Sleep and Cognition in Children with Down Syndrome and Williams Syndrome

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"It is a common experience that a problem difficult at night is resolved in the morning after the committee of sleep has worked on it."

~John Steinbeck, 1902 – 1968, American writer

Abstract

This thesis provides a novel contribution to cognitive and developmental psychology by investigating the relationship between sleep, behaviour and cognition in 41 healthy typically developing (TD) children, 22 children with Down syndrome (DS) and 22 with Williams syndrome (WS). In addition, developmental changes in sleep and cognition, and the importance of sleep for consolidation of new memories were assessed in these groups. Finally, the influence of children's sleep and behaviour on their mothers' sleep and wellbeing were examined. The research used a battery of standardised and novel cognitive tasks, objective measures of sleep, and questionnaires.

Sleep problems were syndrome-specific, with poor sleep quality and oxyhaemoglobin desaturation occurring more frequently in DS, suggestive of breathing difficulties during sleep, and long sleep latencies in the WS group. TD children performed well on cognitive tasks of short term memory, working memory and sustained attention compared to children with DS and WS, and their performance generally improved with increasing age, which tended not to be the case for the clinical groups. In the TD group, improved sleep quality and higher, less variable oxyhaemoglobin saturation related to better performance on cognitive tasks and fewer behavioural problems. Few associations between sleep, cognition and behaviour were found in the DS and WS groups. TD children and children with WS showed evidence of sleep-dependent memory consolidation for explicitly learnt material on two tasks. Mothers of children with DS had the poorest sleep and most daytime sleepiness, though not related to children's sleep or daytime behaviour.

The findings indicate that sleep problems should be assessed and managed in clinical groups. Educational strategies should be implemented to reinforce sleep-related learning gains. Future research could examine whether sleep-dependent learning occurs in relation to specific aspects of sleep architecture in children with DS and WS, as it does in adults and TD children.

Declaration

I, Anna Fiona Ashworth, confirm that the work presented in this thesis is entirely my own. Where information has been derived from other sources, explicit attribution is made.

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List of Terms and Abbreviations

Adenotonsillectomy. *tonsil and adenoid removal*
ADHD. *Attention deficit/hyperactivity disorde*
AHI. *Apnoea-hypopnoea index*
ANCOVA. *Analysis of covariance*
ANOVA. *Analysis of variance*
Apnoea. *Cessation of breathing*
AVSD. *Atrioventricular septal defect*
Bruxism. *Teeth grinding*
BSP. *Behavioural sleep problems*
CA. *Chronological age*
CBQ. *Children's Behaviour Questionnaire*
CDI. *Communicative Development Inventory*
CPAP. *Continuous positive airway pressure*
CPT. *Continuous performance task*
CRP. *C-reactive protein*
CSHQ. *Children's Sleep Habits Questionnaire*
DS. *Down syndrome*
EEG. *Electroencephalogram*
ESS. *Epworth Sleepiness Scale*
FISH. *Fluorescence in situ hybridisation test*
GH. *Growth hormone*
Hypercarbia. *Increased blood circulation of carbon dioxide*
Hypopnoea. *Abnormally shallow breathing or low respiratory rate*
Hypoxia. *Decrease in blood oxygen levels*
ID. *Intellectual disabilities*
MA. *Mental age*
MDI. *Major Depression Inventory*
MMS. *Mini-Mental State*
MSLT. *Multiple sleep latency test*
Nocturnal enuresis. *Bed-wetting*
NREM. *Non-rapid eye movement*
OR. *Outliers removed*
OSAS. *Obstructive sleep apnoea syndrome*
PET. *Positron emission tomography*
PLMD. *Periodic limb movement disorder*
PSG. *Polysomnography:, a full overnight sleep study*
PSQI. *Pittsburgh Sleep Quality Index*
RCPM. *Raven's Coloured Progressive Matrices*
REM. *Rapid eye movement*
RLS. *Restless legs syndrome*
RPM. *Ravens Progressive Matrices*
RT. *Reaction time*
SCN. *Suprachiasmatic nucleus*
SDB. *Sleep-disordered breathing*
SDQ. *Strengths and Difficulties Questionnaire*
Sleep latency. *Time taken to fall asleep*
Somnambulism. *Sleep walking*
Somniloquy. *Sleep talking*
SpO_2. *Oxyhaemoglobin: Haemoglobin oxygen saturation in the blood*
SRTT. *Serial reaction time task*
STM. *Short term memory*
SVAS. *Supravalvular aortic stenosis*
SWS. *Slow wave sleep*
TMCQ. *Temperament in Middle Childhood questionnaire*
WASO. *Wake after sleep onset*
WISC-R. *Wechsler Intelligence Scale for Children – Revised*
WS. *Williams syndrome*
ηp^2. *Partial eta squared*

Thesis Overview

The main aims of this thesis were to investigate sleep characteristics in TD children and children with DS and WS, and the relationship between sleep, behaviour and cognitive functioning.

This thesis is divided into six chapters. Chapters 1 and 2 provide an introduction to the topic and review of the literature. Chapter 1 describes sleep architecture and the importance of sleep for healthy physiological and psychological functioning whilst Chapter 2 introduces DS and WS including what little is known about sleep characteristics in these disorders. Chapter 3 describes the extensive pilot studies that were conducted in order to plan this project. Chapter 4 presents the main methodology used in this thesis, including descriptions of the experimental paradigms, methods of data collection and statistical analysis. Chapter 5 presents the results, showing task performance, group comparisons and developmental trajectories. Finally, Chapter 6 discusses the findings in light of current theories surrounding the functions of sleep. Further suggestions are made for future research.

1. Sleep and Learning

1.1 Introduction

Sleep is not simply an inactive state, but a necessary physiological process practised by all mammals and birds, as well as most reptiles, amphibians and fish. Historically, it was thought of as a state of rest for the mind and body but the advent of electroencephalogram (EEG) to record brain activity revealed a distinct cyclical pattern of activation and deactivation of cortical and subcortical structures during sleep.

Although humans spend almost one third of their lives asleep, the precise purpose of sleep has not been identified. Its many functions are a hot topic of current research and we now know that sleep is essential for optimum physiological and psychological functioning. Sleep problems can therefore have a detrimental effect on health, behaviour and cognition. Tired children perform less well at school, are more hyperactive and have poorer attention and memory than well-rested children. Sleep is also an active state whereby new memories are reinforced and preferentially consolidated compared to the wake state. This phenomenon is known as 'sleep-dependent learning'.

Sleep problems appear to be more common in children with developmental disorders than in typically developing children, yet relatively little research investigates the specific problems and the impact that sleep problems have on the child's development. If sleep is so important for normal, healthy development and optimum functioning, then behavioural problems and learning difficulties experienced by children with disabilities could be exacerbated by their sleep problems.

The current thesis aims to provide an in-depth analysis of sleep and its impact on behaviour, attention and learning in children with developmental disorders Down syndrome and Williams syndrome compared to typically developing children. It uses objective measures, parent report, and a range of established and novel tasks.

This chapter provides a detailed account of sleep, its measurements and its functions. In order to gain a thorough understanding of children's sleep it is also important to consider distinctions between adults and children. For this reason, adult sleep is described, followed by a description of how sleep in childhood differs from this. Since the study of children is often lacking in the area of sleep research, in some places it has been necessary to focus on adult sleep.

1.2 Sleep Physiology

1.2.1 History of sleep research

Sleep occurs, often uncontrollably, on a daily basis. It is characterised by a reduced state of consciousness with limited bodily movement or responsiveness to external stimuli. In 1937, Loomis, Harvey and Hobart were the first to describe five distinct phases of sleep and a cyclic movement between the stages in human adults. Later, Aserinsky and Kleitman (1953) elaborated on this model, reporting four stages (I to IV) of non-rapid eye movement (NREM) sleep which correspond to increasing depths, and a fifth stage of rapid eye movement sleep (REM). These stages are outlined in more detail below, first describing adult sleep architecture to then highlight developmental differences. As first proposed by Loomis et al. (1937), sleep does follow a predictable recurring pattern throughout the night, with each stage having its own characteristic physiological features. Rechtschaffen and Kales (1968) later devised a system for scoring sleep stages which is still used today.

1.2.2 Adult sleep architecture

During the aroused wake state, neural electrical activity is characterised by low-amplitude, irregular beta waves of around 13-30 Hz. As adults begin to fall asleep, they enter stage I of NREM sleep, considered a transition phase between wake and sleep and characterised by high-amplitude, synchronised alpha waves in the 8-12 Hz range that occur during periods of relaxation, rest and drowsy wakefulness. During this stage a person may experience hypnagogic hallucinations and hypnic jerks. These are sudden muscle contractions as the muscles relax, often associated with vivid imagery, which are more frequent during times of stress or irregular sleep schedules. Stage I lasts for only around five to ten minutes before progressing to stage II where conscious awareness of the environment disappears. This is the most prevalent stage of sleep, accounting for around half of the total sleep time of adults. Activity is mainly in the 4-7 Hz theta range but littered with bursts of activity known as K-complexes and sleep spindles. A K-complex consists of a sharp, high-amplitude slow wave reflecting cellular hyperpolarisation, immediately followed by a larger negative deflection reflecting cellular depolarisation (Amzica & Steriade, 1998). Sleep spindles often, but not always, follow a K-complex; these are clusters of rhythmic EEG waves between 12 and 15 Hz that progressively increase and then gradually decrease in amplitude (De Gennaro & Ferrara, 2003). See Figure 1.1 for an illustration of EEG signal in wake and the various sleep stages.

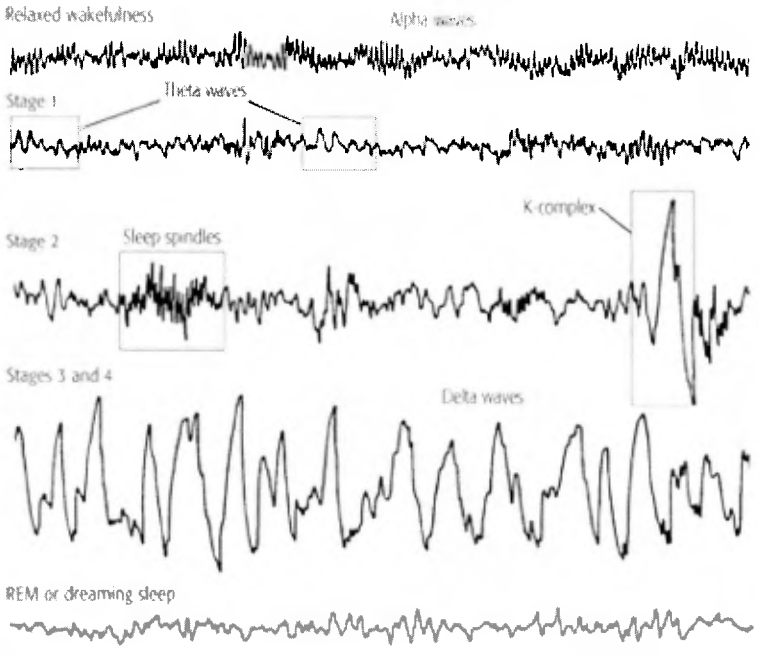

Figure 1.1. Showing EEG signal of wakefulness and sleep stages.

As sleep becomes deeper it progresses to stages III and IV, known jointly as deep sleep or slow wave sleep (SWS) because of the slow but high-amplitude delta waves (<4 Hz) that accompany them. Since 2007 The American Academy of Sleep Medicine has recommended scoring stages III and IV together, as stage III lasts for only a few minutes and was considered as a transition into stage IV. SWS in adults occurs around 30-40 minutes after sleep onset and lasts for about 20 to 40 minutes in the first sleep cycle. This is the deepest stage of sleep where neural activity is least like wake. Consequently it is the most difficult stage from which to rouse somebody, and in young children it is almost impossible. If awakened they are likely to be sleepy and disorientated. It is the stage in which parasomnias such as sleep terrors, somnambulism (sleep walking), somniloquy (sleep talking) and nocturnal enuresis (bed-wetting) may occur. SWS is thought to be the most restorative phase of sleep due to its benefits for the immune system and tissue repair, described in more detail later (Section 1.4.7). During sleep deprivation SWS is better preserved than other phases, showing increased pressure for SWS relative to other sleep stages (Brunner, Dijk, Tobler, & Borbély, 1990).

The final stage of sleep, REM sleep, accounts for around 20 to 25% of total sleep time in adults and is characterised by rapid eye movements, a fast, low voltage EEG similar to stage I but with higher and more variable heart and respiratory rates, and higher metabolic rate. This is the stage during which most memorable dreaming occurs, and is accompanied by paralysis of skeletal muscles to prevent individuals from physically acting out their dreams. REM sleep is not well preserved during sleep deprivation but rebounds on recovery nights (Spiegel, Leproult, & Van Cauter, 1999).

In adults the sleep cycle follows a predictable cyclic pattern, beginning in NREM and progressing through deeper NREM stages before entering REM sleep around 80 to 100 minutes later. The whole cycle then repeats throughout the night, taking around 90 minutes to complete (see Figure 1.2). The first half of the night is dominated by SWS but in later cycles, SWS diminishes and REM and stage II dominate, with REM periods becoming longer and more intense as the sleep period progresses. Short awakenings often occur during the night, especially around the transitions in and out of REM sleep, but these are usually too brief to be remembered in the morning.

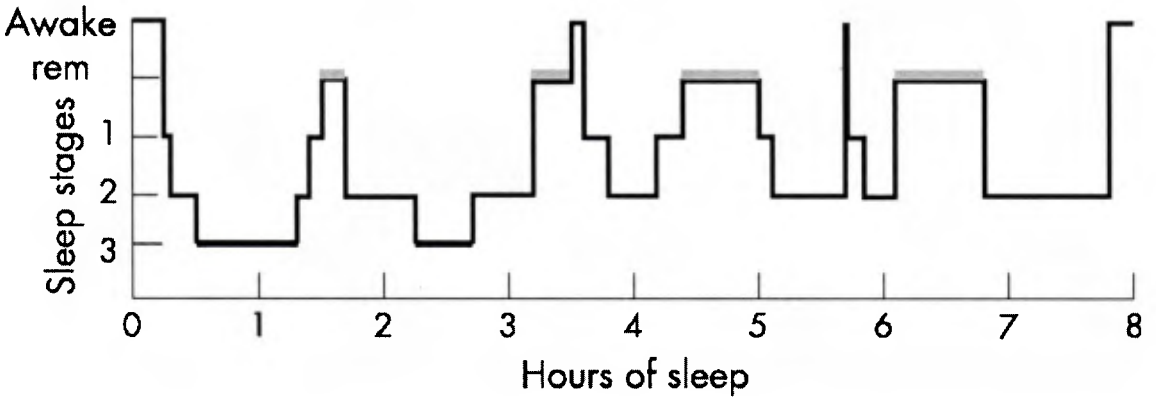

Figure 1.2. Hypnogram showing typical adult sleep architecture (adapted from Hill, Hogan, & Karmiloff-Smith, 2007).

The optimal amount of sleep is hard to define as it varies greatly between individuals. Indicators of insufficient sleep include daytime sleepiness and sleep latency (time taken to fall asleep) of under five minutes, whereas long sleep latencies can suggest too much sleep. For adults, six and a half to seven and a half hours is thought to be sufficient, with much more or less having detrimental effects on health and cognition (Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002; Patel et al., 2004; Youngstedt & Kripke, 2004). The invention of electricity bringing artificial extension of light hours and the advent of a 24-hour society has meant curtailment of sleep to a minimum in order to maximise work and leisure activities. Some individuals claim to be able to gradually reduce their sleep requirement with no ill effects, (e.g., Aitchison, 2012), yet no scientific study backs these claims. Nevertheless, some individuals may be better-able to tolerate inadequate sleep than others.

1.2.3 The development of sleep architecture from infancy to old age

Children's sleep is both qualitatively and quantitatively different from that of adults. It changes considerably throughout infancy and childhood, with lesser changes continuing throughout the lifespan.

During early development sleep is the primary activity, suggesting that it is essential for the developing brain and body. Newborns spend around 16-17 hours of each 24-hour period in sleep, following an ultradian cycle of around four hours that seems to be organised around the feeding cycle. From around 6 weeks of age longer sleep cycles increasingly occur at night time, so that by around 12 months of age children are sleeping for around eight to nine hours during the night whilst still having daytime naps. Total sleep time slowly decreases throughout infancy and early childhood, due mainly to the reduction in daytime sleep. Children aged 2 to 5 years spend around 12 hours each day asleep, slowly decreasing to around 10 hours in later childhood and nine hours during adolescence (See Figure 1.3) (Davis, Parker, & Montgomery, 2004; Mindell & Owens, 2003).

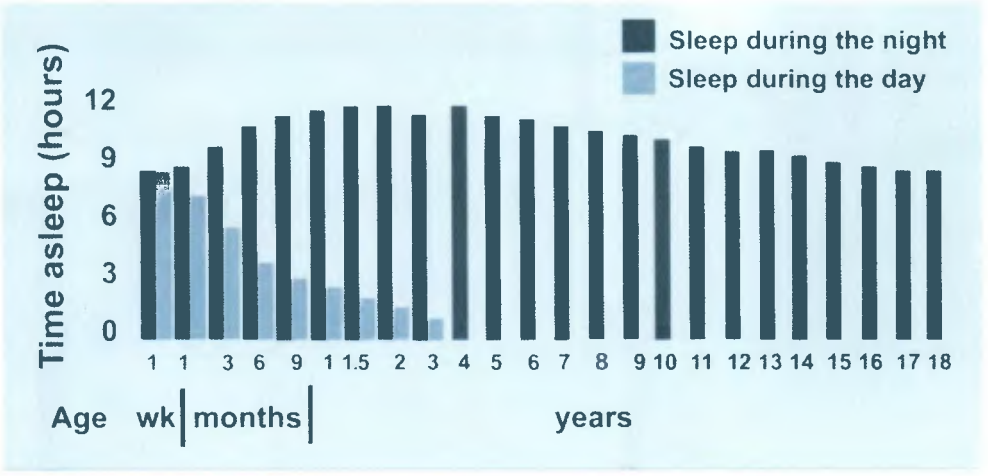

Figure 1.3. Developmental changes to duration of daytime and night-time sleep.

Adult-type sleep states are not apparent in newborns and only emerge as the brain matures during the first year of life. Quiet and active sleep are discernible, each accounting for around 50% of infant sleep time. During active sleep eye movements can be seen under closed lids, and smiling, grimacing, twitching, stretching, tremors and sucking movements occur along with irregular heart rate and respiration. In contrast to adults, infants enter sleep directly through REM sleep before NREM (Pegg, 2006). REM latency increases and the percentage of time spent in REM or active sleep gradually decreases throughout infancy and childhood to 20-25% in adulthood (Kahn, Dan, Groswasser, Franco, & Sottiaux, 1996; Montgomery-Downs, O'Brien, Gulliver, & Gozal, 2006).

During infancy, as active sleep diminishes, quiet NREM sleep is the dominant sleep phase, consisting mainly of SWS, which decreases considerably through childhood and adolescence with a corresponding increase in stage II (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004; Pegg, 2006). By late adolescence, percentages of REM and NREM reach adult levels. In old age, SWS almost completely disappears (see Figure 1.4).

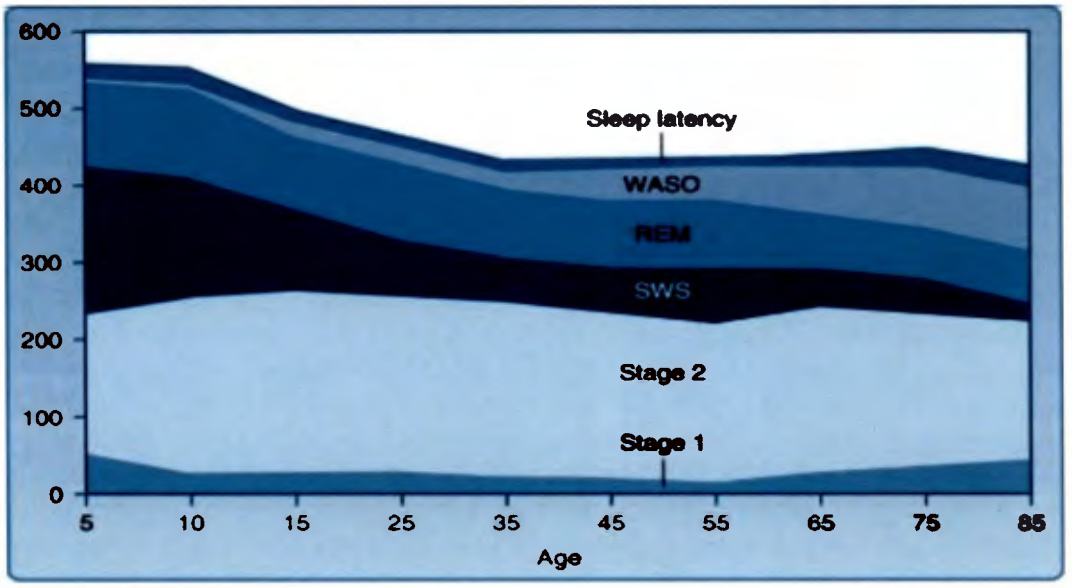

Figure 1.4. Graph showing time (minutes) spent in each sleep stage, sleep latency and wake after sleep onset over the lifespan. Source: Carskadon & Dement (2005).

In infancy sleep cycles occur around every 40 to 50 minutes, gradually increasing in average length to 60 minutes at 4 years of age, and stabilise at around 75 minutes in mid childhood through to 90 minutes in adulthood. In young children cycles repeat seven to ten times per night, whilst adults have around four or five cycles. Sleep latency in infants gradually decreases from around 30 minutes at 2 months of age, to 15 minutes at 9 months, but is inconsistent throughout childhood and adulthood (Carskadon & Dement, 2005; Kahn et al., 1996; Mindell & Owens, 2003).

1.2.4 Physiological regulation of sleep

Sleep timing is controlled by two principle mechanisms. One is a homeostatic drive for sleep which increases throughout the day and is relieved by sleep. The longer the period of wakefulness, the stronger the drive to sleep. It occurs due to build-up of adenosine and other chemicals in the brain that promote sleep and suppress arousal (Mindell & Owens, 2003). The other is an intrinsic circadian clock driven by the suprachiasmatic nucleus (SCN) of the hypothalamus; a tiny region of the brain directly above the optic chiasm. The circadian rhythm in the SCN is influenced by external time-

keeping cues or 'zeitgebers', the main one of which is daylight that it receives from the retina via the retinohypothalamic pathway. During the dim evening light there is a gradual decrease in core body temperature and cortisol levels along with the release of the sleep-promoting hormone melatonin, which work together to cause sleepiness. The circadian clock is then reset in the morning light, prompting the release of wake-promoting chemicals such as serotonin and cortisol, so encouraging alertness (Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010; Datta & Maclean, 2007). In constant dim light with the absence of a light/dark cycle and time-keeping, the circadian cycle runs at a little over 24 hours (Czeisler et al., 1999).

1.2.5 Functional neuroanatomy during sleep

In addition to EEG, activity in the brain during sleep can now be investigated using functional neuroimaging techniques. Positron Emission Tomography (PET) is often used for this purpose and can be used to produce three dimensional functional processes in the brain by measuring cerebral blood flow. This can be considered a marker for neuronal activity (Maquet, 2000). During the aroused wake state regional cerebral blood flow is widely distributed and highly variable, dependent on the engagement of cognitive tasks (Maquet, 2000).

During SWS blood flow is reduced, especially in the frontal lobes, which appear to disconnect and particularly benefit from sleep (Braun et al., 1997; Maquet, 2000). Activity in cortical and subcortical regions is reduced by around 40% compared to the wake state (Dang-Vu et al., 2010), though some areas show relatively increased activation after controlling for overall reduced activation. These include the hippocampus (involved in memory) and the amygdala (involved in emotion) (Nofzinger et al., 2002). Sleep rhythms are generated in the cortex, organising the thalamically-generated sleep spindles and regular delta waves (Dang-Vu et al., 2010; Maquet, 2000). In addition, deactivation of the brainstem structures is thought to modulate sleep, whilst its activation promotes alertness (Fuller, Gooley, & Saper, 2006; Maquet, 2000).

In contrast, REM sleep is characterised by sustained neuronal activity and blood flow in much of the cortex, including the hippocampus, the amygdala and occipital areas (involved in vision), whilst certain parts of the cortex such as the dorso-lateral prefrontal cortex (involved in motor planning, organisation and regulation of intellectual function and action) and parietal cortex (involved in integrating sensory input and viuospatial processing) show reduced activity. The motor cortex is functionally disconnected during REM to inhibit the physical acting-out of dreams (Dang-Vu et al., 2010; Maquet, 2000).

1.2.6 Ethnic and cultural differences in sleep

While some ethnic differences in sleep have been reported, they are typically found to be very small. Quan et al. (2003) found differences in sleep architecture between Caucasian and Hispanic children, with Hispanic children having around 20 minutes less SWS and correspondingly more stage II sleep ($p \leq .02$). Also, white children have been found to have a slightly higher stage I per cent and lower stage II per cent than their black peers (Montgomery-Downs et al., 2006). These differences may relate to cultural differences in sleep practices rather than inherent differences in the neurophysiology of sleep per se. For example, parent report studies have found black children to be eight times more likely to take daytime naps than white children at age 8 years (Crosby, LeBourgeois, & Harsh, 2005). Chinese children sleep for around one hour less per night and have more sleep problems than American children (Liu, Liu, Owens, & Kaplan, 2005), whilst in Japan, children co-sleeping with parents is the norm (Latz, Wolf, & Lozoff, 1999). These differences may then be reflected in children's sleep architecture.

1.3 Sleep Problems in Typical Development

Sleep problems in children are common, with around one third of children experiencing some kind of sleep disturbance at some point during childhood (Mindell & Owens, 2003; Owens, Spirito, McGuinn, & Nobile, 2000; Pegg, 2006). These may be more common in boys than girls (Paavonen et al., 2000) and in children with older parents, since younger parents seem to be stricter with children's bedtimes (Sadeh, Raviv, & Gruber, 2000). Other factors that have been associated with better sleep quality include having better educated parents, living with both parents and having little family stress (Lam, Hiscock, & Wake, 2003; Paavonen et al., 2000; Sadeh et al., 2000). Sleep problems in infancy are often an early predictor of later sleep problems, for example, of 114 infants with sleep problems identified by parent report, 32% still had sleep problems at 3-4 years (Lam et al., 2003).

A distinction should be drawn here between sleep problems and sleep disorders. Sleep problems are often minor, transient annoyances that everyone experiences from time to time. It is important to note that sleep problems may be culturally defined and are often reported by parents when there is a mismatch between the child's behaviour and the parents' expectations, or when the child's behaviour causes significant disruption to the parents' sleep (Mindell & Owens, 2003). In contrast, sleep disorders are defined by the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2005), tend to be more serious and may interfere with daily life. Eight categories of sleep disorders are defined: insomnias, sleep-related breathing disorders, hypersomnias of central

origin, circadian rhythm disorders, parasomnias, sleep-related movement disorders, isolated symptoms, and other sleep disorders. Some of the most common childhood disorders will be discussed here in more detail.

1.3.1 Insomnias

Insomnia is defined as a difficulty initiating and/or maintaining restorative sleep or by short sleep duration, despite adequate opportunity for a full night's sleep (Colten & Altevogt, 2006; Morin, 2000). In a large scale longitudinal study of 1.1 million American adults, Kripke et al. (2002) reported it to be the commonest sleep disorder in adults, with a prevalence of 4.3% in women and 2.6% in men. It can be a primary disorder or may occur secondary to another disorder such as depression, stress or pain, or other factors such as a disturbance to the circadian rhythm by irregular sleep patterns, changes to the sleep environment, psychoactive drugs or stimulants, or poor sleep hygiene (Morin, 2000). In children, too, the vast majority of cases of persistent insomnia have been accompanied by a psychiatric condition such as depression or aggression (Ivanenko, Barnes, Crabtree, & Gozal, 2004).

Behavioural insomnia is by far the most common childhood sleep complaint, characterised by bedtime struggles, trouble settling and difficulty initiating and/or maintaining sleep. The child may refuse and resist going to bed and staying in bed, be unable to self-soothe to sleep, awaken repeatedly throughout the night requiring parental attention, and/or require special conditions to fall asleep, such as certain toys, blankets, music, or the parent being in the room. This is generally accompanied by distress and impaired daytime functioning (Hill, 2011). These characteristics occur frequently in children, especially toddlers and preschool children and, although often transient, can exert great pressure and distress on the family if left unmanaged (Owens, Spirito, McGuinn, & Nobile, 2000).

1.3.2 Sleep-disordered breathing

Sleep-disordered breathing (SDB) refers to a spectrum of disorders that range in severity from primary snoring to severe obstructive sleep apnoea syndrome (OSAS), a condition where the upper airway becomes occluded causing difficulty breathing during sleep. Prevalence estimates vary depending on the type of diagnostic tools used, but it is likely that snoring occurs in around 11% of children aged 4 to 11 years (Ali, Pitson, & Stradling, 1993; Ali, Pitson, & Stradling, 1994; Goodwin et al., 2003; Gozal, 2008), declining to around 6% in adolescence (Johnson & Roth, 2006). OSAS is thought to affect around 1 to 3% of children (Brunetti, 2001; Sogut et al., 2005). It occurs most often during REM sleep due to the associated loss of muscle tone in the pharynx and upper airway (Royal

College of Paediatrics and Child Health, 2009). The apnoea-hypopnoea index (AHI) can be calculated by measuring chest and abdominal excursion with nasal airflow and calculating the number of abnormal respiratory events per hour of sleep to give a figure indicating OSAS severity. Associated features of OSAS include loud snoring, mouth breathing and often a decrease in oxygen levels (hypoxia) and increased circulation of carbon dioxide (hypercarbia) in the blood, which may or may not lead to arousal. Some sufferers may also experience arousals without associated hypoxia and hypercarbia. Sufferers may experience severe daytime sleepiness which in children may manifest itself as irritability, bad behaviour, impulsivity and poor school performance. Other common features in children include daytime mouth breathing, difficulty swallowing, poor speech articulation, a 'dull' facial expression, unusual sleep postures (American Academy of Sleep Medicine, 2001), restless legs, difficulty falling asleep and bruxism (teeth grinding) (Gregório, Athanazio, Bitencourt, Terse, & Hora, 2008). OSAS is frequently caused by enlarged tonsils and adenoids and so can be treated by adenotonsillectomy (tonsil and adenoid removal). Other etiologies include craniofacial abnormalities, obesity and neuromuscular weakness. It can also be treated with a continuous positive airway pressure (CPAP) ventilation, which keeps the airway open by delivering a stream of compressed air via a hose to a face or nasal mask. Ethnic differences have also been found, with African Americans twice as likely as Caucasians to have SDB (Johnson & Roth, 2006; National Sleep Foundation, 2010), and Hispanic children significantly more likely to snore than white children (11.4 vs 7.4%) (Goodwin et al., 2003).

1.3.3 Parasomnias

Parasomnias are abnormal behaviours during sleep that cause full or partial arousal, such as somnambulism, sleep terrors, nightmares, bruxism and nocturnal enuresis. They often reflect immaturity of the central nervous system so are common in early and mid-childhood but are generally outgrown and are rare in adulthood (Thiedke, 2001). The Tucson Children's Assessment (Goodwin et al., 2004) used polysomnography (PSG, a full overnight sleep study; see Section 1.6.1) and parental report to study sleep in 480 healthy children aged 6 to 11. Parent report indicated that the most common parasomnias were somniloquy (11.3% of the sample), sleep terrors (6.3%) and enuresis (9.6% boys, 5.4% girls). Parasomnias did not tend to disrupt sleep architecture, with the exception of enuresis, which was associated with shorter sleep latency and increased stage II sleep, and somniloquy and sleep terrors which were associated with more frequent shifts from REM to stage I. A parent report study of 971 Turkish children aged 7 to 11 reported similar findings, with a total 14.4% prevalence estimate of parasomnias (Agargun et al., 2004). Parasomnias are often

associated with other factors such as SDB, a history of physical illness and learning difficulties (Agargun et al., 2004; Goodwin et al., 2004).

1.3.4 Periodic limb movement disorder

Periodic limb movement disorder (PLMD) is a sleep disorder characterised by involuntary, repetitive and highly stereotyped limb movements whilst asleep, often with no realisation or recollection. Movements typically occur 20 to 40 seconds apart and are most common in stage II sleep. For diagnosis, at least three episodes must occur during the night, each containing at least 30 movements. These movements are often associated with fragmented and restless sleep with frequent arousals and consequent daytime sleepiness. Prevalence increases with age, occurring in around 10% of children and up to 34% of those over 60 (American Academy of Sleep Medicine, 2001; Crabtree, Ivanenko, O'Brien, & Gozal, 2003). In children PLMD is often associated with other conditions such as attention deficit/hyperactivity disorder (ADHD), SDB and insomnia (American Academy of Sleep Medicine, 2001; Crabtree et al., 2003). In around 50% of cases there is a parental history of PLMD or restless legs syndrome (RLS), an irresistible urge to move limbs to stop uncomfortable sensations (Picchietti, Rajandran, Wilson, & Picchietti, 2009).

1.3.5 Daytime sleepiness

Daytime sleepiness is a common occurrence in today's society due to individuals not getting sufficient or good quality night time sleep. This may be related to poor sleep hygiene, voluntary sleep restriction, or another sleep disorder or medical condition. Daytime sleepiness is a significant risk factor for traffic accidents and occupational injuries so is a condition to be taken seriously (Mathis, Seeger, & Ewert, 2003; Melamed & Oksenberg, 2002). It is also associated with impairments in behaviour and cognitive ability, which could significantly affect children's academic performance (Fallone, Owens, & Deane, 2002).

The extent of daytime sleepiness can be measured using the Multiple Sleep Latency Test (MSLT), consisting of four or five 20-minute nap opportunities at two-hour intervals. Sleep latency at each nap opportunity is monitored by measuring neural, ocular (eye movements) and muscular activity (Carskadon et al., 1986; Carskadon & Dement, 1977). Short sleep latencies of less than five minutes are viewed as an indicator of severe daytime sleepiness, whilst 15 to 20 minutes is the norm.

1.4 Functions of Sleep

Sleep has always been the subject of great interest and has triggered considerable research into its functions. It is now recognised that sleep is more than just a passive process that prevents daytime

sleepiness, but its precise functions, whether there is a 'core function', and the necessity for the two different types of sleep (NREM and REM), still remain unclear. Our understanding of sleep has largely been based on observations of the effects of sleep deprivation or disruption. What has become increasingly clear is that sleep is critical for numerous health and cognitive functions and that sleep problems adversely affect physiological and psychological functioning. We turn now to these functions, concentrating mainly on cognitive functions as they are the focus of this thesis, whilst also summarising some of the main physiological changes that occur during sleep.

Sleep is necessary for optimum cognitive functioning, affecting attention, mood, behaviour and our ability to form and retrieve memories. Although most research focuses on adult sleep, it has more recently turned to children, with the rationale that if sleep affects children's cognition, then children who sleep well will perform better academically and have greater achievements than those who do not sleep well. Even a minor sleep disruption can have detrimental effects. In both adults and children this can impact on daytime behaviour and the ability to maximise potential at school or work. Sleep problems can often be treated so, if diagnosed early, correct management could improve a child's chances in life.

1.4.1 Executive functions

Many experimental studies have demonstrated that both adults and children suffer problems with executive functions following sleep disruption (Jones & Harrison, 2001; Karpinski, Scullin, & Montgomery-Downs, 2008; Sadeh, Gruber, & Raviv, 2003; Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010). Executive functions are neural processes mediated by the prefrontal cortex that are responsible for higher functions such as working memory (the ability to hold and manipulate information in short term memory), planning, problem solving, goal-directed behaviour, cognitive flexibility, abstract thinking, initiation and inhibition. Changes to the structure of the prefrontal cortex occur throughout childhood, including an increase in both grey and white matter volume, growth of dendrites and a reduction in synaptic and neuronal density. These changes are thought to be associated with cognitive maturation of functions related to the prefrontal cortex (Tsujimoto, 2008).

In a sample of 60 children aged 6 to 13 years (mean 9.90 ± 1.91), Steenari et al. (2003) studied the relationship between sleep and performance on auditory and visual working memory tasks, assessed using n-back tasks with three difficulty levels. Poorer performance on the tasks was associated with lower sleep efficiency, longer sleep latencies and shorter sleep duration measured by actigraphy (movement monitoring; see section 1.6.3). This was particularly evident for the hardest tasks and

auditory tasks were impaired more than visual tasks. The n-back tasks also pose significant demands on attention. As attention was not assessed, it cannot be ruled out that this study shows not a link between sleep and working memory, as the authors suggest, but a relationship between sleep and attention.

Even a modest sleep restriction can significantly impact on daytime behaviour. Sadeh et al. (2003) assessed neurobehavioural functioning and used actigraphy to measure the normal sleep habits of 77 children aged 9 (N = 42, M = 9.8 ± .64) and 11 (N = 35, M = 11.58 ± .50) years. Children were then asked to either extend or restrict their sleep for one hour per night for three consecutive nights. The extended sleep group slept an average of 35 minutes longer than baseline and were found to improve their reaction time (RT) on a sustained attention task as well as recall on the digit span forwards task. These improvements were similar to, or greater than, the difference between the two age groups (9 and 11 year olds) at baseline. The sleep restricted group reduced their sleep by an average of 41 minutes. Interestingly, the quality of their sleep significantly improved, with reduced night wakings and movement, and increased sleep per cent. The opposite pattern occurred in the sleep extension group. This shows evidence of physiological compensatory mechanisms in place to adapt sleep quality in response to changes in sleep time. Despite this, the sleep restricted group performed worse than baseline on a simple RT test, which involved pressing a button as quickly as possible every time a square appeared on the computer screen. The study shows how sensitive children are to even a modest alteration of their natural sleep patterns. The neurobehavioural improvements that emerged after a 35 minute extension in sleep, comparable to fluctuations in everyday life, were analogous with those gained by two years of development. This is worrying since in all children bedtime struggles and early school start times often mean that children's sleep is chronically restricted.

Executive functioning difficulties have also been associated with sleep fragmentation, characterised by multiple and/or prolonged night wakings. One hundred and thirty-five healthy children from three age groups ≈ 8, 10 and 12 years were monitored for five nights using actigraphy, and were tested on a range of neurobehavioural tasks (Sadeh, Gruber, & Raviv, 2002). Children with the most fragmented sleep also showed the poorest performance, especially on the more cognitively demanding tasks such as sustained attention and the symbol-digit substitution test where they needed to respond as quickly as possible with the number that corresponded with each presented symbol. These children also exhibited the worst behaviour, as reported by parents. These findings were particularly evident in the youngest children, aged 7 and 8 years. The finding that poor sleepers were worse than good sleepers at inhibitory control may help to explain their bad behaviour.

Causality cannot be concluded as the study was correlational by design and did not assess whether sleep fragmentation was confounded by co-morbid symptoms such as SDB, puberty, stress, or medical complaints, but the authors interpret the results as showing that compromised neurobehavioural functioning is a result of tiredness and reduced alertness that occurs as a consequence of sleep fragmentation.

In a sample of 39 preschool children aged 3 to 5 years (M = 4.3 ± .6) executive function difficulties were related to fragmented sleep due to SDB. Karpinski et al. (2008) tested the children on planning, inhibition and working memory tasks and parents completed a questionnaire relating to SDB symptoms. After controlling for age, children who were reported to be frequent snorers scored significantly less than occasional- and non-snorers on all dimensions of the tasks. It is important to note the clinical value of this single item, 'how often does your child snore?', as it is simple to administer, and highly predictive of SDB. Without having tested for oxygen desaturations, it is impossible to know here whether performance deficits were most influenced by the sleep disruption caused by SDB, or by the hypoxia and hypercarbia. Beebe and Gozal (2002) suggest that the relatively late maturation of the prefrontal cortex makes this brain area particularly sensitive to sleep loss and the neurochemical and metabolic imbalance caused by hypoxia, hypercarbia and sleep fragmentation associated with SDB. When apnoeic (cessation of breathing) or hypopnoeic (abnormally shallow or slow breathing) episodes occur during sleep, oxygen delivery to the brain is diminished. In rat models this leads to cell death and reduced long term potentiation, which can have significant lasting effects for neurocognition in the developing brain. It is probable that this model is generalisable to humans. In a review paper, Blunden and Beebe (2006) assess the arguments for each case. Whilst there is much evidence to suggest that neurobehavioural deficits occur in children suffering mild levels of nocturnal oxygen desaturation, even without upper airway obstruction or respiratory arousals, there is also evidence that performance problems are associated with disturbed sleep architecture and observable SDB symptoms, but not hypoxia. Also, sleep problems such as PLMD/RLS, insufficient sleep, sleep fragmentation, and experimental sleep disruption or restriction create problematic cognitive and behavioural effects, even in the absence of SDB and hypoxia. The authors conclude that sleep disruption, deprivation and intermittent hypoxia may be independently sufficient to cause daytime deficits, whilst in combination their effects may be more severe. This is an important consideration in developmental disorders where OSAS is a particular problem in, for example, Down Syndrome, and snoring is relatively more common in Williams Syndrome compared to typically developing children (Annaz, Hill, Ashworth, Holley, & Karmiloff-Smith, 2011; Goldman, Malow, Newman, Roof, & Dykens, 2009). Adverse cognitive effects of OSAS and SDB may be reversible following CPAP treatment or adenotonsillectomy. This could

have a significant beneficial influence on learning and academic performance (see Jones & Harrison, 2001, for a review).

The difficulty with testing for deficits in executive functioning is that most tests were designed for patients with frontal lobe lesions who show severe deficits in performance. Sleep restriction, however, does not cause deficits to the same extent and so it is possible that these tasks are not always sensitive enough for assessing sleep-deprived participants. Tests are generally highly repetitive and boring, so it is also important to note that participants may not perform so well when tests form part of a large test battery, as this decreases motivation. Also, sometimes tests must be repeated to assess performance before and after an experimental manipulation. This removes the novelty value so important to executive function tests, and participants may experience either improved performance through practice, or fatigue effects through boredom.

1.4.2 Attention

Of particular importance in the sleep literature and especially relevant to the current thesis is the effect of sleep disturbance on attention, a vital cognitive process involved in most higher-order cognitive demands. The ability to selectively concentrate on important stimuli whilst ignoring other competing aspects of the environment is a necessary life-skill and a precursor to learning. It is therefore a critical aspect of a child's development. It is generally agreed that the concept of attention encompasses a number of separate components, for example, vigilance or sustained attention, inhibition, shifting of attention and selective attention (Bull & Scerif, 2010; Manly et al., 2001). Tasks used to test these constructs generally involve recording participants' ability to attend to stimuli and respond over a prolonged period of time. One of the most-used tasks is the computerised Continuous Performance Task (CPT). This requires sustained and selective attention to a repetitive and unrewarding task in order to respond to an infrequently occurring target whilst inhibiting the response to non-targets. Omission and commission errors can then be recorded as measures of sustained attention and inhibition respectively (Gruber et al., 2011; Sullivan et al., 2007). Attentional skill generally improves with age but with great individual variability (Scerif, 2010; van de Weijer-Bergsma, Wijnroks, & Jongmans, 2008). Attention is one of the most widely researched topics in the field of cognitive psychology, yet relatively little research has explored its relationship with sleep in typically developing children.

Insufficient sleep is common among children and adolescents, owing to early school start times, increased homework, academic expectations and leisure opportunities outside school (Wolfson & Carskadon, 1998; Zhang, Li, Fok, & Wing, 2010). Sleep is often forfeited during the week and then

caught up at the weekends. Kim et al. (2011) surveyed 2638 Korean adolescents on their sleep habits to find that weekday sleep time was only 5:42 hours (±1:00) whilst weekend catch up sleep was 2:42 hours longer (± 1:42), compensating for the insufficient sleep during the week. Participants also completed a ten-minute visual CPT and a more complex divided attention task that involved tending to auditory and visual stimuli simultaneously. After controlling for potential confounders such as age and gender, results showed no relationship between amount of sleep and performance, but the need for increased weekend catch-up sleep was significantly associated with more omission errors on both tasks. This provides evidence of individual variability in the amount of sleep needed, where increased catch-up sleep can be used as an indicator of insufficient weekday sleep. In a sample of 35 healthy children without sleep problems aged 7 to 11 (M = 8.6 ± 1.12) Gruber et al. (2012) used actigraphy and home-PSG to monitor sleep, and children's teachers completed a questionnaire rating children's cognitive problems, hyperactivity, impulsivity and inattention. Using multiple regression analysis they found that shorter sleep duration significantly predicted teacher-reported cognitive problems and inattention, with 27% shared variance, but not hyperactivity or impulsivity. Children with shorter sleep duration were also reported to have more problems with learning, memory and organisation. The application of the findings to healthcare and sleep education would be beneficial to students, parents and teachers, since optimising sleep could have advantageous effects on attention and school performance. Conversely, a recent meta-analysis of 86 studies on 35,936 children found that sleep duration was not associated with sustained attention, rather, short sleep duration was related to deficits in higher order, complex cognitive processes such as executive functions, behaviour, and school performance (Astill, Van der Heijden, Van Ijzendoorn, & Van Someren, 2012). Why there should be a disparity in findings remains unclear, but could be due to methodological differences between studies and the types of attention tasks used.

Children who snore often display deficits in daytime behaviours such as impaired attention, learning, memory and school performance, lower IQ, and increased hyperactivity and problem behaviour. In 64 children aged 6 to 16 (mean 10.4 ± 3.0), snoring was found to be significantly predictive of lower IQ, poorer attention, impulsivity, less competent behaviour and more problem behaviour (Blunden, Lushington, Lorenzen, Martin, & Kennedy, 2005). Comparatively, behavioural sleep problems (BSP), which disrupt sleep architecture but are non-hypoxic, were associated with increased risk of attention and memory deficits along with problem behaviour. Children suffering from both snoring and BSP therefore had significantly greater detrimental effects than children with only one of these sleep problems. It is not clear why these different types of sleep disruption are associated with different effects on daytime functioning. Other studies report similar findings, with children who snore noted to have significant deficits in sustained and selective attention, with these problems

being specifically linked to oxygen desaturations and associated night wakings (Archbold, Giordani, Ruzicka, & Chervin, 2004; Kennedy et al., 2004). Sleep fragmentation secondary to bruxism has too been associated with parentally reported attentional problems in 5 to 15 year olds ($M = 9.2 \pm 3.2$) (Herrera et al., 2006). The experimental groups in these studies were all small, ranging from 9 to 13 participants, so the results should be interpreted with caution. Nevertheless, together they provide convincing evidence that sleep problems are associated with attentional deficits in children.

Fallone, Acebo, Arnedt, Seifer and Carskadon (2001) investigated the effects of experimental sleep extension and restriction on a group of 87 children aged 8 to 15 years. Following five nights of baseline recording by actigraphy, children spent a night in a sleep laboratory where their sleep was either optimised to ten hours, or restricted to only four hours. The following day, sleep deprived children were still able to maintain attention and inhibit incorrect responses on a nine-minute visual CPT, despite objective and subjective evidence of sleepiness as well as observer-ratings of sleepy behaviours and inattention. Attentional difficulties are also not seen following three consecutive nights of minor (*M* 41 minutes) sleep restriction (Sadeh et al., 2003). Together, findings suggest that acute sleep restriction is not sufficient to disrupt attention in otherwise well-rested children with intellectual abilities in the normal range. Attention problems must therefore arise from long-term sleep disturbance, such as nocturnal restlessness, SDB or chronic curtailment of sleep.

Perhaps the clearest indication of the effects of sleep on attention comes from studies of ADHD, a neurobehavioural disorder characterised by difficulties with inattention or hyperactivity/impulsivity or a combination of the two. It is one of the most prevalent psychiatric conditions, affecting around five per cent of children and causing significant impairment to the child's performance at school and socialisation (Gruber, 2009; Scahill & Schwab-Stone, 2000). Up to half of children and adolescents with ADHD also suffer from sleep problems, of which the main ones appear to be increased nocturnal movement and SDB. Konofal, Lecendreux, Bouvard and Mouren-Simeoni (2001) found that 30 children with ADHD showed increased number and duration of nocturnal movements compared to controls. In a review of the literature Cortese, Konofal, Yateman, Mouren and Lecendreux (2006) concluded that children with ADHD show more movement during sleep, more restless sleep, increased incidence of OSAS and greater daytime sleepiness than controls. Children with ADHD are also more likely to suffer sleep onset insomnia, bedtime refusal, increased night waking and difficulty getting up in the morning. It is not clear whether ADHD is a 24-hour disorder that causes increased movements during sleep, whether sleep disruption due to night-time movements influences the daytime symptoms of ADHD, or whether a third factor underlies both ADHD and nocturnal movements. Of all the studies reviewed, the authors found no evidence of

differences in sleep architecture in ADHD. More recently, in a home-PSG study of 15 children with ADHD and 23 healthy control children aged 7 to 11, Gruber et al. (2009) found that control children slept for over half an hour longer and had a greater amount and percentage of REM sleep than those with ADHD. This difference in sleep architecture could suggest an intrinsic sleep problem symptomatic of ADHD. The authors did not find evidence of any other sleep problems in the ADHD group, and their findings are incongruent with previous research as reviewed by Cortese et al. (2006), and with research by Kirov, Kinkelbur, Banaschewski and Rothenberger (2007) who found that children with ADHD actually showed an increase in REM sleep.

It is interesting that there seems to be a complex association between sleep problems and ADHD symptoms. This could be due to problems with the clinical diagnosis of ADHD, which is made through behavioural observation rather than genetic testing. In some children sleep problems can aggravate ADHD symptoms. Yet not all children with ADHD have sleep problems, and not all children with sleep problems have ADHD. Deficits often improve after adenotonsillectomy, but with some residual long-lasting effects that may reflect damage to the frontal lobes caused by prolonged apnoeic episodes and disruption to sleep architecture during the critical stages of neural development (Andreou & Agapitou, 2007; Blunden, Lushington, Lorenzen, Martin, & Kennedy, 2005; Gozal & Pope, 2001; Gozal, 2008).

1.4.3 Behaviour

Much evidence supports the notion that sleep and behaviour problems are related to one another. Ali et al. (1994) surveyed 507 parents when their children were 4 to 5 years old, and again two years later. Prevalence of snoring was around 12% at each time point, although around half of the cases spontaneously resolved over the two years, whilst new cases emerged. They confirmed a relationship between snoring and hyperactive behaviour, and in those children whose snoring resolved, behaviour also improved, suggesting a causal link.

In a large scale study of 635 children aged 6 to 8 years ($M = 7.00 \pm .42$), Smedje, Broman and Hetta (2001) also report a link between parentally reported sleep problems and behavioural difficulties. They used a questionnaire relating to children's sleep habits over the last six months, and the Strengths and Difficulties questionnaire (SDQ) which screens for behavioural problems in children and adolescents. The authors found many significant links between sleep characteristics and problem behaviour across all variables covered by the SDQ. For example, hyperactivity and conduct problems were related to increased tossing and turning in bed and bedtime resistance, whilst emotional symptoms were related to night terrors and difficulty falling asleep. Overall, 36% of

children with global reports of sleep problems also had significant behavioural problems. Their sample included around 5% of children who had significant health or learning difficulties, which could have adversely affected the sleep and/or behavioural data for this group. Nevertheless, the findings are supported by other researchers. Sadeh et al. (2002), for example, found greater evidence of parentally reported behavioural problems, in particular with thought disorders and delinquency, in children who were poor sleepers (low sleep efficiency and/or at least three night wakings lasting five minutes or longer). Blunden et al. (2005) also found that both snoring and BSP, in isolation and combined, were related to increased parentally-reported problem behaviours. Snoring was also predictive of impulsivity and less competent behaviour.

Calhoun et al. (2012) measured sleep using PSG in 508 children aged 6 to 12 years (M = 8.5). They report that excessive daytime sleepiness (EDS) but not night-time sleep quality or duration predicted parentally reported learning, attention, hyperactivity and conduct problems. The authors suggest that EDS in this group may be a manifestation of obesity, depression or asthma, rather than poor night-time sleep.

In a review of 17 articles published between 1966 and 2001 addressing the impact of SDB on neurocognition and/or behaviour, Ebert & Drake (2004) found that every study reported some association between SDB and either cognition deficits or behavioural problems, yet they criticise most studies for having inadequate sampling methods, not assessing confounding factors and/or using inappropriate methods or statistical techniques. Nevertheless, the link between SDB and problem behaviour is clear, paving the way for future studies to investigate this link with more stringent methodology.

Garetz and Arbor (2008) reviewed 25 articles published between 1950 and 2007 on the topic of adenotonsilectomy for SDB and behaviour, cognition or quality of life. Twelve of these evaluated behaviour change following surgery, finding that adenotonsilectomy led to better behaviour, less aggression and less hyperactivity; benefits which appear to be long-lasting. They note however that none of these studies were randomised and the efficacy of surgery for minority groups, such as different ethnicities and obese children, needs to be explored in more detail. In addition, it was not determined whether behaviour was related to sleep fragmentation or to oxygen desaturations associated with SDB.

1.4.4 Mood

One of the well-known daytime psychological consequences of sleep deprivation is the detrimental effect that it has on mood. In their survey of over 3,000 adolescents, Wolfson and Carskadon (1998)

found that higher levels of depressive mood were reported by students who slept for less than 6:45 hours than those sleeping more than 8:15 hours. This was true for both males and females. Female students with longer weekend bedtime delays also reported greater depressive mood than students with less fluctuation between weekday and weekend nights. Insufficient sleep has also been linked with extreme irritability, fussiness, low tolerance for frustration, inconsolable distress, depressed mood and loss of interest in daytime activities (Dahl, 1996).

Sleep problems in childhood may also be predictive of later anxiety disorders. Gregory et al. (2005) surveyed parents of 943 children aged 5, 7 and 9. When these children were questioned at ages 21 and 26, those who had experienced persistent sleep problems as children were 60% more likely to have developed anxiety disorders compared to individuals without sleep problems. Conversely, sleep problems in childhood did not predict adulthood depression.

In a review of the literature, Chorney, Detweiler, Morris and Kuhn (2008) found strong evidence for anxiety, stress, depression and panic in children who had sleep disturbance. They note, however, that most studies were questionnaire-based and methods for determining sleep or psychological disturbance were not always validated or fully described. In addition, different criteria and cut-off scores are used for distinguishing good sleepers from poor sleepers, and children with psychological disturbance from those without.

The main issue with these studies is that they cannot determine causality, as sleep problems and sleep loss can be both a cause and a symptom of depression and other mood disturbances. However, treatment of sleep problems often leads to improvements in mood, suggesting a causal link (Dahl, 1996).

1.4.5 School performance

The evidence described previously shows that a range of sleep problems can be associated with impairment of executive tasks such as planning, inhibition and working memory. These play a central role in school preparedness and have also been linked with classroom behaviour problems and poorer achievement. Arcia, Ornstein, and Otto (1991) found that in 88 children aged 7 to 10 years, performance on digit span and a symbol-digit substitution test was predictive of reading and mathematical ability. Reading ability was also predicted by performance on a simple RT task. If small alterations in sleep habits can have such a positive effect on children's executive functioning (Sadeh et al., 2003), then this could in turn benefit their reading and mathematical abilities and school performance in general. Parents and professionals should be aware of the potential benefits of sleep extension.

Wolfson and Carskadon (1998) surveyed 3,120 adolescents on their sleep habits and found that in general, students with higher grades reported longer, more regular sleep and earlier bedtimes on school nights than their peers with poorer grades. Students scoring A and B grades also reported slightly less weekend fluctuation from their normal sleep pattern than students scoring <Cs (1.8 hour bedtime delay compared to 2.3 hour delay, $p<.001$ but low effect size).

In a meta-analysis of 50 studies with over 36,000 participants, Dewald, Meijer, Oort, Kerkhof, and Bögels (2010) examined the effects of sleep quality, sleep duration and daytime sleepiness on school performance in healthy typically developing children and adolescents. In general, daytime sleepiness increased with age during puberty, and some studies showed greater daytime sleepiness in girls than in boys. After controlling for these age and gender differences, all sleep variables were significantly but modestly associated with school performance. The strongest relationship was for daytime sleepiness ($r = -.13$), followed by sleep quality ($r = .10$) and sleep duration ($r = 0.07$). These variables were not related to one another and relationships were stronger in younger children suggesting their greater vulnerability to the effects of sleep problems. This means that sleep problems in early childhood could significantly hinder later life chances due to early low achievement at school. Subjective rather than objective measures of sleepiness also showed a stronger correlation with school performance, possibly due to individual differences in amount of sleep needed.

In contrast, Eliasson, Eliasson, King, Gould and Eliasson (2002) found no relationship between self-reported sleep quality or duration and school grades in 1,200 U.S. middle and high school students. Rather, school grades were better predicted by the amount of time spent on homework.

1.4.6 Speech and language

Andreou and Agapitou (2007) examined the effects of snoring in 20 snoring adolescents compared with 20 controls (M age = 18.41 ± 0.37) of equal socioeconomic status. All adolescents from the snoring group had apnoeic episodes and oxygen desaturations defined as abnormal, assessed by PSG. Poorer performance on phonemic and semantic verbal fluency as well as marks in Greek language tests at school correlated strongly and significantly with lower oxygen saturation, more apnoeic episodes, and snoring. The study lends weight to the argument that OSAS compromises daytime functioning. The authors suggest that prolonged apnoeic episodes and disruption to sleep architecture suffered during the critical growth stages of childhood and adolescence can severely affect the frontal lobes, causing an information processing deficit which can have long-lasting detrimental effects on verbal abilities and language. Treatment of sleep problems at an early age

could therefore have beneficial effects on language ability in adolescence (see Gozal, 2008 for a review).

In contrast, Archbold et al. (2004) assessed verbal reasoning and reading ability in 12 children aged 8 to 11.9 years (M = 9.0 ± .85) who had mild SDB. Children's performance was comparable to normative data, suggesting that mild SDB does not affect language ability. It may be that impairments are related to more severe sleep disruption than that covered in this study.

1.4.7 Physiological functions of sleep

In addition to the cognitive effects described above, sleep is vital for good health, having wide-ranging effects on functions such as tissue and muscular growth and repair, metabolism and immune function. In some areas it has been necessary to focus on adults as little research in children exists.

A number of hormones are modulated by sleep, including growth hormone (GH), which assists in the growth and repair of tissues and muscles. GH is released at the onset of SWS and sleep deprivation inhibits its secretion (Davidson, Moldofsky, & Lue, 1991; Redwine, Hauger, Gillin, & Irwin, 2000). A deficiency of GH in childhood may result in growth failure and short stature as well as a delayed pubertal development. Subcutaneous or intramuscular injections of GH have been found to significantly increase the rate of burn healing in children, reducing the length of hospital stays by 25% (Gilpin, Barrow, Rutan, Broemeling, & Herndon, 1994). Maximising GH secretion through adequate sleep could therefore have significant health benefits.

In both adults and children, OSAS has been associated with increased levels of C-reactive protein (CRP), a marker of inflammation that can promote cardiovascular system problems. In 81 children aged 3 to 18 years, increased plasma CRP was associated with both hypoxia and arousals related to sleep-disordered breathing (Tauman, Ivanenko, O'Brien, & Gozal, 2004). OSAS also causes intermittent elevation and dysregulation of blood pressure, which could put sufferers at risk of cardiovascular disease and organ damage later in life (Amin et al., 2004)

Shorter sleep duration has been linked with reduced leptin (an appetite suppressing hormone) and elevated ghrelin (an appetite stimulating peptide), which centrally control appetite and energy expenditure. This leads to increased levels of subjective hunger and appetite, especially for carbohydrate-rich foods. Chronic sleep loss could therefore lead to an increased likelihood of obesity, which is in turn a risk factor for OSAS (Spiegel, Tasali, Penev, & Van Cauter, 2004; Van Cauter, Spiegel, Tasali, & Leproult, 2008). This risk is seen even in early infancy where positive correlations have been found between short sleep duration and infant body size (weight to length ratio), even after controlling for possible confounding factors such as socioeconomic status, birth

weight, age at gestation and breast feeding (Tikotzky et al., 2010). Short sleep duration in childhood has also been associated with a greater chance of obesity. For example, Lumeng et al. (2007) assessed sleep and behaviour through parent report in 785 U.S. school children at ages 9 and 12. After controlling for race, gender, maternal education and numerous other covariates, they found that short sleep duration at both ages was associated with increased chance of being overweight at age 12, independent of weight at age 9. A meta-analysis of 17 observational studies indicated that children with shorter sleep duration were 58% more likely to be overweight or obese than children with longer sleep duration (Chen, Beydoun, & Wang, 2008). This relationship appears to begin in early childhood (Bayer, Rosario, Wabitsch, & Von Kries, 2009; Hiscock, Scalzo, Canterford, & Wake, 2011) and continues into young adulthood before diminishing in later adulthood and old age (Gottlieb et al., 2005; Hasler et al., 2004).

Weight gain associated with sleep duration can also be a precursor to development of type II diabetes (Ayas et al., 2003). In addition reduction of SWS slows the insulin response to glucose and impairs glucose and carbohydrate tolerance which can lead to type II diabetes (Spiegel, Leproult, & Van Cauter, 1999; Van Cauter et al., 2007).

Sleep is essential for regulating immune parameters and maintaining good health. Sleep deprivation leads to an alteration in the body's immune response, including an increase in circulating white blood cells which are normally only produced to defend the body in response to an infection or foreign material (Ruiz et al., 2012). In addition, in adults sleep loss leads to increased concentrations of the stress hormone cortisol in the late afternoon and early evening, a time when it would normally be declining to minimum levels (Spiegel, Leproult, & Van Cauter, 1999). Even just one night of sleep restriction is sufficient to create an increase in evening cortisol the following evening (Leproult, Copinschi, Buxton, & Van Cauter, 1997). This could have detrimental effects on health as cortisol plays a role in suppressing the immune system. It also counteracts insulin and raises blood pressure, so long-term exposure is a risk factor for type II diabetes, obesity and cardiovascular illness.

Serious cases of sleep deprivation are fatal. In a series of experiments, Rechtschaffen and colleagues showed that total sleep deprivation or REM deprivation in rats would certainly lead to death, usually within one month, but with no attributed anatomical cause (Everson, Bergman, & Rechtschaffen, 1989; Kushida, Bergmann, & Rechtschaffen, 1989; Rechtschaffen, Gilliland, Bergmann, & Winter, 1983). In humans, sleep duration is also associated with mortality. Two large scale longitudinal studies found that adults sleeping less than five hours per night were at 15% increased risk of mortality compared with those sleeping seven hours (Kripke et al., 2002; Patel et al., 2004). These

studies also reported risk of mortality to increase by 15% and 42% respectively for individuals sleeping longer than nine hours. The mechanism for the association between long sleep duration and mortality remains unclear and could not be explained by controlling for possible confounding factors such as age, smoking, obesity and history of cancer or cardiovascular disease (Patel et al., 2004). Possibly some other associated factor is to blame, such as low socioeconomic status and depression are associated with increased mortality as well as long sleep duration (Patel, Malhotra, Gottlieb, White, & Hu, 2006; Winkleby & Cubbin, 2003).

As in rats, total sleep deprivation in humans is fatal. Individuals suffering from fatal familial insomnia initially present with a difficulty initiating sleep, followed by a total lack of sleep within a few months. Patients also suffer from extreme body wasting, infections, and kidney and autonomic dysfunctions. The disorder is always fatal, usually within 7 to 13 months after the onset of symptoms (American Academy of Sleep Medicine, 2001). No human is known to have died of intentional sleep deprivation. The world record for the longest time kept awake without using stimulants of any kind was held by Randy Gardner, a 17-year-old college student who stayed awake for 264 hours (eleven days). Although in the final days of the study Randy was still able to function, he suffered serious cognitive and behavioural changes, including loss of concentration and short-term memory, moodiness, short temper, paranoia, hallucinations and delusions (Gulevich, Dement, & Johnson, 1966). News reports suggest that this record has since been beaten several times, and that the record currently stands at 449 hours (18 days and 17 hours) (The National Sleep Research Project, 1998). However, Gardner's effort was closely monitored by researchers, so remains the most documented case. Moreover, close monitoring ensured there were no microsleeps, which could not be ruled out in later attempts.

1.5 Sleep-Dependent Memory Consolidation

In addition to its influence on daytime behaviour and health, sleep is now also known to be an active state promoting certain types of memory consolidation. Newly acquired memory traces are unstable and susceptible to interference, requiring strengthening in order to be integrated into long term memory and be accessible for future retrieval (Walker & Stickgold, 2006). Evidence suggests that this consolidating process occurs preferentially during sleep as opposed to wake, through a phenomenon known as sleep-dependent learning. This may occur by strengthening connections through reactivation of neural pathways during sleep (Maquet et al., 2000; O'Neill, Pleydell-Bouverie, Dupret, & Csicsvari, 2010; Peigneux et al., 2003). This leads to improved performance following a retention interval of sleep, even without further physical practice (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002; Wilhelm, Diekelmann, & Born, 2008).

In order to assess the effects of sleep on learning, the common procedure is to train participants on the task and test them after equal-length retention intervals of wake and sleep. For example, participants may be trained in the evening before bed and be tested the next morning following sleep, and again that evening after an equal amount of time spent awake. This is the Sleep-wake group. Ideally, in order to control for circadian time-of-day effects (Schmidt, Collette, Cajochen, & Peigneux, 2007), a counterbalanced Wake-sleep group will begin training in the morning and be tested that evening and again the next morning. This means that the improvement in performance can be measured following intervals of both wake and sleep, and due to the repeated testing each participant acts as his/her own control. Other procedures have been used to investigate more precisely the effects of sleep on learning, for example by selective disruption; awakening the participant each time they enter a particular sleep stage to assess the contribution of this stage to memory consolidation (e.g., Karni, Tanne, Rubenstein, & Askenasy, 1994). If selective disruption of a certain stage interferes with learning on a task then it is assumed that this stage is necessary for the consolidation of that task. A problem here is that continuous awakenings lead to extremely fragmented sleep, which in itself could disrupt learning. Participants tend to have a propensity to return to the sleep stage that they were awakened from, leading to increased awakenings as the night progresses. To overcome this problem, other researchers have trained participants on a task before sleep, then awakened and tested them after just three or four hours of sleep and again following another three or four hours. This enables a comparison to be made in performance following early sleep which is rich in SWS, compared to late sleep rich in REM (Plihal & Born, 1997).

Broadly, two types of memory can be defined: declarative and non-declarative or procedural memories. Declarative memory is that which can be explicitly recalled such as semantic knowledge for general facts, vocabulary, places, etc, or episodic memories referring to personal experience. Procedural memory is the implicit knowledge of skills. It involves both cognitive and motor processes but is often below the level of conscious awareness and cannot easily be verbalised, for example, how to ride a bike, or how to read. Procedural skills are learnt through repeated practice until they become automatic, without the need for conscious control or attention and can be measured by gains in speed and/or accuracy on a skill-based task. Both declarative and procedural memories have been found to be sleep-dependent in some cases. As the majority of research focuses on adults, these will be discussed in relation to adults and children.

1.5.1 Sleep-dependent declarative memory consolidation

To test sleep-dependent consolidation of declarative memory, a word pairs task is commonly used in which participants are presented with a set of paired words to learn and must subsequently recall

the second word of each pair when prompted with the first. Tasks differ in the number of pairs to be learnt and the association between the words, with some using associated words (e.g., dog – bone) and others using unrelated words (e.g., dog – kettle). In a sample of 20 healthy men, Plihal and Born (1997) found that recall for associated word pairs significantly improved following a full night of sleep but not following a corresponding period of wakefulness. The experimenters also awakened and tested participants after three hours of sleep and again three hours later. They found a 5.7 word improvement following early sleep compared with a further 2 word improvement following late sleep, suggesting that declarative memory is more dependent upon mechanisms active during SWS. Declarative memory relies on the hippocampus which reactivates wake experiences during subsequent sleep, allowing new memories to be transferred to neocortical regions (Dang-Vu et al., 2010). These consolidation mechanisms may replay most efficiently during SWS when there is little other interfering background electrical activity in the brain and low levels of acetylcholine in the hippocampus, a neurotransmitter known to be involved in memory (Gais & Born, 2004).

Learning of novel words, too, has been found to be dependent on sleep. Gaskell and colleagues (Davis, Di Betta, Macdonald, & Gaskell, 2009; Gaskell & Dumay, 2003; Henderson, Weighall, Brown, & Gaskell, 2012) used a lexical competition task, training participants on novel spoken words that overlap with familiar words, for example *cathedruke* competes with *cathedral*. This has the effect of slowing recognition of the familiar words, which emerges only after a period of sleep, suggesting that novel words are consolidated overnight. Functional magnetic resonance imaging (fMRI) in 16 right-handed native English speakers aged 18 to 40 revealed differential neural responses to novel words learnt on the previous day and those learnt on the same day, consistent with overnight consolidation of these words and resulting in a more word-like neural response (Davis et al., 2009). The authors advocate the initial involvement of the hippocampus in learning novel words. Reactivation of new memories in the hippocampus during SWS allows transference of memory representations to neocortical networks for long term storage and hippocampal independence (Born & Wilhelm, 2012; Marshall & Born, 2007).

In contrast, De Koninck, Lorrain, Christ, Proulx and Coulombe (1989) used a small sample of 10 students taking an intensive six-week foreign language learning course to find that language learning efficiency significantly correlated with an increase in the percentage of REM sleep from baseline. This was possibly due to increased demands on REM-dependent consolidation such as learning grammar patterns and word meanings, which were not used in Gaskell et al.'s studies. Greater learning was also positively correlated with dream content, with more verbal communication and foreign language incorporations in dreams (De Koninck, Christ, Hébert, & Rinfret, 1990). Fogel, Smith

and Cote (2007) also found a significant increase in theta power in central brain regions during REM sleep following learning on a word associate task, but found no evidence of differences in sleep architecture.

It has been questioned whether sleep actively promotes consolidation of new declarative memories, or whether it transiently protects information from interference from other sources that would occur during waking (Ellenbogen, Payne, & Stickgold, 2006). To test this hypothesis, Ellenbogen, Hulbert, Jiang and Stickgold (2009) employed a robust behavioural method that investigated the protecting properties of sleep to interference on a word pairs task. Young adult participants ($N = 45$) learnt a list of 60 unrelated word pairs prior to a retention interval of wake or sleep. On retesting 12 hours later, participants who had slept performed significantly better than those who had not. More interestingly, participants then studied an interfering word list, where the original cue words were paired with novel word associates, and were tested for both the original and novel pair. Participants who had not slept showed significantly greater interference, only being able to recall 44% of the original word pairs, compared to 71% in the group who had slept. The authors conclude that sleep is an active process that strengthens the memory trace and protects it from interference.

Research into sleep-dependent memory consolidation in adults seems to yield fairly consistent findings that sleep is essential for enhanced declarative learning and memory. But what about children? Children have a longer total sleep time than adults and differences in sleep architecture, with particularly high amounts of SWS which may be important for declarative memory consolidation. Research has only recently begun to investigate sleep-dependent memory consolidation in children, bringing to light some key developmental differences.

One of the first of these experiments was carried out by Backhaus, Hoeckesfeld, Born, Hohagen and Junghanns (2008). Twenty-seven children aged 9 to 12 years were presented with 40 word pairs of concrete nouns displayed on screen and were trained until they could orally recall at least 20 pairs (50%) correctly. As with adults, children's retention of word pairs across a retention interval of sleep was better than retention over an equivalent period of wake, regardless of whether initial training took place in the morning or evening. This increase in recalled word pairs could not simply be due to new learning during the first retest, as no feedback was given during the retests. This points to an active role of sleep in declarative memory consolidation. PSG showed that retention of word pairs across sleep correlated positively with the percentage of total NREM sleep, but not with individual stages, and negatively with the percentage of REM sleep. This is in line with Plihal and Born's (1997) research in adults that found that declarative memory improved following SWS. The results highlight the importance of NREM sleep for declarative memory consolidation in children. Similarly, Potkin

and Bunney (2012) trained 40 young adolescents on ten associated word pairs either in the evening or the morning. When tested 12 hours later, those who had slept during the intervening period remembered 20.6% more words than those who had not slept, a significant difference. This study compared a Sleep group to a Wake group, rather than creating counterbalanced Sleep-wake and Wake-sleep groups to control for circadian effects. Instead, participants also completed a working memory task to ensure that performance was equal between groups and between evening and morning testing sessions and therefore comparable. Wilhelm, Diekelmann, and Born (2008) also found beneficial effects of sleep on retention for two declarative tasks (word pairs and 2D object location) in both children and adults.

A recent study by Gaskell's group used the lexical competition task with 53 children aged 7 to 12 years (Henderson et al., 2012). Children learnt 32 novel spoken words that overlapped highly familiar words, e.g., *biscal* (biscuit). After sleep, children's recognition memory of the novel words significantly improved. In addition, similarly to adults, lexical competition between novel and existing words increased and was still evident one week later. Children also completed a 2D object location task based on that used by Wilhelm et al. (2008) where they learnt the positions of ten picture-card pairs on a computerised four by five matrix. Although children's memory for the locations did not improve following sleep, their performance did not decline, as it did over the daytime period, so suggesting a protective role of sleep, rather than an active consolidation process. The disparity here between the active process of consolidating novel words and the protective role in the object location task suggests that different learning mechanisms are involved.

Sleep research has also been applied to emotional recognition. Prehn-Kristensen et al. (2009) investigated emotional declarative memory consolidation in children. Participants were 20 boys to control for gender-dependent emotional effects (*M* age = 11.6 years ± .82). Participants rated a set of 120 emotional and neutral images for their degree of arousal and were then given a recognition memory test which included the 120 previously seen pictures interspersed with 60 novel images. Recognition was better for emotional images than for neutral images, and was greatly enhanced by sleep, especially recognition of emotional images. Sleep-dependent improvement on neutral image recognition was non-significant, possibly due to insufficient number of participants.

Based on knowledge that sleep is necessary for strengthening memory traces, Voderholzer et al. (2011) studied the effects of different extents of sleep restriction over four consecutive nights on memory consolidation in 88 healthy 14 to 16 year olds (*M* = 15.0 ± .9). Participants were trained on two tasks: a declarative word pairs task, and a procedural mirror tracing task where they traced line drawings whilst only having visual feedback via a mirror. After one adaptation night of nine hours'

sleep in the laboratory, participants' time in bed was constrained to 5, 6, 7, 8, or 9 hours for the following four nights. They were tested on the tasks after two nights' recovery sleep, and again one month later. Results showed no stepwise association between sleep restriction and performance on either task, with all groups showing similarly high levels of memory consolidation. PSG showed that SWS was relatively well preserved in all groups, whilst REM sleep declined as sleep deprivation mounted, suggesting that adolescents have a high resilience to acute sleep loss. These findings replicate those of Kopasz et al. (2010) who trained 22 healthy 14 to 16 year olds on a word pairs task, before curtailing their sleep to only four hours, followed by a recovery night of nine hours' sleep. Post-recovery, participants' performance on the recall test correlated positively with the percentage of NREM sleep on the recovery night, and did not seem to be decremented by the sleep deprivation. Again, this suggests that adolescents are able to cope with acute sleep restriction and that the relative preservation of SWS is sufficient for declarative memory consolidation.

Perhaps these findings can be explained by the notion that even a short post-training nap is sufficient to increase memory consolidation. Lahl, Wispel, Willigens and Pietrowsky (2008) presented 26 students aged 20 to 29 years (M = 24.8) with a list of 30 adjectives and allowed them two minutes to memorise as many as possible. All participants took part in a nap and a wake condition, each one week apart, with different words each time. After learning the words they either napped whilst being monitored with EEG, or remained awake for 50 minutes. Average nap time was 25.5 minutes (±10.5). In a free recall test participants remembered significantly more words after napping (8.08 ± 2.58) than they did in the wake condition (6.48 ± 2.93). Recall was not associated with total nap time, sleep onset latency, or time spent in SWS. A second group of 14 students (M age = 23.7) took part in the no nap and the nap conditions and a third short nap condition where they napped for an average of 6.3 minutes (± 1.7). Students recalled 6.86 words (± 2.68) in the wake condition, 8.07 (± 3.71) after a short nap, and 9.21 (± 2.69) after a long nap, showing a stepwise increase in recall between the three conditions. ANOVA analysis revealed that all three results were significantly different from one another. The study shows that even a short six-minute nap is enough to promote memory consolidation.

It is clear from extensive research in adults and from the small amount in children, that consolidation of declarative memory is dependent upon sleep, with improvements in recall following sleep compared to wake. Which stage of sleep this depends on remains unclear, although most evidence points to a role of SWS, when reactivation of new memories in the hippocampus allows for transference into neocortical structures. It is probable that learning is dependent on the precise

nature of the task, for example its emotional salience, and that different types of learning involve different mechanisms active during sleep.

1.5.2 Sleep-dependent procedural memory consolidation

Alongside the studies on declarative memory, a considerable body of research has focused on sleep-dependent procedural memory. In adults, evidence fairly consistently finds that a wide variety of functional domains rely on sleep, including visual, auditory and motor systems with tasks such as texture discrimination (Karni et al., 1994), pursuit rotor (Smith & MacNeill, 1994), speech perception (Eisner & McQueen, 2006), mirror tracing (Plihal & Born, 1997), and triggering insight into a hidden rule (Wagner, Gais, Haider, Verleger, & Born, 2004), to name but a few. Sleep-dependent learning is particularly evident in motor skill learning in adults. Karni et al. (1995) developed a sequential finger-to-thumb opposition task where participants were requested to touch each finger of the non-dominant hand to their thumb in the order 4-1-3-2-4, where 1 was the index finger and 4 was the little finger. Participants were marked for speed and accuracy and were reliably found to improve over time. A number of researchers have used this task to assess the impact of sleep on motor memory consolidation. Walker et al. (2002) trained 62 adult participants either in the morning or the evening on a computerised finger tapping version of the task. They found that retesting after a period of wake produced a non-significant improvement of 3.9%, which was no greater than could be predicted by repeated practice. However, following a night of sleep, participants showed an improvement in speed of 18.9% with no loss of accuracy. This enhancement following sleep is well documented and occurs regardless of whether initial training takes place in the morning or evening (Fischer, Hallschmid, Elsner, & Born, 2002; Korman et al., 2007). Fischer et al. (2002) also showed that sleep on the first night post-training is essential for consolidation and that improvement on the finger tapping task significantly correlated with time spent in REM sleep (r = .61, P<.004) in 20 young adult participants. In addition, consolidation was specific to the trained sequence and could not be generalised to other similar sequences.

It is suggested that consolidation of motor memories requires plastic changes in the primary motor cortex (M1) which may occur through reactivation of neural circuits involved in recent learning, promoting brain plasticity and increased consolidation. PET imaging studies show that this reactivation is most pronounced during post-training REM sleep and applies to the acquisition of basic visuo-motor skills (Maquet et al., 2000) as well as implicit learning of a probabilistic sequence (Peigneux et al., 2003). Consolidation may also occur through cholinergic activity in the neocortex. During REM sleep, cholinergic neurons in the basal forebrain fire to the cortex, hippocampus and amygdala at a high rate similar to the wake state. Acetylcholine has long been known to enhance

attention, learning and memory consolidation and facilitate experience-dependent plasticity in the brain by enhancing the amplitude of synaptic potentials and promoting long term potentiation (Hasselmo & McGaughy, 2004; Warburton et al., 2003).

Support for this theory comes from studies that have found an association between procedural memory consolidation and REM sleep. For example, Plihal & Born (1997) found that performance on a mirror tracing task improved following a full night of sleep, and was especially pronounced following sleep during the second half of the night, rich in REM, compared to the first half, rich in SWS. In addition, selective deprivation of REM can disrupt improvements usually seen following sleep on a basic texture discrimination task (Karni et al., 1994) and the Tower of Hanoi task, a cognitive procedural learning task which tests participants' planning ability (Smith, 1995). It also appears that there are learning-related changes to sleep architecture. For instance, Fogel et al. (2007) found that following learning on the mirror tracing task, REM density increased from baseline in eight out of nine participants. This functional change in sleep architecture may be responsible for the improvement in performance. Smith, Nixon and Nader (2004) had similar results. They trained 18 healthy adults on the mirror tracing and Tower of Hanoi task and monitored sleep using PSG. The number of REMs (not REM periods) and REM density increased on the post-learning night, whereas time spent in REM and % of REM did not change from baseline. They also found that the 6 individuals with the highest IQ, and therefore assumed to have the greatest learning potential, showed the greatest increase in REMs and REM density from baseline, which correlated significantly with improvement on the task. This suggests a strong, possibly two-way, relationship between intelligence and sleep architecture. As previously discussed, differences in REM sleep have been found in children with ADHD. It would be interesting to know whether these differences bore any relation to intelligence.

Sleep can also protect procedural memory from interference. In a finger tapping study with 67 young adults, a 90-minute post-training nap led to improved performance and protected the original memory trace from an interfering sequence that was introduced later (Korman et al., 2007). Cajochen et al. (2004) have also investigated the benefit of naps on learning using the serial reaction time task (SRTT). The task requires the participant to respond as quickly as possible to the spatial location of a pseudo-random sequence. The sequence does, in fact, follow a repetitive pattern so implicit learning can be gauged by faster RTs to sequenced compared to random trials. Sixteen adults aged 20 to 31 (M = 25.1 ± 3.4) participated in two counterbalanced conditions, each two to four weeks apart. In one condition participants were sleep deprived for 40 hours, in the other they spent the same period alternating between 150 minutes of wakefulness and 75-minute naps. Before

each nap, or at the equivalent time in the sleep deprivation condition, they were trained on a new sequence and tested post-nap. Although performance on the task remained constant in the sleep deprivation condition, improvement in RTs for each sequence only occurred when participants napped during the retention interval. EEG recordings also showed that improved performance correlated with increased REM sleep in some of the naps, supporting the hypothesis that procedural memory consolidation occurs during REM. In addition, Mednick, Nakayama and Stickgold, (2003) studied the effects of a 60 or 90-minute afternoon nap on a visual discrimination task. Participants who had a 60 minute nap which contained SWS but no REM showed no improvement on the task, whereas those who had a 90-minute nap with both SWS and REM performed significantly better on the task post-nap. This improvement was comparable to that seen after a full night of sleep, leading the authors to conclude that a nap containing both SWS and REM is as good as a night's sleep. This also helps to explain the findings of Voderholzer et al. (2011) who found that when adolescents' sleep was curtailed to five hours, REM sleep dropped to a minimum, yet performance on the mirror tracing task still improved. These participants did, however, still obtain some REM sleep and were allowed two nights of recovery sleep supporting the notion that short sleep duration is indeed sufficient to strengthen learning on the task.

The evidence so far seems to point to a clear role of REM sleep in procedural memory consolidation. In contrast, Walker et al. (2002) found that overnight improvement on the finger tapping task correlated strongly and significantly with the percentage of stage II sleep, especially during the final quarter of the night (the first three quarters alone were not significant). This explained 52% of inter-subject variance. Stage II has also been implicated in procedural memory consolidation since sleep spindles, a characteristic of stage II sleep, have been found to be strongly correlated with intelligence and increase by over 40% following training on both procedural (Fogel & Smith, 2006; Fogel, Jacob, & Smith, 2001) and declarative memory tasks (Schabus et al., 2004). Gais, Plihal, Wagner and Born (2000) describe a complex interplay between sleep stages. Performance on a visual discrimination task improved following early SWS-rich sleep, improved still further following late REM-rich sleep, yet did not improve after late sleep alone. They suggest a two-step consolidation process, whereby early night SWS is necessary for initiating memory consolidation, which is then promoted by late night REM-rich sleep. The product of these two sleep parameters can explain over 80% of inter-subject variance. The pursuit rotor task has also been found to be more dependent on stage II sleep than on REM. Gais et al. (2000) explain this by suggesting that REM becomes increasingly necessary for procedural memory consolidation as task difficulty progresses. For example, cognitively demanding tasks such as mirror tracing and Tower of Hanoi are more heavily dependent on REM than simple tasks, such as visual discrimination and rotor pursuit, where

processing is thought to take place at pre-attentive levels. It may be the case that REM is important for learning new skills, whereas stage II is necessary for the reinforcement of existing skills.

It is clear that in adults procedural memory traces are preferentially consolidated during sleep compared to wake. The scant research in children suggests that in contrast to adults, children do not always show a sleep-dependent improvement on procedural tasks.

Prehn-Kristensen et al. (2009) used a mirror tracing task to assess sleep-dependent learning in 20 healthy boys aged 10 to 13 years. Following sleep, participants performed better on the task due to practice effects, but this was not sleep dependent. The authors propose that during childhood, procedural learning tasks have to compete with overall learning for offline consolidation and so do not improve following sleep. In line with adult studies, they did observe improvement on the hippocampus-dependent emotional recognition task. Similarly, Fischer, Wilhelm and Born (2007) and Henderson et al. (2012) have found that in contrast to adults, children do not show a sleep-dependent improvement on the SRTT. In fact, Fischer et al. (2007) found that children's performance actually deteriorated following sleep but remained unchanged over a daytime retention interval; the direct opposite of the pattern observed in adults. Wilhelm et al. (2008) also did not find evidence in children of sleep-dependent learning on a finger tapping task for learning a motor sequence which, in adults, consistently improves following sleep (Fischer et al., 2002; Walker et al., 2002). Conversely, they found that children's accuracy on the task significantly improved after a period of wake. Our group however did find a significant sleep-dependent improvement on the finger tapping task in 15 children aged 6 to 12 years (Annaz & Ashworth, 2011; Dimitriou, Hill, Ashworth, & Karmiloff-Smith, 2013). Dorfberger, Adi-Japha and Karni (2007) used the original finger-to-thumb opposition task in children aged 9 (N = 21), 12 (N = 21) and 17 (N = 20). Participants were trained on a sequence then trained on a conflicting sequence two hours later. When tested for the first sequence only the 17 year olds showed interference, whilst the younger groups showed a significant gain in performance. This supports the findings of Wilhelm et al. (2008), together suggesting that consolidation of procedural memories in children occurs during the wake state. Some shifting process must therefore occur during puberty. This may reflect an important developmental change in sleep architecture where children's greater amount of SWS might selectively consolidate hippocampus-dependent, explicit, declarative information, thereby interfering with implicit learning.

Conversely, Wilhelm, Metzkow-Mészàros, Knapp and Born (2012) argue that implicit sleep-dependent learning requires a certain level of pre-existing knowledge that children do not have. They used a modified motor sequence learning task with large buttons and found a sleep-dependent improvement only in young children (aged 4 to 6 years) who had been previously trained to an

intermediate level of performance. Low-performing children did not significantly improve on the task following sleep. The authors suggest that the pre-sleep skill level has an impact on newly-learned information which must be combined with an already-stored representation of the task in order for implicit learning to occur. As children have much lower resources of pre-existing knowledge compared to adults then the opportunity for implicit learning is also lower and offline learning prioritises explicit aspects of the task. This is in line with the work of Smith et al. (2004) who found that in adults the most able individuals (i.e., those with the highest IQ) showed the most sleep-related improvement on the mirror tracing and Tower of Hanoi tasks, seemingly because they had greater pre-existing knowledge on which to anchor their new learning.

Since the majority of procedural tasks rely on implicit learning, the development of internal representations and prior knowledge could help to explain the disparity in performance between adults and children for procedural sleep-dependent learning (see also Wilhelm, Prehn-Kristensen, & Born, 2012 for a review). In addition, this new research suggests that the simple declarative-procedural dichotomy is no longer sufficient and that the explicit-implicit aspect needs to also be considered when researching sleep-dependent learning in children.

1.6 Measurements of Sleep

The final section of this chapter describes some of the methods used to measure sleep quality and duration that can be implemented in a research or clinical setting in order to better understand sleep and sleep problems. A number of measures exist, ranging from full overnight studies in a sleep laboratory to simple questionnaires.

1.6.1 Polysomnography

PSG is a detailed, overnight assessment monitoring numerous body functions, including neural, cardiac and muscular activation, eye movements and respiration during sleep. Due to its comprehensive range of measures, it is seen as the gold standard for measuring sleep and is required for the diagnosis of sleep disorders particularly where sleep architecture needs to be quantified. Although PSG can be carried out at home, it generally involves the participant having to spend one or two nights in a sleep laboratory with electrodes attached to the head and body. Consequently, a PSG study is intrusive, expensive, time-consuming and labour-intensive to run. Additionally, it may not always be the most appropriate method for measuring sleep, for example, in children with developmental disorders who do not understand the necessity for the study, become distressed at sleeping in a strange environment, or who are very tactile sensitive (as in WS) and

cannot sleep with electrodes attached to them. A number of alternatives exist to monitor sleep in the home environment.

1.6.2 Video recording

One alternative to PSG is home video recording, which can be used to provide rich qualitative information on sleep. Participants sleep in their own bed so this method is far less distressing than PSG. Morielli, Ladan, Ducharme and Brouillette (1996) compared the reliability of video recording to PSG. Overnight video recordings were taken for 20 children aged 2 to 12 (M = 5.6 ± 3.1) and were analysed by trained technicians in 30-second epochs. Recordings showed excellent predictive value of sleep/wake, being 95% accurate in determining sleep epochs and 80% accurate for wake epochs, compared with PSG. Video has also been used successfully to diagnose OSAS in children. In a sample of 58 children aged 2 to 6 (median = 4.3) who snored, home video recording was correct in 84% of cases for diagnosing OSAS (Sivan, Kornecki, & Schonfeld, 1996). Although simple and highly economical, in order to be practical some data reduction is required as studying a night of video recording of eight to ten hours is impractically time consuming. Sivan et al. (1996) found that studying just 30-minutes was an adequate alternative to PSG for diagnosing OSAS in children, when parents were requested to record periods of snoring, laboured breathing or when they considered that their child had a breathing problem. Their assessments showed high sensitivity with a relatively low false-negative rate (child rated as normal on video but PSG shows OSAS). However, as video cannot be used to distinguish sleep stages, Sivan et al. (1996) could not be sure that the selected 30-minute segments contained REM sleep, the stage most likely to be associated with OSAS in children. The authors conclude that home video recording can be used as a reliable screening tool but should not replace PSG.

1.6.3 Actigraphy

Activity monitors such as the actiwatch (a wristwatch-like device) can be worn to continuously assess activity levels in a naturalistic setting over an extended period of time. The data collected by actigraphy are transferred to computer, where an algorithm is used to automatically score each epoch (usually one minute intervals) as sleep or wake. Similarly to videoing, actigraphy cannot be used to distinguish sleep stages. Actigraphy has been shown to be a valid and reliable method for assessing sleep quality and duration, being more than 80% in agreement with PSG for non-disorder groups (Littner et al., 2003; Sadeh, Hauri, Kripke, & Lavie, 1995). Due to individual variability across nights, it is recommended that actigraphy be used for at least five and preferably seven nights to reliably score a person's normal sleep patterns (Acebo et al., 1999). Although activity monitors can

be expensive, actigraphy provides a valuable research tool for assessing sleep relatively cheaply and easily compared to PSG, and is less time consuming to analyse than both PSG and video recording. It can be used for large scale studies and its non-intrusive nature and simplicity of use make it ideal for use with infants, children and other groups who may not be able to endure the PSG (Morgenthaler et al., 2007).

A negative point is that when used to assess circadian patterns over several days, actigraphy tends to overestimate sleep, incorrectly scoring periods of daytime wakeful inactivity as sleep (Sadeh et al., 1995). Therefore actigraphy may not always be appropriate for certain groups, for example insomniac patients or people with a movement disorder who may be awake but remain still for long periods of time. Agreement with PSG for night-time sleep scoring, however, is consistently more accurate than for wake scoring, being over 80% correct (Pollak, Stokes, & Wagner, 1998; Pollak, Tryon, Nagaraja, & Dzwonczyk, 2001; Sadeh, Sharkey, & Carskadon, 1994). It should ideally be used in conjunction with a self- or parent-reported sleep diary so that daytime naps are recorded and sleep onset latency can be quantified.

1.6.4 Pulse oximetry

Pulse oximeters use an infrared sensor usually worn on the finger or toe to record heart rate and oxyhaemoglobin (SpO_2: the haemoglobin oxygen saturation in the blood). It can be carried out in the home using a portable monitor and shows good sensitivity of around 85% when compared to arterial blood sampling methods (Khemani, Patel, Bart, & Newth, 2009). The Association for Respiratory Technology and Physiology (2009) recommend that pulse oximetry be used as a minimum approach for identifying hypoxia associated with OSAS. Although some individuals may object to wearing the sensor, pulse oximetry provides a non-invasive, straightforward technique that is considerably less time-consuming and expensive than PSG. A limitation of using SpO_2 alone to identify OSAS, without monitoring chest movements or airflow, is that OSAS is likely to be under-diagnosed, since hypoxia is not always present. Therefore a negative pulse oximetry study cannot rule out OSAS as it may only detect around two thirds of cases. It does, however, provide a useful screening tool (Golpe, Jiménez, Carpizo, & Cifrian, 1999; Magalang et al., 2003; Netzer, Eliasson, Netzer, & Kristo, 2001; Williams, Yu, Santiago, & Stein, 1991). Another limitation of the methodology is that it is sensitive to the effects of poor blood flow and body movements, although new models are better at correcting for this (Netzer et al., 2001).

Urschitz and colleagues (2003) have published reference values for home pulse oximetry in school-aged children and recommend that at least five hours of artefact-free data be analysed since

apnoeas often occur in REM sleep which is greater in the latter part of the night, so it is important to obtain some recording from this time.

1.6.5 Questionnaires

Despite the benefits of objective methods, they involve the use of specialist equipment and are often time consuming as they require data to be gathered for several nights. Questionnaires provide a more efficient and cost-effective method for gathering a large amount of data quickly and easily. In the developmental literature a widely used questionnaire is the Children's Sleep Habits Questionnaire (CSHQ; Owens, Spirito, & McGuinn, 2000), a 33-item parent-report questionnaire covering the major clinical symptoms of childhood sleep problems. Its scores can consistently differentiate between children with sleep disorders and children without, though it has not yet been quantified for atypical populations. Although the CSHQ provides an excellent measure for assessing sleep, parent report is not always entirely accurate as parents are not always aware of their children's sleep problems. Large inconsistencies have been found between sleep diaries, questionnaires and actigraphy data. Generally, parents are able to be relatively accurate when reporting bedtime, wake time and assumed sleep time, but their reports are less consistent with actigraphy when recording actual sleep time, night wakings and sleep quality, especially if the child does not cry out for parental attention when they wake during the night. Therefore it is recommended that objective methods be used in conjunction with parent reports in order to gain reliable information about children's sleep (Corkum, Tannock, Moldofsky, Hogg-Johnson, & Humphries, 2001; Holley, Hill, & Stevenson, 2010; Sadeh et al., 2000; Sadeh, 2004; Shott et al., 2006; Werner, Molinari, Guyer, & Jenni, 2008).

1.7 Chapter summary

This chapter has provided a detailed description of sleep and its functions. Sleep stages I, II, SWS and REM repeat in a cyclical pattern throughout the night, with a greater amount of SWS during the first part of the night, and increasing REM later. Compared to adults, children's greater sleep time with especially high amounts of SWS and greater REM in infancy may be a reflection of their increased need for acquiring new knowledge and skills. PET studies of regional blood flow show globally reduced neural activity during SWS in contrast to sustained activity during REM, though some regions, including the hippocampus and amygdala, remain relatively active. During SWS the frontal lobes appear to disconnect and particularly benefit from rest.

Around one third of children experience problems with sleep at some point during childhood. The most common include behavioural insomnia and SDB which can lead to excessive daytime sleepiness.

Clearly the purpose of sleep reaches far beyond simply protecting us from daytime sleepiness. Although its precise functions are poorly understood, it has become increasingly clear that sleep is involved in numerous physiological and psychological domains. It is known to affect daytime functioning in both adults and children. Although many studies are correlational by design, studies which have experimentally manipulated sleep or examined cognitive improvements following treatment of sleep problems have suggested a causal effect whereby sleep problems create daytime deficits. These include executive functioning, attention and behaviour problems, which can in turn affect a child's academic abilities. Cognitive problems appear to arise more from chronic poor sleep than from experimentally manipulated sleep, although there is evidence that acute sleep restriction also has detrimental effects. It is noteworthy that daytime disruption relating to sleep problems is found regardless of whether children have SDB or not. Although hypoxia has often not been confirmed in the reviewed studies, it appears evident that both non-hypoxic sleep disruption and SDB (which may or may not be hypoxic) are sufficient to create daytime deficits in children.

In addition, sleep is vital for good health, with sleep problems and short sleep duration being associated with a wide range of health complaints such as delayed healing, cardiovascular events, obesity, diabetes, immune system abnormalities and increased risk of mortality.

Recent research has found that during sleep, new memories are actively consolidated. For declarative memories this strengthening process appears to depend on SWS when the hippocampus replays new memories, transferring information to the neocortex for long-term storage. It seems that simple procedural memories such as pursuit rotor are dependent on Stage II, and more complex tasks involving integration of rules, such as mirror tracing or the Tower of Hanoi, rely more upon REM sleep for consolidation. In contrast to adults, during childhood procedural memories may be preferentially consolidated during wake, possibly due to increased demands on sleep for consolidating explicit, declarative memories. Some developmental shift occurs during puberty towards sleep- not wake-dependent procedural memory consolidation, which may reflect an increase in pre-existing knowledge on which to anchor new implicit skills. Very little research in children exists and the developmental change fundamental to childhood means that findings from adults cannot be generalised. Further research is needed to better understand the role of sleep in memory consolidation in children and to determine whether people with sleep problems suffer a memory consolidation deficit due to those sleep problems. Although sleep duration has not been

associated with consolidation, it is possible that hypoxia associated with SDB and sleep fragmentation could have a detrimental effect on sleep-dependent learning. This is particularly important when considering that sleep problems are common in childhood and many children do not obtain sufficient sleep.

A number of methods exist for measuring sleep. Although PSG is the gold standard, it is expensive and time consuming and not appropriate for all groups, for example children with developmental disabilities who may not tolerate sleeping in a strange environment with electrodes attached to them. Some reliable alternatives are available for measuring dimensions of sleep in the home, such as video, actigraphy and pulse oximetry for SpO_2, although these cannot be used to determine sleep stages. Questionnaires also provide a valuable tool for extracting a large amount of data quickly and easily but should be used in conjunction with objective methods as parent report is not always reliable.

2. Down Syndrome and Williams Syndrome

2.1 Introduction

It is now well established that sleep problems are common in individuals with intellectual disabilities (ID), including Down syndrome (DS), Williams syndrome (WS), Autism Spectrum Disorder, cerebral palsy, Prader-Willi syndrome and other non-specific IDs. In these cases, sleep problems tend to be more persistent and severe than those in typically developing (TD) children and are often not addressed appropriately, if at all (Annaz et al., 2011; Cotton & Richdale, 2006, 2010; Newman, O'Regan, & Hensey, 2006; Stores & Stores, 1999).

This thesis focuses on sleep in two developmental disorders: DS and WS. By having a developmental disorder an individual is predisposed to certain physiological and behavioural qualities that are characteristic of that disorder. The disorder outcomes, or phenotypes, are not deterministic but probabilistic so an individual may express many of these qualities or only a few. Consequently, there is a considerable range of individual variability within the same disorder with some individuals being high and some low functioning, irrespective of their chronological age (CA). However, some traits are common for different disorders such as hyperactivity and attentional problems, whilst some are syndrome-specific, such as hypersociability in WS.

DS and WS provide good comparison groups due to their similar mental ages (MA) and common features such as executive function and attention difficulties. In addition, they have complementary patterns of cognitive strengths and weaknesses, such as better visuospatial skills in DS and verbal ability in WS, which also make them interesting groups to compare. Although physiological and cognitive aspects of these disorders have been well characterised in the wake state, there is relatively little information available characterising sleep patterns in these groups.

A cross-syndrome comparison of sleep problems in children with DS and WS will determine whether there are characteristic patterns specific to each disorder, or whether problems are common to both groups and could therefore be more general to IDs. This thesis intends to address this issue and also assess the effects that sleep may have on cognition, behaviour and sleep-dependent learning in these groups, an area which has been under-researched.

This chapter provides a summary of the physical and cognitive characteristics as well as a description of sleep in these disorders. Proposals for further investigation and hypotheses are also made.

2.2 Down Syndrome

DS was first described by Edouard Onesimus Seguin in 1846, but named after John Langdon Down, who further described the syndrome in 1866. Both noted a cluster of symptoms, physical characteristics and intellectual impairment in their patients.

By 1959 Lejeune and colleagues discovered the genetic basis for DS, which is usually caused by non-dysjunction in meiosis (may be mitosis) leading to the presence of three free copies of chromosome 21 (trisomy 21) (Fidler & Daunhauer, 2011). In 4 to 5% of cases an additional portion of chromosome 21 is permanently attached to another chromosome (translocation). Less than 1% of cases occur as mosaic Down syndrome where some cells contain extra genetic material whilst others do not (Sherman, Freeman, Allen, & Lamb, 2005). In around 90 to 94% of cases the extra genetic material comes from the mother (Sherman et al., 2005). The diagnosis of DS is made by chromosome karyotyping for duplication of the 21st chromosome and by identifying characteristic physiological features in infants with DS.

DS is the most common sporadic genetic disorder and the leading genetic cause of intellectual disability. A large scale study covering around 94% of all DS pregnancies (N = 11,683) in England and Wales between 1989 and 1998 provided a thorough prevalence estimation taking consideration of confounding factors such as maternal age and terminated pregnancies following antenatal screening (Morris, Mutton, & Alberman, 2002). The study reported the frequency of DS pregnancies to be 1 in 1441 at maternal age of 20 years, rising to 1 in 959 at 30 and 1 in 32 at age 45. Eighty-two per cent of DS pregnancies were terminated following antenatal screening, around 57% of which would have resulted in a miscarriage or stillbirth had they been continued to term. It is not clear why DS pregnancies are more likely in older women but this could be due to hormonal change affecting the ovaries or uterine environment, the accumulation of environmental toxins over time or poorer performance of the ovaries (Fidler & Daunhauer, 2011). Due to this increased risk pregnant women over the age of 35 are routinely screened for DS. Whilst the mean age of pregnancy has increased in recent years, so has the number of terminated pregnancies, leading to a prevalence estimate of around 1 in 1000 live births (Roizen & Patterson, 2003).

Many other risk factors proposed to play a role in the prevalence of DS births have been extensively studied, though none have been convincingly linked to DS. Examples include chromosome and gene variants, differences in folic acid metabolisation, use of oral contraceptives, consumption of caffeine, tobacco, alcohol and drugs, and environmental or occupational exposure to radiation, pesticides and chemicals (Hassold & Sherman, 2002).

DS occurs in all racial groups but prevalence has been noted to vary, with a higher frequency in Hispanics (1.12:1) and lower in Blacks (.77:1) compared to Whites (Canfield et al., 2006; Shin et al., 2009). These studies, however, calculated data only for live births, not controlling for terminations, which are also found to vary by ethnicity with Whites more likely to abort affected pregnancies than both Blacks (Siffel, Correa, Cragan, & Alverson, 2004) and Hispanics (Bishop, Huether, Torfs, Lorey, & Deddens, 1997) within the same country. The ethnic variation may therefore be explained by differences in terminations, prenatal care, genetics or environmental factors.

2.2.1 Clinical features

Individuals with DS tend to have distinctive physical characteristics, though not all features are always present. Kava, Tullu, Muranjan and Girisha (2004) investigated the frequency of physical features in 524 Indian patients with DS, finding that the most common characteristics were a mongoloid eye slant (83.9% of cases), hypotonia (76.3%), ear abnormalities (66.9%), epicanthic skin folds of the upper eyelid (56.9%) and flat facial profile (50.9%) (see Figure 2.1). Other common features included a protruding tongue and abnormalities of the hands, feet, eyes and neck. Hearing and vision problems including congenital cataracts and glaucoma, as well as other eye conditions which worsen with age should be closely monitored and managed (Roizen & Patterson, 2003).

Figure 2.1. Images of children with Down syndrome.

Congenital heart defects affect around half of individuals with DS, with the most frequent being atrioventricular septal defect (AVSD), secundum atrial septal defect, and ventricular septal defect (Freeman et al., 2008; Roizen & Patterson, 2003). There are likely to be ethnic differences in prevalence of heart defects. Freeman et al. (2008) studied ethnic variation in 1469 infants with DS in

America. They found that, compared to Whites, Black infants were twice as likely to have AVSD, whilst Hispanics were half as likely.

Resting metabolic rate is reduced in individuals with DS along with frequent occurrence of hypothyroidism (around 15%), contributing to increased levels of obesity. It is recommended that diet, behavioural interventions and exercise be integrated into the lifestyle in childhood to avoid weight gain (Roizen & Patterson, 2003).

Neural abnormalities have also been noted in DS. Infants with DS show slower dendritic growth and synaptic formation compared to TD infants as well as reduced myelination in frontal and temporal lobe pathways, resulting in fewer and slower neuronal connections (Becker, Mito, Takashima, & Onodera, 1991). Studies of adults with DS have revealed reductions in frontal lobe, hippocampus, neocortex, brainstem and cerebellum volumes as well as overall reduced brain volume (Kesslak, Nagata, Lott, & Nalcioglu, 1994; Raz et al., 1995). The parahippocampal gyrus is larger and its size has been found to correlate positively with general intelligence and language ability in 13 adults with DS (Raz et al., 1995). In children too, hippocampal, cerebellar and frontal lobe volumes have been found to be reduced, whilst grey matter in the parietal lobe and white matter in the temporal lobe appear to be preserved. Total brain volume is around 82% that of TD CA-matched controls (Pinter, Eliez, Schmitt, Capone, & Reiss, 2001; Pinter, Brown, et al., 2001; Schmidt-Sidor, Wisniewski, Shepard, & Sersen, 1990).

There is a significantly increased risk for early-onset Alzheimer's disease in individuals with DS, often beginning in the fourth or fifth decade of life, but with first symptoms often evident from the third decade. A study of 201 adults with DS reported age-specific prevalence estimates of clinical dementia as 9.4% at 40 to 49 years of age, rising to 54.5% at 60 to 69 years (Prasher, 1995). Functions which are served by the frontal lobes are usually early targets for decline, which may be a result of a pre-existing reduction to this area. These include changes to personality and behaviour as well as problems with orientation, visuospatial memory and executive functions (Holland, Hon, Huppert, & Stevens, 2000; Oliver, Crayton, Holland, Hall, & Bradbury, 1998).

Many other disorders that are more common in DS than in the general population include arthritis, atlanto-axial subluxation (instability in the top vertebrae), gastroesophageal reflux, diabetes, seizures, alopecia and skin complaints. Leukaemia, especially in childhood, is more common in people with DS, however they are less susceptible to hard tumours at all ages (Roizen & Patterson, 2003).

Mortality in the first year of life is higher in DS than TD infants (4% vs .48%) (Weijerman et al., 2008) but life expectancy has increased dramatically over the past 50 years, due largely to advances in cardiac surgery and medical care. A Western Australian study of 1332 people with DS reported 273 deaths and an average life expectancy of 58.6 years, with the oldest living person aged 73 years (Glasson et al., 2002).

2.2.2 Cognitive features

Although there is great individual variability in DS, virtually all individuals have intellectual impairments with IQs usually in the 30 to 70 points range. In 965 adults with DS, Glasson et al. (2002) reported that around half (52.4%) had a moderate level of impairment with IQs in the range of 40 to 54 points, 23.3% had mild impairment with IQs between 55 and 69 points, whilst 22.1% had severe disability with IQ below 40 points. Only 2.2% of individuals had a borderline level of intellectual impairment, with IQs ranging from 70 to 85 points. The cognitive profile comprises a distinct pattern, with relative strengths in visual and spatial domains along with weaknesses in verbal abilities.

The dissociation between verbal and spatial short term memory (STM) in DS is well documented. These constructs are usually measured using digit span and spatial span tasks respectively, where the experimenter reads a sequence of numbers or taps a set of blocks on a board and the participant must repeat the sequence in the correct order. The maximum number of remembered items is their span length. In individuals with DS, verbal STM span is generally lower than what would be expected given their intellectual ability in other areas and when compared with TD children matched for MA, and with individuals with other types of ID (Jarrold & Baddeley, 2001; Wang & Bellugi, 1994). The verbal STM deficit cannot be explained by hearing or speech production problems as a number of task manipulations that have been used to overcome these have yielded similar results (Jarrold & Baddeley, 2001, 2002). In contrast, spatial span in DS is relatively unimpaired compared to MA-matched controls (Hick, Botting, & Conti-Ramsden, 2005; Lanfranchi, Jerman, & Vianello, 2009). This suggests a specific problem with verbal STM that does not extend to spatial memory. These findings may be explained by differences in neuroanatomy in individuals with DS, namely the relative preservation of the parietal lobes and diminished cerebellar volume (Pinter, Eliez, et al., 2001); areas which are known to play a part in visuospatial processing and verbal STM respectively (Jonides et al., 1993; Smith, Jonides, & Koeppe, 1996).

Problems with verbal STM mean that children with DS often have difficulty remembering instructions or directions. In the classroom this can hinder learning so teachers should avoid relaying

complex instructions and instead keep them short and limited in number. In addition, children could benefit from a more hands-on approach to learning rather than extensive verbal instruction, with education plans tailored to exploit their strengths in the visual-motor domain (Hughes, 2006).

It is probable that verbal STM is associated with general verbal skills and vocabulary acquisition as new words need to be held in STM before they can be transferred to long term memory. Lanfranchi, Jerman and Vianello (2009) found an association between expressive language skills and verbal word span length in 20 children and adolescents with DS (*M* age = 13.10 ± 3.1) and a younger TD control group matched for verbal level. In addition, a review by Ypsilanti and Grouios (2008) highlights the differences in language ability between individuals with DS, WS and specific language impairment. Individuals with WS do not exhibit problems with verbal STM and have relatively good expressive language, whilst individuals with DS and specific language impairment have deficits in both verbal STM and language, further suggesting a role for verbal STM in language skills and development.

Indeed, expressive language is a particular problem for individuals with DS, whilst receptive language skills are relatively less compromised (McCann, Wood, Hardcastle, Wishart, & Timmins, 2008). Production of intelligible speech is problematic due to fluency, articulation and phonology difficulties that are exacerbated by physiological features such as a small oral cavity with a large tongue, poor voice quality and muscle tone (Martin, Klusek, Estigarribia, & Roberts, 2009). Deficits in certain linguistic areas such as syntax and pragmatics are also evident, with individuals with DS producing shorter and less complex utterances than TD children of the same nonverbal MA, and being less able to understand grammatical rules regarding tense, possession, passive voice and indirect objects. In contrast, their vocabulary knowledge is relatively good, albeit lower than what would be expected based on MA (Chapman, Seung, Schwartz, & Kay-Raining Bird, 1998; Martin, Klusek, Estigarribia, & Roberts, 2009; Rice, Warren, & Betz, 2005). Hearing problems may also contribute to delays in language development (Chapman, Schwartz, & Bird, 1991).

A developmental study of 12 children with DS (CA range 8 to 11, *M* = 9.75 ± .23 at baseline) assessed verbal and nonverbal abilities at three time points, each six months apart and compared these with a TD control group matched for nonverbal MA (*M* MA = 4.33 ± .33). Expressive and receptive vocabulary skills were similar at baseline, however, in comparison to the TD group, these developed more slowly in children with DS and their performance plateaued between the final two time points. In addition, verbal STM span for digits and words did not improve over time, with an average span length of around 2.5 items at each time point. In contrast, visuospatial STM for recall of the positions of pictures on a grid was relatively unimpaired and showed improvement over time similar to the TD

group (Hick et al., 2005). This highlights the importance of studying developmental trajectories for different skills when investigating atypical development.

Jarrold and colleagues have further tested the role of verbal STM in vocabulary development by studying new word learning in children with DS. They used a series of well-designed studies training participants on novel names of cartoon creatures. Jarrold, Thorn and Stephens (2009) compared the performance of 22 individuals with DS aged 14.42 to 29 years to 64 TD children with a similar level of vocabulary knowledge. Participants were trained on two tasks by sequentially showing three monsters and three aliens and presenting their names auditorily. In the monsters task, participants were then presented with the three monsters and heard a name. They had to match the name they heard to the correct monster. In the aliens task participants heard a selection of three non-words: the target and two foils that differed by only one phoneme. In order to overcome issues with speech production they were asked to select the correct name. They completed each procedure ten times or until they completed two consecutive trials correctly. The monsters task therefore relies less on phonological awareness since the three names were distinct from one another so even a relatively degraded memory trace for the phonemes should be sufficient to allow participants to select the correct monster when presented explicitly with the name. In contrast, the aliens task required an accurate phonological memory to distinguish between the target and similar foils. As expected, compared to the control group, children with DS were unimpaired on the monsters recognition task but were markedly impaired on the aliens phonological task. This impairment was related to poorer verbal STM, but performance was better for names that sounded more word-like, suggesting that individuals with DS compensate for their poorer verbal STM by matching novel words with their existing linguistic knowledge. New words that bear a higher resemblance to already known words should therefore be easier to remember for individuals with DS. This has implications for language learning strategies that could be employed to aid vocabulary acquisition. The results also go some way to explaining the contradiction between relatively poor expressive language which is related to poor verbal STM, and good receptive vocabulary which places a lighter load on verbal STM as it is not necessary to remember the precise phonological form of the new word. Jarrold et al. (2009) propose that phonological ability underpins both verbal STM and new word learning, since both skills are dependent upon the ability to accurately encode and maintain phonological information. Phonological deficits in DS could therefore be responsible for their poorer verbal STM and consequent difficulties with vocabulary acquisition. Indeed, a five-year longitudinal study of 30 children and adolescents with DS (CA range 5 to 19 years, $M = 11.23 \pm 3.92$ at baseline) found that better early phonological awareness strongly predicted higher levels of vocabulary knowledge later ($r = .51$, $p < .01$) (Laws & Gunn, 2004). This study also found that phonological awareness actually

declined with age, but this may have been due to confounding factors such as increased hearing problems and moving schools.

In light of their problems with verbal STM, vocabulary acquisition and expressive language, along with relative strengths in motor expression, it is recommended that signed language be taught as an alternative means of communication for individuals with DS. This could relieve frustration for children not being able to communicate effectively, enabling social inclusion and integration, facilitating relationships and cognitive and social learning. Along with enabling children to communicate, use of signed language can aid spoken language (Foreman & Crews, 1998; Millar, Light, & Schlosser, 2006). Most young children with DS are able to produce signs well before they are able to use speech (Martin et al., 2009), although they do experience difficulties with fine motor control relative to gross motor movements (Spanò et al., 1999). Use of gestures appears to develop similarly to TD children with strengths in nonverbal social interaction, although infants with DS have been found to show deficits in nonverbal requesting for objects and for help with objects. This deficit has been associated with both current and subsequent development of expressive verbal skills, suggesting that problems with expression begin to occur prior to development of spoken language (Mundy, Kasari, Sigman, & Ruskin, 1995; Mundy, Sigman, Kasari, & Yirmiya, 1988).

Individuals with DS also suffer problems with executive functions, for example, working memory. Similarly to STM, the impairment is greater for verbal than for visuospatial information but is not related to general verbal abilities (Lanfranchi, Cornoldi, & Vianello, 2009; Lanfranchi, Jerman, et al., 2009). A relatively straightforward test of working memory is the backwards span for verbal or spatial information. Vicari, Carlesimo and Caltagirone (1995) tested the forward and backwards verbal and spatial spans of a group of 15 adolescents with DS (*M* age = 16.6 ± 2.9 years, *M* MA = 5.2 ± 1.2) who were matched for CA and MA with a group of 14 adolescents with unspecific ID, as well as 24 TD children matched for MA. The DS group achieved significantly lower scores on the backwards spans compared to both other groups, showing that a working memory deficit is not uniform to all IDs. In TD children working memory deficits are associated with academic underachievement due to a combination of forgetfulness, disorganisation, inattention, difficulty solving problems and making careless mistakes. Teachers report that TD children with working memory problems often fail to complete tasks or remember instructions, lose track of what they are currently doing and forget things they have learnt (Alloway, Gathercole, Kirkwood, & Elliott, 2009).

Lanfranchi, Baddeley, Gathercole and Vianello (2012) studied verbal and visuospatial STM and the effects of completing two tasks simultaneously, so requiring greater executive control. A sample of 45 individuals with DS (*M* age 13.67 ± 3.17) was compared with a group of TD children matched for

vocabulary knowledge (*M* age 5.17 ± .58). Children with DS were significantly impaired on the verbal STM task of remembering the first word of a list of orally-presented words. Performance on a visuospatial STM task, which involved remembering the movements of a frog on a 4x4 matrix, was equivalent to the control group. On the dual task paradigms participants completed the same tasks, and in addition were asked to tap the table when they heard the word *ball* or when the frog jumped into a red square. Individuals with DS suffered a greater interference effect from the competing task than did the TD group. Lanfranchi et al. (2012) suggest that a deficit exists in the executive control of working memory in individuals with DS.

Other executive function deficits have been found on tasks assessing set shifting, planning, problem solving, inhibition and perseveration (Lanfranchi, Jerman, Dal Pont, Alberti, & Vianello, 2010; Rowe, Lavender, & Turk, 2006). Lanfranchi et al. (2010) measured executive functions in 15 adolescents with DS aged 11 to 18 years (*M* = 15.17 ± 2.2) compared with 15 TD children aged 4 to 6 (*M* = 5.75 ± .67) matched for logical thinking ability. Participants completed a battery of executive function tests including verbal and visuospatial working memory, the Day and Night Stroop test for inhibition, card sorting tasks assessing rule shifting and set shifting, word listing tasks for phonological and semantic verbal fluency, a sustained attention task, and the Tower of London task: a cognitive procedural task based on the Tower of Hanoi that involves problem solving and planning to arrange a set of balls on three pegs according to a given model. Individuals with DS performed less well than the TD children on all assessed tasks, with the exception of verbal fluency. The greatest impairments relative to the TD group were on the set shifting and the Tower of London tasks. The result that verbal fluency was unimpaired is surprising given the weak verbal abilities in DS, but perhaps this is an aspect of executive function that is relatively preserved, or the result could be due to poorer vocabulary knowledge in the much younger control group who were not matched for verbal ability.

Individuals with DS have problems within the attentional domain. Based on the hypothesis that attention of individuals with DS would be better for visual rather than auditory material, due to their known pattern of strengths and weaknesses, Trezise, Gray and Sheppard (2008) investigated sustained attention in the two sensory domains in 11 children and adolescents with DS and 16 children with unspecific ID (CA range 7 to 18 years, *M* = 12.59) matched for nonverbal MA (*M* = 6.71 years). They used two computerised CPTs: one visual and one auditory. The visual task presented a sequence of 225 line drawings of nine animals over a period of 6.3 minutes. Each animal was presented for 500ms with an interstimulus interval of 1200ms. The auditory task was identical except that the name of the animal was presented auditorily through speakers instead of the visual display. The tasks used an alternative approach to the traditional CPT, whereby participants were

requested to respond using the keyboard to non-target stimuli, but withhold their response to the target dog. This variation is thought to require more vigilance to avoid responses becoming automatic. As expected, children with DS were better at the visual than the auditory CPT, and were also better at the visual task than the comparison group. No group differences were evident for auditory attention. The authors reported that the relative preservation of visual skill over verbal abilities extends beyond STM. However, it should be noted that the study would benefit from a TD control group to gain further insight into sustained attention abilities in DS.

2.2.3 Behavioural characteristics

Problems with attention and hyperactivity are the most commonly reported behavioural problems in DS. Although individuals with DS are generally judged to be sociable, happy and affectionate, many do also have considerable behavioural problems. Prevalence estimates vary but average around 33% compared with around 10% of TD children (Coe et al., 1999). Coe et al. (1999) conducted a parent- and teacher-report study of 44 children with DS (CA range 6 to 15 years, $M = 9.7 \pm 2.7$) matched for age, sex and family socioeconomic status with 44 TD children. Compared to the TD group, children with DS were reported to have significantly poorer communication, daily living skills, socialisation skills and overall competency, as well as greater problems with conduct, attention, psychotic behaviours such as repetitive speech and major thought preoccupations, social withdrawal and other behavioural problems. According to parents, 32% of children with DS had severe behaviour problems, compared to 14% of TD children. Another parent-report and interview study of 193 children with DS also identified that 38% of children with DS had behavioural problems in contrast to 49% of 154 children with similar level of ID of other aetiologies. Deviant behaviour was significantly more frequently expressed by children with DS than by their siblings (Gath & Gumley, 1986). This suggests that, although behavioural problems are more prevalent in DS than in the general population, they are actually less frequent than one would expect given their level of impairment. Behavioural problems in DS are not surprising given the challenges to develop cognitively and behaviourally, whilst suffering atypical brain function, frequent medical complaints and poor sleep, as described in the next section. Behaviours are often attention-seeking, disobedient, stubborn or impulsive, or are disruptive strategies to manipulate caregivers or avoid cognitive challenges (Capone, Goyal, Ares, & Lannigan, 2006). Psychiatric conditions are also more commonly expressed in DS than in the general population. Prevalence estimates vary widely, averaging around 25% (Coe et al., 1999) for example, ADHD, autism and mood disorders are each evident in around 10% or less of children with DS (Capone et al., 2006; Fidler & Daunhauer, 2011; Gath & Gumley, 1986).

2.2.4 Sleep

Almost all individuals with DS experience sleep disturbances (Carter, McCaughey, Annaz, & Hill, 2009; Cotton & Richdale, 2006). The most common of these is OSAS, causing both disruption of sleep and intermittent hypoxia. This results in sleep fragmentation manifested in frequent awakenings, a higher percentage of wake after sleep onset (WASO), and thus lower sleep efficiency. It is thought to affect between 30 and 60% of people with DS (Dyken, Lin-Dyken, Poulton, Zimmerman, & Sedars, 2003; Marcus, Keens, Bautista, von Pechmann, & Ward, 1991; Stebbens, Dennis, Samuels, Croft, & Southall, 1991). Craniofacial and upper airway abnormalities, obesity, tonsil and adenoid encroachment, generalised hypotonia and recurrent upper respiratory tract infections could all contribute to OSAS (Churchill, Kieckhefer, Landis, & Ward, 2011; Marcus et al., 1991).

Levanon, Tarasiuk and Tal (1999) used parent-report and PSG in a sleep laboratory to examine sleep in 23 children with DS (CA range 1 to 8 years, M = 4.8) and 13 CA-matched TD children who were mild snorers but did not have evidence of OSAS. Due to difficulties with patient cooperation, 12 children with DS underwent only partial PSG which monitored airflow, chest movements, SpO_2, leg movements and snoring, but not EEG, eye movements or muscular activity. Without the full PSG, sleep stages could not be scored for these participants and arousals and awakenings needed to be scored based on movement rather than EEG. This was thought to be more than 83% accurate based on comparison of both scoring systems in children who underwent the full PSG. Cooperation with the study procedure can often be a problem when working with children with developmental disorders as they have limited capacity to understand the reason for the study and may become distressed at having electrodes attached to them. Results showed that both groups were comparable for the time in bed, total sleep time and sleep efficiency. Time spent in each stage of sleep was also similar; however, children with DS had 30% more stage shifts from deeper to lighter sleep stages and more disrupted stage II sleep than the TD group. The AHI was significantly elevated for children with DS (2.8 ± 2.3 events/h vs 0.6 ± 0.4 events/h, $p < .05$) and mean SpO_2 during sleep was slightly lower, though this difference was not significant (94.0% ± 4.3% vs 96.6% ± 1.3%). It should be noted that the comparison group here were mild snorers, thus they may also have experienced mild respiratory disturbance. Children with DS also had more arousals (>1.5s of alpha activity) and awakenings (>15s of alpha activity) per hour of sleep (24.6 vs 17.6), which were often associated with jerks (45.2% vs 10.2%) rather than respiratory events (8.6% vs 1.5%). Leg movements were also common (8.3 vs 1.8 leg movement events/h). In the DS group these were associated with arousals or awakenings in 82% of occurrences, compared with 52.8% in the TD

group, suggesting that children with DS have a lower arousal threshold than TD children. The authors reported that eight children with DS showed patterns suggestive of PLMD. Children with DS had the most restless sleep, indicated by frequent and abrupt position changes and awkward body positions, such as sleeping seated or with the legs and feet propped upright against the wall. Arousals and awakenings were infrequently associated with respiratory events, suggesting that that the frequent night wakings so often reported in DS may be due to factors other than OSAS, such as jerks and leg movements.

In a PSG study of 56 young children with DS, Shott and collegues (2006) found abnormal PSG results in 32 children (57%), defined by abnormal AHI (38%), hypercarbia (30%), and/or hypoxia (20%). Sixty-one percent of children had elevated arousal indexes. Parent reports of their children's sleep were relatively inaccurate. Of 35% of parents who reported SDB symptoms (snoring, gasping, stopping breathing), only 36% of these children had abnormal PSG results, whilst the other 69% of parents reported no SDB symptoms, yet 54% of their children had abnormal PSGs. Parents had both over- and under-reported problems, with only 23% being concordant with PSG. The high incidence of OSAS and the inaccuracy of parent reports together underline the importance of objective methods for studying sleep in individuals with DS and necessitate that respiratory sleep studies should be recommended for all children with DS. PSG also showed a lower percentage of REM sleep than would be expected in young children; a finding echoed by Miano et al. (2008), who also found increased stage I and II percentages in nine individuals with DS (*M* CA = 13.8 years, range 8 to 20) relative to a healthy control group. As discussed in Chapter 1, differences in sleep architecture are related to sleep-dependent learning. Therefore, decreased REM sleep in children with DS could reflect reduced consolidation of new procedural memories.

Many studies have used parent report to gain an understanding of sleep problems in children with DS, finding that settling, sleep maintenance and early morning waking are particular problems in this group (Breslin, Edgin, Bootzin, Goodwin, & Nadel, 2011; Cotton & Richdale, 2006; Stores, Stores, Fellows, & Buckley, 1998). In a parent report cross-syndrome comparison of 3 to 18 year olds with DS, autism, Prader-Willi syndrome and unspecific ID, Cotton and Richdale (2006) found significant sleep problems in all groups. Children with autism were the most likely to have sleep problems (73%), relative to only 11% of a TD control group. Forty per cent of children with DS were reported to have a sleep problem and of these, around one third had two or more problems, highlighting the complexity and comorbidity of sleep disturbance. Although the parentally-rated severity of sleep problems did not differ between the groups, different types of problems were reported in each group, suggesting that the nature and prevalence of sleep problems is dependent upon the aetiology

of different developmental disorders. Problems with sleep maintenance were common in children with DS and ID, whilst settling difficulties and co-sleeping were more likely in autism. Excessive daytime sleepiness and daytime naps were common in children with Prader-Willi syndrome but rare in the other groups, although in a later study the same authors did find that parents reported daytime sleepiness in children with DS (Cotton & Richdale, 2010). In contrast with other studies (e.g. Stores et al., 1998), the authors did not find early morning waking to be a problem in DS. This may reflect the large age range used in this study, which may have reduced the possibility of finding sleep problems that are common in younger children but outgrown in adolescence. Parents also expressed worry that other family members were affected by the child's sleep problems, especially when the problem was one of sleep maintenance leading the child to disturb other family members during the night. They were also concerned that sleep problems were adversely affecting their child's welfare.

Another parent-report study of 58 children with DS aged 0 to 18 years (M = 8.6) used the CSHQ to assess sleep problems in a community sample (Carter et al., 2009). Compared to published data for 469 TD children (Owens, Spirito, & McGuinn, 2000), parents reported significantly greater bedtime resistance, sleep onset delay, sleep anxiety, night waking, parasomnias, sleep disordered breathing and day-time sleepiness, whilst sleep duration was similar to population control children. In addition, of school aged children, 33% fell asleep in a parent's or sibling's bed and 48% moved to someone else's bed after waking in the night on at least two nights per week compared with only 11% in the TD comparison group. Fifty-eight per cent (vs 26%) were described as having restless sleep. Common parasomnias included bruxism (45% vs 10%), somniloquy (45% vs 13%) and nocturnal enuresis in 26% (vs 5%) of children aged 7 and above. Forty-five per cent of children were reported to snore heavily relative to 14% in the comparison group.

The majority of these studies have used a wide age range to assess sleep from infancy to late adolescence. We know that considerable changes occur in sleep architecture during childhood and adolescence and that many sleep problems, such as parasomnias, occur frequently in childhood but are often outgrown. Studies with wide age ranges should therefore consider investigating developmental changes that may occur in sleep in children with DS, rather than only investigating group differences in a developmentally diverse group.

The wide variability in reported figures for the prevalence of sleep problems in DS could be due, in part, to differences in methodology, definition and parent perception of sleep problems. Parents are not always able to accurately report their children's sleep problems (Shott et al., 2006) and may not be aware of actual sleep time or night wakings if their children do not disturb them in the night (Werner et al., 2008). Parent-report studies are therefore likely to show different results to objective

methods but can be useful for reporting behaviours that may not otherwise be recorded. Therefore the two methodologies should be used in conjunction.

2.2.5 Sleep and cognition

As previously discussed (Section 1.4), sleep problems in TD children can have a detrimental effect on their daytime behaviour and cognition. Despite strong evidence that sleep problems and cognitive and behavioural deficits are common in children with DS, little research has investigated whether they could be related to one another.

One of the earliest studies was conducted by Stores and colleagues (1998), who obtained parent-reports for 91 children with DS. Parents completed three questionnaires: one relating to children's general sleep habits and the frequency of sleep problems over the past four weeks; one on daytime behaviours of irritability, lethargy, stereotypies (i.e., repetitive behaviours), hyperactivity and inappropriate speech; and a measure of maternal stress. Sleep problems were evident in 66% of the sample, with the most common being difficulties initiating sleep (9%), sleep maintenance (8%), and SDB (9%). These three problems were associated with differential daytime behaviours. All were associated with increased hyperactive behaviour, and problems with sleep maintenance and SDB were both related to increased levels of irritability, total behavioural problems score and increased maternal stress. Problems with sleep maintenance were associated with the highest scores for behavioural problems across all factors. Children with no sleep problems were reported to have better behaviour and lower maternal stress scores than children with sleep problems.

Richdale, Francis, Gavidia-Payne and Cotton (2000) used parent reports and found a high level of sleep problems in children with ID. They surveyed parents of 52 children with ID, nine of whom had DS, and 25 parents of TD children. Children with ID who had sleep problems also had significantly worse behaviour than those without sleep problems. They were likely to be disruptive, attention-seeking and self-absorbed, have tantrums, mood changes and other challenging behaviours. In TD children, having a sleep problem was associated only with anxiety. Parents were more likely to rate sleep problems as a 'source of hassle' than parents of TD children, and this stress was greater for parents of children with more severe intellectual impairment. A critique of this study is that children with DS, fragile-X syndrome, autism, cerebral palsy and other IDs were assessed as a group that did not account for syndrome-specific sleep problems and differential effects of sleep problems in different groups.

Cotton and Richdale (2010) studied the relationship between sleep and daytime behaviour using parent-report in 12 children with DS (CA range 3 to 13 years, $M = 8.7 \pm 2.8$) compared to 33 CA-

matched TD children. Parents completed sleep diaries and daily logs of their child's behaviour over a two week period. Daytime sleepiness was significantly more common in DS and this was associated with less energy and less excitable behaviour during the day, whilst daytime sleepiness in TD children was associated with more hyperactive behaviour. This dissociation highlights the complex interplay between sleep problems and aetiology of developmental disorders.

Andreou et al. (2002) investigated the impact of sleep problems on cognitive functioning in DS by testing 12 young adults (*M* CA = 21.66 ± 4.11) with PSG for breathing related problems. Subjects also completed the Ravens Progressive Matrices (RPM) to assess visuospatial skills associated with normal right hemisphere functioning (set A), and analogical reasoning associated with normal left hemisphere processing (sets B and B1); the Mini-Mental state (MMS) to assess a set of cognitive functions, and the Epworth Sleepiness Scale. All 12 participants were found to have sleep apnoea (more than 10 apnoeas per hour and blood oxygen saturation <95%), but did not report daytime sleepiness. Total scores on the RPM and MMS were very low. Regression analysis showed that total scores did not correlate significantly with PSG parameters, however apnoea was significantly correlated with set A of the RPM ($r = .79$, $p < .002$), which in turn was associated with orientation on the MMS ($r = .65$, $p < .002$). The findings suggest that sleep apnoea may be linked to visuo-perception problems including orientation.

Finally, in a PSG study of eight young adults with DS (*M* CA = 22.5 years, range 17 to 30), Diomedi et al. (1999) found reduced REM percentage and fewer REM cycles relative to a CA-matched TD control group. REM percentage also correlated positively and significantly with participants' IQ. The authors propose that this relationship could reflect reduced ability to organise new information during REM sleep and reduced neural plasticity.

Clearly, sleep problems in individuals with DS have a negative impact on their daytime behaviour, but no other known studies have investigated the impact of sleep problems on cognition or on sleep-dependent learning.

2.3 Williams Syndrome

WS has been recognised only since 1961 when cardiologist J. C. P. Williams first described four children with a specific heart defect, supravalvular aortic stenosis (SVAS), noting that they all had similar facial characteristics and 'mental deficiency' (Williams, Barratt-Boyes, & Lowe, 1961). Shortly thereafter, it was similarly described by cardiologists Beuren, Apitz and Harmjanz (1962), leading it to also be known as Williams-Beuren syndrome.

WS is a rare neurodevelopmental disorder caused by a deletion of some 28 genes on the long arm of one copy of chromosome 7 at q11.23 (Donnai & Karmiloff-Smith, 2000). The genetic basis of WS was reported in 1993 with the detection of deletion of the elastin gene at the centromere of deletion (Ewart et al., 1993). Elastin can be marked to assess whether only one copy is present using a fluorescence in situ hybridisation test (FISH) (Schubert, 2009).

Early studies of WS noted its association with infantile hypercalcaemia, describing patients of both disorders as having mild to moderate learning difficulties, poor motor coordination, along with unusual command of language, outgoing personalities, and elf-like facial features. It is probable that individuals with WS formed a subgroup of patients with infantile hypercalcaemia, thus historically the two disorders were frequently described together without differentiation (Jones, 1990; Martin, Snodgrass, & Cohen, 1984; Udwin, Yule, & Martin, 1987).

The most recent prevalence estimation of WS comes from a large-scale epidemiological study in 1993 of 30,037 children born in Norway between 1980 and 1985, which assessed the cognitive profiles of all children referred through healthcare or education systems for learning disabilities. Of 213 referred cases, four were found to have FISH-determined WS, thus leading to the prevalence estimate of 1.33 per 10,000 (95% *CI* = 0.0 – 2.6) or approximately 1 in 7,500 (Strømme, Bjømstad, & Ramstad, 2002). This figure is almost three times higher than the previous estimate of 1 in 20,000 that is generally quoted in the literature (Morris, Demsey, Leonard, Ditts, & Blackburn, 1988). This may reflect more recent advances in screening and previous under diagnosis. Before the availability of genetic testing, the average age of diagnosis was 6.4 years (Morris et al., 1988). WS occurs in all racial groups. No known etiological causes have yet been determined so presumably WS occurs as a sporadic mutation of the gene.

2.3.1 Clinical features

Individuals with WS have distinctive facial features, often described as 'elf-like' in early papers, with bitemporal narrowing of the skull, broad forehead, wide-set eyes with periorbital fullness and strabismus squint, short nose with full tip, depressed nasal bridge, heavy cheeks, wide mouth with fleshy lips and long philtrum, small jaw, dental malocclusion with small, widely spaced teeth, prominent earlobes and curly hair (see Figure 2.2). Expression of these features ranges from subtle to very prominent (Donnai & Karmiloff-Smith, 2000; Morris, 2006; Williams et al., 1961).

Figure 2.2. Images of children with Williams syndrome.

Average birth weight is around .5kg lower than that of TD infants (Martin et al., 1984). Growth during infancy and childhood is slow, due in part to feeding difficulties in infancy, with frequent vomiting, refusal of feeds, difficulty swallowing and thus failure to gain weight (Martin et al., 1984). Many individuals with WS fail to reach the full adult height though around two thirds of adults with WS are overweight, which may be related to subclinical hypothyroidism (Cherniske et al., 2004). Gastrointestinal difficulties continue into adulthood and include gastroesophageal reflux, constipation, chronic abdominal pain, hernias and rectal prolapse (Morris, 2006; Pober, 2010). Frequent urination is thought to affect around half of individuals with WS, often with no physiological cause, though sometimes associated with bladder diverticulae or frequent urinary tract infections (Cherniske et al., 2004).

Elastin deficiency underpins much of the phenotype, including connective tissue, cardiovascular and musculoskeletal abnormalities, such as lax skin, premature aging, hypotonia, and abnormal curvature of the spine (Cherniske et al., 2004; Morris, 2006; Morris & Mervis, 2000). Around 70% of individuals with WS experience cardiovascular symptoms that necessitate surgical intervention in around 40% of cases. The most common and clinically significant is SVAS, occurring in 75% of individuals with cardiac anomalies, though stenosis (narrowing) may occur in any artery (Eronen et al., 2002; Pober, Johnson, & Urban, 2008).

The endocrine system, which controls hormone release in the body, also suffers disruption in WS. Hypercalcaemia occurs in up to 50% of cases. It is more prevalent during infancy though may also be present in adulthood and can be controlled through limiting vitamin D and calcium intake (Pober, 2010). A study of 20 adults with WS reported that abnormal glucose tolerance or type I diabetes was

present in 75% of cases (Cherniske et al., 2004). In addition, puberty may begin around two years early, though truly precocious puberty is rare.

A formal assessment of life expectancy is lacking in WS, though they may live into old age if they do not experience cardiovascular complications, which provide the highest risk factor for mortality (Pober, 2010; Wessel et al., 2004).

Increased sensitivity and aversion to sound (hyperacusis) is thought to affect 80-90% of individuals with WS, with many having a fear of particular load noises such as thunder, fireworks, machinery or balloons bursting (Einfeld, Tonge, & Florio, 1997; Klein, Armstrong, Greer, & Brown, 1990). Sensory sensitivity also extends to tactility which can lead to feeding difficulties induced by disliked food textures (Morris, 2006).

Neuroimaging and autopsy studies have consistently shown that individuals with WS have small brains with reduced cerebral volume and hypoplasia of the parietal and occipital lobes, but relative preservation of the cerebellum (see Martens, Wilson, & Reutens, 2008, for a review). Two high resolution neuroimaging studies of a total 54 young adults with WS (*M* CA = 29 ± 9 years) matched for age and sex with normal controls found that the WS group had decreased cerebral (13% reduction) and brainstem (20% reduction) volumes, and overall brain volume was reduced by 13% relative to controls. The thalamus and basal ganglia were also disproportionately reduced in volume in the WS participants. The frontal lobe, cerebellum, amygdala, superior temporal gyrus, anterior cingulate, and fusiform gyrus volumes were relatively preserved (Chiang et al., 2007; Reiss et al., 2000). Tissue composition analysis indicated that lower cerebral volume was due to a reduction in white matter, whilst grey matter volume was relatively preserved, except in the right occipital lobe, where excessive grey matter volume was lost (Reiss et al., 2000). Chiari I malformation (displacement of the cerebellar tonsils), which may be due to reduced size of the skull compartment holding the cerebellum (Mercuri et al., 1997; Pober & Filiano, 1995), as well as reduced size and differential shape of the corpus collosum have also been reported (Tomaiuolo et al., 2002).

2.3.2 Cognitive features

WS has a complex and uneven psychological profile with an unusual pattern of strengths and weaknesses. Most individuals have mild to moderate ID with an average IQ between 50 and 60 points. IQ can range from 40 to 100 though few individuals with WS score higher than 70 (Martens et al., 2008). For individuals with WS, their strengths lie with selected facets of language, facial recognition, and social and interpersonal skills, combined with weaknesses in visuospatial processing and visuomotor abilities (Martens et al., 2008; Meyer-Lindenberg, Mervis, & Berman, 2006).

Early studies of individuals with WS indicated that language ability was an island of *preserved* skill amid severe cognitive impairment, noting that expressive language was complex and grammatically correct. Individuals with WS were found to be able to show proper use of a full range of complex grammatical structures such as inflections, tenses, passive voice, conditionals, pronouns, plurals and negation. They were described as loquacious, with fluent expressive language and much use of unusual, though correct, low-frequency vocabulary (Bellugi, Bihrle, Neville, Doherty, & Jernigan, 1992; Bellugi, Marks, Bihrle, & Sabo, 1993; Rossen, Klima, Bellugi, Bihrle, & Jones, 1996). This phenomenon came to be researched in depth as it was assumed to provide proof that language was a neural module that develops independently, even in the face of ID. However, more recent, in-depth research suggests that individuals with WS are not as proficient with language as was previously thought (Brock, 2007; Karmiloff-Smith et al., 1997; Martens et al., 2008). Whilst it is true that their knowledge of vocabulary is a relative strength and they do often use unusual, low-frequency words, there is actually little evidence to suggest that other language skills are much better than what would be expected given their overall or nonverbal MA. For example, difficulties are evident with oral fluency, reciprocal conversation skills, and understanding and conveying context (Brock, 2007; Martens et al., 2008). In addition, individuals with WS have problems understanding morphosyntactical grammatical rules governing the structure of words and sentences. In a group of 18 individuals with WS aged 8.33 to 34.08 years (M = 18.17 ± 7.92), Karmiloff-Smith et al. (1997) found a mean MA of only 6.25 (± 1.66) years on a test of morphosyntax which TD children, matched for vocabulary level, find easy. Clearly grammatical ability is not, in fact, intact. Nevertheless, individuals with WS have relatively good receptive and expressive vocabulary, mean length of utterances, and they are able to correctly use some grammatical constructs such as irregular past tense and plurals. An interesting point is that visuospatial deficits in WS seem to be mirrored by problems with grammatical constructs involving spatial or relational terms (Brock, 2007; Martens et al., 2008). Language onset is also atypical. Whereas TD infants engage in joint attention and pointing at around 10 months of age, infants and toddlers with WS show more interest in faces than objects and do not tend to initiate or respond to pointing. In TD infants, pointing serves as an important precursor to language comprehension, with the provision of labels in response to pointing enabling the young child to establish reference between the object and its label. Despite their deficiency in joint attention and pointing, toddlers with WS still develop language and, in fact, have higher levels of vocabulary than nonverbal MA-matched TD controls. This suggests that individuals with WS develop language using a different strategy that does not involve reference to the object (Laing et al., 2002).

Previous arguments for the intact language abilities in WS may have stemmed from often being compared to individuals with DS, for whom expressive language is a weakness. The disparity between the disorders thereby becomes all the more clear. Vicari, Caselli, Gagliardi, Tonucci and Volterra (2002) compared the language abilities of 12 young children with DS (*M* CA = 5.60 ± .83 years), 12 with WS (*M* CA = 4.85 ± 1.87 years) and 12 TD children (*M* CA = 2.48 ± .29 years). The groups had comparable non-verbal MA of around 2.5 years, as well as similar levels of vocabulary knowledge as reported by mothers. Differences emerged between the groups in their use of language. Children with DS used significantly more simple sentences (e.g., *Medicine no!*) and fewer full sentences (e.g., *I don't want any medicine*) relative to controls. Children with WS were not significantly different from either group in their use of both simple and full sentences, perhaps because sample sizes were small. Similarly, on a verbal comprehension test where the child was asked to respond to requests such as pointing to body parts or selecting the correct toy from an array, children with DS performed significantly less well than the TD group, whilst children with WS scored between the DS and TD groups, not being significantly different from either group. On a phrase repetition task, children with DS recited significantly fewer phrases correctly than both other groups. The TD group had slightly, but not significantly higher scores than the WS group, but their pattern of types of mistakes made was different. Specifically, children with WS were significantly more likely than TD children to omit nouns, verbs and modifiers (words that add meaning to, or qualify the sense of another word or word group), but not articles (indicators of nouns, e.g., *a, an, the*) or prepositions (a word or phrase indicating relation, e.g., *at, by, with, from*) when repeating phrases. When the mean length of utterances from spontaneous speech was compared, children with WS had the longest utterances, which were significantly longer than those produced by children with DS. The TD group did not significantly differ from either the DS or WS groups. Finally, the researchers found that vocabulary size correlated strongly and significantly with children's use of full sentences, the number of correctly repeated phrases and with mean length of utterances in children with DS and WS. The authors did not comment on whether or not these relationships existed in their TD group, but did cite other work which has found this effect. To summarise, the findings show that language ability in DS is significantly poorer than that of MA matched controls. Children with WS generally performed better than those with DS, although not as well as TD children who were chronologically younger but matched for nonverbal MA. Although these group differences tended not to reach significance, they suggest that language ability in young children with WS is slightly, though not significantly, worse than what would be predicted given their MA. This further lends weight to the argument that language ability in WS is not as intact as was previously thought.

In direct contrast to DS, individuals with WS display relative strengths in verbal STM whilst their performance on spatial span tasks is consistently below what would be expected based on their CA, MA, or overall level of cognitive impairment (Rowe & Mervis, 2006). Wang & Bellugi (1994) compared the performance of nine adolescents with DS to nine age- and IQ-matched individuals with WS on the digit and spatial span tasks. A dissociation emerged whereby the WS group performed significantly better than the DS group on the digit span forwards (4.56 vs 2.89), whilst the DS group performed best on the spatial task (3.00 vs 3.78). The group difference on digit span backwards was not significant (2.67 vs 2.00), suggesting that the verbal advantage of individuals with WS does not transfer to working memory. This double dissociation of the two groups for phonological and visuospatial STM provides strong evidence for the neurobiological and genetic separation of these two functions. Similarly, Klein and Mervis (1999) tested 13 CA-matched pairs of 9 and 10 year old children with DS and WS on a range of cognitive and language abilities. As they predicted, the WS group showed relative strengths in the verbal and memory domains (verbal and numerical memory) compared to the DS group, whereas children with DS showed relative strengths in perceptual and performance tasks (block building, draw-a-child, draw-a-design). There was no difference between groups on tasks of puzzle solving, word knowledge, number questions, tapping sequence, right/left orientation, verbal fluency, opposite analogies, conceptual grouping, counting and sorting, or vocabulary knowledge. Results should be interpreted with caution due to the low sample size and consequent low power, but they do suggest that by 10 years of age, children with WS show strong verbal memory skills and weak visuospatial constructive skills compared to children with DS. The pattern of results seen in this study suggests that the linguistic strengths seen in the WS group are likely to be due to their memory for verbal material, rather than their semantic abilities, as there was no difference between groups on receptive vocabulary tasks or on verbal semantic tasks not involving STM (e.g., word knowledge, number questions, opposite analogies, and verbal fluency). The results also highlight the importance of reviewing subscales when investigating atypical groups; here the DS and WS groups were matched for overall cognitive ability, yet detailed analysis revealed that they achieved their scores by different means. In contrast, (Cherniske et al., 2004) found a mean full scale IQ of 68 in 20 adults with WS, and that verbal and performance scale scores were comparable. Only one participant had a significantly higher verbal than performance score.

Other executive functions are also affected in WS. Menghini, Addona, Costanzo and Vicari (2010) used a large battery of standardised neuropsychological tests to assess executive function in 15 adolescents and young adults with WS (*M* CA = 19.92) relative to 15 TD children matched for non-verbal MA (*M* CA = 7.5, *M* MA = 6.75). Participants with WS performed well on tasks that relied on verbal material, such as a colour Stroop task, verbal fluency and verbal shifting categories. These

latter two tasks involve listing as many items as possible in two minutes from a given semantic category, e.g., animals or fruits. The shifting task involved alternating between the two categories. Conversely, ability to shift between different rules when sorting objects according to size, shape, colour, and symbol, and to switch between reading numbers and letters were deficient, relative to controls. Individuals with WS also showed deficits on tasks of visuospatial selective attention on a visual search task, and sustained auditory attention that involved listening to and counting tones. Planning ability was assessed using the Tower of London task. Individuals with WS took more moves to complete the puzzle and made more errors than the TD group, although they were just as fast, suggesting impulsive responding that is fast but inaccurate. In addition, they made significantly more errors on a CPT that involved responding to all stimuli except a red circle, again showing problems with inhibition.

Rhodes, Riby, Park, Fraser and Campbell (2010) found contrasting results using the Stockings of Cambridge task, a computerised version of the Tower of London. The performance of 19 individuals with WS aged 11 to 29 (M = 18.08 ± 5.58) was compared with two TD control groups, one matched for CA, the other matched for receptive vocabulary knowledge (M CA = 9.25 ± 1.0). Whilst their performance was comparable to the verbal-matched group, the WS group took significantly more moves to complete the model than the CA-matched group when the solution necessitated making three or more moves. It is possible that differences in findings reflect the task methodology. Individuals with WS are known to have problems with visuomotor skills, so using a computerised version of the task may decrease the task demands by removing the motor aspect, thereby allowing individuals with WS to perform at the same level as verbal-matched controls (Farran, Jarrold, & Gathercole, 2003). Participants with WS also performed similarly to the verbal-matched group on a computerised spatial working memory task which involved a visual search of an array of boxes that could be opened to collect tokens. Individuals with WS were more likely than both other groups to return to boxes that had already been checked, showing a memory deficit. They were as likely as the verbal-matched group to develop a search strategy, but not as likely as the CA-matched group. The WS group also showed significantly impaired performance relative to both control groups on their ability to shift attention. In general, the results suggest that executive functions in WS are below what would be expected based on MA. Particular problems are noted with attention, planning, inhibition and shifting, but functions involving language skill appear to be better preserved.

Individuals with WS have been found to be unable to understand the Piagetian concepts of conservation (that properties such as volume and weight remain constant when an object's shape, colour, position or other properties are altered) and seriation (ability to order objects according to a

common property). In TD children this concept is usually mastered by around age 7 or 8 years, however it has been found that individuals with WS never master these or other simple concepts, for example, in a seriation task they are unable to align a set of rods in order of size, tending to focus on only two rods at a time (Bellugi et al., 1993).

One of the specific problems with visuospatial processing in WS is their tendency to focus on local rather than global aspects of a problem. For example, faced with Navon hierarchical figures (e.g., the letter *A* composed of small *Ss*), they are able to recognise both the local (*Ss*) and global (*A*) levels, but when asked to draw the figure they focus only on the local elements, drawing the *Ss*, but usually arranging them in lines rather than the global *A*. Their difficulty may therefore lie in planning and executing motor responses, rather than in visuospatial perception per se (Bellugi et al., 1992, 1993; Farran et al., 2003; Martens et al., 2008). This is quite the opposite of the pattern seen in DS, where subjects draw the *A* whilst ignoring the *Ss*. Similarly, when asked to draw an object, individuals with WS draw each part of the object without relation to one another, creating an image that is unrecognisable, yet which they can describe fluently (Bellugi, Wang, & Jernigan, 1994). In addition, individuals with WS fail the block design task of the Wechsler Intelligence Scale for Children – Revised (WISC-R) which involves arranging the patterns on a series of black and white blocks into a model configuration. Again, individuals with WS focus on the local elements, arranging parts of the pattern but ignoring the global aspect. Individuals with DS focus on the overall configuration but ignore the elements. Consequently, both DS and WS groups fail on the task, but it highlights the importance of investigating the types of mistakes made, since both groups have remarkably different strategies for solving the puzzle (Bellugi et al., 1994; Bihrle, Bellugi, Delis, & Marks, 1989). This local bias in WS may explain their poor performance on spatial span tasks as they focus only on each individual block, ignoring the global configuration. The local bias and inability to fully attend to global elements in WS is a problem also seen in patients with right hemisphere brain damage. Indeed, this could be explained by the reduction of grey matter in the right occipital lobe in WS, an area involved in visual processing (Reiss et al., 2000, 2004). In terms of neural pathways, this also suggests that the ventral stream functions normally for processing what visual information is, whilst there may be an abnormality in the dorsal stream which processes spatial location (Meyer-Lindenberg et al., 2006).

The global processing deficit also extends to facial recognition, an area of relative skill in WS. Individuals with WS are better able to recognise faces than MA-matched TD children, though not as well as CA-matched controls (Gagliardi et al., 2003). However, their strategy for recognising faces appears to be different. Karmiloff-Smith et al. (2004) conducted a face processing study with 12

adult participants with WS (*M* CA = 30.0 ± 11.92) compared with a control group matched for sex, CA and socioeconomic status. Participants completed a task where they were asked to make a decision on whether two faces were the same or different. A photograph of a real female face was used which was adjusted by making changes either to the features (e.g., replacing the eyes or nose with the eyes or nose from another face) or to the configuration of the distance between features. In addition, in half of the 120 trials, the faces were presented upside-down. Results showed that both groups were equally good for judging differences in features between two upright faces, being 85% accurate, whereas when differences were configural, the WS group were significantly less accurate than the control group (51% vs 75%). Configural processing of features requires expertise in face recognition. The fact that individuals with WS perform well on the featural task but poorly on the configural task suggests that their strategy for detecting differences in faces depends on local processing of the features, rather than higher order holistic processing of their arrangement. Further evidence for this comes from studying the effect of inverted faces on task performance. In TD participants inversion did not disrupt featural processing, but led to a 46% reduction in accuracy for detecting configural differences. This is because holistic face processing requires the face to be upright, the way that we normally view faces, and inversion interferes with the familiar pattern of facial features thus allowing them to only be processed at the features level. Interestingly, inversion led to only a 20% drop in accuracy of detecting configural differences for the WS group, showing that they were less sensitive to the inversion effect and therefore atypical in configural processing.

Some methodological issues exist when conducting research with atypical groups. Firstly, the selection of an appropriate control group is an important factor. Many studies choose to compare atypical individuals to a TD control group who are matched for MA. Whilst this is sometimes necessary to avoid a ceiling effect in a CA-matched control group who may be completing tasks that are well below their ability, it raises the issue that life experience and other developmental markers may not yet be present when using a much younger control group. A useful approach is to analyse the developmental trajectories of the atypical groups compared with a CA-matched TD control group in order to see whether development is atypical, delayed or both. This is likely to give richer, more informative data than simply comparing group means, especially when the study covers a wide age range. Another option is to compare developmental disorders with another disorder. This is especially useful when two disorder groups can be matched for both CA and MA, although a control group of TD children should still also be used. Due to the rarity of WS, most studies have small sample sizes, for example, a review of 178 peer-reviewed research articles reported that the majority of studies (57%) had utilised fewer than 15 participants and that larger studies tended to be parent-report questionnaire-based studies rather than empirical research (Martens et al., 2008). It

should also be noted that participants of studies prior to at least 1993 would not have had WS confirmed by FISH, thus participant selection for studies was less rigorous than it can be today.

Recently research has begun to investigate the precise genetic causes of abnormalities by using mouse models and by studying the physiology and behavioural phenotype of individuals with smaller WS deletions relative to those with large deletions (Karmiloff-Smith et al., 2012; Meyer-Lindenberg et al., 2006; Tassabehji, 2003). For example, a larger deletion may be associated with lower IQ (Morris & Mervis, 2000).

2.3.1 Behaviour

Most individuals with WS are highly friendly, empathic and fascinated with the social world around them, often leading to distraction. They generally appear charming, engaging and chatty; eagerly participating in social interaction, even with strangers. In a study of 70 adults with WS, their parents and caregivers reported this hypersociability to be a problem, since social disinhibition, over-friendliness and trust leaves individuals vulnerable to exploitation and abuse. In fact, 20% of the sample had been alleged victims of sexual assault (Davies, Udwin, & Howlin, 1998). Despite their friendly and sociable characters, almost all adults with WS were reported to have problems establishing friendships and three quarters were socially isolated. In addition, it was reported that nearly all the adults with WS suffered with anxiety, preoccupations, obsessions, distractibility, and repetitive or stereotyped movements such as rocking or hand wringing/rubbing. In the same sample, irritability, a low threshold for annoyance and phobias were evident in around two thirds. These were likely to cause disruption to daily activities, for example five of the 70 participants had a phobia of balloons, probably due to hyperacusis and fear of them popping, which prevented them from attending parties. Anxiety tended to be anticipatory worry and focussed around uncertainty and perceived threat of future events, even for enjoyable events and relatively minor incidents such as a change in routine, staff or the environment. Twenty-one per cent of the sample had been referred to mental health services but families were generally unsatisfied with the interventions and results. Similar findings have been reported by Cherniske et al. (2004) in a comprehensive study of 20 adults with WS and also by Einfeld et al. (1997) in 70 children and adolescents with WS, suggesting that the psychological profile of WS is fairly consistent throughout the lifespan. In addition, a five year follow-up of 53 of these young people with WS suggested that behavioural and emotional problems were persistent over time, although there was a reduction in self-absorbed behaviours such as preoccupations and being a loner (Einfeld, Tonge, & Rees, 2001). Leyfer, Woodruff-borden, Klein-Tasman, Fricke and Mervis (2006) found a high prevalence of psychiatric disorders in children and adolescents with WS. Of an initial sample of 128 4 to 16 year olds with WS, nine (7%) met the criteria

for an autism spectrum disorder. Structured diagnostic interviews designed to diagnose childhood and adolescent anxiety disorders were conducted with parents of the remaining 119 individuals (*M* CA = 9.1 ± 3.3 years). Specific phobias occurred in 53.8% of the sample, with the most common being a fear of loud noises (27.7%). Although anxiety was common and prevalence increased with age, only 12% of the sample met the DSM-IV criteria for generalised anxiety disorder. ADHD was diagnosed in 64.7% of the sample; of these 68.8% were predominantly inattentive, 3.9% were predominantly hyperactive/impulsive, and the remaining 25.9% were both inattentive and hyperactive/impulsive. This is far higher than the prevalence rate of around 5% reported in TD children (Scahill & Schwab-Stone, 2000) Interestingly, with increasing age, ADHD of the inattentive type became increasingly more common relative to other types, whilst there was a corresponding decrease in the proportion of hyperactive/impulsive and combined ADHD types. This highlights the importance of studying developmental trajectories for atypical groups as these can reveal significant changes across the age range. Simply reporting the mean group scores reduces the quality of the data and interest of the findings. ADHD was not related to children's intellectual ability.

The anxiety profile in WS may be explained by abnormal activity in the amygdala, an area of the brain involved in the fear response. In 13 adults with WS, Meyer-Lindenberg et al. (2005) found significantly diminished amygdala activation when viewing images of threatening or angry faces, relative to CA and gender-matched healthy control participants. This reduction in the responsiveness to social danger may contribute to the social disinhibition and diminished fear of strangers that is characteristic of WS. Conversely, participants with WS showed abnormally increased activation when viewing threatening non-social scenes, suggesting a likely neural basis for the high levels of non-social anxiety in WS.

2.3.2 Sleep

Although sleep disorders are common in a number of developmental disorders, experimental research in WS is lacking. Similarly to the DS population, much previous data on sleep in WS has been acquired solely from parent-report questionnaires. Parents of children with WS informally report that their children have problems with sleep, and these have often been noted in WS as an aside to papers covering a range of other behavioural and cognitive phenomena. For example, early general questionnaire studies described settling problems and night waking (Udwin et al., 1987), as well as bed wetting, getting up for the bathroom, and sleep anxiety (Sarimski, 1996). Parents and caregivers have reported that around one third of 70 children with WS (Einfeld et al., 1997) and one quarter of 70 adults with WS (Davies et al., 1998) have sleep problems such as restlessness and nightmares. In adults these were disruptive to daily life in only three cases. Only recently has

research focused specifically on sleep problems in WS and there are now several research groups investigating the issue.

We conducted the first large-scale questionnaire study, to our knowledge, specifically investigating sleep problems in school-aged children with WS. Parents of 64 children aged 6 to 12 with WS (*M* CA = 8.3 ± 2.07 years) and 94 parents of TD children completed the CSHQ and a medical history questionnaire (Annaz et al., 2011). Ninety-seven per cent of parents reported their child with WS to have problems with sleep, which included long sleep latencies, sleep anxiety, night wakings and bedtime resistance. Nocturnal enuresis was reported in half of the children with WS, irrespective of age, and a third were reported to snore. Sixty-one per cent complained of daytime tiredness, likely as a result of these sleep problems. Sleep problems tended not to be related to medical conditions; however, asthma and allergies were strong predictors of sleep onset delay in the WS group. In TD children sleep problems improved with age. This change was not evident in the WS group suggesting that sleep problems in WS decrease at a much slower rate and may be enduring into adulthood. These subjective reports were supported with actigraphy data from a subgroup of 22 children which showed long sleep latencies (*M* = 46 minutes) with six children taking more than one hour to fall asleep (Annaz & Ashworth, 2011; Dimitriou et al., 2013).

Objective measures have found evidence for increased PLMD (Arens et al., 1998; Gombos, Bódizs, & Kovács, 2011) as well as significant differences in sleep architecture, specifically decreased sleep efficiency, decreased REM sleep and increased slow wave sleep (Gombos et al., 2011; Mason et al., 2011). Although research thus far indicates significant sleep problems in WS, more in-depth research is needed.

Arens et al. (1998) investigated the prevalence of PLMD in children with WS. Based on parent reports of children with WS struggling to initiate and maintain sleep, the researchers interviewed parents of 28 children with WS (CA range 1.5 to 10 years, *M* = 4.7 ± 2.3) in order to screen children for symptoms suggestive of a movement arousal disorder. Of 16 children (57%) identified as having suggestive symptoms, seven agreed to testing by PSG. Compared with ten healthy TD children matched for CA, the children with WS spent a greater percentage of the sleep period in wake (10% vs 4%) and SWS (34% vs 20%), whilst spending a smaller percentage in stages I and II (41% vs 59%). As expected, the WS group also showed more leg movements than controls (158 vs 65), including more arousals and awakenings due to movements. These differences were all significant ($p < .05$).

The authors note the significance of finding PLMD in all seven children, but considering that these children were antecedently screened, and only studied with PSG if there was a possibility of a limb

movement disorder, then it is not quite so surprising that all showed PLMD. What is perhaps surprising is that 57% of the original sample were screened as having possible PLMD, a syndrome thought to affect only 10% of TD children (Crabtree et al., 2003). Nevertheless, the conclusion cannot be drawn that all individuals with WS suffer from PLMD as children without risk factors were screened out of the tested subsample.

This group later expanded their findings using PSG and parent-report with a larger sample of 35 children and adolescents with WS (CA range 2 to 18 years, $M = 9.34 \pm 4.89$) who were not pre-selected for a history of sleep problems (Mason et al., 2011). A TD control group were matched for age, gender and ethnicity. The researchers found reduced sleep efficiency, increased WASO and increased SWS in the WS group. Parents of children with WS reported problems with initiating and maintaining sleep, general restlessness and an inability to keep still before sleep. Parents also reported repetitive leg movements and although their reports did correlate with objectively measured leg movements, these were actually no more prevalent than in the control group. Parent report was, on the whole, not very concordant with PSG for reporting of sleep efficiency or SDB, although a regression model of parent-report variables relating to night wakings and arousals yielded a significant relationship with sleep efficiency. There was a slightly elevated AHI in the WS group (2.3 v .03) but this difference was not significant.

Almost identical findings have been reported by Gombos, Bódizs, and Kovács (2011), who measured sleep patterns using PSG in nine adolescents and young adults with WS and an age- and gender-matched healthy control group (CA range 14-29 years, $M = 20.76$). Individuals with WS showed lower total sleep time (7:03 vs 8:50) and sleep efficiency (80.2 vs 94.4%), with increased WASO (68.6 vs 16.4 minutes) as well as an increase in SWS (24.8 vs 14.4%). There were no group differences in stage I or II but REM latency was increased (138.0 vs 85.1 minutes) and REM per cent was decreased in the WS group (19.2 vs 27.6%). Uni- and bi-lateral leg movements were also observed in the WS group. These occurred largely during NREM sleep and were not periodic but often led to sleep disruption, perhaps accounting for the sleep maintenance difficulties in WS. Differences in EEG activity were also observed, including significantly increased delta and slow wave activity with decreased alpha and sigma activity in WS sleep, together suggesting deeper sleep. Considered with the finding of increased percentage of SWS the results indicate an increased sleep propensity, possibly due to chronic sleep disruption or fatigue as a result of increased cognitive overload during the day.

Goldman et al. (2009) used structured interviews and wrist actigraphy to investigate sleep patterns and daytime sleepiness in 23 young adults with WS (CA range 17 to 35 years, $M = 25.5 \pm 8.0$) with an

overall mean IQ of 66.1 (±14.5). Almost all participants reported feelings of tiredness and sleepiness during the day, with over one third suffering excessive daytime sleepiness (ESS ≥ 10) and three quarters wanting to change their sleep. Nocturnal bathroom visits were the norm for almost all participants, with two thirds having to get up twice during the night for this reason. Fourteen per cent indicated symptoms of restless legs, a similar figure to that which would be expected in the general population, although without objectively measuring these it is impossible to determine PLMD. Twenty-three per cent had been told that they snored, a common symptom of OSAS. Seventeen individuals also agreed to wear an actiwatch for seven nights in order to objectively measure sleep patterns. Actual sleep time totalled 7.6 (± 1.2) hours but with low sleep efficiency (74.4%) due to long sleep latencies (37.7 ± 37.3 minutes) and WASO (56.1 ± 17.6 minutes). It seems that there is a disparity here, with participants having an adequate amount of sleep but the majority still reporting feelings of tiredness and sleepiness during the day. The authors propose that daytime tiredness is due to sleep disruption caused by multiple factors including urinary frequency, restless legs, SDB or other factors intrinsic to Williams syndrome. Without a control group it is difficult to note the significance of these results and establish how they differ from those of healthy typical subjects. The subjectivity of self-reported sleep information here may be particularly biased due to the characteristic WS symptom of the desire to please others so giving the answers they think others want to hear. This could lead to an inflated number of 'yes' answers. However, actigraphy data here does appear to support the subjective findings.

These studies are the only known research into sleep characteristics in WS. Most cover large age ranges but do not address developmental changes known to occur in sleep habits and sleep architecture. Nonetheless, they consistently reveal low sleep efficiency due to long sleep latencies and WASO. Bedtime resistance, sleep anxiety, restlessness, increased urinary frequency and snoring are also regular features. PLMD may be more common in WS, though evidence is conflicting and thus inconclusive. Individuals with WS also commonly report feeling sleepy during the day, indicating the consequences of disturbed night-time sleep.

2.3.3 Sleep and cognition

Sleep problems are common in individuals with WS, as are disorders such as ADHD, anxiety, learning difficulties and other behavioural problems. In TD children these are known to be related to sleep and improve when sleep problems are treated (O'Brien et al., 2003); however, few studies have investigated whether a relationship exists between sleep problems, behaviour and cognition in individuals with WS.

Arens et al. (1998) found evidence of PLMD in seven children with WS. Five children were then treated with clonazepam, a drug known to relieve PLMD symptoms in adults so allowing sleep patterns to return to normal. Four of the treated children showed an immediate and sustained improvement in sleep with fewer and shorter awakenings. In addition, parents reported them to be less irritable during the day. Repeated PSG in three of these children 3 to 6 months after treatment showed a significant decrease in PLMD (from 13.4 ± 6.7 to 2.8 ± 2.2 per hour) and PLMD-related arousals (from 3.4 ± 0.9 to 1.2 ± 0.9 per hour) and awakenings (from 1.4 ± 1.0 to 0.4 ± 0.5), all similar to the control group.

More recently this research group investigated sleep patterns using PSG in a larger sample of 35 children and adolescents with WS (Mason et al., 2011). Parents also completed questionnaires relating to their child's sleep habits and symptoms of ADHD. In addition, all participants completed two versions of a CPT using a specialised response box. One version required responding to a target number, the other required responding to all digits except the target. These tasks measured sustained attention and inhibition respectively and each lasted under nine minutes. Parent ratings yielded a 52% prevalence of ADHD in the WS group, which was predominantly of the inattentive type, echoing the findings of Leyfer et al. (2006). Parent-report of ADHD symptoms did not correlate with any sleep variables (sleep efficiency and percentage of SWS from PSG, and parentally reported sleep problems), and children with ADHD symptoms did not show increased evidence of sleep problems relative to children without ADHD symptoms. The authors do not report the results of the CPTs, only that they found a significant negative correlation of -.48 (p = .01) indicating that reduced ability to inhibit responses was linked to greater stage I sleep. Also, they do not explain this finding.

Based on the hypothesis that sleep problems may affect sleep-dependent learning we investigated the impact of sleep on a motor memory task: the finger tapping task, in 12 children with WS and 15 TD children (CA range 6 to 12 years, M = 8.6) (Annaz & Ashworth, 2011; Dimitriou et al., 2013). Children were trained on the task in the evening and retested the following morning and afternoon. Following sleep, the control group dramatically improved in speed and accuracy but we found no evidence of sleep-related learning in WS. However, the lack of improvement in the WS group cannot be attributed to sleep problems before we first exclude possible difficulties with fine motor movements that are needed to perform the finger-tapping task.

Aside from these, no other known studies have investigated the effects that sleep problems may have on daytime behaviours and cognitive functioning or sleep-dependent learning in WS. Clearly more research is needed to assess a range of functions with rigorous methodology and adequate reporting of findings.

2.4 Problems for Parents of Children with Developmental Disorders

Raising a child with a developmental disorder such as DS or WS necessarily creates increased demands on parents compared to rearing a TD child. In addition to having to manage behavioural problems with the child, parents also face increased difficulties finding suitable schools, activity groups and learning support for their child. This burden leads parents of children with ID to be more likely to suffer with stress and depression than parents of TD children, with mothers often experiencing feelings of self-blame and chronic sorrow (Damrosch & Perry, 1989). Stress and depression appear to be strongly correlated with child behavioural problems, though not dependent upon maternal age, gender of the child or the level of the child's cognitive delay (Abbeduto et al., 2004; Baker et al., 2003; Baker, Blacher, Crnic, & Edelbrock, 2002; Fidler, Hodapp, & Dykens, 2000). This trend is especially seen in mothers of younger children with ID, but continues into older age groups. Mothers report greater stress and tendency to seek out-of-home care when behavioural or mental health problems are also present in their young adult offspring with ID (McIntyre, Blacher, & Baker, 2002). Studies investigating this link tend to be questionnaire studies and although many have investigated the wellbeing of parents of children with DS, very few have focused on WS. This is necessary as results cannot be generalised to mothers with children of different disorders. Parents of children with DS have been reported to experience less pessimism than parents of children with WS (Fidler et al., 2010) and less stress than mothers of children with other types of learning difficulty (Hodapp, Ricci, Ly, & Fidler, 2003). Eisenhower, Baker and Blacher (2005) conducted a longitudinal study of maternal wellbeing in 215 mothers of preschool children at ages 3, 4 and 5 years. Children were either TD (n = 136), or had DS (n = 12), CP (n = 10), ID (n = 43) or autism (n = 14). Parent-reports revealed that children with autism and CP had the most behavioural problems and their mothers experienced the highest levels of stress. Conversely, TD children and children with DS were the best behaved and parents reported the lowest stress. Between the ages of 3 and 5 years behaviour problems, particularly aggression, increased in the DS group and there was a corresponding increase in maternal stress, with mothers feeling that their child had a negative impact on their social relationships and feelings about parenting. Group differences were evident in maternal stress, even after controlling for mothers' level of education, child's behavioural problems and child's level of intellectual impairment. This suggests that maternal well-being is influenced by other factors specific to the syndrome, such as sleep problems, insistence on routines, personality, social problems, physical limitations or health problems.

A questionnaire survey of 114 mothers of 3 and 4 year old TD children found that mothers of children with sleep problems were more likely to experience depression and have physical health

problems affecting their daily functioning than those whose children did not have sleep problems (Lam et al., 2003). Children with sleep problems also tended to have higher rates of problem behaviour than children without sleep problems, which could also contribute to maternal depression. In addition, children's poor sleep quality is associated with maternal negative emotions, sensitivity and conflict (Bell & Belsky, 2008) and with maternal poor sleep quality, which in turn is a significant predictor of maternal stress, mood and fatigue (Meltzer & Mindell, 2007). It may not be possible to determine causation of the relationship between parent and child sleep problems since children with poor sleep may disturb their parents in the night, or their some sleep problems (such as SDB) may be related to genetic factors (Holberg, Natrajan, Cline, & Quan, 2000).

Treatment of a child's sleep problems can have a marked beneficial effect on the mother's emotional well-being, energy levels and family relationships (Pritchard & Appleton, 1988). Stores et al. (1998) found increased levels of maternal stress in mothers of children with DS who had sleep problems relative to those who did not, especially when the sleep problem was one of sleep maintenance or SDB. Therefore the presence and extent of sleep problems is an important consideration when investigating maternal wellbeing in mothers of children with developmental disorders. Sleep problems have also been found to create more stress for parents when they are also associated with higher levels of intellectual impairment, suggesting a complex relationship between parental stress, ID and sleep problems (Richdale et al., 2000).

Maternal depression can have a negative impact on a child's development through undesirable parenting practices such as negative perceptions of the child, poor discipline, unresponsiveness and inattention, leading to an increased incidence of behavioural, adjustment, cognitive and health problems in children of depressed mothers, which could in turn contribute to further maternal stress and depression (Bagner, Pettit, Lewinsohn, & Seeley, 2010; Cummings & Davies, 1994; Gelfand & Teti, 1990; Turney, 2012; Weaver, Shaw, Dishion, & Wilson, 2008).

Clearly, then, a complex relationship exists between characteristics of a child and the well-being of their mother. There is a need for further research to establish how syndrome-specific factors other than behavioural problems and cognitive level may impact on mothers' well-being. This study intends to use questionnaires to investigate depressive symptoms and sleep problems in parents of children with DS and WS compared with TD children, and to examine the relationship between child sleep and behaviour and their mothers' sleep and wellbeing.

2.5 Chapter summary

This chapter has discussed physiological and cognitive phenotypes of individuals with DS and WS as well as sleep characteristics and the limited research on the effects of sleep. It is clear that whilst the two syndromes are very different from one another, there are also many similarities.

Cognitively, each syndrome has a distinctive pattern of strengths and weaknesses. IQ is usually around 50 to 60 points although with a great deal of individual variability. Whilst their MAs based on full-scale IQ scores are quite well matched, individuals with WS perform relatively well on verbal tasks and poorly on procedural and visuospatial tasks, whilst the opposite is true of individuals with DS. Attentional difficulties are common to both groups. Ability across cognitive domains in children with DS and WS often develops slowly and/or atypically relative to TD children.

Sleep problems are evident in both groups, though the types of difficulties differ considerably. Individuals with DS often have breathing difficulties during sleep, ranging from snoring to OSAS, and related to increased restlessness and night wakings. Individuals with WS have difficulties initiating and maintaining sleep which may be related to anxieties, an inability to keep still at bedtime and/or PLMD. Both groups suffer with daytime sleepiness, a clear indication of inadequate night-time sleep. Parent reports of sleep problems may not be entirely accurate for reporting certain aspects of their children's sleep if their children do not disturb them during the night, so should be used alongside objective measures. However, one of the problems with research in developmental disorders is children's non-compliance with testing procedures. Often PSG is not possible as children will not co-operate with having electrodes attached to them, so less intrusive measures such as actigraphy provide a useful alternative.

The effects of sleep problems in TD children are wide-ranging, yet precious little research has focused on the effects of sleep problems in children with disorders. In DS sleep problems have been associated with increased behavioural problems and more hyperactive behaviour. One study also suggested that OSAS severity in DS may be linked to visuospatial skills. In children with WS successful treatment of PLMD led to an improvement in daytime behaviour and reduced irritability. In contrast with TD research, no evidence has been found showing a relationship between sleep problems and ADHD symptoms. We investigated sleep dependent learning on a procedural finger tapping task and found no evidence of a sleep-related improvement in children with WS, relative to a significant increase in the control group.

Sleep problems, behavioural problems, and having a child with a disability all contribute to maternal stress and depression. Further cross-syndrome comparisons are needed as it appears that

syndrome-specific factors other than behavioural problems and cognitive level may affect maternal well-being.

Sleep and its consequences is an area that requires thorough investigation in children with DS and WS as these groups clearly experience significant sleep problems. Since sleep problems have such a wide-ranging impact, they could at least partly contribute to many of the cognitive and behavioural difficulties experienced by children with DS and WS. As has been shown, sleep problems are often amenable to treatment, so alleviating the sleep problems could have a beneficial effect on daytime functioning and a knock-on effect on children's families and maternal well-being. This makes it particularly important to assess sleep problems in disorder groups in sufficient detail. Many studies have used only small groups, usually less than 15 participants per group. Matching participants in terms of age or ability is often a problem. Sleep research though tends to match participants by CA, as developmental changes to sleep architecture could confound results if working with participants from different age groups. Nevertheless, it is important to take a measure of MA in order to control for level of ability. Assessing MA of children with DS and WS is also an issue, tasks should not be verbal or visuospatial so as not to advantage or disadvantage either group. The Ravens Coloured Progressive Matrices is often used as it is non-verbal and measures reasoning ability so groups can be fairly well-matched.

2.6 Aims and Hypotheses

The aims of this study are:

1. To objectively define sleep quality and quantity using actigraphy and compare to parent-reported sleep data for school-aged TD children and children with DS and WS.

2. To quantify nocturnal oxyhaemoglobin desaturation and indices that can predict OSAS in these groups.

3. To examine performance on a selection of cognitive and sleep-dependent learning tasks.

4. To gather parentally-reported data on behaviour.

5. To examine how sleep quality, duration and oxyhaemoglobin saturation might be related to cognition, behaviour and sleep-dependent learning.

6. To assess whether there are age-related changes in sleep quality/duration and cognitive performance.

7. To assess maternal depression and sleep quality.

8. To investigate the effects of children's sleep and behaviour on maternal sleep and well-being.

It is predicted that:

1. Sleep problems in developmental disorders are syndrome-specific.

2. Children with DS will have significantly more SpO_2 desaturations, greater sleep fragmentation and lower sleep efficiency than TD children, as determined by pulse oximetry and actigraphy (Dyken et al., 2003; Marcus et al., 1991; Stebbens et al., 1991).

3. Children with WS will have longer sleep latencies, increased night waking and lower sleep efficiency than TD children (Annaz et al., 2011; Arens et al., 1998; Dimitriou et al., 2013; Mason et al., 2011).

4. TD children will have better cognitive performance than children with DS and WS (Menghine et al., 2010; Rowe and Mervis, 2006)

5. Children with DS and WS will have more behavioural problems than TD children (Capone et al., 2006; Coe et al., 1999; Einfeld et al., 1997).

6. Children with WS will show relative proficiency on verbal aspects of tasks, along with poorer performance on spatial aspects. The opposite will be true of children with DS (Klein & Mervis, 1999; Wang & Bellugi, 1994).

7. Task performance of TD children will be related to age, with older children performing better than younger children (Scerif, 2010; Tsujimoto, 2008).

8. Developmental performance gains will be reduced in children with DS and WS, relative to TD children, and will be related to MA rather than CA (Hick et al., 2005; Jarrold & Baddeley, 2001; Van Herwegen, Farran, & Annaz, 2011).

9. After controlling for age, better performance on cognitive tasks will be related to better sleep quality and/or duration (Archbold et al., 2004; Gruber et al., 2012; Kennedy et al., 2004; Sadeh et al., 2002).

10. Parent reports of children's sleep will not correspond well with objective measurements of sleep (Holley et al., 2010; Shott et al., 2006).

11. Parent report of children's daytime functioning will be more reliable than their sleep reports.

12. Parent reports of their child's behaviour will relate to children's sleep and SpO_2 measures, with greater sleep quality and/or duration and better SpO_2 being associated with better behaviour (Ali et al., 1994; Sadeh et al., 2002; Smedje et al., 2001).

13. Children will show evidence of sleep-dependent learning on memory tasks and this improvement may be related to their sleep quality and/or duration (Backhaus et al., 2008; Henderson et al., 2012; Wilhelm et al., 2008).

14. Depressive symptoms and sleep problems will be more prevalent in parents of children with developmental disorders than parents of TD children, and these will be related to their child's sleep and behavioural problems (Baker et al., 2003; Lam, Hiscock, & Wake, 2003; Meltzer & Mindell, 2007).

3. Pilot Studies

3.1 Introduction

Pilot studies were conducted to devise a set of tasks assessing attention and sleep-dependent learning for declarative and procedural memory. The tasks needed to be of an appropriate standard for performance not to be at floor or ceiling level for any children, and test sessions needed to be as brief as possible. This was especially important as some of the test sessions would be late in the evening when children may already be tired.

Initially pilot studies were carried out with TD children, including a wider age range than the intended study age of 6 to 12. This was to ensure that tasks would not be at floor or ceiling level for children who were either developmentally delayed or advanced for their CA. Once tasks had been selected (as described below), they were conducted with the full age range of children with DS and WS as part of the main study and the results were monitored to ensure that the tasks were also suitable for these groups. They were found to be appropriate, so these results were included in the main study. This procedure was adopted because of the difficulty in recruiting children with DS and WS to the study, so as to allow the inclusion of the most possible children into the main study.

All TD children who took part in the pilot studies were recruited by word-of-mouth through friends and colleagues. All children were tested individually in a quiet room, usually in their own home. This chapter describes the pilot studies with TD children along with their results and a brief discussion of each task.

3.2 Declarative Memory Task

A declarative memory task was developed to assess sleep-dependent learning in children. Firstly, a word pairs task was tested, as sleep-dependent learning on this task has previously been demonstrated in children (Backhaus et al., 2008; Wilhelm et al., 2008). Following pilot studies using related and unrelated word pairs, it was developed into a non-word learning task. The reasoning for this is discussed in the following sections.

3.2.1 Associated word pairs task

An associated word pairs task was developed using words selected from the MacArthur-Bates Communicative Development Inventory (CDI; Fenson et al., 2006). This is a checklist of words used and understood by TD children aged 8 to 30 months. Sixty nouns were selected to create 30 matched pairs (e.g., paper-glue, tree-flower; see Appendix A1).

The learning session was administered using a Dell Vostro laptop computer with 15.5 inch screen. Children sat approximately 45cm from the screen. Word pairs were presented auditorily through headphones at a rate of one pair every five seconds. A visual cue of a white circle on a black background appeared on the screen 500ms before each word pair in order to focus attention. The listening exercise lasted approximately two minutes in total.

The task was completed by nine children aged 5 to 14 years (M = 7.9). The number of word pairs was varied between 20 and 30 to establish an appropriate level of difficulty. Children were told, "*You are going to hear some pairs of words, such as dog-bone. Try to remember which words go together. There will be a test at the end*". After completing the listening exercise, children were told the first word of each pair, asked if they remembered the paired word and were given feedback on the correct response. Children then completed another task so that immediate rehearsal was not possible. Finally they were tested and given no feedback on their answers. Children were first trained either in the morning or evening and were retested twice, following approximately equal retention intervals of wake and sleep. During each retest, children were told the first word of each pair and were asked if they could remember the paired word. They were not given feedback.

3.2.1.1 Results

Children's performance was assessed by how many word pairs they could correctly recall. The percentage change in score from one session to the next was calculated using the equation $((Y - X) / X) \times 100$, where X = score at first test and Y = score at retest. At baseline children remembered an average of 15.2 word pairs, which increased to 15.4 following sleep (.73% increase), and decreased to 15 word pairs after the wake retention interval (-1.4%).

3.2.1.2 Discussion

The associated word pairs task did not provide evidence for sleep-dependent memory consolidation, either by providing an active process to strengthen the memory traces, protecting from forgetting, or by blocking interference to the memory traces that could occur during the day.

In addition, three important points arose that warrant consideration.

Firstly, children reported finding the listening exercise very long, boring and quite difficult so lost concentration before it finished. In order to be appropriate for children with DS and WS, who have problems with attention and memory, the task needed to be shorter and interactive so that the experimenter could allow for distractions and lapses in concentration and divert the child's attention

back to the task when necessary. In this way, failure on the task could not be due to its attentional demands.

Secondly, a problem with creating a word pairs task is the subjective level of association between the words. Many tasks use associated words (such as 'arm-blood'; Wilhelm et al., 2008), whereas others use non-associated words (such as 'blanket-rubber'; Ellenbogen et al., 2009). Creating associations and categories for children is challenging because young or developmentally delayed children may not have fully formed semantic categories necessary to understand the association between two words. To illustrate this, in the present pilot study, most of the incorrect answers given by younger children (approximately 5 to 8 years) tended to be words that rhymed with the cue word, such as jelly-belly instead of jelly-donut. In contrast, mistakes made by older children (aged 9+) were more likely to be guesses at a semantic association, e.g., jelly-ice-cream. This difference suggests that semantic categories are better formed in older children, which lessens the task demands as children develop. Another problem with associated words is that in contrast to TD children, children with WS are more likely to base their associations on how similar two objects look, rather than making functional associations, for example, an orange would be more associated with the sun than with a banana (Thomas et al., 2010).

Finally, although simple words were selected from the CDI, children with a language delay as in DS and WS may not have pre-existing knowledge of some of the words. This would incorporate language learning into the task, therefore changing the task demands for some children.

3.2.2 Unrelated word pairs task

An unrelated word pairs task was developed to overcome problems with creating semantic categories that were encountered with the previous task. A set of 20 unrelated word pairs were created using words from the CDI (e.g., bus-glue, apple-hat; see Appendix A2). Using the same methodology as the associated word pairs task, four adults aged 23 to 54 years (M = 39.5) were trained on the unrelated word pairs around one hour before bedtime. They were retested the following morning after sleep, and evening after wake.

3.2.2.1 Results

Participants remembered an average of 1.75 word pairs at the end of the training session. This declined to 1.25 pairs following sleep, and 1 pair following the wake retention interval.

3.2.2.2 Discussion

As with the associated word pairs task, this task did not show evidence of sleep-dependent learning. It was a very difficult task for adults to complete so would have been harder still for children, especially the youngest and those with DS and WS. These children would be less able to use their imagination to create a link between the words and would find it challenging to focus attention on such a complex task. Therefore a pilot study for the unrelated word pairs task was not conducted with children.

The two word pairs tasks described above were unsuitable for the purposes of this study as participants did not show evidence of sleep-dependent learning. In order to address this as well as to avoid problems associated with developmental differences in language knowledge and word associations, the task was further developed using non-words, based on previous research finding improvements in foreign language learning following sleep (Davis et al., 2009; De Koninck et al., 1989).

3.2.3 Novel Animal Names task

Based on the literature review and results of the pilot studies with word pairs tasks, a task was developed that incorporated elements of both word pair and novel non-word learning. This task was specifically designed to improve on the frequently-used word pairs task for testing children. The instructions were simpler, the concept of personal names could be easily understood, and its nature made it more interesting and engaging for children. Farm and domestic animals were chosen as an anchor for learning non-words as animals' names, e.g., Orin the Horse and Kobi the Dog (see Appendix A3). It was thought that even young children would know these animals. The non-words were selected from an online dog names dictionary ("Puppy and Dog Names," 2010) so as to sound more realistically like names than non-words. None of the names were longer than two syllables, began with the same letter, rhymed with another or began with the same letter as their paired animal.

Attractive, coloured images of the animals were printed and laminated onto A6-sized white flashcards. See Figure 3.1 for an example. Prior to being taught the names it was ensured that children were familiar with, and could recognise, all of the animals. All cards were displayed on the table and children were asked to point to each of the animals as it was listed, for example, *"Show me the horse"*.

Figure 3.1. Example of Animal Names Flashcard Images: Basco the Cat and Jaala the Pig.

Children were told that they were going to be taught the personal names of the animals. Stimuli were presented one by one in a random order at a viewing distance of approximately 45cm. Children were told each animal's name, for example, the experimenter would say *"This is Dax the Rabbit"*. They were asked to repeat each name to ensure they had heard and could pronounce it correctly. The experimenter then repeated, *"Yes, Dax the Rabbit"* or *"No, Dax. Can you say it?"* if the child said the name incorrectly, and allowed approximately three seconds pause before continuing to the next animal. Once complete for all cards, they were shuffled to randomise the order and minimise primacy and recency effects. Children were shown the cards a second time, asked if they could remember the name of each animal, and given feedback with the correct name. This was repeated a further one to five times with 8 to 15 names to gauge the difficulty level of the task for children of different ages. This took around 15 minutes to complete. Following the final review of the names children completed a different task in order to remove any chance of immediate rehearsal. Children were then tested a final time on the animal names and were not given feedback. Children were first trained either in the morning or evening and were retested twice, following approximately equal retention intervals of wake and sleep. At the first retest they were not given feedback on their response. At the second retest they were told the correct name. Children then completed another task and finally they were tested once again to assess improvement within one session.

The scoring system was two points for a correct answer and one point for an almost correct answer if one phoneme was incorrect, for example, *"Tobi the Dog"* (instead of Kobi) or *"Basca the Cat"* (instead of Basco). Points were not awarded where children gave a correct name for the wrong animal. If children were unable to correctly pronounce the name during the learning trials their best consistent attempt was accepted as correct.

Ten children aged 3 to 14 years (M = 8.3) completed the pilot study.

3.2.3.1 Results

Two children were removed from the analysis because they were brother and sister and confessed to having discussed the names with one another. The final sample therefore consisted of eight children (*M* age = 8.25, range 3 to 14).

The changes in children's scores from one session to the next were calculated as a percentage using the equation $((Y - X) / X) \times 100$, where X = score at first test and Y = score at retest. Results showed that the number of names correctly remembered increased from 6.5 to 8.5 (30.8%) after the retention interval of sleep then decreased slightly to 8.13 names (-4.4%) following wake. The improvement following sleep was similar to the improvement of 32.50% seen on the final 'within session' test.

3.2.3.2 Discussion

The results suggest that a night of sleep can aid the consolidation of non-word learning at a rate comparable to that of a further learning trial. Sleep provides an active process to preferentially consolidate memory compared to the wake state.

The pilot study also showed that ten animals was an appropriate level of difficulty for children of all ages when they were shown each card five times in total prior to the first test. This procedure ensured that the test was not at floor level for the youngest children or ceiling level for the oldest. With this procedure all children remembered between two and eight names.

The Animal Names task was therefore considered appropriate for assessing sleep-dependent declarative memory in TD children and was used for this purpose in the main study.

3.3 Procedural memory task

Pilot studies were conducted using three procedural tasks to assess whether learning was sleep-dependent. These were Don't Buzz the Wire, a contour integration task, and the Tower of Hanoi. These will now be discussed.

3.3.1 Don't Buzz the Wire!

Don't Buzz the Wire! (Spears Games; Figure 3.2) is a steady-hand game where the participant must use a hooped wand to follow a length of wire around a series of curves and corners. If the wand come into contact with the wire the game emits a buzzing sound. Participants were initially trained on the task either in the morning or evening. They were asked to follow the wire as quickly as possible without 'buzzing the wire'. Their speed and number of errors were recorded for five trials.

Participants were retested following intervals of wake and sleep. This procedure was initially carried out with three adults aged 23 to 28 years (M = 25.33) in order to determine the method and scoring guidelines. Following this, three children aged 7 to 12 years (M = 9.3) took part in the pilot study.

Figure 3.2. Image of Don't Buzz the Wire steady-hand game.

3.3.1.1 Results

At the end of the training session the average speed for adults was 66 seconds with 1.9 errors. Retests following intervals of wake and sleep did not alter these figures dramatically (64s, 1.7 errors following wake; 67s, 2.0 errors following sleep). The children however were much quicker at the task (average speed 34 seconds during training, 37s following wake, 33s following sleep). Errors made by children were impossible to count as often the task was completed with constant buzzing. In addition, the child who took the longest to complete the task also made the fewest errors as he was taking more time to be careful.

3.3.1.2 Discussion

The task did not show evidence of sleep dependent learning in adults or children, although with such small groups it is not possible to be conclusive. For this reason and because of the difficulty with error counting the task was deemed to be unsuitable. It would also have been difficult for the children with DS and WS who would have been disadvantaged by their poorer skills in fine motor control.

As an alternative, pattern recognition tasks and perceptual integration tasks were considered, yet these generally rely on measuring performance by RT. It was thought that this was not a suitable gauge for children with slower processing speeds (as in DS and WS) and therefore slower RTs.

3.3.2 Contour integration task

A contour integration task was found that did not rely on RT or motor skill (Kozma-wiebe et al., 2006). The task is a perceptual task that requires implicit learning to improve. As procedural memories are implicit, the task was included here as a procedural learning task. The stimuli consisted of Gabor patches making an egg shaped contour amidst a noisy background. The participant must locate the egg and indicate on the computer keyboard which direction it is pointing in. The paradigm was forced choice, right or left, so participants should achieve 50% correct by chance. Each stimulus appeared on the screen for 2500ms followed by a grey screen which remained until the child responded. The task comprised six levels of increasing difficulty with 40 trials at each level, lasting for a total of around 10 minutes. Difficulty level was increased by introducing more jitter into the contour elements (see Figure 3.3).

The task was piloted with a group of ten TD children aged 6 to 12 years (mean: 9.13).

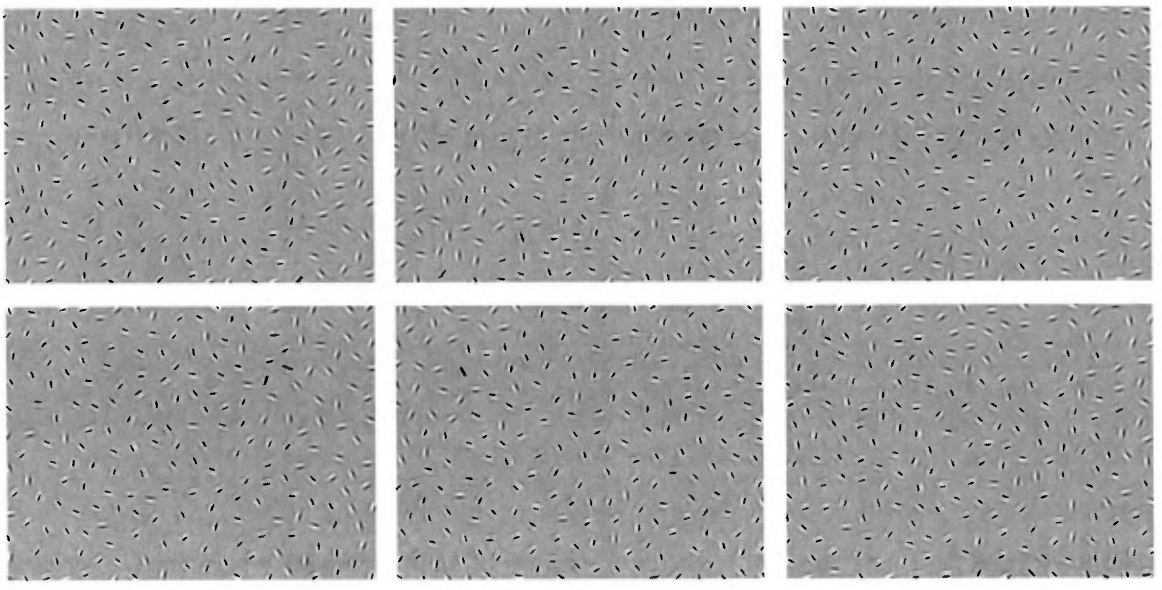

Figure 3.3. Example of Contour Integration Stimuli: Levels 1 to 6.

3.3.2.1 Results

The changes in children's scores from one session to the next were calculated as a percentage using the equation $((Y - X) / X) \times 100$, where X = score at first test and Y = score at retest. Performance on

the task increased from 63.55 to 70.69 (11.24% improvement) after the sleep retention interval and declined to 67.78 (-4.13%) following wake.

3.3.2.2 Discussion

The results show an improvement on the task following sleep, which may be evidence of sleep-dependent learning. The main problem with the task was that children reported it to be very boring and often simply alternated their responses between right and left without looking at the stimuli. A disadvantage with the design of the program was that a response could be recorded from the moment that the stimulus appeared on the screen, meaning that the child could repeatedly press a key and the experiment would advance through all the stimuli without the child attending to each image. Children often did this when bored, especially during the retests, and during the later, more difficult levels. For these reasons the task was deemed inappropriate for use in the present study.

3.3.3 Tower of Hanoi

The Tower of Hanoi is a mathematical puzzle invented by Eduardo Lucas in 1883 (see Figure 3.4). This cognitive procedural task has shown evidence of sleep-dependent learning related to REM sleep in adults (Smith et al., 2004; Smith, 1995) but, to our knowledge, has not yet been used to assess sleep-dependent learning in children. The puzzle consists of three pegs and a number of stackable disks of different diameters that can be slid onto any peg. It starts with the disks stacked in ascending order on the leftmost peg. The task objective is to move the entire stack of disks to the rightmost peg in as few moves as possible whilst following a strict set of rules: only one disk may be moved at a time and no disk may be placed on top of a smaller disk. The fewest possible number of moves is $2^n - 1$ where n is the number of disks.

Figure 3.4. Image of Tower of Hanoi Task.

The experimenter explained the rules to the child and ensured they understood by demonstrating legal and illegal moves and asking if each move was allowed, until the child was sure of the rules.

Children were told that they should plan their moves carefully and try to complete the puzzle in as few moves as possible. They completed the task using between three and five disks to determine an appropriate level of difficulty.

Children were trained by completing the task five times. This took around 30 minutes. They were retested following retention intervals of wake and sleep, where they completed the task twice during each session. Retests took around 10 to 15 minutes each. The rules were reiterated at the start of each session. This procedure was designed to allow children to become familiar with the task during the first session and then not have too much practice in the following sessions so that improvement could not be due to rehearsal.

Children's moves and rule violations were counted. If a child lifted the disk from a peg and placed it back on the same peg, it was counted as one move. If they touched a disk or lifted it slightly but it remained on the peg, it was not counted as a move.

Ten children aged 3 to 14 years ($M = 8.3$) completed the pilot study.

3.3.3.1 Results

The three disk task (seven moves) was very easy and children reached ceiling level at around age seven. With four disks (15 moves) all children were able to complete the task. The two youngest children (aged 3 and 5) made numerous rule violations, whereas older children reached ceiling level at around nine years old. The five disk task (31 moves) was at floor level for the two youngest children. All other children were able to complete it and no children reached ceiling level.

Analysis using the equation $((Y - X) / X) \times 100$, where X = score at first test and Y = score at retest, showed that children's performance improved by 18.67% following sleep but declined by 11.23% after the wake retention interval, possibly due to fatigue in the evening testing session. Percentage improvement within the learning session was calculated by comparing the first two trials with the fourth and fifth trials. Within this session children improved by 6.87%.

3.3.3.2 Discussion

The results suggest that an active process occurs during sleep that enhances performance to a greater extent than further practice. All children were able to complete the task and enjoyed doing so. It was therefore decided that the Tower of Hanoi was a suitable procedural task for assessing sleep-dependent learning in children. It was relatively quick to administer and has previously shown sleep-dependent learning in adults. In order to not reach ceiling level it was decided that a five disk task was the appropriate level for TD children but that children with DS and WS would complete the

task with four disks since they have a younger MA. Once the main study began, this procedure was monitored to determine that four disks was indeed the correct level for children with DS and WS.

3.3.4 Continuous Performance Task

In order to assess children's sustained and selective attention and impulsivity, a visual CPT was designed based upon other CPTs that have been used with young children and children with developmental disorders (Manly et al., 2001; Steele, Karmiloff-Smith, Cornish, & Scerif, 2012; Trezise et al., 2008). The task was developed using DMDX (Forster, 2009), a Win32-based system that can be used to present stimuli and accurately record RTs. It was presented on a Dell Vostro laptop with 15.5 inch screen and a viewing distance of around 45cm. The task required the child to respond to an infrequently occurring target whilst ignoring competing non-targets. Stimuli were attractive, coloured images of zoo animals where the targets were two different monkeys amongst eight other distracter animals (lion, tiger, anteater, leopard, giraffe, elephant, hippo and octopus) (see Figure 3.5).

Figure 3.5. Target Images in the Continuous Performance Task.

Stimuli were presented sequentially in a randomised order in the centre of a white background. They were arranged in blocks of 20, and randomised within blocks so that the maximum number of targets that could appear consecutively was eight, although the probability of this is low. The order that these blocks were presented was also randomised. Children were given written and verbal instructions, *"In this game you will see some pictures. You need to catch the naughty monkeys. Click every time you see a monkey"*. They were presented with images of the target monkeys, and were

told to press the left touchpad button to 'catch' the monkeys. Children were asked and shown to rest the index finger of their dominant hand on the response key and, if necessary, were reminded to do so throughout. There was a practice session of 20 trials where stimuli were presented slowly to ensure that children understood the instructions before completing the full test. During the practice a target always occurred as the second stimuli as an early reminder of the task demands. Following this, the block was randomised. During the test they were given verbal appraisals (e.g., *"Well done"*) when they clicked the target, and were reminded to *"Only catch the monkeys"* if they clicked non-targets. This was similar to the procedure used by Steele et al. (2012), where the computer made a 'reward' or 'error' sound in response to hits or incorrect clicks.

The number of stimuli, stimulus display time and interstimulus interval were varied in order to establish the optimum parameters.

Omission errors (where children missed targets), commission errors (incorrect hits) and RTs were recorded.

The CPT pilot study was completed by 12 children aged 3 to 14 (M = 7.9).

3.3.4.1 Results

The optimum temporal parameters derived from the pilot study were a 300ms stimulus display time with an interstimulus interval of 2000ms. The target was increased from one to two different monkeys based on feedback from children, and targets occurred on 20% of 200 trials. The full test lasted for 7:36 minutes.

Using these parameters, the mean number of omission errors was 5.25 (range 0 to 20) and mean commission errors was 13.5 (range 4 to 29).

3.3.4.2 Discussion

This pilot study allowed for the temporal parameters, number of targets, and number of trials to be adjusted in order to allow sufficient processing time between trials without bringing the task to ceiling level for more attentive children, and to allow enough time to show lapses in attention. Young children were able to complete the task and all children made some errors, so the task was not at floor or ceiling level.

3.4 Chapter Summary

Results of the pilot studies described in this chapter enabled the selection and development of appropriate tasks for assessing sleep-dependent learning and attention in children. The tasks carried forward to investigate sleep-dependent learning are the Animal Names declarative memory task and the Tower of Hanoi cognitive procedural task. Pilot testing also enabled temporal parameters to be established for the CPT. These tasks were suitable for TD children aged 3 to 14 and were therefore assumed to also be appropriate for testing children aged 6 to 12 with DS and WS. Nevertheless, the tasks continued to be monitored once the main study began in order to ensure this. No further changes to the tasks were necessary so results for the clinical groups are included only in the main results chapter. The general methodology is described in Chapter 4.

4. Methodology

This chapter discusses the general methodology used in the research, including an overview of the participants and a detailed description of experimental tasks, sleep recording and questionnaires used.

4.1 Ethical approval

The study was approved by The Institute of Education Research Ethics Committee and Middlesex University Research Ethics Committee. It was supported by grants from The Williams Syndrome Foundation UK and Down Syndrome Education International.

All parents were provided with full details of the study and gave written informed consent for their child to take part (Appendix B1). Children were asked for their assent verbally.

4.2 Participants

Participants were TD children and children with DS and WS, aged 6 to 12 years. This age group was chosen so that children would be old enough to understand the task instructions, and also to avoid the disruptive effects that adolescence has upon sleep patterns (Ohayon et al., 2004).

All children in the DS group had previously tested positive for trisomy of chromosome 21. Children with WS had been diagnosed clinically and by FISH analysis for the detection of hemizygosity at the elastin locus (7q11.22-11.23).

4.2.1 Exclusion criteria

Children were not included in the study if they had co-morbid medical or psychiatric disorders likely to affect sleep such as epilepsy, poorly controlled asthma or eczema; if they were taking any hypnotic medication and if English was not their first language. In addition, children needed to have functional hearing and vision.

4.2.2 Recruitment

TD children were recruited through three primary schools in North and East London, UK. Parents of children with DS were contacted through mailing lists of local support groups, special needs schools and other groups such as sports clubs and speech and language classes for children with disabilities. TD and DS families were given written information stating that the study was investigating normal sleep patterns, learning and attention in children (see Appendix B2 and B3). They were invited to respond to the school or to the researcher if they wished to take part. Sixty parents of TD children

responded to recruitment information; of these, five were excluded (one had a medical condition, two did not have English as their first language, and two later declined to take part). Of the 40 DS families who responded, 15 were excluded (six lived too far away, two would not tolerate the actiwatch, four had comorbid disorders or medical conditions, and three later declined to take part). Of the remaining 55 TD children and 25 children with DS who met the inclusion criteria, participants were selected based on age and sex in order to create balanced groups.

Contact details for parents of children with WS were made available by the Williams Syndrome Foundation UK. These parents had previously agreed to be contacted for research purposes. Parents were given study information over the telephone and later in writing (Appendix B3). Of all WS families contacted only two declined to take part in the study.

4.2.3 Sample

The final sample consisted of 41 TD children, 22 children with DS and 22 with WS. The majority of children were from middle socioeconomic background and were predominantly white. Their details are provided in Table 4.1. A one-way between-groups ANOVA indicated no significant difference in age between the three groups (F (2, 82) = .09, p = .92, η_p^2 <.01) and a Chi-square test showed no sex differences (χ^2 (2, 85) = .11, p = .95, phi = .04).

Table 4.1. *Participant details*

Group	*n*	Male/female	Age (*M* (SD))	Age range
TD	41	19 / 22	9.44 (1.70)	6.19 – 12.90
DS	22	11 / 11	9.42 (1.98)	6.09 – 12.23
WS	22	10 / 12	9.24 (2.13)	6.08 – 12.58

4.3 Materials

The study used objective measures for monitoring sleep and made use of several questionnaires to assess parentally reported sleep and behaviour. A battery of tests was also used for assessing cognition and sleep-dependent learning. These are described in detail below.

4.3.1 Sleep measures

Although parent reports are cheap and simple to administer and offer a wealth of valuable information, objective measures are undoubtedly more credible in research. Children's sleep was therefore also assessed using actigraphy, and pulse oximetry was used to measure SpO_2.

4.3.1.1 Actigraphy

Each child wore an Actiwatch Mini (CamNTech, Cambridge, UK; see Figure 4.1) on the non-dominant wrist, as if wearing a watch. They were requested to wear it continuously for one week, as is recommended by Acebo et al. (1999). Data were downloaded to computer and analysed using Sleep Analysis 7 (CamNTech, Cambridge, UK) at the default 'medium' sensitivity level (refer back to Section 1.6.3 for a description of actigraphy)

Figure 4.1. Actiwatch mini.

The child's bedtime and getting up time (as reported by parents) are entered into the program as shown in Figure 4.2. The program uses an algorithm to score each one-minute epoch as sleep or wake based on movement during that minute, as well as the two preceding and two successive minutes. Sleep start and sleep end were marked as the start and end respectively of a period of 10 or more minutes of immobility. The program also produces an actigram: a graphic representation of activity (movement) throughout the day (see Figure 4.3) where black bars indicate the amount of movement in each epoch.

Figure 4.2. Screen shot of Sleep Analysis 7 (CamNTech, Cambridge, UK).

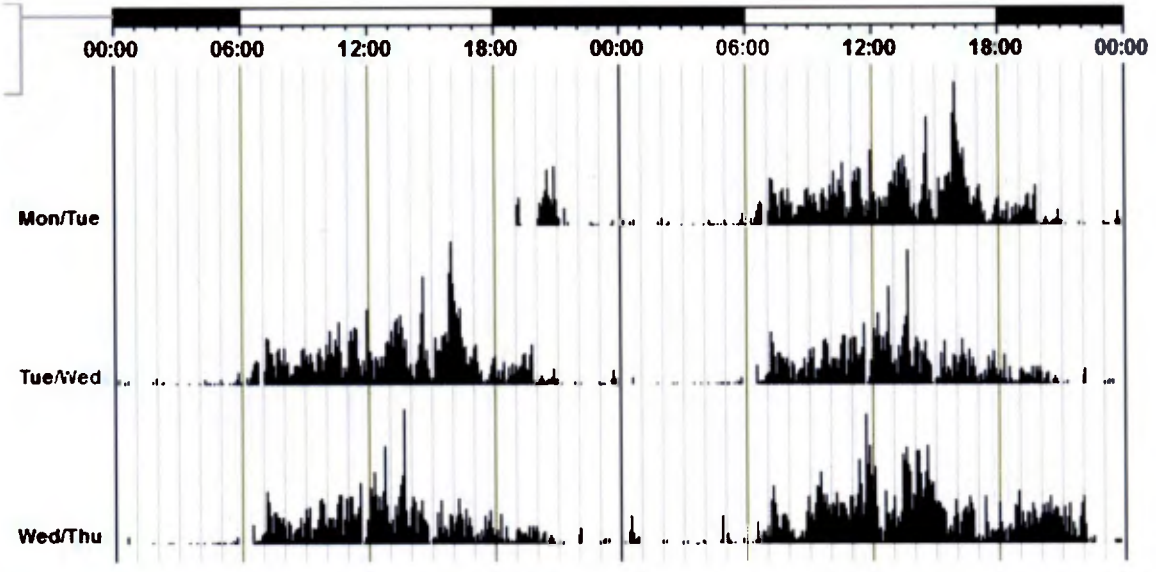

Figure 4.3. Example actigram. Black bars indicate movement during each epoch.

4.3.1.2 Sleep diary

Parents completed a sleep diary recording their child's bed time, getting up time, and any daytime naps or night-time awakenings for the duration of the study. These diary parameters were used to support analyses of actigraphy data.

4.3.1.3 Masimo pulse oximetry

As obstructive sleep apnoea is common in DS, heart rate and SpO_2 were measured in the child's home using Masimo Radical 8 monitors (see Figure 4.4). Recordings were taken through an infrared sensor attached to the toe; usually the second toe. Parents were shown how to use the device correctly and were given opportunity to ask any questions. They were requested to use the monitor overnight for three consecutive nights (refer back to section 1.6.4 for a description of pulse oximetry).

Figure 4.4. Masimo Pulse Oximetry Rad 8 Device.

Devices were set to a two-second averaging time and sampled SpO_2 saturation at 1 Hz. Data were analysed using Visi-Download software (Stowood Scientific Instruments, Oxford, UK)(Stowood Scientific Instruments, 1997). They were visually screened prior to analysis and artefacts such as low signal strength or periods of instability were removed from the analysis. The programme was set to automatically detect and remove artefacts where there was too much ambient light, low signal, low perfusion, interference, no pulse, and when the sensor was defective, not connected or not on the patient. Figure 4.5 shows a screen shot from Visi-Download showing SpO_2 (top row), pulse (middle) and perfusion (signal strength; bottom). This example shows several clear oxygen desaturations, usually coinciding with a peak in heart rate.

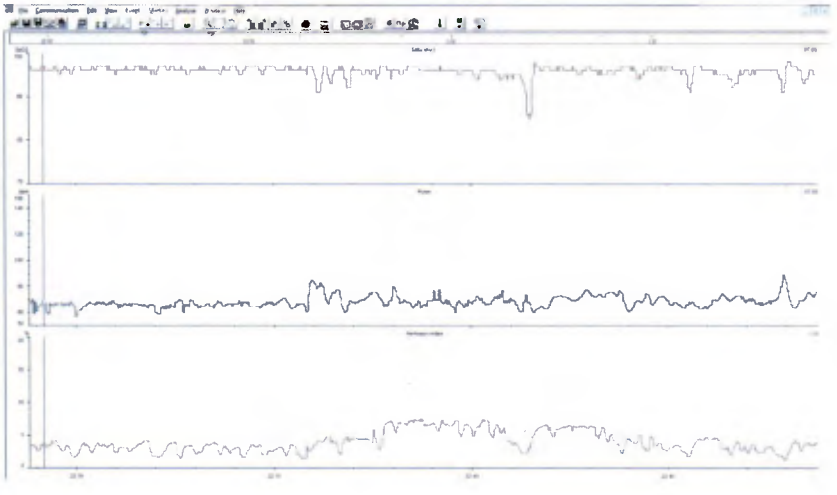

Figure 4.5. Screen shot from Visi-Download software (Stowood Scientific Instruments, Oxford, UK).

4.3.2 Experimental tasks

During the week in which children's sleep was examined, they also completed the test battery assessing sleep-dependent learning, attention, MA and short term memory tasks. In order to counterbalance groups, half of the children were trained on the learning tasks in the morning (Wake-sleep group), the other half trained in the evening (Sleep-wake group). They were then tested twice following approximately equal intervals of both wake and sleep. After completing the Animal Names and Tower of Hanoi tasks, children completed the CPT, Raven's Coloured Progressive Matrices, STM and working memory tests (described in the following sections) during either the second or third testing session, whichever was in the morning, to avoid fatigue effects (see Figure 4.6). Evening test times varied depending on the child's bedtime, morning sessions usually occurred at the child's school. To avoid interference that may occur by wake during the sleep retention interval, children were tested as early in the day as possible, usually as soon as they arrived at school or just after registration. They were also requested not to partake in any cognitively demanding activities, such as school work or music practice, between the evening and following morning test sessions.

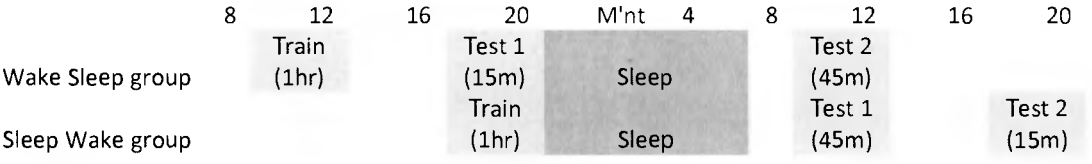

Figure 4.6. Testing schedule for Wake-sleep and Sleep-wake groups.

Ideally the time difference would have been 12 hours between each testing session in order to have a balanced sleep and wake interval. However, these differences were unavoidable due to variations in children's bedtimes and school start times and the need to minimise disruption to normal routines. The time differences between each session are presented in Table 4.2.

ANOVAs showed that the sleep interval was significantly longer than the wake interval for all groups (Table 4.2). In addition, the TD sleep interval was significantly shorter (F (2, 73) = 6.19, p = .003, η_p^2 = .15) and wake interval was significantly longer (F (2, 73) = 4.33, p = .02, η_p^2 = .11) than the corresponding intervals for the DS group.

Table 4.2. *Time duration between test sessions for sleep and wake retention intervals. Including ANOVA results comparing the sleep and wake retention interval length for each group*

	Sleep interval		Wake interval				
	M	Range	*M*	Range	*F*	*p*	η_p^2
TD	13:15	12:05 - 15:00	10:26	9:00 - 11:45	177.36	<.001	.83
DS	13:56	12:25 - 15:15	9:52	8:45 - 11:30	174.64	<.001	.90
WS	13:34	11:55 - 15:00	10:08	8:30 - 11:20	150.24	<.001	.88

4.3.3 Animal Names declarative learning task

Following pilot studies (Chapter 3), the Animal Names task was used to assess sleep-dependent declarative learning. As per the procedure described in Section 3.2.3, children were shown each animal five times in total. Following the final review of the names in this task, children completed the Tower of Hanoi task (described in the next section) in order to remove any chance of immediate rehearsal. Children were then tested a final time on the animal names and were given no feedback. The ten animals and their names are presented in Table 4.3.

Table 4.3. *Animal Names*

Animal	Name	Animal	Name
Cat	Basco	Horse	Orin
Chicken	Razz	Mouse	Galba
Cow	Artoo	Pig	Jaala
Dog	Kobi	Rabbit	Dax
Goat	Spyro	Sheep	Eagus

Children were retested twice, following intervals of wake and sleep. During the first retest they were shown the cards in a random order and asked if they could remember each name. They were not given feedback. During the second retest they were tested on the names and given feedback with

the correct name. They then completed the Tower of Hanoi task, before a final retest of the names to assess learning within one testing session.

4.3.4 Tower of Hanoi cognitive procedural learning task

The Tower of Hanoi task was conducted as per the procedure described in Section 3.3.3. TD children completed the task with five disks whereas children with DS and WS used four disks. All children completed the task five times during the training session, then twice during each session following retention intervals of wake and sleep.

4.3.5 Continuous performance task

To assess sustained and selective attention and inhibition, children completed the CPT as described in Section 3.3.4 with the parameters defined in 3.3.4.1.

4.3.6 Raven's Coloured Progressive Matrices

Raven's Coloured Progressive Matrices (RCPM; Raven, Raven, & Court, 1998) is a popular, standardised test of fluid intelligence that is often used to give a non-verbal reasoning score for children. This correlates well with IQ in TD children so can be used to give a child's non-verbal MA. This is necessary when researching with developmental disorder groups whose MA is discordant with their CA. The RCPM is designed for use with children aged 3 to 12 and has also been used with children with DS (Laws, Buckley, Bird, Macdonald, & Broadley, 1995) and WS (Van Herwegen, Farran, et al., 2011). The test consists of 36 abstract figures, arranged in three sets of increasing difficulty (Sets A, AB, B). Each figure has a section missing and the child must select the missing piece out of six options (see Figure 4.7 for an example). The task was conducted according to the manual, with no time limits, and it was ensured that all children understood the instructions before progressing.

In a normative sample of 618 Australian school-children, good split-half reliability (Spearman-Brown $r = .91$) and internal consistency (K-R formula 20 = .89) were reported (Cotton et al., 2005).

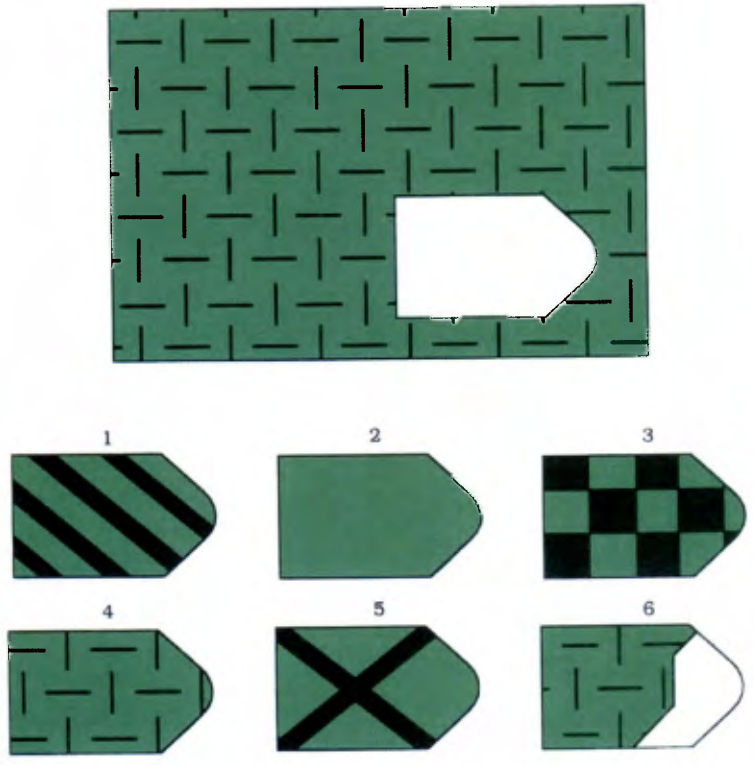

Figure 4.7. Ravens Coloured Progressive Matrices: #A1.

4.3.7 Short term and working memory span

Short term memory span was assessed using the digit span and block tapping tasks from the Wechsler Memory Scale (WMS; Wechsler, 1997). Together these two tasks provide comparable measures of verbal and non-verbal STM span. Both have been used with children with DS (Laws, 2002) and WS (Van Herwegen, Rundblad, Davelaar, & Annaz, 2011; Vicari, Brizzolara, Carlesimo, Pezzini, & Volterra, 1996) and may highlight specific differences between the groups, who tend to have relative strengths in spatial skills and verbal skills, respectively (Edgin, Pennington, & Mervis, 2010).

In the digit span task, the researcher read digits aloud and children were requested to immediately recite the sequence as accurately as possible. The block tapping task was conducted using the Spatial Span Board (The Psychological Corporation); a 28 by 22 cm (11 by 8.5 inch) white plastic base, with an irregular array of 10 blue blocks, each 3cm (1.2 inch) square. The experimenter tapped blocks with a finger and the child responded by repeating the sequence. One variation of the task involves

tapping the blocks with a pen but in this case a finger was used as this was how the child was expected to respond. Other experimenters have used a computerised version, but the physical version was used here to avoid possible difficulties with mouse control (see Berch, Krikorian, & Huha, 1998, for other variations).

For both tasks children were given a practice trial to ensure that they understood the instructions. Sequence length ranged from two to eight items. Two trials were administered at each level at a rate of one item per second. The child needed to pass at least one trial at each level so the tasks were administered until they failed both trials at a given level. They were awarded one point for each correctly completed sequence and span length was calculated as the length of the longest sequence that the child could correctly complete.

To assess working memory, the procedure was repeated for backwards digit and spatial spans, whereby the child was requested to repeat the sequences backwards.

4.4 Questionnaires

Parents were requested to complete a set of six questionnaires: three regarding their child's sleep and behaviour and three covering their own sleep and symptoms of depression. Please see appendices for copies of the questionnaires.

4.4.1 Children's Sleep Habits Questionnaire

The CSHQ (Owens, Spirito, & McGuinn, 2000) is a 33-item caregiver response questionnaire which screens for the occurrence of common sleep problem symptoms in school-aged children (See Appendix C1). Parents indicate whether each listed characteristic occurs usually (5-7 nights per week), sometimes (2-4 nights per week) or rarely (0-1 nights per week), for behaviours such as going to bed at the same time each night, sleepwalking, bruxism or snoring. Items are then scored from one to three, where higher scores signify greater problems with sleep. Scores are added to yield scores on eight subscales: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep disordered breathing and daytime sleepiness, as well as a total sleep disturbance score. Psychometric properties of the CSHQ have been published for a community sample of 469 TD children aged 4 to 10, and 154 children attending a sleep disorders clinic (Owens, Spirito, & McGuinn, 2000). Cronbach's alpha coefficients showed satisfactory internal consistency of .68 for the community sample and .78 for the clinical group. The questionnaire expressed adequate validity, with the clinical group scoring significantly worse than the community group (all p values < 001) on all subscales and 30 of the 33 individual items except 'wakes by him/herself', 'others wake child' and 'has a hard time getting out of bed in the morning'. Pearson's correlations for retest

reliability of 60 children after a two week interval ranged from .62 for the sleep onset delay subscale to .79 for sleep anxiety. T-tests showed no significant differences between the two ratings for any subscale. Although there are no established norms for total or subscale scores, Owens and colleagues (2000) found that a cut-off score of 41 yielded the best diagnostic confidence by correctly identifying 80% of the clinical sample. They recommend the questionnaire is most useful in comparing groups or assessing pre- and post-intervention. Although the CSHQ has not been validated for atypical populations, no specific tools yet exist for monitoring sleep in these groups. Hence the this questionnaire was selected as it has been widely used in TD populations.

4.4.2 Temperament in Middle Childhood Questionnaire

The Temperament in Middle Childhood questionnaire (TMCQ; Simonds & Rothbart, 2004) is a 157-item caregiver response questionnaire assessing temperament in normal development (See Appendix C2). Parents indicate on a five-point scale whether each statement is 1 almost always untrue, 2 usually untrue, 3 sometimes true and sometimes untrue, 4 usually true, or 5 almost always true of their child, for items such as 'is afraid of heights', 'likes poems', 'likes to plan carefully before doing something' and 'likes to be in charge'. It yields scores on 17 subscales: activation control, activity level, affiliation, anger/frustration, assertiveness/dominance, attention focusing, discomfort, fantasy/openness, fear, high intensity pleasure, impulsivity, inhibitory control, low intensity pleasure, perceptual sensitivity, sadness, shyness, and soothability/falling reactivity. See Appendix C3 for a definition of each subscale. The average score of all items relating to each subscale is calculated so that each subscale is scored from 1 to 5. In a sample of 193 TD children aged 7 to 10 years Cronbach's alphas were > .63 for every subscale, showing satisfactory internal consistency (Simonds & Rothbart, 2004). Other psychometric data are not available for the TMCQ.

Although the TMCQ is aimed at children aged 7 to 10, a slightly narrower age range than this study's sample, it was used for all children so that they could be equally compared rather than using different questionnaires for children who fell outside this age bracket.

4.4.3 Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) is a brief 25-item parent response questionnaire that screens for behavioural problems (See Appendix C4). Parents record whether each item is 0 not true, 1 somewhat true or 2 certainly true of their child for statements such as 'often has temper tantrums or hot tempers', 'constantly fidgeting or squirming', 'generally liked by other children' and 'often volunteers to help others'. Items are added to give scores on five subscales; emotional symptoms, conduct problems, hyperactivity, peer problems and pro-social

behaviour. In addition, an 'impact score' shows how the child's problems impact on their daily life. Higher scores indicate increased problems, except the pro-social scale, where a higher score depicts better behaviour. Scores for each subscale can then be categorised as normal, borderline or abnormal, according to the scoring guidelines. Approximately 10% of a community sample scores in the abnormal range, with a further 10% scoring in the borderline range for any given scale (Goodman, 2001). The SDQ has satisfactory validity, being able to distinguish between a community and psychiatric sample with 87% accuracy (Goodman, 1997). A nationwide study of over 10,000 British children aged 5 to 15 years found that the scale shows good internal consistency (Cronbach's alpha = .73), and retest reliability (r = .62) (Goodman, 2001). The SDQ also correlates highly with the often-used Child Behaviour Checklist (Goodman & Scott, 1999) and Rutter questionnaires (Goodman, 1997), whilst benefitting from being shorter and focusing on the child's strengths as well as problem behaviour. In this case the SDQ was selected for its brevity to measure behavioural problems in the sample.

4.4.4 Pittsburgh Sleep Quality Index (for parents)

Parents completed the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) regarding their own sleep (See Appendix C5). This is a 19-item self-rated questionnaire which assesses sleep quality and disturbances over the previous month. Items such as 'have to get up to use the bathroom', 'cannot breathe comfortably' and 'had bad dreams' are rated on a four-point scale dependent on their frequency of occurrence (0 not during the past month, 1 less than once a week, 2 once or twice a week, or 3 three or more times a week). Scores from 0 to 3 are generated for seven subscales; subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction; as well as a global score from the sum of the subscales. Higher scores signify increased sleep problems. A study of 52 healthy adults and 63 adult patients from a sleep clinic showed that the PSQI has acceptable levels of reliability and validity (Buysse et al., 1989). Cronbach's alphas for each subscale ranged from .35 for sleep disturbances to .76 for habitual sleep efficiency and subjective sleep quality, and had an overall score of .83 indicating high internal consistency. A cut-off total score of 5 was able to correctly identify 88.5% of patients and controls. Retest reliability was good, with no significant differences between scores after an average interval of 28.2 days.

4.4.5 Epworth Sleepiness Scale (for parents)

The Epworth Sleepiness Scale (ESS; Johns, 1991) is a short and simple questionnaire which provides a measure of general daytime sleepiness (See Appendix C6). Parents indicated on a scale of 0 (would

never doze) to 3 (high chance of dozing) the likelihood of them dozing or falling asleep in eight different everyday situations such as sitting and reading, watching TV, and sitting quietly after a lunch without alcohol. The total score of summing all items can reliably distinguish non-sleep disordered subjects from a range of diagnostic groups including patients with OSAS, narcolepsy and idiopathic hypersomnia, but not from primary snoring, insomnia or PLMD (Johns, 1991). Retest reliability after five months is good (Pearson's r = .82) and the ESS has high internal consistency (Cronbach's alpha = .88) (Johns, 1992). Although the ESS alone is not a diagnostic tool for sleep disorders, it correlates well with objective measures of sleep latency. It is suggested that a score greater than 10 is indicative of excessive daytime sleepiness which may be the result of nocturnal sleep problems.

4.4.6 Major Depression Inventory (for parents)

The Major Depression Inventory (MDI; Bech, Rasmussen, Olsen, Noerholm, & Abildgaard, 2001) is one of the most widely used standardised instruments for measuring the severity and depth of depressive symptoms (See Appendix C7). It contains 12 items addressing the DSM-IV and ICD-10 depression criteria. Parents rated on a scale of 0 (at no time) to 5 (all of the time) how much of the time during the last two weeks they have, for example, felt in low spirits or sad, lost interest in daily activities and had a bad conscience or feelings of guilt. The MDI can then be scored according to DSM-IV or ICD-10 algorithms, or a simple total score for depression severity can be calculated. A higher total score indicates increased depressive symptoms. In 43 psychiatric patients, those who were depressed scored significantly higher than non-depressed patients for each individual item, as well as the total score. A cut-off total score of 26 was recommended for distinguishing between depressed and non-depressed psychiatric patients with a sensitivity of .86 and specificity of .82 (Bech et al., 2001). In a sample of 30 depressed patients and 68 control participants, Fountoulakis et al. (2003) reported high internal consistency (Cronbach's alpha .89), and excellent retest reliability for 18 of these participants after 1-2 days, with Spearman's r ranging from .53 to .96 for individual items, and .89 for total score.

4.5 General Procedure Summary

Parents were contacted by telephone to ensure that children met inclusion criteria, were in good health, and to arrange a suitable time for each child to participate in the study. Schools were also contacted by telephone to arrange testing sessions. The experimenter visited all families at home either on the first evening of the experimental tasks or up to one week before. Parents gave written informed consent for their child to take part in the study and children gave their verbal assent.

Parents were provided with the questionnaires and sleep diary along with instructions for their completion. In a parent's presence, children were given an actiwatch and were requested to wear it for one week. The pulse oximetry equipment was also provided. Parents were shown how to use the equipment correctly, given opportunity to ask any questions and a contact phone number in case of any problems. They were requested to use the pulse oximetry monitor overnight for three consecutive nights. The experimenter arranged to collect the equipment and completed questionnaires at the end of the study.

Children were individually tested in a quiet room. This was always during school term time in order to avoid irregular routines and sleep schedules that may occur during school holidays. Sometimes in the cases of children with DS and WS, their learning support assistant was present and sat quietly without intervening with the testing. All children were trained on the Animal Names and Tower of Hanoi tasks either in the morning or evening and were retested after retention intervals of wake and sleep. During the second or third session (whichever was in the morning) children also completed the CPT, digit and spatial spans and RCPM.

4.6 Statistical analysis

Data were analysed using IBM Statistical Package for Social Sciences V.20. Outlying scores were identified using Cook's distance. Analyses where the significance of results changed after excluding outliers will be explicitly mentioned by denoting 'OR' (Outliers Removed) beside the variable. In all other instances outliers were not excluded (see Thomas et al., 2009).

Children's results on the cognitive tasks and questionnaires were examined by comparing group means, age-related effects and sleep-related effects.

4.6.1 Group means

Data on tasks and measures were investigated using one-way between-groups Analysis of Variance (ANOVA) tests to compare the TD, DS and WS groups. For all ANOVAs, Levene's test was used to assess the assumption of homogeneity of variance. This is sometimes violated when studying atypical groups however ANOVAs were still used in this thesis to avoid losing power associated with nonparametric tests. The Bonferroni correction was used in post hoc analysis except where equal variances could not be assumed the Games-Howell test was used, as recommended by Field (2005). The effect size is reported as partial eta squared (ηp^2).

4.6.2 Age-related effects

Ideally, the study of development would be based on longitudinal data. This is costly and time-consuming so an alternative method is to use a cross-sectional design in a group with a range of ages. Linear regression is used to plot a typical developmental trajectory of performance on a particular task. The trajectories of clinical groups can also be plotted and compared to the typical trajectory to see whether or not the performance of these groups is delayed, atypical or both. In addition, one can establish where the score of an individual fits on the typical trajectory, and whether this position is what would be predicted, given their CA (Karmiloff-Smith et al., 2004; Thomas et al., 2001, 2009).

The current thesis used this approach to investigate the relationship of age with cognition, behaviour and sleep. First, the relationship between each dependent variable (scores on tasks and sleep variables) and increasing CA (independent variable) was investigated by plotting developmental trajectories for the TD, DS and WS groups. If CA was able to explain a significant amount of the variance in any group then the trajectories for the three groups were compared to one another using the developmental trajectory approach described by Thomas et al. (2009). Cross-sectional Analysis of Covariance (ANCOVA) models within the General Linear Model were conducted with age as a covariate. (Thomas et al., 2009). The group by age interaction was studied, which assesses whether the trajectories followed by each group are significantly different from one another. MA-related changes were investigated using the same method with MA determined by total score on the RCPM.

4.6.3 Sleep-related effects

Group comparisons for sleep characteristics were investigated using one-way between-groups ANOVAs, as described above. Actigraphy variables were selected to give a broad overview of sleep parameters that have previously been associated with children's cognitive performance (Gruber et al., 2012; Holley, 2009; Sadeh et al., 2002). These related to sleep duration: bed time, getting up time, assumed sleep (total time from falling asleep to waking up) and actual sleep time (assumed sleep minus any periods of wake) as well as sleep quality: sleep efficiency (percentage of time spent asleep from sleep onset to wake up), sleep latency (time from lights out (parentally-reported) to sleep onset), number and duration of night wakings, and fragmentation (an indication of restlessness where a higher figure indicates increased restlessness). Pulse oximetry variables were selected that have been demonstrated in previous studies to be indicators of sleep apnoea (Urschitz, Brockmann, Schlaud, & Poets, 2010). These were mean SpO_2, median SpO_2, SpO_2 dips per hour

greater than 4%, % time spent below 90% SpO_2, and delta 12 (an index of SpO_2 variability over each 12-second epoch where a higher figure indicates increased variability). Refer back to Sections 4.3.1.1 (actigraphy) and 4.3.1.3 (pulse oximetry) for descriptions of the methodology.

Performance on the Animal Names (described in Sections 3.2.3 and 4.3.3) and Tower of Hanoi (Sections 3.3.3 and 4.3.4) learning tasks was assessed using repeated-measures ANOVAs with performance scores at each test session (train, test 1, test 2) as the dependent variables and Group (TD, DS, WS) and Condition (Sleep-wake, Wake-sleep) as the independent variables. Performance of the three groups was then compared across sleep and wake intervals to investigate whether any performance gains were related to sleep.

The relationship between sleep and cognition was investigated for the sleep-dependent learning tasks, the CPT (described in Sections 3.3.4 and 4.3.5), the digit and spatial spans (Section 4.3.7), and the parent-reported SDQ (Section 4.4.3) for each Group (TD, DS, WS). For this purpose, hierarchical linear regression was used. Performance score on the task in question was the dependent variable.

CA and MA were controlled for in the first block of the model. The second and third blocks respectively included actigraphy variables relating to sleep duration (actual sleep time) and quality (sleep efficiency, number of night wakings, mean duration of night wakings). These actigraphy variables were selected based on those that have previously been associated with children's cognitive performance (Gruber et al., 2012; Holley, 2009; Sadeh et al., 2002) and that did not strongly correlate with one another so that the assumption of no multicollinearity was not violated (all <.7) (Field, 2005). The order of blocks here was important. Firstly, it was necessary to control for CA and MA due to their influences on task performance and sleep parameters in some groups. Second, it was necessary to control for sleep duration before investigating sleep quality because in children with short sleep duration sleep quality improves, whilst in children with long sleep duration sleep quality is reduced. This is due to a physiological compensatory mechanism that adapts sleep quality in response to changes in sleep duration (Sadeh et al., 2003).

SpO_2 variables were not included in the model due to some missing data. Instead, a second model was created, also controlling for CA and MA in block 1, then including mean SpO_2, dips per hour >4%, delta 12 index, and % time spent below 90% SpO_2 in block 2. Again, the assumption of no multicollinearity was not violated.

5. Results

This chapter describes the participants and results of the study. Firstly children's performance on the standardised tests (RCPM, STM, working memory) is described in order to provide a description of children's general cognitive ability before discussing their performance on the experimental tasks.

Broadly, there are four sections: Sleep measures, Standardised tests, Experimental tasks and Questionnaires. Each section investigates similarities and differences between the TD, DS and WS groups, as well as the effects of development and of sleep, where appropriate.

5.1 Sleep Measures

5.1.1 Actigraphy

In order to monitor their sleep patterns, all children were requested to wear an actiwatch continuously for one week (see Section 4.3.1.1 for a description of the methodology). One child from the TD group refused to wear the actiwatch. All other children had four or more days and nights of actigraphy data and the majority (78%) had seven or more, as requested. One-way between-groups ANOVA showed no significant difference in compliance between the groups (F (2, 94) = 1.72, p = .19, ηp^2 = .04)

Key actigraphy variables were selected to give a broad overview of sleep characteristics across the three groups. Variables of interest include those relating to sleep duration (bed time, getting up time, assumed sleep and actual sleep time) and sleep quality (sleep efficiency, sleep latency, number and duration of night wakings, and fragmentation; see Section 4.6.3 for a description of variables). ANOVA results comparing groups on these variables are presented in Table 5.1.

Table 5.1. *Mean scores (SD) and group differences using ANOVA for selected actigraphy variables*

	TD (n = 40)	DS (n = 22)	WS (n = 22)	*F*	*p*	η_p^2
Bed time (hh:mm)	**21:18** (0:42)	20:30 (0:37)	20:48 (0:38)	10.74	<.001[ab]	.21
Getting up time (hh:mm)	**7:33** (0:31)	7:06 (0:37)	7:04 (0:41)	6.08	<.01[ab]	.13
Assumed sleep time (hh:mm)	9:28 (0:42)	**10:06** (0:43)	9:21 (1:01)	5.82	<.01[ac]	.13
Actual sleep time (hh:mm)	8:19 (0:37)	8:22 (0:50)	8:18 (0:55)	.06	.94	.00
Sleep efficiency (%)	87.66 (3.61)	**82.99** (5.45)	88.79 (3.28)	13.03	<.001[ac]	.24
Sleep latency (mm:ss)	27:40 (11:11)	23:23 (15:53)	**46:30** (37:34)	3.44	.04[c]	.08
Number of night wakings	31.91 (7.97)	**39.50** (9.19)	28.00 (6.10)	12.30	<.001[ac]	.23
Mean night waking duration (mm:ss)	2:08 (0:24)	**2:35** (0:30)	2:14 (0:26)	7.60	.001[ac]	.16
Fragmentation index	29.70 (8.14)	**41.77** (8.74)	31.84 (6.31)	17.26	<.001[ac]	.30

Significant differences in bold

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

5.1.1.1 Age and actigraphy

Actigraphy variables were investigated for developmental changes using linear regression. It was expected that increasing age would be related to shorter sleep duration.

Only variables that showed a significant relationship with age are reported. These were bedtime, assumed sleep and actual sleep time (reported below). For scatterplots see also Figure 5.1. No reliable trajectories were found for getting up time, sleep efficiency, sleep latency, number or duration of night wakings, or fragmentation; indicating that these sleep parameters are not related to age.

5.1.1.1.1 Bed time

Bed time was significantly related to CA in the TD group with older children going to bed later. This relationship was not significant in the DS or WS groups (TD: $R^2 = .17$, F (1, 38) = 7.97, $p = .01$; DS: $R^2 = .15$, F (1, 20) = 3.49, $p = .08$; WS: $R^2 = .25$, F (1, 20) = 1.35, $p = .26$).

The ANCOVA model showed no significant difference between the trajectories of the three groups (F (2, 78) = .63, $p = .53$, $\eta_p^2 = .02$).

5.1.1.1.2 Assumed sleep time

In the WS group but not the TD or DS groups, assumed sleep time was significantly related to CA, with older children having less sleep than younger children (TD: $R^2 = .07$, F (1, 38) = 2.72, $p = .11$; DS: $R^2 = .12$, F (1, 20) = 2.59, $p = .13$; WS: $R^2 = .32$, F (1, 20) = 9.34, $p = .01$).

The ANCOVA model showed no significant difference between trajectories of the three groups (F (2, 78) = 1.41, $p = .25$, $\eta_p^2 = .04$).

5.1.1.1.3 Actual sleep time

In the DS and WS groups but not the TD group, CA was significantly related to actual sleep time, with older children having less sleep than younger children ($R^2 = .06$, F (1, 38) = 2.45, $p = .13$; DS: $R^2 = .20$, F (1, 20) = 5.05, $p = .04$; WS: $R^2 = .32$, F (1, 20) = 9.52, $p = .01$).

The ANCOVA model showed no significant difference between trajectories of the three groups (F (2, 78) = 1.20, $p = .31$, $\eta_p^2 = .03$).

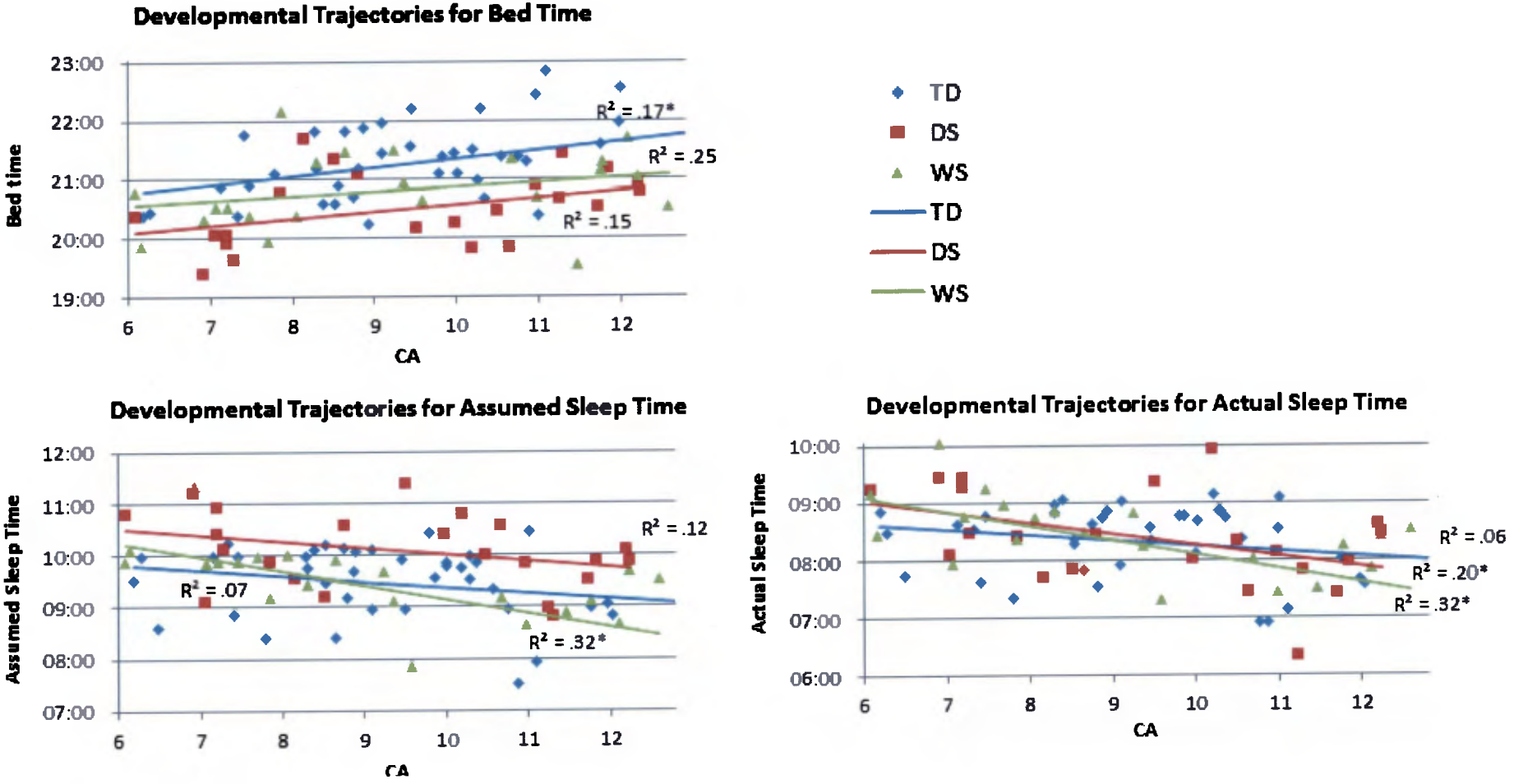

Figure 5.1. Developmental trajectories showing relationship of CA with bed time, assumed sleep time and actual sleep time for each group (TD, DS, WS). * = significant effect of CA.

5.1.2 Pulse oximetry

Children were requested to use the pulse oximetry monitor for three consecutive nights in order to measure pulse and SpO_2 saturation (see Section 4.3.1.3 for a description of the methodology and Section 4.6.3 for the variables). Data were extracted from the pulse oximetry results to show key variables indicative of SDB in children. It was predicted that children with DS would have lower and more variable SpO_2 than TD children and children with WS.

Pulse oximetry data were not available for all children. In the cases of six TD children (20%) this was due to lack of equipment and two cases data on the machine was corrupted. Three children (14%) with DS and ten with WS (45%) refused to wear the pulse oximeter probe. Further, data were removed for five children with DS (23%) and two with WS (9%) whose recordings were less than the five hours minimum duration (Urschitz et al., 2003). Hence the final sample was 33 TD children (80%), 14 children with DS (64%) and 10 children with WS (45%). There was no difference between groups for the total amount of artefact-free recording time that was analysed (Table 5.2).

One way between groups ANOVAs showed greater evidence of possible SDB in the children with DS, with lower SpO_2, more dips per hour and a higher delta 12 index. The WS group had a significantly higher heart rate than the other two groups (see Table 5.2).

Table 5.2. *Mean scores (SD) and group differences using ANOVA for SpO_2 saturation variables*

	TD (n = 33)	DS (n = 14)	WS (n = 10)	*F*	*p*	η_p^2
Time analysed	28:22 (10:59)	24:09 (8:27)	22:43 (8:36)	1.65	.21	.06
Mean SpO_2 OR	97.81 (.71)	**96.80** (0.84)	**96.83** (.71)	10.12	<.001[ab]	.31
Median SpO_2 OR	98.03 (.72)	**97.00** (0.77)	**96.88** (.83)	12.27	<.001[ab]	.35
SpO_2 dips per hour >4% OR	1.96 (1.26)	**4.35** (1.37)	2.36 (.34)	16.70	<.001[ac]	.42
% time SpO_2 below 90 %	0.79 (2.00)	2.22 (5.14)	0.96 (.54)	1.06	.36	.04
Delta 12	0.41 (.13)	**0.52** (0.12)	0.43 (.12)	4.02	.02[a]	.13
Pulse OR	73.37 (4.52)	**79.24** (4.22)	**85.63** (.84)	22.28	<.001[abc]	.51

Significant differences in **bold.**

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

Age-related changes in SpO_2 saturation were not investigated as there is no known good evidence that OSAS is associated with age in children.

5.2 Standardised Tests

5.2.1 Raven's Coloured Progressive Matrices

The RCPM was used to assess non-verbal MA (see Section 4.3.6). Group differences on each set of the RCPM and total score were investigated using one way repeated measures ANOVAs. Post hoc comparisons were made using the Bonferroni correction.

RCPM data were not available for two children with DS who were unable to complete the task. The RCPM total score (out of a possible 36) can be used to give a child's non-verbal MA from 5 to 12 years. As some children scored below the minimum age-equivalent score on the RCPM, this thesis uses the total raw scores, rather than the age-equivalent scores (Van Herwegen, Farran, et al.,

2011). The TD group had a significantly higher score, and therefore MA, than both other groups ($p < .001$ for each). The DS and WS groups did not differ significantly from one another, indicating a good match for MA (see Table 5.3). These are typical cognitive profiles of these two clinical groups (Hick et al., 2005, Van Herwegen et al., 2011). Scores and ANOVA results are shown in Table 5.3 and illustrated in Figure 5.2.

Table 5.3. *Cross-syndrome comparison of scores (Mean (SD)) on the RCPM using ANOVA*

	TD (n = 41)	DS (n = 20)	WS (n = 22)	*F*	*p*	η_p^2
Total score range	15 - 36	6 - 18	9 - 21			
Mean MA	≈ 11	Under 5	≈ 6			
Set A (/12)	9.54 (1.42)	**5.55 (1.73)**	**7.00 (1.23)**	56.30	<.001[abc]	0.58
Set AB (/12)	9.59 (2.16)	**3.65 (1.42)**	**4.18 (1.68)**	94.00	<.001[ab]	0.70
Set B (/12)	8.56 (2.59)	**3.40 (1.43)**	**3.45 (1.37)**	63.12	<.001[ab]	0.61
Total score (/36)	27.68 (5.35)	**12.60 (3.53)**	**14.64 (3.02)**	104.77	<.001[ab]	0.72

Significant differences in **bold**

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

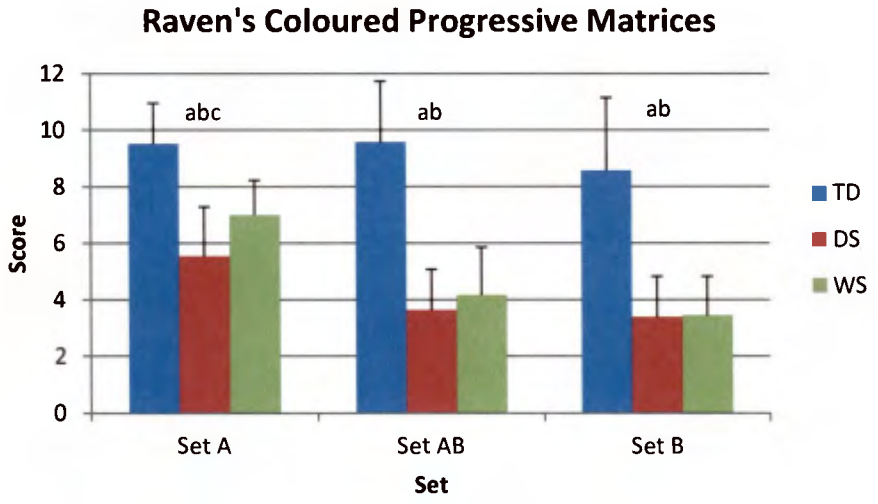

Figure 5.2. Histogram of scores by group for RCPM sets. Error bars show standard deviation. Maximum possible score of 12 for each set.

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

5.2.1.1 Relationship between sleep and mental age

Linear regression was used to investigate any association of actigraphy and SpO_2 variables with MA (based on RCPM total score). Only variables that showed a significant trajectory are reported (actigraphy: bed time, sleep latency; pulse oximetry: median SpO_2 and % time spent below 90% SpO_2). For clarity, significant relationships between MA, actigraphy and SpO_2 variables are also summarised in Table 5.4.

No significant MA trajectories were found for actigraphy variables of get up time, assumed sleep, actual sleep time, sleep latency, number or duration of night wakings and fragmentation; or pulse oximetry variables of mean SpO_2, pulse and SpO_2 dips per hour.

Where significant associations between sleep and MA were found, the ANCOVA model previously described (Section 4.6.2) was used to assess whether the trajectories of the three groups were significantly different from one another.

5.2.1.1.1 Bed time

MA (RCPM total score) was significantly associated with bed time in the DS group with MA-older children going to bed later than MA-younger children (R^2 = .38, F (1, 18) = 11.12, p = .004). There was no relationship between MA and bed time in either the TD or WS groups (TD: R^2 = .03, F (1, 38) = 1.16, p = .29; WS: R^2 = .05, F (1, 20) = .97, p = .34).

An ANCOVA model was used to compare MA developmental trajectories for bedtime but showed no significant difference between groups (F (2, 76) = 2.85, p = .06, η_p^2 = .07)

5.2.1.1.2 Sleep latency

In the DS group there was a significant relationship between MA and sleep latency whereby MA-older children had longer sleep latency than MA younger children (R^2 = .21, F (1, 18) = 4.77, p = .04). Sleep latency was not related to MA in the TD and WS groups (TD: R^2 < .001, F (1, 38) = .003, p = .96; WS: R^2 = .08, F (1, 20) = 2.16, p = .16)

ANCOVA showed no significant difference between the MA trajectories of the three groups for sleep latency (F (2, 76) = 1.64, p = .20, η_p^2 = .04).

5.2.1.1.3 Median SpO_2

In the TD group, higher MA was associated with higher median SpO_2 saturation (R^2 = .15, F (1, 31) = 5.24, p = .03). There was no relationship between MA and median SpO_2 in the DS or WS groups (DS: R^2 = .11, F (1, 10) = 1.17, p = .31; WS: R^2 = .003, F (1,8) = .03, p = .87)

5.2.1.1.4 Percentage time spent below 90% SpO_2

In the TD group increased MA was significantly related to reduced % time spent below 90% SpO_2 saturation (R^2 = .19, F (1, 31) = 7.47, p = .01). No relationship existed in the DS or WS groups (DS: R^2 = .001, F (1, 10) = .02, p = .91; WS: R^2 = F (1, 8) = .12, p = .74).

ANCOVA models showed no significant differences between the trajectories of the three groups (F (2, 49) = .48, p = .62, η_p^2 = .02).

Table 5.4. *Summary of relationship between MA, actigraphy and SpO_2 saturation variables. Figures show significant R^2 values (ns = no significant difference, - = negative relationship).*

Sleep and MA	TD	DS	WS	MA trajectory comparison
Bed time		.38		ns
Sleep latency		.21		ns
Median SpO_2	.15			ns
% time spent below 90% SpO_2	.19 (-)			ns

5.2.1.2 Relationship between chronological and mental age

To investigate the relationship between CA and MA, linear regression was used to plot developmental trajectories for each group. Total score on the RCPM was the dependent variable.

There was a significant relationship between age and RCPM score (and therefore MA) in the TD and DS groups (TD: $R^2 = .37$, F (1, 39) = 22.73, $p < .001$; DS: $R^2 = .28$, F (1, 18) = 6.82, $p < .02$) but not the WS group ($R^2 = .01$, F (1, 20) = .20, $p = .66$)

The ANCOVA model to compare groups showed a significant difference between the trajectories of the three groups (F (2, 77) = 5.85, $p = .004$, $\eta_p^2 = .13$). Pairwise comparisons showed a significant difference between the trajectories of the TD and WS groups (F (1, 59) = 10.54, $p = .002$, $\eta_p^2 = .15$) There was no significant difference between the trajectories of the TD and DS groups (F (1, 57) = 2.81, $p = .10$, $\eta_p^2 = .05$) or the DS and WS groups (F (1, 38) = 2.74, $p = .11$, $\eta_p^2 = .07$). See Figure 5.3.

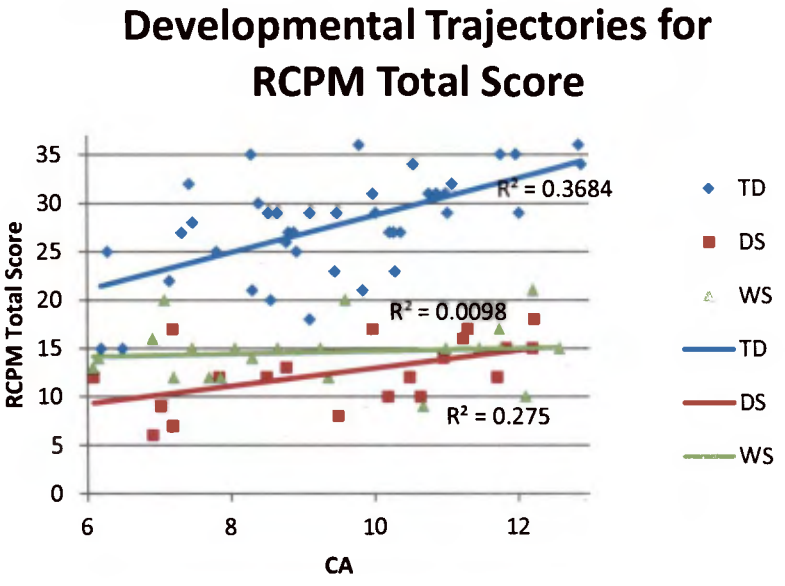

Figure 5.3. Developmental trajectories of the TD, DS and WS groups on RCPM total score (maximum possible score of 36).

5.2.2 Short-Term and working memory span

Children completed the digit and spatial spans forwards and backwards to assess STM and working memory, respectively (Section 4.3.7). It was predicted that TD children would perform significantly better on the task than children with DS and WS. It was also predicted that children with WS would perform better on the digit span than on the spatial span, whilst the opposite would be true of children with DS. Scores on the tasks include span length (maximum number of correct items recalled) and raw score (one point awarded for each correct trial with two trials at each span length).

Digit and spatial span data were not available for all children with DS and WS as some children were unable to complete the task. The final sample numbers for each test are shown in Table 5.5.

Using one-way between-groups ANOVAs, significant group differences emerged on all digit and spatial span tasks. As predicted, the TD children outperformed children with DS and WS on all tasks. The WS group also performed significantly better than the DS group on the digit span forwards task. Span lengths are illustrated in Figure 5.4 as they are thought to be most meaningful but span lengths, raw scores along with ANOVA results also are reported in Table 5.5.

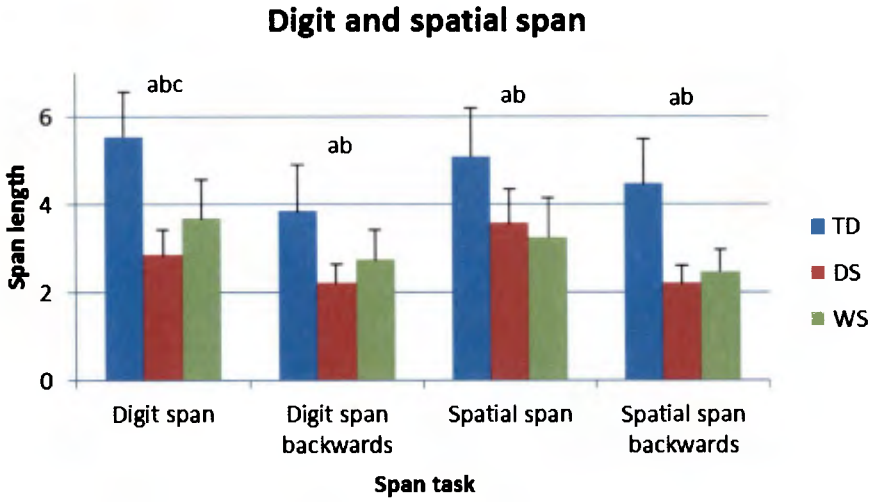

Figure 5.4. Histogram of digit and spatial span lengths by group. Error bars show one standard deviation above the mean. Possible score range of 2 to 8.

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

Table 5.5. *Cross-syndrome comparison of span length and raw scores (Mean (SD)) on the digit and spatial spans, forwards and backwards, using ANOVA.*

	TD		DS		WS				
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	*F*	*p*	η_p^2
Digit span	41	5.54 (1.03)	20	**2.85 (.59)**	22	**3.68 (.89)**	68.60	<.001[abc]	.63
Digit span backwards	41	3.85 (1.04)	5	**2.20 (.45)**	15	**2.73 (.70)**	12.66	<.001[ab]	.30
Spatial span	41	5.10 (1.09)	19	**3.58 (.77)**	20	**3.25 (.91)**	30.16	<.001[ab]	.44
Spatial span backwards	41	4.46 (1.03)	10	**2.20 (.42)**	15	**2.47 (.52)**	45.82	<.001[ab]	.59
Digit score OR	38	8.08 (1.50)	19	**3.05 (.97)**	18	**4.67 (.97)**	112.40	<.001[abc]	.76
Digit score backwards OR	40	4.88 (1.64)	5	**1.60 (.89)**	12	**3.00 (1.04)**	15.65	<.001[ab]	.37
Spatial score	41	7.10 (1.87)	19	**5.00 (2.98)**	20	**4.20 (2.07)**	13.34	<.001[ab]	.26
Spatial score backwards	41	6.10 (1.67)	11	**3.36 (4.23)**	15	**3.27 (2.15)**	11.17	<.001[ab]	.26

Significant differences in **bold**

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

Repeated-measures ANOVAs showed that TD children and children with WS scored significantly higher on the digit span than on the spatial span (TD: Wilks' Lambda = .88, F (2, 40) = 5.26, p = .03, η_p^2 = .17; WS: Wilks' Lambda = .75, F (2, 19) = 6.33, p = .02, η_p^2 = .25), whilst children with DS scored higher on the spatial span than they did on the digit span (Wilks' Lambda = .64, F (2, 18) = 9.94, p = .01, η_p^2 = .36).

5.2.2.1 Are there developmental effects on short term and working memory?

Linear regression was used to assess the relationship between age (CA and MA) and span length on the STM and working memory tasks. If a reliable age-related effect was found, ANCOVA models were used to investigate whether trajectories for the three groups significantly differed from one another. See Figure 5.5 for scatterplots of CA developmental trajectories for each STM and working memory task.

5.2.2.1.1 Digit span forwards

5.2.2.1.1.1 *Chronological age*

In the TD and WS groups but not the DS group, increased CA was significantly related to longer digit span forwards (TD: R^2 = .23, F (1, 39) = 11.41, p = .002; DS: R^2 = .01, F (1, 18) = .21, p .65; WS: R^2 = .40, F (1, 20) = 13.44, p = .002).

ANCOVA model showed significant differences between the three trajectories for digit span forward (F (2, 77) = 4.19, p = .02, η_p^2 = .10). Pairwise comparisons using the ANCOVA model showed a significant difference between the TD and DS groups (F (1, 57) = 6.38, p = .01, η_p^2 = .10). There was no significant difference between the TD and WS groups (F (1, 59) = .89, p = .35, η_p^2 = .02) or between the DS and WS groups (F (1, 38) = 2.65, p = .11, η_p^2 = .07).

5.2.2.1.1.2 *Mental age*

In the TD and WS groups, longer digit span forwards was significantly related to increased MA (RCPM total score). This effect was not significant in the DS group. (TD: R^2 = .14, F (1, 39) = 6.48, p = .02; DS: R^2 = .03, F (1, 18) = .55, p = .47; WS: R^2 = .20, F (1, 20) = 5.07, p = .04).

ANCOVA model showed no significance between the MA trajectories of the three groups for digit span forwards (F (2, 77) = .80, p = .45, η_p^2 = .02).

5.2.2.1.2 Digit span backwards

5.2.2.1.2.1 *Chronological age*

In the TD group increased CA was significantly related to longer digit span backwards. There was no significant relationship between age and digit span backwards in the DS or WS groups (TD: $R^2 = .14$, $F(1, 39) = 6.12$, $p = .02$; DS: $R^2 = .24$, $F(1, 3) = .95$, $p = .40$; WS: $R^2 < .001$, $F(1, 13) < .001$, $p = .99$).

ANCOVA model showed no significant differences between the three MA trajectories for digit span backwards ($F(2, 55) = 1.49$, $p = .24$, $\eta_p^2 = .05$).

5.2.2.1.2.2 *Mental age*

In the TD group increased MA was related to better performance on the digit span backwards task. This effect was not significant for the DS or WS group (TD: $R^2 = .26$, $F(1, 39) = 13.64$, $p = .001$; DS: $R^2 = .60$, $F(1, 3) = 4.49$, $p = .12$; WS: $R^2 = .03$, $F(1, 13) = .45$, $p = .52$).

ANCOVA model showed no difference between the MA trajectories of the three groups for digit span backwards ($F(2, 55) = .29$, $p = .75$, $\eta_p^2 = .01$).

5.2.2.1.3 Spatial span forwards

5.2.2.1.3.1 *Chronological age*

In the TD group increased CA was significantly related to longer spatial span forwards. There was no significant relationship between age and spatial span forwards in the DS or WS groups (TD: $R^2 = .24$, $F(1, 39) = 12.50$, $p = .001$; DS: $R^2 = .01$, $F(1, 17) = .16$, $p = .70$; WS: $R^2 = .12$, $F(1, 18) = 2.50$, $p = .13$).

The ANCOVA model showed no significant differences between the CA trajectories of the three groups ($F(2, 74) = 2.21$, $p = .12$, $\eta_p^2 = .06$).

5.2.2.1.3.2 *Mental age*

In the TD group, increased MA was related to longer spatial span forwards. This relationship was not significant in the DS or WS group (TD: $R^2 = .31$, $F(1, 39) = 17.63$, $p < .001$; DS: $R^2 = .02$, $F(1, 17) = .29$, p .60; WS: $R^2 = .003$, $F(1, 18) = .06$, $p = .82$).

ANCOVA model showed no difference between the MA trajectories of the three groups for spatial span forwards ($F(2, 74) = 1.56$, $p = .22$, $\eta_p^2 = .04$).

5.2.2.1.4 Spatial span backwards

5.2.2.1.4.1 *Chronological age*

In the TD group increased CA was significantly related to longer spatial span backwards. There was no significant relationship between age and spatial span backwards in the DS or WS groups (TD: R^2 = .24, F (1, 39) = 12.61, p = .001; DS: R^2 = .01, F (1, 8) = .09, p = .78; WS: R^2 = .01, F (1, 13) = .13, p = .72).

ANCOVA showed a significant difference between the three trajectories (F (2, 60) = 3.43, p = .04, η_p^2 = .10). Pairwise comparisons using the ANCOVA model showed a significant difference between the TD and DS groups (F (1, 48) = 22.02, p < .001 , η_p^2 = .31) and between the TD and WS groups (F (1, 52) = 9.99, p = .003 , η_p^2 = .16), but no significant difference between the trajectories of the DS and WS groups (F (1, 22) = 3.12, p = .09, η_p^2 = .12).

5.2.2.1.4.2 *Mental age*

Linear regression showed no significant relationship between MA and spatial span backwards for any group, although the relationship for the TD group approached significance (TD: R^2 = .09, F (1, 39) = 4.00, p = .053; DS: R^2 = .01, F (1, 8) = .07, p = .80; WS: R^2 = .01, F (1, 13) = .14, p = .72).

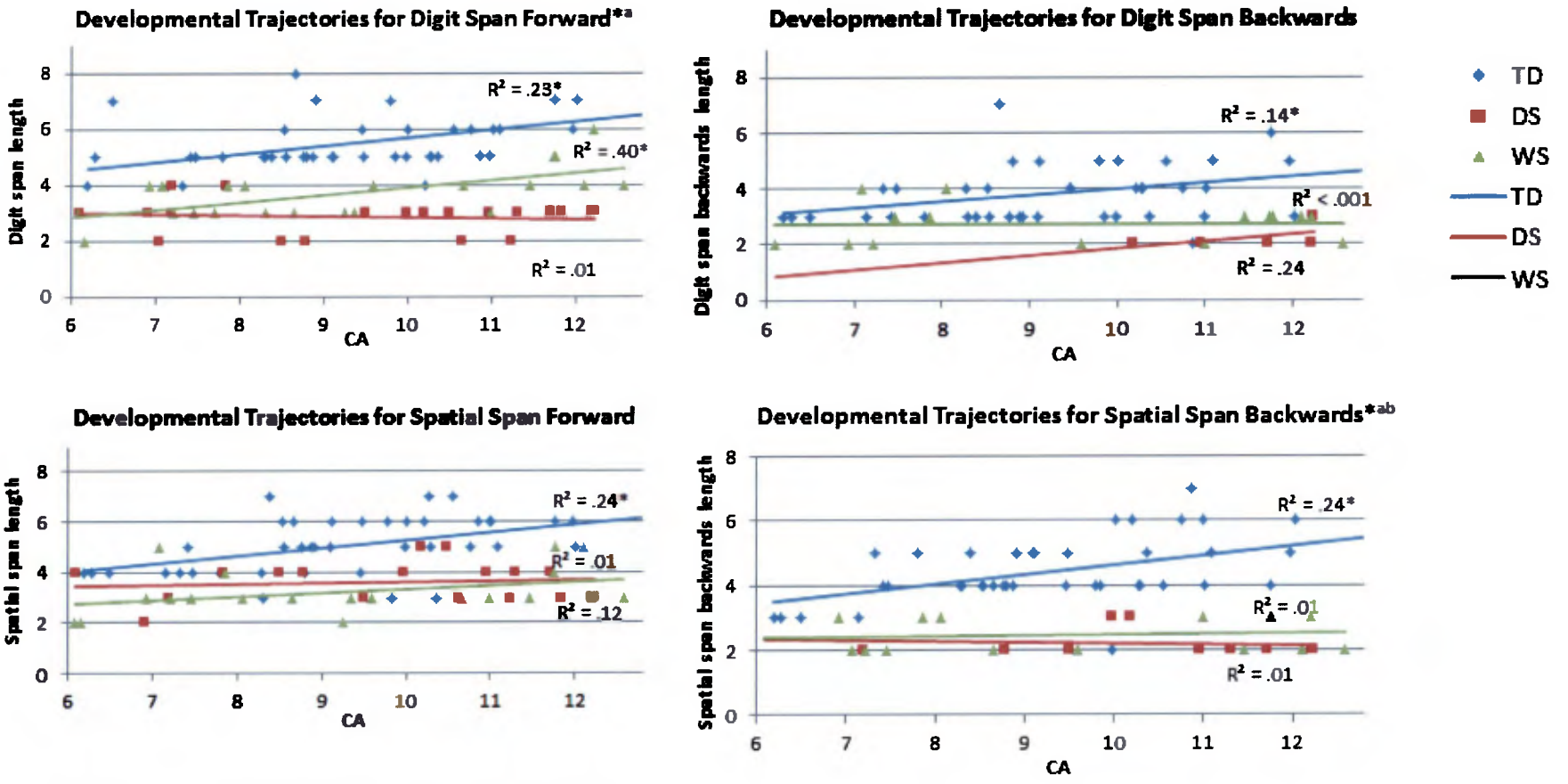

Figure 5.5. Developmental trajectories for the TD, DS and WS groups on the digit and spatial, forwards and backwards span tasks (verbal and spatial short term memory and working memory for number of items correctly recalled). Maximum possible score was 8. * = significant effect. a = Significant difference between TD and DS ($p < .05$). b = Significant difference between TD and WS ($p < .05$).

5.2.2.2 Sleep and short term memory

Hierarchical multiple regression was used to investigate whether actigraphy and SpO_2 saturation variables were related to STM and working memory, whilst controlling for the effects of CA and MA (RCPM total). Firstly a model was created to investigate actigraphy variables relating to sleep duration (actual sleep time) and sleep quality (sleep efficiency, number of night wakings, mean duration of night wakings). Block one was used to control for CA and MA (RCPM total), and blocks 2 and 3 related to sleep duration and sleep quality respectively, as discussed in Section 4.6.3. Table 5.6 shows results of the first regression model. Note that the regression model could not be completed for the DS group for digit span backwards due to insufficient sample size.

A second hierarchical multiple regression model was created to investigate the influence of SpO_2 on short term and working memory. Block 1 controlled for CA and RCPM total. Block 2 included the SpO_2 variables of mean SpO_2, dips per hour >4%, delta 12 index, and % time spent below 90% SpO_2. (discussed in Section 4.6.3). In the TD group, the SpO_2 variables block explained 32% of the variance in spatial span length, after controlling for age (R^2 change = .32, *F* change (4, 26) = 4.97, p = .004). SpO_2 variables were unable to explain STM or working memory scores in the DS or WS groups.

Table 5.6. *Hierarchical multiple regression analysis showing influence of age (CA and MA), sleep duration (actual sleep time) and sleep quality (sleep efficiency, number of night wakings, mean duration of night wakings) on short term and working memory tasks*

		Block 1: age			Block 2: Sleep duration			Block 3: sleep quality		
Group	n	R^2	*F*	*p*	R^2 change	*F* change	*p*	R^2 change	*F* change	*p*
Digit span forwards										
TD	40	**.20**	4.69	.02	.05	2.24	.14	**.16**	3.05	.04
DS	20	.08	.77	.48	**.33**	9.01	.01	.04	.33	.80
WS	22	**.55**	11.76	.001	.00	.15	.70	.15	2.48	.10
Digit span backwards										
TD	40	**.24**	5.92	.01	.00	.07	.79	**.25**	5.51	.004
DS (NA)	5									
WS	15	.03	.21	.81	.03	.34	.57	.30	1.23	.36
Spatial span forwards										
TD	40	**.34**	9.53	.001	.02	.90	.35	.04	.78	.51
DS	19	.02	.15	.86	.00	.06	.81	.23	1.21	.35
WS	20	.12	1.19	.33	.04	.71	.41	.04	.19	.90
Spatial span backwards										
TD	40	**.30**	7.97	.001	.03	1.48	.23	.04	.61	.62
DS	10	.02	.06	.94	.06	.38	.56	**.87**	15.48	.02
WS	15	.02	.12	.89	.00	.00	.96	**.74**	8.09	.01

Significant results in **bold**

5.3 Experimental Tasks

This section includes group comparisons, age-related effects and sleep-related effects on the Animal Names task, Tower of Hanoi and CPT.

Animal Names (described in Sections 3.2.3 and 4.3.3) and Tower of Hanoi (Sections 3.3.3 and 4.3.4) data were analysed using repeated-measures ANOVAs, as described in the following sections. The independent variables were the three groups (TD, DS, WS) and two conditions (Sleep-wake, Wake-sleep). Dependent variables were scores on the tasks at each session. For the Animal Names task there were four sessions: training, test 1, test 2 and within the final trial. Post-hoc tests were conducted using the Bonferroni correction. For repeated measures ANOVAs, multivariate statistics are reported as these are more robust than univariate tests since they are not dependent upon the assumption of sphericity (Field, 2005).

5.3.1 Animal Names declarative learning task

To assess whether sleep was related to declarative learning, children were trained on the Animal Names task and were retested after retention intervals of sleep and wake, and once again within the final session after they had heard the animals' names one more time. They were awarded two points for a correct answer and one point for an almost correct answer; hence the maximum score was 20 points. It was predicted that children would show a sleep-related improvement on the task.

Data on the Animal Names task were not available for all children. This included seven TD children who were not tested due to time constraints, and two children with DS who were unable to complete the task.

There was a significant effect of Group (F (2, 70) = 22.63, $p < .001$, $\eta_p^2 = .39$), where the TD group had significantly higher scores than both the DS and WS groups ($p < .001$ for each), who did not significantly differ from one another ($p = .99$). The effect of Condition was not significant (F (1, 70) = .05, $p = .82$, $\eta_p^2 = .001$) indicating comparable scores between the Sleep-wake and Wake-sleep conditions. Scores are presented in Table 5.7 and illustrated in Figure 5.6.

Table 5.7. *Mean scores at each Session and within the final session by Group (TD, DS, WS) and Condition (Sleep-wake, Wake-sleep) on the Animal Names task (maximum possible score of 20)*

Condition/ group	n	Train	Test 1	Test 2	Within trial
Sleep-wake		PM	AM	PM	PM
TD	17	10.53 (5.06)	12.29 (5.12)	12.41 (5.18)	14.94 (4.53)
DS	10	5.60 (3.03)	4.80 (3.19)	4.40 (2.72)	5.70 (3.89)
WS	10	5.30 (4.27)	7.20 (5.25)	6.20 (5.29)	9.20 (5.41)
Wake-sleep		AM	PM	AM	AM
TD	17	10.65 (4.40)	11.06 (3.40)	12.29 (3.67)	15.12 (3.33)
DS	10	5.80 (3.19)	5.70 (3.97)	6.90 (4.56)	8.80 (4.59)
WS	12	4.92 (2.87)	6.17 (2.72)	6.00 (3.38)	7.67 (4.05)

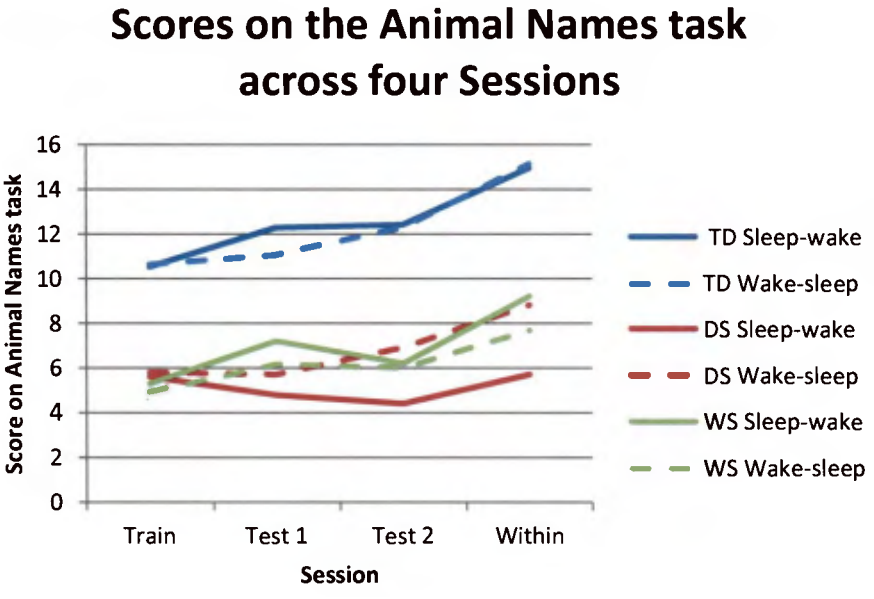

Figure 5.6. Scores across four sessions on the Animal Names task for each Group (TD, DS, WS) and Condition (Sleep-wake, Wake-sleep). Maximum possible score of 20.

There was a significant main effect of Session (Wilks' Lambda = .42, F (2, 68) = 31.08, p < .001, η_p^2 = .58). There was a significant interaction effect between Group and Session (Wilks' Lambda = .70, F (6, 136) = 4.51, p < .001, η_p^2 = .16) and between Condition and Session (Wilks' Lambda = .85, F (3, 68) = 3.89, p = .01, η_p^2 = .15), however the Group by Condition by Session interaction was not significant (Wilks' Lambda = .88, F (6, 136) = 1.49, p =.19, η_p^2 = .06).

These interactions were investigated in further detail by conducting the repeated measures ANOVA for each Group with the between-subjects factor of Condition. For this purpose, Training, Test 1 and Test 2 were investigated in one ANOVA to study the interaction between sleep and wake. The within trial improvement was assessed in a separate repeated measures ANOVA comparing performance at Test 2 with the final test.

For the TD and WS groups but not the DS group there was a significant main effect of Session (TD: Wilks' Lambda = .58, F (2, 31) = 11.31, p < .001, η_p^2 = .42; DS: Wilks' Lambda = .90, F (2, 17) = .98, p = .40, η_p^2 = .10; WS: Wilks' Lambda = .36, F (2, 19) = 16.94, p < .001, η_p^2 = .64).

For the TD group, the interaction between Session and Condition approached significance (Wilks' Lambda = .85, F (2, 31) =2.83, p = .08, η_p^2 = .15). This interaction was significant for the DS group (Wilks' Lambda = .60, F (2, 17) = 5.76, p = .01, η_p^2 = .40) but not for the WS group (Wilks' Lambda = .88, F (2, 19) =1.30, p = .30, η_p^2 = .12).

Results of the within-trial repeated measures ANOVA showed that all groups significantly improved on the Animal Names task within the final trial (TD: Wilks' Lambda = .40, F (1, 32) = 49.11, p < .001, η_p^2 = .61; DS: Wilks' Lambda = .63, F (1, 18) = 10.59, p = .004, η_p^2 = .37; WS: Wilks' Lambda = .51, F (1, 20) = 19.37, p < .001, η_p^2 = .07). There was no significant difference between the Sleep-wake and Wake-sleep conditions for any group (all p values > .05).

Finally, repeated measures ANOVAs were conducted for each Group and Condition in order to determine performance changes between each Session. The TD group in both Conditions showed a significant improvement on the task following the sleep retention interval but no significant change after wake. They also significantly improved on the final within trial test. Children with DS showed no significant change in scores after wake or sleep, but children in the Wake-sleep condition improved within the final trial. Children with WS significantly improved on the task following their first retention interval, i.e., after sleep for the Sleep-wake condition and after wake for the Wake-sleep condition. Children with WS in both conditions also significantly improved on the task within the final trial. Table 5.8 shows the change in score following each retention interval with repeated-measures ANOVA results.

Table 5.8. *Changes in score and repeated-measures ANOVA results for each Group (TD, DS, WS) and Condition (Sleep-wake, Wake-sleep) on the Animal Names task*

Group	Condition	n	Interval	Change in score	*F*	*p*	η_p^2
TD	Sleep-wake	17	Sleep	**1.76**	24.16	<.001	.60
			Wake	.12	.27	.61	.02
			Within	**2.53**	20.66	<.001	.56
	Wake-sleep	17	Sleep	**1.23**	7.03	.02	.31
			Wake	.41	.38	.55	.02
			Within	**2.83**	29.12	<.001	.65
DS	Sleep-wake	10	Sleep	-.80	3.27	.10	.27
			Wake	-.40	3.27	.10	.27
			Within	1.30	4.21	.07	.32
	Wake-sleep	10	Sleep	1.20	4.38	.07	.33
			Wake	-.10	.02	.88	.00
			Within	**1.90**	6.38	.03	.42
WS	Sleep-wake	10	Sleep	**1.90**	25.19	.001	.74
			Wake	-1.00	5.00	.05 ns	.36
			Within	**3.00**	13.07	.01	.59
	Wake-sleep	12	Sleep	-.17	.13	.72	.01
			Wake	**1.25**	11.30	.01	.51
			Within	**1.67**	6.04	.03	.36

Significant differences in **bold**

5.3.1.1 Are there developmental effects on the Animal Names task?

Age-related effects on score on the Animal Names task were investigated using linear regression. For this purpose, each child's mean score across the four tests was calculated and used to examine developmental trajectories for CA and MA for each group.

5.3.1.1.1 Chronological age

In the TD group but not the DS or WS groups there was a significant positive relationship between CA and mean score on the Animal Names task (TD: $R^2 = .22$, F (1, 32) = 9.02, $p = .01$; DS: $R^2 = .01$, F (1, 18) = .14, $p = .71$; WS: $R^2 = .03$, F (1, 20) = .58, $p = .46$)

The ANCOVA model showed no significant difference between the developmental trajectories of the three groups on the Animal Names task (F (2, 70) = 2.83, $p = .07$, $\eta_p^2 = .08$).

5.3.1.1.2 Mental age

Similarly, in the TD group but not the DS or WS groups, increased RCPM total was significantly related to higher score on the Animal Names task (TD: $R^2 = .13$, F (1, 32) = 4.87, $p = .04$; DS: $R^2 = .01$, F (1, 18) = .20, $p = .66$; WS: $R^2 = .09$, F (1, 20) = 1.88, $p = .19$).

Again, the ANCOVA model showed that the MA trajectories did not significantly differ from one another (F (2, 70) = 1.16, $p = .32$, $\eta_p^2 = .03$).

5.3.1.2 Sleep and sleep-dependent learning

To investigate whether sleep quality or duration might be related to the extent of sleep dependent learning, the change in score following the sleep retention interval was calculated for the Animal Names task using the equation 'score after sleep minus score before sleep'. The influence of sleep duration, quality and SpO_2 on these scores was investigated using hierarchical multiple regression as described in Section 4.6.3. There were no significant effects.

5.3.2 Tower of Hanoi procedural learning task

The Tower of Hanoi task was used to assess whether children's learning on a cognitive procedural task was related to sleep. It was predicted that children would improve on the task following sleep but not wake.

Due to test differences between the typical and clinical groups on the Tower of Hanoi, firstly scores were transformed to be comparable between groups. The TD group completed the task with five disks hence the minimum possible number of moves was 31 ($2^n - 1$ where n is the number of disks).

For the DS and WS groups completing the four-disk task, the minimum possible number of moves was 15. The constant here is 2.067 (calculated as 31/15) meaning that the five-disk task takes 2.067 times more moves than the four-disk task. The scores of the DS and WS groups were therefore multiplied by 2.067 to make them comparable to the TD group. All mention of scores hereafter refers to the transformed scores.

Table 5.9 and Figure 5.7 show the number of moves taken at each Session by each Group and Condition, after transformation of scores. Note that fewer moves indicates better performance.

Data on the Tower of Hanoi task were not available for all children. This included seven TD children who were not tested due to time constraints, as well as five children with DS and one with WS who were unable to complete the task.

Table 5.9. *Number of moves taken (Mean (SD)) at each Session by Group (TD, DS, WS) and Condition (Sleep-wake, Wake-sleep) on the Tower of Hanoi task*

Condition/ group	n	Train	Test 1	Test 2
Sleep-wake		PM	AM	PM
TD	17	57.91 (14.29)	49.38 (15.53)	46.06 (9.11)
DS	8	66.66 (33.49)	54.65 (13.26)	59.68 (28.17)
WS	10	54.05 (9.30)	51.68 (8.76)	59.94 (19.23)
Wake-sleep		AM	PM	AM
TD	17	66.94 (19.30)	69.09 (18.20)	50.62 (15.23)
DS	9	61.44 (25.86)	59.37 (14.75)	56.04 (16.24)
WS	11	60.22 (27.38)	67.18 (18.80)	50.74 (10.56)

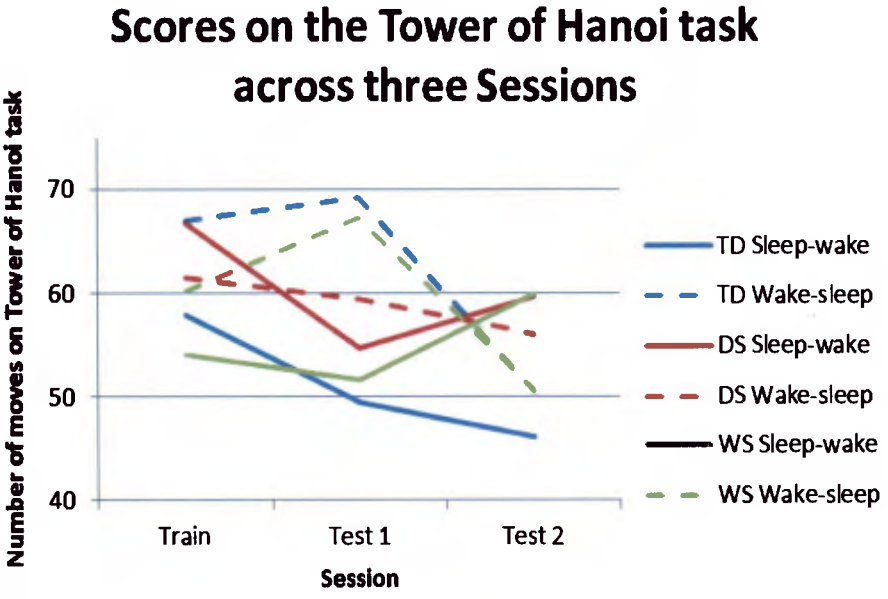

Figure 5.7. Number of moves taken across three sessions on the Tower of Hanoi task for each Group (TD, DS, WS) and Condition (Sleep-wake, Wake-sleep). Note that fewer moves indicates better performance. Minimum possible moves is 31.

Data for the Tower of Hanoi task were explored using a repeated measures ANOVA with the within-subjects factor of Session (three levels: training, test 1 and test 2) and two between-subjects factors (Group and Condition).

The effects of Group (F (2, 66) = .26, p = .78, η_p^2 = .01) and Condition (F (1, 66) = 1.77, p = .19, η_p^2 = .03) were not significant indicating comparable scores between the TD, DS and WS groups and between the Sleep-wake and Wake-sleep conditions. This shows that the converting the scores of the DS and WS groups made them comparable to the scores of the TD group.

There was a significant main effect of Session (Wilks' Lambda = .86, F (2, 65) = 5.12, p = .01, η_p^2 = .14). There was a significant interaction effect between Condition and Session (Wilks' Lambda = .82, F (2, 65) = 7.29, p = .001, η_p^2 = .18) but not between Group and Session (Wilks' Lambda = .89, F (4, 130) = 2.21, p = .07, η_p^2 = .06). The Group by Condition by Session interaction was also not significant (Wilks' Lambda = .96, F (4, 132) = .72, p =.58, η_p^2 = .02).

These interactions were investigated in further detail by conducting the repeated measures ANOVA for each Group with the between-subjects factor of Condition.

In the TD group but not the DS or WS groups there was a main effect of Session (TD: Wilks' Lambda = .64, F (2, 31) =8.91, $p < .001$, $\eta_p^2 = .37$; DS: Wilks' Lambda = .84, F (2, 14) = 1.35, $p = .29$, $\eta_p^2 = .16$; WS: Wilks' Lambda = .89, F (2, 18) = 1.15, $p = .34$, $\eta_p^2 = .11$). The interaction between Session and Condition was significant only in the WS group (TD: Wilks' Lambda = .86, F (2, 31) =, 2.46, $p = .10$, $\eta_p^2 = .14$; DS: Wilks' Lambda = .92, F (2, 14) = .64, $p = .54$, $\eta_p^2 = .08$; WS: Wilks' Lambda = .48, F (2, 18) = 9.65, $p = .001$, $\eta_p^2 = .52$).

Finally, repeated measures ANOVAs were conducted for each Group and Condition in order to determine performance changes between each Session. The TD group in both Conditions showed a significant improvement on the task following the sleep retention interval, indicated by a reduction in the number of moves, but no significant change after wake. Children with DS showed no significant change in scores after wake or sleep. Children with WS in the Wake-sleep condition significantly improved on the task following sleep but not wake. Performance of children with WS in the Sleep-wake condition did not significantly change following sleep or wake, however the decline in performance following wake approached significance ($p = .08$). The change in number of moves and ANOVA results are presented in Table 5.10.

Table 5.10. *Changes in number of moves and repeated-measures ANOVA results for each Group (TD, DS, WS) and Condition (Sleep-wake, Wake-sleep) on the Tower of Hanoi task*

Group	Condition	n	Interval	Change in number of moves	*F*	*p*	η_p^2
TD	Sleep-wake	17	Sleep	**-8.53**	9.35	.01	.37
			Wake	-3.32	.59	.45	.04
	Wake-sleep	17	Sleep	**-18.47**	12.55	.003	.44
			Wake	2.15	.09	.77	.01
DS	Sleep-wake	8	Sleep	-12.01	2.23	.18	.24
			Wake	5.04	.50	.50	.07
	Wake-sleep	9	Sleep	-3.33	1.41	.27	.15
			Wake	-2.07	.10	.76	.01
WS	Sleep-wake	10	Sleep	-2.38	.33	.58	.03
			Wake	8.27	3.83	.08	.30
	Wake-sleep	11	Sleep	**-16.44**	18.40	.002	.65
			Wake	6.95	1.37	.27	.12

Significant differences in **bold**

5.3.2.1 Rule violations

Rule violations on the Tower of Hanoi task were explored using a repeated-measures ANOVA with the within-subjects factor of Session (three levels: training, test 1 and test 2) and two between-subjects factors (Group and Condition). Fourteen TD children who did not commit any rule violations were not included in the analysis. All children with DS and WS made rule violations. Mean number of rule violations at each session are shown in Table 5.11 and Figure 5.8.

Table 5.11. *Number of rule violations made at each Session by Group (TD, DS, WS) and Condition (Sleep-wake, Wake-sleep) on the Tower of Hanoi task*

Condition/ group	n	Train	Test 1	Test 2
Sleep-wake		PM	AM	PM
TD	10	.85 (.97)	.05 (.16)	.25 (.63)
DS	8	5.31 (1.60)	3.50 (1.77)	4.56 (2.77)
WS	10	7.60 (2.83)	4.25 (2.78)	4.10 (2.27)
Wake-sleep		AM	PM	AM
TD	10	.80 (.42)	.40 (.81)	.05 (.16)
DS	9	8.17 (3.00)	7.22 (3.31)	5.94 (3.57)
WS	11	7.82 (3.78)	8.14 (3.46)	4.59 (2.51)

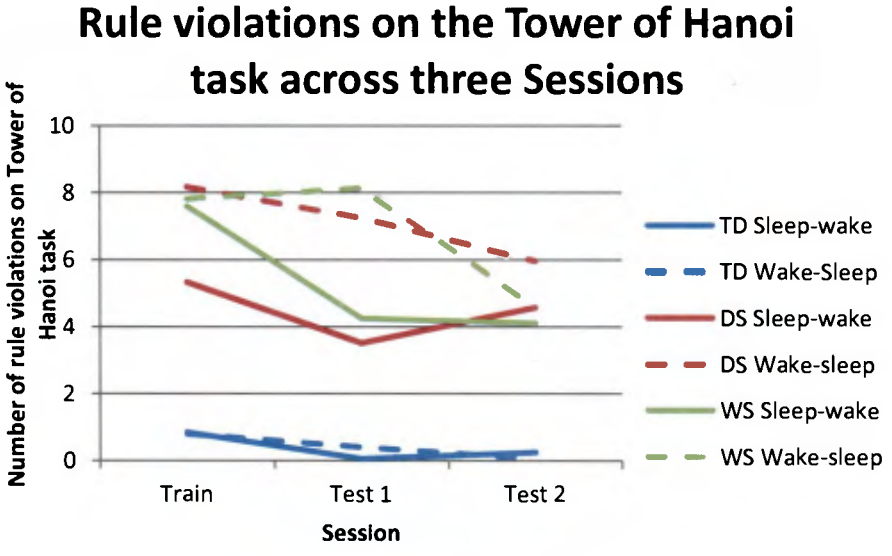

Figure 5.8. Number of rule violations made across three sessions on the Tower of Hanoi task for each Group (TD, DS, WS) and Condition (Sleep-wake, Wake-sleep).

There was a significant effect of Group (F (2, 52) = 45.19, p < .001, η_p^2 = .64) whereby the TD group committed significantly fewer rule violations than children with DS and WS. The effect of Condition was significant (F (1, 52) = 6.35, p = .02, η_p^2 = .11), with fewer rule violations made by the Sleep-wake than the Wake-sleep condition.

There was a significant main effect of Session (Wilks' Lambda = .54, F (2, 51) = 21.52, p < .001, η_p^2 = .46). There was a significant interaction effect between Condition and Session (Wilks' Lambda = .67, F (2, 51) = 12.70, p < .001, η_p^2 = .33) and between Group and Session (Wilks' Lambda = .69, F (4, 102) = 5.21, p = .001, η_p^2 = .17). The Group by Condition by Session interaction was also significant (Wilks' Lambda = .80, F (4, 102) = 3.01, p =.02, η_p^2 = .11).

These interactions were investigated in further detail by conducting the repeated measures ANOVA for each Group with the between-subjects factor of Condition.

The main effect of Session was significant in the TD and WS groups and approached significance in the DS group (TD: Wilks' Lambda = .30, F (2, 17) = 20.05, p < .001, η_p^2 = .70; DS: Wilks' Lambda = .69, F (2, 14) = 3.18, p = .07, η_p^2 = .31; WS: Wilks' Lambda = .35, F (2, 18) =16.65, p < .001, η_p^2 = .65). The interaction effect between Session and Condition was significant only in the WS group (TD: Wilks' Lambda = .80, F (2, 17) = 2.11, p = .15, η_p^2 = .20; DS: Wilks' Lambda = .75, F (2, 14) = 2.38, p = .13, η_p^2 = .25; WS: Wilks' Lambda = .38, F (2, 18) = 14.57, p < .001, η_p^2 = .62).

Finally, repeated measures ANOVAs were conducted for each Group and Condition in order to determine performance changes between each Session. The TD Sleep-wake group showed a significant improvement on the task following the sleep retention interval, indicated by a reduction in the number of rule violations, but no significant change after wake. The TD Wake-sleep group showed no significant change in number of rule violations after either sleep or wake. Children with DS showed no significant change in scores after wake or sleep. Children with WS in both conditions had significantly reduced number of rule violations following sleep, but not wake. The change in number of rule violations and ANOVA results are presented in Table 5.12.

Table 5.12. *Changes in number af rule vialatians and repeated-measures ANOVA results far each Graup (TD, DS, WS) and Canditian (Sleep-wake, Wake-sleep) an the Tawer af Hanai task*

Group	Condition	n	Interval	Change in number of rule violations	*F*	*p*	η_p^2
TD	Sleep-wake	10	Sleep	**-.80**	9.44	.01	.51
			Wake	.20	1.71	.22	.16
	Wake-sleep	10	Sleep	-.35	2.00	.19	.18
			Wake	-.40	2.09	.18	.19
DS	Sleep-wake	8	Sleep	-1.81	4.33	.08	.38
			Wake	1.06	2.72	.14	.28
	Wake-sleep	9	Sleep	-1.28	2.47	.16	.24
			Wake	-.94	1.08	.33	.12
WS	Sleep-wake	10	Sleep	**-3.35**	30.13	<.001	.77
			Wake	-.15	.12	.73	.01
	Wake-sleep	11	Sleep	**-3.55**	29.59	<.001	.75
			Wake	.32	.21	.66	.02

Significant differences in **bold**

5.3.2.2 Are there developmental effects on the Tower of Hanoi task?

Linear regression was used to investigate the effects of CA and MA on number of moves taken and rule violations on the Tower of Hanoi task.

5.3.2.2.1 Number af maves taken

Linear regression showed no significant relationship between children's CA or RCPM total score with their average score on the Tower of Hanoi task for any group, therefore individual developmental trajectories are not reported.

5.3.2.2.2 Rule Violations

5.3.2.2.2.1 *Chronological age*

For number of rule violations, TD children made significantly fewer rule violations with increasing CA. CA was not significantly related to rule violations in the DS and WS groups (TD: R^2 = .22, F (1, 18) = 5.07, p = .04; DS: R^2 = .04, F (1, 15) = .66, p = .43; WS: R^2 = .04, F (1, 19) = .74, p = .40).

The ANCOVA model showed that the trajectories of the three groups were not significantly different from one another for rule violations (F (2, 52) = .08, p = .93, η_p^2 = .003).

5.3.2.2.2.2 *Mental age*

In the TD and WS groups, rule violations were significantly related to MA. This relationship was not evident in the DS group (TD: R^2 = .42, F (1, 18) = 12.91, p = .002; DS: R^2 = .10, F (1, 15) = 1.63, p = .22; WS: R^2 = .27, F (1, 19) = 7.09, p = .02).

The ANCOVA model showed a significant difference between the MA trajectories of the three groups (F (2, 52) = 6.41, p = .003, η_p^2 = .20).

Pairwise comparisons showed no significant difference between the TD and DS groups (F (1, 33) = 1.60, p = .25, η_p^2 = .05)

There was a significant difference between the MA trajectories of the TD and WS groups (F (1, 37) = 12.44, p = .001, η_p^2 = .25) and between the DS and WS groups (F (1, 34) = 7.45, p = .01, η_p^2 = .18). Figure 5.9 shows that this was due to the increase in rule violations made by children with WS with increasing MA, whilst children with DS and TD children made fewer rule violations with increasing MA.

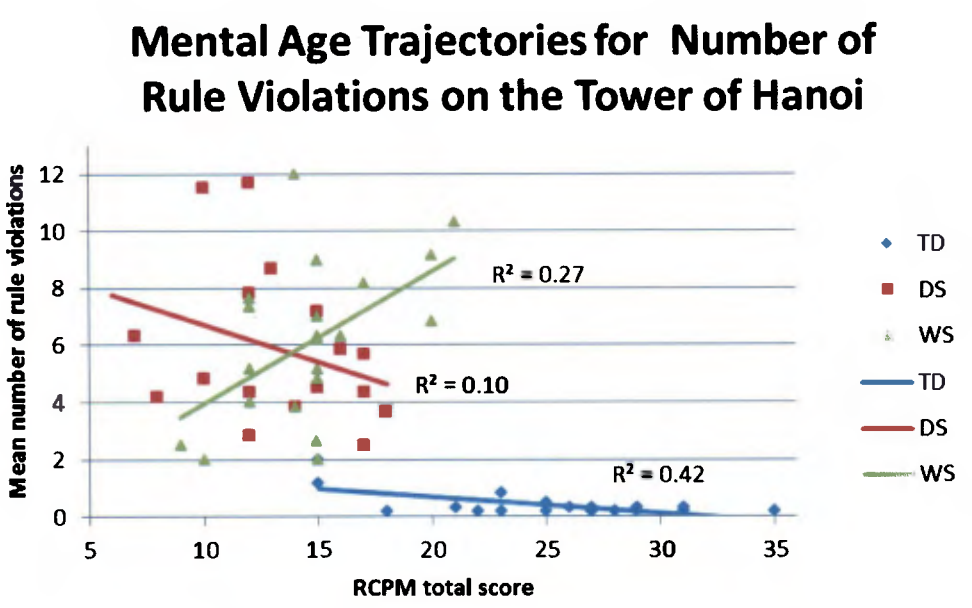

Figure 5.9. Mental age trajectories for the TD, DS and WS groups for number of rule violations made on the Tower of Hanoi task.

5.3.2.3 Sleep and sleep-dependent learning

To investigate possible relationships between sleep characteristics and sleep-dependent learning, the change in score following the sleep retention interval was calculated for the number of moves and rule violations on the Tower of Hanoi task using the equation "score after sleep minus score before sleep". The influence of sleep duration, quality and SpO_2 on these scores was investigated using hierarchical multiple regression as described in Section 4.6.3. There were no significant effects.

5.3.3 Continuous Performance Task

Children completed a CPT in order to measure their sustained and selective attention to respond to two infrequently occurring targets (monkeys) (Sections 3.3.4 and 4.3.5). It was predicted that TD children would perform better on the CPT than children with DS or WS.

Data from one child with DS were removed as they did not adhere to the instructions of the CPT.

One-way between-groups ANOVAs were computed to compare group scores for number of correct hits, commission errors and reaction times (RTs) for hits and errors. Significant group differences were evident with the two disorder groups performing significantly less well than TD children on all variables. In addition, children with DS achieved significantly fewer hits and their RT for errors was significantly slower than both other groups (see Table 5.13).

Table 5.13. *Group differences for correct hits, commission errors and reaction times on the CPT*

	TD (n = 41)	DS (n = 21)	WS (n = 22)	*F*	*p*	ηp^2
Correct hits (/40)	37.79 (3.87)	**19.58 (11.51)**	**30.05 (8.87)**	35.13	<.001[abc]	.48
Commissions (/160)	8.58 (9.19)	**21.00 (18.27)**	**18.82 (17.53)**	6.21	<.01[ab]	.14
RT hits	619.18 (69.90)	**837.60 (179.23)**	**786.35 (148.73)**	23.16	<.001[ab]	.38
RT errors	484.06 (80.34)	**714.70 (146.13)**	**615.11 (110.60)**	31.10	<.001[abc]	.45

Significant differences in **bold**

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

5.3.3.1 Are there developmental effects on the CPT?

Linear regression was used to investigate individual trajectories (CA and MA) for each variable of the CPT. These are reported below and CA trajectories are illustrated in Figure 5.10.

5.3.3.1.1 Correct hits

5.3.3.1.1.1 *Chronological age*

In the TD group but not the DS or WS groups there was a significant positive relationship between CA and number of correct hits (TD: $R^2 = .11$, F (1, 39) = 4.80, $p = .04$; DS: $R^2 = .14$, F (1, 19) = 2.4, $p = .14$; WS: $R^2 = .04$, F (1, 20) = 2.56, p .13).

The ANCOVA model showed no significant difference between the developmental trajectories of the three groups for correct hits on the CPT (F (2, 78) = .68, $p = .51$, $\eta_p^2 = .16$).

5.3.3.1.1.2 *Mental age*

Similarly, in the TD group but not the DS or WS groups, increased RCPM total was significantly related to increased correct hits on the CPT (TD: $R^2 = .22$, F (1, 39) = 11.07, $p = .002$; DS: $R^2 = .10$, F (1, 17) = 1.95, $p = .18$; WS: $R^2 = .003$, F (1, 20) = , $p = .82$).

Again, the ANCOVA model showed that the MA trajectories did not significantly differ from one another (F (2, 76) = 1.45, p = .24, η_p^2 = .04).

5.3.3.1.2 Commission errors

5.3.3.1.2.1 *Chronological age*

In the TD group there was a significant relationship between increased CA and reduced number of commission errors (TD: R^2 = .10, F (1, 39) = 4.21, p < .05; DS: R^2 = .03, F (1, 19) = .62, p = .44; WS: R^2 = .02, F (1, 20) = .35, p = .56).

The ANCOVA model showed no significant difference between the trajectories of the three groups for number of commission errors made on the CPT (F (2, 78) = 1.35, p = .27, η_p^2 = .03).

5.3.3.1.2.2 *Mental age*

MA was not significantly related to commission errors for any group.

5.3.3.1.3 Reaction time hits

5.3.3.1.3.1 *Chronological age*

In the TD and WS groups but not the DS group, increased RCPM total was significantly related to faster RT for correct hits on the CPT (TD: R^2 = .69, F (1, 39) = 35.81, p < .001; DS: R^2 = .12, F (1, 19) = 2.51, p = .13; WS: R^2 = .48, F (1, 20) = 18.53, p < .001).

ANCOVA model showed no significant difference between the trajectories of the three groups for RT hits (F (2, 78) = .99, p = .38, η_p^2 = .02).

5.3.3.1.3.2 *Mental age*

There was a significant relationship between RCPM total and RT for correct hits in the TD group but not the DS or WS groups (TD: R^2 = .35, F (1, 39) = 21.09, p < .001; DS: R^2 = = .01, F (1, 17) = .19, p = .67; WS: R^2 = .002, F (1, 20) = .03, p = .86).

ANCOVA showed that the MA trajectories for the three groups for RT hits did not significantly differ from one another (F (1, 76) = 1.17, p .32, η_p^2 = .03).

5.3.3.1.4 Reaction time errors

5.3.3.1.4.1 *Chronological age*

In the TD and WS groups, faster RT for commission errors was significantly related to increasing age. This relationship was not significant in the DS group (TD: R^2 = .14, F (1, 36) = 5.99, p = .02; DS: R^2 = .09, F (1, 17) = 1.57, p = .23; WS: R^2 = .33, F (1, 20) = 9.85, p = .01).

The ANCOVA model showed no significant difference between the trajectories of the three groups for RT errors (F (2, 73) = .40, p = .67, η_p^2 = .01).

5.3.3.1.4.2 *Mental age*

MA was not significantly related to RT for errors for any group.

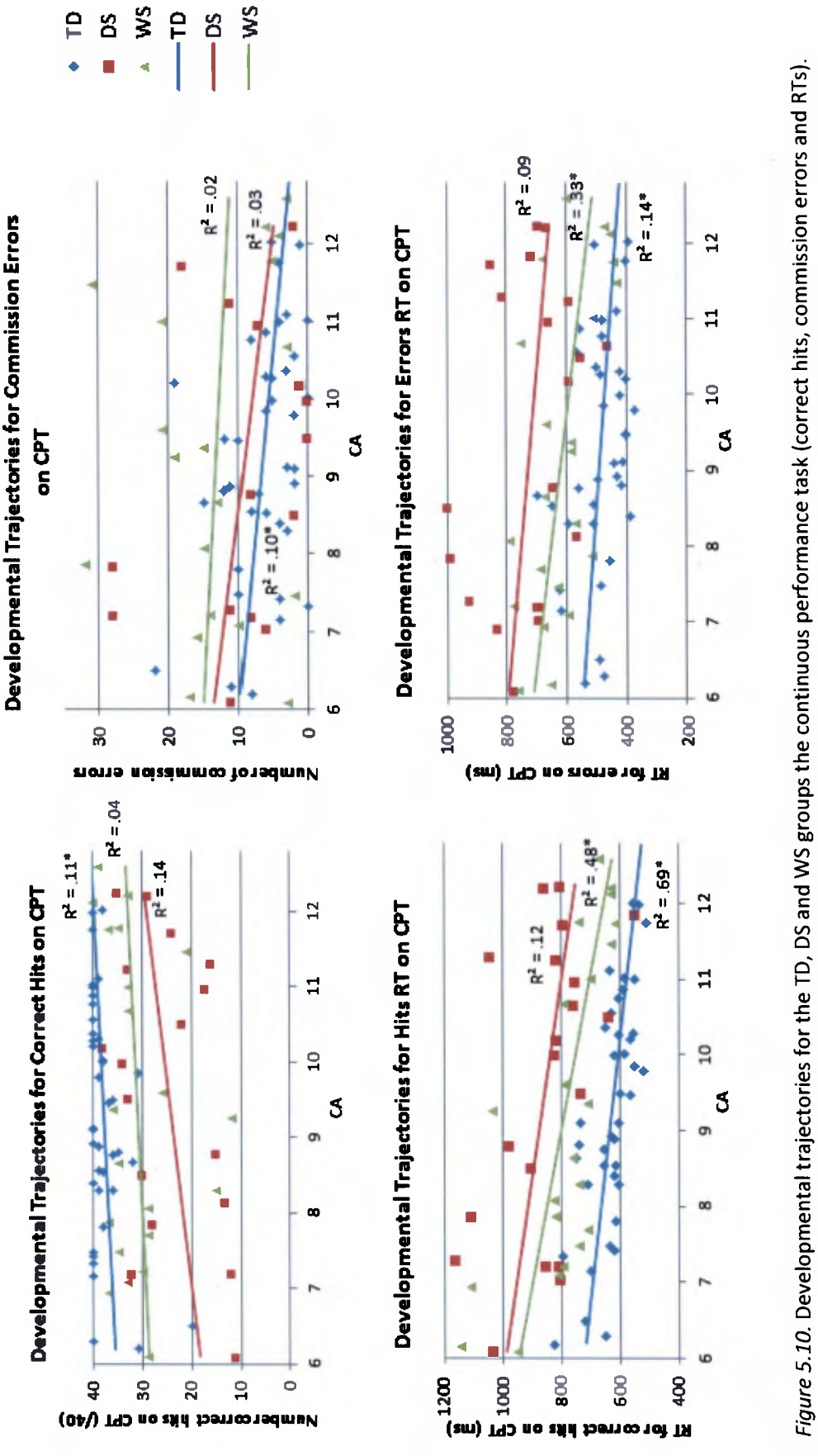

Figure 5.10. Developmental trajectories for the TD, DS and WS groups the continuous performance task (correct hits, commission errors and RTs).

* = significant effect.

5.3.3.2 Sleep and attention

It was predicted that children with longer sleep duration and/or better quality sleep would perform better on the CPT than children with short or poor quality sleep.

In order to investigate this, hierarchical linear regression was used. As described in Section 4.6.3, two models were created: one investigating the influence of sleep duration and quality, the other examined SpO_2 variables. For both models, CA and MA (RCPM total) were controlled in the first block. Omission errors, commission errors and their RTs on the CPT were entered individually as dependent variables.

The first model (actigraphy) included actual sleep time in block 2 (sleep duration block), and sleep efficiency, number of night wakings and mean duration of night wakings in block 3 (sleep quality block). After controlling for CA and MA, significant findings in the TD group showed that block 3 (sleep quality) was able to predict 16% of the variance in number of correct hits (R^2 change = .16, F change (3, 30) = 2.97, p = .046) and 27% of the variance for RT errors (R^2 change = .27, F change (3, 30) = 5.07, p = .01). Children with better sleep quality achieved more correct hits on the task and had quicker reaction times for commission errors. The model was not able to significantly predict performance on the task for the DS or WS groups.

The second model included SpO_2 variables in block 2. These were mean SpO_2, dips per hour >4%, delta 12 index, and % time spent below 90% SpO_2. In the TD group, the SpO_2 variables block explained almost half of the variance in number of commission errors (R^2 change = .48, F change (2, 30) = 7.30, $p < .001$). Children with better (higher and less variable) SpO_2 saturation made fewer commission errors on the tasks than children with poorer SpO_2.

5.4 Questionnaires

Parents completed questionnaires relating to their child's sleep, behaviour and temperament as well as their own sleep and wellbeing (Section 4.4).

All questionnaires were analysed using one-way between-groups ANOVAs with questionnaire scores as the dependent variables and Group (TD, DS, WS) as the fixed factor. This section outlines the results of individual questionnaires. Due to the great number of variables covered by the questionnaires are reported in histograms for clarity. Tables with F ratios, η_p^2 and observed power are also provided.

Questionnaires were missing for six TD children and two children with DS whose parents did not complete them.

5.4.1 Children's Sleep Habits Questionnaire

The CSHQ (Section 4.4.1) was used to assess parentally reported sleep problems. It was predicted that parents of children with DS and WS would report more sleep problems than parents of TD children.

ANOVA analyses of the CSHQ revealed significant group differences in subscale scores between the TD, DS and WS groups. Specifically, children with DS had elevated scores on the subscales of Sleep anxiety OR, Night wakings, Parasomnias and SDB. Compared to the TD group, children with WS scored highly on the Night wakings subscale. In addition children with DS had a significantly higher Total problems score than both other groups. The Total problems scale has been used to distinguish children with sleep problems from those without by applying a cut-off score of 41 (Owens, Spirito, & McGuinn, 2000). According to this criterion, 68.6% of TD children, 100% of children with DS and 86.4% of children with WS were found to have sleep problems. Chi Squared analysis showed that the difference between groups was significant, with more children with DS falling in the problem score range than TD children (χ^2 (2, 77) = 8.88, p = .01, phi = .34). Results of the subscales are shown in Figure 5.11 with significant group differences marked. Further details of the ANOVA results are in Table 5.14.

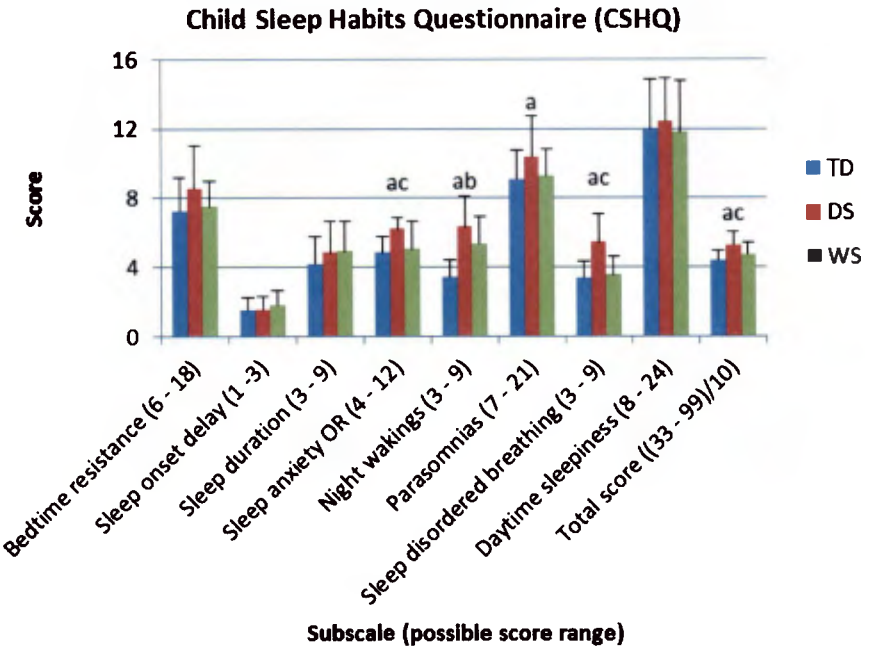

Figure 5.11. Histogram of scores by group for CSHQ subscales. Error bars show standard deviation. Possible score range is shown in brackets for each variable. Higher scores correspond with greater sleep problems. Total score is scaled (/10) to fit the chart.

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

Some interesting data are lost through amalgamating scores to subscales, particularly for the Parasomnias subscale which includes unrelated items. Therefore individual items of the Parasomnias scale and items that have been reported by others to be specific problems in children with DS or WS were investigated in further detail to establish whether group differences were apparent (Annaz et al., 2011; Breslin et al., 2011; Stores et al., 1998). The results in Table 5.15 indicate the percentage of parents who reported sleep characteristics occurring sometimes and usually (two or more nights per week). ANOVAs were then used to compare groups on these variables.

Table 5.14. *Cross-syndrome comparison of scores (mean (SD)) on the CSHQ using ANOVA. Higher scores indicate increased sleep problems*

Subscale (possible score range)	TD (n = 35)	DS (n = 20)	WS (n = 22)	*F*	*p*	η_p^2
Bedtime resistance (6 - 18)	7.26 (1.95)	8.55 (2.48)	7.50 (1.50)	2.79	.07	.07
Sleep onset delay (1 -3)	1.54 (0.70)	1.55 (0.76)	1.82 (0.80)	1.06	.35	.03
Sleep duration (3 - 9)	4.20 (1.55)	4.85 (1.81)	4.91 (1.77)	1.57	.22	.04
Sleep anxiety OR (4 - 12)	4.83 (.95)	**6.19 (.66)**	5.05 (1.64)	7.55	.001[ac]	.19
Night wakings (3 - 9)	3.46 (0.95)	**6.35 (1.73)**	**5.36 (1.56)**	31.56	<.001[ab]	.46
Parasomnias (7 - 21)	9.11 (1.62)	**10.40 (2.30)**	9.27 (1.55)	3.46	.04[a]	.09
Sleep disordered breathing (3 - 9)	3.37 (0.94)	**5.45 (1.64)**	3.55 (1.10)	20.94	<.001[ac]	.36
Daytime sleepiness (8 - 24)	12.00 (2.86)	12.45 (2.48)	11.77 (3.01)	.31	.73	.01
Total score (33 – 99)	43.86 (5.44)	**52.90 (7.57)**	47.23 (7.28)	12.00	<.001[ac]	.24

Significant differences in **bold**

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

Table 5.15. *Cross-syndrome comparison of the percentage of children expressing parasomnias on two or more nights per week and group differences determined by ANOVA*

	TD (n = 35)	DS (n = 20)	WS (n = 22)	*F*	*p*	η_p^2
Wets the bed?	8.57	30.00	**36.36**	3.22	<.05[b]	.08
Talks during sleep?	**54.29**	30.00	13.64	6.02	<.01[b]	.14
Restless during sleep?	60.00	**95.00**	68.18	10.76	<.001[ac]	.23
Sleepwalks?	5.71	10.00	4.55	.28	.76	.01
Grinds teeth during sleep?	25.71	47.37	13.64	2.37	.10	.06
Awakens screaming/ sweating/ inconsolable?	2.94	10.53	4.55	1.20	.31	.03
Has frightening dreams?	14.29	26.32	27.27	.62	.54	.02
Moves to someone else's bed?	11.43	**60.00**	**54.55**	11.64	<.001[ab]	.24
Snores loudly?	20.00	**70.00**	22.73	12.93	<.001[ac]	.26
Wakes very early?	28.57	**75.00**	54.55	4.38	.02[a]	.11
Seems tired during the day?	34.29	**85.00**	54.55	7.05	<.01[a]	.16
Sleepy when watching TV?	2.86	**40.00**	18.18	6.15	<.01[a]	.14
Sleepy when riding in a car?	14.29	**65.00**	22.73	8.72	<.001[a]	.19

Significant differences in **bold**.

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

5.4.1.1 Comparison of parent report with objective measures of sleep

Where analogous variables existed, Pearson's product moment correlations were used to investigate the similarity between parent report (CSHQ) and objective measures of sleep (actigraphy and pulse oximetry). This was conducted for sleep duration, sleep onset latency, number and duration of night wakings and fragmentation/restlessness by correlating CSHQ data with actigraphy variables. Parentally reported SDB was correlated with mean SpO_2 as measured by pulse oximetry. Correlation results showed little agreement between parent-report and objective measures (Table 5.16).

Table 5.16. *Pearson's product moment correlations between parent report and objective actigraphy and pulse oximetry measures*

	TD (n = 34)			DS (n = 20)			WS (n = 22)		
	n	*r*	*p*	n	*r*	*p*	n	*r*	*p*
Sleep duration	32	**.53**	.002	17	**.65**	.01	20	.32	.17
Sleep latency	34	**.43**	.01	20	-.30	.20	22	-.38	.08
Number of night wakings	34	-.30	.09	20	-.09	.72	22	-.33	.14
SDB/ SpO_2 dips per hour >4%	29	-.08	.70	13	-.26	.39	10	.34	.33
Restlessness	34	-.31	.08	20	-.15	.54	22	-.10	.65
Night waking duration	15	-.26	.35	19	.01	.96	15	.17	.54

Significant results in **bold**

5.4.2 Temperament in Middle Childhood Questionnaire

The TMCQ was used to give an overview of temperament in children with DS and WS compared to TD children. The TMCQ gives scores on 17 different aspects of child behaviour, each with a possible score range of 1 to 5. ANOVAs revealed significant group differences on all but three variables of the TMCQ. Figure 5.12 shows the mean score for each group, standard deviations and significant group differences for each subscale. ANOVA results are presented in Table 5.17.

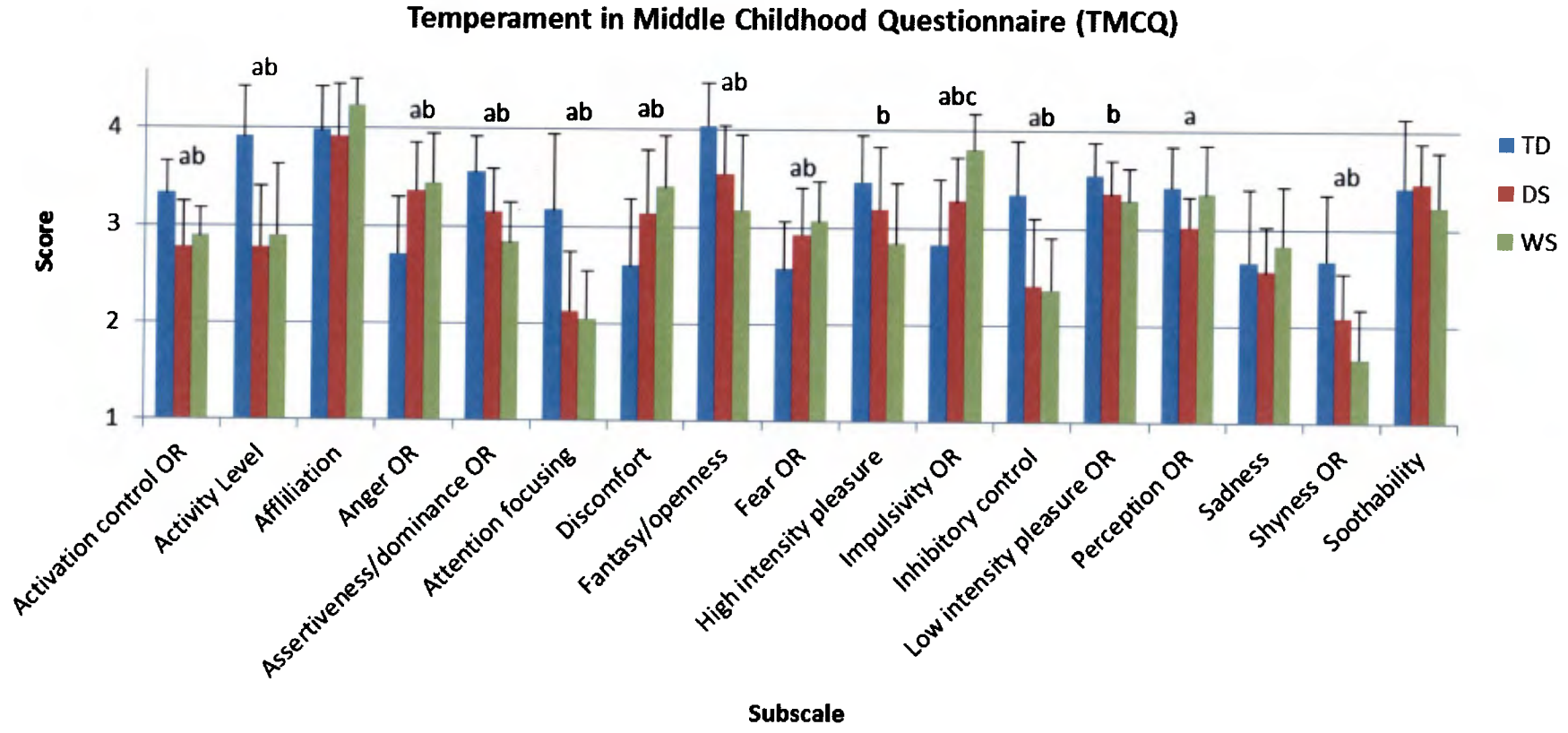

Figure 5.12. Histogram of scores by group for TMCQ subscales. Error bars show standard deviation. Higher scores indicate greater expression of that trait. Score range is 1 to 5 for each subscale.

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

Table 5.17. *Cross-syndrome comparison of scores (Mean (SD)) on the TMCQ using ANOVA. Higher scores indicate greater expression of that trait. Score range is 1 to 5 for each subscale*

	TD (n = 35)	DS (n = 20)	WS (n = 22)	*F*	*p*	η_p^2
Activation control OR	3.33 (.33)	**2.78 (.47)**	**2.89 (.29)**	16.24	<.001[ab]	.33
Activity Level	3.91 (.51)	**2.78 (.62)**	**2.90 (.73)**	13.88	<.001[ab]	.28
Affliliation	3.98 (.45)	3.92 (.53)	4.24 (.27)	3.27	.05 ns	.08
Anger OR	2.71 (.59)	**3.36 (.49)**	**3.44 (.51)**	13.42	<.001[ab]	.30
Assertiveness/dominance OR	3.55 (.37)	**3.14 (.45)**	**2.84 (.41)**	18.77	<.001[ab]	.38
Attention focusing	3.17 (.78)	**2.13 (.61)**	**2.05 (.50)**	24.72	<.001[ab]	.41
Discomfort	2.60 (.68)	**3.14 (.65)**	**3.41 (.52)**	11.83	<.001[ab]	.25
Fantasy/openness	4.04 (.44)	**3.55 (.49)**	**3.18 (.77)**	15.57	<.001[ab]	.30
Fear OR	2.57 (.49)	**2.92 (.48)**	**3.06 (.40)**	7.39	<.001[ab]	.19
High intensity pleasure	3.47 (.48)	3.19 (.64)	**2.84 (.62)**	8.09	<.001[b]	.18
Impulsivity OR	2.84 (.67)	**3.28 (.45)**	**3.81 (.37)**	18.71	<.001[abc]	.37
Inhibitory control	3.35 (.54)	**2.41 (.69)**	**2.37 (.53)**	25.42	<.001[ab]	.41
Low intensity pleasure OR	3.55 (.33)	3.35 (.34)	**3.29 (.33)**	3.89	.03[b]	.16

Table 5.17. *Continued*

	TD (n = 35)	DS (n = 20)	WS (n = 22)	*F*	*p*	η_p^2
Perception OR	3.43 (.42)	**3.02 (.31)**	3.35 (.51)	4.73	.01[a]	.14
Sadness	2.66 (.74)	2.56 (.46)	2.83 (.61)	1.01	.37	.03
Shyness OR	2.67 (.68)	**2.09 (.46)**	**1.67 (.50)**	18.59	<.001[ab]	.38
Soothability	3.43 (.70)	3.47 (.41)	3.23 (.56)	1.04	.36	.03

Significant differences in **bold**

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

5.4.2.1 Comparison of parent report TMCQ with experimental CPT

Pearson's product moment correlations were used to investigate whether parent report of the attention focusing, impulsivity and inhibitory control subscales of the TMCQ were related to the same objective variables measured by the CPT.

Attention focussing was correlated with number of CPT hits, inhibitory control with number of commission errors, and impulsivity with RT for errors. No significant correlations were found.

5.4.3 Strengths and Difficulties Questionnaire

The SDQ was used to assess behaviour problems and prosocial behaviour in children. It was predicted that children with DS and WS would have more behavioural problems than TD children.

ANOVA analyses on the subscales of the SDQ showed significant group differences on the subscales of Conduct problems OR, Hyperactivity/inattention, Peer relationship problems, Pro-social behaviour, Total difficulties and Impact OR, with children with DS and WS having more problems than TD children.

Subscale scores are shown in Figure 5.13 with significant group differences marked. See also Table 5.18 for ANOVA results. Higher scores on the SDQ indicate greater behavioural problems, with the exception of the prosocial scale, which is reversed. Each of the subscales has a possible score range of 0 to 10 though the Total difficulties scale is the sum of the four other problem scales so ranges from 0 to 40. Note that it has been scaled here (/4) to fit the chart.

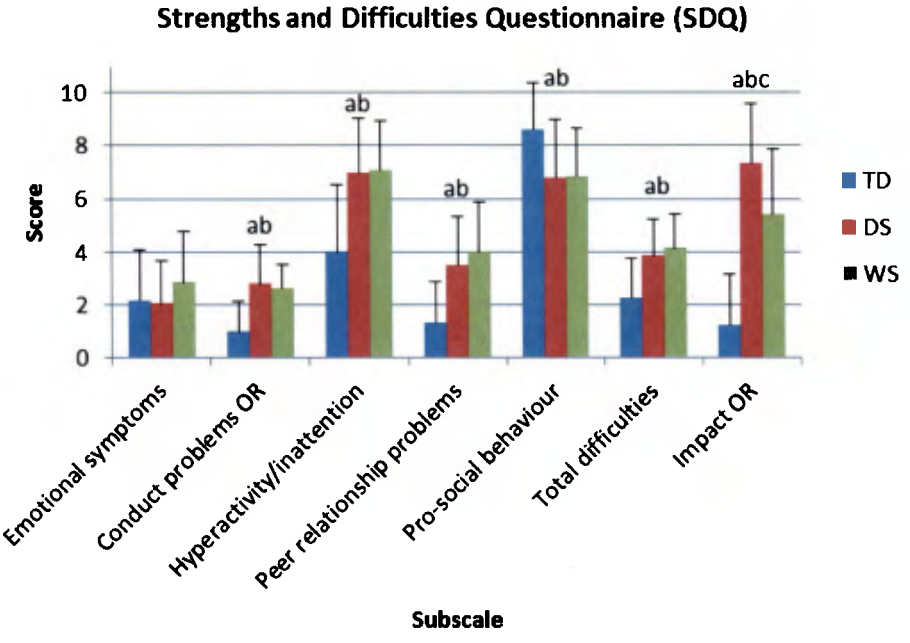

Figure 5.13. Histogram of scores by group for SDQ subscales. Error bars show standard deviation.

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

Table 5.18. *Cross-syndrome comparison of scores (Mean (SD)) on the SDQ using ANOVA*

	TD (n = 35)	DS (n = 20)	WS (n = 22)	*F*	*p*	η_p^2
Emotional symptoms	2.15 (1.94)	2.05 (1.61)	2.82 (1.97)	1.13	.33	.03
Conduct problems OR	0.97 (1.15)	**2.79 (1.48)**	**2.63 (.89)**	16.19	<.001[ab]	.37
Hyperactivity/ inattention	4.00 (2.52)	**7.00 (2.05)**	**7.09 (1.85)**	17.37	<.001[ab]	.33
Peer relationship problems	1.33 (1.55)	**3.50 (1.85)**	**4.00 (1.90)**	18.40	<.001[ab]	.34
Pro-social behaviour	8.61 (1.77)	**6.80 (2.19)**	**6.86 (1.83)**	8.00	.001[ab]	.18
Total difficulties	9.00 (6.00)	**15.45 (5.46)**	**16.55 (5.18)**	14.58	<.001[ab]	.29
Impact OR	1.23 (1.93)	**7.35 (2.23)**	**5.42 (2.46)**	49.93	<.001[abc]	.61

Significant differences in **bold**

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

The SDQ also gives suggested bands for normal, borderline and abnormal scores. According to these criteria both the DS and WS children scored in the borderline range for Conduct problems OR and in the abnormal range on the Hyperactivity/inattention scale and Impact score. On the Peer relationships and Total difficulties subscales children with DS scored in the borderline range, whilst children with WS scored in the abnormal band. Despite scoring significantly lower than the TD group for prosocial behaviour, scores for the DS and WS groups were within the normal range for this characteristic.

5.4.3.1 Relationship between sleep and behaviour

It was predicted that, after controlling for potentially confounding factors of CA and MA, children with shorter sleep duration and/or poorer sleep quality would have more behavioural problems and less prosocial behaviour than children who slept for longer and had good sleep.

Hierarchical multiple regression was used to investigate these associations. Due to the great amount of data here, non-significant results are not reported.

A regression model was used to investigate the influence of sleep duration and quality (as measured by actigraphy) on each subscale of the SDQ. CA and MA (RCPM total) were controlled in the first block. The second block included only actual sleep time; the third block included sleep efficiency, number of night wakings and duration of night wakings, as described in Section 4.6.3.

In the TD group, sleep duration (block 2) was able to predict 15% of the variance in scores for the hyperactivity subscale after controlling for CA and MA (R^2 change = .15, F change (1, 28) = 5.47, p = .03). Children who had short sleep duration were reported to be more hyperactive than children who slept for longer.

A second regression model was constructed to investigate the influence of SpO_2 variables on the SDQ subscales. As before, CA and MA (RCPM total) were controlled in the first block. The second block included mean SpO_2, dips per hour >4%, delta 12 index, and % time spent below 90% SpO_2. In the TD group, SpO_2 variables significantly related to conduct problems (R^2 change = .38, F change (4, 21) = 3.49, p = .03) and to prosocial behaviour (R^2 change = .59, F change (4, 21) = 10.54, p < .001). For both subscales, better behaviour was predicted by better sleep (i.e., higher and less variable SpO_2).

5.4.4 Parent questionnaires

Parents answered three questionnaires relating to their own sleep, daytime sleepiness and depressive symptoms. These were the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS) and the Major Depression Inventory (MDI) respectively. It was predicted that parents of children with DS and WS would have more disturbed sleep, daytime sleepiness and depression than parents of TD children.

Of the returned questionnaires, the majority were completed by children's mothers. To avoid potential confounding factors between mothers and fathers, five fathers who responded were not included in the analysis (1 TD, 2 DS, 2 WS).

Possible scores on the PSQI ranged from 0 to 3 for each subscale, along with a total score sum of the subscales, where higher scores indicated increased sleep problems. One-way between-groups ANOVAs showed that parents of children with DS had significantly higher scores than both other groups on the subscales of Sleep quality, Sleep latency and sleep efficiency. Parents of TD children had the highest score for the Sleep disturbances scale, which relates to night wakings associated with factors such as feeling too hot/cold, snoring and having to use the bathroom. See Figure 5.14 and Table 5.19 for further details.

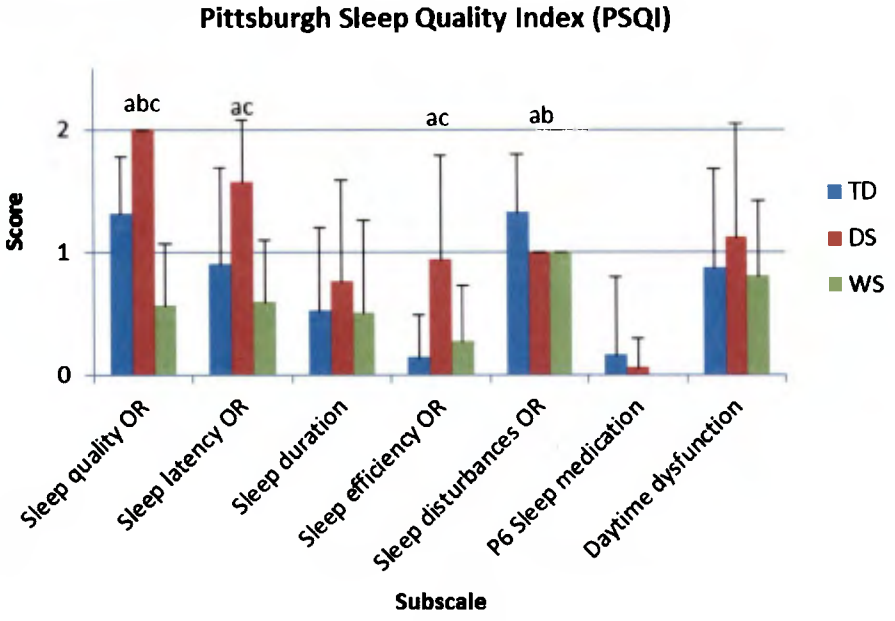

Figure 5.14. Histogram of scores by group for PSQI subscales. Error bars show standard deviation. Possible score range is 0 to 3, higher scores indicate increased problems.

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

Total score OR on the PSQI also showed a significant group difference, with parents of children with DS having a significantly higher score than both other groups.

On the ESS OR, too, parents of children with DS had the highest score, whilst parents of children with WS had the lowest score (Table 5.19). This difference was significant though scores did not indicate excessive daytime sleepiness (>10). Chi-squared was used to analyse how many mothers scored above the cut off-score of 10. Seven (22.6%) mothers of TD children, six (35.3%) mothers of children

with DS and one (5%) mother of a child with WS had scores of 10 or higher. The between-groups difference was not significant (χ^2 (2, 65) = 5.30, p = .07, phi = .28).

Parents of children with DS also had the highest scores on the MDI, though group differences were not significant (Table 5.19). Also, using Bech et al.'s (2001) criteria for scoring depression, two (6.2%) mothers of TD children, two (11.8%) mothers of children with DS and one (5%) mother of a child with WS scored above the cut-off score of 26, though Chi-squared analysis showed that this difference was also not significant (χ^2 (2, 65) = .69, p = .71, phi = .10). Of these five depressed mothers, four also scored above 10 on the ESS.

Table 5.19. *ANOVA group comporison of porents' scores (Meon (SD)) on the PSQI, ESS ond MDI*

	TD (n = 34)	DS (n = 18)	WS (n = 20)	*F*	*p*	η_p^2
P1 Sleep quality OR	1.31 (.47)	**2.00 (.00)**	**.56 (.51)**	36.15	<.001[abc]	.58
P2 Sleep latency OR	.90 (.79)	**1.57 (.51)**	.59 (.51)	8.63	.001[ac]	.23
P3 Sleep duration	.52 (.68)	.76 (.83)	.50 (.76)	.75	.47	.02
P4 Sleep efficiency OR	.14 (.35)	**.94 (.85)**	.27 (.46)	11.30	<.001[ac]	.28
P5 Sleep disturbances OR	1.32 (.48)	**1.00 (.00)**	**1.00 (.00)**	6.05	<.01[ab]	.19
P6 Sleep medication	.16 (.64)	.06 (.24)	.00 (.00)	.83	.44	.02
P7 Daytime dysfunction	.87 (.81)	1.12 (.93)	.80 (.62)	.82	.44	.02
P8 Total OR	4.85 (1.81)	**6.46 (1.98)**	3.94 (1.91)	6.55	<.01[ac]	.20
Epworth sleepiness scale OR	5.48 (3.04)	**7.55 (2.50)**	4.37 (2.83)	4.24	.02[c]	.14
Major depression inventory	9.13 (7.54)	14.00 (8.54)	8.95 (8.26)	2.43	.10	.07

Significant differences in **bold**

a = Significant difference between TD and DS ($p < .05$)

b = Significant difference between TD and WS ($p < .05$)

c = Significant difference between DS and WS ($p < .05$)

5.4.4.1 Relationship between child sleep and behaviour, and maternal sleep and wellbeing

It was predicted that mothers' sleep would be related to their child's sleep and that maternal depression would be related to children's sleep and behaviour problems. Pearson's product moment correlation coefficients were used to investigate these relationships within each group. There were a great number of variables here and high interrelationships between the subscales of the PSQI (for each group, total score significantly correlated with at least five of the seven subscales). Therefore, initially only the total PSQI score was correlated with children's sleep characteristics. Subscales were only examined if there was a significant effect for total PSQI score.

Firstly, total PSQI and ESS were correlated with key actigraphy and SpO_2 saturation variables previously discussed (Section 4.6.3). In the TD group, higher PSQI total score correlated with longer child wake bouts (r (30) = .37, p = .04). The subscales driving this relationship were parents' sleep duration and sleep disturbances, suggesting that children's longer night wakings are related to parents' shorter sleep duration and increased sleep disturbance. Linear regression showed that children's mean wake bout time predicted 14% of the variance in mother's PSQI total score for the TD group (R^2 = .14, F (1, 28) = 4.53, p = .04). No significant correlations were found between parents' and children's sleep in the DS or WS groups.

Next, parents' scores on the MDI were correlated with children's actigraphy and SpO_2 saturation variables as well as scores on the SDQ. No significant relationships were found except that in the WS group there was a positive correlation between mothers' MDI scores and children's emotional symptoms scores on the SDQ (r (20) = .47, p = .04). Linear regression showed a shared variance of 23% between children's emotional score and mothers' MDI score in the WS group (R^2 = .23, F (1, 18) = 5.23, p = .04).

6. Discussion

6.1 Summary

The primary aims of this thesis were to investigate sleep characteristics and how they might affect behaviour, cognition and sleep-dependent learning in healthy TD children and children with DS and WS. In addition, it aimed to examine age-related changes to sleep and cognition as well as study the relationship between children's sleep and behaviour, and maternal sleep and wellbeing. It was successful in meeting these aims. Sleep characteristics and SpO_2 for all groups were established using actigraphy and pulse oximetry. Children's cognitive abilities and sleep-dependent learning were assessed and parents completed questionnaires relating to their child's sleep and behaviour as well as their own sleep and wellbeing. Group differences, age-related changes and the relationship between sleep and performance were then examined.

This chapter contains a discussion of the research findings and how they relate to the hypotheses (Section 2.4) and existing research. It covers the limitations and implications of the present study and suggestion are made for future research.

6.2 Sleep

6.2.1 Actigraphy and pulse oximetry

Actigraphy and pulse oximetry data were consistent with previous reports of sleep problems in children with DS and WS (e.g., Annaz et al., 2011; Carter et al., 2009). These sleep characteristics were syndrome-specific, so supporting Hypothesis 1. Children with DS had increased night wakings and fragmented sleep, which could be related to OSAS as these children also had lower SpO_2, increased SpO_2 dips and delta 12 indices (SpO_2 variability) compared to TD children, supporting Hypothesis 2. These signs are suggestive of OSAS, which is known to be common in DS (Churchill et al., 2011; Dyken et al., 2003; Ng et al., 2006; Shott et al., 2006). Hypothesis 3 was part-supported as children with WS had long sleep latencies, consistent with previous parental reports (Annaz et al., 2011; Udwin et al., 1987). In the current study, mean sleep latency was over 46 minutes. This was 19 minutes longer than the TD group and 23 minutes longer than the DS group, although there was also wide inter-individual variability. Children with WS had a significantly lower mean and median SpO_2 than the TD group which, to my knowledge, has not been previously reported. Children with WS also had a significantly higher heart rate during sleep than both other groups, possible due to known cardiovascular problems in this group (Eronen et al., 2002; Pober et al., 2008). Contrary to the prediction of Hypothesis 3, night wakings and sleep efficiency in the WS group were comparable to TD. The pulse oximetry data for the TD group are comparable to reference values reported by

Urschitz et al. (2003) in a large random sample of 100 healthy TD children so we can assume that these children form a representative comparison group.

In the current study, actigraphy data showed that the three groups were remarkably similar in the actual amount of sleep they achieved. The mean actual sleep times of the three groups were within four minutes of one another but standard deviations were larger in the clinical groups, indicating greater variability. Despite the resemblance, the DS group had considerably more night wakings, wake after sleep onset, and lower sleep efficiency, therefore having significantly longer assumed sleep to achieve this actual sleep time (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2013).

Actigraphy data also showed that TD children went to bed later and got up later than both other groups. This may be a reflection of their journey-to-school time. TD children usually lived within walking distance of their school so their journey time was short. Conversely, many children with DS and WS attended specialist schools for children with learning difficulties, often with a long journey in a school bus or taxi. It may also take these children longer to get ready for school in the morning than TD children, hence needing to get up half an hour earlier.

The age range of the study is a developmental period associated in TD populations with a mean reduction in night sleep of 1.7 hours (Iglowstein, Jenni, Molinari, & Largo, 2003). It was expected that this decline in sleep time would be apparent in the present study. In general there was a trend for children having less sleep with increasing CA, which was significant in the DS and WS groups: older children with WS had less assumed sleep and children with DS and WS had reduced actual sleep time, although this was not associated with bedtime or getting up time. Children in the TD group went to bed later with increasing age, but this was not related to their total sleep time as older children did not also sleep for longer than younger children. In the DS group, later bedtimes were related to increased MA, not CA, and MA-older children took longer to fall asleep than MA-younger children but did not have shorter sleep duration. This shows an interesting developmental difference between the DS and TD groups and suggests that children in all groups adjust their sleep time to suit their needs, irrespective of bedtime. In addition, it suggests that bedtime is driven by brain maturation as well as biological factors. Also in the TD group, increased MA was associated with higher median SpO_2 and less time spent below 90% SpO_2. This indicates that SpO_2 desaturations may have a negative impact on the advancement of children's MA, delaying them developmentally. This supports previous research, for example, in a large sample of 205 5 year-old TD children, Gottlieb et al. (2004) found that children with SDB (N = 61; determined by parent report and PSG) had a significantly lower IQ than children without SDB, as well as poorer performance across a range of cognitive ability tasks. Others, too, have found a link between SDB and intelligence in otherwise

healthy TD children (Kaemingk et al., 2003; O'Brien et al., 2004). The link between cognitive function and SDB is well-documented in TD children, indicating that associated hypoxia, hypercarbia and sleep fragmentation can lead to disturbed cognition and behaviour (Blunden & Beebe, 2006). This association was not evident in the DS group but has been reported previously in 12 young adults with DS using the RPM (Andreou et al., 2002). The relationship between sleep and ID is particularly intricate, with a possible two-way interaction. Alterations of sleep architecture and disturbed sleep may interfere with normal development of cognition and behaviour, whilst cognitive processes may also drive the sleep requirement. In addition, cognitive impairments and sleep problems may both arise from underlying neural abnormalities (Dan & Boyd, 2006).

Aside from a gradual decline in sleep time during childhood usually seen in TD children, though not evident in the present study (Iglowstein et al., 2003) there are also considerable changes to sleep architecture throughout childhood (refer to Section 1.2.3): sleep cycles become longer and SWS diminishes with a corresponding increase in stage II (Ohayon et al., 2004; Pegg, 2006). Although actigraphy cannot detect these changes, it was thought that some might be reflected in the actigraphy recording, for example increased fragmentation or night wakings associated with lighter stages of sleep. Interestingly, there were no age-related changes to sleep quality in any of the three groups.

Actigraphy is a useful tool for monitoring movement and studying sleep-wake cycles. It was particularly valuable for the present study as its simplicity made it ideal for use with children with ID. Indeed only two children with DS were excluded from the study because they would not tolerate wearing the actiwatch, and one TD child later refused after wearing it for only a few hours. This contrasts with the three children with DS and ten with WS who refused to wear the pulse oximetry probe. It is probable that these children would also have objected to PSG; hence, actigraphy provides a valuable tool for measuring sleep and wake in these groups.

Nevertheless, this method also has important limitations. Although the Actiwatch Mini is assumed to be comparable to other validated devices, to my knowledge, there are no published validation studies. Sensitivity and specificity for use with children in clinical groups are unknown. Meltzer and Westin (2011) compared two different scoring algorithms for scoring sleep onset and offset (respectively, the first and last of 15 consecutive minutes of sleep; or the first of three and the last of five consecutive minutes of sleep). Although the two algorithms gave different results, the disparities were not clinically meaningful so data may still be compared across studies. Pollak et al. (2001) also studied two actigraphy devices compared to PSG. Although both were reasonably accurate for predicting sleep (86.6% concordance with PSG), they tended to overestimate sleep

efficiency due to scoring epochs of wakeful inactivity as sleep. Neither of these was the Actiwatch Mini used in the present study. Furthermore, actigraphy is limited in its ability to accurately measure sleep latency as this depends on parents accurately reporting 'lights out' time in a sleep diary. We know that parent report is not always accurate (Holley et al., 2010; Shott et al., 2006); hence sleep latency is the least objective of the actigraphy measures. Despite these limitations, the use of a TD group gives a useful comparison in this case, so the data are valuable even if they cannot necessarily be compared to the wider literature. Clearly there is the need for validation of actigraphy devices and scoring algorithms in order for findings to be comparable across studies (Littner et al., 2003).

It is unfortunate that pulse oximetry data were not available for all children. In some cases this was due to the child refusing to wear the oximeter probe, a common occurrence when working with children with disabilities (C.M. Hill, personal communication, May 9, 2012). Also, although parents were shown how to use the device correctly, it is thought that some inadequate recordings were due to incorrect placement of the sensor. In some cases this meant that children's data could not be used due to insufficient artefact-free recording time. The use of actigraphy, however, meant that detailed information on sleep quality and quantity could still be gathered from all children, even when pulse oximetry was not possible or not sufficient. In addition, although pulse oximetry is a useful screening tool for SDB, it has relatively low sensitivity: 64% when compared to PSG for accurate detection of OSAS related SpO_2 desaturations (Brouillette et al., 2000). It must be remembered that it is not possible to determine OSAS from SpO_2 alone as SpO_2 desaturations could also be linked to central apnoea or hypoventilation. Furthermore some children with OSAS arouse with apnoea and so avoid desaturation.

A confounding factor that may have affected sleep quality, which was not controlled for in the present study was that whilst all TD children and the majority of children with DS lived in London, the rarity of WS necessitated recruiting children from further afield (up to 220 miles away). Some lived in rural areas away from street lights, traffic and other noise; hence their sleep may have been less interrupted than that of children who live in the city. This means that groups were not as well matched as they could have been. This is an important consideration for future research, which could perhaps test the siblings of atypical children in order to ensure better-matched groups. It would then have to be ensured that children would not confer or practice memory tasks with one another. This could be achieved by having different but matched lists of to-be-remembered material. Also, the possibility of a response bias in the TD and DS groups cannot be ruled out. Although parents were told that the study was investigating normal sleep patterns, it is conceivable that parents whose children experienced sleep problems were more inclined for their children to

participate; therefore, sleep problems in these groups may be worse here than would normally be found in a random sample. Nevertheless, the findings in these groups were consistent with previously reported data (Churchill et al., 2011; Urschitz et al., 2003) so it can be assumed that these were representative groups. For the WS group, we are more confident that the findings are generalisable to the WS population, since only two families declined to take part due to current family circumstances.

6.2.2 Children's Sleep Habits Questionnaire

Data from the CSHQ also showed that children with DS experienced greater problems with sleep than the WS and TD groups. Compared to TD children, children with DS had significantly higher scores on four of the eight subscales as well as total CSHQ score. Atypically high scores on the sleep anxiety, parasomnias and night wakings subscales are consistent with previous literature describing settling and sleep maintenance difficulties in DS (Stores, Stores, Fellows, & Buckley, 1998). Parents of children with DS also reported a higher incidence of SDB symptoms on the CSHQ, consistent with the actigraphy data showing fragmented sleep with increased night wakings, and the pulse oximetry data showing decreased and more variable SpO_2 compared to TD.

Mean score on the daytime sleepiness subscale of the CSHQ was not significantly elevated for children with DS, who scored only marginally higher than the other two groups. This is in contrast to most previous research which found daytime sleepiness to be a particular problem for individuals with DS. For example, Breslin et al. (2011) used the CSHQ and found that their sample of 35 children with DS aged 7 to 18 (mean age 12.65) had a significantly elevated mean score for the daytime sleepiness subscale and 60% routinely fell asleep whilst riding in the car or watching television. When individual items were investigated, the current study showed similar findings. Children with DS were more than twice as likely as TD children to appear sleepy during the day, particularly whilst riding in the car and watching television, but this did not significantly increase the mean subscale score. These symptoms could also be a manifestation of OSAS. Breslin et al. (2011) found significant sleep problems in almost all areas, with 85.7% of the DS sample having sleep disturbance scores in the clinical range. This is slightly lower than the 100% found in the present study, yet is probably accounted for by the slightly higher age range and their finding that some sleep problems (e.g., sleep anxiety) decline with age.

Although parents reported night wakings to be a problem in the WS group, this was not reflected in the actigraphy data, and in fact the WS group had fewer night wakings than the TD group. This inconsistency may be due to a reduced ability in the WS group to self-soothe back to sleep,

therefore demanding more attention from parents and leading to increased parental report of night waking, despite objective measures being comparable to the TD group. TD children learn to self-soothe in infancy, with around 60 to 70% of infants being able to self soothe by 12 months of age (Anders, Halpern, & Hua, 1992). This also highlights the great difference between actigraphic night wakings, which may be brief, and behavioural night wakings that would be evident to a parent.

The present findings are not completely consistent with previous CSHQ data from 64 children with WS, where particular problems were found on the bedtime resistance, sleep onset delay, sleep anxiety, night waking and daytime sleepiness subscales (Annaz et al., 2011). Perhaps this disparity is due to the greater effect of a much larger sample. Both studies found a high level of bedwetting in children with WS, showing a maturational contrast with TD children.

6.2.3 Comparison of parent report, actigraphy and pulse oximetry

As predicted (Hypothesis 10), parent report was not always in agreement with actigraphy data. It was expected that parent report would be quite precise for sleep latency, and although positive correlations were found for all groups, only the TD group reached the significance level of .05. Parents were reasonably accurate at reporting how long children had slept in the TD and DS groups but no other correlations were found between actigraphy and CSHQ. One reason for this may be that the CSHQ subscale for sleep onset delay consists of only one item (Child falls asleep within 20 minutes), yielding a score of 1 (rarely), 2 (sometimes) or 3 (usually). This is perhaps not detailed enough to correlate with the range of sleep latency times experienced by children. Parent report was also inconsistent with actigraphy data for restlessness and night wakings, possibly because without constant watch over the child, it would be impossible to know the frequency of these behaviours. These findings support previous research suggesting that parents are not always aware of characteristics of their children's sleep (Shott et al., 2006; Wiggs, Montgomery, & Stores, 2005) and that whilst parents are reasonably good at reporting sleep start and finish times, they are less accurate in other areas (Holley et al., 2010; Lam, Mahone, Mason, & Scharf, 2011). Other studies have compared parent reports to the child's own reports of their sleep, finding that children report significantly more problems and night wakings than their parents do (Muris, Merckelbach, Ollendick, King, & Bogie, 2001; Wiechers et al., 2011). Perhaps, then, children's reports of their sleep need to also be considered, although this may not be appropriate for children with ID.

Despite its inaccuracy on these subjective issues, it was thought that parent report might be more useful for uncovering specific information regarding sleep, for example parasomnias such as bed-wetting or grinding teeth. Indeed, Mason et al. (2011) found significant correlations between

parental reports of repetitive leg movements during sleep and periodic limb movements measured by PSG in children. Hence, in the present study, parasomnias and other items were investigated individually. This is particularly important for the parasomnias subscale, where items are unrelated so rich information is lost by amalgamating scores. This analysis revealed key differences between groups. Children with DS and WS were much more likely than typical children to move to another person's bed during the night. Bedwetting was a particular problem for children with WS, whilst restlessness, loud snoring and early waking were problems for the DS group. More than half of the TD children were reported to talk in their sleep. Parent report is useful for gaining information on these parameters since most cannot be measured by actigraphy. In addition, a well-kept sleep diary is necessary for analysis of actigraphy data so parent report should still be valued. However, due to its inaccuracy for reporting subjective sleep characteristics, it should not be used as a substitute for objective measures, but ought to be used in conjunction. The present study benefits from using both objective and subjective techniques to support one another.

Although there are no established norms, Owens and colleagues (2000) have reported CSHQ results from a sample of 494 healthy school-aged children. For the TD group the current findings are quite similar, except that our sample scored much higher on the Daytime Sleepiness subscale (12.00 compared to 9.63) and total sleep problems score (43.86 compared to 38.80). In addition, two thirds of the TD group scored above the suggested cut-off score (41) for determining the best diagnostic confidence for clinical sleep problems in a TD population. Similar findings have been reported by Holley et al. (2010) in a UK-based study in TD children. Almost half of their sample of 91 6 to 11 year olds scored above the cut-off, relative to 23% reported by Owens et al. (2000). These differences may represent cultural sleep differences between our UK populations and the US sample on which the original data were based.

6.3 Sleep-dependent learning

Sleep is an active state that has been linked with the consolidation of newly acquired memories. Research in adults demonstrates sleep-dependent memory consolidation for both declarative and procedural tasks (Karni et al., 1994; Walker & Stickgold, 2004, 2006), whilst in children sleep-dependent learning has been demonstrated for declarative tasks, with mixed results on procedural learning (Annaz & Ashworth, 2011; Backhaus et al., 2008; Dimitriou et al., 2013; Wilhelm et al., 2008; Wilhelm, Metzkow-Mészàros, et al., 2012). The present study successfully implemented a novel declarative (Animal Names task) and a cognitive procedural memory task (The Tower of Hanoi) in a group of 34 TD children, 20 children with DS and 22 children with WS.

6.3.1 Animal Names task

The newly developed Animal Names declarative task was adapted from word pairs and non-word learning tasks in order to be more appealing and engaging for children whilst still adhering to the principles of a declarative learning task. This child-friendly task showed to be easy to implement. Of children who completed the task, only one child was at ceiling level and none were at floor level, so it can be assumed to be of appropriate difficulty for the age range targeted, i.e., children aged 6 to 12, including those with developmental delay. Similarly to word pair studies in children (Backhaus et al., 2008; Wilhelm et al., 2008), performance scores increased significantly following sleep compared to wake in the TD group, so supporting Hypothesis 13 and indicating reliability of the Animal Names task. The results suggest that in TD children the memory traces for the Animal Names were actively reinforced during sleep so that children were able to achieve a higher score following a retention interval of sleep. This effect was evident regardless of whether initial training took place in the morning or evening (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, under review).

In contrast, children with DS did not show any significant change in memory performance between each session on the Animal Names task. Verbal memory and expressive language are particular problems for individuals with DS (Hick et al., 2005; Ypsilanti & Grouios, 2008). Future studies of declarative sleep-dependent learning in individuals with DS could use tasks adapted to place fewer demands on these problem areas. The 2D object location task used by Wilhelm et al. (2008) may be suitable as a non-verbal declarative task. Alternatively, (Jarrold et al., 2009) used an Alien Names task to assess short term verbal memory in children with DS, but reduced the demands on expressive language by providing multiple choice answers of similar sounding names. A task such as this may help children with DS to perform well, thus sleep-dependent gains could become apparent.

Children with WS remembered more animal names on their first retest than they had at baseline, regardless of whether sleep or wake occurred in the retention interval. This pattern of findings is interesting and difficult to explain since it did not appear to be related to sleep or wake, as predicted; nor was it related to the time of day (e.g., better performance in the morning). Further studies are needed to establish why the declarative memory of children with WS improved between one session and the next, and indeed, whether this is a reliable finding. No children were reported to take a nap on the study day, nor did actigraphy show napping, so it cannot be assumed that consolidation occurred during daytime sleep. It is possible that memory consolidation in children with WS happens between sessions, regardless of whether sleep occurs. Daytime consolidation has been demonstrated in TD children, though only for implicit procedural learning, not declarative tasks (Fischer et al., 2007; Wilhelm et al., 2008). Alternatively, children with WS were better-able to

remember the names at the beginning of the second session when they were refreshed then they had been at the end of the first session.

Finally, all groups except the DS Sleep-wake group showed improvement on the Animal Names task within the final trial, showing that children did have the cognitive capacity for increased learning. That the DS Sleep-wake group did not significantly improve ($p = .07$) could reflect that this task was late in the day when children may be tired and not concentrate as well as they might in the morning. This suggests that tiredness or accumulated sleep propensity throughout the day may have more impact on the learning of children with DS than it does on children with WS or TD children. In addition, although baseline performance of the DS Sleep-wake and Wake-sleep conditions was comparable, there was a significant interaction between Session and Condition in this group whereby the Wake-sleep group (who were trained in the morning) gradually improved on the task at each session, whilst performance of the Sleep-wake group (who were trained in the evening) progressively declined so that performance at the second retest was much better for the Wake-sleep group (6.90 points) than the Sleep-wake group (4.40 points). Thus, although learning for the DS group did not appear to depend on sleep, these children seemed to benefit from being trained in the morning as opposed to the evening.

6.3.2 Tower of Hanoi

The present study was the first to use the Tower of Hanoi task to assess cognitive procedural sleep-dependent learning in children (Ashworth et al., under review). In general, all groups showed a trend towards greater improvement (reduction in their number of moves taken to complete the task) following sleep than they did after the wake retention interval, though this was only significant for the TD groups and the WS Wake-sleep group. In fact, performance often declined slightly over the wake interval, which may have been due to fatigue in the evening test session. Additionally, a significant interaction between Session and Condition in the WS group indicated an overall improvement in performance following sleep and a decline after the wake retention interval. Children in the DS Sleep-wake group reduced their mean score by 12 moves (after adjustment) following sleep. Compare this to the significant reduction of 8.53 moves in the TD Sleep-wake group after sleep and this seems a considerable improvement, yet it is not significant, probably due to greater variability in performance and only having 8 participants in the DS Sleep-wake group. A similar pattern of findings was revealed when rule violations were investigated. TD children made very few rule violations, significantly fewer than both other groups. Rule violations made by the TD Sleep-wake group significantly declined following sleep, but not wake. There was no change in the number of rule violations made following sleep or wake for the TD Wake-sleep group, probably

because children made so few that differences between sessions were small. For children with DS there was no significant change in the number of rule violations made following sleep or wake, though the reduction following sleep for the Sleep-wake group approached significance (p = .08; similarly to the reduction in number of moves for this group). Children with WS showed a significant interaction between Session and Condition for rule violations, driven by significantly reduced rule violations following sleep but not wake. This shows evidence of sleep-dependent learning for the rules of the task. For the TD and WS groups, these results support Hypothesis 13.

On completing the Tower of Hanoi task the improvement following sleep seen in both TD conditions and the WS Wake-sleep condition is in contrast with most other published data for procedural tasks (Fischer et al., 2007; Prehn-Kristensen et al., 2009; Wilhelm et al., 2008), though there is some recent controversy in the literature (Annaz & Ashworth, 2011; Dimitriou et al., 2013; Wilhelm, Metzkow-Mészàros, et al., 2012). There are a number of possible explanations for this finding. Firstly, it may relate to the task demands. The Tower of Hanoi is not a purely procedural task. It also involves a cognitive aspect in order to discover the rule to complete the task in the fewest moves. It is possible that this cognitive learning is sleep-dependent, whereas *purer* procedural tasks, which rely on implicit learning gains, such as mirror tracing or a SRTT used in other studies, may not be sleep-dependent in children. This suggests that sleep-dependent learning is affected by specific features of the learning task. A theory proposed by Gais et al. (2000) goes some way to explaining this difference. They suggest that, in adults, as task difficulty progresses, so the dependence on sleep for memory consolidation shifts from stage II to REM. Thus, complex tasks that involve learning new skills, such as the Tower of Hanoi, are consolidated during REM sleep whilst simple, purely motor tasks such as rotor pursuit or visual discrimination are dependent upon stage II for reinforcement of existing skills. Children have a particularly high percentage of REM, though it is not yet known whether this is involved in complex procedural learning as it is in adults. Nevertheless, the current findings in the TD group do appear to support this theory. Together, the previous literature and the present thesis indicate that the REM-dependent learning occurs during sleep in children, whilst stage II-dependent learning does not. In addition, Smith et al. (2004) found that adults improved their performance on the Tower of Hanoi task following sleep, and that improvement was related to an increase in REMs and REM density. Improvement was also related to IQ; adults with the highest IQs showed greater improvement on the task and also a greater increase in REMs and REM density from baseline on the post-learning night, compared to adults with the lowest IQs. PSG studies have found evidence of reduced REM sleep in children with DS and WS (Gombos et al., 2011; Miano et al., 2008; Shott et al., 2006). Thus, it would be interesting to research whether, firstly, the relationship between learning, REM and IQ could be generalised to TD children; secondly, whether the known

reduction of REM sleep in individuals with DS and WS might be related to their ability to consolidate new procedural memories during sleep; and thirdly, whether IQ might be related to memory consolidation and REM in DS and WS. Indeed, in a sample of eight young adults with DS, Diomedi et al. (1999) found that lower IQ was related to reduced REMs and REM percentage. They propose that this reflects a reduction in neural plasticity and the ability to consolidate new information during REM sleep, although they did not research sleep-dependent learning directly. This suggestion appears to be supported by the current research. Further, it is likely that the sleep-dependent learning deficit in individuals with DS reaches far beyond performance on the present task and may also help to explain their difficulties in other areas, for example, fine motor control (Spanò et al., 1999).

Secondly, as Wilhelm and colleagues suggest, childhood sleep preferentially enhances explicit rather than implicit memory, since implicit knowledge must be merged with pre-existing knowledge in order to be remembered (Born & Wilhelm, 2012; Fischer et al., 2007; Wilhelm, Metzkow-Mészàros, et al., 2012; Wilhelm, Prehn-Kristensen, et al., 2012). In the present study children were told to complete the task in as few moves as possible, requiring conscious effort to discover the correct sequence of moves. This could be construed as explicit learning, therefore leading to greater enhancement by sleep. In support of this theory, an observation was noted when conducting the Tower of Hanoi with children: once they had discovered a sequence of moves that 'worked' they seemed reluctant to change it, even when there was a quicker method. This suggests explicit learning as children were remembering a set sequence, rather than learning the implicit hidden rule, again supporting suggestions made by Wilhelm and colleagues and further highlighting a distinction between the learning methods of adults and children. As this was an observation and the order of moves was not recorded, it cannot be confirmed. Hence, future studies could use video when conducting this task with children to investigate how often children repeat a sequence of moves that they have used previously, even when a shorter sequence is available.

The lack of sleep-dependent learning in DS in the present study could reflect that children with DS did not have a sufficient level of prior knowledge to be able to benefit from sleep on the task. Alternatively, children with ID have reduced resources available to devote to offline consolidation so sleep preferentially consolidates more recent or more salient aspects of the day. Studies could be devised to test this by assessing children on days when they are not at school, so reducing competition from other learning activities. In addition, the use of tasks that involve only one aspect of memory would enable better understanding of how different skills are enhanced by sleep. In the

real world, learning rarely relies only on a single type of memory, so learning techniques could then be maximised to make use of off-line memory consolidation.

Wilhelm, Metzkow-Mészàros, et al.'s (2012) theory is also supported by the results of the rule violations on the Tower of Hanoi task. Children in the TD Wake-sleep group and both WS conditions improved following sleep. Remembering the rules and putting them into action is an explicit aspect of a procedural task, thus, the task showed evidence of explicit learning in TD and WS.

Contrary to Hypothesis 7, the number of moves taken to complete the Tower of Hanoi task was not related to CA or MA for any group. In contrast, Hypothesis 7 was supported for the number of rule violations: in TD children, CA- and MA-older children made fewer rule violations than younger children. Children with DS made fewer rule violations with increasing MA, though this relationship was not significant. Interestingly, children with WS made significantly more rule violations with increasing MA, with MA explaining 27% of the variance in score. This would suggest reduced inhibition with increasing MA in children with WS, a finding counter to the expected direction of this relationship (Hypothesis 8).

6.3.3 General comments on sleep-dependent learning

Sleep problems and restricted sleep in childhood can impair neurobehavioural performance (O'Brien et al., 2004; Sadeh et al., 2003), school achievement (Dewald et al., 2010; Wolfson & Carskadon, 1998) as well as IQ and attention (Archbold et al., 2004; Blunden et al., 2005). It was therefore expected that performance on the learning tasks would be related to sleep quality or duration. However, this was not the case. The children in the TD group were selected to exclude those with known sleep problems. That their sleep was in the normal range is likely to explain why we failed to show any association between sleep and performance as it is probable that all were engaging in adequate sleep to perform well on the tasks. Alternatively, it could be that a relationship between sleep quality/duration and learning simply does not exist but it is related to sleep stages or other fine physiological sleep variables. Other research has shown that a short nap may be just as effective for memory consolidation as a whole night of uninterrupted sleep (Lahl et al., 2008; Mednick et al., 2003).

Generally, TD children and children with WS remembered more Animal Names, took fewer moves to complete the Tower of Hanoi task and made fewer rule violations after a night of sleep. Thus, it appears that both groups have benefitted from sleep for the consolidation of declarative and cognitive procedural memories. As previously discussed, it is possible that improved performance on the Tower of Hanoi task actually reflects the consolidation of explicit aspects of the task; hence it is

proposed that TD children and children with WS in the current study benefitted from sleep for the consolidation of explicit memories.

One could argue that the overnight gains seen in TD children in the present study were simply due to children being tested in the morning when they were less tired than in the evening, though one would also then expect to see a decline in performance over the daytime, which is not reflected in the data. In addition, this explanation does not fit the WS data for the Animal Names task. Future studies could employ a group of children who were first retested 24 hours after training, so controlling for time-of-day effects (e.g., Kuriyama, Stickgold, & Walker, 2004).

In the TD group, but not the DS or WS groups, better performance on the Animal Names task was related to increased CA and MA, supporting Hypotheses 7 and 8. In contrast, performance on the Tower of Hanoi was not related to CA or MA in any group, though TD children made fewer rule violations with increasing CA and MA. Interestingly, children with WS tended to make more rule violations with increasing MA, though there is also a lot of variability within the group.

The finding of an age-related association with performance for CA and MA in the TD group on the Animal Names task but not on the Tower of Hanoi is an interesting one. It may reflect the greater pre-existing knowledge base in older children on which to anchor the newly learned Animal Names, whilst the Tower of Hanoi was a novel task for all children so none could rely on pre-existing knowledge (Wilhelm, Metzkow-Mészàros, et al., 2012).

6.4 Continuous Performance Task

The present study used a CPT and objective sleep measures to investigate the relationship between sleep and sustained and selective attention in children with DS and WS compared to TD children.

The findings from the CPT support Hypothesis 4 and previous research showing that children with DS and WS suffer problems with attention (Greer, Brown, Pai, Choudry, & Klein, 1997; Munir, Cornish, & Wilding, 2000; Rhodes, Riby, Matthews, & Coghill, 2011; Trezise et al., 2008), as they displayed clear deficits across all elements of the task, having fewer hits, more commission errors and longer RTs. Particular problems were noted in the DS group, who performed significantly less well than both other groups on their ability to respond to the target, achieving ten fewer hits than the WS group, and 18 fewer than the TD children.

In general, children tended to improve on all areas of the CPT with increasing CA and MA, though this was not always statistically significant. In comparison to the two disorder groups, TD children showed the strongest age-related effects on the task, supporting Hypothesis 7. In the TD group there

was a significant relationship with CA on all variables, and significant association with MA for number and RT of correct hits. There was more variability in CPT performance in the DS and WS groups, shown by the increased standard deviations, so it is no surprise that the strength of developmental trajectories was weaker in these two groups.

The RTs for hits and commission errors become quicker with increasing age for the TD and WS groups, supporting previous research that RT decreases with age (Steele et al., 2012). The TD group also had a significantly faster mean RT for commission errors than the other two groups. Quick RTs for incorrect responses often indicate reduced inhibition, however in this case we suspect that this is either due to better motor skill in this group, which also improves with age, so allowing for a faster response; or that the greater variability in the two disorder groups led to an increased mean score for this variable. It is not proposed that the TD group were actually less inhibited than the DS and WS groups because their absolute number of commission errors was fewer. In fact, it is likely that the quickening of RT with age is related to increased motor speed which has developed in TD and WS.

Sleep parameters assessing sleep duration, sleep quality and SpO_2 variables were examined for possible influences on task performance using hierarchical multiple regression controlling for effects of CA and MA. The models showed that performance was not related to sleep or SpO_2 in the DS or WS groups; however, in the TD group, children with better sleep quality and higher, less variable SpO_2 had improved performance on the task compared to children with poorer sleep quality and SpO_2. For the TD group, these results support Hypothesis 9; that better task performance will be related to improved sleep quality or duration. Specifically, better sleep quality was related to more correct hits and faster RT for commission errors. This is in contrast with results reported by Holley (2009), who found that increased sleep time, but not sleep quality, was related to better executive function performance in children, including measures of attention. Gruber et al. (2012) also reported that children with short sleep duration had more cognitive problems and inattention than children with long sleep duration. Others, however have reported similar findings to the current study: that children with sleep problems causing disrupted sleep architecture suffer problems in the attentional domain (Blunden et al., 2005; Herrera et al., 2006). The present study also found that higher, less variable SpO_2 was associated with fewer commission errors, accounting for almost half (48%) of the variance in commission errors in the TD group. This directly supports previous research that has reported that children who snore have problems with sustained and selective attention, which were related to SpO_2 desaturations and associated night wakings (Archbold et al., 2004; Kennedy et al., 2004). The multiple regression models were not able to predict CPT performance for the DS or WS groups. This was somewhat surprising since, in general, the DS group had the worst sleep and also

performed the poorest on the CPT. Hence it was expected that there would be a strong relationship between sleep and performance. The lack of significant findings here is probably partly accounted for by the fact that there was more variability in the CPT scores of the DS group. In a complex disorder with a spectrum of behavioural and cognitive problems, it is likely that other confounding factors were not accounted for in the present study, for example demographic data, motor ability, motivation or parental smoking, which are known to affect attention (Hackman & Farah, 2009; Hofhuis, de Jongste, & Merkus, 2003). In addition, some pulse oximetry data were missing, so group sizes were smaller in the DS and WS groups (14 and 10 respectively) so power was reduced, though others have found significant effects with such sample sizes (e.g., Archbold et al., 2004; Blunden et al., 2005). In fact, the sample size in this thesis is larger than much other research in the field and effect sizes were generally good. Nevertheless, it is probable that it would have benefitted from a greater number of participants in order to add power to analyses where significant effects were expected but not found. Due to time constraints as well as the unavailability of participants and equipment, this was not possible.

Manly et al. (2001) argue that the type of test used in the present study is not, in fact, a measure of attention, but a measure of visual detection, response speed and response inhibition, which are constructs believed to be affected by separable attentional mechanisms. There is also the question of whether the task measures attentional constructs, or motivation to complete a repetitive and unrewarding task. Although TD children were motivated by a desire to perform well on the task, it is unlikely that all children with intellectual delay were motivated in this way, especially the DS group, who had the lowest MA. Perhaps the promise of a tangible reward for good performance would have better served to encourage them.

A limitation was that the CPT task was subject to a ceiling effect in the TD group, with 19 children (46%) making no omission errors. This can often be a problem with researching attention as tasks often need to be quite long or more demanding in order to avoid ceiling effects in the most able children. However, standard CPT tests have been found to be unsuitable for testing children with developmental delay as they are too long or difficult so many children lose interest and do not or cannot complete the task, thus data are not meaningful (Knox et al., 2012; Sullivan et al., 2007). At 7:36 minutes, the present task was already longer than some other CPTs that have been used with children with disorders (e.g., Trezise et al., 2008; 6:20 minutes with 7 to 18 year olds with DS). Additional work should be done to construct a CPT that is suitable for TD children as well as the broad spectrum of abilities encompassed by developmentally delayed children, whilst also addressing the issue of motivation. Despite the ceiling effect, the CPT task is still useful for

understanding developmental delay in children with DS and WS. The fact that these children did not reach the test ceiling is interesting in itself, showing atypical development of sustained/selective attention.

6.5 Short term and working memory

Children completed digit and spatial spans both forwards and backwards to measure verbal and spatial STM and working memory. As predicted, TD children performed significantly better than children with DS and WS on all four tasks (Hypothesis 4). In addition, children with WS performed significantly better than DS on the digit span forwards task, and better on the digit span than on the spatial span, whilst children with DS performed better on the spatial span than they did on the digit span. These findings support Hypothesis 6 and current knowledge of relative language strength in WS and weakness in DS (Brock, 2007; Hick et al., 2005; Martens et al., 2008; Ypsilanti & Grouios, 2008).

An important point to note here is that many children with DS and WS were unable to complete even the simplest trial (two items) of the backwards span tasks because they were unable to understand or follow the instructions, even when given examples. This meant that only five children with DS and 15 with WS completed the backwards digit span, and only ten children with DS and 15 with WS completed the backwards spatial span. Results for these tasks should therefore be interpreted with caution due to the small numbers of participants. The fact that more children with DS were able to complete the backwards spatial than the backwards digit span again supports knowledge of their relative strength for spatial relative to verbal tasks (Lanfranchi, Cornoldi, et al., 2009; Lanfranchi, Jerman, et al., 2009).

In the TD group, developmental trajectories showed that performance on all short term and working memory tasks was significantly related to CA and MA (with the exception of spatial span backwards and MA which was close to significance (p = .053)), meaning that CA- and MA-older children performed better than younger children on the tasks. In the DS and WS groups there was no relationship with CA or MA on any of these tasks, except that in the WS group digit span forwards was significantly related to CA (R^2 = .40) and MA (R^2 = .20). The finding that digit span was not related to age in the DS group is consistent with the findings of Hick et al. (2005), who conducted a longitudinal study with 12 school-aged children with DS. They found that verbal span for digits and words did not improve over an 18 month period; however, spatial span was unimpaired and showed improvement over time relative to MA-matched TD children. This latter finding is in contrast with the results of the present study.

Comparison of the three groups on the digit span forwards task using the developmental trajectory approach (Figure 5.5) showed that the WS group had a typical but delayed trajectory, with age explaining 40% of the variability in span length. In contrast, there was no relationship between age and performance in the DS group. This task clearly illustrates how the performance of one group is delayed but typical (WS) whilst the other is delayed and atypical (DS). In contrast, a comparison of the developmental trajectories for the spatial span backwards task (Figure 5.8) showed that in the TD group age explained 24% of the variance in scores, whilst in the DS and WS groups there was no relationship with age, showing delayed and atypical performance on this task by both groups. These tasks highlight the importance of investigating developmental trajectories in addition to group means, exposing patterns in the data.

6.5.1 Sleep, short term and working memory

Hierarchical multiple regression models were used to examine the influences of sleep quality, duration and SpO_2 on short term and working memory. It was predicted that, after controlling for CA and MA, children with better sleep quality or duration would perform better on the tasks than children with poorer sleep (Hypothesis 9). In the TD group, sleep quality significantly predicted 16% of the variance in digit span forwards, and 25% of the variance in digit span backwards scores, with children with better sleep quality having longer digit spans. In the DS group, digit span forwards was predicted by longer sleep duration, which accounted for 33% of the variance in span length. In the DS and WS groups but not the TD group, backwards spatial span length was very strongly related to better sleep quality, which predicted 87% and 74% of the variance in scores for the DS and WS groups respectively. These findings are supportive of previous research, for example Steenari et al. (2003) found that better performance on working memory tasks was related to longer sleep duration, and more to higher sleep efficiency. With this in mind, assessments of sleep should focus on the quality of sleep, rather than just the duration.

In addition, the present study found that in the TD group, spatial span forwards was significantly predicted by SpO_2 variables, which accounted for 32% of the variance in scores. This supports previous research, for example Karpinsky et al. (2008) reported that poorer working memory was related to snoring in preschool children. STM and working memory are mediated by the prefrontal cortex, which continues to mature throughout childhood (Tsujimoto, 2008). Beebe and Gozal (2002) suggest that its relatively late maturation makes the prefrontal cortex particularly vulnerable to the effects of sleep loss, sleep disruption, hypoxia and hypercarbia. This area of the brain appears to functionally disconnect from other brain regions during sleep and particularly benefit from SWS. After around 21 hours of total sleep deprivation glucose uptake in the prefrontal cortex is reduced,

activation in response to cognitively demanding tasks is diminished, and theta waves increase showing a slowing of activity in this area. These changes correspond with a decrease in working memory function and vigilance. Chronic sleep restriction (<6 hours sleep per night for two weeks) and sleep fragmentation (with or without hypoxia) create similar performance deficits to acute total sleep deprivation (for reviews see Beebe & Gozal, 2002; Durmer & Dinges, 2005; Jones & Harrison, 2001).

It is not clear why these relationships are inconsistent across the three groups, showing that STM and working memory can be related to sleep duration, quality and SpO_2, though Blunden and Beebe (2006) have suggested that sleep disruption, deprivation or hypoxia may each be independently sufficient to create cognitive deficits in children.

6.6 Behavioural questionnaires

This thesis used two behaviour questionnaires to assess temperament (TMCQ), behaviour problems and prosocial behaviour (SDQ) in children. It was predicted that children with DS and WS would have more behavioural problems than TD children (Hypothesis 5).

Group comparisons on the TMCQ showed significant differences between groups on almost all of the 17 subscales, whereby the DS and WS groups scored similarly to one another, but significantly higher or lower than the TD group. According to parents, TD children had higher activation control, activity level, assertiveness/dominance, attention, fantasy/openness, inhibitory control and shyness, with less anger, discomfort, fear and impulsivity than children with DS and WS. The TD group also scored significantly higher than WS for both high and low intensity pleasure, and higher for the DS group for perception. In addition, the WS group scored higher for impulsivity than both other groups. There was no significant difference between groups for the subscales of affiliation, sadness and soothability. See Appendix C3 for a definition of all subscales.

The TMCQ has no published norms but if the scores of the TD group here can be taken to be 'typical' then the results clearly show differing temperament between TD and disorder groups. Interestingly, the DS and WS groups scored similarly on all but a few variables, suggesting that some characteristics could be common to developmental disorders. To my knowledge this is the first study to use the TMCQ with individuals with DS and WS. Other studies have, however, used the Children's Behaviour Questionnaire (CBQ; Rothbart, Ahadi, Hershey, & Fisher, 2001) which is similar but aimed at a slightly younger age range (3-7 vs 7-10). Using the CBQ, children with WS have been reported as being less shy and more empathic than children with intellectual disabilities of unspecific ID. These two traits together characterised 96% of a sample of 23 8 to 10 year olds with WS (Klein-tasman &

Mervis, 2003). The TMCQ does not contain a subscale on empathy so we cannot compare on this variable. The finding of reduced shyness in WS is comparable to the present study and also what would be expected, given what is known about the unique personality profile and hypersociability of WS. Children with DS aged 4 to 11 years (N = 55) have been found to have less attention focusing, inhibitory control and sadness on the CBQ than a slightly younger TD control group (age 5 to 7 years, N = 91) (Nygaard, Smith, & Torgersen, 2002). In comparison, the current thesis did not find a significant difference between groups for sadness, however in the cases of the attention focusing and inhibitory control subscales, some of the biggest differences between the TD and DS groups were seen compared to other subscales, both in favour of the TD group.

In general, parent reports of their children's sleep are not always reliable (Section 6.2.3) since parents are not always in the room whilst their children sleep. It was predicted that parent reports would be somewhat more credible for reporting children's daytime behaviour (Hypothesis 11). Thus, parentally reported data on attention and inhibition from the TMCQ were correlated with like variables from the CPT. No significant correlations were found, suggesting that parent report is also not reliable for daytime behaviours.

Comparable to the TMCQ, parent reports on the SDQ revealed significant differences between groups for almost all subscales. Again, the DS and WS groups had similar scores, which were significantly different from those of the TD group. All subscales indicated significantly more problem behaviours and less prosocial behaviour expressed by children with DS and WS compared to the TD group. This supports Hypothesis 5 and previous research finding problems with conduct, hyperactivity and peer relationships in children with DS (Capone et al., 2006; Coe et al., 1999) and WS (Einfeld et al., 2001; Martens et al., 2008). The exception was emotional symptoms, where there was no significant difference between groups and all groups scored within the 'normal' range. This is in contrast to other researchers who have found higher rates of emotional problems in children with WS compared to TD children and children with DS (Papaeliou et al., 2012). Finally, the impact score, which indicates how much of an impact the child's difficulties have on their daily life, showed that the WS group scored significantly higher than the TD group, and the DS group scored significantly higher than both groups. This indicates that the problems experienced by children with DS have the greatest impact on their daily lives.

It would be interesting to conduct the TMCQ and SDQ with children with intellectual disabilities of other aetiologies, such as Fragile X syndrome or Autism, to see similarities and differences between groups compared to TD children and to further characterise temperament in children with developmental disorders.

6.6.1 Sleep and behaviour

Based on previous research showing a relationship between sleep and behaviour problems in children (Ebert & Drake, 2004; Smedje et al., 2001), it was predicted that there would be a relationship between sleep and behaviour (Hypothesis 12).Thus, hierarchical multiple regression was used to control for CA and MA and investigate the influence of sleep duration, quality and SpO_2 on individual subscales of the SDQ. This showed that in the TD group, shorter sleep duration was related to increased hyperactive behaviour, whilst lower and more variable SpO_2 was related to increased conduct problems and decreased prosocial behaviour. These relationships were not evident in the DS or WS groups, which may reflect that other confounding factors were not controlled for.

The findings in the TD group support Hypothesis 12 and previous research. For example, Sadeh et al. (2002) found that childhood delinquent behaviour was related to low sleep efficiency and long night wakings. Behavioural problems and hyperactivity in children have also been associated with SDB (Ali et al., 1994; Ebert & Drake, 2004). Although the precise findings are not identical, these studies and the current thesis have all found an association between poor sleep and behavioural problems. In contrast, in a large sample of 6 to 12 year old TD children (N = 508) Calhoun et al. (2012) found that parentally reported attention, hyperactivity and conduct problems were related to excessive daytime sleepiness, not sleep duration or quality.

6.7 Parent questionnaires

Parents completed three questionnaires relating to their own sleep (PSQI), daytime sleepiness (ESS) and depression (MDI). It was predicted that parents of children with DS and WS would have poorer night time sleep and increased daytime sleepiness and depression than mothers of TD children (Hypothesis 14). Indeed, it was found that parents of children with DS reported poorer sleep quality and sleep efficiency and longer sleep latency than both the TD and WS groups. They also had the highest total sleep problems score and the highest daytime sleepiness score on the ESS. In contrast, parents of TD children reported greater sleep disturbance than both other groups, waking in the night for reasons such as being too hot/cold, or having to use the bathroom. Parents of children with WS reported significantly better sleep quality and lower daytime sleepiness than parents of TD children and children with DS. Group differences on the MDI were not significant, though there was a trend for mothers of children with DS to have higher scores than both other groups. This is in contrast with other research which has shown that mothers of children with DS experience less stress and pessimism than mothers of children with WS and other IDs (Eisenhower et al., 2005;

Fidler et al., 2010). A confounding factor here which was not considered was whether children had younger siblings who might interfere with the parents' sleep and wellbeing to a greater extent than the child being studied.

Previous research has found strong links between maternal sleep and wellbeing, and child sleep and behavioural problems (Abbeduto et al., 2004; Baker et al., 2003, 2002; Fidler et al., 2010; Meltzer & Mindell, 2007; Stores et al., 1998). Hence it was predicted that maternal sleep and depression would be related to sleep and behavioural difficulties in children in the present study (Hypothesis 14). In fact, there was little evidence for this. In the TD group there was a relationship between mothers' reports of disturbed sleep and children's mean night waking duration. It would be tempting to suppose that mothers have disturbed sleep because the child wakes them in the night. However, as mentioned earlier, the parental sleep disturbance score is based on night wakings due to discomfort, rather than external interruption (which the PSQI does not cover), with the exception of 'other reasons'. Perhaps, then, there exists a familial or environmental pattern of sleep disturbance, and that children wake during the night for similar reasons to parents.

Research suggests that a reciprocal relationship exists between parent and child sleep and behaviour whereby child sleep and behavioural problems have a negative impact on mothers' sleep and wellbeing, leading to maternal negative affect, increased stress and poorer parenting, which in turn leads to increased sleep and behavioural problems in the child (Bagner et al., 2010; Bell & Belsky, 2008; Turney, 2012). That this relationship is not evident in the data of the present study is beneficial for the families involved, though contrasts with existing literature. A possible reason for this is that families in the present study were self-selecting; therefore mothers experiencing exceptional stress or depression may have been under-represented in the sample.

Future research could give questionnaires or short interviews to children to ask them the reasons for their night wakings. In the WS group there was a relationship between the child's emotional symptoms and maternal depression. These two scales both target mood disturbance, hence high emotionality/depression may be familial.

6.8 Developmental effects

Children with developmental disabilities generally have a lower MA than CA. However as syndrome severity is independent of CA, it is necessary to also assess a child's MA, as there may be a great deal of variability within a disorder group.

The present study benefitted from having groups that were matched for CA but whilst also considering and being able to control for the effects of MA, which was especially important as

children's performance on tasks would be affected by their cognitive level. In addition, the similar MAs in the DS and WS groups meant that these groups could be compared as MA matched groups. Many studies have used a control group of children with non-specific ID (Trezise et al., 2008; Vicari et al., 1995). This makes any comparisons hard to interpret as children's patterns of relative strengths and weaknesses are not known. As the cognitive traits of DS and WS have been well-characterised, comparisons can be meaningfully drawn.

Furthermore, matching children only on MA is problematic as a suitable test for MA must be selected. As tests and MA norms are generally based on TD children, few can account for the different pattern of strengths and weaknesses seen across domains in children with developmental disabilities. It is for this reason that the digit and spatial span were not used to determine children's MA in the present study. Instead, the RCPM was used because it is a standardised test of fluid intelligence and yields a score equating to the child's non-verbal MA. It has been used successfully with children with DS and WS in the past and, because it is non-verbal, children with language difficulties (DS) are able to complete the task, whilst those with language strengths (WS) cannot rely on language to do well. All but two children in the present study were able to complete to RCPM but it was necessary to use the raw scores for further analysis rather than the MA due to the fact that many children scored below the minimum MA score.

In the TD and DS groups, there was a strong and significant relationship between CA and MA, with CA explaining 37% and 28% of the variance in RCPM scores in the TD and DS groups respectively. In the WS group there was no association between CA and MA. Comparison of the trajectories using the ANCOVA model, and inspection of the scatterplots showed that children with WS had a significantly slower rate of MA development than TD children; in fact, their trajectory for the RCPM showed no development with increasing age. This contrasts with other research which has found that the RCPM performance of individuals with WS follows a delayed, but typical, trajectory (Van Herwegen, Farran, et al., 2011). The present study had a smaller sample size (22 vs 53) and age range (6 to 12 vs 5 to 41) compared to the Van Herwegen et al. (2011) study, which could help to explain the disparity. Alternatively, as CA is not related to syndrome severity, relationships between CA and MA may not always be found in cross-sectional research with children with ID.

On some tasks, such as the CPT, spatial span forwards and digit span backwards, there was a significant relationship with age in the TD group, though when ANCOVA models were used there was no significant difference between the trajectories of the three groups. So even though the DS and WS groups did not always show a significant improvement on the task with increasing age, their

trajectory was not significantly different from TD. Perhaps with larger groups there would be significant effects.

Of course, using a cross-sectional approach rather than longitudinal research to study development is not ideal. In TD groups the investigation of developmental trajectories can be successfully implemented using a cross-sectional design, as in the present study. It has also been widely used successfully in clinical groups (Karmiloff-Smith et al., 2004; Thomas et al., 2009; Van Herwegen, Farran, et al., 2011). Nevertheless, the variability in atypical groups and the fact that level of impairment is not related to age means that a cross-sectional approach may not be appropriate. For example, (Cornish, Cole, Longhi, Karmiloff-Smith, & Scerif, 2013) conducted CPTs with children aged 4 to 10 with fragile-X syndrome. Older children were not better at the task than younger children, suggesting that attention does not improve with age in this group. This finding is consistent with the lack of age-related improvement in the DS and WS groups in the present study. However, when the children with fragile-X syndrome were followed longitudinally over three years, each child showed an attentional improvement comparable to MA-matched TD children. This highlights the limitations of drawing conclusions from cross-sectional data, which cannot account for individual differences. It would be interesting to retest children who participated in this thesis to gather longitudinal, developmental data as each individual child may still improve with age (see also Scerif, 2010, for a discussion of the developmental trajectory approach in disorder groups).

6.9 Implications

Research into the effects of sleep problems in children with developmental disorders is severely lacking. With the known wide-ranging effects of sleep in TD children, it is imperative that we understand sleep in children with DS and WS and the effect that sleep may have on their health, behaviour and cognitive ability. This is the first direct cross-syndrome comparison of sleep in atypically developing populations and shows clear evidence of sleep problems in children with DS and some disruption in WS. These sleep problems should be considered in terms of the child's health and wellbeing, thus should be managed accordingly. Paediatricians should ensure that sleep problems are examined in all children with developmental disorders in order to rule out sleep as a potential influencing factor on other health issues. Examination should use objective measures as parent reports of both sleep and daytime behaviours may not be completely reliable.

Attention is an important aspect of normal healthy development, affecting the way in which an individual interacts with their environment and therefore learns from it. Ability to maintain attention in the classroom has important implications for learning as children who are able to focus and

maintain attention on the current task will undoubtedly learn more than children who are unable to do so.

In TD children, better sleep quality and higher, less variable SpO_2 significantly predicted better performance on the CPT, a task of sustained and selective attention and inhibition. In light of these findings as well as the known physiological and psychological benefits of sleep, it should be ensured that any problems with sleep quality or SDB are successfully managed. This will enable children to maximise attention and achieve optimum cognitive performance, which would have a dramatic impact in the classroom and on educational attainment. This not only important for the here-and-now, but children's life chances rest upon their early attainment, thus correct management of sleep problems could have far-reaching consequences. This study is unique in investigating relationships between sleep and attention in children with DS and WS and opens the way for future research.

Diamond (2010) argues for an educational approach that addresses the whole child, focusing not just on their general ability, but on interrelated factors that drive that ability. These factors include the child's cognitive, emotional, social and physical health, *each* of which need to be encompassed and developed in order for *all* to develop, enabling the child to excel academically. Sleep is an important contributor to each of these areas; hence inadequate sleep can impede a child's all-round development.

The current study supports the notion that sleep is necessary for enhanced memory consolidation in TD children and, to some extent, in children with WS. This has far-reaching implications for child development. Childhood is period characterised by a vast expansion of both declarative and procedural learning, necessary for all-round functioning, including academic knowledge, social skills and motor ability. It is therefore essential that consolidation of new information during sleep occurs on a daily basis in order for the individual child to develop at the same rate as their peers. In order to optimise learning, effective educational programs should be designed and implemented which factor in children's night-time sleep; for example by testing children on their homework the following morning or revisiting the previous day's work to reinforce any sleep-related gains. This should enable optimal academic performance. The present thesis is the first to investigate sleep-dependent learning in children with DS and WS. It did not find evidence of sleep-related gains in children with DS, and the evidence in WS was inconclusive although was suggestive of a sleep-dependent memory improvement. This does not prove that memory consolidation does not occur during sleep in children with DS, but perhaps the tasks, study design or sample size used here were not sensitive enough to show it. Children with developmental delay may also consolidate memories differently to TD children, and a lack of sleep-related learning gains could contribute to learning difficulties.

Further research with larger groups and different tasks is necessary to elucidate whether offline learning occurs in these groups as it does in TD children. The fact that the extent of sleep-dependent learning did not appear to be related to sleep quality or duration is reassuring, as it means that even children with poor sleep consolidate new memories during sleep. This is, at least, the case in TD; for children with DS and WS further research is needed.

In addition, on the Animal Names task, although baseline performance of the DS Sleep-Wake and Wake-sleep groups was comparable, children with DS appeared to benefit more from being trained in the morning compared to the evening, i.e., the group who trained in the morning achieved a greater improvement on the task than the group who trained in the evening on this declarative learning task. If further research were to demonstrate that this is a consistent finding in children with DS, then it has strong implications for education. This 'morning advantage' could be exploited in the classroom to benefit children with DS by teaching them more challenging or important information in the morning.

STM and working memory performance have previously been linked to reading and mathematical ability in school-aged children (Arcia et al., 1991). The present thesis found that in TD children, those with better sleep quality performed better on the digit span forwards and backwards, whilst children with DS and WS with better sleep quality had increased spatial span backwards compared to children with poorer sleep quality. In addition, children with DS who slept for longer had increased digit span relative to children with shorter sleep duration. So, this study and previous research (e.g., Sadeh et al., 2003) have found that sleep is related to children's STM and working memory, which could have a knock-on effect on their school performance.

6.10 Future directions

Suggestions for future research have been provided throughout this chapter in order to address the limitations of the research, for example by making adjustments to the tasks, benefitting from a larger sample size and taking a detailed account of the child's background in order to control for factors such as demographics, medical history or family circumstances. In addition, the research would benefit from a longitudinal approach to investigate development, since the variability within groups with ID makes it difficult to draw conclusions based on cross-sectional research.

It was predicted that sleep would have a strong, significant influence on cognitive performance and behaviour in children. These relationships were not always evident, even after controlling for CA and MA. Future research could use a repeated measures design to investigate children's performance on cognitive tasks after sleep extension and restriction. Such a design would need to be ethically

cautious, though such studies have previously been conducted with TD children. For example, Sadeh et al. (2003) asked children to extend or restrict their sleep by one hour per night for three nights. This repeated-measures methodology allows direct comparison of sleep extension and restriction in each child, thus confounding factors are better-controlled. Nevertheless, such a design would only be able to investigate the effects of acute sleep loss rather than chronic sleep problems.

The present study used actigraphy to monitor sleep but this cannot be used to measure sleep stages. Although the results did not show a specific sleep variable related to learning, they did show sleep-dependent learning in TD children and children with WS. In adults, sleep-dependent learning may be related to particular sleep stages or sleep spindles (Backhaus et al., 2008; Fischer et al., 2002; Fogel & Smith, 2006). Hence it would be interesting to see whether children show the same learning-dependent relationship to sleep as adults, given their developmental difference for consolidating procedural skills. The present study found no evidence for sleep-dependent learning in children with DS, and conflicting findings in the WS group; hence, using PSG to measure sleep stages and spindles in response to learning would allow more specific investigation of whether learning is related to sleep at all in children with developmental disabilities. Further, neuroimaging could be used to assess learning-dependent neural changes during sleep. PSG studies have shown altered sleep architecture in individuals with DS and WS; specifically reduced REM in both groups, increased SWS in WS and increased stage I and II in DS. It would be interesting to see whether these differences might relate to altered sleep-dependent memory consolidation. In typical adults, SWS is necessary for enhanced consolidation of declarative memories (Plihal & Born, 1997), and in children NREM has been associated with declarative memory consolidation (Backhaus et al., 2008). Perhaps, then, the increased SWS in WS could be beneficial for declarative learning. Indeed, the present study did find that children with WS in the Sleep-wake condition improved on the Animal Names task following sleep, and both conditions reduced their rule violations on the Tower of Hanoi after sleep. These are both examples of explicit declarative learning, which could be enhanced by SWS, thought to be increased in WS. Of course, without EEG it is not possible to know whether the WS group in the present study had increased SWS. Although it would be useful to know whether sleep-dependent memory consolidation is related to sleep stages in DS and WS, these types of studies may not be practical for children with ID. Compliance was low in the present study for wearing the pulse oximetry probe in the clinical groups, thus compliance with PSG or neuroimaging studies may also be low, although they have previously been used successfully (Arens et al., 1998; Bódizs, Gombos, & Kovács, 2012; Shott et al., 2006).

6.11 Conclusions

This study effectively used actigraphy to study sleep patterns over the course of one week, and pulse oximetry to monitor SpO_2 for three nights, in children with DS and WS as well as a large control group. This approach offers considerable benefits in such children who are challenging to study in a laboratory environment. Much previous research has relied solely upon parent report, but this study has demonstrated that its inaccuracy necessitates the concurrent use of objective measures (see also Ashworth et al., 2013).

The research suggests that sleep problems are syndrome-specific. Children with DS experience the most disrupted sleep, most likely due to SDB. Children with WS experience long sleep latencies, although are not reported by parents to be resistant to settling. Once asleep, their sleep quality is remarkably good although they do experience some parasomnias. The study extends previous work in WS, where research on sleep is limited, and provides a direct cross-syndrome comparison as well as a control group. The findings show that sleep problems are common and highlight the need for objective assessment in atypical groups.

Clear difficulties were found in the two disorder groups on all cognitive tasks, with children with DS generally experiencing the greatest problems. Some associations with sleep suggested that sleep quality and SpO_2 may be related to cognitive ability in TD children, though few associations were found in children with DS and WS. In addition, whilst TD children tended to have better cognitive ability with increasing CA and MA, this was not always the case for children with DS and WS due to the great variability in syndrome severity. DS and WS are complex disorders with a varied pattern of strengths and weaknesses. Therefore it is likely that cognitive performance is also influenced by other confounding factors that were not accounted for in the present study.

This thesis provides unique contributions to the fields of developmental and cognitive psychology. It is the first study to investigate sleep-dependent learning in children with DS or WS and also the first to study the effects of sleep on other areas of cognition in these groups. In addition, it is the first, to my knowledge, to use the Tower of Hanoi task to investigate sleep-dependent learning in children, finding a sleep-dependent improvement on the task in the TD and WS groups. In light of recent theories suggesting an implicit/explicit distinction for sleep-dependent learning in children, this finding suggests that children preferentially consolidate explicit aspects of the task during sleep. Therefore, although both adults (Smith et al., 2004; Smith, 1995) and children show improvement on this task following sleep, it seems that learning is achieved through different cognitive means.

In light of the findings of the current thesis, and accounting for its limitations, it seems clear that there is a complex interplay between cognition and sleep; hence parents, educationists and researchers must understand the importance of sleep for children's healthy all-round development.

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Appendix A. Pilot study materials

A1. Related word pairs

Soap – Pillow
Shoe – Sock
Cat – Tiger
Sun – Rain
Chair –TV
Face – Head
Bike – Car
Monkey – Squirrel
Doll – Bricks
Cheek – Nose
Jeans – Pants
Brush – Mop
School – Home
Blanket – Towel
Stick – Rock
Zip – Belt
Hand – Arm
Apple – Grapes
Farm – Zoo
Oven – Sink
Dish – Cup
Bus – Train
Jelly – Donut
Drum – Ball
Tree – Flower
Paper – Glue
Goose – Hen
Coat – Hat
Toe – Leg
Peas – Beans

A2. Unrelated word pairs

Cat – Flower
Monkey – Bricks
Goose – Train
Bus – Glue
Bike – Donut
Paper – Beans
Drum – Grapes
Doll – Rain
Apple – Hat
Peas – Cup
Jelly – Leg
Zip – Car
Shoe – Tiger
Coat – Sink
Jeans – TV
Face – Home
Hand – Zoo
Toe – Mop
Cheek – Rock
Dish – Belt

A3. Animal Names

Orin the Horse
Razz the Chicken
Jaala the Pig
Galba the Mouse
Eagus the Sheep
Kobi the Dog
Paco the Duck
Dax the Rabbit
Spyro the Goat
Basco the Cat
Tabeel the Frog
Cabo the Donkey
Notus the Fox
Artoo the Cow

Appendix B. Recruitment material

B1. Consent form

CONSENT FORM

Sleep and Cognition in Children

Researcher: Anna Ashworth MSc

Please initial box

1. I confirm that I have read and understand the information sheet dated March 2010 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐

3. I agree to take part in the above study. ☐

4. I agree that this form that bears my name and signature may be seen by a designated auditor. ☐

_____	_____	_____
Name of participant	Date	Signature

_____

Email address (optional if you would like the final findings)

Anna Ashworth	_____	Anna Ashworth
Researcher	Date	Signature

One copy for participant; one copy for researcher.

B2. Invitation letter to parents

Dear Parents,

I am writing to invite you to take part in research being carried out at Middlesex University investigating sleep problems in children with Down syndrome and Williams syndrome and the effect that sleep patterns have on their learning, memory and attention.

We know that sleep problems in children can have a detrimental effect on their behaviour, health and psychological and social functioning. Tired children perform less well at school, are more hyperactive and have poorer attention and memory than well rested children. Many parents report that children with developmental disabilities have a number of problems with sleep. By studying children's normal sleep patterns, the aim of this study is to investigate whether sleep patterns could contribute to learning difficulties in children aged six to twelve.

The study would involve your child being monitored for one week using an actiwatch. This is a small accelerometer worn as a wristwatch to measure activity levels throughout the day and movement during sleep. For three nights they would also be monitored overnight at home with a pulse and oxygen sensor to assess any sleep related breathing disorder.

The cognitive tests would be completed in three testing sessions. One or two of these would be completed early in the morning at school, the remaining one or two would be at your home, just before bedtime. Each session should last between 15 minutes and 1 hour (depending on the child). The tests are designed to be like games and, so far, all children have enjoyed taking part.

You would also be asked to complete some questionnaires about your child's sleep and behaviour.

If you would like further information or are interested in taking part please contact me using the details below.

Thank you for taking the time to read and consider this information, I am sure that it will be an interesting project to participate in, and you will be informed of the results.

e: a.ashworth@mdx.ac.uk

t: 020 8411 6221 or 07971 613 323

m: Hatchcroft, Middlesex University, The Burroughs, Hendon, NW4 4BT

Thank you for your time.

Yours faithfully,

Anna Ashworth, MSc

B3. Participant information sheet

Note: Sections in grey were not included in the information given to parents of TD children.

January 2011. V.3

Sleep and cognition in children

I am writing to invite you to take part in research being carried out at Middlesex University, part of which will be for my doctoral thesis. Please take time to read the following information to help you decide whether to take part, discuss it with others if you wish and please contact me for any further information. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What is the purpose of the study?

The purpose of the study is to investigate sleep in children with Down syndrome and children with Williams syndrome and to see how sleep affects learning, memory and attention. We know that sleep problems can have a detrimental effect on behaviour, health and psychological and social functioning. Tired children perform less well at school, are more hyperactive and have poorer attention and memory than well rested children. Many parents report that children with developmental disabilities have problems with sleep. This study aims to investigate normal sleep patterns and what the specific sleep problems are in children with Down syndrome and Williams syndrome and whether sleep problems could be partly responsible for learning difficulties.

Why have I been chosen?

Local schools and support groups have been contacted to pass on information to parents.

What will I have to do?

Your child will be asked to wear an actiwatch for one week to measure their sleep quality and quantity. This is a small accelerometer worn around the wrist in order to assess activity levels during the day, and movement during sleep.

Your child will also be monitored overnight with pulse oxymetry for three nights. This involves wearing a small infrared sensor on the finger or toe, which measures heart rate and the oxygen level in the bloodstream to detect any sleep related breathing disorder such as sleep apnoea.

Your child will also complete a set of cognitive tasks during three sessions to test memory, learning and attention. Each session should take between 15 minutes and 1 hour, depending on the child. One or two of these sessions will be completed first thing in the

morning (probably at school), with the remaining one or two sessions to be completed at home before bed. I will visit your child at home and school for these sessions.
You will also be asked to complete some questionnaires about your child's sleep and behaviour.

What are the possible disadvantages and risks of taking part?
Testing may disrupt your child's routine, but every effort will be taken to ensure that testing occurs at a time that is convenient for you.

What are the possible benefits of taking part?
It is hoped that the information gained from this study will lead to a broader understanding of children's sleep and the affect that it has on their behaviour. This knowledge will be beneficial to future research, understanding and treatment. Parents will of course be informed of their child's results.

Will my taking part in this study be kept confidential?
All data will be stored, analysed and reported in compliance with the Data Protection Act 1998. This means that all information collected about your child during the course of the research will be kept strictly confidential. Data and computers are password protected, and any information about your child which is used will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
This study will be published as my doctoral thesis and shorter articles will be written for academic journals. This is likely to be in 2012 and 2013. It will also be presented at relevant conferences, and short articles will be written for newsletters. Individual children and families will not be identified in any report or publication.

Who has reviewed the study?
This project has been approved by Middlesex University, School of Health & Social Sciences, Natural Sciences Ethics sub-Committee.
It has also received approval and funding from Down Syndrome Education International and The Williams Syndrome Foundation.

Contact for further information

Anna Ashworth MSc
a.ashworth@mdx.ac.uk
Hatchcroft, Middlesex University, The Burroughs, Hendon, NW4 4BT
020 8411 6221

Dr Dagmara Annaz (supervisor)
d.annaz@mdx.ac.uk
The Town Hall, Middlesex University, The Burroughs, Hendon, NW4 4BT
020 8411 4695

Thank you for taking the time to read this information sheet. Please do not hesitate to contact me with any questions, and let me know if you do wish to take part.

Best wishes,

Anna Ashworth

Appendix C. Questionnaires

C1. Children's Sleep Habits Questionnaire (CSHQ)

Child's Sleep Habits
(Preschool and School-Aged)

Coding _____

The following statements are about your child's sleep habits and possible difficulties with sleep. Think about the past week in your child's life when answering the questions. If last week was unusual for a specific reason (such as your child had an ear infection and did not sleep well or the TV set was broken), choose the most recent typical week. Answer USUALLY if something occurs **5 or more times** in a week; answer SOMETIMES if it occurs **2-4 times** in a week; answer RARELY if something occurs **never or 1 time** during a week. Also, please indicate whether or not the sleep habit is a problem by circling "Yes," "No," or "Not applicable (N/A).

Bedtime

Write in child's bedtime: _____

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child goes to bed at the same time at night	☐	☐	☐	Yes	No	N/A
Child falls asleep within 20 minutes after going to bed	☐	☐	☐	Yes	No	N/A
Child falls asleep alone in own bed	☐	☐	☐	Yes	No	N/A
Child falls asleep in parent's or sibling's bed	☐	☐	☐	Yes	No	N/A
Child falls asleep with rocking or rhythmic movements	☐	☐	☐	Yes	No	N/A
Child needs special object to fall asleep (doll, special blanket, etc.)	☐	☐	☐	Yes	No	N/A
Child needs parent in the room to fall asleep	☐	☐	☐	Yes	No	N/A
Child is ready to go to bed at bedtime	☐	☐	☐	Yes	No	N/A
Child resists going to bed at bedtime	☐	☐	☐	Yes	No	N/A
Child struggles at bedtime (cries, refuses to stay in bed, etc.)	☐	☐	☐	Yes	No	N/A
Child is afraid of sleeping in the dark	☐	☐	☐	Yes	No	N/A
Child is afraid of sleep alone	☐	☐	☐	Yes	No	N/A

Sleep Behavior

Child's usual amount of sleep each day: _____ hours and _____ minutes
(combining nighttime sleep and naps)

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child sleeps too little	☐	☐	☐	Yes	No	N/A
Child sleeps too much	☐	☐	☐	Yes	No	N/A
Child sleeps the right amount	☐	☐	☐	Yes	No	N/A
Child sleeps about the same amount each day	☐	☐	☐	Yes	No	N/A
Child wets the bed at night	☐	☐	☐	Yes	No	N/A
Child talks during sleep	☐	☐	☐	Yes	No	N/A
Child is restless and moves a lot during sleep	☐	☐	☐	Yes	No	N/A
Child sleepwalks during the night	☐	☐	☐	Yes	No	N/A
Child moves to someone else's bed during the night (parent, brother, sister, etc.)	☐	☐	☐	Yes	No	N/A

CSHQ- Rev 4/1/09

Coding _____

Sleep Behavior (continued)

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child reports body pains during sleep. If so, where?	☐	☐	☐	Yes	No	N/A
_____						
Child grinds teeth during sleep (your dentist may have told you this)	☐	☐	☐	Yes	No	N/A
Child snores loudly	☐	☐	☐	Yes	No	N/A
Child seems to stop breathing during sleep	☐	☐	☐	Yes	No	N/A
Child snorts and/or gasps during sleep	☐	☐	☐	Yes	No	N/A
Child has trouble sleeping away from home (visiting relatives, vacation)	☐	☐	☐	Yes	No	N/A
Child complains about problems sleeping	☐	☐	☐	Yes	No	N/A
Child awakens during night screaming, sweating, and inconsolable	☐	☐	☐	Yes	No	N/A
Child awakens alarmed by a frightening dream	☐	☐	☐	Yes	No	N/A

Waking During the Night

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child awakes once during the night	☐	☐	☐	Yes	No	N/A
Child awakes more than once during the night	☐	☐	☐	Yes	No	N/A
Child returns to sleep without help after waking	☐	☐	☐	Yes	No	N/A

Write the number of minutes a night waking usually lasts: _____

Morning Waking

Write in the time of day child usually wakes in the morning: _____

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child wakes up by him/herself	☐	☐	☐	Yes	No	N/A
Child wakes up with alarm clock	☐	☐	☐	Yes	No	N/A
Child wakes up in negative mood	☐	☐	☐	Yes	No	N/A
Adults or siblings wake up child	☐	☐	☐	Yes	No	N/A
Child has difficulty getting out of bed in the morning	☐	☐	☐	Yes	No	N/A
Child takes a long time to become alert in the morning	☐	☐	☐	Yes	No	N/A
Child wakes up very early in the morning	☐	☐	☐	Yes	No	N/A
Child has a good appetite in the morning	☐	☐	☐	Yes	No	N/A

Coding

Daytime Sleepiness

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
Child naps during the day	☐	☐	☐	Yes	No	N/A
Child suddenly falls asleep in the middle of active behavior	☐	☐	☐	Yes	No	N/A
Child seems tired	☐	☐	☐	Yes	No	N/A

During the past week, your child has appeared very sleepy or fallen asleep during the following (check all that apply):

	1 Not Sleepy	2 Very Sleepy	3 Falls Asleep
Play alone	☐	☐	☐
Watching TV	☐	☐	☐
Riding in car	☐	☐	☐
Eating meals	☐	☐	☐

C2. Temperament in Middle Childhood Questionnaire (TMCQ)

Temperament in Middle Childhood Questionnaire (Version 3.0)

Child's name: Today's date

Instructions: Please read carefully before starting:

On the next pages you will see a set of statements that describe children's reactions to a number of situations. We would like you to tell us what your child's reaction is likely to be in those situations. There are of course no "correct" ways of reacting; children differ widely in their reactions, and it is these differences we are trying to learn about. Please read each statement and decide whether it is a "true" or "untrue" description of your child's reaction within the past six months. Use the following scale to indicate how well a statement describes your child:

Circle #	If the statement is:
1	Almost always untrue of your child
2	Usually untrue of your child
3	Sometimes true, sometimes untrue of your child
4	Usually true of your child
5	Almost always true of your child

If you cannot answer one of the items because you have never seen the child in that situation, for example, if the statement is about the child playing wildly and recklessly and you have never seen your child play that way, then circle NA (not applicable).

Please be sure to respond by circling a number or NA for every item. If you find an item objectionable or upsetting, you may make an exception to this instruction and skip the item.

	My Child…	Almost always untrue	Usually untrue	Sometimes true, sometimes untrue	Usually true	Almost always true	Does Not Apply
1	Likes poems.	1	2	3	4	5	NA
2	Likes to be physically active.	1	2	3	4	5	NA
3	Likes going down high slides or other adventurous activities.	1	2	3	4	5	NA
4	Greatly enjoys playing games where s/he can win.	1	2	3	4	5	NA
5	Is bothered by pain when s/he falls down.	1	2	3	4	5	NA
6	Can stop him/herself when s/he is told to stop.	1	2	3	4	5	NA
7	Is easily distracted when listening to a story.	1	2	3	4	5	NA
8	Has a hard time settling down after an exciting activity.	1	2	3	4	5	NA
9	Likes rough and rowdy games.	1	2	3	4	5	NA
10	Likes the crunching sound of leaves in the fall.	1	2	3	4	5	NA
11	Is afraid of fire.	1	2	3	4	5	NA
12	Likes to think of new ideas.	1	2	3	4	5	NA
13	Is afraid of heights.	1	2	3	4	5	NA
14	Can't help touching things without getting permission.	1	2	3	4	5	NA
15	Is always on the move.	1	2	3	4	5	NA
16	Tends to say the first thing that comes to mind, without stopping to think about it.	1	2	3	4	5	NA
17	Looks around the room when doing homework.	1	2	3	4	5	NA
18	Would like to be friends with lots of people.	1	2	3	4	5	NA
19	Is very difficult to soothe when s/he has become upset.	1	2	3	4	5	NA
20	Can make him/herself do homework, even when s/he wants to play.	1	2	3	4	5	NA
21	Prefers playing outdoors to indoors when weather permits.	1	2	3	4	5	NA
22	Interrupts others when they are talking.	1	2	3	4	5	NA
23	Would rather play a sport than watch TV.	1	2	3	4	5	NA
24	Tends to become sad if plans don't work out.	1	2	3	4	5	NA
25	Says the first thing that comes to mind.	1	2	3	4	5	NA
26	Can say hello to a new child in class, even when feeling shy.	1	2	3	4	5	NA
27	Sometimes appears to be downcast for no reason.	1	2	3	4	5	NA
28	Has a hard time speaking when scared to answer a question.	1	2	3	4	5	NA
29	Cheers up quickly.	1	2	3	4	5	NA
30	Cries when given an injection.	1	2	3	4	5	NA
31	Becomes sad when told to do something s/he does not want to do.	1	2	3	4	5	NA

	My Child...	Almost always untrue	Usually untrue	Sometimes true, sometimes untrue	Usually true	Almost always true	Does Not Apply
32	Likes to play quiet games.	1	2	3	4	5	NA
33	Would like to spend time with a good friend every day.	1	2	3	4	5	NA
34	Likes the sound of poems.	1	2	3	4	5	NA
35	Cries sadly when a favorite toy gets lost or broken.	1	2	3	4	5	NA
36	Notices the color of people's eyes.	1	2	3	4	5	NA
37	Likes to get out of the house and do something physical.	1	2	3	4	5	NA
38	Becomes quite uncomfortable when cold or wet.	1	2	3	4	5	NA
39	Can take a Band-Aid® off when needed, even when painful.	1	2	3	4	5	NA
40	Can stop him/herself from doing things too quickly.	1	2	3	4	5	NA
41	Enjoys exciting and suspenseful TV shows.	1	2	3	4	5	NA
42	Usually stops and thinks things over before deciding to do something.	1	2	3	4	5	NA
43	Likes to run.	1	2	3	4	5	NA
44	Notices the sound of birds.	1	2	3	4	5	NA
45	Likes exploring new places.	1	2	3	4	5	NA
46	Can make him/herself run fast, even when tired.	1	2	3	4	5	NA
47	Becomes self conscious when around people.	1	2	3	4	5	NA
48	Likes to make up stories.	1	2	3	4	5	NA
49	Becomes tearful when tired.	1	2	3	4	5	NA
50	Enjoys making her/his own decisions.	1	2	3	4	5	NA
51	Is warm and friendly.	1	2	3	4	5	NA
52	Would find moving to a new, big city exciting.	1	2	3	4	5	NA
53	Gets very angry when another child takes his/her toy away.	1	2	3	4	5	NA
54	Likes reading or listening to make believe stories.	1	2	3	4	5	NA
55	Is shy with new people.	1	2	3	4	5	NA
56	Has an easy time waiting to open a present.	1	2	3	4	5	NA
57	Notices odors like perfume, smoke, and cooking smells.	1	2	3	4	5	NA
58	Likes to make others feel good.	1	2	3	4	5	NA
59	Can generally think of something to say, even with strangers.	1	2	3	4	5	NA
60	Is followed by other children.	1	2	3	4	5	NA
61	Gets angry when called in from play before s/he is ready to quit.	1	2	3	4	5	NA
62	Can tell if another person is sad or angry by the look on their face.	1	2	3	4	5	NA
63	Is scared of injections by the doctor.	1	2	3	4	5	NA
64	When s/he cries, tends to cry for more than a couple of minutes at a time.	1	2	3	4	5	NA

	My Child...	Almost always untrue	Usually untrue	Sometimes true, sometimes untrue	Usually true	Almost always true	Does Not Apply
65	Enjoys exciting places with big crowds.	1	2	3	4	5	NA
66	Is energetic.	1	2	3	4	5	NA
67	Likes listening to music.	1	2	3	4	5	NA
68	Remains upset for hours when someone hurts his/her feelings.	1	2	3	4	5	NA
69	Is bothered by loud or scratchy sounds.	1	2	3	4	5	NA
70	Has a hard time making him/herself clean own room.	1	2	3	4	5	NA
71	Enjoys drawing pictures.	1	2	3	4	5	NA
72	Calls out answers before being called on by a teacher or group leader.	1	2	3	4	5	NA
73	Enjoys looking at books.	1	2	3	4	5	NA
74	Makes up mind suddenly.	1	2	3	4	5	NA
75	Is afraid of burglars or the "boogie man."	1	2	3	4	5	NA
76	When a child is left out, can ask that child to play.	1	2	3	4	5	NA
77	Touches fabric or other soft material.	1	2	3	4	5	NA
78	When working on an activity, has a hard time keeping her/his mind on it.	1	2	3	4	5	NA
79	Has a hard time waiting his/her turn to talk when excited.	1	2	3	4	5	NA
80	Has a hard time paying attention.	1	2	3	4	5	NA
81	Is bothered by light or color that is too bright.	1	2	3	4	5	NA
82	Needs to be told by teacher to pay attention.	1	2	3	4	5	NA
83	Often rushes into doing new things.	1	2	3	4	5	NA
84	Is first to speak up in a group.	1	2	3	4	5	NA
85	Is afraid of sleeping over at someone's house.	1	2	3	4	5	NA
86	Likes quiet reading time.	1	2	3	4	5	NA
87	Gets angry when s/he can't find something s/he is looking for.	1	2	3	4	5	NA
88	Is very careful and cautious when crossing the street.	1	2	3	4	5	NA
89	Has a hard time working on an assignment s/he finds boring.	1	2	3	4	5	NA
90	Is afraid of loud noises.	1	2	3	4	5	NA
91	Goes to school nurse's office for very minor complaints.	1	2	3	4	5	NA
92	Likes the feel of warm water in a bath or shower.	1	2	3	4	5	NA
93	Does a fun activity when s/he is supposed to do homework instead.	1	2	3	4	5	NA
94	Gets angry when s/he has trouble with a task.	1	2	3	4	5	NA
95	Likes to look at trees.	1	2	3	4	5	NA
96	Likes to play so wildly and recklessly that s/he might get hurt.	1	2	3	4	5	NA

	My Child ...	Almost always untrue	Usually untrue	Sometimes true, sometimes untrue	Usually true	Almost always true	Does Not Apply
97	Is told by others to "cheer up" and be happier.	1	2	3	4	5	NA
98	When with other children, is the one to choose activities or games.	1	2	3	4	5	NA
99	Gets angry when s/he makes a mistake.	1	2	3	4	5	NA
100	Her/his feelings are easily hurt.	1	2	3	4	5	NA
101	Can make him/herself get out of bed, even when tired.	1	2	3	4	5	NA
102	Likes active games.	1	2	3	4	5	NA
103	Can apologize or shake hands after a fight.	1	2	3	4	5	NA
104	Has a big imagination.	1	2	3	4	5	NA
105	When angry about something, s/he tends to stay upset for five minutes or longer.	1	2	3	4	5	NA
106	Places great importance on friends.	1	2	3	4	5	NA
107	Seems to feel down when unable to accomplish a task.	1	2	3	4	5	NA
108	Gets into trouble because s/he does things without thinking first.	1	2	3	4	5	NA
109	Notices small changes in the environment, like lights getting brighter in a room.	1	2	3	4	5	NA
110	Has temper tantrums when s/he doesn't get what s/he wants.	1	2	3	4	5	NA
111	Notices things others don't notice.	1	2	3	4	5	NA
112	Has a hard time going back to sleep after waking in the night.	1	2	3	4	5	NA
113	Likes to sit under a blanket.	1	2	3	4	5	NA
114	Notices even little specks of dirt on objects.	1	2	3	4	5	NA
115	Enjoys playing chase.	1	2	3	4	5	NA
116	Likes to pretend.	1	2	3	4	5	NA
117	Gets nervous about going to the dentist.	1	2	3	4	5	NA
118	Is shy.	1	2	3	4	5	NA
119	Likes to go high and fast on the swings.	1	2	3	4	5	NA
120	Needs to be told to pay attention.	1	2	3	4	5	NA
121	Would think that skiing or snowboarding fast sounds scary.	1	2	3	4	5	NA
122	Usually wins arguments with other children.	1	2	3	4	5	NA
123	Likes to run his/her hand over things to see if they are smooth or rough.	1	2	3	4	5	NA
124	Grabs what s/he wants.	1	2	3	4	5	NA
125	Becomes upset when hair is combed.	1	2	3	4	5	NA
126	Enjoys riding bicycle fast and recklessly.	1	2	3	4	5	NA
127	Likes to run around outside.	1	2	3	4	5	NA
128	Decides what s/he wants very quickly and then goes after it.	1	2	3	4	5	NA

	My Child...	Almost always untrue	Usually untrue	Sometimes true, sometimes untrue	Usually true	Almost always true	Does Not Apply
129	Would like to confide in others.	1	2	3	4	5	NA
130	Usually rushes into an activity without thinking about it.	1	2	3	4	5	NA
131	Likes to be in charge.	1	2	3	4	5	NA
132	Can make him/herself take medicine or eat food that s/he knows tastes bad.	1	2	3	4	5	NA
133	Feels sad frequently.	1	2	3	4	5	NA
134	Likes hugs and kisses.	1	2	3	4	5	NA
135	Likes to plan carefully before doing something.	1	2	3	4	5	NA
136	Acts insecure with others.	1	2	3	4	5	NA
137	Feels nervous for a long time after being scared.	1	2	3	4	5	NA
138	Is quite upset by a little cut or bruise.	1	2	3	4	5	NA
139	Can make him/herself pick up something dirty in order to throw it away.	1	2	3	4	5	NA
140	Is afraid of the dark.	1	2	3	4	5	NA
141	Is able to keep secrets.	1	2	3	4	5	NA
142	Is bothered by bath water that is too hot or too cold.	1	2	3	4	5	NA
143	Has a hard time slowing down when rules say to walk.	1	2	3	4	5	NA
144	Tends to feel sad even when others are happy.	1	2	3	4	5	NA
145	Loves pets and other small animals.	1	2	3	4	5	NA
146	Gets mad when provoked by other children.	1	2	3	4	5	NA
147	When s/he sees a toy or a game s/he wants, is eager to have it right away.	1	2	3	4	5	NA
148	Likes to feel close to other people.	1	2	3	4	5	NA
149	Gets distracted when trying to pay attention in class.	1	2	3	4	5	NA
150	Notices when parents are wearing new clothing.	1	2	3	4	5	NA
151	Likes to make things.	1	2	3	4	5	NA
152	Has a hard time getting moving when tired.	1	2	3	4	5	NA
153	Is very frightened by nightmares.	1	2	3	4	5	NA
154	Is likely to cry when even a little bit hurt.	1	2	3	4	5	NA
155	Enjoys winning arguments.	1	2	3	4	5	NA
156	Likes just being with other people.	1	2	3	4	5	NA
157	Can make him/herself smile at someone, even when s/he dislikes them.	1	2	3	4	5	NA

C3. Definitions of TMCQ subscales

- **Activation Control:** The capacity to perform an action when there is a strong tendency to avoid it.
- **Activity Level:** Level of gross motor activity including rate and extent of locomotion.
- **Affiliation:** The desire for warmth and closeness with others, independent of shyness or extraversion.
- **Anger/Frustration:** Amount of negative affect related to interruption of ongoing tasks or goal blocking.
- **Assertiveness/Dominance:** Tendency to speak without hesitation and to gain and maintain control of social situations
- **Attentional Focusing:** Tendency to maintain attentional focus upon task-related channels.
- **Discomfort:** Amount of negative affect related to sensory qualities of stimulation, including intensity, rate or complexity of light, movement, sound, and texture.
- **Fantasy/Openness:** Active imagination, aesthetic sensitivity, intellectual curiosity.
- **Fear:** Amount of negative affect, including unease, worry or nervousness related to anticipated pain or distress and/or potentially threatening situations.
- **High Intensity Pleasure:** Amount of pleasure or enjoyment related to situations involving high stimulus intensity, rate, complexity, novelty, and incongruity.
- **Impulsivity:** Speed of response initiation.
- **Inhibitory Control:** The capacity to plan and to suppress inappropriate approach responses under instructions or in novel or uncertain situations.
- **Low Intensity Pleasure:** Amount of pleasure or enjoyment related to situations involving low stimulus intensity, rate, complexity, novelty, and incongruity.
- **Perceptual Sensitivity:** Amount of detection of slight, low intensity stimuli from the external environment.
- **Sadness:** Amount of negative affect and lowered mood and energy related to exposure to suffering, disappointment, and object loss.
- **Shyness:** Slow or inhibited approach in situations involving novelty or uncertainty.
- **Soothability/Falling Reactivity:** Rate of recovery from peak distress, excitement, or general arousal.

C4. Strengths and Difficulties Questionnaire (SDQ)

Strengths and Difficulties Questionnaire P 4-16

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months.

Child's Name ..... Male/Female

Date of Birth.....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Do you have any other comments or concerns?

Please turn over - there are a few more questions on the other side

Overall, do you think that your child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes- minor difficulties	Yes- definite difficulties	Yes- severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress your child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
HOME LIFE	☐	☐	☐	☐
FRIENDSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐
LEISURE ACTIVITIES	☐	☐	☐	☐

- Do the difficulties put a burden on you or the family as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature ..... Date .....

Mother/Father/Other (please specify:)

Thank you very much for your help

C5. Pittsburgh Sleep Quality Index (PSQI)

Pittsburgh Sleep Quality Index of Parents' Sleep

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, what time have you usually gone to bed at night?
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, what time have you usually gotten up in the morning?
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 spent 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 to help you sleep (prescribed or "over the counter")?
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 room mate?
No bed partner or room mate _____ Partner/room mate in other room _____
Partner in same bed _____ Partner in same room, but not same bed _____

If you have a room mate or bed partner, 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_____

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

C6. Epworth Sleepiness Scale (ESS)

Epworth Sleepiness Scale

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 haven't 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 = would never doze

1 = slight chance of dozing

2 = moderate chance of dozing

3 = high chance of dozing

It is important that you answer each question as best you can.

Situation	Chance of Dozing (0-3)
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (e.g. a theatre or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____

C7. Major Depression Inventory (MDI)

The Major (ICD-10) Depression Inventory (MDI)

The following questions ask about how you have been feeling over the last two weeks.

Please put a tick in the box which is closest to how you have been feeling.

Example: If you have felt in low spirits or sad slightly more than half of the time during the last two weeks put a tick in the third box from the left in the first row.

	How much of the time...	All of the time	Most of the time	More than half of the time	Less than half of the time	Some of the time	At no time
1	Have you felt in low spirits or sad?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
2	Have you lost interest in your daily activities?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
3	Have you felt lacking in energy and strength?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4	Have you felt less self-confident?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
5	Have you had a bad conscience or feelings of guilt?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

6	Have you felt that life wasn't worth living?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
7	Have you had difficulty in concentrating, e.g. when reading the newspaper or watching television?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
8a	Have you felt very restless?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
8b	Have you felt subdued?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
9	Have you had trouble sleeping at night?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
10a	Have you suffered from reduced appetite?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
10b	Have you suffered from increased appetite?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0