questionnaire for purposes of research, the questionnaire was accessed via a link within the e-mail. The epilepsy sample were recruited via the website of Epilepsy Action, a UK epilepsy charity with a dedicated website providing information and support for people with epilepsy (www.epilepsy.org.uk). Epilepsy Action posted an invitation to participate in the research on their website, with the questionnaire accessible via a web link. Epilepsy Action also advertised the study via their on-line community, directing members to the appropriate web-link if they wished to participate.

4.2.5 Variables and Analyses

Sub-sections 3 to 7 of the questionnaire generated twenty one final outcome measures. These comprised four QOLIE-10 measures (Epilepsy Effects, Mental Effects, Role Functioning, and Total Score), nine PSQI measures (Subjective Sleep Quality, Sleep Latency, Sleep Duration, Sleep Efficiency, Sleep Disturbances, Sleep Medication, Daytime Dysfunction, Global Score, and Partner Rating), a single ESS measure, five MASQ measures (Language, Visuo-Perceptual Memory, Verbal Memory, Visual Memory, and Attention), and two PANAS measures (Positive Affect and Negative Affect). On all QOLIE-10, PSQI, ESS, MASQ, and PANAS

(negative affect) measures, variables were coded so that higher scores indicated more problems. On the PANAS (positive affect) measure, higher scores indicated fewer problems (i.e. a more positive mood).

Variables were assessed for normality and those displaying significant skew were subject to a log transformation (after the addition of a constant where necessary). Log transformed variables comprised all PSQI measures, the ESS measure, all MASQ measures, and both PANAS measures.

Standard multiple regression analyses were performed in order to assess whether various factors were able to predict memory/cognitive function, in healthy participants and in participants with epilepsy. Independent *t*-tests were also undertaken to compare sleep problems, memory/cognitive problems, and mood in epilepsy and controls, Bonferroni corrections were applied for multiple *t*-tests. ANOVA's were also used to assess the effect of various epilepsy variables on sleep problems.

4.3 Results

4.3.1 Relationships between sleep and mood variables, and memory/cognitive function variables in healthy subjects

Initially, a standard multiple regression analysis was carried out to assess whether self-reported sleep disturbances could significantly predict memory and cognitive function problems in healthy adults. As the associations between sleep and mood have also been well documented, mood variables were also used as predictors in these analyses. Predictors entered into the model consisted of two sleep variables and two mood variables. The sleep variables consisted of PSQI Total Score and ESS, these two variables were selected as they were thought to best represent general aspects of sleep disturbance (PSQI Total Score gives a general measure of sleep at night, whilst ESS gives a measure of the daytime effects of sleepiness). The correlation between the two predictors was small but significant ($r = 0.271$), however both predictors were included in order to provide some distinction between the daytime and night time effects of sleep and sleepiness. The mood variables consisted of PANAS positive and PANAS negative, giving measures of both positive and negative affect. A small but significant correlation also existed between the two

PANAS variables (r = 0.229), but they were both included in order to gain some distinction between affectual responses. Separate regressions were performed for each of the MASQ variables. Participants with epilepsy were excluded from these analyses in order that a specific assessment of memory/cognitive function in healthy subjects could be made. Participants who failed to complete relevant sections of the questionnaire were also excluded from analyses.

For the MASQ Language variable, the regression model was significant $F(4,1805) = 125.16$, $p < 0.001$, with the predictors explaining 21.6% of the variance. All predictor variables were significant individual predictors (table 4.1). For the MASQ Visuo- Perceptual variable, the regression model was significant $F(4,1811) = 66.81$, $p < 0.001$, with the predictors explaining 12.7% of the variance. All predictors were individually significant (table 4.1). For the MASQ Verbal Memory variable, the model was significant $F(4, 1807) = 98.06$, $p < 0.001$, the predictors explained 17.7% of the total variance. All predictors were significant (table 4.1). For the MASQ Visual Memory variable the model was again significant $F(4,1805) = 72.04$, $p < 0.001$, with the predictors explaining 13.6% of the variance. All predictors were significant (table 4.1). For the MASQ Attention variable the model was significant $F(4,1807) = 180.23$, $p < 0.001$, with predictors explaining 28.4% of the variance. All predictors were significant (table 4.1).

Outcome Variable	Adjusted R^2	Predictor variables	Beta	*p*
MASQ Language	0.216	PSQI Total Score	0.104	$p < 0.001$
		ESS	0.092	$p < 0.001$
		PANAS positive	-0.203	$p < 0.001$
		PANAS negative	0.278	$p < 0.001$
MASQ Visuo-Perceptual	0.127	PSQI Total Score	0.061	$p < 0.05$
		ESS	0.066	$p < 0.005$
		PANAS positive	-0.182	$p < 0.001$
		PANAS negative	0.209	$p < 0.001$
MASQ Verbal Memory	0.177	PSQI Total Score	0.073	$p < 0.005$
		ESS	0.108	$p < 0.001$
		PANAS positive	-0.228	$p < 0.001$
		PANAS negative	0.214	$p < 0.001$
MASQ Visual Memory	0.136	PSQI Total Score	0.059	$p < 0.05$
		ESS	0.085	$p < 0.001$
		PANAS positive	-0.204	$p < 0.001$
		PANAS negative	0.194	$p < 0.001$
MASQ Attention	0.284	PSQI Total Score	0.074	$p < 0.005$
		ESS	0.135	$p < 0.001$
		PANAS positive	-0.273	$p < 0.001$
		PANAS negative	0.299	$p < 0.001$

Table 4.1: Regression of sleep and mood variables on MASQ variables in 2698 healthy adults.

4.3.2 Relationships between sleep variables and mood variables in healthy subjects

A standard multiple regression analysis was also carried out to assess whether self-reported sleep disturbances could significantly predict mood in healthy adults. Predictors entered into the model again consisted of PSQI Total Score and ESS, separate regressions were performed on the two outcome measures PANAS Positive and PANAS Negative. For PANAS Positive the regression model was significant $F(2,2000) = 122.57$, $p < 0.001$, with predictors explaining 10.8% of the variance, both predictors were individually significant (table 4.2). For PANAS Negative the model was also significant $F(2,2000) = 190.53$, $p < 0.001$, with predictors explaining 15.9% of the variance, both predictors were again significant (table 4.2). Examination of the beta weights indicates that an increase in scores on predictor variables (i.e. worse sleep) predicts a decrease in positive affect, and a decrease in scores on predictor variable (i.e. better sleep) leads to a decrease in negative affect.

Outcome Variable	Adjusted R^2	Predictor variables	Beta	*p*
PANAS Positive	0.108	PSQI Total Score ESS	-0.291 -0.098	p < 0.001 p < 0.001
PANAS Negative	0.159	PSQI Total Score ESS	0.348 0.126	p < 0.001 p < 0.001

Table 4.2: Regression of sleep variables on PANAS variables in 2698 healthy adults.

4.3.3 Nature of the epilepsy group

After having shown that self-reported sleep disturbances are predictive of memory/cognitive function problems and poor mood in healthy subjects, an assessment of sleep in adults with epilepsy is reported. Table 4.3 shows descriptive information for the epilepsy sample. The epilepsy sample was 36% male, with a mean age of 35.59 years (SD = 13.76). An independent *t*-test confirmed the epilepsy sample were significantly older than the control sample (mean age = 27.12 years) (t = 7.81, df = 3057, $p < 0.001$). There were no significant differences between epilepsy and controls in terms of sex distribution. Inspection of the epilepsy variables revealed a relatively long mean epilepsy duration (14.45 years), and nearly a third of participants (26%) reported more than one seizure per fortnight. Epilepsy type was broadly categorised into partial and generalised epilepsies, with the largest group consisting of generalised epilepsies, accounting for 49% of all epilepsy types.

Comparison with large scale population data indicates that our sample is reasonably representative in terms of epilepsy duration, seizure frequency, number of medications, and type of medication. Prevalence studies suggest that 70% of patients with epilepsy will have had the condition for over five years, up to 53% of patients report having more than one seizure a month (Sander, 2005), while 8% of patients report approximately one seizure per week (Hart & Shorvon, 1995). Most prevalence studies indicate that partial seizures account for most cases of epilepsy, with partial seizures accounting for between 52% (Sander & Shorvon, 1996) and 72% (Hart & Shorvon, 1995) of cases. Our sample appears to show a reversal of this trend with generalised seizures the most commonly reported. The general incidence of antiepileptic monotherapy is around 65% of patients, with 35% on polytherapy. In terms of medication type, lamotrigine, carbamazepine, sodium valproate, and levitaracetam are all common first line AED's used to treat both partial and

generalised epilepsies, with the exception of leviteracetam which is considered only for partial seizures and partial with secondary generalisation (Information on epilepsy: AED's used in adults, 2007).

Male	36%	
Age	mean = 35.59 years, SD = 13.76	
Duration of epilepsy	mean = 14.45 years, SD = 13.81	
Epilepsy Type	Generalised	49%
	Partial	32%
	Unspecified	19%
Seizure Frequency	> one/fortnight	26%
	< one/fortnight	59%
	Unspecified	15%
Number of medications	0	4%
	1	47%
	2	17%
	3	14%
	>3	4%
	Unspecified	14%
Types of medication	Lamotrigine	27%
	Carbamazepine	20%
	Sodium Valproate	15%
	Levitaracetam	13%
	Other/None	25%

Table 4.3: Descriptive information for the epilepsy sample (n = 99).

4.3.4 Comparisons of sleep problems in epilepsy and controls

In order to compare incidence of sleep disturbances across the two groups, independent *t*-tests were performed to compare PSQI and ESS sleep factors in epilepsy and controls, a Bonferroni correction for multiple *t*-tests was applied (i.e. a significance threshold set at $p < 0.005$). As described previously, items from the PSQI were grouped into nine factors, corresponding to different areas of sleep disturbance, the ESS generated a single item. Adults with epilepsy were found to have significantly higher scores than controls on all sleep factors, with the exception of sleep medication. Mean values, standard deviations and *t* values are presented in table 4.4.

	Epilepsy		Controls		
	Mean	S.D	Mean	S.D	*t*
Subjective sleep quality	0.386	0.212	0.321	0.189	*3.09
Sleep latency	0.501	0.275	0.426	0.279	*2.50
Sleep duration	0.202	0.224	0.126	0.187	*2.98
Sleep efficiency	0.271	0.243	0.167	0.209	**4.26
Sleep disturbances	0.970	0.219	0.791	0.273	**5.74
Sleep medication	0.082	0.198	0.041	0.143	1.81
Daytime dysfunction	0.530	0.214	0.426	0.245	**3.78
Partner rating	0.740	0.314	0.465	0.312	**5.19
Total score	1.257	0.237	1.094	0.255	**5.19
Epworth Sleepiness Scale	0.915	0.351	0.799	0.351	**3.51

*Table 4.4: Comparison of epilepsy and control scores on sleep measures. *$p <$ 0.005; **$p < 0.001$*

4.3.5 Comparisons of memory/cognitive function and mood in epilepsy and controls

In addition to the assessment of sleep problems, both epilepsy and control participants completed measures of memory and cognitive abilities (MASQ), and mood (PANAS). As memory and mood are both predicted to be associated with sleep, independent *t*-test comparisons were made between MASQ variables (Language, Visuo-Perceptual, Verbal Memory, Visual Memory and Attention) and PANAS variables (Positive affect and Negative affect), in epilepsy and controls. A Bonferroni correction for multiple *t*-tests was applied (i.e. a significance threshold set at $p < 0.07$). People with epilepsy had significantly higher scores than controls on all MASQ variables (table 4.5), indicating people with epilepsy have more problems with memory and cognitive abilities than controls. People with epilepsy also had significantly higher scores on measures of negative affect, and lower scores on measures of positive affect, than controls (table 4.5) indicating epilepsy is associated with more negative mood than controls.

	Epilepsy		Controls		
	Mean	S.D	Mean	S.D	*t*
MASQ language	1.29	0.136	1.20	0.116	5.78*
MASQ visuo-perceptual	1.14	0.017	1.08	0.133	4.05*
MASQ verbal memory	1.35	0.113	1.28	0.111	5.88*
MASQ visual memory	1.27	0.014	1.19	0.116	5.48*
MASQ attention	1.35	0.106	1.28	0.103	6.22*
PANAS negative	1.39	0.165	1.31	0.145	4.58*
PANAS positive	1.43	0.150	1.51	0.111	-4.40*

*Table 4.5: Comparisons of log scores on memory/cognitive function and mood variables. *$p < 0.001$*

4.3.6 Within the epilepsy group: variables associated with sleep problems

In order to assess the impact of epilepsy variables on sleep, ANOVA's were performed on each of the PSQI and ESS sleep variables with independent variables consisting of seizure frequency, seizure type, number of AED's, and epilepsy duration. As indicated previously, seizure frequency was classified as > one per fortnight or < one per fortnight, and seizure type was classified as partial or generalised. For the purposes of these analyses, number of AED's was categorised into either monotherapy (one AED), or polytherapy (> one AED). The epilepsy duration variable was subdivided into four categories; 0-5yrs, 5-10yrs, 10-15yrs, and > 15yrs. Post-hoc comparisons were made using Scheffe's test.

With all variables included in the analyses, the epilepsy scores for subjective sleep quality, sleep latency, sleep duration, sleep medication, partner rating, and ESS were not significantly affected by seizure frequency, seizure type, number of AED's, or epilepsy duration. However, sleep efficiency was significantly affected by epilepsy duration $F(3,41) = 4.63$, $p < 0.01$. Although post-hoc comparisons were not significant, analysis of the descriptive statistics indicates a duration of 0-5yrs is associated with worst sleep efficiency, whilst a duration of 10-15 yrs is associated with the best sleep efficiency. Sleep disturbances were found to be significantly affected by number of medications $F(1,41) = 4.46$, $p < 0.05$, with those on polytherapy suffering more disturbed sleep than those on monotherapy. Daytime dysfunction was also significantly affected by number of medications $F(1,46) = 7.94$, $p < 0.01$, with polytherapy associated with more daytime dysfunction than monotherapy. There was also a significant interaction between epilepsy duration and

seizure frequency $F(3,46) = 3.63$, $p < 0.05$. Total scores on the PSQI were significantly affected by number of medications $F(1,34) = 15.30$, $p < 0.001$, with those on monotherapy reporting less total problems than those on polytherapy.

4.3.7 Relationships between sleep, mood, QoL variables, and memory/cognitive function variables, within the epilepsy sample

In order to investigate the effect of sleep disturbance on memory and cognitive function within the epilepsy group, standard multiple regression analyses were conducted to assess the predictive relationship between sleep variables and MASQ variables. Mood and quality of life variables were also included as predictors as they have potential associations with memory and cognition. Predictors entered into the model consisted of PSQI Total Score, ESS, PANAS positive, PANAS negative, and QOLIE-10 Total. Separate regressions were performed for each of the MASQ variables. Participants who did not complete relevant sections of the questionnaire were excluded from analysis of those variables. For MASQ Language, the regression model was significant $F(5,53) = 7.42$, $p < 0.001$, with predictors explaining 37.7% of the variance, the ESS and QOLIE-10 Total variables were the only significant individual predictors. For the MASQ Visuo-Perceptual variable, the model was significant $F(5,53) = 4.71$, $p < 0.005$, with predictors explaining 23.8% of the variance. However, none of the variables were significant individual predictors. For MASQ Verbal Memory, the model was significant $F(5,52) = 8.56$, $p < 0.001$, with predictors explaining 42.1% of the variance. QOLIE-10 Total was the only significant individual predictor. For MASQ Visual Memory, the model was significant $F(5,50) = 4.22$, $p < 0.005$, with predictors explaining 24.3% of the variance. None of the predictors were individually significant. Finally, for the variable MASQ Attention, the model was significant $F(5,52) = 5.32$, $p < 0.005$, with predictors explaining 29.4% of the variance. None of the predictors were individually significant (table 4.6).

Outcome Variable	Adjusted R^2	Predictor variables	Beta	*p*
MASQ Language	0.377	PSQI Total Score	-0.056	p = 0.733
		ESS	0.350	p < 0.01
		PANAS positive	-0.089	p = 0.494
		PANAS negative	0.151	p = 0.233
		QOLIE-10 Total	0.380	p < 0.05
MASQ Visuo-Perceptual	0.238	PSQI Total Score	0.041	p = 0.823
		ESS	0.132	p = 0.344
		PANAS positive	-0.189	p = 0.190
		PANAS negative	0.223	p = 0.113
		QOLIE-10 Total	0.199	p = 0.216
MASQ Verbal Memory	0.421	PSQI Total Score	0.238	p = 0.142
		ESS	0.129	p = 0.289
		PANAS positive	-0.092	p = 0.478
		PANAS negative	0.139	p = 0.267
		QOLIE-10 Total	0.310	p < 0.05
MASQ Visual Memory	0.243	PSQI Total Score	0.254	p = 0.180
		ESS	0.203	p = 0.161
		PANAS positive	-0.050	p = 0.728
		PANAS negative	0.056	p = 0.700
		QOLIE-10 Total	0.168	p = 0.302
MASQ Attention	0.294	PSQI Total Score	0.291	p = 0.106
		ESS	0.095	p = 0.483
		PANAS positive	-0.253	p = 0.074
		PANAS negative	0.138	p = 0.311
		QOLIE-10 Total	0.013	p = 0.936

Table 4.6: Regression of sleep, mood, and quality of life variables, on MASQ variables within the epilepsy group (n = 99).

4.3.8 Relationships between sleep variables and mood variables, within the epilepsy sample

A further standard multiple regression was carried out in order to assess the effect of disturbed sleep on mood, within the epilepsy sample. Predictors consisted of PSQI Total Score and ESS, separate regressions were carried out for both PANAS Positive and PANAS Negative. For PANAS Positive, the regression model was significant $F(2,56) = 6.03$, $p < 0.005$, with predictors explaining 14.8% of the variance. Of the two predictors, only PSQI Total Score was individually significant. For PANAS Negative, the model was also significant $F(2,53) = 8.20$, $p < 0.005$, with predictors explaining 23.6% of the variance. Once again, PSQI Total Score was the only significant individual predictor (table 4.7). Examination of the beta weights indicates that an increase in scores on predictor variables (i.e. worse sleep), predicts a

decrease in positive affect, and a decrease in scores on predictor variables (i.e. better sleep) leads to a decrease in negative affect.

Outcome Variable	Adjusted R^2	Predictor variables	Beta	*p*
PANAS Positive	0.148	PSQI Total Score ESS	-0.411 -0.022	$p < 0.005$ $p = 0.874$
PANAS Negative	0.236	PSQI Total Score ESS	0.469 0.034	$p < 0.001$ $p = 0.807$

Table 4.7: Regression of sleep variables on PANAS variables, within the epilepsy group (n = 99).

4.3.9 Relationships between sleep and mood variables, and quality of life variables

In order to investigate the impact of sleep and mood on quality of life in those suffering from a chronic medical condition, a standard multiple regression was performed to assess whether sleep disturbances and poor mood could significantly predict quality of life in epilepsy scores. As the QOLIE-10 measure is specific to epilepsy, only those participants with epilepsy were included in these analyses. Predictors entered into the model consisted of PSQI Total Score, ESS, PANAS positive, and PANAS negative. Separate regressions were performed on each of the QOLIE-10 variables. For QOLIE-10 Epilepsy Effects, the regression model was significant $F(4,54) = 12.57$, $p < 0.001$, with predictors explaining 46.2% of the variance. PSQI Total Score was the only individually significant predictor (table 4.8). For QOLIE-10 Mental Effects, the model was again significant $F(4,54) = 4.30$, $p < 0.005$, with predictors explaining 19.6% of the variance. PANAS negative was the only significant individual predictor (table 4.8). For QOLIE-10 Role Functioning the model was significant $F(4,53) = 3.12$, $p < 0.05$, with predictors explaining 13.8%of the variance. The PSQI Total Score predictor was the only significant individual predictor (table 4.8). For QOLIE-10 Total Score the regression model was significant $F(4,53) = 9.11$, $p < 0.001$, with predictors explaining 38.0% of the variance. PSQI Total Score was the only significant individual predictor (table 4.8).

Outcome Variable	Adjusted R^2	Predictor variables	Beta	*p*
QOLIE-10 Epilepsy Effects	0.462	PSQI Total Score	0.556	$p < 0.001$
		ESS	-0.046	$p = 0.700$
		PANAS positive	0.132	$p = 0.257$
		PANAS negative	-0.166	$p = 0.157$
QOLIE-10 Mental Effects	0.196	PSQI Total Score	-0.277	$p = 0.106$
		ESS	0.271	$p = 0.059$
		PANAS positive	0.256	$p = 0.074$
		PANAS negative	-0.382	$p < 0.01$
QOLIE-10 Role Functioning	0.138	PSQI Total Score	0.433	$p < 0.05$
		ESS	-0.115	$p = 0.437$
		PANAS positive	-0.007	$p = 0.964$
		PANAS negative	-0.110	$p = 0.458$
QOLIE-10 Total Score	0.380	PSQI Total Score	0.484	$p < 0.005$
		ESS	-0.043	$p = 0.728$
		PANAS positive	0.109	$p = 0.385$
		PANAS negative	-0.207	$p = 0.104$

Table 4.8: Regression of sleep and mood variables on QOLIE-10 variables, within the epilepsy group (n = 99).

4.4 Discussion

4.4.1 Relationships between sleep variables, mood variables, and memory/cognitive function variables

Recent research findings, including those discussed in chapters one and two, have provided robust evidence that sleep plays an important role in learning and memory. Specifically, a night of sleep has been shown to lead to performance improvements on learning and memory tasks that are not matched by improvements seen over similar periods awake. In order to explore whether disturbances to sleep can lead to detrimental effects on learning and memory, the current study assessed the relationship between sleep variables and memory/cognitive function variables in a large sample of healthy adults, and in a smaller sample of people with epilepsy. Mood variables were also included as predictors in order to assess any additional accountability for mood.

A standard multiple regression was performed to determine whether sleep quality and mood could significantly predict self-reported memory and cognitive functioning difficulties in healthy adults. The four predictors as a set significantly predicted scores on all MASQ variables, with predictors explaining between 12.7% and 28.4% of the total variance in MASQ variables. The findings indicate that sleep

disturbances and poor mood are predictive of problems with memory and cognitive function, and those people who sleep badly and/or have poor mood are at greater risk of memory problems and cognitive difficulties. Results from studies described in chapter two showed that sleep is vital for the consolidation and improvement of procedural and declarative memories, findings from this study were in line with a large body of evidence linking sleep to the consolidation of memory (e.g. Walker et al., 2002, Stickgold et al., 2000). Given these findings, we predicted that chronic sleep disturbances could lead to impaired memory and deficits in cognitive function. The current study establishes a significant relationship between sleep disturbance and memory/cognitive function problems and provides further evidence for the role of sleep in learning and memory. It can be speculated that the disruption to sleep architecture brought about by chronic sleep disturbance, impairs the ability to consolidate material learnt in the preceding wake period, and leads to persistent deficits in areas of memory and functioning that are dependent on sleep.

However, the current study also established that mood is a significant predictor of memory and cognitive function, and any conclusions regarding the accountability of sleep have to take this into account. The findings showed that those people who report high levels of negative affect, or low levels of positive affect, are significantly more likely to report subjective difficulties in areas of memory and cognitive function. Although an association was established between mood and memory/cognitive function, it is unclear whether people who report poor mood have genuinely impaired cognitive abilities, or whether they have false beliefs regarding the capabilities of their memory and cognitive functions. The current study was only able to generate data from subjective self-report measures, such measures are clearly vulnerable to bias and do not represent the most reliable or accurate method of data collection. The use of objective measures of memory/cognitive function would assist in determining the true nature of the relationship between mood and memory/cognitive function. It would allow an investigation of whether poor mood genuinely impairs memory/cognition, or whether poor mood leads to an inappropriate belief that memory and cognitive abilities are impaired. Whatever the causality, it is interesting to note that both sleep variables and mood variables contribute to memory and cognitive function abilities. Although it was suggested that sleep quality is the key factor in predicting memory and cognitive function, the

results demonstrate that mood factors are also of importance. Other variables not included in these analyses may also contribute to memory and cognitive function, and the accountability of sleep should not be overestimated. It is quite plausible that factors such as IQ, social factors, level of education etc. could explain some of the variability in scores of memory/cognitive function. Further research including a more comprehensive set of predictor variables would help to further elucidate the precise relationship between disturbed sleep and memory/cognitive function.

Separate regressions were performed on each of the MASQ variables, of the five outcome variables examined, predictors explained over 20% of the variance in only MASQ Attention (28.4%), and MASQ Language (21.6%). The findings indicate that sleep quality and mood exert their influence most strongly in the areas of attention and language. The fact that sleep quality predicts scores on attention measures is not surprising given the clear link between disturbed sleep and daytime fatigue and somnolence. Sleep deprivation has long been known to result in patterns of daytime fatigue and drowsiness (e.g. Oginska et al., 2006; Stepanski et al., 2000). Our finding confirms that chronic sleep disturbances also contribute to problems with attention and concentration, presumably as a result of fatigue and daytime drowsiness. Sleep and mood variables also predicted 21.6% of the variance in scores on MASQ Language, this implies that people who sleep badly have worse language abilities. Whilst the relationships between sleep and procedural and declarative learning have been well documented, evidence for the involvement of sleep in language learning is less abundant (e.g. Fenn et al., 2003). However, as a skill involving multiple skills it would be expected that language learning may in some way be mediated by sleep, and the finding that sleep quality to some extent predicts language skills adds further support to theories of sleep dependent learning. As discussed above, the contribution of mood to attention and language, is more difficult to explain. Although poor mood and depressive episodes could conceivably lead to difficulties with attention and language, it is also plausible that poor mood or depression could lead to dysfunctional beliefs regarding cognitive abilities, and may lead to an under-reporting of ability.

On the other three MASQ variables, predictors explained between 12.7% and 17.7% of the variance. Although accounting for a lesser proportion of the total variance, we

can still conclude that sleep quality and mood are significant predictors of scores across all the memory/cognitive function domains. Examination of the regression beta weights indicates that all sleep and mood variables make significant individual contributions to all outcome measures. However, mood variables make greater individual contributions to the outcome measures than do sleep variables, as assessed by the beta weights. This would indicate that mood is more important as a predictor of memory/cognitive function than is sleep, and mood holds the strongest influence over scores on the MASQ measures. However, calculation of beta weights only provides an index of the unique contribution of each predictor, and does not account for any contribution shared with other predictors. As the two sleep variables used in this analysis were correlated, as were the two mod variables, we must be cautious when drawing conclusions regarding the importance of individual predictors on the basis of beta weights.

4.4.2 Relationships between sleep variables and mood variables

A standard multiple regression was performed to determine whether sleep quality could significantly predict positive and negative affect in healthy adults. The two predictors (PSQI Total Score and ESS) as a set significantly predicted scores on both PANAS Positive and Negative variables, with predictors explaining 10.8% and 15.9% respectively of the total variance. The results indicate that sleep disturbances are predictive of poor mood, with those people who sleep badly more likely to report high levels of negative affect, and low levels of positive affect. These findings support a large body of evidence linking sleep disturbance to disorders of mood and negative affect. Sleep abnormalities have repeatedly been reported in major depression, with over 80% of patients with depression reporting significant sleep disturbance (Armitage, 2007). Reductions in sleep efficiency and total sleep time have been shown in patients with affective disorders, and several abnormalities are known to characterise the sleep of patients with major depression (Benca et al., 1992; Kupfer, 1995; Hubain et al., 2006). In addition to the evidence linking sleep to depression and affective disorders, many studies have also shown sleep deprivation is associated with negative mood (e.g. Scott et al., 2006). The findings from the current study support an important role for sleep in mood and affect. Although much of the previous research has concentrated on sleep disturbances in clinical affective

disorders, the results presented here confirm that sleep can have substantial effects on mood in non-depressed and otherwise healthy subjects.

Examination of the regression beta weights indicates that of the two predictors, PSQI Total Score accounts for more of the variance than ESS, on both PANAS measures. It appears that, as for MASQ variables, PANAS variables are more greatly affected by disturbances of night-time sleep, than they are by daytime effects such as sleepiness and drowsiness. Research investigating sleep in depressed populations has shown that sleep disturbances are a common consequence of depression, and occur in a large proportion of sufferers (Armitage, 2007). Evidence such as this leads us to question whether the finding that sleep disturbance is predictive of mood, is correct in terms of the direction of prediction. Although we have assessed sleep and mood in a non-depressed population, it can be speculated that the mechanisms linking sleep and mood in depressed patients also occur within a normal population. As such, further investigations should be undertaken to more reliably define the direction of causation between sleep and affect. Further analyses would also benefit from the inclusion of a larger set of predictor variables, it can be presumed that there are many factors that influence mood, and the inclusion of predictors that take this into account would provide more robust analyses.

4.4.3 Comparisons of sleep problems in epilepsy and controls

This study examined sleep and the prevalence of sleep disturbances in a sample of healthy controls and in a diverse sample of epilepsy patients with both partial and generalised epilepsies, varying seizure frequencies, on both monotherapy and polytherapy. The findings show that on self-report measures, people with epilepsy report significantly more sleep disturbances than healthy controls. In addition, those participants on polytherapy generally reported more sleep disturbances than those on monotherapy, no differences were found between partial and generalised epilepsies, or between seizure frequency groups. The results of this study support and extend the limited earlier research in which sleep disturbances were found to be more prevalent in people with epilepsy than in controls. DeWeerd et al., (2004) reported a twofold higher prevalence for sleep problems in people with partial epilepsy when compared to controls, and Xu et al. (2006) reported patients with partial epilepsy had considerably worse sleep than the general population. The current study indicates

that self-reported sleep problems in epilepsy are not just confined to the partial epilepsies, indeed no differences were observed between partial and generalised epilepsies on self-reported sleep problems. As the literature relating to self-reported sleep problems in epilepsy is so limited, it is reassuring to report similar results here to those previously published, and in a sample of unselected epilepsy patients. The findings are also in line with the generally accepted belief that sleep and epilepsy have important associations. Although few studies to date have investigated the subjective report of sleep in epilepsy patients, the relationship between sleep and epilepsy has long been recognised, the occurrence of seizures can have profound effects on sleep architecture (Bazil, 2003; Dinner, 2002), and anti-epileptic medications can alter sleep architecture (Placidi et al., 2000[b]; Foldvary, 2002). The present study confirms that sleep disturbance is a common occurrence in epilepsy, irrespective of epilepsy type or seizure frequency.

A discussion of the causes of disturbed sleep in epilepsy involves an assessment of multiple factors. Ictal and interictal epileptiform activity can have important associations with sleep. It has long been established that sleep deprivation can increase the chances of seizure activity (Bazil, 2000), interictal discharges are more commonly recorded at night than during the day, and specific increases in spike and wave activity have been demonstrated in relation to various stages of sleep (Bazil, 2000). The wealth of evidence associating sleep and epileptiform discharges leads us to speculate that although epilepsy may disrupt sleep through the effects of epileptiform discharges, sleep states are also capable of inducing epileptiform activity and seizures, and the relationship between sleep and epileptiform activity may be reciprocal. In addition to the effects of seizures and epileptiform activity, interactions between AED's and sleep have been reported both acutely and chronically. Although some AED's (e.g. gabapentin and lamotrigine) have been reported to have a beneficial effect on sleep (Placidi et al., 2000[b]), many others, particularly the older classes of AED's, have well documented detrimental effects on sleep (Dinner, 2003). Primary sleep disorders are also more common in people with epilepsy, research confirms that sleep disorders and epilepsy commonly co-exist but often go undiagnosed (Bazil, 2000). Sleep has also been identified as a risk factor for sudden unexpected death in epilepsy (SUDEP), with patient profiles revealing SUDEP is more likely to occur during sleep (Opeskin & Berkovic, 2003). The

combined evidence indicates that complex interactions between many aspects of epilepsy lead to chronic sleep disturbances, but that sleep itself also has important effects on the epilepsy state. It is clear that further research is needed to more fully investigate interactions between sleep and epilepsy, in particular the relationship between self-perceived sleep disturbances and epilepsy. In addition to the effects of various epilepsy related factors on sleep, we also have to consider that the epilepsy sample in this study was significantly older than the control sample (35.59 years vs. 27.12 years). In general, older people sleep less and have more fragmented sleep than younger people (Rama et al., 2006), however these changes in sleep patterns do not usually occur until later life and would not be expected to lead to significant differences in people in their 20's and 30's such as those described here.

Findings from this study also indicate that polytherapy is a particular risk factor for sleep disturbance in epilepsy. As previously discussed, research has provided evidence that certain anti-epileptic medications can alter sleep architecture and can disrupt the sleep cycle (Fabio et al., 2000; Foldvary, 2002). Our results indicate that in addition to the importance of AED type, the number of AED's is also an important contributor to sleep quality. We speculate that interactions between AED's may lead to the increase in sleep disturbances associated with polytherapy, and cumulative effects of multiple AED's may also account for some of the disruption to sleep patterns. However, an alternative possibility is that patients on polytherapy have more resistant forms of epilepsy, and therefore the higher rate of sleep disturbance is a consequence of the severity of the epilepsy rather than the polytherapy. Although this possibility exists, the finding that seizure severity has no relationship with sleep disturbance makes it unlikely that epilepsy severity is mediating the effect of polytherapy on sleep. We speculate that the effect of polytherapy on sleep is largely a result of the cumulative effects of AED's, and the interactions between multiple AED's, however we acknowledge that epilepsy severity may also play a role.

4.4.4 Comparisons of MASQ and PANAS variables in epilepsy and controls

In addition to the assessment of sleep disturbance, this study also investigated memory/cognitive function and mood in both epilepsy and controls. The findings showed that people with epilepsy reported significantly more problems with memory and cognitive function, and reported significantly worse mood than controls. The

finding that people with epilepsy report more problems with memory functioning than controls, fits into line with the large and robust body of evidence associating epilepsy with self-reported memory problems and cognitive difficulties (e.g. Thompson & Corcoran, 1992; Hermann et al., 1988; Mayeux et al., 1980). However, people with epilepsy can often achieve average or higher than average scores on laboratory memory tests. The discrepancy between self-reported memory and objectively measured memory has been attributed to various factors including exaggerated perception of memory problems due to anxiety or depression, poor correspondence between laboratory tests and everyday memory difficulties, and impairment of other cognitive functions leading to subjective memory problems (Giovagnoli et al., 1997). Whatever the cause, the fact that people with epilepsy complain of persistent and problematic memory difficulties is something that should not be overlooked, and the causes of such self-reported memory problems and cognitive difficulties should be further investigated.

The finding that patients with epilepsy report higher levels of negative affect, and lower levels of positive affect than controls, is in line with a large body of evidence connecting epilepsy to depression and mood disorders (e.g. Mendez et al., 1986; Robertson et al., 1987; Piazzini et al., 2001). Depressive symptoms have often been classified according to the temporal relationship between onset of depressive symptoms and seizure occurrence. Depressive symptoms have been identified in the ictal, post-ictal, and inter-ictal phases, with inter-ictal depression believed to be the most common presentation of affective disorder (Kanner et al., 2000). The current study assessed average mood 'over the past month' without specifically requesting information relating to seizure occurrence, as such we can presume that in addition to (or perhaps as a result of) specific seizure related depression, patients with epilepsy suffer a general and diffuse pattern of more negative emotion than is seen in controls. The causes of depression in epilepsy are not fully understood, epilepsy duration and age of onset appear not to be associated with depression. Decreased seizure frequency has been found to precede the onset of depression in some patients, and seizure type and localisation of focus have also been associated with depression. The effect of AED's on mood has also been investigated and has produced mixed findings, some AED's appear to induce depression, whilst others appear to prevent it (Harden, 2002). The relationship between disturbed sleep and mood has not been

fully investigated in epilepsy, but may have important and unrecognised effects (for example on sleep) which the current study will attempt to clarify.

4.4.5 Relationships between sleep variables, MASQ variables, and PANAS variables, within the epilepsy group.

The findings discussed in section 4.4.1 and 4.4.2 provide evidence that sleep disturbances and poor mood are significantly predictive of deficits in memory/cognitive function and mood, in healthy adults. We have also shown that sleep disturbances, memory/cognitive difficulties, and negative affect are more frequently reported in people with epilepsy than they are in controls (section 4.4.3 and 4.4.4). In an attempt to establish the impact of disturbed sleep and poor mood on memory/cognitive function in people with epilepsy, further standard multiple regression analyses were carried out within the epilepsy group. Variables entered into the regression model as predictors were PSQI Total Score, ESS, PANAS positive, and PANAS negative. As participants with epilepsy had also completed a quality of life measure, the QOLIE-10 Total variable was also used as an additional predictor as this gives a measure of overall quality of life. The five predictors as a set significantly predicted scores on all MASQ and PANAS variables, these findings reflected results from controls. For MASQ variables, predictors explained a higher proportion of variance than they did in controls (between 24.3% - 37.7% in epilepsy group vs. 12.7% - 28.4% in controls). The same was true of the PANAS variables, with predictors explaining more of the total variance than in controls (14.8% and 23.6% in epilepsy group vs. 10.8% and 15.9% in controls).

When we assess the impact of individual predictors on the MASQ variables, it can be seen that predictors are only individually significant on MASQ Visuo-Perceptual , MASQ Visual Memory, and MASQ Attention variables. This indicates that although the regression models are significant, the individual contribution of predictor variables is not always sufficient to predict MASQ scores. It would appear that for the epilepsy group, a combination of sleep, mood and quality of life variables are generally required to predict scores on the MASQ, indicating that a combination of factors are leading to deficits in cognitive function and memory. Examination of the beta weights reveals a variable pattern of predictor contributions across the different outcome variables. It is interesting to note the effect of quality of life on

MASQ variables, QOLIE-10 Total is a significant individual predictor on both MASQ Language and MASQ Verbal Memory. It seems that quality of life may be one of the important contributors to memory and cognitive abilities in people with epilepsy. Although it was predicted that sleep is the important variable in predicting memory and cognitive function, it seems that more research is required to more fully understand the relationship between the various predictors and outcome measures.

An inspection of the contribution of individual predictors on the PANAS variables reveals that, as expected, predictors increase (i.e. sleep worsens) as negative mood increases, and predictors decrease (i.e. sleep improves) as positive mood increases. The results also reveal that the only individually significant predictor for scores on PANAS is PSQI Total Score, indicating that disturbed sleep has a greater relative impact on mood than does daytime sleepiness (as represented by ESS). When the epilepsy group is compared to the control group (section 4.3.2), it can be seen that the relative contributions of disturbed sleep (PSQI) and daytime sleepiness (ESS) on mood are more equal in controls than in epilepsy. It is interesting to speculate as to why the pattern of results observed in epilepsy is different to that seen in controls, on both MASQ and PANAS variables. As previously discussed (section 4.4.3), people with epilepsy report more problems with both night-time sleep and daytime sleepiness than controls, and also have to deal with the effects of seizures, medications, and other epilepsy related factors. It can be speculated that variations in the pattern of results are due to differences in sleep quality, however we cannot exclude the effect of epilepsy factors and these must also be considered as possible contributors to variations in patterns of results. Further research with a larger epilepsy sample would help clarify these results and would also allow comparisons of people with different types of epilepsy, medications, seizure frequency, epilepsy duration etc.

4.4.6 Relationships between sleep and mood variables, and quality of life in epilepsy variables

In order to assess the impact of disturbed sleep on quality of life in epilepsy, standard multiple regressions were performed on each of the QOLIE-10 variables, with PSQI Total Score, ESS, PANAS positive, and PANAS negative as predictors. Regression models for each of the QOLIE-10 variables were significant, with predictors

explaining between 13.8% and 46.2% of the total variance. The results indicate that, within the epilepsy group sleep disturbances and poor mood are predictive of quality of life issues, meaning people who report the most sleep problems and who suffer from poor mood report the most compromised quality of life.

When the QOLIE-10 variables are examined separately, predictors explain the greatest amount of total variance on the QOLIE-10 Epilepsy Effects variable, indicating that effects such as memory, and physical and mental effects of anti-epileptic medication, are most strongly associated with sleep and mood problems. Predictors explained 19.6% of the variance in QOLIE-10 Mental Effects, and 13.8% of the variance in QOLIE-10 Role Functioning. It appears that sleep and mood are relatively poor predictors for these variables when compared with QOLIE-10 Epilepsy Effects. QOLIE-10 Mental Effects includes measures of energy levels, mood and general quality of life, whilst QOLIE-10 Role Functioning encompasses driving, social and work limitations, and seizure worry. The results appear to indicate that the negative impact of sleep disturbance is relatively specific to epilepsy related effects, and other issues affecting quality of life in epilepsy are more robust to sleep disturbances and negative mood.

When we assess the individual contribution of predictors, it seems that the predictor with the greatest individual contribution to outcome scores is PSQI Total Score. This variable is the only significant predictor on three of the four outcome measures. Although an obvious explanation for this finding is that disturbed sleep leads to problems with day-to-day activities that impair quality of life related to epilepsy, we also have to consider the possibility that quality of life issues lead to disturbed sleep (and also to a lesser extent poor mood). Associations between sleep and AED's have long been recognised with studies (as discussed above) suggesting that treatment with AED's can alter sleep architecture both acutely and chronically, and may be detrimental or beneficial. We speculate that our findings represent a bi-directional causality, AED's and medication effects may be a factor leading to disturbed sleep, but the subsequent disturbed sleep may then impair memory functioning, mood, or other aspects of epilepsy related quality of life. The only other significant individual predictor is PANAS negative, which predicts the outcome variable QOLIE-10 Mental Effects. This indicates that negative affect is associated with worse quality of

life relating to the mental effects of epilepsy. This finding is not surprising given QOLIE-10 Mental Effects specifically measures mood, in addition to energy levels and general quality of life. None of other predictors were individually significant in terms of predicting the outcome measures, as such it appears that a combination of sleep and mood variables are required in order for the outcomes to be significantly predicted. Another possibility is that other factors also contribute to the outcome measures, as has been discussed in section 4.4.1, the inclusion of a more comprehensive set of predictors may help clarify the results.

4.5 Conclusions and Implications

The results outlined above provide evidence that sleep disturbances and poor mood are predictive of memory and cognitive functioning problems in healthy adults, the results also provide evidence that sleep disturbances are predictive of negative affect. Within the epilepsy group, it was found that sleep problems are more commonly reported than in controls, the findings established that sleep disturbances are prevalent in people with both partial and generalised epilepsies, varying seizure frequencies, and taking many different classes of AED. The study has also provided evidence that sleep disturbances, mood, and quality of life are important predictors of memory and cognitive function in people with epilepsy. In an assessment of quality of life in epilepsy, it was found that sleep and mood variables (as a set) predicted outcomes on quality of life measures, with disturbed sleep appearing to be the most important individual predictor.

The implications of these findings, if replicable, are potentially great. It appears that sleep problems are vastly underestimated and largely ignored in epilepsy, this is despite the negative impact that such sleep disturbances have been shown to have. A greater awareness of sleep problems in epilepsy, and further objective research into sleep disturbances associated with epilepsy, could potentially lead to interventions that would not only improve sleep, but may also have positive effects on memory, mood, and quality of life. In addition to the finding that sleep disturbances in epilepsy are prevalent, the study has also shown that sleep and mood are predictive of memory/cognitive functioning in a large-scale sample comprising epilepsy and controls. It appears that the negative effects of sleep on day-to-day functioning have been underestimated, and should perhaps receive further research attention.

Before any conclusions can be drawn from this study it is important to recognise the limitations of the methods, and to be cautious when drawing any conclusions regarding the data. As discussed above, the study relies on entirely subjective methods of data collection, and whilst the various measures are validated, there is no objective data available. As such, there is a certain degree of bias that is inevitable in the dataset, and this should be taken into account before any conclusions are made. The use of objective methods, to provide a further validation for self-report measures, would generate a more reliable dataset. Another point to consider is the choice of appropriate predictor variables in the regression calculations, whilst the analyses included predictors such as sleep disturbance, mood, and quality of life, there are other factors that could presumably impact on memory and cognitive function abilities e.g. genetic factors, education, social factors. Further research including a wider range of predictors may help account for a greater proportion of the variance in memory and cognitive function. Whilst the current study provides some preliminary evidence that sleep and mood are important predictors of memory/cognitive function, and that sleep problems are prevalent in epilepsy, further work is clearly required to reach firm conclusions regarding these findings.

Chapter 5

Sleep problems in children with epilepsy: Actigraphic and parental reports of sleep disturbances.

5.1 Introduction

The studies outlined in chapter two provide support for theories suggesting sleep is vital for the promotion of learning and memory. The findings specifically suggest that sleep is important for the consolidation of procedural learning, and for the preservation of declarative memory, in both adults and children. The findings also provide support for earlier research indicating that sleep is involved in the consolidation of learning (e.g. Walker et al., 2002, Stickgold et al, 2000). In addition, the large-scale prevalence study described in chapter four demonstrated that self-reported sleep problems are associated with deficits in memory and mood. The study also provided evidence to suggest that the presence of a chronic clinical disorder (epilepsy) could predispose to sleep problems which were in turn highly predictive of memory, mood, and quality of life problems. This study not only indicated that sleep problems are more common in people with epilepsy than in controls, but that these sleep problems may have negative consequences in terms of other areas of functioning.

The current study aims to further explore the relationship between epilepsy and sleep, specifically in children. As discussed in section 1.5.2, epilepsy has a complex association with sleep, a relationship recognised since antiquity. This relationship varies from one type of epilepsy to another, and can also vary according to factors such as age, medication, epilepsy severity etc. In children, various epilepsies and epilepsy syndromes have important associations with sleep. Examples of epilepsies characterised by nocturnal seizures, or seizures upon wakening include benign rolandic epilepsy (Stores, 2001[b]), mesial frontal seizures, Lennox-Gestaut Syndrome (Amir et al., 1986), and Landau-Kleffner Syndrome (Massa et al., 2000). Other epilepsy types may be linked to the sleep-wake cycle and seizures may be associated with the transition from sleep to wake e.g. juvenile myoclonic epilepsy (Dinner, 2002; Timmings & Richens, 1992). In addition to the presence of clinically relevant seizures during sleep, there is also a close association between EEG activation and sleep. Evidence suggests that sleep has the ability to activate the EEG, an occurrence

common across many kinds of epilepsy, but something that often goes unnoticed due to the subclinical nature of the epileptiform discharges. In addition, both focal and generalised epileptic discharges are common during sleep, even if clinical seizures do not occur (Shouse, 2006).

These examples demonstrate the close associations between epilepsy and sleep, and provide evidence that sleep can have important interactions with childhood epilepsy. However, despite the relatively large quantity of literature describing direct relationships between specific epilepsy variables and aspects of sleep, there is only limited research investigating the subjective quality and quantity of sleep in children with epilepsy. A study by Stores et al. (1998) used a parental report questionnaire to assess sleep disturbances in 79 children with epilepsy (mean age 10.12, range 5–16 years) for comparisons with 73 age and sex matched healthy control children. The daytime behaviour of the children with epilepsy was also assessed by parental report questionnaire. Sleep disturbance was classified into five types on the basis of questionnaire responses (poor quality sleep, anxieties about sleep, disturbances during sleep, symptoms of disordered breathing during sleep and short duration sleep). The behaviour questionnaire provided scores on five factors (conduct problems, hyperactivity, attention problems, anxiety and physical complaints). When compared with healthy controls, children with epilepsy showed much higher rates of sleep disturbances, in particular poor quality sleep and anxieties about sleep. In children aged 5–11 years associations were also found between disturbed daytime behaviour and sleep problems, particularly poor quality sleep. This study was one of the first to investigate the habitual sleep quality of children with epilepsy, and attempted to assess general aspects of sleep and sleepiness via subjective means, rather than investigating specific relationships between epilepsy and sleep. Despite the limitations that exist in a study relying entirely on subjective measures, the findings from this study provide an insight into the sleep experience of parents and children living with epilepsy, and provide data that may be missed when more traditional and objective methods such as PSG or EEG are used to provide information on sleep.

A subsequent study by Cortesi et al. (1999) also used a parental questionnaire, and assessed sleep problems in 89 children with idiopathic epilepsy for comparisons with 49 siblings and 321 healthy control children, equally distributed for age and sex. Sleep problems were clustered into five factors: parasomnias, parent/child interaction during the night, sleep fragmentation, daytime drowsiness, and bedtime difficulties. Daytime behavior and psychological adjustment were also assessed. Results showed that children with epilepsy showed significantly more sleep problems than did both siblings and healthy controls. Within the epilepsy group, children with current seizures reported more sleep problems than did the seizure-free children. In addition, children with epilepsy showed more behavioral problems and maladjustment.

Studies such as those described above provide evidence that children with epilepsy are vulnerable to habitual sleep disturbances, and suffer pervasive and chronic difficulties with sleep. A study by Maganti et al. (2005) has also shown that daytime sleepiness is common in epilepsy, and found that children with epilepsy are much more likely to suffer from excessive daytime sleepiness than are healthy controls (Maganti et al., 2005). However in general, data in this area are lacking, and studies investigating habitual sleep problems and daytime sleepiness in childhood epilepsy are few. The current study aims to address this gap in the literature and will attempt to provide further information regarding sleep and sleepiness in epilepsy. The study will attempt to add to the current literature by assessing sleep in a group of children with a wide range of epilepsy types, generally representing the more severe end of the epilepsy spectrum (in contrast to either of the above studies). The study will involve the use of purely subjective measures, although it is recognised that this design has limitations in terms of validity, potential parental bias etc, the intention is to generate the sort of experiential data not quantifiable by objective means.

Although studies such as those described above have now shown that habitual sleep disturbances seem to occur in children with epilepsy, the studies rely on subjective measures that are dependent on parental input. Although data colleted in this way provide vital insights into the patient experience, methods involving purely subjective means may not represent a completely accurate means of collecting valid and reliable data. Some studies have found that parents can be inaccurate reporters and suggest additional measures should be used alongside parental report measures

(Huybrechts et al., 2006; Sureshkumar et al., 2006). Actigraphy is a useful and relatively new tool in the assessment of sleep, the term refers to methods using miniaturised computerised wristwatch-like devices (called actiwatches) to monitor and collect data generated by movements (Sadeh & Acebo, 2002). An actiwatch can collect data continuously over extended periods (e.g. one week or longer), providing advantages as a method of collecting data on habitual sleep quality. Various studies have assessed the validity of actigraphy and the general conclusion is that the epoch by epoch agreement between actigraphy and PSG is good (Sadeh et al., 1995).

Despite its obvious advantages as a tool for collecting information on habitual sleep patterns and general aspects of sleep and wakefulness, there is no research to date that has used actigraphy in childhood epilepsy. Actigraphy presents various advantages that would be beneficial to the assessment of sleep in epilepsy. As mentioned above actigraphy can collect data for long periods, it can also record continuously during the day and night, allowing for analysis of daytime activity as well as night-time sleep, something particularly pertinent in epilepsy where daytime seizures may result in naps, post-ictal drowsiness etc. Actigraphy is also easy to use and is well tolerated in adults, being easy to wear, unobtrusive, painless, and unrestrictive. The current study will use actigraphy to assess the validity and accuracy of a parental report questionnaire via correlative analyses. It will also investigate both the utility and tolerability of actigraphy in children with epilepsy, assessing its value as both a research tool and as a clinical instrument.

Aims

The primary aim of this study is to assess, via parental report measures, whether children with epilepsy are more vulnerable to sleep problems than are healthy control children. The secondary aim is to compare subjective parental report measures of sleep with a more objective measure (actigraphy), and to assess both the validity and accuracy of parental report and the utility of actigraphy in epilepsy.

Hypotheses

The hypothesis relating to the first aim states that children with epilepsy will be reported as having significantly more sleep problems than healthy controls. The hypothesis relating to the second aim states that significant correlations will exist

between actigraphic and parental report methods of assessing sleep in children with epilepsy.

Investigating the prevalence of sleep problems in children with epilepsy

5.2 Methods

5.2.1 Consent

All parents and children were given information on the study prior to participation, all parents gave informed consent and all children gave informed assent. The study was approved by the NHS South Sheffield Research Ethics Committee.

5.2.2 Participants

A total of 87 children with epilepsy were recruited for the study. Recruitment occurred via two channels, 44 children (50.6%) were recruited via an Epilepsy Clinic at a Sheffield paediatric neurology assessment unit, these children had been referred from their GP or paediatrician for assessment of their epilepsy. A further 43 children (49.4%) were recruited via membership of the charity Epilepsy Action. A short article was published on the charity website and in the members magazine (Epilepsy Today), in which parents of children with epilepsy were invited to join the study. Children with a wide range of epilepsies and epilepsy syndromes were accepted, there were no exclusion criteria based on epilepsy type. The mean age of the epilepsy group was 10.6 years (SD = 3.72), the age range was 3-19 years and 67% were male.

Control participants consisted of 117 healthy children, recruited via a mainstream primary school and a mainstream secondary school in Cheshire. The mean age of the control group was 11.05 years (S.D = 3.41), the age range was 4-16 years and 55.6% were male.

5.2.3 Apparatus

Sleep Questionnaire

Sleep, the primary outcome measure, was assessed by means of a parental report sleep questionnaire. This questionnaire had been developed by Gianotti et al. (1995) to facilitate the investigation of sleep behaviour in a general paediatric population. The questionnaire was designed primarily to assess sleep disturbances and sleep-

related disorders in childhood, not to provide an accurate diagnosis of sleep disorders. It assesses quantity and quality of sleep, as well as factors such as reluctance to go to bed, usual bedtime and wake time, sleep latency, parental involvement at bedtime, night awakenings, naps, daytime drowsiness in different situations and un-refreshing sleep. (Cortesi et al., 1999). Severity of each sleep problem was rated on a 5 point Likert scale from 1 (never) to 5 (always) as to how often each item occurred. On all items (after appropriate recoding), higher scores were correlated with a greater severity of sleep problems. The sum of all questionnaire items relating to sleep gives a total score for sleep problems. In addition, factor analysis of the questionnaire yielded the following five factors.

1. Parent/child interactions during the night
2. Sleep fragmentation
3. Parasomnias
4. Daytime Drowsiness
5. Bedtime difficulties

The sum of factor items gives a score for each sleep factor, higher scores again indicating more severe sleep problems. Some items were not grouped into factors due to their miscellaneous nature (bedwetting, snoring, bad dreams), these were still included in scores of total sleep problems. In addition to the sleep factors listed above the questionnaire also generated parent defined measures of mean sleep time per night, sleep latency, and duration of daytime naps (if taken). The internal consistency of the questionnaire was shown by its authors to be good (Cronbach's $\alpha = 0.70$). 3-week test-retest correlation of total sleep scores also indicates adequate reliability ($r = 0.79$, $p < 0.001$) (Cortesi et al., 1999).

Epilepsy related items

As epilepsy and seizure variables were likely to be related to children's sleep problems, parents were also asked to report on various items relating to epilepsy. These included epilepsy syndrome or type if diagnosed, primary seizure type, secondary seizure type if appropriate, seizure frequency, age of onset, primary medication (plus secondary and tertiary if appropriate). Parents were also asked to report any other significant medical problems (especially ENT related problems or other problems with a known predisposition to sleep problems), and any learning or

behavioural difficulties. Children with a diagnosis of a primary sleep disorder were excluded.

5.2.4 Design and Procedure

For control participants, parents of children from two schools (primary and secondary) were sent a copy of the questionnaire alongside a short information sheet detailing the aims of the study, parents who wished to participate completed the questionnaire in their own time and returned them by freepost to the research team. For epilepsy participants a mailshot was prepared from the Sheffield neurology assessment unit, all parents of children with epilepsy (>5yrs) were sent a questionnaire and information sheet, parents who wished to participate completed the questionnaire in their own time and returned them by freepost to the research team. An article was also published on the website of Epilepsy Action, and in their magazine Epilepsy Today, inviting parents of children with epilepsy to contact the research team if they would like to participate in research. Parents who contacted the research team were sent a questionnaire and information sheet, and completed and returned the questionnaires in their own time. All parents of children were asked to complete the questionnaire as accurately and honestly as possible.

5.2.5 Variables and Analysis

Variables were tested for normality, significant positive skew was found to be present on all six sleep questionnaire variables (parent/child interactions, sleep fragmentation, parasomnias, daytime drowsiness, bedtime difficulties, and total score) so were subjected to natural log transforms. Statistical analyses were performed using independent *t*-tests to compare sleep problems in epilepsy and controls, and chi squared tests to assess the frequency of napping in epilepsy and controls. Independent *t*-tests and ANOVA's were used to assess the effect of non-epilepsy related variables sex and age on sleep problems. Further ANOVA's were used to assess the effect of the various epilepsy variables (seizure frequency, seizure type, medication and presence of SEN) on questionnaire defined sleep problems. Although information relating to age of onset of epilepsy was included the questionnaire, responses were generally vague and uncertain, and as such were unfortunately not suitable for inclusion in further analyses. A small number of participants returned questionnaires with occasional items missing, these were still

included in analyses but only for the sleep factors that could be fully and correctly computed.

5.3 Results

5.3.1 Descriptive information for epilepsy and controls groups

Table 5.1 shows descriptive information for the epilepsy sample. The return rate for questionnaires within the epilepsy sample was 60.8%. Epilepsy variables ranged widely, although unspecified in many cases seizure frequency rose above one per fortnight in 25 cases. Where primary seizure type could be judged with some degree of confidence, the largest group appeared to be generalised seizures, accounting for two thirds of all primary seizure types. The most common generalised seizure type was absences, this seizure type alone accounted for a third of all primary seizures. Other generalised seizures encompassed tonic-clonic, atonic and myoclonic. Partial seizures (simple and complex) were the primary seizure type in 18 children. A total of 43 children experienced more than one seizure type, the most common secondary seizure type was generalised. In addition to seizure type, parents were also asked to define their child's epilepsy type. A wide range of epilepsy types and syndromes were described by parents, the most common epilepsy types were generalised and focal. Of the children classified as 'other epilepsy syndrome/unspecified', a diverse range of epilepsy syndromes was identified. These included Lennox-Gastaut Syndrome and Landau-Kleffner Syndrome. All but 5 of the children were on current epilepsy medication at the time of the survey, the most common primary medications were lamotrigine and sodium valproate. Other primary medications included carbamazepine, levetiracetam, and topiramate. Parents described 42 children as being on current polytherapy, definable as taking two or more anti-epileptic drugs. The most common secondary medication was topiramate. In addition 44 of the children were reported to have a learning disability sufficient to require a statement of special educational needs.

Within the control sample there were 67 males and 50 females, the group mean age was 11.05 years (S.D = 3.41), and the age range was 4-16 years, there was no significant difference between the ages of the epilepsy group and the controls. None of the control children had any significant medical problems or learning difficulties. The return rate for questionnaires within the control group was 55%.

Male		58 (67%)
Age		4-19 years, mean = 10.6 yrs (S.D = 3.72 yrs)
Seizure frequency:	> One/fortnight	37 (42.5%)
	< One/fortnight	25 (28.7%)
	Unspecified	25 (28.7%)
Primary seizure type:	Absences	29 (33.3%)
	Other generalised	29 (33.3%)
	Partial	18 (20.6%)
	Other seizure type/Unspecified	11 (12.6%)
Epilepsy Type:	Generalised	22 (25.3%)
	Focal	10 (11.5%)
	Complex Partial	8 (9.2%)
	Juvenile Myoclonic Epilepsy	6 (6.7%)
	Other syndrome /Unspecified	41 (47.1%)
Primary medication:	Lamotrigine	26 (29.9%)
	Sodium Valproate	21 (24.1%)
	Carbamazepine	10 (11.5%)
	Levetiracetam	9 (10.3%)
	Topiramate	8 (9.2%)
	Other	8 (9.2%)
	None	5 (6.5%)
Polytherapy		42 (48.3%)
Special Educational Needs (SEN)		44 (50.6%)

Table 5.1.1: Parental defined descriptive information for the epilepsy sample (n = 87)

5.3.2 Comparison of sleep problems in epilepsy and controls

As described previously, preference was given to the analysis of items grouped into factors, corresponding to different areas of sleep disturbance. In addition, a total score for sleep disturbances was obtained by summing scores for all questionnaire items. A Bonferroni correction for multiple *t*-tests was applied (i.e. a significance threshold set at $p < 0.006$). Independent *t*-tests showed that children with epilepsy had significantly higher total sleep scores than controls. Children with epilepsy had a mean total sleep score of 64.19 (S.D = 16.19) whilst controls had a mean score of 45.5 (S.D = 8.93) ($t = 8.52$, df = 154, $p < 0.001$). Further independent *t*-tests showed that, as a group, children with epilepsy had higher mean scores than controls on all five sleep factors. With the exception of bedtime difficulties ($p < 0.005$), all factors were significant at the $p < 0.001$ level. Mean values for both groups are shown in table 5.1.2.

	Epilepsy		Controls		
	Mean	S.D	Mean	S.D	*t*
Total score	64.19	16.19	45.5	8.93	**8.52
Parent child interactions	7.79	3.69	5.1	2.1	**6.68
Sleep fragmentation	11.64	3.45	8.36	2.05	**7.52
Parasomnias	16.55	5.61	11.13	5.08	**7.87
Daytime drowsiness	13.26	4.16	5.32	2.65	**9.87
Bedtime difficulties	9.05	3.9	7.29	2.61	*3.39

Table 5.1.2: Comparison of sleep problems in children with epilepsy and controls.
$^{**}p < 0.001$; $^{*}p < 0.005$

Children with epilepsy also reported significantly more time spent in bed than controls. Children with epilepsy spent an average of 10 hrs 23 mins in bed per week night whilst controls spent an average of 9 hrs 57 mins in bed per week night (t = 2.63, df = 199, $p < 0.01$). Conversely, at weekends this trend was reversed and children with epilepsy were reported as spending significantly less time in bed than controls, children with epilepsy spent an average of 10hr 50mins in bed, compared to 12hrs 19mins for controls (t = -2.50, df = 194, $p < 0.05$) controls. Seemingly children with epilepsy show more consistency in their sleep duration, with sleep times differing only slightly between week nights and weekend nights, the relative difference is much greater in the control population, with over 2 hours mean difference in sleep time between week nights and weekend nights.

Parents were also asked whether their child took daytime naps, a significant relationship was found between epilepsy and daytime nap taking with 36.8% of the epilepsy sample taking naps, compared to 1.7% of the control sample (Pearson's χ^2 = 44.19, df = 1, $p < 0.001$). In addition, parents also reported the usual duration of their child's naps (if they napped at all), within the epilepsy sample the majority of children were reported as taking naps lasting longer than 30 mins, both at home and at school (see table 5.1.3).

		Epilepsy	Controls
Children reporting daytime naps:		32 (36.8%)	2 (1.7%)
Usual duration of naps:	0-30 mins	5 (15.6%)	N/A
	30-60 mins	11 (34.3%)	N/A
	1-2 hrs	12 (37.5%)	N/A
	Unspecified	4 (12.5%)	N/A

Table 5.1.3: Frequency and duration of nap taking in children with epilepsy and controls.

5.3.3 Within the epilepsy group: non-clinical variables associated with sleep problems

Further analyses were carried out to assess the effect of the non-epilepsy variables sex and age on sleep problems. With respect to sex of child, an independent *t*-test showed no significant differences between boys and girls on any sleep problems, with the exception of sleep fragmentation, where boys reported significantly higher scores than girls ($t = 2.91$, $p < 0.005$). As there was a large age range (3-19yrs), four age bands were examined separately; 3-6 yrs (n = 16), 7-10 yrs (n = 26), 11-14 yrs (n = 21), 15-19yrs (n = 12). Between-subject ANOVA's were performed on each of the sleep factors and post hoc analyses were performed using Scheffe's test. Significant relationships were found for the following sleep factors (table 5.1.4). Parent/child interactions $F(3,81) = 0.170$, $p < 0.005$, post hoc comparisons showed the youngest children performed worst, with significant differences between 3-6yrs age group, and both 11-14 yrs ($p < 0.05$) and 15-19yrs ($p < 0.01$). Sleep fragmentation $F(3,74) = 0.77$ $p < 0.005$, post hoc comparisons again showed the youngest children performing worst, with significant differences between 3-6yrs and 11-14yrs ($p < 0.01$). Daytime drowsiness $F(3,78) = 0.68$, $p < 0.05$, post hoc comparisons did not show any significant differences between groups but examination of means showed an increase in daytime drowsiness corresponding to increasing age (fig. 5.1.4). No significant relationships were seen between parasomnias and age, bedtime difficulties and age, or total score and age.

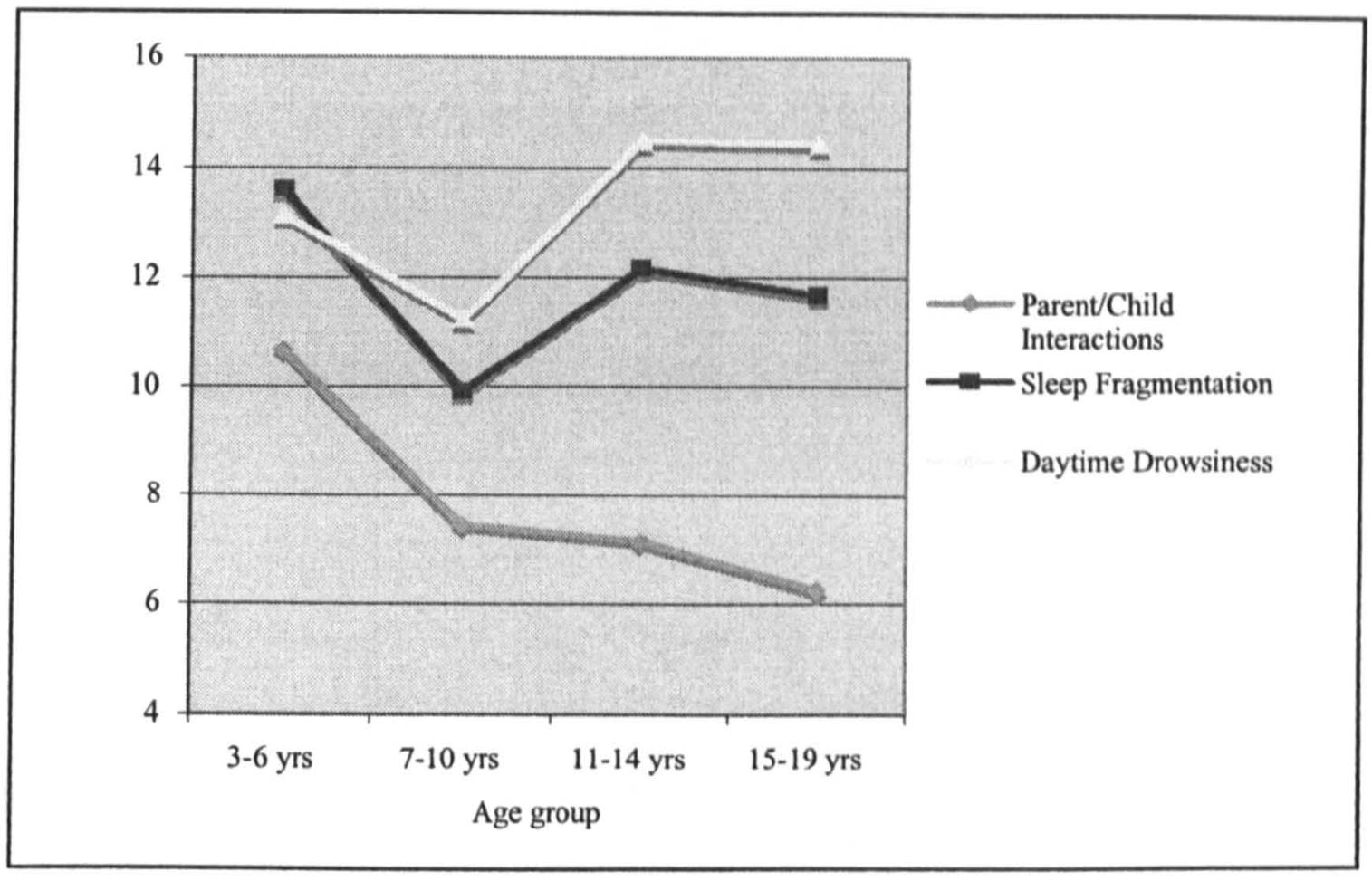


Fig. 5.1.4: Mean scores for factors showing a significant relationship with age (epilepsy group).

5.3.4 Within the epilepsy group: variables associated with sleep problems

In addition to items relating to sleep, the questionnaire also contained items relating to epilepsy. Factorial ANOVA's were performed on each of the sleep factors. Independent variables consisted of seizure frequency, primary seizure type, presence of SEN, and monotherapy vs. polytherapy. As indicated in the descriptive information seizure types were classified as absence, other generalised, or partial. Seizure frequency, presence of SEN and monotherapy vs. polytherapy were coded as simple dichotomous variables. Medication type was not included as an independent variable because the range of medications was so wide, individual AED's did not have sufficient numbers to warrant inclusion in the analysis. Polytherapy or monotherapy was included as a broader measure of medication effects. Post-hoc comparisons were made using Scheffe's test. With all variables included in the model, the epilepsy group scores for sleep fragmentation, parasomnias and bedtime difficulties were not significantly affected by the child's seizure type, seizure frequency, SEN (presence or absence), or mono vs. polytherapy. However, parent/child interactions during the night were significantly affected by both seizure type $F(2,37) = 3.78$, $p < 0.05$ and mono/polytherapy $F(1,37) = 4.33$, $p < 0.05$. Children on polytherapy (mean 8.18, SD = 4.00) reported more sleep interaction problems than those on monotherapy (mean = 7.35, SD = 3.46), and children with generalised seizures (excluding absences) (mean = 8.68, SD = 4.22) reported more

sleep problems than those suffering from either partial seizures (mean = 7.00, SD = 3.14), or absence seizures (mean = 7.24, SD = 3.43). Daytime drowsiness was also significantly affected by seizure type $F(2,35) = 4.95$, $p < 0.05$, with generalised seizures (mean = 14.71, SD = 3.84) associated with significantly higher mean scores than partial seizures (mean = 13.81, SD = 3.66), or absence seizures (mean = 11.90, SD = 4.10). Total sleep scores were also significantly affected by seizure type $F(2,20) = 5.73$, $p < 0.05$ and SEN $F(1,20) = 5.29$, $p < 0.05$. Children suffering generalised seizures (mean = 71.83, SD = 15.88) again reported higher scores than those suffering absences (mean = 61.53, SD = 16.76), and partial seizures (mean = 66.33, SD = 11.99). Children with a diagnosis of SEN reported higher total scores (mean = 70.58, SD = 15.77) than children with no learning difficulties (mean = 61.87, SD = 14.72). There were no significant interactions between epilepsy variables on any of the sleep factors.

5.4 Discussion

5.4.1 Implications of sleep disturbances

The main conclusion from this study is that according to parents, children with epilepsy are much more likely to report a range of sleep problems than controls. Sleep problems were clustered into various factors and whichever way sleep was quantified, the group of children with epilepsy reported a greater occurrence of problems. In addition to the questionnaire defined sleep problems, children with epilepsy were also more likely to take naps, and slept for longer during the week (although at weekends they slept less than controls).

Within the epilepsy group, age was shown to have a significant effect on certain types of sleep problem. In general, it was found that younger children had more sleep problems, the exception was daytime drowsiness were the trend was reversed and older children reported more problems. The group of children with epilepsy was very diverse in terms of epilepsy variables but despite this the group as a whole showed a non-specific vulnerability to sleep problems. Limited associations were also found between epilepsy variables and sleep problems, seizure type appeared to be the variable with the most associations with sleep problems, with generalised seizures leading to the most problems. Children taking more than one medication

and those with learning difficulties (SEN) were also more likely to have problems with parent/child interactions and total sleep scores respectively.

The findings from this study support evidence from two earlier studies, indicating children with epilepsy are particularly vulnerable to a wide range of sleep problems and sleep disturbances (Cortesi et al., 1999; Stores et al., 1998). Although the study conducted by Stores et al. in 1998 used a different questionnaire to that used in the current study, the results were comparable. The Stores et al. (1998) study was also composed of children with relatively stable epilepsy, who represented the less severe end of the epilepsy spectrum. The children in the current study generally suffer from more problematic epilepsy, with a greater number of children reported as having complex epilepsy syndromes, multiple medications, and associated learning difficulties. Despite differences in the samples, both studies reported similar findings in terms of a high prevalence of sleep disturbance compared to healthy children. The 1999 study by Cortesi et al. used the same questionnaire to the current study, and it is reassuring that both studies report similar findings. The sample in the Coretesi et al. (1999) study was restricted to children with idiopathic epilepsy, although the current study was composed of a sample of children with a wide range of epilepsy types, both studies report similar findings in terms of reported sleep disturbance in epilepsy. Our findings provide further evidence that sleep disturbances in epilepsy are highly prevalent, and common across different epilepsy types, epilepsy severities, and medication groups. The finding that children with epilepsy are particularly vulnerable to sleep problems has a number of important implications. Sleep disturbances, problems at bedtime, and the resultant daytime effects of sleep disruption can cause a great deal of distress to a child, particularly in children already dealing with a chronic illness. Sleep disturbance and its consequences may also put pressure on parents and siblings, potentially disrupting the sleep of other family members. In addition to these issues, sleep disturbances can be particularly significant in those with a chronic condition such as epilepsy. Sleep deprivation is known to precipitate seizures, and certain types of sleep disorder have specific links to epilepsy and nocturnal seizures, for example sleep apnea can exacerbate seizures and the treatment of sleep apnoea may have a beneficial effect on seizure control (Koh et al., 2000).

In addition to the possible effects on a child's epilepsy and seizures, sleep problems can also have important consequences on aspects of learning and behaviour. Stores et al. (1998) showed that sleep problems in childhood epilepsy were associated with parental reports of disturbed daytime behaviour. It may be important to further investigate the effects of disturbed sleep on behaviour, and to be aware of interactions between sleep and problematic behaviour. The present study also highlights the problem of daytime drowsiness and daytime napping in epilepsy, a worrying finding in children of school age expected to maintain concentration and alertness at school. Children who are unable to maintain concentration at school, or who are missing out on lesson time due to naps, are at an obvious disadvantage in terms of learning and education.

In addition to the more obvious detrimental effects on learning, the role sleep plays in the consolidation of learning should also be considered. Several studies including those described in chapter two have now shown that sleep is vital for the consolidation of certain types of learning (e.g. Walker et al., 2002; Stickgold et al., 2000). The studies described in chapter two also confirm that the association between sleep and learning exists in children as well as adults. It should be considered that sleep problems in childhood epilepsy may impair learning through the effect of impaired consolidation, and that disturbed sleep architecture may be a particularly important issue when considering the potential implications on learning. Children with epilepsy are known to be particularly vulnerable to learning problems and cognitive difficulties, educational underachievement and poor scholastic performance are commonly associated with epilepsy. The causes of this epilepsy related learning deficit have never been fully and satisfactorily explained, although it is generally accepted that seizure effects, medication, epilepsy related pathology, and social and parenting factors all play a role (e.g. Aldenkamp et al., 1990; Binnie et al., 1990; Stores, 1990). Given the evidence connecting sleep to learning, perhaps sleep should also be considered as an important factor when investigating epilepsy related learning problems. Future research specifically investigating sleep dependent learning in children with epilepsy could help further elucidate the impact of sleep on learning and cognitive function in epilepsy.

5.4.2 Causes of sleep problems

The cause of sleep problems in childhood epilepsy has not been satisfactorily established and is likely to be multi-factorial. Epilepsy variables to be considered may include the direct effect of seizures, epilepsy related anatomical abnormalities, subclinical epileptiform discharges, medication, and social factors such as parenting styles etc. The direct effect of seizures is likely to have an important effect on sleep in epilepsy, both through the effect of nocturnal seizures and through the associative effects of any daytime seizure or epileptiform activity. Nocturnal seizures cause a disruption to normal sleep architecture and to the characteristic EEG patterns associated with normal sleep stages (Bazil, 2003). Even if patients are unaware of night-time seizures, the disruption of normal sleep architecture may lead to abnormal arousals and daytime drowsiness. In addition, night-time seizures of which a child is unaware may be mistaken for parasomnias (e.g. nocturnal partial seizures may be mistaken for sleep walking or night terrors), EEG video-telemetry is often the only way to confirm a diagnosis if there is uncertainty. The increased prevalence of parasomnias in epilepsy may in fact be a reflection of undiagnosed seizures rather than true parasomnias.

Often patients will be woken by a night-time seizure, in cases such as these there is a more obvious disruption to the sleep pattern and often a prolonged arousal or awakening. There may also be problems of returning to sleep, either as a result of the seizure or due to anxiety or post-ictal effects. Fragmented sleep and subsequent daytime drowsiness will be an obvious consequence of these night-time disturbances. In cases were patients suffer from predominantly or exclusively nocturnal seizures, there may also be some anxiety attached to going to bed or falling asleep. Postponement of bedtime or problems maintaining sleep throughout the night may be an indication of anxiety or apprehension regarding sleep.

Even when seizures do not occur at night, they may still have an indirect effect on sleep patterns. Seizures during the day are often associated with a period of post-ictal tiredness or sleepiness. It is tempting to attribute the increased likelihood of daytime drowsiness in epilepsy to the post-ictal effects of seizures, however we found no differences in sleep problems when comparing those with high seizure frequency (> 1 per fortnight) and those with low seizure frequency (< 1 per

fortnight). This indicates that post-ictal effects are not the sole contributor to daytime drowsiness, and we should consider other factors.

The effect of subclinical epileptiform discharges should also be considered as a possible contributor to sleep problems. Subclinical discharges are relatively common in epilepsy, they represent inter-ictal epileptiform activity that is not recognised as a clinical event. Inter-ictal discharges that occur at night will have an obvious disruptive effect on sleep architecture, causing changes to the EEG patterns that characterise sleep stages. Subtle EEG markers that are associated with specific sleep stages (e.g. sleep spindles and K-complexes during stage 2 NREM sleep) may be disrupted by inter-ictal discharges. Disruptions to sleep architecture may lead to increased sleep fragmentation and a greater number of nocturnal arousals, inappropriately staged sleep may also prevent sufficient restoration and may lead to an increase in daytime drowsiness. Inter-ictal discharges during the day may also have an effect on the reported incidence of sleep problems, there is evidence to suggest that children may suffer a transient cognitive impairment when suffering from inter-ictal discharges (Binne & Marston, 1992; Aldenkamp & Arends, 2004). Transient cognitive problems during the day may well be mistaken for inattentiveness or drowsiness, but are unlikely to reflect true sleep problems.

Another factor to consider when evaluating the cause of sleep disturbances in epilepsy is the effect of epilepsy related pathology. Many epilepsies can be traced to a specific area of damage or pathology in an area of the brain. Sleep states are dependant on the functioning of specific brain sites and the effects of certain neuromodulators and neuropeptides (Marks, 2006). Lesions or specific damage to areas of the brain associated with sleep may cause disruption to sleep architecture and could result in abnormal sleep states. Damage such as this may result in epilepsy with a related clinical sleep disorder, with the abnormal brain pathology independently responsible for both the epilepsy and the sleep disorder. Epilepsy related pathology can also result in more subtle effects on sleep, although the complex interactions between specific brain areas and sleep are not fully understood, it is possible that alterations to sleep architecture and disruptions to sleep states occur. However, many epilepsies are not associated with demonstrable pathology and do not appear to show any abnormalities to brain structures, as such it is unlikely

that abnormal brain pathology is solely responsible for the high prevalence of sleep problems seen in epilepsy.

Anti-epileptic drugs (AED's) are widely used in epilepsy, mechanisms of action vary greatly but the effect of AED's on sleep has been documented. However, despite widespread clinical use, the specific effects of AED's on sleep have not been extensively investigated and are not well known. However, studies do exist which enable us to make some assessment of the effect of medication on sleep. Studies have shown that some AED's have detrimental effects on sleep, while others appear to have stabilizing effects. The most commonly taken drug in the present study (lamotrigine) has been shown to significantly increase REM sleep and to have a stabilizing effect on sleep, (Placidi et al., 2000[a]). Studies investigating the effects of sodium valproate have mostly shown minor or no effects on sleep architecture, and have generally resulted in a stabilisation of sleep cycles (Placidi et al., 2000[b]). Research into the effect of carbamazepine is more controversial but suggests disruption to REM sleep can occur after acute administration, however chronic treatment does not result in modifications of sleep or daytime somnolence (Placidi et al., 2000[b]). Studies on the effects of levetiracetam are few but findings have shown a general consolidating effect on sleep, however reports of daytime drowsiness are conflicting with some studies reporting an increase (Bell et al., 2002), and others a decrease (Cicolin et al., 2006). The single small scale study (n = 13) assessing the effect of topiramate reported a decrease in stage 1 sleep and a shorter REM latency (Jennum et al., 2005). In general it seems that the AED's most commonly taken in this study have a consolidating effect on sleep, although as these drugs are also effective anticonvulsants it is possible that sleep is stabilised by the improvement of seizures. As such, it seems unlikely that we can attribute the high prevalence of sleep problems in our sample of children with epilepsy to the use of AED's.

However, our results did show that treatment with polytherapy was associated with more reported sleep problems than monotherapy, a finding confirming previous research (e.g. Bazil et al., 2005). The mechanism for this is unclear, one possibility is that interactions between various drugs lead to detrimental effects on sleep architecture, however another possibility to consider is that those children on polytherapy are those with the most severe and the most drug resistant epilepsy, and

the increased incidence of sleep problems may be a result of the severity of the epilepsy rather than a direct consequence of medication. It is clear that AED's have profound effects on sleep, whether this effect is positive or negative clearly requires further investigation in order to provide a clearer picture of the complex interactions between AED's and sleep.

A final point to consider when evaluating the cause of sleep problems in epilepsy is the contribution of social and behavioural factors such as parental attitudes, child characteristics, attitude towards illness, seizure anxiety etc. Although these factors were not assessed in the current study it can be argued that the presence of epilepsy per se can have a significant and detrimental effect on sleep. For example, anxiety about nocturnal seizures may lead to problems at bedtime and increased sleep latencies, parental concerns over nocturnal seizures may lead to increased vigilance throughout the night and over-reporting of sleep problems. Stores et al. (1998) reported sleep problems in children with epilepsy were associated with behavioural difficulties, this evidence supports the theory that behaviour has important associations with sleep. The question as to whether behaviour is causative of sleep disturbances, or whether sleep problems lead to behavioural difficulties is as yet unanswered and is an obvious direction for future research.

In conclusion, children with epilepsy have been found to be highly susceptible to sleep problems, and report significantly more difficulties with sleep than healthy controls. The high incidence of sleep disturbances reported in childhood epilepsy is likely to have a number of negative consequences, particularly in areas of learning and cognitive function. The cause of sleep disturbances is likely to be multi-factorial, with seizure activity, pathology, medication, and social factors all playing a role. The findings from this study support previous research linking sleep with epilepsy, but outline the need for a more detailed evaluation of sleep in childhood epilepsy, particularly investigating specific parameters of sleep such as total sleep time, sleep latency and sleep efficiency. Parent report measures are also subjective in their nature and as such are vulnerable to bias, validity cannot always be guaranteed as parents may be inaccurate in their reporting of sleep problems, or may be unaware of certain disturbances that occur during the night. Questionnaires assessing sleep are particularly vulnerable to such bias as parents will themselves be

asleep for a proportion of the time their child is in bed, and may be unaware of many night-time events. Objective investigation of the more specific aspects of sleep disturbances in epilepsy will allow a greater understanding of the complex interactions between sleep and epilepsy, and will provide the means to validate parental report questionnaires.

Actigraphic and parental reports of sleep problems in childhood epilepsy.

5.5 Methods

5.5.1 Consent

Within the epilepsy group, parents and children who completed the first part of the study were also invited to participate in further research, those who expressed an interest were given full information regarding the second stage of the study (actigraphy). Informed consent and assent was taken from parents and children respectively. The study was approved by the Department of Psychology Ethics Sub-Committee.

5.5.2 Participants

Of the 87 participants with epilepsy who completed the first (questionnaire) stage of the study and who expressed an interest in further research, 20 children were selected at random to undergo the actigraphy stage of the study. The children were aged between 5 and 14 years (mean age = 10.3, SD = 2.68), 14 boys and 6 girls. All children had a confirmed diagnosis of epilepsy and all children were on antiepileptic medication. A total of 6 of the children had special educational needs, no other learning, behavioural or medical problems were reported in the sample. Children with a diagnosis of a primary sleep disorder were excluded.

5.5.3 Apparatus

Sleep disturbances had already been assessed by means of a detailed but subjective parental report questionnaire (see section 5.2.3). In order to gain more objective data on sleep children were asked to undergo seven nights of actigraphy. Actigraphy is a relatively unobtrusive means of collecting objective data on sleep, it involves a participant wearing a specialised activity monitor or 'actiwatch' (fig. 5.1.5) for seven days. The actiwatch is a wrist mounted device which detects and logs movement

intensity and duration. The data is stored in the watch and can be downloaded to a computer for analysis. The sensor in the actiwatch produces an electrical signal proportional to the g force to which it is subjected. The signal is therefore proportional to the movement intensity. The signal is sampled to determine the peak intensity in each second. The intensity is converted to a digital value referred to as a 'count'. Counts from several seconds are summed together and stored in a time bin called an 'epoch' which is user definable (Cambridge Neurotechnology Ltd, 2005). In the present case epoch length was established at 1 minute for all participants. Actigraphy has been validated against polysomnography the 'gold standard' for use in sleep studies (correlations of > 0.90) (Sadeh et al., 1995). During the seven day period children were wearing the actiwatch, parents were asked to complete a simple sleep diary on behalf of their child. Information recorded in the sleep diary included bedtimes and get-up times for each of the seven days, number of night awakenings, daytime drowsiness ratings, and details of any other events affecting sleep during the seven day period (particularly epilepsy related events such as seizures, post-ictal drowsiness etc). Parents were also asked to report any times the actiwatch was taken off during the test period. After the seven day test period, information from the actiwatch was downloaded onto a computer, bedtimes and get–up times as reported by parents were input into the computer, and the sleep analysis software (Sleep Analysis 5) generated detailed information on various aspects of sleep. Specific variables generated are listed in table 5.1.6 with a brief description of each parameter. As recommended by the manufacturers, each variable was averaged over the seven day period to provide a single mean score for each variable to be used in all subsequent analyses. Further details of actigraphy can be found in section 1.1.7.

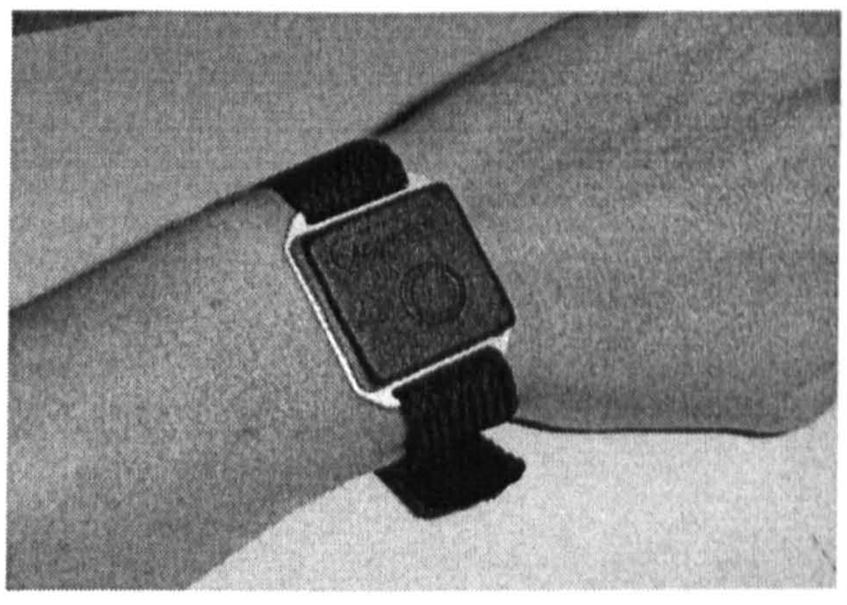


Fig. 5.1.5: A wrist mounted actiwatch.

Actiwatch variables	Description
Time in Bed	The difference between getting up and going to bed as defined by parents
Assumed Sleep	The difference between sleep start and sleep end (sleep start and end determined by the algorithm).
Actual Sleep Time	The amount of sleep determined by algorithm and equivalent to assumed sleep minus awake time.
Actual Awake Time	The amount of time spent awake (determined by the algorithm) within the period of assumed sleep.
Sleep Efficiency	Actual Sleep Time divided by Time in Bed
Sleep Latency	The latency before sleep onset following bed time.
Number of Sleep and Wake Bouts	The actual number of episodes of sleep and wakefulness
Mean Length of Sleep/Wake Bouts	Determined by dividing total duration of sleep and wake by corresponding number of sleep and wake bouts
Number of Minutes Immobile	Number of minutes where an activity score of zero (indicating immobility) was recorded during the assumed sleep period.
Fragmentation Index	An indicator of restlessness, defined by the algorithm
Mean Activity Score	The average value of the activity counts per epoch over the assumed sleep period.

Table 5.1.6: Descriptions of variables generated by the actiwatch

5.5.4 Design and Procedure

Parents of children with epilepsy who had completed a sleep questionnaire were asked if they and their child would be interested in being involved in further research and those who expressed an interest were contacted with details of the actigraphy study. Of the participants who had expressed an interest, 20 were selected at random to be involved. Actiwatches and sleep diaries were posted to participants, children were instructed to wear the actiwatch on their non dominant hand for a seven day period. Children were instructed to wear the actiwatch at all times during this period except for baths/showers or whilst swimming. During the seven day test period, parents were also asked to complete a sleep diary on behalf of their child. After the seven day period parents returned the actiwatch and the diary to the experimenter and were provided with feedback and a summary of the actigraphy data.

5.5.5 Variables and Analyses

As discussed in section 5.2.5, log transformed variables were used for statistical analyses involving all six questionnaire defined sleep factors (parent/child interactions, parasomnias, sleep fragmentation, daytime drowsiness, bedtime

difficulties and total score) in order to reduce positive skew. Other non-transformed questionnaire variables comprised mean sleep time per night and sleep latency. Actigraphy variables are listed in table 5.1.6 and did not require transformations. Initial analyses sought to assess correlations between parent-report measures and actigraphy measures of sleep using Pearson's correlation coefficients. Paired *t*-tests were then used to compare parent-reported and actigraphic mean sleep times and sleep latencies. A case analysis of an actogram was also performed to give general feedback on the use of pictorial information.

5.6 Results

5.6.1 Descriptive information for the sample.

Table 5.1.7 shows descriptive information for the sample. All participants had a diagnosis of epilepsy and of those who specified, 8 reported more then one seizure per fortnight. An assessment of seizure type revealed generalised seizures were the most common with 10 children reporting absences or tonic clonic as the primary seizure type. Complex partial seizures accounted for the primary seizure type in 8 children. Of the 20 children, 7 reported the occurrence of more than one seizure type. In addition to defining seizure type, parents were also asked to define their child's epilepsy type or syndrome (where possible). A diagnosis of focal epilepsy was the most common, and was reported in 8 children, generalised epilepsies accounted for 7 children with various specific epilepsy syndromes diagnosed in 5 children. Lamotrigine and sodium valproate were the most common primary medications, with 6 children each taking one of these, carbamazepine was taken by 3 children with a range of other medications taken by the remaining children. All of the children were taking at least one anti-epileptic medication, 7 of the children were taking two AED's while 2 were taking three AED's. For the purposes of further analyses children were categorised as being on either monotherapy (11) or polytherapy (9). It was reported that 6 of the children had a statement of special educational needs, none of the children had any additional medical disorders predisposing to sleep problems.

Male		14 (70%)
Age		mean = 10.3, SD = 2.68
Seizure frequency:	> One/fortnight	8 (35%)
	< One/fortnight	5 (25%)
	Unspecified	7 (35%)
Primary seizure type:	Absences	5 (25%)
	Tonic Clonic	5 (25%)
	Complex Partial	8 (40%)
	Unspecified/Unknown	2 (10%)
Epilepsy Type:	Generalised	7 (35%)
	Focal	8 (40%)
	JME	2 (10%)
	Landau-Kleffner Syndrome	1 (5%)
	Ring Chromosone 20 Syndrome	1 (5%)
	Panayiotopoulos Syndrome	1 (5%)
Primary medication:	Lamotrigine	6 (30%)
	Sodium Valproate	6 (30%)
	Carbamazepine	3 (15%)
	Levetiracetam	1 (5%)
	Topiramate	1 (5%)
	Ethosuximide	1 (5%)
	Oxcarbazepine	1 (5%)
	Steripentol	1 (5%)
Polytherapy		9 (45%)
Special Educational Needs (SEN)		6 (30%)

Table 5.1.7: Descriptive information of the actigraphy participants (n = 20)

5.6.2 Correlations between parent-report and actigraphy

In order to assess the validity of parent-report measures of sleep in children, correlations were examined between parent-report measures and actigraphy measures using Pearson's coefficients. Parent report variables entered into the correlation matrix consisted of questionnaire defined sleep time per night and sleep latency, as well as the six questionnaire defined sleep factors: parent/child interactions, parasomnias, sleep fragmentation, daytime drowsiness, bedtime difficulties, and questionnaire total score. As the six sleep factors represent more general aspects of a child's sleep they cannot be directly compared to any of the more specific actigraphy variables, however they are included as broader measures of various sleep problems as they are expected to show some correlation with actigraphy parameters. Actigraphy variables entered into the correlation matrix are as listed in table 5.1.6. Significant positive correlations were observed between questionnaire mean sleep time per night and the three actigraphy variables; assumed sleep ($r = 0.815$, $p < 0.001$), actual sleep ($r = 0.758$, $p < 0.001$), and time in bed ($r = 0.802$, $p < 0.001$)

indicating an agreement between subjective and objective measures of mean sleep time. In addition, a significant positive correlation was observed between questionnaire mean sleep time and actigraphy number of minutes immobile ($r = 0.807$, $p < 0.001$). A significant positive correlation was also observed between questionnaire sleep latency and actigraphy sleep latency ($r = 0.465$, $p < 0.05$), indicating an agreement between objective and subjective sleep latency measures. A negative correlation was observed between questionnaire sleep latency and actigraphy sleep efficiency ($r = -0.449$, $p < 0.05$), indicating that sleep efficiency improves as parental reports of sleep latency decrease. There were no other significant correlations between any actigraphy variables and questionnaire mean sleep time or sleep latency.

When correlations between questionnaire defined sleep factors and actigraphy sleep parameters were examined, a significant negative correlation was observed between parasomnias and actigraphy actual wake time ($r = -0.474$, $p < 0.005$), indicating parasomnias are associated with an decrease in the amount of time spent awake per night. Surprisingly, there is no corresponding significant correlation between parasomnias and actual sleep time ($r = -0.222$, $p = 0.348$). A significant positive correlation was observed between daytime drowsiness and actigraphy sleep latency ($r = 0.554$, $p < 0.05$), a result that indicates daytime somnolence may be attributable to longer sleep latencies, however no correlations were observed between daytime drowsiness and actigraphy measures of actual sleep time ($r = -0.118$, $p = 0.619$). Significant positive correlations were observed between bedtime difficulties and both actigraphy sleep latency ($r = 0.629$, $p < 0.005$) and actigraphy mean activity score ($r = 0.511$, $p < 0.05$), these results not surprisingly indicate that difficulties at bedtime are associated with both longer sleep latencies, and increased activity and arousals throughout the night. A significant negative correlation was also observed between bedtime difficulties and actigraphy sleep efficiency ($r = -0.504$, $p < 0.05$), pointing to an association between difficulties at bedtime and a decrease in sleep efficiency. There was a significant positive correlation between the total score on the questionnaire and actigraphy sleep latency ($r = 0.586$, $p < 0.05$), indicating that sleep problems in general are associated with longer sleep latencies. There were no other significant correlations between questionnaire defined sleep factors and actigraphy

variables. Table 5.1.8 shows all correlations between questionnaire defined variables (horizontal) and actigraphy defined variables (vertical).

	Sleep Time per Night	Sleep Latency	Parent/Child Interactions	Parasomnias	Sleep Fragmentation	Daytime Drowsiness	Bedtime Difficulties	Total Score
Time in Bed	**0.80	0.41	0.17	-0.27	0.26	0.14	0.47	0.25
Assumed Sleep	**0.82	0.22	0.17	-0.41	0.15	-0.07	0.21	0.01
Actual Sleep Time	**0.76	0.11	0.26	-0.22	0.02	-0.12	0.02	-0.01
Actual Awake Time	0.46	0.30	0.09	*-0.47	0.33	0.10	0.32	0.03
Sleep Efficiency	-0.22	*-0.45	-0.02	0.12	-0.41	-0.32	*-0.50	-0.32
Sleep Latency	0.35	*0.47	0.02	0.21	0.39	*0.55	*0.63	*0.59
Number of Sleep Bouts	0.38	-0.18	-0.35	-0.29	-0.27	-0.08	-0.23	-0.39
Number of Wake Bouts	0.37	-0.15	-0.36	-0.28	-0.29	-0.08	-0.22	-0.39
Mean Sleep Bout Length	0.02	0.22	0.45	0.23	0.36	0.02	0.21	0.46
Mean Wake bout Length	0.38	0.36	0.22	-0.41	0.44	0.12	0.36	0.17
Number of mins Immobile	**0.81	0.11	0.12	-0.32	-0.11	-0.24	0.06	-0.14
Fragmentation Index	-0.08	0.07	-0.06	0.19	0.19	0.13	0.12	0.15
Mean Activity Score	0.46	0.39	0.33	-0.42	0.42	0.24	*0.51	0.26

*Table 5.1.8: Matrix showing correlations between questionnaire defined variables (horizontal) and actigraphy variables (vertical). ** $p < 0.001$; * $p < 0.05$.*

5.6.3 Comparisons of specific questionnaire and actigraphy measures

The correlational analyses demonstrate associations between various objective and subjective sleep measures, however they are unable to provide any information as to whether scores generated by the questionnaire and by actigraphy are absolutely comparable. Paired *t*-tests were used to examine differences between actigraphy variables and questionnaire defined variables. As three *t*-tests were performed, a Bonferroni correction was applied and provided a significance level at $p = 0.003$. Only two of the questionnaire variables (mean sleep time per night and sleep latency) were directly comparable with actigraphy variables, the other questionnaire measures

representing sums of items scored on non-interval scales. A paired *t*-test performed to compare questionnaire sleep time per night and actigraphy actual sleep time found questionnaire estimates of sleep time were significantly greater than actigraphy actual sleep time $t = -48.18$, $df = 19$, $p < 0.001$. A further paired *t*-test compared questionnaire sleep time with actigraphy assumed sleep time, assumed sleep potentially provides a better comparison with parental reports of sleep time as actual sleep time takes into account all night awakenings which parents would be presumed to miss. The *t*-test revealed that questionnaire reports of sleep time were significantly higher than actigraphy assumed sleep times $t = -43.59$, $df = 19$, $p < 0.001$. A final *t*-test compared questionnaire defined sleep latencies with actigraphy sleep latencies and found no significant differences between the scores $t = 1.947$, $df = 19$, $p = 0.066$. Mean values and standard deviations are shown in table 5.1.9.

Variables Pairs	Mean	Standard Deviation	*t*
Questionnaire Sleep Time (hrs) Actigraphy Actual Sleep Time (hrs)	10.92 8.24	0.91 0.58	*-48.18
Questionnaire Sleep Time (hrs) Actigraphy Assumed Sleep Time (hrs)	10.92 9.48	0.91 0.45	*-43.59
Actigraphy Sleep Latency (mins) Questionnaire Sleep Latency (mins)	42.91 31.65	8.22 19.81	1.947

*Table 5.1.9: Means and standard deviations of sleep times and sleep latencies as defined by both parental report questionnaire and actigraphy. *p < 0.001*

5.6.4 Case analysis of Actogram

In addition to the generation of various sleep parameters, the actiwatch also produces a pictorial representation of patterns of sleep and wakefulness over the seven day test period. This actogram can provide useful information regarding patterns of sleep but is unsuitable for statistical analysis. However, in our sample of children with epilepsy, analysis of an individual's actogram may provide a means for the detection of night time seizures. Parents were asked to note the time and duration of any seizure activity during the seven day test period, although parents may not provide a totally accurate picture of a child's seizures it is possible to compare seizure patterns with an individuals actogram. Fig. 5.2.0 shows the actogram of a 15 year old female with nocturnal complex partial seizures, arrows correspond to nocturnal seizures reported by parents and are clearly visible as brief periods of activity in the

actogram. Although statistical methods cannot be applied in this instance, it is interesting to speculate that actograms may have clinical utility.

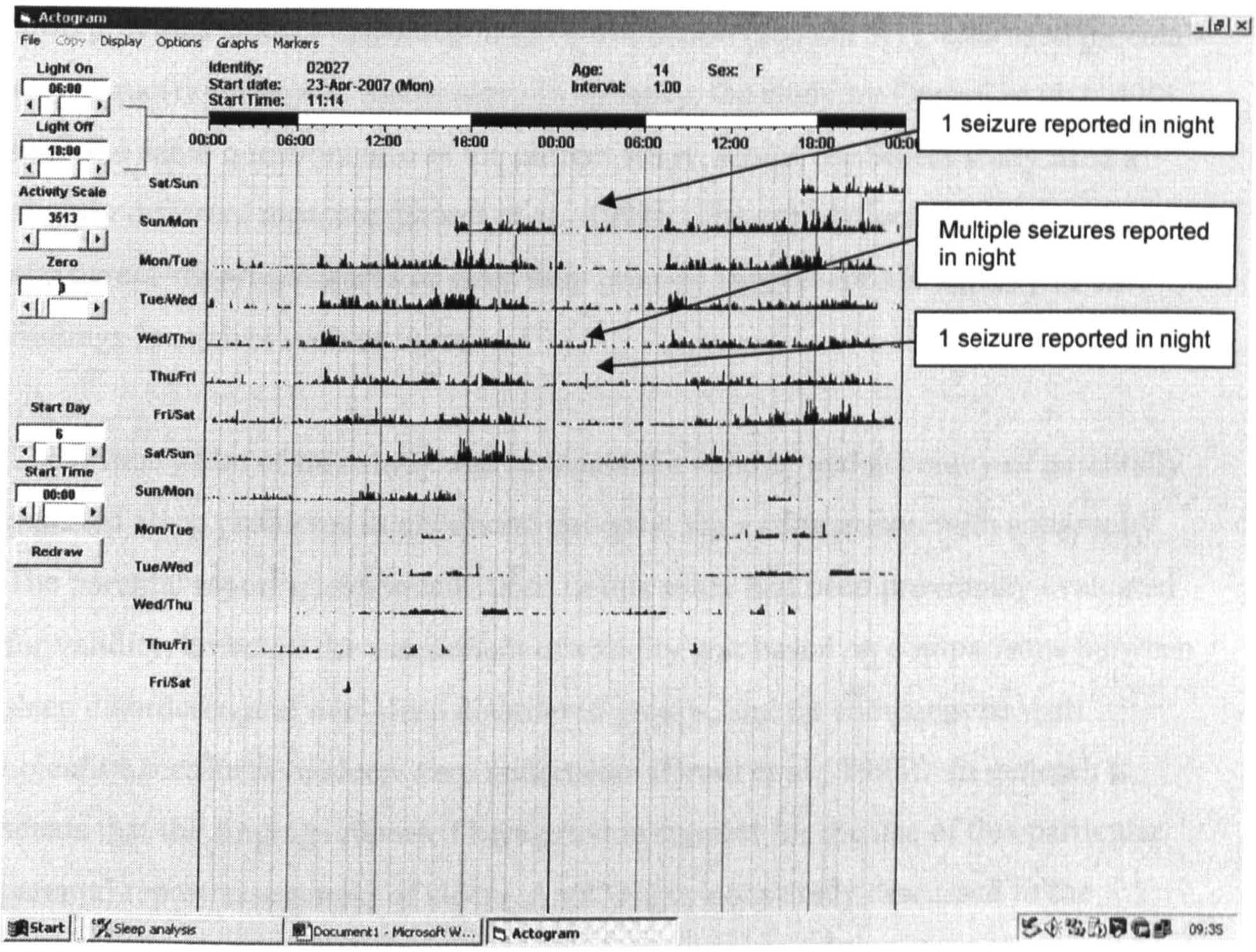


Fig. 5.2.0: Actogram of a 15 year old female with nocturnal complex partial seizures, arrows represent seizures as reported by parents.

5.7 Discussion

5.7.1 Correspondence between parent-report and actigraphy

The results from this study demonstrate a reasonable correspondence between subjective parental report measures of sleep, and objectively derived actigraphic measures of sleep. Significant correlations were observed between actigraphic variables and both questionnaire derived sleep factors, and specific variables such as sleep time and sleep latency. When those variables that could be directly compared were evaluated against one another (i.e. mean sleep time and sleep latency), significant differences were observed between parental and actigraphic estimates of sleep time, with parents consistently overestimating sleep time. However, there were no significant differences between parental and actigraphic estimates of sleep latency. In addition to the evaluation of correlations, this study also suggests that

actigraphy provides a useful means of assessing general patterns of sleep and wake through the analysis of actograms. In general, it seems that the finding reported here provide support for the use of this particular parental report assessment of sleep. Two previous studies discussed in the introduction (section 5.1), also used parental-report questionnaires to assess sleep in epilepsy, the study by Cortesi et al. (1999) used the same questionnaire as the current study, whilst the Stores study used a slightly different measure (Stores et al., 1998). The correlations between actigraphy and parent-report measures of sleep help provide support for the validity of the findings in studies such as these.

The primary aim of this study was to assess the validity and accuracy of parentally reported sleep problems in childhood epilepsy, via a comparison with actigraphy. The parental report questionnaire used in this study had been previously evaluated for validity, however the assessment of validity was based on comparisons between sleep disordered and non-sleep disordered groups, and no comparisons with objective measures of sleep were undertaken (Bruni et al., 1996). In general, it seems that the findings reported here provide support for the use of this particular parental report assessment of sleep. Another previous study discussed in the introduction (section 5.1), also used a parental-report questionnaire to assess sleep in epilepsy (Stores et al., 1998). The correlations between actigraphy and parent-report measures of sleep help provide support for the validity of the findings in studies such as this and the Cortesi et al. (1999) study. The assessment of the validity of parental report questionnaires designed to evaluate various symptoms and behaviour has generated a great deal of research. Many studies have found that parental report measures provide a reasonable approach to collecting data, and have shown satisfactory correlations with objective measures in varying areas of research (e.g. Vernacchio et al., 2007; Varni et al., 2007; Feldman et al., 2005; Wogelius et al., 2005). However, other researchers have found that parents can be inaccurate reporters and suggest additional measures should be used alongside parental report measures (Huybrechts et al., 2006; Sureshkumar et al., 2006). A recent study investigating actigraphic and parent reports of sleep in children with ADHD found a poor correspondence between actigraphy and parent-report, it was suggested that either parents are poor reporters of their child's sleep pattern and/or sleep problems

coming to the attention of parents are not detected by actigraphy (Wiggs et al., 2005).

The results from the current study indicate a reasonable level of correspondence between parent report and actigraphic measures of sleep. Correlations between the directly comparable variables sleep time and sleep latency show that parent reports are highly associated with objective measures. In addition, there were no significant differences between parent reports and actigraphic reports of sleep latency, indicating that parents are providing accurate data for this particular variable. However, when a direct comparison was made between parent reports and actigraphic measures of mean sleep time per night, results demonstrated parents were significantly overestimating their child's sleep time. Parents overestimated their child's actual sleep time by over two hours a night, and the assumed sleep time by over one hour a night. Although we cannot expect parents to provide an accurate figure for actual sleep time (as this takes into account brief night time awakenings and arousals that parents would not be expected to account for), it seems surprising that reports of assumed sleep are so significantly overestimated. Even if we assume that parents are recording times for 'going to bed' and 'getting out of bed', rather than falling 'falling asleep' and 'waking up', we would not expect the times to differ by much more than the mean sleep latency. Even if we take into account the sleep latency, parents are still consistently overestimating the sleep of their children. Two possibilities arise, one that parents are inaccurate in their reporting of these times, perhaps due to poor recall or lack of communication between parent and child. The second possibility is that parents are unaware of a period of wake before arising in the morning, children may wake before parents realise but do not necessarily leave the bedroom or make parents aware of their wake state. Of course the final possibility to consider is that the discrepancy in sleep times is due to inaccuracies in the actigraphic measurement of sleep time, rather than parental inaccuracies. However, this seems unlikely given the high correlations between actigraphy and PSG (the 'gold standard'), correlations of > 0.90 have been shown for healthy subjects, and > 0.75 for sleep disordered subjects (Sadeh et al., 1995). Therefore, it seems a more plausible argument that the discrepancy is due to parental inaccuracies, as discussed above.

In addition to correlations and comparisons involving directly comparable variables, analyses were also conducted to assess whether questionnaire defined sleep factors were concordant with actigraphy measures of sleep. The questionnaire grouped various Likert scaled items into a number of sleep factors, corresponding to different areas of sleep disturbance. These sleep factors, rather than providing data on a specific parameter like the actigraphy variables, provide a more general measure of sleep quality in different areas. Correlational analyses were undertaken to assess if any of the questionnaire defined sleep factors could be associated with the more specific variables generated by the actigraphy. Bedtime difficulties emerged as the factor with the greatest concordance with actigraphy variables, a positive correlation with both sleep latency and mean activity score indicates that children who take longer to fall asleep or are more active at night are those most likely to be reported as having bedtime difficulties by their parents. In addition, children who have a lower sleep efficiency are also more likely to be reported as having difficulties at bedtime. These findings provide support that the grouping of items from the sleep questionnaire into factors is a valid way of providing meaningful data on general sleep quality. Daytime drowsiness and total score on the sleep questionnaire were also both positively correlated with sleep latency, indicating daytime somnolence and global sleep difficulties may be linked to longer sleep latencies.

The only unexpected association is the small but significant negative correlation between parasomnias and actual wake time, indicating that those children reported as suffering from parasomnias spend less time awake. This result seems at odds with what might be predicted, and appears to associate sleep problems as defined by parasomnias, with less time spent awake. Somewhat surprisingly there is no corresponding correlation associating parasomnias with actual sleep time, indicating a potential anomaly in the pattern of results, perhaps requiring further investigation. However, it is interesting to note a similar result in chapter two, where a positive correlation was found between reported parasomnias and overnight improvement on a procedural task. As discussed in chapter two, this result could be explained by the fact that parasomnias do not necessarily impair sleep quantity or quality, and may just represent altered sleep architecture or abnormal sleep behaviours. Clearly the associations between parasomnias and both sleep quality and overnight consolidation require further investigation. Despite the associations that were demonstrated

between these sleep factors and actigraphy variables, the sleep factors parent/child interactions and sleep fragmentation showed no significant correlations with any actigraphy variables. Parent/child interactions is a factor encompassing behaviours such as sleeping in the parental bed, sharing the parental bedroom, requiring parental presence to fall asleep etc. As such, this factor would not be expected to correlated highly with actigraphy variables which assess specific parameters of sleep and do not attempt to record sleep habits or behaviours. This provides evidence that objective measures of sleep may provide benefits over subjective measures like parent report in terms of accuracy and specificity, but in doing so may fail to detect sleep disturbances that are salient to parent and child and can only be identified by communication with the child and family. However the factor sleep fragmentation, which encompasses night time awakenings, waking to eat etc, might be expected to show a higher level of correlation with those actigraphy variables relating to night time activity e.g. fragmentation index, mean activity score etc. The fact that no correlations exist, indicates that parents are inaccurate reporters of fragmented sleep in their children. Of course the nature of fragmented sleep means that it may be difficult for parents to accurately report episodes of arousal or activity during the night. Night time awakenings could potentially go unnoticed by parents, particularly in those children who sleep alone or in children whose arousals are brief and relatively benign.

In addition, our sample is comprised entirely of children with epilepsy, many suffering from nocturnal seizures, and whilst many nocturnal seizures would be recorded as periods of activity by the actiwatch, the reporting of seizures by parents would not be included under the specific items coding for the sleep fragmentation factor. In other words, seizure activity during the night could be accounting for the lack of concordance between questionnaire defined sleep fragmentation and actigraphic measures of fragmentation. Clearly, normalised control data from healthy children is required to draw any further conclusions.

In general, the parent report questionnaire appears to correspond well with actigraphic measures of sleep in children with epilepsy. The questionnaire is well validated against actigraphy but some discrepancies indicate the possibility that

either some behaviours reported by parents are not well detected by actigraphy, or there are some inaccuracies in parental report.

5.7.2 Utility of actigraphy in childhood epilepsy

The secondary aim of this study was to assess the utility of actigraphy in childhood epilepsy, although actigraphy has been confirmed as a useful tool for the assessment of sleep in many populations, it has not to date been formally evaluated in epilepsy. Actigraphy has been validated against polysomnography and has yielded agreement rates of > 90% in normal adult subjects, indicating the use of actigraphy as a useful means of assessing sleep in healthy adults. Research comparing actigraphy and PSG in sleep-disordered subjects has typically yielded lower agreement rates (78-85%) (Sadeh et al., 1995), however actigraphy is still recognised by the American Academy of Sleep Medicine as a useful tool in the assessment of sleep disorders, and has been used to study a range of sleep disturbances including insomnia and circadian rhythm disorder (American Sleep Disorders Association, 1995). Validation with PSG is less widespread in research with children and infants, comparisons with behaviourally determined sleep state classifications are generally more common than direct comparisons with PSG (particularly in infants) (So et al., 2005). However, the use actigraphy is now widespread in children, and is accepted as a valuable and unobtrusive tool in assessing sleep.

To date, there has been no research exploring the use of actigraphy in children or adults with epilepsy, the current study provides some evidence that actigraphy has an important role in epilepsy, and should be considered for wider use. Parents of children with epilepsy frequently voice concerns about sleep disruption caused by seizures or by other epilepsy related factors. The consequences of disturbed sleep should not be underestimated as in addition to direct effects on learning and cognitive function (such as those discussed in chapter two), daytime sleepiness and fatigue can have a detrimental effect on schooling and education. We can also speculate that disturbed sleep in children with epilepsy may impair quality of life and mood, these associations have already been confirmed in adults (see chapter three) and may also exist in children. Given the consequences of disturbed sleep, it seems important to find a reliable and valid way of assessing patterns of sleep and wakefulness in children. Our results show that subjective measures such as parental

report questionnaires are reasonably accurate at providing information on sleep patterns, the correlations with actigraphic measures provide evidence that parent-report is an acceptable method for collecting data. In addition, the use of actigraphy was well tolerated by children and parents in this study, the unobtrusive nature of the device lends itself well to use with children. When used over a seven day period, actigraphy was able to provide averaged scores for various parameters, allowing an assessment of a child's typical sleep patterns. This may be particularly useful in epilepsy where periodic nocturnal seizures can lead to intense sleep disruption on a single night, but may not represent typical sleep patterns.

The majority of people with epilepsy take some form of anti-epileptic medication, and all the children in the current study were taking at least one AED. The choice of AED available to prescribing clinicians is vast, with the constant development of new drugs providing an ever increasing choice. With many AED's now known to have an effect on sleep (Foldvary 2002; Placidi et al., 2000[b]), clinicians should perhaps give further consideration to the consequences on sleep of various medications. Actigraphy may play an important role in assessing the tolerance of various AED's with regard to sleep.

Although actigraphy is unable to formally detect seizure activity via electrophysiological means, it may act as a means of assessing the impact of nocturnal seizures on sleep quality. Analysis of the actogram shown in fig. 5.2.0 allows us to evaluate the impact of seizure activity on night time sleep patterns. If parents are able to record the time and duration of nocturnal seizures (as in this case), we are provided with a means of assessing the effect on sleep. Actiwatches equipped with event markers (a button pressed on an actiwatch to time lock an event) may be especially suited to this role, with parents instructed to event mark any seizure activity.

Although the current study provides us with some evidence to support the use of actigraphy in childhood epilepsy, we are not able to draw any comparisons with a control sample of healthy children. Future research generating normative data from control children would allow the comparison of actigraphy between different clinical groups, and would provide a means to more formally assessing the level of sleep disturbance in various clinical groups.

It should also be pointed out that actigraphy has limitations as a measure of sleep, whilst providing an unobtrusive and objective means of collecting data, it cannot offer the detailed information on sleep and seizure activity that is provided by full PSG. Actigraphy is unable to provide electrophysiological data and as such is unable to accurately stage sleep or detect seizures. However, actigraphy may provide a compromise between the intrusive but detailed PSG, and more subjective measures such as parent or self report. We suggest that actigraphy would be a suitable tool for the assessment of sleep in children with epilepsy, a group in which the consequences of sleep disturbance are so important, and should perhaps be considered for routine use in clinical practice.

5.8 Conclusions and Implications

Results from this study confirm that sleep problems are highly prevalent in childhood epilepsy. When compared with controls, children with epilepsy were consistently reported as having more problems with initiating and maintaining sleep, and complained of more daytime problems associated with sleepiness. Although doubts have been expressed by some investigators as to the validity of parent-report measures, we found adequate correspondence with an objective measure of sleep (actigraphy). In addition we would recommend the use of actigraphy for children with epilepsy, this objective measure of sleep is well tolerated and provides useful information on sleep parameters. When used alongside detailed seizure diaries or with time logged event markers, actigraphy may also have utility as a tool for recording information relating to nocturnal seizures.

Although this study provides us with important information regarding sleep in children with epilepsy, there are limitations that must be acknowledged before any conclusions can be drawn. As the sample of children with epilepsy was relatively unselected, and exclusion criteria were minimal, many of the children had severe and problematic epilepsy types or syndromes, with co-morbid conditions and a high prevalence of learning difficulties. As such, it is difficult to fully dissociate the effects of epilepsy, medication, learning difficulties, and co-morbid conditions; on the child's sleep. In hindsight, more stringent criteria for inclusion in the study may have resulted in more meaningful data transferable to a larger population. It is also

clear that further research is required to increase our knowledge of the mechanisms and implications of sleep disturbance. In particular, further investigation needs to explore the consequences of disturbed sleep in epilepsy, and to assess whether chronically disrupted sleep is a factor predicting a portion of the cognitive impairment and learning difficulties so often associated with epilepsy. Although potential candidates for the causes of sleep problems in epilepsy have been discussed, a more formal assessment of the input of various factors needs to be undertaken in order to develop a better understanding of the mechanisms involved. Actigraphy may prove to be a useful tool for research into sleep in epilepsy, allowing an objective perspective on sleep, however comparisons with actigraphy in healthy children are vital in order to fully validate its use in epilepsy.

Chapter 6

6 General conclusions and directions for future work

Following the literature review presented in chapter one, certain issues were identified for analysis in the subsequent experimental chapters. Although previous research had indicated an important role for sleep in processes of learning and memory, the research was mainly restricted to the procedural domain and only assessed sleep and learning in adults. Gaps in the literature suggested a need for research into sleep and declarative memory (the domain receiving the least research attention to date), an additional lack of research involving children was noted. These two issues provided a starting point for experimental work and were tackled in chapter two. The literature review also outlined the evidence associating the primary sleep disorder OSA with cognitive impairment, this evidence combined with the established links between sleep and learning, lead to the conception of a clinical study investigating sleep dependent learning in OSA. In addition to OSA, epilepsy was also identified as a disorder with complex associations with sleep. Although there are known interactions between epilepsy and sleep, the area has received little research attention, and provides an interesting framework for the assessment of quality of sleep and its impact on learning in non-healthy populations.
Other issues identified in the initial review included a discussion of the relationship between sleep and mood, and prompted a study assessing the way people perceive their own sleep, and the relationships between self-reported sleep and various measures of memory, cognitive function, and affect.

The first experimental study (chapter two) demonstrated the importance of sleep for the enhancement of procedural and declarative memory in adults and children.
These finding supported the previous research indicating a role for sleep in processes of learning and memory (e.g. Walker et al., 2002; Stickgold et al., 2000; Gais & Born, 2004). The importance of sleep for the improvement of procedural performance is well established, and the findings described in this study provide further evidence that a period of sleep leads to greater improvements on a procedural task than does a similar period awake. The evidence for sleep dependent mechanisms for declarative memory enhancement are less conclusive, the findings suggest that recognition is preferentially preserved over sleep when compared to

wake, but recall is not differentially affected by sleep or wake. These findings concur with previous research concluding that the relationship between declarative memory and sleep is complex, and may be sensitive to subtle changes in the type of declarative task performed. Clearly, further research into the relationship between sleep and declarative memory is required, firstly to provide a clearer picture of precisely which aspects of declarative memory are sensitive to sleep, and secondly to assess the processes and mechanisms by which this occurs.

Another important finding is that sleep dependent consolidation occurs in children as it does in adults. This provides support for theories of an early developing system for processes of sleep dependent learning. As this study did not provide information on correlations between sleep stages and learning, this provides an obvious direction for future research and would provide further information into the processes of sleep dependent learning in childhood. Studies investigating the relationships between the various sleep stages and overnight learning have until now been inconclusive, a further assessment of sleep architecture and learning in both children and adults would provide a clearer understanding of the mechanisms involved.

After demonstrating the importance of sleep for the enhancement of procedural and declarative memory, the second study assessed sleep dependent learning in children with sleep disordered breathing suggestive of OSA. Anecdotal evidence suggested that sleep disordered breathing is associated with some impairment to processes of sleep dependent learning, and appears to be a result of sleep fragmentation rather than a result of hypoxia (none of the children had significant gas exchange problems). Although previous research had already suggested that children with sleep disordered breathing (in particular obstructive sleep apnoea) are vulnerable to problems with learning and cognitive function (e.g. Blunden et al., 2001), this case series is the first to investigate the specific relationship between sleep dependent learning and sleep disordered breathing. However, it is clear that although the evidence is suggestive of a relationship between sleep disordered breathing and impaired overnight learning, reliable claims cannot be made using data from only four participants. A clear limitation of this study is the sample size, the assessment of a greater number of participants would justify the use of inferential statistics, and would provide vital statistical support to the speculative claims made in this study.

Despite this limitation, the findings provide interesting preliminary evidence regarding sleep disorders and learning. The implication that chronic sleep disturbances may be damaging not only in terms of sleep quality, but also in terms of learning, should certainly justify further research and may also highlight potential clinical and educational consequences.

The finding that sleep is important for processes of learning and memory, and that sleep disturbances may be associated with impairments to these processes, led to speculation that sleep may be linked to chronic memory impairment. A large-scale questionnaire study revealed that sleep disturbances in healthy adults are predictive of impairments to memory and cognitive function, and are also associated with poor mood. This finding provides strong evidence, and the first of its kind, that chronic sleep disturbances lead to long-term memory difficulties and cognitive impairments. Even though the sleep disturbances reported are relatively subtle and do not constitute clinically relevant problems, we still observe a significant relationship between sleep and memory. Although we speculate that impairments to memory and cognition are a function of deficits to sleep dependent learning, we do not have empirical evidence to support this claim. Future work assessing the specific impact of sleep dependent learning on general cognitive function and memory is vital in order to provide an accurate evaluation of this relationship. The finding that sleep disturbances are associated with poor mood fits into line with a large body of evidence associating poor sleep with depression and anxiety (e.g. Kupfer, 1995; Armitage, 2007). It is interesting to note that even in a sample of healthy adults, disturbed sleep is predictive of poor mood, indicating the functions of sleep are not just restricted to learning and memory processes.

This study also assessed the sleep of people with epilepsy, although this is not classified as a clinical sleep disorder, epilepsy has complex interactions with sleep that are often reported by patients, but despite this has received little research attention. The results demonstrated that people with epilepsy are particularly vulnerable to sleep disturbances, and that sleep disturbances in epilepsy are strongly predictive of memory and cognitive difficulties, poor mood, and impaired quality of life. Although the study only employed subjective self-report measures and may be criticized for its lack of objective assessment, (especially given the known

discrepancies between self-report and standard measures of memory difficulties in epilepsy), the perceived impact of sleep on people with epilepsy is in itself an important finding. An interesting continuation of this study could aim to collect objective information on both sleep and memory, and assess the strength of the predictive relationship using these measures. This would not only provide further information on the relationships between sleep, epilepsy, and memory/cognitive function, but would also offer some evaluation of the validity of the self-report measures used.

The final study attempted to implement some of the suggestions generated by the previous study, and used subjective and objective measures to assess sleep in children with epilepsy. As suggested above, the impact of disturbed sleep and its potential consequences in terms of learning are considerable in school age children, and the final study attempted to make an assessment of the complex relationship between sleep and epilepsy in children. The results confirmed that children with epilepsy report significantly more sleep disturbances, in all areas, than controls. An assessment of sleep with actigraphy provided evidence that agreement with parental-report measures (often claimed to be unreliable) was reasonable. An additional finding was that actigraphy may be useful as a unobtrusive means of recording information on nocturnal seizures. Although this finding was not statistically validated, it certainly provides enough anecdotal evidence to justify further research. Actigraphy is a relatively new tool in the area of sleep research, and its use in the assessment of sleep in epilepsy is unprecedented. Validation with PSG and EEG would provide the necessary information to be able to assess the validity of actigraphy both in terms of sleep variables and with reference to the accurate documentation of seizures.

The findings from this thesis outline the importance of sleep for processes of learning and memory and indicate that clinical sleep disorders may be damaging in terms of learning. Additionally, subtle but chronic non-clinical sleep disturbances can predict memory/cognitive difficulties and poor mood in healthy adults. People with epilepsy are particularly vulnerable to sleep problems and these problems may in turn be associated with a range of memory, mood, and quality of life difficulties. However, objective means of collecting information on sleep may help disentangle

the complex relationship between sleep and epilepsy, and may also be able to identify the presence of nocturnal seizures. Although historically there has been much uncertainty surrounding the functions of sleep, the findings from this thesis provide evidence that sleep is inextricably linked to processes of learning. Future research will undoubtedly provide answers to some of the questions generated by the results reported here, and will hopefully ultimately lead to the conception of an accepted and accurate model for the mechanisms and processes of sleep dependent learning.

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8.0 Appendices

8.1 Stories Subtest of Children's Memory Scale

Story A (5–8 years)

A mother cat had five brown and white kittens. One morning she took the kittens for a walk. The kittens looked for someone to play with. They found some butterflies in a field. A dog came and barked at them. The mother cat did not like the dog. The cat hissed at the dog and the dog ran away.

Recognition Questions

1. Did the cat have six kittens?
2. Were the kittens brown and white?
3. Did the mother cat take the kittens for a walk at night?
4. Did they go for a walk to find something to eat?
5. Were the kittens looking for someone to play with?
6. Did they find some butterflies?
7. Were the butterflies near a river?
8. Were the butterflies in a field?
9. Did the kittens see a dog?
10. Did the dog bark at the kittens?
11. Did the dog play with the mother cat?
12. Did the mother cat like the dog?
13. Did the mother cat hiss at the dog?
14. Did the dog run away?
15. Was the dog afraid of the mother cat?

Story B (5-8 years)

On a sunny day in June, four boys built a clubhouse near a stream in the woods. The boys cut down dead trees and used scrap wood. They built a table and found some old chairs to sit on. When the boys were finished working, their parents took them for ice cream cones.

Recognition Questions

1. Was the story about five boys?
2. Did the boys build a clubhouse?
3. Was the clubhouse near a lake?
4. Was the clubhouse in the woods?
5. Did the story take place in July?
6. Was it raining when they built the clubhouse?
7. Did the boys cut down dead trees?
8. Did the boy use scrap wood to build the clubhouse?
9. Did the story say how long it took to build the clubhouse?
10. Did any girls help build the clubhouse?
11. Did the boys also build a table?
12. Did the boys find some new chairs to put in the clubhouse?
13. Did the parents help the boys build the clubhouse?
14. Did the parents take the boys for ice cream sundaes?
15. Did the the boys finish working before they went for ice cream?

Story C (9-12 years)

Lisa and Melissa were walking past the grocery store on their way to school, when two men ran out with a money bag. The men jumped into a brown car and drove away very fast. When the police came, Lisa told them the colour of the car. Melissa told the police that one man was short and the other man was tall. Because the girls were in the right place at the right time, the men were caught one month later and the money was returned.

Recognition Questions

1. Was one of the girls named Lisa?
2. Was the other girl named Mary?
3. Were the girls walking past a store?
4. Were the girls on their way to the movies?
5. Did three men run out of the store?
6. Were the men in big hurry?
7. Were the men carrying a suitcase?
8. Did the men jump into a brown car?
9. Did the car drive away fast?
10. Did someone call the police?
11. Did Lisa tell the police the colour of the car?
12. Did Melissa tell the police what the men were wearing?
13. Were both men short?
14. Were the robbers caught one year later?
15. Was the money returned to the store?

Story D (9-12 years)

Jessica had taken the lifeguard class at school. One Saturday morning in March, she was walking past Bear Lake and saw two men fishing in a motor boat. The man steering the boat did not see a warning marker and hit a rock that was underwater. The boat began to sink. Jessica jumped in and helped the men swim to shore. After hearing the story, the park ranger offered Jessica a summer job as a life guard.

Recognition Questions

1. Did the story take place in March?
2. Was it a Sunday afternoon?
3. Was the girl's name Jessica?
4. Had Jessica just learned to swim?
5. Did Jessica tae the lifeguard class at the YMCA?
6. Was Jessica walking near a lake?
7. Did Jessica see two men fishing?
8. Were the men fishing at Bear Lake?
9. Were the men fishing on the rocks?
10. Did the boat hit a tree stump?
11. Was the boat damaged?
12. Did Jessica jump in the water?
13. Was Jessica a weak swimmer?
14. Did the park ranger get mad at Jessica for jumping in the water?
15. Did Jessica get a summer job as a park ranger?

Story E (13-16 years)

Over two hundred years ago, the first hot air balloon was built in England. The balloon was made of paper covered with cloth to make it stronger. A large basket made of straw and weighing 20 pounds was attached to it with cables. A long rope anchored the balloon to the ground. On the first flight, the pilot was in the air for 15 minutes. Later he took a friend, and they stayed up for one hour. They traveled 100 miles before landing in a treetop on the side of a hill.

Recognition Questions

1. Is this story about the first flying hot air balloon?
2. Did the story take place in England?
3. Did this story take place over 300 years ago?
4. Was the balloon made out of rubber?
5. Was the balloon covered with cloth to make it stronger?
6. Was the basket made out of wood?
7. Did the basket weigh 15 pounds?
8. Was the basket attached with cables?
9. Was the balloon anchored to the ground for the first flight?

10. On the first trip, did the pilot stay up 10 minutes?
11. Did the pilot later take his friend in the balloon?
12. Did the pilot stay up 2 hours with his friend?
13. Did they travel 100 miles?
14. Did they land in a treetop on the side of a hill?
15. Were flying balloons common at this time?

Story F (13-16 years)

In the 1700's large herds of buffalo roamed the plains of America. Many Native American tribes, like the Sioux and the Blackfoot, followed the herds to survive. They hunted on horseback, killing the buffalo with bows and arrows. They used the meat for food, the bones for tools, and the skins for clothing. During the 1800's, the buffalo were killed in large numbers for sport and money by settlers from the East. Soon the buffalo had vanished, and the Native Americans lost their largest food source.

Recognition Questions

1. Did this story happen in the 1600's?
2. Did the story take place in Canada?
3. Did the Sioux follow the buffalo?
4. Were the Native American tribes following the herds to survive?
5. Did the Blackfoot also follow the herds of buffalo?
6. Did the Native Americans hunt the buffalo with guns?
7. Did the Native Americans use the buffalo bones for tools?
8. Were clothes made from the skins?
9. Does the story say the buffalo were killed in large numbers in the 1700's?
10. Did the settlers kill large numbers of buffalo?
11. Were the settlers from the West?
12. Did the settlers kill the buffalo only for food?
13. Did the settlers from the East kill the buffalo mainly for sport and money?
14. Did the settlers sell the buffalo robes to the Native Americans?
15. Were the buffalo the Native Americans largest source of food?

8.2 PAEDIATRIC SLEEP QUESTIONNAIRE (PSQ)

(Gianotti et al., 1995)

1. Relationship to child of person completing questionnaire (mother, father etc.)

_____

2. Age of child (years) _____

3. Date of birth of child____/____/____

4. Sex of child male ☐ female ☐

5. Height of child _____

6. Weight of child _____

7. Does your child have epilepsy?

yes ☐ no ☐

8. What type of epilepsy/epilepsy syndrome does the child have?

_____

9. What type of seizures does the child have, and how often?

_____

10. What medications is the child taking, and what dosage (if known)?

_____

_____

11. Does the child have any significant allergies or infections of ear, nose or throat?

yes ☐ no ☐

12. Please give the names of any chronic medical problems (except epilepsy) that the child currently has

_____

_____

13. Please give the name of any learning or behavioural disabilities which the child currently has (e.g. ADHD, dyslexia, autism, special educational needs etc.)

_____

_____

My child…

	Always	Quite often	Sometimes	Just a few times	Never
14. Goes to bed willingly	☐	☐	☐	☐	☐
15. Falls asleep alone	☐	☐	☐	☐	☐
16. Falls asleep in his/her own bed	☐	☐	☐	☐	☐

17. Falls asleep in parental bed	☐	☐	☐	☐	☐
18. Wakes up 1-2 times per night	☐	☐	☐	☐	☐
19. Wakes up 3-4 times per night	☐	☐	☐	☐	☐
20. If wakes, remains awake for under 30 mins	☐	☐	☐	☐	☐
21. If wakes, remains awake for over 30 mins	☐	☐	☐	☐	☐
22. If wakes, will only fall asleep again with parental presence	☐	☐	☐	☐	☐
23. After waking in the night goes to parents bed	☐	☐	☐	☐	☐
24. Wakes up to eat	☐	☐	☐	☐	☐
25. Moves a lot while sleeping	☐	☐	☐	☐	☐
26. Sweats a lot while sleeping	☐	☐	☐	☐	☐
27. Shares the bedroom with parents (even if there is another sleeping place)	☐	☐	☐	☐	☐
28. Sleeps in the parental bed	☐	☐	☐	☐	☐
29. Twitches while sleeping or trying to sleep	☐	☐	☐	☐	☐
30. Wakes up from sleep confused and disoriented	☐	☐	☐	☐	☐
31. Talks in sleep	☐	☐	☐	☐	☐
32. Walks in sleep	☐	☐	☐	☐	☐
33. Grinds the teeth during sleep	☐	☐	☐	☐	☐
34. Has problems with bedwetting	☐	☐	☐	☐	☐
35. Wakes up from sleep screaming and confused	☐	☐	☐	☐	☐

36. Has bad dreams	☐	☐	☐	☐	☐
37. Snores while sleeping	☐	☐	☐	☐	☐
38. Is refreshed and in a good mood upon waking in the morning	☐	☐	☐	☐	☐
39. Is sleepy while sitting and/or studying	☐	☐	☐	☐	☐
40. Is sleepy while watching TV	☐	☐	☐	☐	☐
41. Is sleepy whilst sitting and talking to other people	☐	☐	☐	☐	☐
42. Falls asleep at school	☐	☐	☐	☐	☐

43. What time does your child usually go to bed on week nights?

44. What time does your child usually wake up on week days?

45. What time does your child usually go to bed on weekend nights?

46. What time does your child usually wake up at the weekend?

47. How long does it normally take your child to get to sleep?

48. Does your child take naps during the day?

yes ☐ no ☐

49. If yes, for how long?

8.3 GENERAL DEMOGRAPHIC AND EPILEPSY RELATED INFORMATION

1. How old are you?

2. Gender

Male ☐ Female ☐

3. Do you have any medical conditions that affect your sleep?

Yes ☐ No ☐

4. Do you have epilepsy?

Yes ☐ No ☐

5. If yes, what type of epilepsy/epilepsy syndrome do you have?

6. How long have you had epilepsy i.e. how long is it since your diagnosis?

7. What type of seizures do you have?

8. How often do you have seizures?

Less than 1 every fortnight ☐ More than 1 every fortnight ☐

9. Please list all medications that you take for your epilepsy

8.4 QUALITY OF LIFE IN EPILEPSY SCALE (QOLIF-10)

(Cramer et al., 1996)

How much of the time during the past 4 weeks.....	All of the time	Most of the time	Some of the time	A little of the time	None of the time
1 Have you had a lot of energy?	☐	☐	☐	☐	☐
2 Have you felt downhearted and blue?	☐	☐	☐	☐	☐
3 Has your epilepsy or antiepileptic medication caused trouble with driving?	☐	☐	☐	☐	☐

During the past 4 weeks how much have you been bothered by.....	Not at all bothered	A little	Somewhat	A lot	Extremely bothered
4 Memory difficulties?	☐	☐	☐	☐	☐
5 Work limitations?	☐	☐	☐	☐	☐
6 Social limitations?	☐	☐	☐	☐	☐
7 Physical effects of antiepileptic medication?	☐	☐	☐	☐	☐
8 Mental effects of antiepileptic medication?	☐	☐	☐	☐	☐

	Not at all fearful	Mildly fearful	Moderate fearful	Very fearful	Extremely fearful
9 How fearful are you of having a seizure in the next month?	☐	☐	☐	☐	☐

	Very well	Pretty good	Good and bad equal	Pretty bad	Very bad
10 How has the quality of your life been during the past 4 weeks? That is, how have things been going for you?	☐	☐	☐	☐	☐

8.5 PITTSBURGH SLEEP QUALITY INDEX (PSQI)

(Buyusse et al., 1989)

Instructions:
The following questions relate to your usual sleep habits during the past month ONLY. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.
Please answer all questions.

1. During the past month, when have you usually gone to bed at night?
USUAL BED TIME_____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?
NUMBER OF MINUTES_____

3. During the past month, when have you usually gotten up in the morning?
USUAL GETTING UP TIME_____

4. During the past month, how many hours of *actual sleep* did you get at night? (This may be different than the number of hours you spend in bed.)
HOURS OF SLEEP PER NIGHT_____

For each of the remaining questions, check the one best response. Please answer ***all*** questions.

5. During the past month, how often have you had trouble sleeping because you.....

(a) cannot get to sleep within 30 minutes
Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(b) Wake up in the middle of the night or early morning
Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(c) Have to get up to use the bathroom.
Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(d) Cannot breathe comfortably.
Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(e) Cough or snore loudly.
Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(f) Feel too cold.
Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(g) Feel too hot.
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(h) Had bad dreams.
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(i) Have pain.
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

(j) Other reason(s), please describe_____
_____

How often during the past month have you had trouble sleeping because of this?
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?
Very good _____
Fairly good _____
Fairly bad _____
Very bad _____

7. During the past month, how often have you taken medicine (Prescribed or "over the counter") to help you sleep?
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?
No problem at all _____
Only a very slight problem _____
Somewhat of a problem _____
A very big problem _____

10. Do you have a bed partner or share a room?
No bed partner or do not share a room _____
Partner/ flatmate in other room _____
Partner in same room, but not same bed _____
Partner in same bed _____

11. If you have a bed partner or share a room, ask him/her how often in the past month you have had.....
(a) Loud snoring.
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____
(b) Long pauses between breaths while asleep.
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____
(c) Legs twitching or jerking while you sleep.
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____
(d) Episodes of disorientation or confusion during sleep.
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____
(e) Other restlessness while you sleep: please describe_____
Not during the Past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8.6 EPWORTH SLEEPINESS SCALE (ESS)
(Johns, 1991)

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	**Chance of dozing**
1. Sitting and reading	☐
2. Watching TV	☐
3. Sitting inactive in a public place (e.g a theatre or a meeting)	☐
4. As a passenger in a car for an hour without a break	☐
5. Lying down to rest in the afternoon when circumstances permit	☐
6. Sitting and talking to someone	☐
7. Sitting quietly after a lunch without alcohol	☐
8. In a car, while stopped for a few minutes in traffic	☐

8.7 MULTIPLE ABILITY SELF-REPORT QUESTIONNAIRE (MASQ)

(Seidenberg et al., 1994)

Below is a list of 38 statements about different aspects of cognition. Please rate each of the statements as you believe them to be TRUE FOR YOU.

Please rate all of the following items using the following scale
1 = Never
2 = Hardly ever
3 = Sometimes
4 = Frequently
5 = Always

1. When talking I have difficulty conveying precisely what I mean ☐
2. I can follow telephone conversations ☐
3. I find myself searching for the right word to express my thoughts ☐
4. My speech is slow or hesitant ☐
5. I find myself calling a familiar object by the wrong name ☐
6. I find it easy to make sense of what people say to me ☐
7. People seem to be speaking too fast ☐
8. It is easy for me to read and follow a newspaper story ☐

9. I can easily fit the pieces of a jigsaw puzzle together ☐
10. I am able to follow the visual diagrams that are included in "easy to assemble" products ☐
11. I have difficulty locating a friend in a crowd of people ☐
12. I have difficulty estimating distances, for example from my house to a house of a relative ☐
13. I get lost when travelling around ☐
14. It is hard for me to read a map to find a new place ☐

15. I forget to mention important issues during conversations ☐
16. I forget important things I was told just a few days ago ☐
17. I am able to recall the details of the evening news report several hours later ☐
18. I forget important events which occurred over the past month ☐
19. I forget important portions of interesting gossip I have heard ☐
20. I forget to give phone call messages ☐
21. I have to hear or read something several times before I can recall it without difficulty ☐
22. I can recall the names of people who were famous when I was growing up ☐

23. After putting something away for safekeeping, I am able to recall its location ☐
24. When I first go to a new restaurant, I can easily find my way back to the table when I get up ☐
25. I have difficulty finding stores in a shopping centre even if I have been there before ☐
26. I can easily locate an object I know is in my closet ☐
27. I have difficulty remembering the faces of people I have recently met ☐
28. After the first visit to a new place, I can find my way around with little difficulty (e.g. restaurant, department store) ☐
29. I remember the pictures which accompany magazines or newspaper articles I have recently read ☐
30. I can easily pick out my coat from among others on a coat rack ☐

31.	I can do simple calculations in my head	☐
32.	I ask people to repeat themselves because my mind wanders during conversations	☐
33.	I am alert to things going on around me	☐
34.	I have difficulty sitting still to watch my favourite TV programmes	☐
35.	I am easily distracted from my work by things going on around me	☐
36.	I can keep my mind on more than one thing at a time	☐
37.	I can focus my attention on a task for more than a few minutes at a time	☐
38.	I find it difficult to keep my train of thought going during a short interruption	☐

8.8 POSITIVE AND NEGATIVE AFFECT SCHEDULE (PANAS)

(Watson & Clark, 1988)

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you have felt this way in the past few weeks. Use the following scale to record your answers.

1 = very slightly or not at all
2 = a little
3 = moderately
4 = quite a bit
5 = extremely

1. Interested	☐	11. Irritable	☐
2. Distressed	☐	12. Alert	☐
3. Excited	☐	13. Ashamed	☐
4. Upset	☐	14. Inspired	☐
5. Strong	☐	15. Nervous	☐
6. Guilty	☐	16. Determined	☐
7. Scared	☐	17. Attentive	☐
8. Hostile	☐	18. Jittery	☐
9. Enthusiastic	☐	19. Active	☐
10. Proud	☐	20. Afraid	☐