The Paediatric Narcolepsy Project: The relationships between sleep, physical activity, cognitive function and psychosocial well-being in children with narcolepsy

By

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Abstract

Narcolepsy is a lifelong neurological sleep disorder characterised by excessive daytime sleepiness and attacks of muscle weakness triggered by emotions (cataplexy). In 2010, alarms were raised about an increase in the incidence rate of narcolepsy diagnosis in children. Subsequent research has confirmed a causal link between the use of the Pandemrix H1N1 influenza vaccine and cases of narcolepsy in children. Despite the rise in cases, there is limited research investigating the clinical characterisation and functional impact of paediatric narcolepsy. To address this gap in the literature, a systematic review of cognitive function and psychosocial well-being in children with narcolepsy was conducted. The results suggested that children who develop narcolepsy are at significant risk of cognitive impairment in at least one domain and emotional problems including depression, anxiety and low self-esteem.

Based on the systematic review findings, a case-control study was designed to describe the relationships between sleep, physical activity, cognitive function and psychological well-being in children with narcolepsy. 23 children with narcolepsy (aged 8-15 years) and 23 gender, age, I.Q and socioeconomic status (SES) matched healthy controls underwent standardized neuropsychological assessment and home polysomnography (PSG) using a portable PSG system. The children also wore an actigraphy monitor for eight days to measure their daytime sleep and physical activity. 21 out of the 23 children with narcolepsy were treated with medication at the time of the study.

Children with narcolepsy showed more sleep disturbance, spent more time asleep during the day and were less active when awake than controls. Children with narcolepsy reported more feelings of anger and more disruptive behaviour than controls. Children with narcolepsy also reported poorer health-related quality of life than controls. There were no significant differences found in cognitive performance between the two groups, suggesting that well-managed children with narcolepsy do not have significantly impaired cognitive function. Sleep efficiency positively correlated with physical activity and health-related quality of life in children with narcolepsy and controls. Physical activity positively correlated with health-related quality of life and negatively correlated with disruptive behaviour in children with

narcolepsy and controls. These findings will inform the design of intervention studies that aim to optimise the clinical management of paediatric narcolepsy.

Table of Contents

List of Tables

List of Figures

Abbreviations

AASM	American Academy of Sleep Medicine
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS	Attention Deficit Hyperactivity Disorder-Rating Scale
AESS	Adapted Epworth Sleepiness Scale
ASDA	American Sleep Disorder Association
ASD	Autism Spectrum Disorder
ASO3	Adjuvant System O3
BAI-Y	Beck Anxiety Inventory for Youth
BANI-Y	Beck Anger Inventory for Youth
BDBI-Y	Beck Disruptive Behaviour for Youth
BDI-Y	Beck Depression Inventory for Youth
BMI	Body mass index
BSCI-Y	Beck Self Concept Inventory for Youth
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBCL	Achenbach Child Behaviour Checklist
CDI	Child Depression Inventory
CFS	Chalder's Fatigue Scale
CPRS-R	Conner's Parent Rating Scale-Revised
CSF	Cerebral spinal fluid
CSHQ	Child Sleep Habits Questionnaire
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
EMG	Electromyography
EOG	Electrooculography
ESS	Epworth Sleepiness Scale
FSIQ-2	Full Scale IQ-2 Subtests
HLA	Human leukocyte antigen
HRQL	Health-related quality of life
ICSD	International Classification of Sleep Disorders
IED	Intra Dimensional/Extradimensional Set Shift
IHS	Idiopathic Hypersomnia

IMD	Index of Multiple Deprivation
IPA	Interpretative phenomenological analysis
IQ	Intelligence quotient
ISI	Insomnia Severity Index
M	Mean
MEMS	Microelectromechanical system
MOT	Motor Screening Test
MSLT	Mean Sleep Latency Test
NHS	National Health Service
NREM	Non-rapid eye movement
OSAHS	Obstructive Sleep Apnoea-Hypopnea Syndrome
PAL	Paired Associates Learning
PDSS	Paediatric Daytime Sleepiness Scale
PRISMA	Preferred reporting items for systematic reviews and meta analyses
PSG	Polysomnography
QAS	Quality assessment score
QATSDD	Quality assessment tool for reviewing studies with diverse design
REM	Rapid eye movement
ROI	Republic of Ireland
RTI	Reaction Time Task
SE	Sleep efficiency
SES	Socioeconomic status
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SOC	Stockings of Cambridge
SOL	Sleep onset latency
SOREMP	Sleep onset rapid eye movement periods
SOUND	Sufferers of Unique Narcolepsy Disorder
SSP	Spatial Span
SWM	Spatial Working Memory
SWS	Slow wave sleep
TIB	Time in bed
TOWRE-2	Test of Word Reading Efficiency-Second Edition

TST	Total sleep time
UK	United Kingdom
USA	United States of America
USD	United States dollar
VMCPM	Vector magnitude counts per minute
WASI-II	Wechsler Abbreviated Scale of Intelligence-Section Edition
WASO	Wake after sleep onset
WIAT-2	Wechsler Individual Achievement Test-Second Edition
WISC-R	Wechsler Intelligence Scale for Children-Revised
WISC-III	Wechsler Intelligence Scale for Children-Third Edition
WMTB-C	Working Memory Test Battery for Children

Chapter 1 Clinical overview of narcolepsy

1.1 Introduction

Narcolepsy is a chronic and disabling neurological sleep disorder characterised by excessive daytime sleepiness (EDS) and attacks of muscle weakness which are often precipitated by strong emotions (cataplexy). The estimated prevalence of narcolepsy with cataplexy in adults is 25 to 50 cases per 100,000 people (Longstreth, Koepsell, Ton, Hendrickson, & Van Belle, 2007). It is a condition that has traditionally been thought of as a disorder of adulthood (Lecendreux, 2014) however, contrary to this assumption, more than 50% of individuals with narcolepsy report experiencing the onset of symptoms before the age of 18 years (Wijnans et al., 2013), typically during adolescence. The prevalence of narcolepsy in children and adolescents is yet to be determined (Meltzer, Johnson, Crosette, Ramos, & Mindell, 2010; Nevsimalova, 2014). It has been estimated that delays between the onset of symptoms and the diagnosis of narcolepsy can range from 10-15 years (Serra, Montagna, Mignot, Lugaresi, & Plazzi, 2008). Individuals with narcolepsy vary greatly in their presentation and this can lead to the misinterpretation of symptoms and misdiagnosis.

1.2 Narcolepsy in children

In August 2010, concerns were raised in Scandinavian countries about an increase in the incidence rate of narcolepsy diagnosis in children and adolescents after September 2009. The pharmacovigilance authorities in Sweden and Finland were concerned that this increase in the number of narcolepsy cases may be associated with the use of the ASO3 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix) during the H1N1 (swine flu) Pandemic in 2009 and 2010 (Lakemedelsverket Medical Products Agency, 2010). This vaccine was recommended for individuals with high risk clinical conditions and for healthy children under the age of 5 (Miller et al., 2013). Following these concerns, a cohort study was conducted in Finland and the results showed that there was a 13-fold

increased risk of narcolepsy in children aged 4-19 years old who received the vaccination compared to unvaccinated children (Nohynek et al., 2012). These concerns led to further investigations about the incidence of narcolepsy in Europe before, during and after the swine flu pandemic and vaccination campaigns (Miller et al., 2013; National Narcolepsy Study Steering Commitee, 2010; Wijnans et al., 2013). Consistent with the findings of the cohort study conducted in Finland, Miller et al. (2013) found a significantly increased risk of narcolepsy in children who received the vaccine in England. Following an extensive review of the available literature, The European Medicines Agency have confirmed the association between the use of the Pandemrix vaccination and the increased incidence of narcolepsy (Barker & Snape, 2014). It has been estimated that globally more than 1000 children have developed narcolepsy following the vaccination (Thebault, Vincent, & Gringras, 2013).

1.3 The pathophysiology of narcolepsy

The exact cause of narcolepsy is unclear (Thebault et al., 2013), however it is generally considered to arise from a combination of genetic and environmental factors (National Narcolepsy Study Steering Commitee, 2010). The presence of the human leucocyte antigen (HLA) DQB1*0602 is a primary susceptibility factor for the condition (Kadotani, Faraco, & Mignot, 1998) and additional environmental factors have been identified that are commonly reported to precede the onset of symptoms. Frequently reported events in the weeks prior to the development of narcolepsy include: major psychological stress, streptococcal infection, seasonal influenza, a sudden change in sleep patterns and head trauma (Peacock & Benca, 2010).

As mentioned in section 1.2, it has recently been suggested that H1N1 influenza (commonly referred to as swine flu) and the ASO3 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix) have a causal association with narcolepsy (Miller et al., 2013; Thebault et al., 2013; Wijnans et al., 2013). The prevailing hypothesis is that narcolepsy is an autoimmune condition and can be caused by autoimmune response (Dauvilliers et al., 2010). H1N1 influenza and the H1N1 vaccine are reported to be triggers of autoimmune attacks to the central nervous system (CNS) (Coelho et al., 2012). It is reported that individuals carrying the

specific HLA-DQB1*0602 allele (a variant form of a gene) are more likely to have a unique immunological response to the swine flu infection or vaccine. The unique autoimmune response is thought to lead to a hypocretinergic system dysfunction which results in the destruction of the 70,000 hypocretin (also known as orexin) producing cells in the hypothalamus (Partinen, Kornum, Plazzi, Jennum, Julkunen, & Vaarala, 2014). Hypocretin plays a role in stabilising the transition between sleep and wake states, by promoting wakefulness and suppressing rapid eye movement (REM) sleep (Babiker & Prasad, 2015). This loss of hypocretin cells in the hypothalamus is reported to cause the onset of narcolepsy symptoms (Dauvilliers et al., 2010). Before describing the clinical features of narcolepsy in section 1.9, section 1.4 provides an overview of normal sleep in typically developing children.

1.4 Normal paediatric sleep architecture

Sleep is essential for survival and humans spend approximately one third of their life asleep (Stores, 2009). Sleep can be defined by both behavioural and physiological criteria (MacLean, Fitzgerald, & Waters, 2015); it is a state of rest during which consciousness of the world is suspended (Spriggs, 2014) and changes occur to physiological parameters such as brain activity, muscle tone and cardiorespiratory control (MacLean et al., 2015).

Sleep consists of two main stages: non-rapid eye movement sleep (NREM) and rapid eye movement sleep (REM), which typically alternate at approximately 90 minute intervals in healthy adults. NREM sleep is comprised of three stages, progressing from light sleep at stage 1 and 2, to deep slow wave sleep (SWS) at stage 3. REM sleep follows NREM sleep and is characterized by rapid eye movements, muscle paralysis (atonia) and dreaming. NREM sleep typically marks the beginning of sleep and REM sleep is more prevalent towards the end of the night (Babiker & Prasad, 2015). The pattern of sleep stages that humans progress through during their sleep period is best represented by a hypnogram. Figure 1.1 is a hypnogram which shows the typical sleep architecture of a healthy school-aged child.

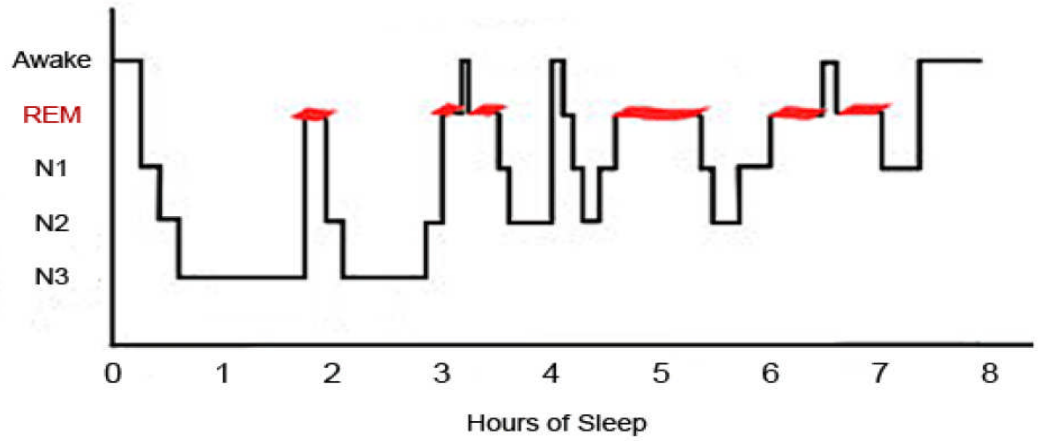

Figure 1.1 A hypnogram showing the characteristic progression of sleep stages overnight in a healthy school-aged child (Dawson, 2012, p. 18). Reprinted with permission.

1.5 Measuring and scoring sleep

Sleep stages can be determined by recording brain activity and other physiological indicators using polysomnography (PSG) equipment (Stores, 2009). Polysomnography recordings involve placing electrodes (sensors) on the scalp to measure brain activity (electroencephalogram or EEG channels), near the eyes to measure eye movements (electrooculography or EOG channels) and on the chin to measure muscle activity and tone (electromyography or EMG channels). An electrode is also placed in the centre of the forehead to act as a common ground (reference electrode) and two further reference electrodes are placed on the mastoid bones behind the ears on either side of the head (M1 and M2). The international 10/20 electrode placement system (Jasper, 1958) is a standard measurement tool which sleep technicians follow in order locate the appropriate areas to place electrodes.

Electrical signals generated by an individual are transmitted through the electrodes to a differential amplifier. A differential amplifier converts two input signals (the electrode of interest and the reference electrode) recorded from the individuals scalp, face or body, amplifies the differing voltages (electrical tension) and sends a resulting output signal to the polysomnogram. Biological potentials are measured in microvolts (μV) (millionths of a volt) (Spriggs, 2014). Each stage of sleep has characteristic EEG waveforms which help the scorer to identify the different sleep

stages within a polysomnography recording. The frequency of a wave is characterised by the number of times it repeats or oscillates in a second and this is measured in Hertz (Hz). The amplitude of the wave is characterised by the height of the wave (Spriggs, 2014). Rechtschaffen and Kales (1968) published a manual which set the standard for scoring sleep stages in adults for over 40 years (Spriggs, 2014) and more recently the American Academy of Sleep Medicine introduced a new standard of scoring which includes paediatric sleep scoring rules (Berry, Brooks, Gamaldo, Harding, Marcus, & Vaughn, 2012).

1.6 Sleep stages

An overview of each sleep stage is provided below. The descriptions are based on sleep in healthy individuals and the figures show a 30 second epoch (one page of the sleep study recording) from a polysomnography recording conducted with a healthy 11 year old male as part of the research described in Chapter 6. The figures show two EOG channels (E1 and E2), six EEG channels (F3, F4, C3, C4, O1, O2) and one EMG channel (Chin left). Odd numbers refer to the electrodes placed on the left side of the head and even numbers refer to those placed on the right side of the head. The percentage of time spent in each stage of sleep reported below are based on healthy adult data (Spriggs, 2014).

1.6.1 Stage W (Wake)

Wake is characterised by frequent movement and muscle activity seen on the polysomnography recording (see Figure 1.2). When an individual is awake but resting with their eyes closed, alpha waves (8-13 Hz) are present in the occipital regions of the brain which indicates that the individual may be preparing to fall asleep (see Figure 1.3).

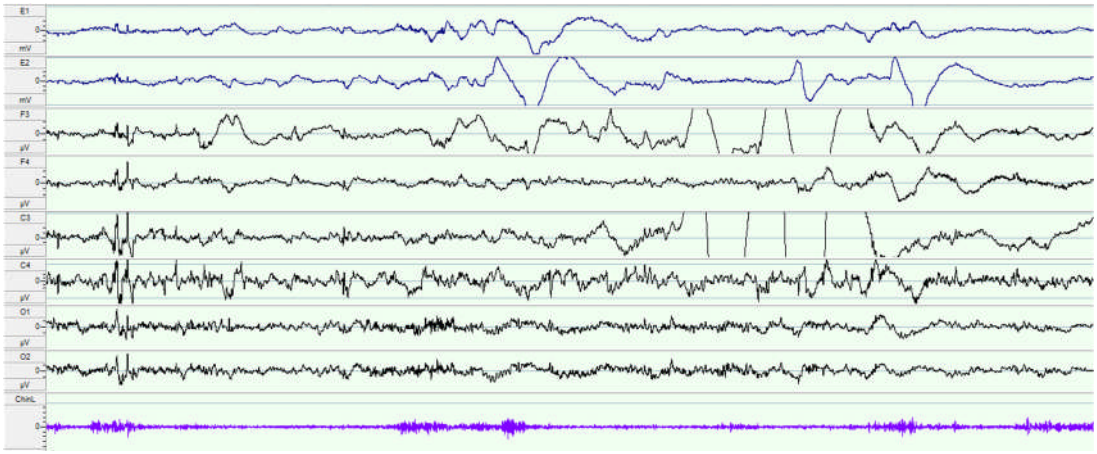

Figure 1.2 A 30 second epoch of wake

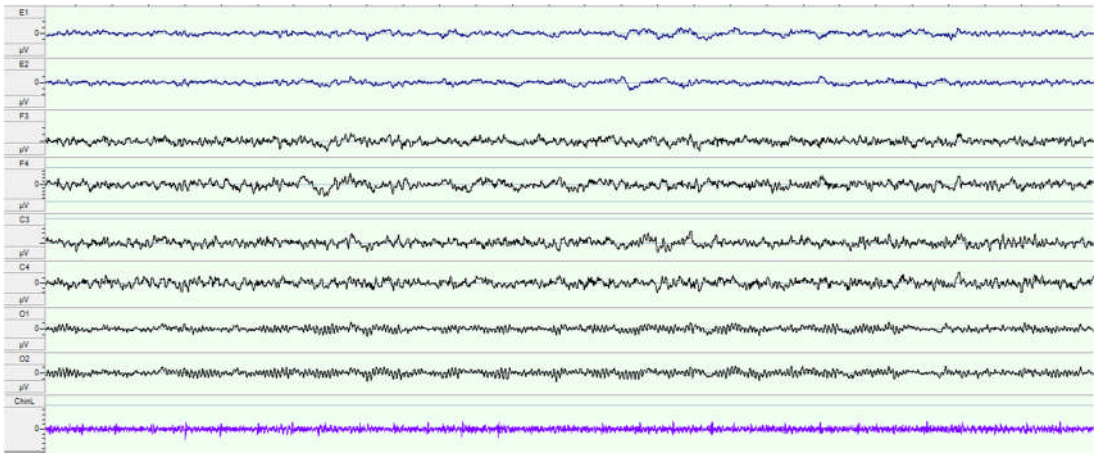

Figure 1.3 A 30 second epoch of relaxed wakefulness

1.6.2 Stage N1

5-10% of total sleep time is spent in stage N1 sleep. Stage N1 sleep is often referred to as a transitional stage because most people enter sleep through stage N1 (Spriggs, 2014). As this is a light stage of sleep, an individual in stage N1 sleep may still be aware of external stimuli. The EOG channels often show slow eye movements (SEMs), as opposed to blinks, which are seen when the individual is awake. In stage N1 sleep the EEG channels show specific wave forms known as theta waves (4-7 Hz) and sharp waves (known as vertex sharps or V waves) (see Figure 1.4).

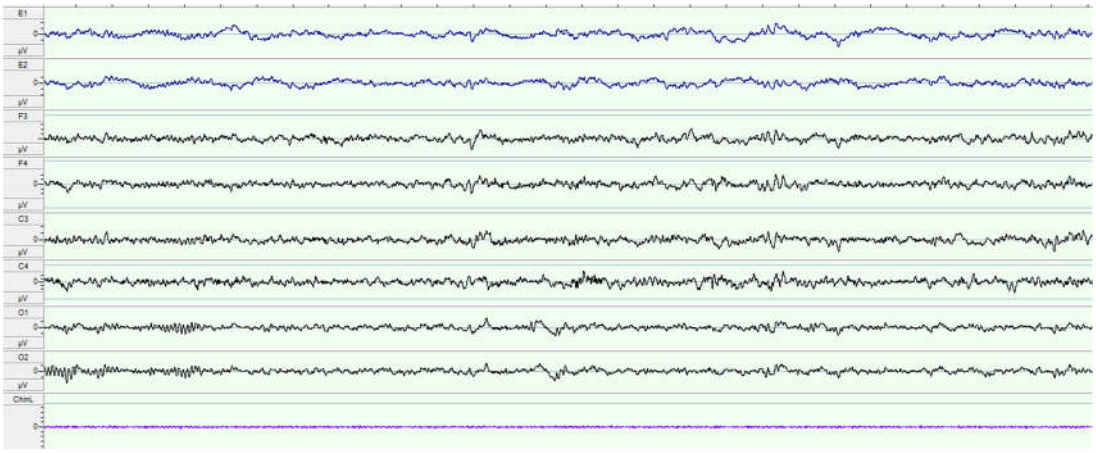

Figure 1.4 A 30 second epoch of stage N1 sleep

1.6.3 Stage N2

40-50% of total sleep time is spent in stage N2 sleep. Stage N2 is identified by the presence of K-complexes (a negative deflection followed by a slower positive component) followed by sleep spindles (a burst of EEG activity (11-16 Hz) lasting at least 0.5 seconds). During stage N2 sleep the individual becomes less aware of external stimuli (see Figure 1.5).

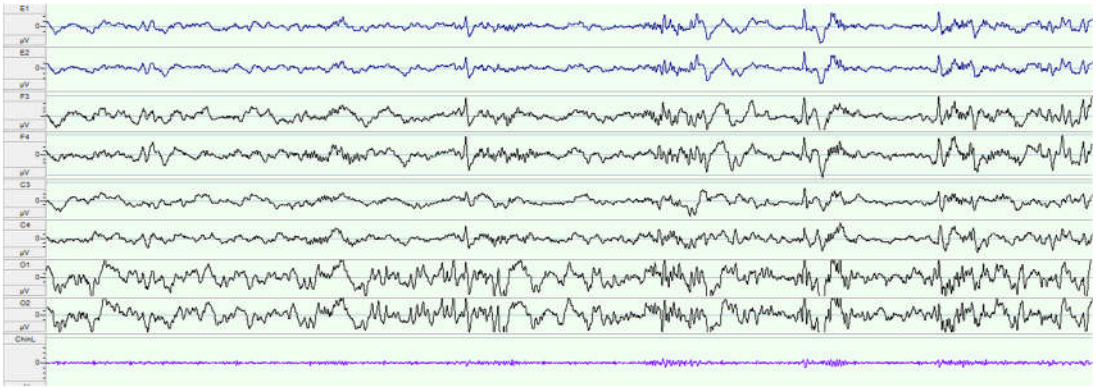

Figure 1.5 A 30 second epoch of stage N2 sleep

1.6.4 Stage N3

20-25% of total sleep time is spent in stage N3 sleep, which is identified by the presence of slow (0.5-2 Hz) high amplitude EEG waves. This is why the stage is also known as slow wave sleep (SWS). This is considered to be the deepest stage of sleep as individuals are more difficult to wake from this stage of sleep (see Figure 1.6).

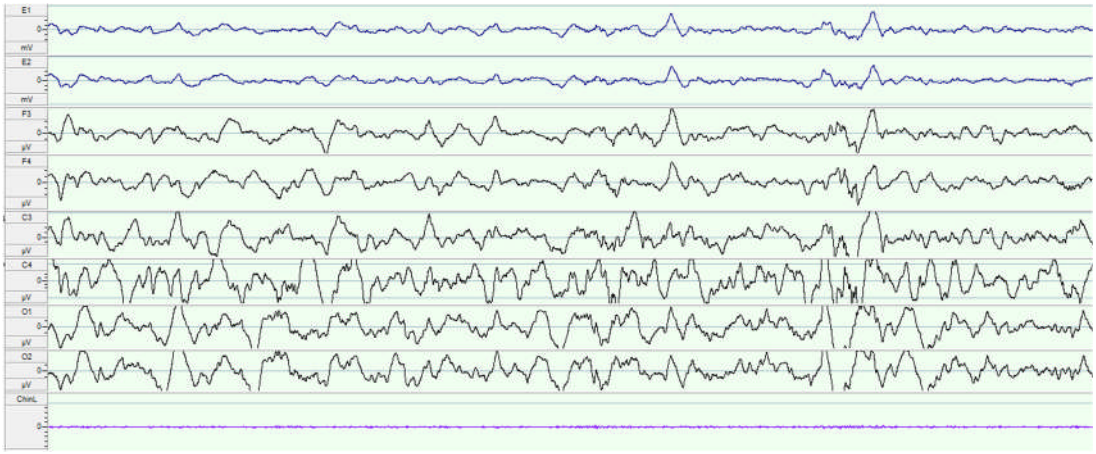

Figure 1.6 A 30 second epoch of stage N3 sleep

1.6.5 Stage R

20-25% of total sleep time is spent in stage R (also known as REM sleep). REM sleep is characterised by rapid eye movements and brain activity that resembles the activity during wakefulness but the muscles are paralyzed (reduced chin tension is shown on the EMG channel). The EEG channels show a low-voltage mixed frequency EEG. Heart rate and breathing tend to be less regular in REM sleep than in other stages of sleep (Stores, 2009) (see Figure 1.7).

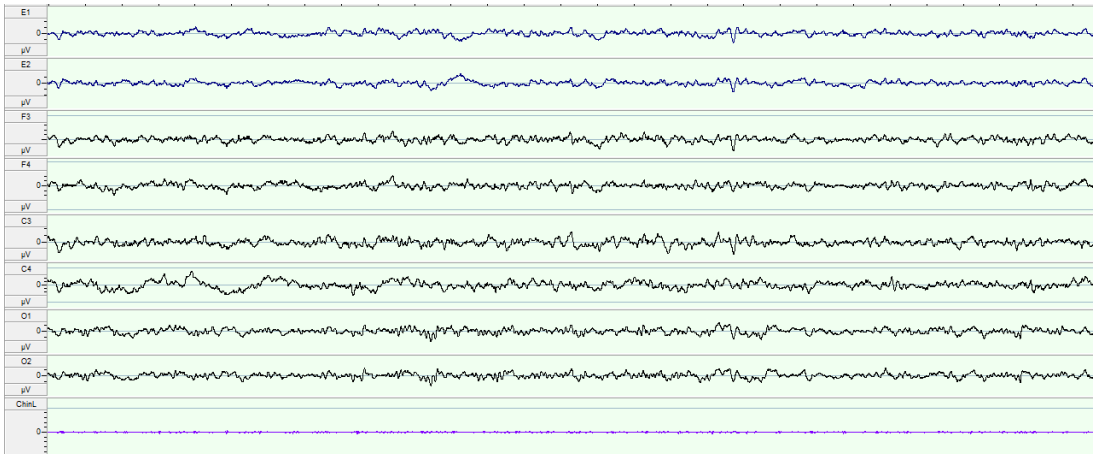

Figure 1.7 A 30 second epoch of REM sleep

1.6.6 Additional polysomnography measures

In addition to providing information about minutes spent in each stage of sleep, polysomnography recordings provide other information that is clinically useful. This includes a measure of sleep onset latency (SOL) which is the time it took an individual to fall asleep, sleep efficiency (SE) which is a calculation of the total sleep time divided by the total time spent in bed and wake after sleep onset (WASO) which is how many minutes an individual spent awake after sleep onset. The recordings also allow the scorer to calculate the number of awakenings and arousals during the recording. In a full polysomnography set up, additional physiological measures can be recorded such as breathing effort, heart rate, body position and leg movements. This information is interpreted by a clinician in order to assess whether a sleep issue is present or not.

1.7 Developmental changes in sleep need

The amount of sleep needed for satisfactory function during the day changes with age (Stores, 2009). On average, new-born babies require 16-18 hours of sleep, infants require approximately 12 hours of sleep, adolescents require 9 or more hours of sleep and adults require approximately 7-8 hours sleep per night. Daytime naps should have stopped in healthy children by the age of 3-4 years (Stores, 2009).

There are also developmental changes in sleep architecture throughout the lifespan (MacLean et al., 2015). New-born infants spend up to 50% of their sleep time in REM sleep (Stores, 2009), however this reduces over the first year of life so that by the age of 1 year, slow wave sleep (N3 sleep) occupies more sleep time than REM sleep. Between the ages of 5-19 years old, the percentage of time spent in REM sleep remains relatively stable and there is an increase in N2 sleep and a decrease in N3 sleep (MacLean et al., 2015). The frequency of arousals also changes at different developmental stages. Arousals are more frequent in new-borns but they decrease by the age of one. The frequency of arousals remains stable during childhood and then increases in adolescence and late adulthood.

1.8 The importance of sleep

1.8.1 Sleep and health

Adequate sleep is needed in order to maintain both physical and psychological health. Routinely getting less than the recommended amount of sleep for your age (as described in section 1.7) can have profound negative effects on health such as increasing the likeliness of diabetes (Cappuccio, D'Elia, Strazzullo & Miller, 2010), cardiovascular disease (Meisinger, Heier, Lowel, Schneider & Doring, 2007), hypertension (Gangwisch, Heymsfeld & Boden-Albala, 2006) and obesity (Cappuccio, Taggart & Kandala, 2008). The mechanisms that underlie these associations are not yet fully understood (Cappuccio, D'Elia, Strazzullo & Miller, 2010). If sleep is disrupted from a young age, physical growth may be affected (Stores, 2009). This is because the production of growth hormone is closely linked to NREM slow wave sleep.

1.8.2 Sleep and cognitive function

The term ‘cognition’ refers to all the processes by which sensory input is transformed, reduced, elaborated, stored, recovered and used (Neisser, 1967). Higher intellectual processes such as thought, memory, language, attention, problem solving, reasoning, decision making and complex perceptual processes are considered ‘cognitive functions’ (Albright, Kandel & Posner, 2000; Andrade & May, 2004). These mental processes underlie the ability to perceive the world, to understand and remember experiences, to communicate and to control behaviour (Andrade & May, 2004). Individuals who are exposed to sleep loss usually experience a decline in cognitive performance (Pilcher & Huffcutt, 1996; Philibert, 2005; Durmer & Dinges, 2005; Lim & Dinges, 2010) therefore sleep is considered to be essential for cognitive performance.

Lim and Dinges (2010) conducted a meta-analysis of the impact of short-term sleep deprivation on cognitive variables and report that sleep deprivation has a deleterious effect across most cognitive domains including attention, executive function, short-term memory, working memory and processing speed. The authors found that there was no effect of sleep deprivation on accuracy measures in tests of reasoning and crystallized intelligence (retrieval of domain-specific knowledge) (Lim & Dinges, 2010), which is unsurprising given that crystallized abilities are considered to be highly stable over a range of cognitive states (Andrade & May, 2004). Simple sustained attention was reported to be the cognitive domain most strongly affected by sleep deprivation (Lim & Dinges, 2010). Simple sustained attention is critical in many everyday tasks such as driving or operating machinery where lapses in attention may pose a significant safety risk. Lim & Dinges (2010) suggest that deficits in sustained attention often precede other observable cognitive effects of sleep deprivation and that deficits in sustained attention may have “considerable utility as an early warning system for imminent cognitive failure” (page 13). Similarly, Alhola & Polo-Kantola (2007) report that both total and partial sleep deprivation induce adverse changes in cognitive performance and that attention is particularly affected by sleep deprivation.

Simple reaction time tests or psychomotor vigilance tests are commonly used to measure simple sustained attention (Alhola & Polo-Kantola, 2007; Lim & Dinges, 2010). The tests usually involve the visual or auditory detection of a single class of

stimuli and provide information about speed, accuracy and lapses in attention (Alhola & Polo-Kantola, 2007). Simple reaction time has been shown to be strongly positively correlated with the level of impairment on neuropsychological tests (Elsass & Hartelius, 1985; Collins & Long, 1996). Hicks & Birren (1970) demonstrated that reaction time deficits tend to be nonspecific in their effects and reflect impairment of some generalized (rather than strictly localised) cognitive ability. These findings suggest that reaction time tasks are a valuable part of neuropsychological assessments and can provide useful information about cognitive functioning (Blackburn & Benton, 1955; DeRenzi & Faglioni, 1965; Elsass, 1986) and the impact of sleep deprivation on attention (Alhola & Polo-Kantola, 2007).

Working memory is also reported to be particularly vulnerable to sleep deprivation (Durmer & Dinges, 2005; Lim & Dinges, 2010; Alhola & Polo-Kantola, 2007). Working memory involves the ability to hold and manipulate information and can involve multiple sensory-motor modalities. Deficits in neurocognitive performance requiring working memory result in difficulty determining the scope of a problem due to changing or distracting information, remembering the temporal order of information, maintaining focus on relevant cues, maintaining flexible thinking and making behavioural modifications based on new information (Durmer & Dinges, 2005).

There are two main theories proposed to explain the mechanism behind the effects of sleep deprivation on cognitive performance (Alhola & Polo-Kantola, 2007). The first theory proposes that cognitive impairments during sleep deprivation are mediated by attentional lapses caused by microsleeps (very short periods of sleep-like EEG activity) (Dinges, Rogers & Dorrian, 2004; Kjellberg, 1977), slowed responses (Kjellberg, 1977; Dorrian et al., 2005) and wake-state instability (where sleep-initiation mechanisms repeatedly interfere with wakefulness) (Doran, Van Dongen & Dinges, 2001). The second theory known as the “sleep-based neuropsychological perspective” (Babkoff et al., 2005) proposes that sleep deprivation has selective effects on the prefrontal cortex and consequently impairs cognitive performances that depend on the prefrontal cortex such as language, executive functions, divergent thinking and creativity.

There is also evidence that insufficient sleep can cause impairments in memory consolidation. Consequently, lack of sleep can have a significant impact on school

work and educational outcomes. Studies have shown that, in healthy children, sleep promotes memory consolidation (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2014; Henderson, Weighall, Brown, & Gaskell, 2012). Memory consolidation is the process by which information becomes stronger, more efficient and more resistant to interference (Cellini, 2017). The dual process hypothesis proposes a differential role of SWS, rapid-eye-movement (REM) sleep and stage N2 sleep for different types of memories (Plihal & Born, 1997). Supporting this hypothesis, there is convincing evidence that SWS is beneficial for declarative memories (knowledge of information that can be put into words easily and tested by direct questioning) (Ackermann & Rasch, 2014). The dual process hypothesis also proposed that REM sleep is important for consolidation of procedural memories (knowledge of procedures or skills), however the evidence for this is scarce (Ackermann & Rasch, 2014). Recent evidence suggests that procedural memory is also dependent on non-REM sleep rather than REM sleep (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). Given that sleep is important for memory consolidation, it is possible that individuals who have disturbed sleep may have an impairment in the ability to consolidate new information (Cellini, 2017).

1.8.3 Sleep and psychosocial well-being

As well as affecting physical health and cognitive function, lack of sleep has been shown to affect psychological well-being (Hamilton, Nelson, Stevens, & Kitzman, 2007; Vandekerckhove & Cluydts, 2010; Walker & Harvey, 2010). Pilcher & Huffcutt (1996) conducted a meta-analysis of the effects of sleep deprivation on performance and found that mood was more affected by sleep deprivation than either cognitive or motor performance. Walker & Harvey (2010) report that nearly all psychiatric disorders co-occur with one or more abnormalities of sleep and researchers have speculated that the relationship between sleep and psychosocial well-being may be bidirectional (Fredriksen, Rhodes, Reddy & Way, 2004). Roberts and Duong (2014) conducted a study to examine the prospective association between sleep deprivation and depression among adolescents and found that reduced quantity of sleep increases risk for major depression, which in turn increases risk for decreased sleep. Similarly, Baglioni et al. (2011) conducted a meta-analysis and found that non-depressed adults with insomnia have a twofold risk to develop depression, compared to people with no sleep difficulties. The psychophysiological

mechanisms through which insomnia predicts depression are still not clear (Bagliono et al., 2011).

1.8.4 The relationship between nocturnal sleep, naps and physical activity

Nocturnal sleep and daytime naps in children

Early childhood is an important time in sleep development in which sleep consolidates into one nocturnal sleep period and napping ceases (Iglowstein, Jenni, Molinari & Largo, 2003). Iglowstein et al. (2003) report that the most prominent decline in napping habits occurs between 1.5 years of age and 4 years of age. Thorpe, Staton, Sawyer, Pattinson, Haden & Smith (2015) conducted a systematic review to assess the evidence regarding the effects of napping in children. An association was found between napping and falling asleep later at night, shorter nocturnal sleep duration and poorer quality of nocturnal sleep in children beyond the age of two years old. Similarly, Lam, Mahone, Mason & Scharf (2011) found that in pre-schoolers, weekday napping and night time sleep were inversely correlated, such that those who napped more slept less at night. The direction of the relationship between nocturnal sleep and daytime naps in children is not clear and it is possible that naps may weaken the sleep drive at night and therefore children may sleep less at night because their sleep debt is decreased by daytime sleep or children who sleep less at night may be partially sleep deficient and require a nap. More research is required to understand the advantages and disadvantages of napping during the day and the relationship between daytime naps and the quality and quantity of nocturnal sleep.

Nocturnal sleep and physical activity in children

Information on the relationship between daytime activity and sleep in pre-adolescents is scarce and contradictory (Ekstedt Nyberg, Ingre, Ekblom & Marcus, 2013). Pesonen et al. (2011) investigated the temporal associations between daytime physical activity and sleep in children using actigraphy and found that physical activity and sleep were significantly related, such that a higher level of physical activity during the day was associated with poorer sleep that night, and poorer sleep during the night was associated with a higher level of physical activity the following day. However, Ortega et al. (2011) examined the association between sleep duration

and time in sedentary, moderate and vigorous activity in children and adolescents and found no significant association between sleep duration and activity level.

There is also evidence to suggest that sleep and physical activity are positively correlated. Ekstedt, Nyberg, Ingre, Ekblom & Marcus (2013) conducted a cross-sectional study which measured sleep and physical activity using actigraphy for seven consecutive days in 1,231 children aged six to ten years old. The results showed that moderate-to-vigorous intense physical activity promoted an increased sleep efficiency the following night, while total sleep time was not affected. Similarly, Stone, Stevens & Faulkner (2013) found that children aged 10 to 12 years old who maintained the recommended amount of sleep for their age (more than 9 hours) through the weekdays and weekend engaged in more intense physical activity than children who got less than the recommended amount of sleep during the week and slept more at the weekend to catch up on their sleep.

Given the contradictory results, more research using objective measurements of physical activity and sleep (actigraphy and polysomnography) are needed to better understand the relationship between sleep and physical activity in children and adolescents.

Previous literature suggest that exercise and physical activity are associated with better quality of life and health outcomes (Penedo & Dahn, 2005; Pretty, Peacock, Hine, Sellens, South, & Griffin, 2007; Steptoe & Butler, 1996) and that there are positive effects of aerobic physical activity on cognition, brain function and academic performance (Coe, Pivarnik, Womack, Reeves, & Malina, 2006; Hillman, Erickson, & Kramer, 2008; Trudeau & Shephard, 2008).

1.9 Clinical features of narcolepsy

The International Classification of Sleep Disorders-Third Edition (ICSD-3) (American Academy of Sleep Medicine, 2014) distinguishes between two types of narcolepsy; narcolepsy type 1 and narcolepsy type 2. Type 1 narcolepsy is also known as 'narcolepsy-cataplexy' because individuals have deficiency of the neuropeptite hypocretin or experience cataplexy. Type 2 narcolepsy is also known as 'narcolepsy without cataplexy' as individuals do not experience cataplexy and the relationship to cerebrospinal levels of hypocretin is less definite than in type 1 narcolepsy. It is also important to note the difference between 'primary/idiopathic' narcolepsy and 'secondary/symptomatic' narcolepsy-cataplexy. Primary narcolepsy is caused by the loss of hypocretin (as previously described in section 1.3), whereas secondary narcolepsy develops as result of other medical conditions (mainly caused by structural brain lesions) and is found in up to 20-33% of all childhood narcolepsy cases (Nevsimalova, 2014).

Children and adolescents with narcolepsy are at increased risk of their condition being unrecognised, misinterpreted and misdiagnosed due to the disorder's wide range of clinical manifestations (Stores, 2006). The symptoms of narcolepsy can have a huge impact on a child and their family's life and are often vastly underestimated (Elphick, Staniforth, Blackwell, & Kingshott, 2017). The full array of narcolepsy symptoms are rarely present in childhood and variations in the development of each symptom (described below) are possible.

1.9.1 Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) is the most commonly reported first symptom of narcolepsy. Particularly in cases of childhood narcolepsy, it can be difficult for clinicians to distinguish between the normal requirement for daytime naps during childhood and excessive need for sleep. The International Classification of Sleep Disorders-3rd Edition (ICSD-3) states that for a diagnosis of narcolepsy the individual must have daily periods of irrepressible need to sleep or daytime lapses into sleep, occurring for at least 3 months (American Academy of Sleep Medicine, 2014). Irresistible urges to sleep can lead young children to nap during the day (Nevsimalova, 2009). Naps can last up to 2-3 hours without being restorative and can result in "sleep drunkenness" after awakening, lasting up to 15-20 minutes (Nevsimalova, 2009). "Sleep drunkenness" can be described as a combination of

confusion on arousal, disorientation and grogginess and it is more frequently reported by children than adults. EDS and the need for long overnight sleep may be the only symptoms present for a number of years, resulting in delayed and inaccurate diagnosis for young individuals.

1.9.2 Cataplexy

Cataplexy is another predominant symptom of narcolepsy experienced by approximately 60-75% of children diagnosed. Cataplexy may not be present initially, but can develop weeks to years after the onset of EDS (National Institute of Neurological Disorders and Stroke, 2017). The best predictor of the development of cataplexy is hypocretin deficiency (American Academy of Sleep Medicine, 2014). A cataplexy attack involves a sudden, temporary loss of muscular control and can be triggered by a range of different emotions (usual triggers are laughter, anger or surprise) (Serra et al., 2008). Attacks are usually short in duration and progress from the facial region down to the lower limbs, which can lead to full-body collapse. Breathing and eye movements are unaffected and the individual remains aware during the episode (Babiker & Prasad, 2015). The severity of the attacks can vary from mild (eye lids drooping, slight buckling of the knees, head drop) to severe (complete loss of muscle tone). Cataplexy represents the intrusion of REM sleep into wakefulness.

1.9.3 Abnormal REM sleep phenomena

Narcolepsy is also characterised by abnormal REM sleep phenomena. Individuals with narcolepsy enter REM sleep more quickly than typically expected during nocturnal sleep and often experience REM sleep at sleep onset. REM sleep early in the night can cause individuals with narcolepsy to experience multisensory hallucinations and sleep paralysis in the transitional period between wakefulness and sleep (Nevsimalova, 2009). Vivid auditory or visual hallucinations that occur at sleep onset are known as hypnagogic hallucinations and those that occur during awakening are known as hypnopompic hallucinations. The visual hallucinations usually consist of simple forms (coloured circles, parts of objects, animals or people) and the auditory hallucinations can range from a collection of sounds to threatening sentences (Guilleminault & Cao, 2011). The hallucinations are reported to be so realistic that children can become terrified and believe they are real (Peterson & Husain, 2008).

Hallucinations are often accompanied by sleep paralysis, which is a temporary inability to move or speak when falling asleep or waking up, possibly with a feeling of being unable to breathe despite respiratory movements being spared (Stores, 2014). The episodes usually last seconds to minutes and end spontaneously. They can be interrupted if the child is touched or spoken to.

It is now well recognised that children with narcolepsy experience disturbed overnight sleep due to their condition affecting the regulation of sleep-wake states (Peraita-Adrados et al., 2011). This can lead to frequent night time awakenings (Serra et al., 2008) which results in fragmented sleep. Some children with narcolepsy show excessive movements during REM sleep which is characteristic of REM sleep behaviour disorder without atonia (Babiker & Prasad, 2015).

1.9.4 Additional features of narcolepsy

The features described above are part of the International Classification of Sleep Disorders (American Academy of Sleep Medicine, 2014) diagnostic criteria for narcolepsy. The additional features described below are not part of the diagnostic criteria but they are commonly reported in the literature (Babiker & Prasad, 2015; Elphick et al., 2017; Nevsimalova, 2009)

1.9.4.1 Automatic behaviour

Automatic behaviour can appear when an individual with narcolepsy is becoming increasingly tired. This often manifests as individuals doing tasks without being able to recall the process of doing them. One example is taking notes in class or completing homework. It becomes obvious that this was an automatic behaviour when the handwriting is completely illegible. It is important that those around individuals with narcolepsy can recognise the signs of automatic behaviour and offer support when needed, particularly in situations where the child could be at risk if they are not fully alert (for example during bath time).

1.9.4.2 Obesity

Obesity is common in narcolepsy and tends to happen quickly and suddenly after the onset of other narcolepsy symptoms (Babiker & Prasad, 2015). The mechanism of weight gain is not clear but may be related to abnormal hypocretin levels leading to impaired energy metabolism. Parents frequently report an increase in their child's snacking which could also contribute to weight gain. Excessive daytime sleepiness

may lead to a reduction in overall activity due to increased time spent resting or sleeping. Current National Health Service (NHS) guidelines recommend that to maintain a basic level of health, children and young people aged 5 to 18 years need to do at least 60 minutes of moderate to vigorous physical activity every day (NHS choices, 2016). There is currently a lack of research that has objectively assessed whether children with narcolepsy are meeting this criteria. It is possible that lack of physical activity may also contribute to weight gain in children with narcolepsy.

1.10 Clinical diagnostic criteria

Diagnosis of childhood narcolepsy is established by clinical evaluation and sleep recordings (Serra et al., 2008). Diagnostic evaluation includes the use of: parental sleep diaries to provide information about the child's sleep patterns, a device worn on the wrist (called an actigraphy watch) to record the child's movements which indicate overall sleep-wake patterns (Meltzer, Montgomery-Downs, Insana, & Walsh, 2012), overnight Polysomnography (PSG) to provide detailed physiological information about sleep, and the multiple sleep latency test (MSLT) to objectively measure EDS. In addition to these investigations, some paediatric sleep centres perform a blood test to look for the HLA-DQB1* 0602 haplotype and a lumbar puncture to look at levels of hypocretin in the cerebrospinal fluid. Additional information on each diagnostic test is provided below.

1.10.1 Sleep diaries

Parents may be asked to complete a sleep diary documenting their child's bedtime, wake time and daytime naps for a period of up to two weeks. This is useful for highlighting poor or inappropriate bedtime routines (Nevsimalova, 2009) or a disordered nocturnal sleep pattern which may result in excessive daytime sleepiness. The limitations of sleep diaries are that they rely on parents estimating details about their child's sleep patterns and these estimates may be prone to error and be biased by socially desirable responding (Short, Gradisar, Lack, Wright, & Chatburn, 2013).

1.10.2 Actigraphy

Actigraphy is an objective method of estimating sleep-wake patterns by recording motor activity over an extended period of time in the child's natural environment (Meltzer et al., 2012). The small device is normally worn on the child's non-

dominant wrist. A two week period of actigraphy is recommended as part of the diagnosis process.

1.10.3 Overnight polysomnography

As described in section 1.5, polysomnography (PSG) is a multi-channel physiological test to monitor sleep patterns, breathing, gas exchange parameters and leg movements during sleep. The results of an overnight polysomnography recording can be used to provide evidence to support a diagnosis of narcolepsy. The presence of the following symptoms can support a diagnosis of narcolepsy:

- A short sleep onset latency (SOL) of up to 8 minutes
- A shortened REM sleep onset latency of 15 minutes or less (SOREMP)
- An increase in leg movements overnight and twitches in REM sleep
- An overall fragmentation of the hypnogram with a high level of sleep disturbance

1.10.4 Multiple Sleep Latency Test

The Multiple Sleep Latency Test (MSLT) involves daytime PSG recording and is an objective measure of EDS. This test is conducted on the day following an overnight polysomnography recording. The MSLT is based on 20 minute polysomnography recordings repeated every 2 hours (four or five times a day) starting about 2 hours after morning awakening. The individual is asked to try and fall asleep at each of these time points. The International Classification of Sleep Disorders-Third Edition (American Academy of Sleep Medicine, 2014) states that the MSLT should show a mean sleep latency of 8 minutes or less and more than two sleep onset REM periods (SOREMPs) for a diagnosis of narcolepsy.

1.10.5 Human leukocyte antigen typing

Human leukocyte antigen (HLA) typing may be used as a diagnostic tool to test for the presence of the HLA-DQB1*0602 haplotype. A blood test with a positive result adds more diagnostic probability of narcolepsy (Nevsimalova, 2014), however the results must be interpreted with caution as the HLA DBQB1*0602 is also present in 18-35% of the general population (Nevsimalova, 2014).

1.10.6 Cerebrospinal fluid hypocretin 1 level

The most valuable diagnostic marker for narcolepsy type 1 is an undetectable hypocretin-1 level (or a level lower than 110 pg/mL) in the cerebral spinal fluid (CSF), which is measured using a lumbar puncture. This procedure is invasive and is currently not widely available (Babiker & Prasad, 2015).

1.10.7 Summary of diagnostic tools

Used in combination, these diagnostic tools allow for the comprehensive assessment of a child experiencing symptoms of narcolepsy. The type of narcolepsy (1 or 2) can be established by the presence of cataplexy and hypocretin deficiency in narcolepsy type 1. Accurate diagnosis is needed so that the most effective pharmacological and non-pharmacological interventions can be provided to sufferers of narcolepsy, which aim to alleviate the physical, psychological and cognitive symptoms and improve outcomes for these individuals.

1.11 Treatment

There is currently no cure for narcolepsy but medications are available to treat the symptoms of the disorder. There are no specific treatments for children with narcolepsy, however the medications used to manage narcolepsy in adults have also been shown to be effective in children. Children diagnosed with narcolepsy are normally recommended a treatment plan that combines pharmacological therapy and non-pharmacological interventions. This condition requires lifelong treatment (Thorpy & Hiller, 2017).

1.11.1 Pharmacological treatments

Medications for narcolepsy are traditionally divided into those that treat EDS and those that improve cataplexy.

1.11.1.1 Treatments for excessive daytime sleepiness

The aim of treating EDS is to restore a normal or sufficient level of alertness and function (Lecendreux, 2014). There are various treatment options for EDS including:

- Central nervous system stimulants (e.g. Methylphenidate, Dextroamphetamine)
- Wake promoting agents (e.g. Modafinil and Armodafinil)
- Nocturnal sleep promoting agent-Sodium oxybate (also treats cataplexy)

Side effects for these medications can include decreased appetite, headaches, dry mouth, weight loss and nausea (British Medical Association, 2009).

Sodium oxybate is the only drug available for use in narcolepsy that has been shown to be effective at simultaneously treating sleepiness in the day, cataplexy and fragmented nocturnal sleep in adults. In 2016 NHS England's specialised services announced that they will routinely commission sodium oxybate for symptom control in post-pubertal children with narcolepsy with cataplexy (NHS England, 2016). In adults with narcolepsy sodium oxybate has been shown to increase slow wave sleep (SWS) and subsequently improve daytime symptoms (NHS England, 2016). However, this medication is linked to frequent negative side effects such nausea, dizziness, headache and bed wetting (Lecendreux, 2014)

1.11.1.2 Treatments for cataplexy

Cataplexy is mainly treated with antidepressant medication which suppress REM sleep.

- Tricyclic antidepressants (e.g. Clomipramine)
- Selective serotonin reuptake inhibitors (e.g. Fluoxetine)
- Serotonin and norepinephrine reuptake inhibitors (e.g. Venlafaxine)

1.11.2 Non-pharmacological treatments

Children with narcolepsy and their families are advised about good sleep hygiene (routines) and the importance of keeping regular sleep wake patterns. They are also often advised to exercise during the day with the aim of promoting wakefulness,

reducing the risk of obesity and improving the quality of their sleep at night. Scheduled brief naps are also recommended, however children can be resistant to having them as they can interrupt their school activities or their free time. Families are educated about the triggers of cataplexy and the nature of the episodes so that the families can learn to support the child during a cataplexy attack and help to eliminate potential triggers where ever possible.

1.12 Comorbidities

Narcolepsy can be associated with a number of other comorbid medical problems (Maski & Heroux, 2016), including comorbid sleep disorders. Unfortunately this is an area that has received little research attention to date (Peraita-Adrados & Martínez-Orozco, 2016). Due to the broad spectrum of symptoms of narcolepsy in childhood, comorbid sleep disorders may be undetected or misdiagnosed. Frequent sleep disorder comorbidities reported in narcolepsy include sleep-related breathing disorders, nightmares and lucid dreaming, sleep walking, REM sleep behaviour disorder, restless legs syndrome and periodic leg movements (Peraita-Adrados & Martínez-Orozco, 2016). Narcolepsy in both children and adults is associated with obesity (Panossian & Avidan, 2016). An increased body mass index (BMI) is frequently associated with upper airway obstruction, increasing the likelihood that individuals with narcolepsy could have comorbid obstructive sleep apnoea-hypopnea syndrome (OSAHS) (Peraita-Adrados & Martínez-Orozco, 2016). The impact of these comorbid conditions can be significant and once they are identified they must be treated alongside the symptoms of narcolepsy to enable the best possible outcomes for the individual.

1.13 Mortality

There is very limited literature available on mortality in narcolepsy. Ohayon, Black, Lai, Eller, Guinta, and Bhattacharyya (2014) conducted a retrospective database evaluation (using a database representative of the general United States (US) population) to characterise the mortality rate in narcolepsy. The authors found a statistically significant 1.5 fold increase in all-cause mortality relative to those without narcolepsy for each of the three consecutive study years studied (Ohayon et al., 2014). The cause of the increased mortality is currently unknown, however the

authors speculate that it may be due to comorbid medical illnesses such as those outlined in section 1.12, rather than narcolepsy having an independent effect on the cause of death. Further research is needed to develop a better understanding of the potential causes of increased mortality in individuals with narcolepsy to enable better care and introduce preventative measures in these patients (Ohayon et al., 2014).

1.14 Summary

Narcolepsy is a chronic disabling condition that requires lifelong treatment. The condition has recently been brought to the attention of the media following an increase in the number of children diagnosed with the condition after receiving the Pandemrix vaccination in 2009/2010. It is important to consider the effect narcolepsy may have on school-age children who are in a stage of their life that is critical to their physical, emotional and social development and their academic attainment. A systematic review of the previous literature which has investigated cognitive function and psychosocial well-being in school-age children with narcolepsy is presented in Chapter 2.

Chapter 2 A systematic review of cognitive function and psychosocial well-being in school-age children with narcolepsy

2.1 Introduction

A prolonged insufficiency or disturbance of sleep can have profound negative effects on health, cognitive function and psychosocial well-being (see Chapter 1 section 1.8). It is therefore reasonable to suppose that children with narcolepsy who consistently experience disturbed night time sleep because of their condition (see section 1.9.3) may have some degree of impairment in their cognitive function and may have poorer psychosocial well-being compared to children without narcolepsy.

Given the recent increase in the number of children and adolescents diagnosed with narcolepsy (Thebault et al., 2013), it is timely to systematically review, critically appraise and summarise the current quantitative and qualitative research that has investigated the consequences of this serious disorder in childhood. This Chapter provides a systematic review of the literature related to cognitive function and psychosocial well-being in school-age children with narcolepsy. The review aims to update understanding of how cognitive function and psychosocial well-being in school-age children with narcolepsy compares with that of school-age children without narcolepsy and to assess what study designs and methods have been used to investigate this. The review also aims to assess the quality of the included studies and to provide recommendations for future research by highlighting gaps in the current evidence base.

2.2 Methods

A systematic review was conducted to assess whether cognitive function and psychosocial well-being is impaired in school-age children with narcolepsy. This review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 checklist and is registered in PROSPERO. The registration number is CRD42015018949 (Blackwell, Alammar, Weighall, Kellar, & Nash, 2015).

2.2.1 Literature search

Electronic databases were searched on 28th August 2015. The databases searched included; The Cochrane Library, EMBASE, Ovid MEDLINE and PsycINFO (see Table 2.1). Records were downloaded and added to EndNote bibliography software. The records were de-duplicated.

The search was structured to combine the following concepts:

(Narcolepsy OR Cataplexy) AND (Children OR Adolescents) AND Cognition OR Psychosocial Well-Being.

Table 2.1 Databases searched

Database	Interface	Date searched
MEDLINE	Ovid MEDLINE(R), 1996 to August week 3 2015	28th August 2015
Embase	OvidSP, 1996 to 2015 week 34	28th August 2015
PsycINFO	OvidSP, 2002 to August week 4 2015	28th August 2015
The Cochrane Library	Cochrane Database of Systematic Reviews, Issue 9 of 12, September 2015	28th August 2015

2.2.2 Inclusion criteria

For this review, one reviewer (JB) screened titles and abstracts. Another reviewer (HA) independently screened 5% of these articles in order to establish agreement about the inclusion and exclusion of studies. The website random.org was used to randomly select 5% of the articles and the inter-rater agreement was 98%. Any disagreements during this process were resolved by discussion and a consensus decision was reached.

Quantitative and qualitative research studies primarily concerned with narcolepsy (and cataplexy) in school-aged children (5-18 years old) and cognitive function or

psychosocial well-being were eligible for inclusion in the review. Research studies written in English language and published in peer-reviewed journals between 2005 and 2015 were included in the review. This inclusion criteria was selected so that only the most current, relevant and high quality research was included within this review.

Full papers that were identified as potentially relevant were retrieved and screened in the same way as previously described based on the inclusion criteria and authors were contacted to clarify any missing information. Inter-rater agreement was 100%.

2.2.3 Data extraction

The Cochrane data extraction form was modified for the purposes of this review. Data were extracted into the standardized form by one researcher (JB) and authors were contacted when insufficient information was provided. 50% of these articles were then double data extracted by another researcher (HA). Any disagreements were resolved by discussion and a consensus decision was reached.

2.2.4 Quality assessment

Individual study quality was assessed with the ‘quality assessment tool for reviewing studies with diverse design’ (QATSDD) (Sirriyeh, Lawton, Gardner, & Armitage, 2012), a 16-item, validated quality assessment tool applicable to research with heterogeneous study designs (qualitative, quantitative and mixed methods). This tool was particularly suitable for assessing the quality of the papers included in this review as it encompasses an evaluation of both quantitative and qualitative aspects of research. Two reviewers (JB and HA) independently awarded each research paper a quality score on a 4-point scale from 0 to 3 for each of the QATSDD criteria (0 = the criterion is totally undescribed, 1 = described to some extent, 2 = moderately described and 3 = described in full). An example criterion from the QATSDD is “description of procedure for data collection”. As none of the studies included in this review employed mixed methods, only 14 out of the possible 16 quality assessment criteria were evaluated for each paper (as the remaining two criteria only addressed mixed-method research). For each paper, the sum of the 14 quality assessment scores indicated the overall quality of the paper (expressed as a percentage of the maximum possible score of 42). Additionally, an overall quality score was assigned for all studies using the same design (e.g. quantitative or qualitative studies) in order to assess the full body of evidence. To do this, an

average of the quality scores was calculated for each group (quantitative and qualitative papers) and was expressed as a percentage of maximum quality score. It was therefore possible to compare the qualities of the quantitative and qualitative studies included in the review. Papers were not excluded based on quality due to the very limited number of studies eligible for inclusion in this review.

Table 2.2 displays the quality assessment scores (QAS) awarded for each paper next to each study reference. There was substantial inter-rater agreement (89.3%) between the two independent reviewers (JB and HA). Discussion following the independent scoring of papers resolved the remaining differences in agreement. Overall study quality for the seven quantitative studies included in the review was rated as 72.4% and the study quality of the one remaining qualitative study was rated as 43.0%, suggesting that the quantitative work was of a higher standard.

The quantitative papers ranged in quality ratings from 61.9 % to 71 % with the highest quality papers scoring particularly highly in criteria relating to: the aims and objectives of the study, description of procedure for data collection, the rationale for the choice of data collection tools and detailed recruitment data. The lowest rated quantitative papers scored especially low on the following criteria: statistical assessment of reliability and validity of measurement tools, explicit theoretical framework, and evidence of user involvement in design. The qualitative paper was of relatively poor quality and scored particularly low in the following areas: clear description of research setting, detailed recruitment data and assessment of reliability of analytic process. The quality assessment revealed that the quantitative research could be improved by future researchers using reliable and valid measurement tools, larger more representative samples and including a matched control group in the design. More well-designed qualitative research is required with this population in order to extend the findings reported in the one included qualitative paper.

2.3 Results

2.3.1 Study selection

Following a systematic search, 710 articles were found from the electronic databases and an additional 3 articles were found from other sources. After exporting the articles to EndNote, 168 duplicates were removed. 545 articles were screened for

relevance and 488 records were excluded after reading the title and abstract. 57 publications were retrieved for more detailed full text screening. 49 studies were excluded at full text screening. Eight studies met the inclusion criteria for the present review (See Figure 2.1).

2.3.2 Summary of papers included within the review

Table 2.2 was produced to summarise the main characteristics of each of the eight studies eligible for inclusion in this review. The table includes all the information provided by each study in regard to: the number of participants, their sex, age, type of narcolepsy, how their diagnosis was confirmed, whether or not a control group was included, the cognitive and psychosocial measures used and the dependent variables. The comments provided in the table consider the individual strengths and weaknesses of each study in terms of design, analysis and conclusions drawn.

Table 2.2 Summary of papers included within the review

	Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
1	Avis, Gamble, and Schwebel (2014)	66.7 %	33 children with EDS (18 narcolepsy, 15 IHS). 16 M, 17 F, mean age 12.93 years, range 8.03-16.84 years. Children met (ICSD-2) criteria for a hypersomnia of central origin (narcolepsy with or without cataplexy, or IHS). The diagnosis was made within three years of study date. 33 control children, 16 M, 17 F, mean age 12.74 years, range 8.83-17.81 years. Matched by age, sex, race and average income in the ZIP code of residence.	USA	Cross sectional-design Case-control study	Simulated injury Attention to traffic Decision making ESS-modified for children.		Children with EDS were clinically sleepy with a mean ESS score of 12.33.The control sample were adequately alert with a mean ESS score of 6.94. Children with EDS experienced collisions and near-collisions on over 10% of crossings in the virtual street environment and at a rate twice that of matched controls.	*Strengths* Children came off medication three days before the study-performance unaffected by medication. Matched controls *Weaknesses* Children with narcolepsy and children with IHS were grouped together. No standardized measure of I.Q.

	Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
			Diagnosis and recruitment occurred at the Paediatric Sleep Disorders Center at Children's of Alabama.						Limitations to the virtual reality environment- bidirectional midblock crossing. Not a perfect replica of a real life situation. Did not measure lower level underlying cognitive processes such as reaction time or visual perceptual skills. Small sample size
2	Dorris, Zuberi, Scott, Moffat, and McArthur (2008)	64.3%	12 children with narcolepsy (11 children reported to have cataplexy), six M, six F, mean age 10.6 years (SD= 2.9), range 7 years to 16 years	UK	Cross-sectional	I.Q: verbal, performance and full scale Wechsler intelligence scale for children-III UK (WISC-III ^{UK})	Clinical psychologist assessed the participants using a clinical interview	11 children obtained an I.Q in the average range on the WISC-III^{UK} (median =10, SD= 10.24, range= 84-116).	*Strengths* Used well validated and reliable measures which have normative data and clinically significant cut off points

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
		All were diagnosed and assessed within a multidisciplinary regional paediatric neuroscience unit on the basis of clinical history. No control group				The parent version of the Achenbach child behaviour checklist (CBCL)	A significant and clinically significant difference was found between verbal (median=98, range= 88-122) and performance (median= 104, range= 77-123) scales in 42% of the children, compared to WISC-III^{UK} normative prevalence rates of 24%.	Tests were alternated in their presentation Children tested during clinical appointment where child was assumed to be at their optimal level of arousal and wakefulness *Weaknesses* No control group Lack of specific measures of attention, learning or neuropsychological measures of executive function

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
							These discrepant profiles did not reflect a consistent pattern of strength and weakness 10/12 children scored in the clinically significant range (64 and above) on the total score index of the CBCL (mean= 64.83, SD= 8.39, range= 49-80).	Cognitive test measurement may be confounded by medication. Seven children were treated with Modafinil (300g) before assessment, five children were untreated. No comparison made between treated and untreated children due to small sample size No empirical assessment of vigilance or wakefulness was employed. Arousal fluctuations may contribute to the uneven cognitive profiles

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
							9/12 children scored in the clinically significant range on the Internalising Index of the CBCL (mean=62.25, SD =11.23, range=32-77). The majority of children presented with difficulties in discussing and describing distressing physical and psychological symptoms with parents and others.	No consideration of SES Used parental accounts of psychosocial problems Small sample size

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
							Over 50% of the children were rated by their parents as having significant difficulties in areas such as social integration and academic attainment.	
3	Inocente et al. (2014)	62%	88 children with narcolepsy (cataplexy was present in 80.7% of the children), 44 M, 44 F, mean age 11. 9 years, range 5 years to 17.5 years	France	Cross-sectional		Children's depression inventory (CDI) Adapted Epworth sleepiness score (AESS)	High levels of depressive symptoms affected 25% of the children There were more females with abnormal CDI scores than boys (*P*=.04)	*Strengths* Relatively large sample Used well validated and reliable measures with normative data available and clinically significant cut off points

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
		All children were diagnosed with primary narcolepsy after a complete clinical evaluation using ICSD-2 and sleep-and wake-monitoring No control group				Paediatric daytime sleepiness scale (PDSS) Cataplexy severity rating score Insomnia severity index (ISI) Conners parent rating scale-revised (CPRS-R) Chalders fatigue scale (CFS)	Depressive children were older at diagnosis than non-depressive children (*P*=.04) The period between disease onset and diagnosis tended to be longer in patients with abnormal CDI scores (*P*=.051) Depressive children had higher fatigue, hyperactivity and insomnia scores but did not have more frequent school difficulties.	*Weaknesses* No consideration of SES

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
4	Inocente. et al. (2014)	71 %	117 children with primary narcolepsy (81% of children reported to have cataplexy), 65 M, 52 F), mean age 11.6 years, range five years to 17 years	France	Cross-sectional	Children's depression inventory (CDI) Conners parent rating scale-revised (CPRS-R) Health-related quality of life (HRQL) questionnaire: -Vécu et santé perçue de l'Adolescent (11-18 years) -Vécu et santé perçur par l'Enfant (8-10 years)	Narcolepsy impacts HRQL in terms of vitality and physical well-being. Children with narcolepsy were more obese than control children (60% vs 1.4 %, P < 0.001).	*Strengths* Control group Relatively large sample Used well validated and reliable measures with normative data available and clinically significant cut off points *Weaknesses* No consideration of SES

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
		All children were diagnosed with primary narcolepsy after a complete clinical evaluation using ICSD-2 and sleep- and wake-monitoring 69 control children (29 M, 40 F), mean age 13.5 years, range seven years to 17 years.				Adapted Epworth sleepiness score (AESS) Paediatric daytime sleepiness scale (PDSS) Chalders fatigue scale Cataplexy severity rating score Insomnia severity index Parent reports of school difficulties, absenteeism and grade repetition Height, weight and body mass index (BMI)	25% of children with narcolepsy has clinically significant depressive feelings on the CDI (CDI≥16) compared to 15.6 % of controls 7% of children with narcolepsy had a high level of Attention Deficit/Hyper activity Disorder symptoms (CPRS-R>75)	

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
							41% of children with narcolepsy reported school difficulties compared to 7.5% of controls (*P*=0.002) (reported by parents) 28 % of children with narcolepsy did not pass a school year and repeated it prior to narcolepsy diagnosis compared to 7.5% of controls (*P*< 0.001)	

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
							30 % of children with narcolepsy compared with 8.9% of controls had high levels of absenteeism (*P*=0.002) Compared with control children, children with narcolepsy(*P*= 0.0001) and adolescents (*P*=0.008) had lower HRQL	
5	Karjalainen, Nyrhilä, Määttä, and Uusiautti (2014)	43%	Six children with narcolepsy (2 M, 4 F), mean age 11 years, range 10 years-13 years.	Finland	Cross-sectional			*Strengths* Produced qualitative and quantitative data

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
		No control group				Questionnaire including structured and open-ended questions aimed for parents children and teachers (data analysed with content analysis) The structured questions followed standardized questionnaires such as the strength and difficulties questionnaire (SDQ) but the open ended questions were composed specifically for this research	Narcolepsy affected children's school work and need for support. There are no established forms of support but solutions vary. Five out of six children had behavioural, emotional and social problems	Detailed evaluation of six children and highlights that concern over well-being of children with narcolepsy is justified *Weaknesses* Small sample Reliance on questionnaires and interview – no objective measures

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
							Symptoms of narcolepsy affect many areas of the children's lives and decrease the general well-being of their families, too. Teachers reported that five children had general support and one child was receiving intensive support	

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
							EDS and fatigue attacks are reported to have affected concentration and attention Illness is reported to have affected the children's overall ability to function and learning processes considerably Skills that were learned previously were lost at the beginning of the illness	

	Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
6	Lecendreux et al. (2015)	64.3%	108 children with narcolepsy, 86 of these children had cataplexy, 22 did not have cataplexy. The median age of children who had narcolepsy with cataplexy was 14 years, age range 6.6-17.8 years. 48 M, 38 F. The median age of children who had narcolepsy without cataplexy was 10.3 years, range 5.9-17.4 years. 10 M, 12 F. 67 healthy controls with a median age of 14.8 years, range 7 years-17.9 years.	France	Cross-sectional	Paediatric daytime sleepiness scale (PDSS) Insomnia severity index (ISI) Chadler's fatigue Scale ADHD-RS Need to repeat a grade in school	Structured interview Physical examination Child depression inventory (CDI) Heath-related quality of life	Paediatric patients with narcolepsy had high levels of treatment-resistant ADHD symptoms. Individuals with narcolepsy were at an increased risk for ADHD symptoms compared to controls (2 fold). They were also at greater risk for depressive symptoms and were reported to have a poorer quality of life	*Strengths* Relatively large sample Used well validated and reliable measures with normative data available and clinically significant cut off points Control group *Weaknesses* ADHD symptoms were not measured before the onset of narcolepsy and after the initiation of psychostimulants therefore the causal relationship between narcolepsy and ADHD cannot be established.

	Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
									No clinical assessment or formal diagnosis of ADHD was undertaken.
7	Posar, Pizza, Parmeggiani, and Plazzi (2014)	61.9%	13 children with narcolepsy with cataplexy (eight M, five F), mean age 10.3 years, range 6.8 years to 13.6 years All children underwent a series of investigations and were included if they met the criteria for narcolepsy with cataplexy according to the ICSD-2. No control group	Italy	Cross-sectional	Academic performance (reading, writing, mathematics) assessed according to familial and personal interview Full I.Q, Verbal I.Q, Performance I.Q: Wechsler intelligence scale for children-revised (WISC-R) Auditory verbal working memory: "Digit span" verbal subtest of WISC-R.	SDQ for parents	All children had normal full I.Q (mean =104, range 87-115) verbal I.Q (mean=105, range 91-117) and performance I.Q (mean=104, range 85-118)	*Strengths* The individual performing the neuropsychological testing was informed so that he could realize even minimal signs of sleepiness in the patient, in order to stop the evaluation if necessary *Weaknesses* Lack of physiological monitoring of sleepiness while testing

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
					Non-verbal reasoning: Raven's progressive matrices (1974) Fepsy (a computerized test battery, Alphers, 1987) tasks: Alertness (auditory and visual reaction times) Attention (binary choice task) Visual verbal and nonverbal working memory (recognition of words and figures, respectively) Abstraction and problem solving (classification task: total and		Comparisons between verbal I.Q and performance I.Q showed that verbal I.Q was similar to performance I.Q in eight cases, whereas it was higher than performance I.Q in three cases and lower than performance in two cases according the WISC-R normative values.	Academic performance was assessed via familial and personal interview rather than standardized measurement Lack of follow up evaluation Not all participants were submitted to all Fepsy tasks because of a lack of available normative values for all the ages. Lack of control group

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
					preservative errors)			
							Nonverbal reasoning was adequate in all children according to Raven's progressive Matrices 7 out of 13 subjects reported academic failure An impairment of at least one of the assessed cognitive aspects was present in nine of 13 cases and in five of seven	

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
							children with academic failure	
							Attention was normal in all of the 11 children tested on the binary choice task Childhood narcolepsy with cataplexy is a risk factor for the development of heterogeneous cognitive problems. No consistent cognitive profile was found in the subgroup of	

	Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
								children with academic failure	
8	Stores, Montgomery, and Wiggs (2006)	61.9%	42 children with narcolepsy (24 male, 18 female), mean age 12.5 years, age range 7.3 years to 17.9 years The child's clinician was contacted and asked to provide as much diagnostic detail as possible about the child's condition. This information was supplemented by the Ullanlinna narcolepsy scale as a check on the original diagnosis	UK Recruitment in: Europe U.S Australia	Cross-sectional	International cross-sectional questionnaire asking teachers to provide information about child's absent days from school in the previous term and their opinion on the child in relation to: -problems with learning -not reaching academic potential	Behaviour: (SDQ) Quality of life: child health questionnaire Mood: child depression inventory (CDI) Ullanlinna narcolepsy scale	Children with narcolepsy and those with EDS reported significantly higher rates of behavioural problems and depression than controls. Their quality of life was significantly poorer and they had more educational problems (as reported by teachers).	*Strengths* Relatively large sample size Precise assessment of the symptoms of children previously given the diagnosis of narcolepsy International questionnaire *Weaknesses* The controls are not matched on age and gender Reliant on teachers responses rather than on standardized

Reference	QAS (%)	Sample	Country	Design	Cognitive measures	Psychosocial measures	Results	Comments
		18 children with excessive daytime sleepiness (EDS) of uncertain origin without definite additional features of narcolepsy (14 male, 4 female), mean age 14.3 years, range 5.1 years to 18.8 years 23 control children (12 male, 11 female), mean age 11.30 years, age range 6.0 years-16.8 years			-not working hard enough -being difficult to teach		The similar profiles of difficulties in the narcolepsy and the EDS groups suggest that excessive sleepiness may be the underlying cause.	assessment of the childrens' abilities

Notes. Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder, ADHD-RS: Attention Deficit Hyperactivity Disorder-Rating Scale, AESS: Adapted Epworth Sleepiness Scale, BMI: Body Mass Index, CBCL: Achenbach Child Behaviour Checklist, CDI: Child Depression Inventory, CFS: Chalder's Fatigue Scale, CPRS-R: Conner's Parent Rating Scale-Revised, EDS: Excessive Daytime Sleepiness, ESS: Epworth Sleepiness Scale, F: Female, HRQL: Health-related quality of life, ICSD-2: International Classification of Sleep Disorders-Second Edition, IHS: Idiopathic Hypersomnia, ISI: Insomnia Severity Index, M:Male, PDSS: Paediatric Daytime Sleepiness Scale, QAS: Quality assessment score, SES: Socioeconomic status, SDQ: Strengths and Difficulties Questionnaire, WISC-III UK: Wechsler Intelligence Scale for Children-Third Edition, WISC-R: The Wechsler Intelligence Scale for Children-Revised.

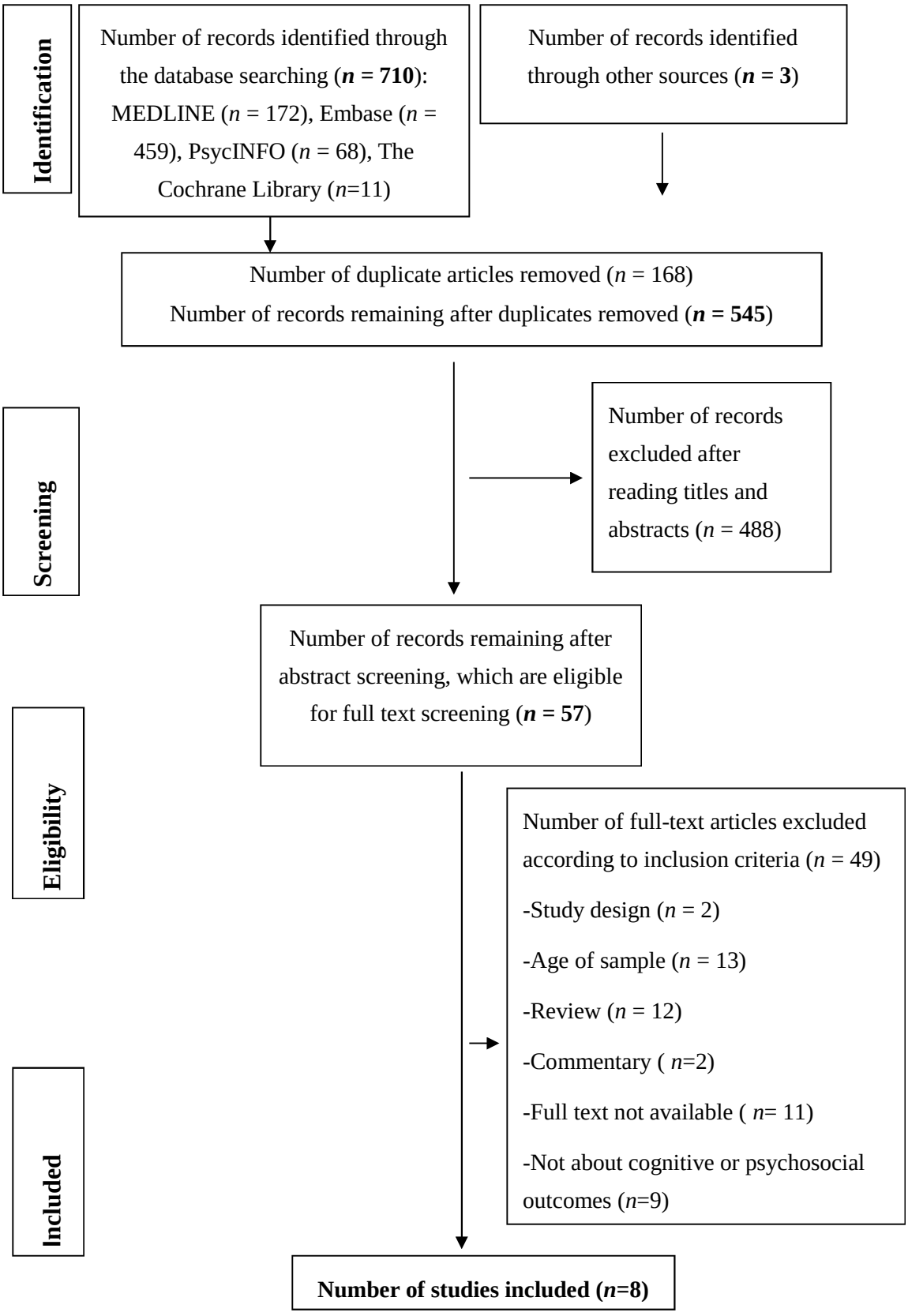

Figure 2.1 Flow diagram for identification of relevant studies (from January 2005 to August 2015).

2.3.3 Sampling

Seven of the studies included in this review were conducted in Europe, with only one of these studies recruiting participants from the USA and Australia (Stores, Montgomery, & Wiggs, 2006). The remaining study was conducted solely in the USA (Avis et al., 2014). The age range of the children varied slightly between studies (range 5-18 years) (see Table 2.2) and, with the exception of one study that did not report full diagnosis information (Karjalainen et al., 2014), the majority of participants had narcolepsy with cataplexy. The studies included both treated and untreated children with narcolepsy. The type of medication and the time since starting treatment varied between participants. Two studies reported that none of the children were taking medication at the time of the study (Avis et al., 2014; Posar et al., 2014), five studies reported that some of the participating children were taking medication at the time of the study (Dorris et al., 2008; Inocente et al., 2014; Inocente. et al., 2014; Lecendreux et al., 2015; Stores et al., 2006) and one study did not report whether or not the children were medicated (Karjalainen et al., 2014). Sample sizes varied dramatically between studies, with the smallest sample being six participants (Karjalainen et al., 2014) and the largest being 117 participants (Inocente et al., 2014; Inocente. et al., 2014). All studies included approximately equal numbers of male and female participants.

2.3.4 Design

A cross sectional-design was employed by all the studies included in this review (seven quantitative studies and one qualitative study). Of the seven quantitative studies, only four included a control group and/or a comparison group (Avis et al., 2014; Inocente. et al., 2014; Lecendreux et al., 2015; Stores et al., 2006). When evaluating whether or not cognitive function and psychosocial well-being in school-age children are affected by having narcolepsy, the absence of a control group is a key limitation. This is because it is not possible to compare the cognitive and psychosocial profiles of children with narcolepsy to that of healthy matched controls. In the absence of any better quality empirical research, details of the four quantitative studies that lack a control/comparison group are included in this review as they have produced interesting and relevant findings.

Of the eight studies, two studies were primarily concerned with cognitive outcomes (Avis et al., 2014; Posar et al., 2014), three studies were primarily concerned with psychosocial outcomes (Inocente et al., 2014; Inocente. et al., 2014; Karjalainen et al., 2014) and the remaining three studies reported on both cognitive and psychosocial outcomes in school-age children with narcolepsy (Dorris et al., 2008; Lecendreux et al., 2015; Stores et al., 2006).

2.4 Cognitive outcomes

The five studies that examined cognitive function in school age-children with narcolepsy used a variety of different measures to assess participants' functioning. This makes it difficult to draw conclusions about the overall cognitive profile of children with narcolepsy. Two studies examined cognitive function (Dorris et al., 2008; Posar et al., 2014) using a standardized measure of intelligence (The Wechsler Intelligence Scale for Children) alongside one or more additional measures of working memory, non-verbal reasoning, attention, alertness or problem solving. Overall, the results of these studies showed that the children with narcolepsy had an I.Q within the average range (with the exception of one child (Posar et al., 2014)), however clinically significant discrepancies between verbal I.Q and performance I.Q were reported in both studies (Dorris et al., 2008; Posar et al., 2014). Posar et al. (2014) found that verbal I.Q was similar to performance I.Q in eight out of their 13 cases. However, in three cases verbal I.Q was higher than performance I.Q and in two cases verbal I.Q was lower than performance I.Q. The authors also reported that each child had impairments in at least one of the other cognitive domains assessed (verbal working memory, non-verbal working memory, alertness, problem solving). Similarly, (Dorris et al., 2008) found a significant difference between verbal and performance I.Q in five out of their 12 participants. For three of the participants verbal I.Q was higher than performance I.Q, whilst for the other two participants performance I.Q was higher than verbal I.Q. These results highlight that although participants obtain an I.Q within the average range, uneven cognitive profiles are frequently observed across studies.

Academic performance (reading, writing and maths) was also assessed according to teacher and family reports in two studies (Posar et al., 2014; Stores et al., 2006). It was found that seven out of 13 children with narcolepsy had failed academically

(Posar et al., 2014) and that teachers rated children with narcolepsy as having significantly more educational difficulties than children without narcolepsy (problems with learning, not reaching academic potential, not working hard enough and being difficult to teach) (Stores et al., 2006).

The additional two studies that assessed cognitive function in school-age children with narcolepsy (Avis et al., 2014; Lecendreux et al., 2015) did not include a standardized measure of I.Q. Avis et al. (2014) assessed decision making and attention in unmedicated children with narcolepsy using a virtual reality pedestrian environment. Children were immersed in a virtual environment, watching vehicles pass bi-directionally. Children were asked to decide when it was safe to cross a virtual road by stepping off a simulated curb and walking along a pressure plate without getting hit. Attention to traffic was monitored using head tracking equipment, decision making was assessed by the average latency to start crossing the road and the sum of the car hits and close calls assessed pedestrian injury risk. Avis et al. (2014) found that children with narcolepsy and children with idiopathic hypersomnia were twice as likely to be struck by a virtual vehicle in the virtual pedestrian environment than healthy controls. They found that although attention to traffic was not impaired, decision making was significantly impaired. However, Lecendreux et al. (2015) found that inattention and impulsivity (as measured using the Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS)) were significantly higher in children with narcolepsy than healthy controls. Additionally, although not statistically significant, Lecendreux et al. (2015) found that the children with clinically significant ADHD symptoms were more likely to have needed to repeat a school year. It is important to note that the ADHD-RS is completed by parents and therefore ADHD symptoms were scored by parents alone. No clinical assessment or formal diagnosis of ADHD was undertaken by a clinician and therefore the results may have been affected by response bias.

The discrepant profiles of impairment described above do not reflect a consistent pattern and therefore a ‘narcolepsy-specific’ cognitive profile has not been established. Across the studies, the most commonly reported problems by the children were persistent sleepiness, lack of alertness and lack of concentration which are likely to impact on cognitive function and may be the underlying cause of the high levels of academic failure reported in the children with narcolepsy included in these studies. The consequences of having impaired areas of cognitive function (e.g.

decision making and attention) in children with narcolepsy can be serious, as demonstrated by performance in the virtual reality environment. The reviewed research suggests that narcolepsy in school-age children is a risk factor for the development of heterogeneous cognitive problems that can impact on academic attainment, daytime functioning and safety.

2.5 Psychosocial outcomes

Six studies examined psychosocial well-being in school age children with narcolepsy (Dorris et al., 2008; Inocente et al., 2014; Inocente. et al., 2014; Karjalainen et al., 2014; Lecendreux et al., 2015; Stores et al., 2006). One study used qualitative methods (semi-structured interviews only) (Karjalainen et al., 2014), and the remaining studies employed quantitative methodology (standardized assessment tools and psychological assessment). Within the studies using quantitative methodology, the range of standardized assessments used to assess psychosocial well-being varied (Achenbach Child Behaviour Checklist (CBCL), Child Depression Inventory (CDI), health-related quality of life questionnaires (HRQL), Conner's Parent Rating Scale-Revised (CPRS-R), Strengths and Difficulties Questionnaire (SDQ)) making it difficult to directly compare results across studies.

Karjalainen et al. (2014) published a qualitative study that collected information about how children's lives have changed after receiving the diagnosis of narcolepsy. Content analysis revealed that all parents reported that their child displayed changes in behaviour and mood around the time they developed narcolepsy and reported that these symptoms were the most difficult to manage. One parent claimed that their child's ability to function is "limited" and that their child is "tinged with aggression and disappointment several times a day" (Parent no.4) (Karjalainen et al., 2014). Five out of the six children in the sample had behavioural, emotional and social problems.

Three of the quantitative studies concerned with psychosocial outcomes included a control group or groups (Inocente. et al., 2014; Lecendreux et al., 2015; Stores et al., 2006). Stores et al. (2006) included 42 children with narcolepsy, 18 children with excessive daytime sleepiness of uncertain origin and 23 healthy control children. Inocente. et al. (2014) included 117 children with narcolepsy and 69 healthy control

children. Lecendreux et al. (2015) included 108 children with narcolepsy and 67 healthy controls. All three studies included the Child Depression Inventory and a health related quality of life questionnaire suitable for children. The studies showed that compared to control children, children with narcolepsy had significantly poorer quality of life and significantly higher rates of depression. Stores et al. (2006) found that children with narcolepsy and EDS had similar profiles of difficulties (significantly higher rates of behavioural problems and depression, which were above the population norms), suggesting that EDS may be the underlying cause of psychosocial impairment.

Similarly, Dorris et al. (2008) reported that nine out of twelve children with narcolepsy scored highly on internalizing behaviour measures (withdrawal, depressive behaviour and anxiety) of the Achenbach Child Behaviour Checklist (CBCL) and that ten out of twelve children scored in the clinically significant range on the total score index of the child behaviour. Together these findings support the hypothesis that narcolepsy puts children at significant psychological risk.

2.6 Discussion

A systematic review of cognitive function and psychosocial-well-being in school aged children with narcolepsy was conducted. Seven quantitative studies and one qualitative study published between 2005-2015 were eligible for inclusion in this review.

2.6.1 Summary of findings

Collectively the results of the qualitative and quantitative research reviewed above provide evidence to suggest that children who develop narcolepsy are at significant cognitive and psychological risk. The findings suggest that narcolepsy puts children and adolescents at particular risk of cognitive impairment in at least one domain (e.g. decision making, verbal I.Q, performance I.Q). A consistent pattern of impairment has not been identified across the reviewed studies. Children with narcolepsy are also at risk of emotional problems including depression, anxiety and low self-esteem which may consequently lead to poorer quality of life. Despite the limited research into the cognitive and psychological consequences of childhood narcolepsy, the current findings have provided insight into the daily struggles experienced by children with narcolepsy and the consequences of this chronic

disorder. These findings are particularly useful for parents, doctors and teachers so that they can work together to carefully monitor school-age children with narcolepsy and effectively manage any impairments present.

2.6.2 Limitations of existing evidence

The current studies suffer limitations that need to be considered when interpreting the results. Of the eight studies reviewed, only four studies recruited more than 40 children and adolescents with narcolepsy. Small sample sizes limit the generalisability of the results to the wider population of young individuals with narcolepsy. The use of different assessments and standardized tests in the existing studies makes comparison and the determination of a narcoleptic profile difficult. Ideally, agreement needs to be reached about which standardized assessments are appropriate for adequately exploring the cognitive and psychological consequences of developing narcolepsy in childhood and this would allow for direct comparisons of results between studies. Academic attainment was investigated by asking parents or teachers to provide a description of the childrens' academic strengths and weaknesses and their general performance at school (e.g. the need to repeat a school year). The use of a standardized test of academic attainment (for example the Wechsler Individual Achievement Test-Second Edition (WIAT-II) at the time of the study would have provided a more accurate and reliable assessment of ability and allowed for direct comparison between the participating children and between studies. The reviewed studies lacked objective and subjective measures of sleep quality and duration (polysomnography, actigraphy or sleep diaries), making it difficult to assess how the participants' overnight sleep and daytime naps may be affecting cognitive and psychosocial outcomes. The reviewed studies also did not include any objective or subjective measures of alertness and sleepiness during testing so it is not clear whether participants were performing at an optimal level during the assessments. Some of the studies included both treated and untreated children with narcolepsy, however, due to the small sample sizes it was not possible to compare performance between these groups. It is therefore unclear how medication may have affected individual profiles. This information would be useful for doctors to know when prescribing medication to children with narcolepsy so that they are aware of any positive or negative side effects on cognitive function and psychosocial well-being. If medication was shown to have any negative effects on

cognitive function, teachers should be aware that the academic performance of medicated children with narcolepsy may be adversely effected.

2.6.3 Future research and recommendations

In order to gain further understanding about the cognitive and psychological consequences of childhood narcolepsy, future research must address the following key issues. Ideally, future studies should aim to recruit large, representative samples of children and adolescents with narcolepsy. Controls matched on age, gender, socioeconomic status (SES) and I.Q should be recruited and included in the studies. Childrens' and adolescents' progress should be monitored using standardized assessment tools so that changes in cognitive and psychological difficulties can be measured objectively. Mixed-method research would be useful for investigating this population so that qualitative data (for examples interviews with children and parents) can be used to support quantitative results (objective sleep measurement and standardized cognitive and psychological assessment).

Research should aim to clarify whether any particular symptom or consequence of narcolepsy (for example EDS, disturbed night time sleep, reduced daytime activity) is the root cause of cognitive and psychological difficulties. If support is found for a particular symptom being the cause of cognitive and psychological difficulties in children and adolescents with narcolepsy, treatment and interventions must focus on alleviating this symptom in order to prevent or reduce its consequences.

Longitudinal research is needed to follow up children and adolescents with narcolepsy and provide insights into how cognitive and psychological difficulties change over the lifespan. Longitudinal data is critical to understanding the relationship between the symptoms of narcolepsy and cognitive and psychological outcomes and will help establish a cognitive and psychological profile of children with narcolepsy. Understanding how sleep quality and duration and daytime activity levels affect cognitive and psychosocial outcomes in this population may inform the design of effective interventions to improve daytime functioning.

2.7 Conclusion

The reviewed literature has highlighted that school-age children with narcolepsy are at significant risk of cognitive and psychosocial impairment. These impairments are

hypothesised to impact on academic performance, quality of life, daytime functioning and safety and therefore these children should be carefully monitored by doctors, parents and teachers. This review has highlighted that the current literature is limited by small sample sizes, lack of longitudinal data and lack of standardized measures. Future research should aim to determine the underlying cause of cognitive and psychosocial impairments as this will enable the most effective treatment and interventions to be put in place for these children so that they can achieve their full potential.

The aim of this thesis is to build upon the existing research by addressing some of the key limitations of previous work and employing novel methods to investigate whether any particular clinical symptom of narcolepsy (for example disturbed overnight sleep) or any observed change in behaviour (for example reduced daytime physical activity) is associated with cognitive and psychological difficulties. Chapter 3 outlines the main aims of this thesis.

Chapter 3 The aims and hypotheses of the thesis

3.1 Structure of the thesis

Chapter 1 describes the debilitating symptoms of narcolepsy which include excessive daytime sleepiness, cataplexy and abnormal REM sleep. Chapter 2 has shown that school-age children with narcolepsy are at significant risk of cognitive and psychosocial impairment. The overall aim of this thesis is to clarify whether any significant unresolved symptoms in clinically treated narcolepsy (for example disturbed overnight sleep) or any significant change in behaviour (for example reduced daytime physical activity) are associated with cognitive or psychological difficulties. If evidence of an association between sleep, physical activity, cognitive function and psychosocial well-being is found, this may inform the development of effective interventions designed to alleviate the symptoms and functional impact of paediatric narcolepsy.

Chapter 4 describes the research methodology employed to address the research questions outlined below and Chapter 5 describes the characteristics of the sample recruited for this study.

3.2 The key research questions

The seven key research questions addressed in this thesis and their associated hypotheses are outlined below.

Q1. How does overnight sleep in children with narcolepsy compare with that of gender and age matched healthy controls?

This research question is addressed in Chapter 6. Based on the literature reviewed in Chapter 1 (Peraita-Adrados et al., 2011; Serra et al., 2008; Babiker & Prasad, 2015), it was hypothesised that children with narcolepsy will have significantly poorer sleep efficiency, significantly shorter sleep onset latency and spend significantly more time awake after sleep onset

compared to matched controls. It was also hypothesised that children with narcolepsy will spend significantly more time in sleep stages N1 and N2 and have more arousals per hour than matched controls.

Q2. How does daytime sleep in children with narcolepsy compare with that of gender and age matched healthy controls? What proportion of children with narcolepsy nap during the day? What is the average frequency and length of the naps?

This research question is addressed in Chapter 7. It was hypothesised that the healthy controls will not nap and that the majority of children with narcolepsy will nap because of their excessive daytime sleepiness (Nevsimalova, 2009) and because planned naps are often recommended as part of their treatment plan (Elphick et al., 2017). It was hypothesised that the frequency and the length of naps will vary between children because symptom severity and willingness to nap is known to vary between children.

Q3. How do daytime physical activity levels in children with narcolepsy compare with that of gender and age matched healthy controls?

This research question is addressed in Chapter 7. It was hypothesised that when awake, children with narcolepsy will be significantly less active throughout the day compared to matched controls. This may be associated with their excessive daytime sleepiness. This hypothesis was based on the research discussed in section 1.8.4 in Chapter 1 (Ekstedt Nyberg, Ingre, Ekblom & Marcus, 2013).

Q4. What is the relationship between overnight sleep efficiency, time spent asleep during the day and physical activity in children with narcolepsy and healthy controls?

This research question is addressed in Chapter 7. The first hypothesis was that there will be a negative correlation between sleep efficiency and total sleep time during the day (as sleep efficiency increases, total sleep time

during the day decreases). This hypothesis was based on the research discussed in section 1.8.4 in Chapter 1 (Lam, Mahone, Mason & Scharf, 2011). The second hypothesis was that there will be a positive correlation between sleep efficiency and daytime physical activity (as sleep efficiency increases, daytime physical activity increases). This hypothesis was based on the research discussed in section 1.8.4 in Chapter 1 (Ekstedt Nyberg, Ingre, Ekblom & Marcus, 2013). The third hypothesis was that there will be a negative correlation between the time spent asleep during the day and physical activity (as total sleep time during the day increases, physical activity decreases).

Q5. How does cognitive function in children with narcolepsy compare with that of gender and age matched healthy controls?

This research question is addressed in Chapter 8. Based on the previous literature summarised in Chapter 2, it was hypothesised that children with narcolepsy (even those who are clinically managed and medicated) will have normal full scale I.Q's (within the average range) (Dorris et al., 2008; Posar et al., 2014) but they will have significantly impaired attention and executive functions compared to healthy controls (Avis et al., 2014; Lecendreux et al., 2015).

Q6. How does psychosocial well-being in school-age children with narcolepsy compare with that of gender and aged matched healthy controls?

This research question is addressed in Chapter 9. Based on the previous literature summarised in Chapter 2 (Dorris et al., 2008; Inocente et al., 2014; Inocente. et al., 2014; Karjalainen et al., 2014; Lecendreux et al., 2015; Stores et al., 2006), it was hypothesised that children with narcolepsy will be significantly more likely to report feelings of depression, anxiety and anger than healthy controls. It was also hypothesised that children with narcolepsy will report more disruptive behaviours, lower self-esteem and poorer health-related quality of life than healthy controls.

Q7. Are any observed case-control differences in cognitive function and psychosocial well-being associated with sleep efficiency, total sleep time during the day and physical activity?

Based on the previous literature summarised in Chapter 1 (see section 1.8.2, 1.8.3 and 1.8.4), it was hypothesised that any observed difficulties in cognitive function or psychosocial well-being will be associated with poor sleep efficiency, total sleep time during day (Pilcher & Huffcutt, 1996; Philibert, 2005; Durmer & Dinges, 2005; Lim & Dinges, 2010) and lower levels of physical activity (Coe, Pivarnik, Womack, Reeves, & Malina, 2006; Hillman, Erickson, & Kramer, 2008; Trudeau & Shephard, 2008).

Chapter 4 Research design and methodology

This chapter describes the research design and methodology employed to address the research questions outlined in Chapter 3. Consent was obtained from all parents and the children (where possible) before including the photographs in this Chapter.

4.1 The design of The Paediatric Narcolepsy Project

A gender and age matched case-control study was designed to describe the relationship between sleep, daytime physical activity, cognitive function and psychological well-being in children with narcolepsy. This study was entitled 'The Paediatric Narcolepsy Project' and a study logo was created to represent this research (see Figure 4.1). The study involved recruiting children with and without narcolepsy (and their families) from the United Kingdom (UK) and The Republic of Ireland (ROI). The researcher (JB) visited the children in their homes over two days and the children underwent standardized neuropsychological assessment, a full polysomnography recording and were asked to wear an activity monitor for eight days and eight nights. The procedure is described in section 4.7.

Figure 4.1 The Paediatric Narcolepsy Project Logo (created by Jane Katherine Houghton Designs).

4.2 Ethical approval

Ethical approval was obtained from the Board of Ethics at the School of Psychology prior to the start of the study (reference number: 15-0198, approval date: 03.08.15).

4.3 Funding

A University of Leeds 110 Anniversary Research Scholarship was awarded to cover the research degree fees and living expenses of the researcher. This scholarship also provided a small research budget of £750 per year to support the research costs associated with the study.

The researcher sought additional funding from multiple external sources in order to purchase the equipment required in The Paediatric Narcolepsy Project and to support the travel expenses associated with conducting this research. Funding was awarded from Child Brain Research, The British Psychological Society, Narcolepsy UK, Sufferers of Unique Narcolepsy Disorder (S.O.U.N.D.) Ireland, The Max Hamilton Fund at the University of Leeds, The Psychology Postgraduate Affairs Group (PsyPAG) and The British Sleep Society. The total funding awarded from these sources was £15,282.

In addition, fundraising activities were also organised to raise money for The Paediatric Narcolepsy Project. The events included a music tribute evening, a football tournament, sponsored races and a cake sale (see Figure 4.2). The total funding raised from these activities was £2,559.

Figure 4.2 Fundraising activities organised to raise money for The Paediatric Narcolepsy Project.

4.4 Participant recruitment

The majority of children with narcolepsy and their families who participated were recruited through two charities. The charity Narcolepsy UK assisted with recruitment in the UK and the charity Sufferers of Unique Narcolepsy Disorder (S.O.U.N.D.) assisted with recruitment in the ROI.

The following social media pages were also created to advertise the project, provide updates on the study progress and to share the results. Over 500 individuals currently follow these pages.

 www.facebook.com/ThePaediatricNarcolepsyProject

 www.twitter.com/ThePNarcolepsyP

The families that were not recruited through the charities were recruited either through the social media pages, word of mouth or through the connections of the researcher.

4.4.1 Recruitment in the UK

In October 2014, the researcher presented an overview of the aims of The Paediatric Narcolepsy Project at the Narcolepsy UK conference held in Birmingham. A recruitment poster advertising the study was also displayed at this conference. Attendees were given the opportunity to ask any question about the study and it was made clear that participation in the study was entirely voluntary. Those interested in participating in the study were asked to register their interest with the researcher. Following this conference, Narcolepsy UK uploaded the participant information sheets onto their website and additional recruitment advertisements were posted on the social media pages designed for this project.

The children without narcolepsy (healthy controls) and their families were mainly recruited by asking parents of the children with narcolepsy to pass on the study information sheets to families (with a child of the similar age) who they thought may be willing to participate in the research. The parents asked the families to get in touch with the researcher if they were interesting in finding out more or were willing to take part. Using this method of recruitment made it easier to find children matched on age and gender and to find children that were likely to have a similar socio-economic background to the child with narcolepsy. Children and their families known to the researcher and families that came forward through the social media pages were also recruited as part of the control group. The majority of families recruited for the control group lived in Yorkshire, which reduced travel and accommodation expenses.

Potential participants who expressed an interest in taking part were screened for eligibility. Eligible participants were contacted via email or letter and were sent the relevant participant information sheets (one suitable for their child to read and one suitable for parents/legal guardians) and the assent (for the child) and consent forms (for the parents). The participant information sheets provided detailed information about the study procedures so that the families could decide whether or not they were willing to participate. The participants were asked to read the information carefully, take time to consider taking part and contact the researcher to ask any questions. If they were willing to take part they were asked to complete the assent/consent forms and return them to the researcher. A self-addressed stamped envelope was provided for participants to return the forms or they could choose to return the forms electronically. The researcher sent a follow up email if there had been no response after two weeks.

All participants provided informed consent prior to the commencement of the study. As part of the consent process, participants were informed of their right to withdraw from the study at any point during the study. The participants were made aware that if they withdrew from the study before data analysis began, their identifiable data forms and anonymized data would be destroyed. However, if they withdrew from the study after data analysis began, their identifiable data forms would be destroyed and the researchers would need to use the anonymised data collected up to their withdrawal. Participants were made aware that all personal (identifiable) information collected about them or their child during would be kept strictly confidential and that this information would be retained for at least 2 years after the study is published.

4.4.2 Recruitment in The Republic of Ireland

A similar method of recruitment was followed in The Republic of Ireland. The researcher presented at The Sufferers of Unique Narcolepsy Disorder (S.O.U.N.D) Annual General Meeting in Dublin in November 2014 and families who were interested in taking part registered their interest and were contacted as described in section 4.4.1 above.

4.5 Inclusion and exclusion criteria

In order to be considered for inclusion in the study, participants were required to meet the following criteria:

- The child must be aged between 8-16 years old
- The child and their family must be fluent in English
- The families must be UK or Republic of Ireland citizens
- To participate in the clinical group, the child must have a medically confirmed diagnosis of narcolepsy with or without cataplexy (parents/legal guardians to provide evidence of this)
- To participate in the control group, the child must not have a diagnosis of a sleep disorder, developmental disorder or specific learning difficulty. The child must not have an I.Q score that is classified as 'borderline' (70-79) or 'extremely low' (69 and below) according to the WASI-II manual (Wechsler, 2011).

The following criteria were used to exclude potential children with narcolepsy from the study:

- Location of the child's home. Due to the limited funding that was available to support the travel and accommodation costs in the ROI, only the children who lived within 45 minutes of central Dublin (where the researcher was based) were included in the research.

There was no discrimination or exclusion due to gender, race, religion, belief or sexual orientation. The inclusion and exclusion criteria described above were required for the following reasons:

- An adequate comprehension of English was required because the cognitive tests involved understanding verbal instructions and the psychosocial measures involved reading.

- It was important that the children participating in the clinical group had a medically confirmed diagnosis of narcolepsy and that parents/legal guardians could provide evidence of this so that the clinical group is representative of the disorder of interest (narcolepsy with or without cataplexy).

- Excluding children from the control group with sleep disorders, developmental disorders or specific learning difficulties made it possible to investigate differences between children with and without narcolepsy without having to account for these additional factors. Excluding children from the control group with an I.Q score that is classified as 'borderline' (70-79) or 'extremely low' (69 and below) ensured that the control group had average I.Q scores and were able to understand the task instructions during the testing session.

- Children under the age of 8 years and over the age of 16 years were excluded from the study because the target population was school-aged children. School-aged children between the ages of 4-7 years were excluded because some of the standardized tests used in this study were only suitable for children aged 8-16 years old. A larger age range would also have increased the individual differences in scores.

- When funding was sought from the charity S.O.U.N.D Ireland, it was made clear that the researcher would not be able to include all children with narcolepsy who are supported by their charity due to time and financial constraints. The charity board approved this exclusion criteria.

4.6 Sample size

To determine the minimum sample size required in this study, an a priori power analysis was performed using the data from a previous study included in the systematic review in Chapter 2 (Stores et al., 2006). Stores et al. (2006) compared behaviour, mood and quality of life in children with narcolepsy and healthy controls. The authors presented sufficient information for the researcher (JB) to calculate the effect sizes for the differences between the two groups in Child Depression Inventory scores (d = 1.24, a large effect size), the Strengths and Difficulties Questionnaire total difficulties scores (d = 1.51, a large effect size) and the Child Health Questionnaire mental health subscale scores (d = 1.23, a large effect size). Using these results, the a priori power analysis revealed that a sample size of 26 children with narcolepsy and 26 healthy controls was required for an effect size of

0.8 with adequate statistical power of 80 % at 0.05 probability level (*p* value). Due to the time and financial constraints of this project, 46 families in total were recruited for this study. This included 23 children with narcolepsy and 23 gender and aged matched healthy controls. The characteristics of the participants are described in Chapter 5.

4.7 Procedure

This section will describe how the research was conducted.

4.7.1 Before the visit to the participants' homes

Once the families had completed the informed consent and assent forms and returned them to the researcher, a visit to the participant's home was arranged for a date and a time which was convenient for the family. The visit was usually arranged to take place over a weekend (Saturday and Sunday) or on a weekday during the school holidays. This provided more time for the testing to take place than would be available on a school day and ensured that the child was not over tired from school during the visit.

Nine days prior to the visit, a package containing details about the upcoming visit, a background questionnaire, a watch to measure activity levels (actigraphy watch) and two sleep diaries were sent to the participant. The questionnaire, diaries and actigraphy watch are described in detail below (see sections 4.8.1.1, 4.8.2.1 and 4.8.2.2). Clear instructions outlining how to fit the watch were included in the package and the parents/legal guardians were asked to complete the questionnaire before the researcher's visit to their home and to store it safely. This gave the parents/legal guardians time to complete the questionnaire carefully and find the information they needed to complete the questionnaire (for example the child's date of diagnosis and information about the diagnostic tests the child underwent).

4.7.2 During the visit to the participants' homes

For the majority of the visits, the researcher arrived at the participants home around 1pm. This allowed time for the researcher to travel to the participants home in the morning. Figure 4.3 displays the locations of the visits to the children with narcolepsy.

Although informed consent had already been provided, on arrival at the home the researcher read through the appropriate information sheets with the child and their parents so that they could ask any questions face-to-face. Parents and the children were asked to provide their verbal consent to participate before any data collection began. The researcher took some time to talk to the child, explain who they are and build rapport and trust before the testing began.

During the visit, the families were asked to maintain their usual routine as much as possible. A parent was always present during the visit and parents of the children with narcolepsy administered medication as usual. The child was also asked to nap at their usual time. Data collection on the first day took approximately 2-3 hours and further time was required for the child to take breaks and nap. The length of the naps and breaks required varied between children. During the visit the parents/legal guardians were asked to complete three questionnaires about their child (described in section 4.8). The measurements completed by participants during the visit are described in detail below. During the design of the study a set order for administering the tasks was decided on, however in practice this sometimes had to vary to suit the needs of the particular child.

The researcher would usually leave the house when the family had their evening meal and return to the home once the child was ready for bed to set up the polysomnography recording. The timing of this varied between families. After the polysomnography equipment was set up, the researcher would leave and stay in accommodation close to the participant’s house. The researcher would return in the morning to remove the equipment at a time that was convenient for the families. Data collection on the second day usually took 1-2 hours.

Figure 4.3 The locations of the visits to the children with narcolepsy.

4.7.3 After the visit to the participants' homes

At the end of the testing session, participants were given a debrief form to read. The children received a £10 amazon voucher for taking part.

4.8 Methods of measurement

This section will describe the tests and techniques used in this research to measure sleep, daytime physical activity, cognitive function and psychosocial well-being. For brevity, any measures that were completed by parents or legal guardians will be referred to as measures completed by parents.

4.8.1 Child and family background information

4.8.1.1 Background questionnaire

Parents were asked to complete a questionnaire to provide background information on the child and the family. The questionnaire covered:

- Part A: Family background
- Part B: Child background
- Part C: Child development
- Part D: Home environment

The questionnaire was designed based on the 'Stanford Sleep Inventory' (Anic-Labat, Guilleminault, Kraemer, Meehan, Arrigoni, & Mignot, 1999) which is used to gather background information on individuals who are suspected of having a sleep disorder. These data were used to characterise the sample that participated in this research (see Chapter 5).

4.8.1.2 Medical information

As part of the background questionnaire, parents were asked to provide information about their child's diagnosis including; the diagnosis (narcolepsy with or without cataplexy), how the child was diagnosed (which tests they underwent), who diagnosed the child and the date of diagnosis.

Parents were also asked to list all of the medications that their child takes (for sleep related conditions and for other conditions). They were asked to provide the drug name, the dosage, the time that it is taken and what the medication is taken for. If the participants were unsure of how to complete this section, the researcher assisted the parents during the visit by looking at the medication packaging and noting down the information. These data are presented in Chapter 5.

4.8.2 Measuring sleep

4.8.2.1 Objective measures

Actigraphy

Background

One of the aims of The Paediatric Narcolepsy project was to objectively measure the children's daytime activity levels, naps and overnight sleep for at least a week in their natural environment. Although polysomnography recordings (described in Chapter 1) are considered the gold standard method for measuring sleep, they are costly to conduct, children may not tolerate wearing the equipment and they are not a convenient method for long term continuous sleep monitoring (McCall & McCall, 2012). Actigraphy monitors provide a more convenient and non-invasive alternative to polysomnography as they estimate sleep-wake patterns based on movement. As described in Chapter 1, actigraphy devices are typically worn on the waist or on the non-dominant wrist and can be worn continuously over a period of time.

The validity of actigraphy as an instrument to assess sleep is usually established by comparing the outcomes of actigraphy recordings and polysomnography recordings that were conducted simultaneously. Validation studies often report correlational statistics and more detailed studies also report the sensitivity, specificity and accuracy of actigraphy. Sensitivity reflects the proportion of epochs scored as sleep using polysomnography that are accurately identified as sleep by actigraphy, whereas specificity reflects the proportion of epochs scored as wake using polysomnography that are accurately identified as wake by actigraphy (Meltzer et al., 2012). Accuracy is the ability of actigraphy to detect both sleep and wakefulness compared to polysomnography (de Souza, Benedito-Silva, Pires, Poyares, Tufik, & Calil, 2003). Guidelines by the American Sleep Disorder Association (ASDA) state that actigraphy provides an acceptably accurate estimate of sleep patterns in normal, healthy adult populations and in patients suspected of certain sleep disorders (Morgenthaler et al., 2007). Two studies of adults with narcolepsy found that actigraphy measures of daytime and night time uninterrupted immobility (mean duration) were able to distinguish between unmedicated adults with narcolepsy and controls (Bruck, Kennedy, Cooper, & Apel, 2005; Middelkoop, Lammers, Hilten, Ruwhof, Pijl, & Kamphuisen, 1995). Bruck et al. (2005) also found that the

actigraphy variable of uninterrupted immobility is sensitive enough to successfully differentiate between medicated and unmedicated adults with narcolepsy.

Despite these promising findings, a recent review has highlighted that the main methodological problem associated with the validity of actigraphy sleep-wake scoring is the relatively low ability to detect wakefulness during sleep periods (Sadeh, 2011). In response to the increased popularity of using actigraphy in paediatric sleep research, Meltzer et al. (2012) conducted a review investigating the validity of actigraphy in paediatric populations. In line with the findings of Sadeh (2011), Meltzer et al. (2012) found consistent reports that actigraphy is good at identifying sleep periods (high sensitivity) but less accurate in identifying wake after sleep onset (WASO) (low specificity) among paediatric populations. It is important that this limitation is taken into consideration when analysing actigraphy data collected from both adult and paediatric populations. The results of the review highlight the need for other subjective and objective measures of sleep (such as sleep diaries and polysomnography) which can be used to guide the actigraphy analysis.

Despite the limitations of actigraphy for assessing sleep in paediatric populations, actigraphy does provides a more objective measure of a child's sleep than parent-report (Meltzer et al., 2012). Filardi, Pizza, Bruni, Natale, and Plazzi (2016) used actigraphy to measure the rest-activity rhythm of both unmedicated children with narcolepsy and of age and sex matched controls. The main aim of this study was to compare circadian rest-activity rhythm and actigraphy estimated measures of sleep between the two groups. The secondary aim was to explore whether actigraphy assessment shows good discriminatory capabilities in paediatric narcolepsy cases. The authors found that the children with narcolepsy showed enhanced motor activity throughout the night and a decrease in activity in the early afternoon compared to controls. The study highlighted that actigraphy was a useful assessment measure as it was able to depict the marked impairment of both nocturnal sleep and daytime wakefulness in unmedicated children with narcolepsy (Filardi et al., 2016).

Acebo et al. (1999) investigated how many nights of actigraphy recording are necessary for reliable actigraphy measures of sleep for children and adolescents. The authors conclude that five or more nights of usable recordings are required and they recommend recording for at least one week as they found that up to 28% of weekly

recordings may be unacceptable for analysis because of illness, technical problems and participant noncompliance (Acebo et al., 1999).

Based on this background literature, in the current study both actigraphy and polysomnography recordings were used to objectively measure the sleep of children with narcolepsy and the controls. The validity of actigraphy versus polysomnography has not yet been established in children with narcolepsy, therefore by conducting a polysomnography recording alongside an actigraphy recording as part of this research, the concordance between these two objective measures in this population could be better understood and enabled more accurate interpretation of the actigraphy data.

Actigraphy monitor

10 actigraphy devices known as 'ActiGraph wGT3X-BT' activity monitors (ActiGraph, Pensacola, Florida, USA) were used in this research (see Figure 4.4).

Figure 4.4 The actigraphy monitor known as the 'ActiGraph wGT3X-BT' (ActiGraph, Pensacola, Florida, USA).

ActiGraph wGT3X-BT activity monitors contain a 3-axis (vertical, horizontal and perpendicular) microelectromechanical system (MEMS) accelerometer which measures body movements in terms of acceleration. The data can then be used to estimate the intensity of physical activity over time (Chen & Bassett, 2005). Acceleration data are sampled by a 12 bit analog to digital converter at user specified rates ranging from 30 Hertz (Hz) (30 samples per second) to 100 Hz (100 samples per second) and stored in a raw, non-filtered/accumulated format in the units of gravity (G's) (Actigraph, 2014). The raw outputs of accelerometers are

known as counts. The value of the counts varies based on the frequency and intensity of the raw acceleration. The data is then filtered and accumulated into user-selected epoch sizes (60seconds). Computerized scoring algorithms then translate the data into sleep-wake scores (Sadeh, 2011).

The ActiGraph wGT3X-BT devices also contain a metallic plate on the back of the battery near the cover which can be used to detect removal of the monitor when worn against the skin. The wear sensor data is useful as it can detect short device removals (for example for a 10 minute long shower), whereas the built-in algorithms have difficulty with detecting non-wear periods shorter than an hour in length. This wear sensor data was particularly important for detecting the difference between non-wear time and sedentary periods during the day.

Data are stored directly into a non-volatile flash memory and can then be downloaded onto a laptop. 'ActiLife' (ActiGraph, Pensacola, Florida, USA) is the software package used for initialising recordings, downloading and analysing the actigraphy data. During the download the software produces an *.agd file (epoch-level file) which can then be processed inside of ActiLife.

The wGT3X-BT monitors must be worn on the wrist to obtain accurate readings from the wear time sensor and to obtain accurate sleep score information (Actigraph, 2014)

Actigraphy sleep outcomes

Sleep times (time in and out of bed) were manually entered during the actigraphy sleep analysis using the information reported in the sleep diaries (described in section 4.8.2.2) as the software could not automatically detect time in and out of bed. The Actilife software includes two algorithms that are primarily used to perform sleep scoring on actigraphy data captured by ActiGraph devices. The validated Sadeh algorithm (Sadeh, Sharkey, & Carskadon, 1994) was used to determine minute by minute asleep/awake status. This algorithm was chosen because it is considered appropriate for younger populations as it was developed using subjects ranging from 10 to 25 years of age (Actigraph, 2010).

The Sadeh algorithm (Sadeh et al., 1994) yields the following information for each sleep period:

- **Latency-** The first minute that the algorithm scores as sleep.
- **Sleep efficiency (SE)-**The number of sleep minutes divided by the total number of minutes the participant was in bed.
- **Total sleep time (TST)-**The total number of minutes scored as sleep.
- **Total time in bed (TIB)-** The time in minutes the participant spent in bed.
- **Wake after sleep onset (WASO)-**The total number of minutes the participant was awake after sleep onset occurred.
- **Number of awakenings-**The number of different awakening episodes as scored by the algorithm.
- **Average awakening length-** The average length, in minutes, of all awakening episodes.

Initialisation

The watch was initialised by the researcher using Actilife software (version 6.13.2) (ActiGraph, Pensacola, Florida, USA) on a HP 650 ProBook Laptop. Initialisation involves selecting the recording start and stop date and time, the sampling frequency and the wear location. As the children were asked to wear the device on their non-dominant wrist, the researcher also entered information about whether the device will be worn on their right or left wrist and whether this was their dominant or non-dominant hand. Further information was also entered about the participant including the participants code, their date of birth, their height and their weight (when available) so that the file was easily identifiable during download.

The following initialisation settings were applied:

- The device was set to record for eight days and eight nights continually (start time was 6am on the first day and stop time 6pm on the last day). This recording length was based on the previous literature which recommends recording for at least one week in order to obtain five nights of useable recordings (Acebo et al., 1999).

- The device was always worn on the child's non-dominant wrist. As previously mentioned the device must be worn on the wrist to obtain accurate sleep score information and accurate readings from the wear time sensor.

- Activity counts per second were collected at a sampling frequency of 30 Hz and then were summed across a period of time (epoch) for data analysis. The data were analysed using a 60 second epoch because the sleep algorithms within ActiLife require a 60 second epoch to be applied to the data files.

Once initialisation was complete, the watch was sent via special delivery to the participant in the post. This was timed so that the watch arrived the day before the child was asked to fit the watch and the recording began (9 days before the researcher's visit to the home). The researcher contacted the participant to check that the watch had arrived safely and on time.

Fitting the monitor

Full instructions on how to fit and use the monitor safely were sent with the device. The children were asked to wear the actigraphy monitor securely on their non-dominant wrist for eight consecutive days and eight nights and to remove it when participating in water based activities (for example showering, swimming and bathing). For their safety, children were also asked to remove the device during contact sports such as rugby and to comply with any school rules that prohibit them wearing the device during P.E. lessons. Parents were asked to record the time and reason for the removal of the device.

Removal of the monitor

The eighth night of the child wearing the monitor generally coincided with the researcher's visit to the participants home, therefore for one night the child wore the actigraphy monitor and the polysomnography equipment simultaneously. The correlation between the polysomnography recording outcomes and the actigraphy recording outcomes are presented in Chapter 6. The researcher collected the watch the following morning at the end of the visit. The procedure for processing and analysing the actigraphy data is described in Chapter 6.

Polysomnography

As previously described in Chapter 1, polysomnography is the gold standard method of measuring sleep (see section 1.5). Routinely polysomnography is conducted in a sleep laboratory, however it is also possible to record sleep in the home environment using portable equipment. The advantages of home sleep studies include the convenience for families, children can sleep in their own bedroom (which can reduce anxiety about the procedure) and the approach can be cost-effective. In addition, sleep recorded in the home environment is likely to be more representative of a child's typical sleep quality than when recorded in a sleep laboratory (Moss et al., 2005). Studies using home polysomnography equipment with children are increasing in popularity, however, to date there have been no studies that have evaluated portable polysomnography monitoring in children with narcolepsy.

One of the aims of The Paediatric Narcolepsy Project was to investigate the differences in sleep architecture between children with and without narcolepsy and also to investigate the technical feasibility and acceptability of conducting unattended home sleep studies for research purposes in children with and without narcolepsy. To address these aims, the children underwent home polysomnography (PSG) using a portable PSG system (see Figure 4.5). The Embla® Systems-Embletta MPR PG & ST+ Proxy was used with 41 children and the Micromed-Morpheus was used with 3 children when the Embletta was not available. A standard montage (as described in Chapter 1 section 1.5) was used to measure sleep architecture, with nine EEG channels (F3, F4, C3, Cz, C4, O1, O2, M1, M2), two electrooculography (EOG) and two electromyography (EMG) channels.

The polysomnography equipment

The equipment was set up by the researcher approximately 1 hour before the child's bedtime. Target areas of the face/scalp/chin were cleaned with an exfoliating agent (Nuprep skin prep gel) before the electrodes (9mm diameter chlorided silver with 1.5m cables) were fixed in place with an electroconductive cream (EC2 electrode cream) and medical tape (Mefix or Micropore tape). Once the electrodes were in place, the child was free to move around until they were ready to settle in their bed. Data was recorded for 10 hours as this was the maximum possible recording length of the Embletta equipment. The equipment was set to record from the child's usual bed time.

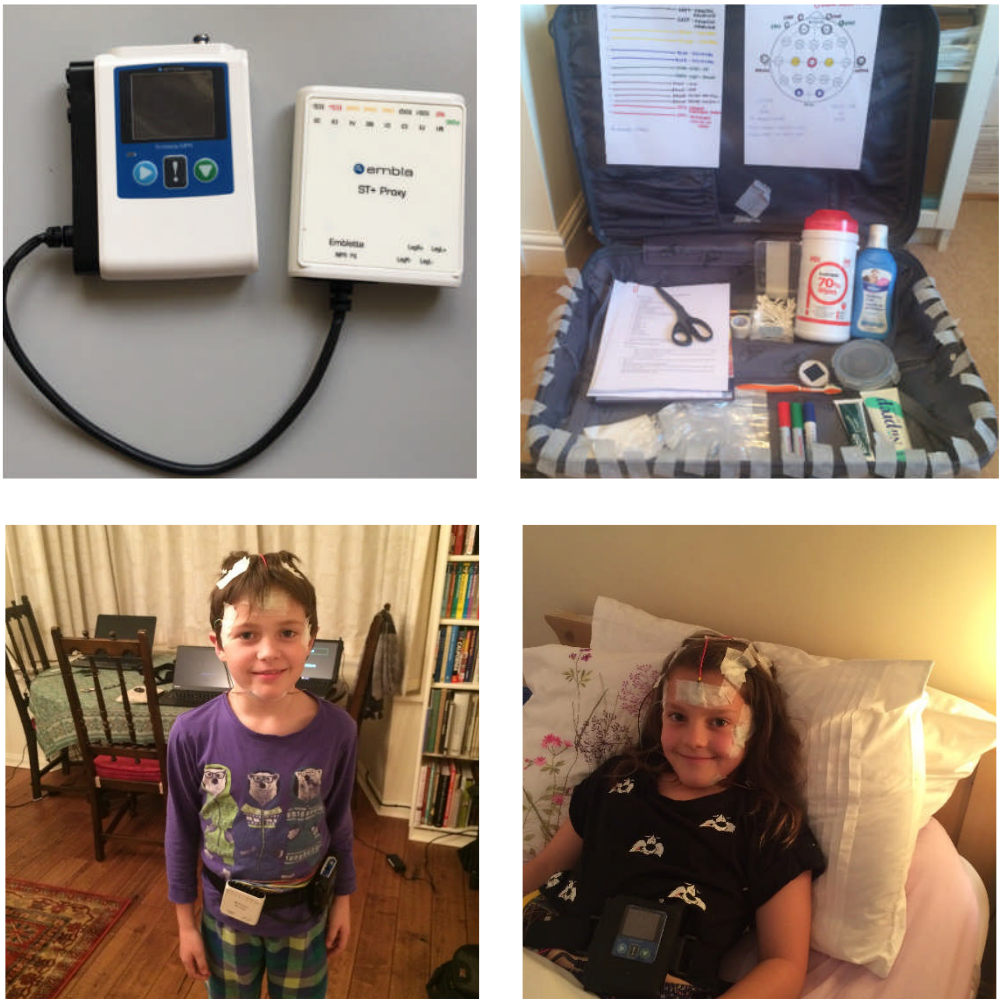

Figure 4.5 The Embla® Systems Embletta MPR + ST Proxy polysomnography equipment set up on two children and the consumables needed to apply the equipment.

Polysomnography sleep outcomes

The procedure for scoring polysomnography data has been described briefly in Chapter 1 (see section 1.5) but is also described in detail in Chapter 6. The polysomnography recording produces the same sleep related outcomes as the actigraphy recording (sleep onset latency (SOL), SE, TST, WASO, number of awakenings, average awakening length) but is also able to produce more detailed information about sleep architecture:

- **N1 sleep % of total sleep time**
- **N2 sleep % of total sleep time**
- **N3 (SWS) sleep % of total sleep time**
- **REM sleep % of total sleep time**
- **Arousal Frequency Index (arousals/hr slept)**

The polysomnography data is described in Chapter 6.

4.8.2.2 Subjective measures

Sleep diaries

Parents and children were asked to complete a daily sleep diary during the week the actigraphy device was worn. The sleep diaries were designed by the researcher based on those used in sleep clinics. Parents were asked to report the time their child started trying to fall asleep, the time they woke up and whether this was a typical night's sleep for their child. They were also asked to report information on their child's naps (time of nap and whether this was a usual day of naps for their child). This information was critical for guiding the actigraphy data analysis (described in section 4.8.2.1)

Children were asked to rate how well they slept each night on a 10-point scale (1 = very bad, 10 = very good) and also report if they remember experiencing nightmares, sleep paralysis, hallucinations, night-time eating/drinking or waking up to go to the toilet . This information was collected to assist with the polysomnography data scoring. For example, if the EEG channels showed a long period of awake in the middle of the night with a lot of chin movement (on the EMG channels) and the diary reported that the child had eaten during this night, this information helped the scorers estimate that this was the period of time that the child was eating during the night.

The Paediatric Daytime Sleepiness Questionnaire (Drake, Nickel, Burduvali, Roth, Jefferson, & Badia, 2003)

The Paediatric Daytime Sleepiness Questionnaire was used to measure and compare daytime sleepiness in the children with narcolepsy and healthy controls. This is an eight item self-report questionnaire that was chosen because it is quick and easy to administer and has robust psychometric properties (Drake et al., 2003). Drake et al. (2003) report that the internal consistency (Chronbach's alpha) for the final 8-item scale was .80. Children were asked to respond to eight statements such as 'how often do you get sleepy or drowsy while doing your homework?' and 'how often are you ever tired and grumpy during the day?' by circling either 'always', 'frequently', 'sometimes', 'seldom' or 'never'. Each response is scored (never = 0, seldom = 1, sometimes = 2, frequently = 3, always = 4). Higher scores indicated greater levels of sleepiness. The data is presented in Chapter 7.

The Child Sleep Habits Questionnaire (CSHQ) (Owens, Spirito, & McGuinn, 2000)

The CSHQ is a sleep screening instrument used to identify both behaviourally based and medically based sleep problems in school-aged children (Owens et al., 2000). Owens et al. (2000) report adequate internal consistency for a community sample (parents of healthy school aged children) ($p = 0.68$) and a clinical sample (parents of children diagnosed with sleep disorders) ($p = 0.78$). Alpha coefficients for the various subscales of the CSHQ ranged from 0.36 (Parasomnias) to 0.70 (Bedtime Resistance) for the community sample, and from 0.56 (Parasomnias) to 0.93 (Sleep-Disordered Breathing) for the clinical sample. Owens et al. (2000) also report that the test-retest reliability was acceptable (range 0.62 to 0.79) and that the CSHQ individual items, as well as the subscale and total scores were able to consistently differentiate the community sample from the clinical sample, demonstrating validity. The parents of the children with narcolepsy and healthy controls were asked to complete the CSHQ so that the total sleep disturbance scores could be compared between the two groups. They were asked to think about the previous week when responding to statements such as the 'child falls sleep within 20 minutes of going to bed' and the 'child awakens in the night screaming, sweating, and inconsolable'. They were asked to answer 'usually' if something occurs 5 or more times in a week, 'sometimes' if it occurs 2-4 times in a week and 'rarely' if something never occurs or only happens once during the week. A higher CSHQ score indicates more sleep problems. The data is presented in Chapter 6.

Stanford Sleepiness Scale (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973)

The aim of The Paediatric Narcolepsy Project was to assess cognitive function in the children with and without narcolepsy at their optimal performance. Therefore before each of the cognitive tasks (described in section 4.8.4), the researcher assessed the child on the Stanford Sleepiness Scale to measure their current sleepiness. The scale has an average test-retest rating of $r = .88$ (Maclean, Fekken, Saskin & Knowles, 1992). If the child rated him/herself as a '4' on the scale or higher ('somewhat foggy', 'foggy', 'sleepy' or 'sleep onset soon'), the researcher asked the child if they would like to nap, take a break and checked with the parents if they were due medication (this only occurred when testing the children with narcolepsy).

4.8.3 Measuring daytime activity

Actigraphy

In addition to using actigraphy to measure sleep, the ActiGraph wGT3X-BT monitors (ActiGraph, Pensacola, FL, USA) were also used to measure levels of activity during the day over an eight day period. These monitors are described in detail in section 4.8.2.1. The aim was to compare the activity levels of children with narcolepsy and healthy controls across eight days in their natural environment. The Actilife software (version 6.13.2) (ActiGraph, Pensacola, Florida, USA) includes a data scoring tool which enables users to break down the proportion of time (total epochs) within each dataset the participant spent in different categories of intensity using 'cut points'. Cut points categorize the data collected from the wGT3X-BT monitors (known as counts) into different intensity categories (sedentary, light, moderate, vigorous, very vigorous). One of the validated cut point sets available within Actilife called 'Freedson Children 2005' (Freedson, Pober, & Janz, 2005) was chosen for use in the study because it was most suitable for the age range of the participants recruited. The five cut points are displayed in Figure 4.6.

Cut Point	Min	Max
Sedentary	0	149
Light	150	499
Moderate	500	3999
Vigorous	4000	7599
Very Vigorous	7600	and above

Figure 4.6. Freedson Children (2005) cut points for daytime activity analysis.

The outcomes of interest for daytime activity levels during the day are:

- **% time spent sedentary**
- **% time spent in light activity**
- **% time spent in moderate activity**
- **% time spent in vigorous activity**
- **% time spent in very vigorous activity**
- **Overall physical activity (counts per min)**

The procedure for processing and analysing the data is described in Chapter 7.

4.8.4 Measuring cognitive function

This section describes the battery of tasks chosen to assess and compare cognitive function in children with narcolepsy and healthy controls. The tasks were generally completed in the order listed below, however this varied occasionally to suit the particular needs of the child and their family. The data from the following tasks will be presented in Chapter 8.

Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II) (Wechsler, 2011)

The vocabulary and matrix reasoning subtests of the WASI-II were administered to estimate the general cognitive function (I.Q) of the children with narcolepsy and the healthy controls. The WASI-II has strong internal consistency, with the average reliability coefficients ranging from 0.87 to 0.91 for children (Wechsler, 2011). The research described in Chapter 2 suggested that children with narcolepsy have I.Q's within the average range. By including a standardised measure of intelligence in this study it enables comparisons between the results of this study and the previous research.

The vocabulary subtest is designed to measure the participants' word knowledge and verbal concept formation. It also measures crystallized intelligence, learning ability, long term memory and the degree of language development (Wechsler, 2011). The subtest includes 3 picture items and 28 verbal items. For verbal items, the participant was asked to the define words that were presented visually and orally. All participants in this study started on item 4 (start point for ages 6-90). The researcher queried marginal responses (for example 'swimmer' instead of fish), generalized responses ('animal' instead of fish), functional responses ('it digs dirt' instead of shovel) or hand gestures (pretending to dig) using a neutral inquiry such as 'tell me more about it' according to the instructions in the manual. The answers were scored as either 2 (shows a good understanding of the word), 1 (in general the response is correct but shows poverty of content) or 0 (no clear understanding of the word or is obviously incorrect). Testing ended after 3 consecutive scores of 0. A total raw score was calculated by summing the item scores and this score was converted to a *T* score using the child's age and the conversion table in the manual.

The matrix reasoning subtest is designed to measure fluid intelligence, broad visual intelligence, classification and spatial ability and perceptual organisation (Wechsler,

2011). The subtest includes 30 items which display incomplete matrices. The participant views them and completes them by selecting one of five response options. Responses were scored as either 1 for a correct response or 0 for an incorrect response. Testing ended after 3 consecutive incorrect answers. As above, a total raw score was calculated and this was converted to a *T* score.

The *T* scores from the vocabulary and matrix reasoning subtest were then summed. The sum of the *T* scores was converted using another conversion table in the manual to obtain a Full Scale I.Q-2 Subtests (FSIQ-2). This provided a general estimate of cognitive functioning based on the results of two subtests. An average I.Q score is 100 and I.Qs between 90-109 are within the average range.

The subtests took between 15-30 minutes to administer depending on the ability of the child.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, 2017)

The CANTAB is a computerised neuropsychological test battery developed by Trevor Robbins and Barbara Sahakian at the University of Cambridge in 1985. The battery was originally designed to define cognitive impairments in individuals with Alzheimer's disease and Parkinson's disease (Sahakian et al., 1988). Over the last 30 years, the CANTAB has become recognised as a gold standard cognitive assessment and data collection software as it includes highly sensitive, precise and objective measures of cognitive function, correlated to neural networks (Cambridge Cognition, 2017). CANTAB tests have demonstrated sensitivity to detecting changes in neuropsychological performance (Sahakian et al., 1988). The validity of the CANTAB for assessing brain-behaviour relations in adults has been supported by numerous studies of individuals with degenerative disorders, brain lesions, attention deficit hyperactivity disorder (ADHD) and psychiatric illness (Chamberlain et al., 2011; Downes, Roberts, Sahakian, Evenden, Morris, & Robbins, 1989; Kehagia, Murray, & Robbins, 2010; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Sahakian et al., 1988).

The CANTAB has also been widely used to study executive functioning in paediatric populations (Luciana, 2003) and is suitable for use with children over the age of 4 years old. By comparing the performance of a clinical group (for example

children with narcolepsy) to an age matched healthy control group the nature of any neurocognitive impairments present can be better understood. In 4–12-year-old children, internal consistency coefficients are uniformly high, ranging from .73 for a measure of reaction time latency to .95 for performance on the self-ordered search task (Luciana, 2003). Luciana (2003) reports that retest reliability studies in children have not yet been published, but stability coefficients for CANTAB's measures of executive function in adult samples are moderate in magnitude and generally range from .60 to .70 (Lowe & Rabbitt, 1998).

In this study, a version of the battery called CANTABeclipse (Cambridge Cognition, 2012) was used. This is a windows-based program that operates on a PC platform and utilizes touch screen technology (Luciana, 2003). The equipment needed to administer the CANTAB tests chosen for this study included a touch screen computer (PaceBlade technology, Slimbook 200 Series), a keyboard, a mouse and a press pad.

The CANTAB was chosen for use in this study because it consists of modules for assessing a range of cognitive functions, including memory and attention, planning and reasoning abilities, psychomotor and motor speed, and temporal and frontal dysfunctions. As discussed in Chapter 1, simple sustained attention and working memory are reported to be the cognitive domains most strongly affected by sleep deprivation (Lim & Dinges, 2010). A battery of seven cognitive tests was chosen to assess a range of cognitive functions in children with narcolepsy and healthy controls, including those known to be most strongly affected by sleep deprivation. The tests were chosen based on the 'core cognition' battery provided and recommended by Cambridge Cognition which incorporates the core cognitive domains often impaired in brain disorders, as well as those affected by cognitive enhancing drugs or interventions (Cambridge Cognition, 2017). The cognitive domains assessed using CANTAB were attention, reaction time, accuracy, working memory, executive function, planning and learning. The aim of measuring these cognitive domains was to better understand the cognitive profile of children with narcolepsy and how it compares to healthy control children. All task stimuli are nonverbal consisting of geometric designs or simple shapes and therefore an adequate comprehension of English is only necessary to understand the instructions prior to the start of the task (Luciana, 2003). All of the tasks chosen were age

appropriate for the sample recruited. The battery lasted on average one hour but this varied depending on the ability of the child.

The equipment was set up in a quiet room on a table and the child sat directly in front of the screen. The researcher sat next to the child throughout the testing session and administered the test instructions. The tests chosen and the main outcomes of interest for each test (based on the CANTAB guidelines) are described below (in the order that they were administered). The description of the tasks, the outcome measures and the images are from the CANTABeclipse test administration guide and have been reprinted with permission from Cambridge Cognition ltd.

1. Motor Screening Test (MOT)

The MOT was administered first as it is a brief exercise designed to familiarise participants with the touch screen interface. Participants touch a series of 10 flashing crosses shown in different locations on the screen (see Figure 4.7). Participants are instructed to use the tip of their forefinger of their dominant hand to touch the screen. If the cross is touched properly a sound plays and the cross disappears, if it is not touched properly no sound is heard and the cross remains on the screen. This test simultaneous screens for difficulties with vision, movement, comprehension and checks that the participant can follow simple instructions. This task took 3 minutes to complete.

Figure 4.7 The Motor Screening test (MOT) (Cambridge Cognition, 2012)

The main outcomes of interest for MOT are:

Total correct: The total number of correct responses made by the participant over the 10 assessed trials in the test. A higher score is better.

Mean error: This is a measurement of the accuracy of the participant's pointing. It measures the mean distance between the centre of the cross and the location the

participant touched on the screen. The distance is measured in pixel units and a lower score is better.

MOT latency: This is the time taken for the participant to touch the cross after it appeared on the screen (reaction time for correct responses only). Reaction time is measured in milliseconds and a lower reaction time is better.

2. Reaction Time (RTI)

RTI is a measure of a participant's speed of response to a visual target where the stimulus is either predictable (simple reaction time) or unpredictable (choice reaction time). The participants are asked to hold down a press pad button until a yellow spot appears at the top of the screen. They then must touch the yellow spot as quickly as possible. The spot appears in a single location during the simple reaction time phase (see Figure 4.8) and in one of five locations in the 5-choice reaction time phase. This tasks took approximately 5 minutes to complete.

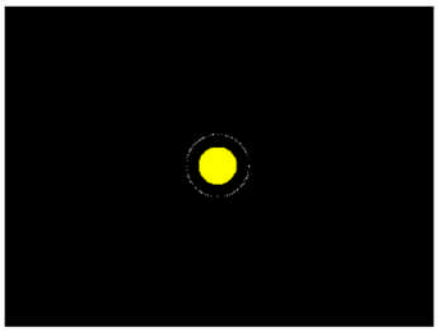

Figure 4.8 Reaction time task (RTI) (Cambridge Cognition, 2012)

The main outcomes of interest for RTI are:

Simple reaction time: The speed with which the participant releases the press pad button in response to the onset of a stimulus in a single location. This is measured in milliseconds and lower is better.

Simple movement time: This is the time taken to touch the stimulus after the press pad has been released in trials where the stimuli appear in one location only. This is measured in milliseconds and lower is better.

Five choice reaction time: The speed with which the participant releases the press pad button in response to the onset of a stimulus in any one of five locations. This is measured in milliseconds and lower is better.

Five choice movement time: This is the time taken to touch the stimulus after the press pad has been released in trials where the stimuli appear in one of five possible locations. This is measured in milliseconds and lower is better.

Simple accuracy score: This is the total number of trials where the response is recorded as correct where the stimuli appear in one location only. Higher is better.

Five choice accuracy score: This is the total number of trials where the response is recorded as correct where the stimuli appear in one location of five locations. Higher is better.

3. Spatial span (SSP)

SSP is a test of working memory capacity. In this task a pattern of white boxes is shown on the screen (see Figure 4.9) and some of the squares briefly change colour, one by one, in a variable sequence. The participant must remember the sequence and then touch the squares in the same order as they opened. The sequence length increases throughout the test. The participant is given up to 3 attempts at each sequence length and the test terminates if all three are failed. This task took approximately 6 minutes to complete.

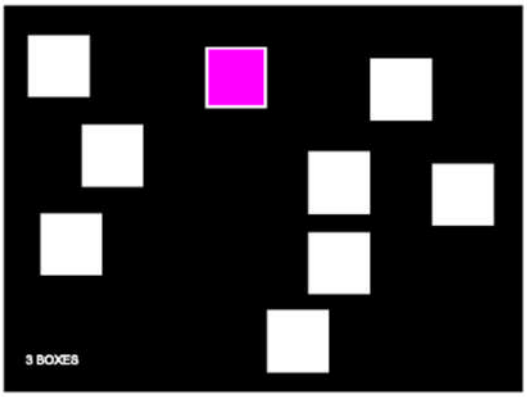

Figure 4.9 Spatial span task (SSP) (Cambridge Cognition, 2012)

The main outcomes of interest for SSP are:

Span length: This is the longest sequence successfully recalled by the participant. The participant has three attempts at each level. The maximum possible score is 9 and a higher score is better.

Number of attempts: This measure reports the total number of attempts that the participant made across all spans. Lower is better.

Total errors: This is defined as the number of times the participant selected an incorrect box. The maximum score is 97 and a lower score is better.

Total usage errors: This measure reports the number of times the participant selected a box not in the sequence being recalled. The maximum scores is 39 and a lower score is better.

4. Stockings of Cambridge (SOC)

SOC is a test of executive function, planning and spatial working memory. The participant sees two displays containing three coloured balls and must move the balls in the lower display to copy the arrangement in the upper display (see Figure 4.10). The balls must be moved one at a time by touching the required ball, then touching the position to which it should be moved. This tasks took approximately 10 minutes to complete.

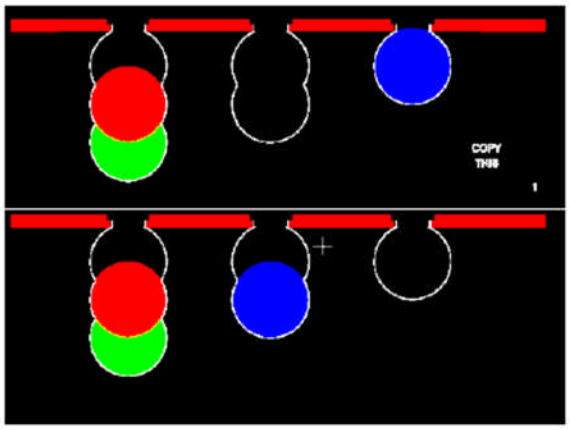

Figure 4.10. Stockings of Cambridge (SOC) (Cambridge Cognition, 2012)

The main outcomes of interest for SOC are:

Problems solved in minimum number of moves: This is the fundamental measure, recording the number of occasions upon which the participant has successfully completed a test problem in the minimum possible number of moves. A higher score is better.

Mean moves (2, 3 and 4 move problems): The mean number of moves required by the participant to solve 2, 3 and 4 move problems. A lower score indicates better performance.

Initial thinking time (2, 3, 4 and 5 move problems): The participants are encouraged to plan their moves before actually enacting the solution to the problem. This measure gives an indication of the time taken to plan the problem solution.

5. Intra-Dimensional/Extra-dimensional Set Shift (IED)

IED is a test of rule acquisition, reversal learning and attentional set shifting. In this test participants are required to make a series of two-choice visual discriminations. The test starts with the presentation of two simple, colour-filled shapes (block 1) (see Figure 4.11). The participant must touch the shapes and learn which of the stimuli is 'correct' using the feedback from the computer. After 6 consecutive correct responses, the stimuli and/or rules are changed. For example, in block two, the rule is reversed so that the previously incorrect stimulus is now correct. There are nine stages that the participants can progress through by satisfying the set criterion of learning at each stage (6 consecutive correct responses) and blocks 3-9 include compound stimuli (colour-filled shapes and white lines). The key stages of this task are the 'Intradimensional (ID) shift' (block 6) and the 'Extradimensional (ED) shift'(block 8). The ID shift is when the stimuli change but the previously relevant feature may still be relevant and the ED shift is when the previously relevant feature is no longer relevant and the participant must redirect responding to the other stimulus feature. If at any stage the participant fails to reach the learning criterion after 50 trials, the test terminates. This task took approximately 7 minutes to complete.

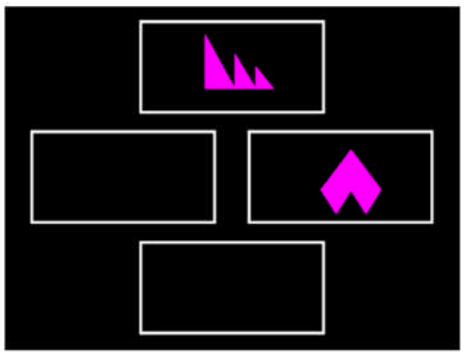

Figure 4.11 Intra-Dimensional/Extra-dimensional Set Shift (IED) (Cambridge Cognition, 2012)

The main outcomes of interest for IED are:

Stages completed: This is the total number of stages the participant completed successfully. There are 9 stages in total.

Total errors adjusted: This is a measure of the participant's efficiency in attempting the test. Although a participant may pass all nine stages, a substantial number of errors may be made in doing so. It is crucial to note that participants failing at any stage of the test by definition have had less opportunity to make errors. Therefore, this adjusted score is calculated by adding 25 for each stage not attempted due to failure. This value of 25 is used since participants must complete 50 trials to fail a stage and half of these could be correct by chance alone. Lower is better.

Pre ED errors: This measure records the number of errors made prior to the extra-dimensional shift of the task. Errors are defined as instances when the participant fails to select the stimulus that is compatible with the current rule. Lower is better.

EDS errors: Errors made in the extra-dimensional stage of the task are labelled EDS errors, as they have been committed at the stage where the participant is required to make an extra-dimensional shift. Errors committed at the reversal stage following the EDS stage are not included. Lower is better.

6. Spatial Working Memory (SWM)

SWM measures the ability to retain spatial information and manipulate it in working memory. It is a task that also assesses the use of strategy. The test begins with a number of coloured boxes being shown on the screen (See Figure 4.12). Participants must search for blue tokens hidden within the coloured boxes by touching them to open them. Once the token has been found the participant must use them to fill up an empty column on the right hand side of the screen. The task becomes more difficult as the number of boxes increases. The critical instruction is that the participant must not return to a box where a token has previously been found. This tasks took approximately 8 minutes to complete.

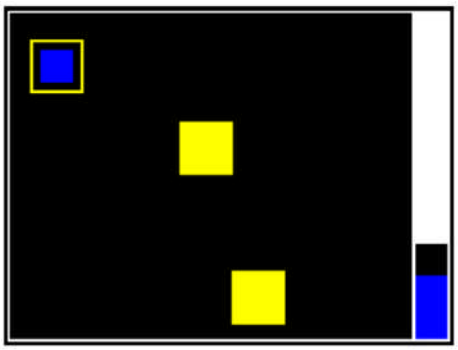

Figure 4.12 Spatial Working Memory (SWM) (Cambridge Cognition, 2012)

The main outcomes of interest for SWM are:

Between errors: Between errors are defined as times the participant revisits a box in which a token has previously been found. This is calculated for all trials of four or more tokens only. Lower is better.

Within errors: Within errors are defined as the number of errors made within a search, i.e., the number of times a participant revisits a box already found to be empty during the same search. This is calculated for all trials of four or more tokens only. Lower is better.

Strategy: It is suggested that an efficient strategy for completing this task is to follow a predetermined sequence by beginning with a specific box and then, once a blue token has been found, to return to that box to start the new search sequence.

An estimate of the use of this strategy is obtained by counting the number of times the participant begins a new search with a different box for 6 and 8 box problems only. A high score represents poor use of this strategy and a low score equates to effective use.

7. Paired Associates Learning (PAL)

PAL assesses visual associative learning and memory. Boxes are displayed on the screen and are automatically opened in a randomized order (see Figure 4.13). One or more of the boxes will contain a pattern. Participants must learn to associate the patterns with locations on the screen. After all the boxes have been opened each pattern is then shown in the centre of the screen and the participant must touch the

box where that pattern was located. There are 8 stages in this task and the participant is given 10 attempts at each stage before the test terminates. Stages 1 and 2 include 1 pattern, stages 3 and 4 include 2 patterns, stages 5 and 6 include 3 patterns, stage 7 includes 6 patterns and stage 8 includes 8 patterns. This task took approximately 10 minutes to complete.

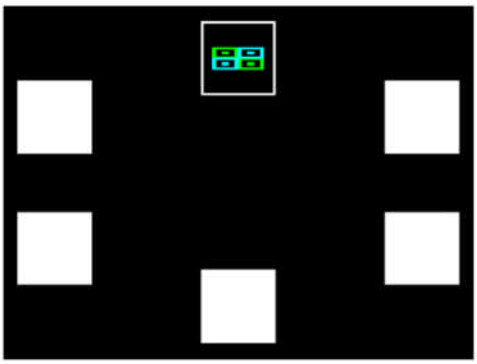

Figure 4.13. Paired Associates Learning (PAL) (Cambridge Cognition, 2012)

The main outcomes of interest for PAL are:

Stages completed: This is a key indicator of the participants overall success, recording how many stages were successfully completed. When analysing other outcome measures from PAL it is crucial that analyses are conducted with reference to the number of stages completed. A participant that fails prior to the successful completion of the 8-pattern stage will have had less opportunity to make errors than a participant who completes the test. A higher score is better.

First trial memory score: This measure is the number of patterns correctly located after the first trial, summed across the stages completed (range 0-26, with 26 meaning all the patterns were correctly located for all stages first time). Higher is better.

Total errors adjusted: This measure reports the total number of errors across all assessed problems and all stages, with an adjustment for each stage not attempted due to previous failure. Lower is better.

The results of the seven CANTAB tests described above are reported in Chapter 8.

Working Memory Test Battery for Children (WMTB-C) (Pickering & Gathercole, 2001)

As discussed in Chapter 1, working memory is reported to be one of the cognitive domains most strongly affected by sleep deprivation (Lim & Dinges, 2010). In order to measure verbal working memory the following two tests were administered from the WMTB-C.

Digit recall

Each trial involved the spoken presentation of sequences of digits for immediate recall by the participant. Digits were presented in an even monotone and at a rate of 1 per second. The child was asked to repeat back exactly what they heard and in exactly the same order. The sequences gradually increased in length and the trial terminated when the child could not recall the sequence or made errors 3 times within one span block. A correct response is scored as 1 and an incorrect response is scored as 0. A total raw score is calculated and is converted to a standardized score. Pickering & Gathercole (2001) report a test-retest reliability coefficient of .81 for the digit recall task.

Backwards digit recall

As above, each trial involved the spoken presentation of sequences of digits for immediate recall by the participant and digits were presented in an even monotone and at a rate of 1 per second. The child is required to recall the list in reverse order (the recalled list should begin with the last item heard and end with the first item heard). The sequences gradually increased in length and the trial terminated when the child could not recall the sequence or made errors 3 times within one span block. A correct response is scored as 1 and incorrect response is scored as 0. A total raw score is calculated and is converted to a standardized score. Pickering & Gathercole (2001) report a test-retest reliability coefficient of .53 for the backwards digit recall task.

Wechsler Individual Achievement Tests-Second Edition (WIAT-2) (Wechsler, 2002)

As discussed in Chapter 2, two studies assessed academic performance (reading, writing and maths) according to teacher and family reports (Posar et al., 2014; Stores et al., 2006). It was found that seven out of 13 children with narcolepsy had

failed academically (Posar et al., 2014) and that teachers rated children with narcolepsy as having significantly more educational difficulties than children without narcolepsy (problems with learning, not reaching academic potential, not working hard enough and being difficult to teach) (Stores et al., 2006). In the current study the standardised Wechsler Individual Achievement Test-Second Edition (WIAT-2) was chosen to assess numerical and language attainment rather than teacher and family reports in order to provide a more accurate and reliable assessment of ability and allow for direct comparison between the participating children and between studies. The WIAT-2 has strong inter-item consistency within subtests with average reliability co-efficients ranging from .80 to .98 (Wechsler, 2002).

Numerical operations

Numerical attainment was assessed using the numerical operations measure from the WIAT-2 battery which assesses number discrimination, addition, subtraction, division, multiplication and calculating percentages. This measure includes 54 items and the starting point is determined by the age of the child. Each correct answer was scored as 1 and the each incorrect answer was scored as 0. The task ended after 6 incorrect answers. The scores were summed to obtain a total raw score and this was converted into a standard score using the WIAT-2 manual.

Spelling

Written language attainment was assessed using the spelling measure from the WIAT 2 battery which assesses the ability to spell dictated letters, letter blends and words. The inclusion of homonyms requires that the participant uses context clues from the dictated sentences to spell the appropriate word. This measure includes 53 items and as above the starting point is determined by the age of the child. Each correct answer was scored as 1 and the each incorrect answer was scored as 0. The task ended after 6 incorrect answers. The scores were summed to obtain a total raw score and this was converted into a standard score using the WIAT-2 manual.

Test of Word Reading Efficiency-Second Edition (TOWRE-2) (Torgesen, Rashotte, & Wagner, 2012)

The Test of Word Reading Efficiency–Second Edition (TOWRE-2) is a measure of an individual’s ability to pronounce printed words (sight word efficiency) and phonemically regular non-words (phonemic decoding efficiency) accurately and

fluently. These are two kinds of word reading skill that are critical in the development of overall reading ability. The TOWRE-2 was chosen to assess word reading skill rather than teacher and family reports in order to provide a more accurate and reliable assessment of ability and allow for direct comparison between the participating children and between studies. The test developer reports high average test–retest reliability for the same form (exceeds .90) and high alternate form reliability on the subtests (.87) (Torgesen, Rashotte & Wagner, 2012).

The participant was instructed to read aloud the list of printed words for a period of 45 seconds. Practice items were provided and testing only proceeded if the participant was able to respond accurately to at least one item. In subtest 1, 'sight word efficiency', the participant reads a list of words that gets progressively more difficult and in subtest 2, 'phonemic decoding efficiency' the participant reads aloud non-words. A total raw score was calculated for sight word efficiency and phonemic decoding efficiency and these scores were converted into standardized scores.

4.8.5 Measuring psychosocial well-being

4.8.5.1 Quantitative methods

The Beck Youth Inventories-Second Edition for Children and Adolescents (Beck, Beck, Jolly, & Steer, 2005)

Given the evidence described in Chapter 1 which suggests that lack of sleep effects psychological well-being (Hamilton, Nelson, Stevens, & Kitzman, 2007; Vandekerckhove & Cluydts, 2010; Walker & Harvey, 2010) (see section 1.8.3), The Beck Youth Inventories were used to assess symptoms of depression, anxiety, anger, disruptive behaviour, and self-concept in the children with narcolepsy and the healthy controls. The Beck Youth Inventories shows good to excellent internal consistency, with alpha coefficients ranging from 0.86 to 0.96 (Beck, Beck, Jolly & Steer, 2005). The Beck Youth Inventories are 5 self-report scales that are suitable for use with children and adolescents between the ages of 7 and 18 years old. A combination booklet which includes the following 5 self-report scales was administered as it provides a comprehensive evaluation of the child's current level of distress.

The 5 self-report scales:

- **Beck Self-Concept Inventory for Youth (BSCI-Y)**- The items explore self-perceptions, such as competence and positive self-worth.
- **Beck Anxiety Inventory for Youth (BAI-Y)-** The items reflect children's fears, worries and physiological symptoms associated with anxiety.
- **Beck Depression Inventory for Youth (BDI-Y)**- The items reflect the respondent's negative thoughts about themselves or their lives, feelings or sadness and physiological indications of depression.
- **Beck Anger Inventory for Youth (BANI-Y)-** The items include perceptions of mistreatment, negative thoughts about others, feelings of anger and physiological arousal.
- **Beck Disruptive Behaviour for Youth (BDBI-Y)**-Behaviours and attitudes associated with conduct disorder and oppositional-defiant behaviour are included in this inventory.

The inventories are administered in the order above and each scale includes 20 items. Children are asked to respond to a 'list of things that happen to people and that people think or feel' such as 'I work hard', 'I feel strong', 'I like myself" by circling either 'never', 'sometimes', 'often' or 'always'. The instructions remind the children there are no right or wrong answers. For both the depression and anxiety inventory children are asked to think especially about the last two weeks.

Each response is scored (never = 0, sometimes = 1, often = 2, always = 3) and a total raw score is calculated by adding the scores of the 20 items. The range of possible total raw score on each inventory is 0-60.

Total raw scores were converted to standardized scores (*T* scores) using the child's age and gender and the table provided in the manual. For the depression, anxiety, anger and disruptive behaviour inventories, the higher the *T* score, the higher the distress the youth is reporting. For the self-concept inventory, a higher score indicates a more positive self-concept.

The Beck Youth Inventory was chosen for use in this study because it has been widely used in paediatric mental health research and has good reliability and validity (Beck, Beck, Jolly, & Steer, 2005). The combination booklet took the child approximately 45 minutes to complete. This questionnaire was not completed directly in front of parents, siblings or friends unless absolutely necessary so that the

child could respond openly. If the child struggled to read the items, the researcher would read each item to them and ask for a response. The data will be reported in Chapter 9.

Paediatric Quality of life Inventory (PedsQL) (Varni, Seid, & Rode, 1999)

The PedsQL 4.0 generic core scales (Varni et al., 1999) were used to compare health-related quality of life (HRQOL) in children with narcolepsy and healthy controls. This measure is suitable for children aged between 5-18 years old with and without acute and chronic health conditions.

Age-appropriate versions of the inventory (8-12 years and 13-18 years) were administered. The parent versions of the inventory correspond to the version completed by their child. Each inventory is composed of 23 items comprising 4 dimensions: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items). Participants are instructed that they will see a list of things that might be a problem for them (or for their child in the parent version). They are asked to report how much of a problem each one has been during the past month by circling either: 0 if it is never a problem, 1 if it is almost never a problem, 2 if it is sometimes a problem, 3 if it is often a problem, 4 if it is almost always a problem. The participants are told that there are no right or wrong answers. An example statement is ‘problems with participating in sports activities or exercise’. Scores are transformed and reverse scored on a scale from 0 to 100 (0=100, 1=75, 2=50, 3=25, 4=0). The total scale score is the sum of all the items (max score 2300) divided by the number of items answered on all the scales (23 if all items have been answered). Higher scores indicate better HRQQL.

The PedsQL was chosen for use in this research as previous studies have reported excellent internal consistency reliability for the total scale score (alpha = 0.88 child, 0.90 parent report) and that the PedsQL can distinguish between healthy children and children with chronic health conditions (Varni, Burwinkle, Seid, & Skarr, 2003; Varni, Seid, & Kurtin, 2001). Children and parents were able to complete this questionnaire in under 5 minutes. The data will be reported in Chapter 9.

The Strengths and Difficulties Questionnaire (SDQ) (Goodman, Meltzer, & Bailey, 1998)

The SDQ was used to compare the psychological well-being of children with narcolepsy and controls. The SDQ is a brief behavioural screening questionnaire

suitable for 4-17 year olds. In this research, the children who were 11 years of age and above were asked to complete the self-report questionnaire (suitable for 11-17 year olds) and all parents/legal guardians were asked to complete the version suitable for parents of 4-17 year olds.

All versions of the SDQ contain 25 items on psychological attributes which comprise the following 5 scales (each with 5 items):

- Emotional problems scale
- Conduct problems scale
- Hyperactivity scale
- Peer problems scale
- Prosocial scale

The child or parent is asked to think about the last 6 months and mark ‘not true’, ‘somewhat true’ or ‘certainly true’ next to each item. Although both versions of the questionnaire ask about the same 25 traits, the wording is slightly different An example item from the self-report version is ‘I get very angry and often lose my temper’ and an example from the parent version is ‘(the child) often has temper tantrums or hot tempers’.

An impact supplement was also included with each questionnaire which asks the child/parent whether they think that they/their child has difficulties in one or more of the following areas: emotions, concentration or being able to get on with other people. The participant can respond ‘no’, ‘yes-minor difficulties’, ‘yes-definite difficulties’ or ‘yes-severe difficulties’. If they mark ‘yes’, they are asked to respond to four further items which enquire about:

- How long the difficulties have been present (possible responses: less than a month, 1-5 months, 6-12 months or over a year)
- Whether the difficulties upset or distress them/their child (possible responses: not at all, only a little, quite a lot or a great deal).
- Whether the difficulties interfere with everyday life (home life, friendships, classroom learning, leisure activities). Participants are asked to respond either ‘not at all’, ‘only a little’, ‘quite a lot’ or ‘a great deal’ for each of the four areas of everyday life.
- Whether the difficulties make it harder for those around you (family, friends, teachers etc.). The possible responses are ‘not at all’, ‘only a little,’ ‘quite a lot’ or ‘a great deal’.

‘Somewhat true’ is always scored as 1, but the score given to a ‘not true’ or a ‘certainly true’ response varies with the item. Due to the complexity of scoring the SDQ, the SDQ scoring website was used to score the questionnaires and generate the reports (www.sdqscore.org). Scoring by hand is not recommended as it is very time consuming and prone to human error. The SDQ scoring website charges 0.50 USD (~£0.36) per questionnaire scored and downloaded.

A total difficulties score is generated by summing scores from all the scales except the prosocial scale. The scores can range from 0-40. A higher score represents more total difficulties. An impact score ranging from 0 to 10 is generated by summing items on overall distress and impairment. The impact score is automatically 0 if the participant did not perceive themselves (child version) or their child (parent version) as having any emotional or behavioural difficulties because they are not asked to complete the additional four items on distress or impairment. A higher score represents a larger impact.

The SDQ was chosen for use in this research as previous studies have reported satisfactory reliability and validity (Goodman, 2001), whether judged by internal consistency (mean Cronbach’s alpha: .73), cross-informant correlation (mean: 0.34), or retest stability after 4 to 6 months (mean: 0.62) (Goodman, 2001). It has been established as the most widely used instrument in child mental health research (Vostanis, 2006). It is easy and quick to complete, allows comparisons to be made between different populations and it is sensitive to change. The data will be reported in Chapter 9.

4.8.5.2 Qualitative methods

Semi-structured interview with the children with narcolepsy

A semi-structured interview using open-ended questions was conducted with each child with narcolepsy (if they were willing to participate). If the child and their parents gave their consent, the interview was audio recorded. The purpose of the interview was to ask the child about their experience of living with narcolepsy and about the impact they think the disorder has on their school and home life. This gave the children with narcolepsy the opportunity to express their own opinions, experiences, ideas and perspectives and raise any issues that are important to them. The children were always given the option of their parents sitting with them while

they were interviewed. The interview questions were pre-defined but as the interview was semi-structured, the following questions only acted as a topic guide:

1) Please can you tell me a bit about yourself? (warm up question)
2) Can you tell me about a usual school day for you?
3) Do you think that having narcolepsy has an effect on school?
4) Do you think that there is anything the school could do to make things better for you?
5) Can you tell me about a usual day when you are not in school (weekend or holiday)?
6) Do you think narcolepsy has an effect on your family life, social life or leisure activities?
7) Do you think there is anything at home that could be done to make things better for you?
8) What have been the biggest changes in your life since being diagnosed with narcolepsy compared to before?
9) What are the hardest parts about having narcolepsy (if there are any)?
10) What are the easier or nicer parts about having narcolepsy (if there are any)?
11) If there was just one thing you could tell other children/young people going through the same experiences as you, what might it be?

The length of the interview varied between children but it typically lasted 30 minutes.

Semi-structured interview with the parents of the children with narcolepsy

Parents were also asked to participate in a semi-structured interview. The purpose of this interview was to ask parents about their experiences of having a child with narcolepsy. They were asked 11 questions which mirrored those asked to the children apart from a slight change of wording to make them appropriate for addressing parents. Parents were usually interviewed when the child was napping, taking a break or had gone to bed so that the parents could speak freely. The length of the interview varied between families but it typically lasted 45 minutes-1 hour.

The aim of conducting the interviews was to document and better understand the experiences of both children living with narcolepsy and their parents. Consequently, interviews were only conducted with the families affected by narcolepsy. Unfortunately due to the time and financial constraints of this project, the interview

data will not be presented in this thesis but the interviews have been transcribed and will be analysed using interpretive phenomenological analysis (IPA) in 2018 and submitted for publication.

4.9 General statistical approach

Statistical analysis was performed using IBM SPSS Statistics 23 (Chicago, Illinois, Version 23) installed on a HP 650 Probook laptop. All variables were inspected visually for potential outliers and normality was assessed using the Shapiro-Wilk test prior to running any analysis. For normally distributed variables, comparisons between the two groups were performed using independent two-tailed *t*-tests and for non-normally distributed data the non-parametric alternative to the independent *t*-test (known as Mann-Whitney *U* test) was used. For normally distributed variables, the associations between the variables were investigated using Pearson's correlation coefficients and for non-normally distributed data Spearman's correlation coefficients were used. Effect sizes are reported for each comparison. Cohen's *d* is reported for normally distributed variables (Cohen, 1988) and *r* is reported for non-normally distributed variables (Rosenthal, 1991).

The chapters in this thesis describe and compared overnight sleep (Chapter 6), daytime sleep (Chapter 7), physical activity (Chapter 7), cognitive function (Chapter 8) and psychosocial well-being (Chapter 9) in children with narcolepsy and healthy controls. Consequently multiple comparisons were performed in each Chapter which increases the risk of type I error (concluding that a significant difference is present when it is not). In order to reduce the risk of type I error, Bonferroni corrections were applied to all of the analyses in the thesis. Significant results after correcting for multiple comparisons are indicated by an asterisk in the result tables throughout the thesis.

Limitations of applying Bonferroni corrections

It is important to note some of the limitations of applying Bonferroni corrections to analyses. Despite the widespread use of the Bonferroni method, there has been continuing controversy regarding its use (Armstrong, 2014). One of the main criticisms of the Bonferroni method is that it is overly conservative (Perneger, 1998) and increases the likelihood of type II error (Garamszegi, 2006), such that real differences may not be detected (Armstrong, 2014). The interpretation of result

depends on the number of other tests performed, so that as the number of tests increase, the value of the adjusted *p* that has to be achieved to consider a result significant decreases markedly, lowering the power of a test (Armstrong, 2014). Perneger (1998) highlighted that type II errors are no less false than type I errors and states that simply describing what tests of significance have been performed, and why, is generally the best way of dealing with multiple comparisons rather than using Bonferroni corrections. Nakagawa (2004) recommends reporting effect sizes for all group comparisons along with exact *p* values. This enables the readers to evaluate the importance of the findings. Moderate or large effect sizes indicate that the significant differences found between the two groups are likely to represent genuine group differences. Based on this recommendation, in this thesis effect sizes for all group comparisons are reported along with exact *p* values.

4.10 Summary

This Chapter has described the research design and methodology employed in The Paediatric Narcolepsy Project. Chapter 5 describes the sample of participants recruited to take part in this study.

Chapter 5 The characteristics of the study population

This Chapter describes the sample of participants recruited to take part in The Paediatric Narcolepsy Project.

5.1 Study population

Data were collected from 46 children in total, 23 children with narcolepsy and 23 gender and age matched healthy controls.

Two of the children in the control group were excluded from all of the analyses in the thesis based on the exclusion criteria outlined in Chapter 4 (see section 4.5). The first child was excluded as information provided in the child and family background questionnaire revealed that the child had a diagnosis of dyslexia. The researcher was not aware of this diagnosis at the time of testing. The second child was excluded because their Full Scale IQ-2 Subtests (FSIQ-2) score was 76. The FSIQ-2 score provides a general estimate of cognitive functioning and composite scores between 70-79 are classified as 'borderline' intellectual functioning in the WASI-II manual (Wechsler, 2011). Therefore the child's FSIQ-2 score of 76 indicates that they had lower than average intellectual functioning. As described in Chapter 4, it was important that the children in the control group did not have a specific learning difficulty such as dyslexia or an I.Q score classified as 'borderline' or 'extremely low' because the aim of the study was to directly compare the performance of children with narcolepsy to typically developing children.

Table 5.1 displays details of the 44 participants included in the analyses in the thesis. The two groups were matched as closely as possible on age and gender. An independent *t*-test revealed that there was no significant difference in the age of the children in the two groups, $t(42) = -.36$, $p = .72$. There were 15 males in both groups and there were 8 females with narcolepsy and 6 females in the control group (due to the exclusion of two females in the control group).

Table 5.1 Participant details

Participant characteristics	Children with narcolepsy (*n* = 23)	Healthy controls (*n* = 21)
Mean age	11 years 6 months	11 years 8 months
(SD)	(1.85)	(1.84)
Range	8 years 0 months- 15 years 8 months	8 years 8 months- 15 years 5 months
Sex	15 male 8 female	15 male 6 female

Note. SD = Standard deviation.

Four of the 23 children with narcolepsy were recruited from The Republic of Ireland. All of the children in the control group were recruited from England.

The home postcodes of the children recruited from England were entered into the governments 'English indices of deprivation 2015 postcode lookup tool' (Department for Communities and Local Government, 2015) to give an indication of socioeconomic status (SES). This tool provides an 'Index of Multiple Deprivation' (IMD) score for each postcode entered. The IMD scores are an overall relative measure of deprivation which combine information from seven different domains of deprivation. The domains of deprivation are: income deprivation, employment deprivation, education, skills and training deprivation, health deprivation and disability, crime, barriers to housing and services and living environment deprivation. The Index of Multiple Deprivation ranks every small area in England from 1 (most deprived area) to 32,844 (least deprived area) (Department for Communities and Local Government, 2015). IMD scores were only available for the children recruited from England and therefore the four children with narcolepsy recruited from The Republic of Ireland were excluded from this analysis. The 19 children with narcolepsy had a mean IMD score of 22,178 (*SD* = 8747) and the 21

children in the control group had a mean IMD score of 25,116 (*SD* = 7711). An independent *t*-test revealed that there was no significant difference between the IMD scores in the two groups, $t(38) = -1.13$, $p = .27$.

5.1.1 Children with narcolepsy

19 of the 23 children with narcolepsy were diagnosed with narcolepsy with cataplexy (type 1) and 4 children were diagnosed with narcolepsy without cataplexy (type 2). 12 of the 23 children with narcolepsy had received the ASO3 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix). One child was diagnosed with Autism Spectrum Disorder (ASD) as well as narcolepsy following receiving the Pandemrix vaccination. Following discussions with paediatric sleep consultants who are experts in the field of paediatric narcolepsy, it was considered unrealistic within the time frame of this project to achieve the minimum sample size required for this study if only treatment naive children with narcolepsy were recruited. The research team also felt that it was impractical and inappropriate to ask children with narcolepsy to withdraw from their medication in order to take part in the study, as participation lasted over a week. The aim of the study was to compare children with narcolepsy to healthy controls when the children were following their usual routine, so that the results are more representative of how the children are on a day to day basis. Therefore, all children with narcolepsy who met the inclusion criteria for the study were recruited for the study, regardless of whether they were treated with medication. 21 of the 23 children with narcolepsy were being treated with medication when they participated in the study. 18 out of the 21 children treated with medication were taking a combination of medications to treat both excessive daytime sleepiness and cataplexy. Details of the medications taken by the 21 children with narcolepsy are provided in the Table 5.2. Chapter 1 provides further details about the two types of narcolepsy (see section 1.9), the Pandemrix vaccination (see section 1.2) and the medications used to treat individuals with narcolepsy (see section 1.11.1).

Table 5.2 Medications taken by the children with narcolepsy (*n* = 21)

Medication	Indication	Number of children taking the medication
Methylphenidate (immediate release)	Excessive daytime sleepiness	13
Methylphenidate (modified release)	Excessive daytime sleepiness	13
Modafinil	Excessive daytime sleepiness	4
Dexamphetamine	Excessive daytime sleepiness	1
Sodium oxybate	Excessive daytime sleepiness & cataplexy	6
Venlafaxine	Cataplexy	4
Fluoxetine	Cataplexy	1
Clomipramine	Cataplexy	2
Clonidine	Restless legs	3
Iron supplements	Iron deficiency	1
Cetirizine	Hay fever	1

5.1.2 Healthy controls

18 of the 21 children in the control group did not have any medical diagnoses and were not taking any medication. Two children in the control group had asthma and were taking medication to treat it when needed. Another child in the control group had hypermobility but was not taking any medication. As asthma and hypermobility are not known to affect the outcomes of interest in this study, the children were included in the analyses in the thesis. Five of the children in the control group were siblings of a child with narcolepsy. Since the recruitment stage of this project in 2014 and 2015, there has been some published evidence to suggest that there may be a "narcolepsy spectrum disorder" in family members of patients with type 1 narcolepsy (Wang, Yan, Han, Lin, & Mignot, 2017). In the study, 378 parents of children with narcolepsy underwent HLA typing, polysomnography, multiple sleep latency test (MSLT) and questionnaire evaluations. Wang et al. (2017) found that in

parents of children with cataplexy, 0.8% had narcolepsy with cataplexy and an equivalent or larger number (0.5-1.6%) had mild type 1 narcolepsy due to hypocretin deficiency. The authors suggest that mild symptomatology may explain why the parents of children with narcolepsy are rarely diagnosed in sleep centres (Wang et al., 2017). Based on this recent publication, the data collected from the five siblings of a child with narcolepsy were looked at in detail before deciding whether or not to include the siblings as part of the healthy control group in the analyses in the thesis. The sibling data did not differ significantly from the healthy control data and therefore the sibling data were included in the analyses in this thesis. For completeness, the analyses described in Chapters 6, 7, 8 and 9 were also conducted with siblings excluded. The overall pattern of case-control differences were unaffected by the exclusion.

Chapter 6 Characterisation of overnight sleep in children with narcolepsy

6.1 Introduction

As discussed in Chapter 3, one of the main aims of The Paediatric Narcolepsy Project was to investigate how overnight sleep in children with narcolepsy compares with that of gender and age matched healthy controls. Chapter 2 highlighted that children with narcolepsy are at risk of cognitive and psychological impairment even when treated with medication (see section 2.3.3). The overall aim of this thesis is to clarify whether any significant unresolved symptoms in clinically treated narcolepsy (for example disturbed overnight sleep) or any significant change in behaviour (for example reduced daytime physical activity) are associated with cognitive or psychological difficulties. In order to address this aim, it was important to measure the sleep of children with narcolepsy and healthy controls to investigate whether there were any differences between the two groups. In this study, sleep disturbance was measured by The Child Sleep Habits Questionnaire, sleep-wake patterns were measured by actigraphy and sleep architecture was measured by polysomnography. There is currently very limited research that has measured the sleep of children with narcolepsy treated with medication. As outlined in Chapter 5, 21 out of the 23 children with narcolepsy in this study were treated with medication. To the researcher's knowledge, this is the first study which has conducted unattended home polysomnography recordings in children with narcolepsy.

Based on the literature reviewed in Chapter 1, it was hypothesised that children with narcolepsy will have significantly poorer sleep efficiency, significantly shorter sleep onset latency and spend significantly more time awake after sleep onset compared to matched controls. It was also hypothesised that children with narcolepsy would spend significantly more time in sleep stages N1 and N2 and have more arousals per hour than matched controls.

This Chapter begins by describing The Child Sleep Habits Questionnaire data (see section 6.2), followed by the polysomnography results (see section 6.3). Before the actigraphy results are reported in section 6.8, section 6.7 describes the agreement between the polysomnography and actigraphy measurements of sleep in children

with narcolepsy and healthy controls. Understanding the agreement between the two measures of sleep enables more accurate interpretation of the actigraphy results reported in section 6.8.

6.2 Subjective measures of sleep

6.2.1 The Child Sleep Habits Questionnaire (CSHQ)

As described in Chapter 4, parents were asked to complete The CSHQ (Owens et al., 2000) which can be used to identify both behaviourally based and medically based sleep problems in school-aged children (see section 4.8.2.2). A total sleep disturbance score is calculated based on the responses provided and a higher score indicates more sleep problems. Scores greater than 41 reflect clinically significant sleep problems (Owens et al., 2000). One set of parents from the narcolepsy group did not complete the questionnaire due to time constraints. The results show that parents of children with narcolepsy reported that their child had a significantly higher number of total sleep problems than parents of children without narcolepsy (see Table 6.1). In the narcolepsy group, total sleep disturbance scores ranged from 45-74 (M = 54.05, SD = 7.43) suggesting that the children with narcolepsy have clinically significant sleep problems. In the control group, total sleep disturbance scores ranged from 31-46 (M = 37.48, SD = 3.88) suggesting that the healthy children do not have clinically significant sleep problems. Only two children in the control group had a total sleep disturbance score above 41.

Table 6.1 The Child Sleep Habits Questionnaire (CSHQ) data

Measurement	Narcolepsy $M \pm SD$ (n = 22)	Control $M \pm SD$ (n = 21)	t	p value	df	Cohen's d
The Child Sleep Habits Questionnaire Total Sleep Disturbance Score	54.05 ± 7.43	37.48 ± 3.88	9.23	<.001	41	2.80

Note. M = Mean, SD= Standard deviation.

6.3 Objective measures of sleep

6.3.1 Polysomnography (PSG) data analysis

Chapter 1 provides an overview of how sleep is measured using polysomnography (PSG) (see section 1.5) and Chapter 4 outlines the procedure the researcher followed when conducting the unattended home polysomnography recordings in this study (see section 4.8.2.1). 22 out of the 23 children with narcolepsy underwent home PSG. One child declined due to a previous negative PSG experience in hospital. Similarly, 22 out of the 23 children in the control group underwent the PSG sleep recording. One child became unwell during the polysomnography equipment set up, so did not proceed with the polysomnography recording.

Embla® RemLogic™ sleep diagnostic software (Embla RemLogic Embla Systems LLC, USA) was used to score the polysomnography data. The software was installed on a HP 650 Probook laptop and the polysomnography recordings were downloaded in REMLogic as soon as possible after each recording ended. During a three month clinical placement at Sheffield Children's Hospital, the researcher was trained to sleep stage and score arousals by Dr Ruth Kingshott (a Senior Sleep Physiologist). The 44 polysomnography studies were scored manually according to the AASM (2012) paediatric scoring criteria (Berry et al., 2012). During the sleep scoring training process, the researcher (novice) scored a polysomnography recording independently before watching the sleep physiologist score the same study so that any discrepancies in the scoring could be discussed and learning goals for the next scoring session set. Dr Ruth Kingshott was blind to whether the polysomnography sleep study was from a child with narcolepsy or a healthy control. The inter-scorer agreement was calculated by exporting the scoring data from the sleep scoring programme into Excel so that 30 second epoch by epoch comparisons and the overall percentage of agreement could be determined. Within 6 months, inter-scorer agreement had improved from approximately 65% to approximately 95%. The learning process was documented and presented in a poster at The British Sleep Society conference in October 2017 (Kingshott & Blackwell, 2017). The initial low agreement was mainly due to artefactual PSG recordings which were difficult to score. Lack of video, pulse rate and respiratory patterns meant that the scorers were completely reliant on sleep channels when analysing the data. The researcher (novice) initially had difficulty distinguishing between drowsiness vs N1

sleep, wakefulness vs REM sleep and vertex sharpes vs K complexes (see section 1.6 for more information on sleep stage). Although all of the sleep recordings were scored by the researcher, the polysomnography outcomes presented in this thesis are based on the scoring of Dr Ruth Kingshott who has 27 years of sleep scoring experience to ensure that the results are as accurate as possible.

Based on existing literature, study failure was defined as a sleep recording with less than four hours of interpretable sleep data. 16 out of the 22 children with narcolepsy (73%) were successfully studied and all 22 of the control children were successfully studied. Failed home studies were classified into three main areas of study failure: sensor removal (n = 4), equipment failure (n = 1) or battery failure (n = 1).

As two of the controls met the exclusion criteria for the study (see Chapter 5 section 5.1), there were 16 children with narcolepsy and 20 healthy control children included in the polysomnography analysis. 14 of the 16 children with narcolepsy were treated with medication.

6.3.2 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 23 (Chicago, Illinois, Version 23) installed on a HP 650 Probook laptop. All variables were inspected visually for potential outliers and normality was assessed using the Shapiro-Wilk test prior to running any analysis. For normally distributed variables, comparisons between the two groups were performed using independent two-tailed *t*-tests and for non-normally distributed data the non-parametric alternative to the independent *t*-test (known as Mann-Whitney *U* test) was used. The Bonferroni-adjusted significance level was $p <. 005$ (0.05/11 = 0.005) (see Chapter 4 section 4.9). Effect sizes are reported for each comparison. Cohen's d is reported for normally distributed variables (Cohen, 1988) and r is reported for non-normally distributed variables (Rosenthal, 1991).

The effect sizes can be interpreted as follows:

Cohen's *d* (Cohen, 1988)

d = 0.2 small effect size

d = 0.5 medium effect size

d = 0.8 large effect size

r (Rosenthal, 1991)

r = 0.1 small effect size

r = 0.3 medium effect size

r = 0.5 large effect size

6.3.3 Polysomnography results

Table 6.2 displays the polysomnography data of 16 children with narcolepsy and 20 healthy controls. The main polysomnography outcomes of interest are described in detail in Chapter 4 (see section 4.8.2.1).

Table 6.2 Polysomnography data

Measurement	Narcolepsy *M* ± *SD* (*n* = 16)	Control *M* ± *SD* (*n* = 20)	*p* value	Cohen's *d or* '*r*'
Sleep onset latency (SOL) (minutes)	23.84 ± 36.30	27.99 ± 18.32	.09[b]	*r* = .28
Sleep efficiency (SE) (%)	80.93 ± 11.67	87.44 ± 9.68	.02[b]	*r* = .38
Total sleep time (TST) (minutes)	465.53 ± 86.25	480.20 ± 66.51	.52[b]	*r* = .11
Wake after sleep onset (WASO) (minutes)	86.33 ± 49.09	27.70 ± 12.75	<.001[b]*	*r* = -.11
Number of awakenings	27.38 ± 11.63	25.25 ±7.43	.53[a]	*d* = .22
N1 % of total sleep time	8.21 ± 5.48	4.12 ± 2.02	.02[b]	*r* = -.39
N2 % of total sleep time	37.18 ± 10.26	48.67 ± 3.79	<.001[a]*	*d* = 1.49
N3 % of total sleep time	40.74 ± 14.66	29.03 ± 5.74	.003[b]*	*r* = -.48.
REM % of total sleep time	15.84 ± 6.64	18.19 ± 4.46	.23[a]	*d* = .42
Wake % of sleep period	15.91 ± 9.47	5.34 ± 2.42	<.001[a]*	*d* = 1.53
Arousal frequency index (arousals/hour)	7.05 ± 4.03	7.50 ± 1.26	.68[a]	*d* = .15

Note. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.005) (0.05/11 = 0.005). M = Mean, SD= Standard deviation.

[a] Independent *t*-test

[b] Mann-Whitney *U* test

The results show that the children with narcolepsy were awake three times as long after sleep onset than healthy controls (measured by WASO). Children with narcolepsy spent significantly more of their sleep in stage N3 sleep. However, they spent significantly less of their sleep in stage N2 sleep compared to healthy controls. There were no significant differences found between the two groups in sleep onset latency, sleep efficiency, total sleep time, number of awakenings, N1% of total sleep time, REM % of total sleep time and arousal frequency index.

In order to examine whether or not having two children who were not treated with medication in the narcolepsy group had an effect on the overall results, statistical analyses were also performed without these two children (narcolepsy group $n = 14$, control group $n = 20$). The group differences that persisted were WASO ($p = < .001$), N2 % of total sleep time ($p = < .001$) and wake % of sleep period ($p = < .001$).

Statistical analyses were also performed when only gender and aged matched pairs were included, in order to investigate whether or not having different group sizes had an effect on the results. There were 15 gender and aged matched pairs with successful PSG recordings (narcolepsy group $n = 15$, control group $n = 15$). The group difference that persisted were WASO ($p = <.001$).

6.4 Summary of findings

6.4.1 Findings from The Child Sleep Habits Questionnaire (CSHQ)

- The CSHQ was completed by the parents of 22 children with narcolepsy and the parents of 21 healthy children. 20 of the children were treated with medication.
- Parents of children with narcolepsy reported that their child had a significantly higher number of total sleep problems than parents of the healthy children ($p = <.001$).
- The mean total sleep disturbance score in the narcolepsy group ($M = 54.05$, $SD = 7.43$) suggests that the children with narcolepsy have clinically significant sleep problems (as the mean is higher than the clinically significant cut off of 41). In the narcolepsy group, total sleep disturbance scores ranged from 45-74.

- The mean total sleep disturbance score in the control group (*M* = 37.48, *SD* = 3.88) suggests that the healthy children do not have clinically significant sleep problems (as the mean is lower than the clinically significant cut off of 41). In the control group, total sleep disturbance scores ranged from 31-46.

6.4.2 Polysomnography findings

- 44 children underwent home polysomnography (children with narcolepsy *n* = 22, healthy controls *n* = 22).
- 16 out of the 22 children with narcolepsy (73%) were successfully studied and all 22 of the control children were successfully studied.
- The results of the main comparison (children with narcolepsy *n* = 16, healthy controls *n* = 20) showed that children with narcolepsy had three times as much wake after sleep onset (WASO) than healthy controls. Children with narcolepsy spent significantly more of their sleep in stage N3 sleep than healthy controls. However, they spent significantly less of their sleep in stage N2 sleep compared to healthy controls. There were no significant differences found between the groups for any of the other sleep variables.

6.5 Discussion

The aim of this study was to investigate how overnight sleep in children with narcolepsy compares with that of gender and age matched healthy controls. To the researcher's knowledge, this is the first study which has conducted unattended home polysomnography recordings in children with narcolepsy. This research has shown that conducting unattended home sleep studies to measure sleep architecture in children with narcolepsy and healthy controls for research purposes is feasible and is tolerated by the majority of children. It is reasonable to suppose that the results of the home polysomnography recordings are more representative of a typical night's sleep for the child than if the recording had taken place in a sleep laboratory. However, the data show that unattended home sleep studies carry a risk of data loss, even when set up in the home by a trained researcher. This is due to lack of monitoring during the night, meaning that technical failures cannot be rectified.

The polysomnography results supported the hypotheses that children with narcolepsy spend significantly more time awake after sleep onset. The results also showed that the children with narcolepsy spent significantly more of their sleep in

stage N3 sleep than healthy controls. In line with the polysomnography findings, The CSHQ results indicate that the children with narcolepsy have significantly more sleep disturbance than healthy controls (as reported by parents).

The hypotheses that children with narcolepsy would have significantly poorer sleep efficiency, shorter sleep onset latency, spend more time in N1 and N2 sleep and have more arousals per hour than the matched controls were not supported by the results. The results showed that children with narcolepsy spent significantly less of their sleep in stage N2 sleep compared to healthy controls.

It is perhaps important that although 14 out of the 16 children with narcolepsy were treated with medication, the children spent significantly more time awake after sleep onset compared to healthy controls. It is possible that the stimulant medications that are used to treat excessive daytime sleepiness and the antidepressant medication used to treat cataplexy are having an effect on overnight sleep and resulting in the children spending more time awake after sleep onset compared to controls. The literature examining the effects of these medications on sleep in children with narcolepsy is limited and due to the small numbers of children with narcolepsy included in this study it was not possible to compare the sleep of children treated with different medications.

It is also possible that poor sleep hygiene, such as lack of a bedtime routine or using technology in the bedroom could contribute to the significant differences in sleep outcomes between the two groups. Video recording was not used alongside the home polysomnography recording, therefore it was not possible to assess what the child was doing when awake in the night unless detailed information was provided by the child/parent in the sleep diaries.

6.6 Conclusion

Polysomnography recordings are considered the gold standard method for measuring sleep. The results of the home polysomnography recordings conducted in this study suggest that children with narcolepsy have more disturbed overnight sleep compared to healthy controls even when the majority of the children with narcolepsy in this study were treated with medication. Given the importance of sleep for health, cognitive function and psychosocial well-being (see Chapter 1 section 1.8) it is

likely that the significantly disturbed sleep of the children with narcolepsy will have a significant impact on their life.

6.7 Comparison between polysomnography and actigraphy measurements of sleep

6.7.1 Introduction

As mentioned in Chapter 4, actigraphy and polysomnography recordings were used in this study to objectively measure the sleep of children with narcolepsy and healthy controls (see section 4.8.2.1). To the researcher's knowledge, the ActiGraph wGT3X-BT actigraphy monitors have not been used with children with narcolepsy before and therefore there is no existing literature on how reliable the sleep-wake data produced by these devices is in this population. In order to establish the agreement between the gold standard polysomnography measurement of sleep and the actigraphy measurement of sleep, the children in this study underwent a home polysomnography recording whilst also wearing also the actigraphy monitor on their non-dominant wrist. The purpose of trying to establish agreement between the two measures is to be able to more accurately interpret the results of the actigraphy recordings which were conducted over 8 days and 8 nights for each child (see section 6.8).

6.7.2 Statistical analysis

The polysomnography and actigraphy measurements of sleep provided information on five of the same sleep variables: sleep efficiency (SE), sleep onset latency (SOL), total sleep time (TST), wake after sleep onset (WASO) and the number of awakenings. For each of these variables, agreement between the two measures was evaluated using either paired samples *t*-tests and Pearson's correlation coefficients (for normally distributed data) or Wilcoxon signed-rank tests and Spearman's correlation coefficients (for non-normally distributed data). The Bonferroni-adjusted significance level was $p <. 01$ (0.05/5 = 0.01) (see Chapter 4 section 4.9). In the correlational analysis, correlation coefficients of 1 indicate a perfect positive linear relationship, coefficients of -1 indicate a perfectly negative relationship and correlation coefficients of 0 indicate no linear relationship at all. The strength of the correlations can be interpreted as follows: correlation coefficients of 0.1-0.3 are considered 'weak', correlation coefficients of 0.4-0.6 are considered 'moderate' and

correlation coefficients of 0.7-0.9 are considered ‘strong’. It was beyond the scope of this thesis to establish the sensitivity, specificity and accuracy of the actigraphy monitors by comparing the PSG data and actigraphy data epoch-by-epoch.

6.7.3 Polysomnography vs actigraphy results

31 out of the 44 children included in the study had successful PSG and actigraphy recordings that were conducted concurrently. The data was used to establish the agreement between the two measures. The 31 children in this analysis included 14 children with narcolepsy and 17 healthy controls. Table 6.5 displays the results of the polysomnography vs actigraphy comparison when the children with narcolepsy and the healthy controls are combined (n = 31). The agreement between the two measures was also investigated when looking at the clinical population (children with narcolepsy) and the healthy children separately to establish whether the agreement between the measures is different in children with sleep disorders and healthy children. Table 6.6 displays the results when only the children with narcolepsy were included in the analysis (n = 14) and Table 6.7 displays the results when only the healthy children were included in the analysis (n = 17).

Table 6.3 Polysomnography vs actigraphy (children with narcolepsy and healthy controls combined $n = 31$)

Sleep variables	PSG ***M* ± *SD***	Actigraphy ***M* ± *SD***	***p* value**	Correlation coefficient
Sleep efficiency (%)	86.07 ± 9.57	75.94 ± 9.61	<.001[b]*	r_s = .39, p = .03[c]
Sleep onset latency (mins)	25.14 ± 29.11	17.16 ± 16.60	.07[b]	r_s = .43, p = .02[c]
Total sleep time (mins)	475.90 ± 68.86	451.03 ± 76.21	.02[b]	r_s = .67, p = <.001[c]*
Wake after sleep onset (mins)	52.14 ± 42.11	126.97 ± 61.50	<.001[b]*	r_s = .50, p = .004[c]*
Number of awakenings	26.00 ± 9.35	27.58 ± 9.40	.53[a]	r= -.09, p = .64[d]

Notes. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.01) (0.05/5 = 0.01). [a] Paired samples t-test, [b] Wilcoxon signed-rank test. [c] Spearman's correlation coefficient, [d] Pearson's correlation coefficient. M = Mean, SD = Standard deviation

Table 6.4 Polysomnography vs actigraphy (children with narcolepsy only $n = 14$)

Sleep variables	PSG ***M* ± *SD***	Actigraphy ***M* ± *SD***	*p* value	Correlation coefficient
Sleep efficiency (%)	81.61 ± 12.33	70.09 ± 10.91	.01[a]	r = .33, p =.25[d]
Sleep onset latency (mins)	23.14 ± 38.94	16.20 ± 15.38	.73[b]	r_s = .28, p =.33[c]
Total sleep time (mins)	456.77 ± 82.26	432.07 ± 93.50	.33[a]	r = .46, p = .10[d]
Wake after sleep onset (mins)	79.67 ± 48.96	168.50 ± 64.85	.001[a]*	r = .16, p =.58[d]
Number of awakenings	25.79 ± 11.38	29.71 ± 12.90	.43[a]	r = -.10, p = .74[d]

Notes. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.01) (0.05/5 = 0.01). [a] Paired samples *t*-test, [b] Wilcoxon signed-rank test. [c] Spearman's correlation coefficient, [d] Pearson's correlation coefficient. M = Mean, SD = Standard deviation

Table 6.5 Polysomnography vs actigraphy (healthy controls only $n = 17$)

Sleep variables	PSG ***M* ± *SD***	Actigraphy ***M* ± *SD***	***p* value**	Correlation coefficient
Sleep efficiency (%)	89.74 ± 4.07	80.76 ± 4.68	<.001[a]*	r = .28, p = .28[d]
Sleep onset latency (mins)	26.79 ± 18.73	17.94 ± 17.96	.01[b]	r_s = .64, p = .01[c]
Total sleep time (mins)	491.66 ± 53.00	466.65 ± 56.69	.04[b]	r_s = .72, p = .001[c]*
Wake after sleep onset (mins)	29.46 ± 12.95	92.76 ± 30.40	<.001[a]*	r = .55, p = .02[d]
Number of awakenings	26.18 ± 7.66	25.82 ± 4.81	.88[a]	r = -.04, p = .87[d]

Notes. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.01) (0.05/5 = 0.01). [a] Paired samples t-test, [b] Wilcoxon signed-rank test. [c] Spearman's correlation coefficient, [d] Pearson's correlation coefficient. M = Mean, SD= Standard deviation.

6.7.4 Summary of findings

6.7.4.1 Polysomnography vs actigraphy (children with narcolepsy and healthy controls combined *n* = 31)

The results show that there was a significant difference between PSG and actigraphy measurements for the following sleep variables: sleep efficiency (p = <.001) and wake after sleep onset (p = .001). The actigraphy measure significantly over-estimated wake after sleep onset relative to PSG, which led to the actigraphy measure also significantly underestimating sleep efficiency. There was no significant difference between the two measurements for sleep onset latency (p = .07), total sleep time (p = .02) and the number of awakenings (p = .53).

The results also show that there were significant positive correlations between PSG and actigraphy measurements for the following sleep variables: total sleep time (strong correlation) and wake after sleep onset (moderate correlation). Moderate correlations were also found for sleep efficiency and sleep onset latency but they were not statistically significant after correcting for multiple comparisons. The correlation between the two measurements for number of awakenings was not significant.

6.7.4.2 Polysomnography vs actigraphy (children with narcolepsy only *n* = 14)

The results show that there was a significant difference between PSG and actigraphy measures for wake after sleep onset (p = .001). The actigraphy measure significantly over estimated wake after sleep onset relative to PSG, which led to the actigraphy measure underestimating sleep efficiency. There were no significant differences between the two measurements for any of the other sleep variables.

The results did not show any significant correlations between PSG and actigraphy measurements for the sleep variables in children with narcolepsy. However, sleep efficiency, sleep onset latency and total sleep time had moderate positive correlation coefficients indicating that the measures may be correlated but the sample size may have been too small for the correlation to reach statistical significance. Wake after sleep onset had a weak positive correlation coefficient and the number of awakenings had a weak negative correlation coefficient.

6.7.4.3 Polysomnography vs actigraphy (healthy controls only *n* = 17)

The results show that there was a significant difference between PSG and actigraphy measurements for the following sleep variables: sleep efficiency (p = <.001) and wake after sleep onset (p = <.001). The actigraphy measure significantly over estimated wake after sleep onset relative to PSG, which led to the actigraphy measure significantly underestimating sleep efficiency and total sleep time. There was no significant difference between the two measurements for the number of awakenings (p = .88), total sleep time (p = .04) and sleep onset latency (p = .01).

The results also show that there was a significant positive correlation between PSG and actigraphy measurements for total sleep time (strong correlation). Moderate correlations were also found sleep onset latency and wake after sleep onset but they were not statistically significant after correcting for multiple comparison. There was no significant correlation between the two measures for sleep efficiency or number of awakenings.

6.7.5 Discussion

The aim of the current analysis was to establish the agreement between two objective measures of sleep (polysomnography and actigraphy) in children with narcolepsy and healthy controls.

When the children with narcolepsy and the healthy children were combined, the results showed that there were significant moderate-to-strong positive correlations between PSG and actigraphy measures for measures of total sleep time and wake after sleep onset. However, when the groups were considered separately, the strength of the correlations reduced in the narcolepsy group but not in the control group. The results suggest that actigraphy may be less reliable at estimating sleep-wake patterns in children with narcolepsy than in healthy controls. This may be because the children with narcolepsy have more disturbed overnight sleep and are more restless when asleep than healthy controls. Actigraphy may over estimate wake after sleep onset in this population because the software scores movement during the night as ‘wake’ when in fact the child is asleep but moving around and therefore actigraphy results may underestimate sleep efficiency in children with narcolepsy.

The results indicate that the ActiGraph wGT3X-BT activity monitors are a useful and reliable method for measuring sleep in healthy children over a number of days. However, the results have also shown that actigraphy measurements of wake after sleep onset and sleep efficiency should be interpreted with caution, as the data consistently showed that actigraphy over-estimated wake after sleep onset compared to PSG which led to the measure underestimating sleep efficiency. The results have shown that actigraphy may be less reliable at estimating sleep-wake patterns in children with narcolepsy than healthy controls. It is important to remember that actigraphy monitors estimate sleep-wake patterns based on movement and therefore if a child is restless in the night (whilst asleep) the actigraphy results will report that the child is awake. Conversely, if a child is restless during a polysomnography recording, movement will be detected but the EEG signals will show that the child is still asleep. Polysomnography is therefore a more accurate measure of sleep than actigraphy.

6.7.6 Conclusion

This is the first study to compare polysomnography and actigraphy measures of sleep in children with narcolepsy. The results showed that there were significant moderate-to-strong positive correlations between polysomnography and actigraphy measurements of total sleep time and wake after sleep onset when the data from children with narcolepsy and health controls were combined. However, actigraphy tends to overestimate wake after sleep onset compared to gold standard polysomnography. The findings suggest that the actigraphy devices used in this study are a useful method for measuring sleep in children. However, the results have also highlighted that it is important to consider the limitations of actigraphy devices when interpreting the actigraphy results reported below in section 6.8.

6.8 Actigraphy

6.8.1 Introduction

The aim of this study was to investigate how overnight sleep in children with narcolepsy compares with that of gender and age matched healthy controls by objectively measuring the children's overnight sleep for at least a week in their natural environment using actigraphy. Chapter 4 provides an overview of how sleep is measured using actigraphy, the actigraphy monitors used in this study (ActiGraph wGT3X-BT monitors) and the procedure for collecting the actigraphy data (see section 4.8.2.1). The children were asked to wear the actigraphy monitor securely on their non-dominant wrist for 8 consecutive days and 8 nights as the aim was to collect at least 5 nights of reliable actigraphy data from each child.

As outlined in section 6.1, it was hypothesised that children with narcolepsy will have significantly poorer sleep efficiency, significantly shorter sleep onset latency and spend significantly more time awake after sleep onset compared to matched controls. It was also hypothesised that children with narcolepsy will have a greater number of awakenings than matched controls.

6.8.2 Actigraphy data analysis

22 of the 23 children with narcolepsy agreed to wear the activity monitor. One child refused to wear the monitor but did not give a reason why. All 23 of the children in the control group agreed to wear the activity monitor.

Actilife software (version 6.13.2) (ActiGraph, Pensacola, Florida, USA) was used to download and process the actigraphy data. As described in Chapter 4, the actigraphy monitors contain a wear sensor which detect periods of time that the device was not worn. This wear sensor information was used alongside the sleep diaries to flag data as 'wear time' or 'non-wear time' within Actilife's wear time validation tool. Data flagged as "non-wear time" (invalid data) was then excluded from further analysis. The wear time validation tool provided a summary of the minutes of wear time and non-wear time per day for each child. Actilife's sleep analysis tool was used alongside the information provided in the sleep diaries to determine sleep onset latency (SOL), sleep efficiency (SE), total minutes in bed (TIB), total sleep time (TST), wake after sleep onset (WASO), the number of awakenings and average awakening (minutes) (see section 4.8.2.1). Figure 6.1 shows an example of a graph

produced by the sleep analysis software within Actilife. The graph displays the actigraphy data of a 15 year old female with narcolepsy collected across 8 days and 8 nights. The researcher manually entered the child's 'time in bed' and 'time out of bed' using the information provided in the sleep diary. The sleep periods are highlighted in pink on the graph. The green line represents the period of time scored as sleep using the Sadeh sleep scoring algorithm (Sadeh, 2011). The blue lines represent activity counts.

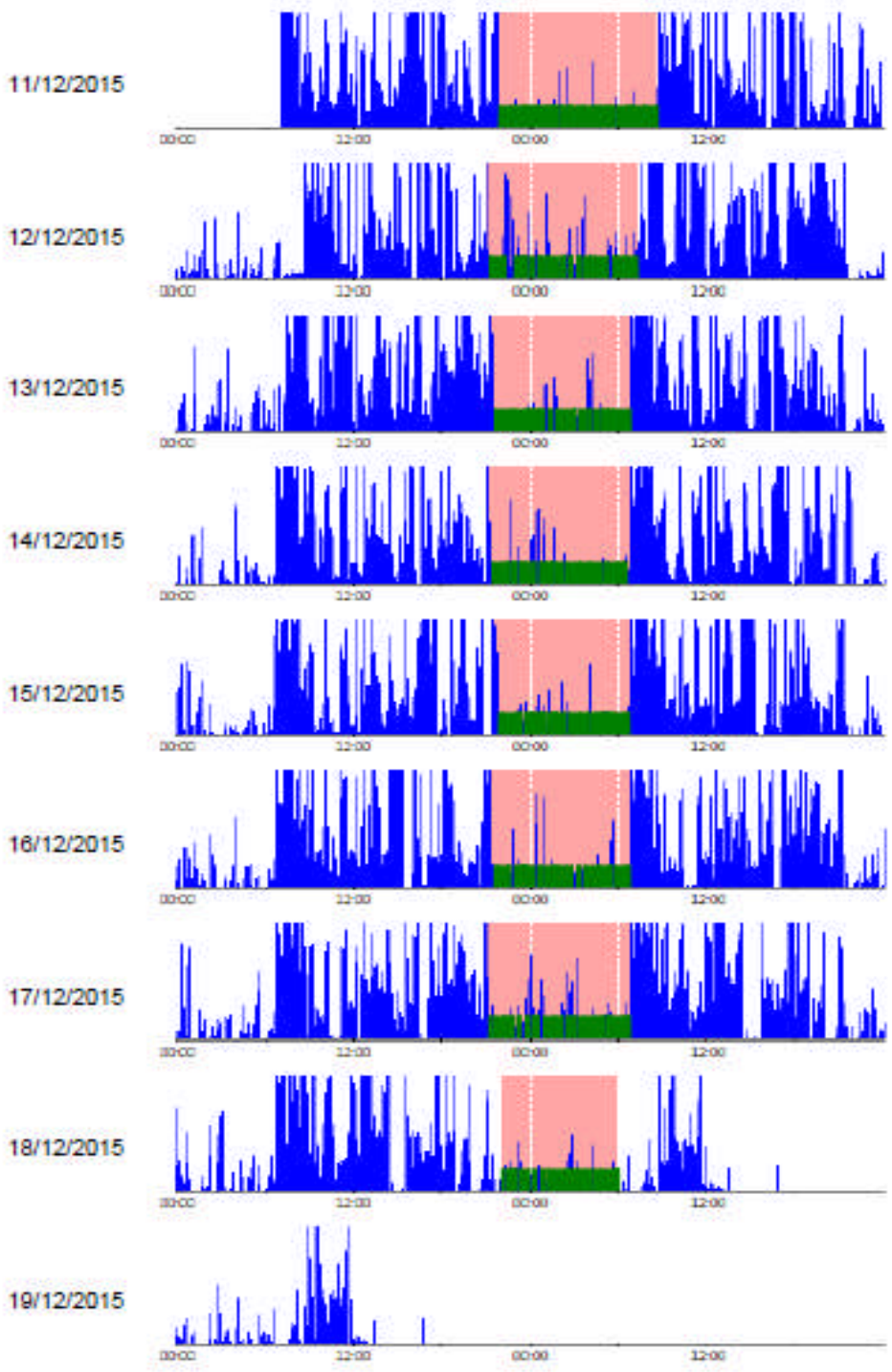

Figure 6.1 Graph displaying the actigraphy data collected from a 15 year old female with narcolepsy across 8 days and 8 nights.

6.8.3 Inclusion criteria

Based on the existing literature which suggests that five nights of recording are necessary for reliable actigraphy measures of sleep in children and adolescents (Acebo et al., 1999), the criteria for inclusion in the actigraphy analysis was children with at least 5 consecutive nights of reliable wear time, where at least one of the nights was a night of the weekend (Friday or Saturday night). For consistency, if a child had more than 5 nights of reliable recording, the first 5 nights of the recording were chosen for inclusion in the actigraphy analysis. If there was any missing data within the first 5 nights of recording, the next available set of 5 consecutive nights was chosen for inclusion in the analysis.

Data were lost from one child with narcolepsy during the download process and another child with narcolepsy was only able to wear the actigraphy monitor for three nights due to the monitor being delayed in the mail to The Republic of Ireland. Consequently these children were excluded from the actigraphy analysis. One child from the control group was excluded from the analysis because they did not wear the watch consistently due to going abroad during the week of the actigraphy recording. As described in Chapter 5, two of the control children met the exclusion criteria for the study and therefore were excluded from all analyses in this thesis. Therefore, in total there were 20 children with narcolepsy and 20 healthy controls included in the actigraphy analysis. Six of the children with narcolepsy and five of the healthy controls wore the actigraphy monitor during the school holidays. All of the other children wore the actigraphy monitor during school term time.

6.8.4 Results

Data consisted of a mean value based on five consecutive nights, where at least one of the nights was a night of the weekend (Friday or Saturday). Table 6.8 displays the actigraphy data.

Table 6.6 Actigraphy data

Measurement	Narcolepsy *M* ± *SD* (*n* = 20)	Control *M* ± *SD* (*n* = 20)	*p* value	Cohen's *d or 'r'*
Sleep onset latency (SOL) (minutes)	24.08 ± 24.46	16.03 ± 8.02	.64[b]	*r* = -.07
Sleep efficiency (SE) (%)	63.83 ± 9.80	78.84 ± 5.40	<.001[a]*	*d* = 1.90
Time in bed (TIB) (minutes)	629.58 ± 73.67	600.29 ± 48.77	.15[a]	*d* = .47
Total sleep time (TST) (minutes)	400.28 ± 70.14	473.52 ± 52.77	.001[a]*	*d* = 1.18
Wake after sleep onset (WASO) (minutes)	205.22 ± 67.99	110.74 ± 33.88	<.001[a]*	*d* = 1.76
Number of awakenings	32.69 ± 9.02	29.85 ± 14.83	.09[b]	*r* = -.27
Average awakening (minutes)	6.75 ± 2.72	4.19 ± 1.00	.001[a]*	*d* = 1.25

Note. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.007) (0.05/7 = 0.007). M = Mean, SD = Standard deviation.

[a] Independent *t*-test

[b] Mann-Whitney *U* test

6.8.5 Summary of findings

- The actigraphy data reveal significant differences between the children with narcolepsy and the healthy controls in four of the sleep variables: sleep efficiency (p = <.001), total sleep time (p = .001), wake after sleep onset (p = <.001) and the average awakening length (p =.001).
- Children with narcolepsy had significantly reduced sleep efficiency compared to healthy controls.
- Children with narcolepsy had significantly less total sleep time than healthy controls.
- The average length of awakenings were significantly longer for children with narcolepsy compared to healthy controls.
- There were no significant differences between the two groups in sleep onset latency (p = .64) and time in bed (p =.15).

6.8.6 Discussion

The aim of this study was to investigate how overnight sleep in children with narcolepsy compares with that of gender and age matched healthy controls by objectively measuring the children's overnight sleep for at least a week in their natural environment using actigraphy.

The actigraphy data supported the hypothesis that children with narcolepsy have significantly poorer sleep efficiency and spend significantly more time awake after sleep onset compared to matched controls. However, as discussed in section 6.7.5, these results must be interpreted with caution because the actigraphy monitors used in this study tend to overestimate wake after sleep onset relative to PSG measures and this may have led to sleep efficiency in children with narcolepsy being underestimated. It is possible that the children with narcolepsy were more restless than controls whilst asleep and this led the monitors to report that the children with narcolepsy were awake more in the night than controls when in fact they were not. On the other hand, the results from the gold standard polysomnography measurement of sleep in children with narcolepsy (reported in section 6.3.3) also show that children with narcolepsy have significantly more wake after sleep onset compared to the healthy controls, which gives more confidence in the actigraphy findings.

The actigraphy data did not support the hypothesis that children with narcolepsy have shorter sleep onset latency and more awakenings than healthy controls. However, the actigraphy results did show that the awakenings of children with narcolepsy were significantly longer than the awakenings of the controls. The actigraphy results also show that total sleep time was significantly greater in healthy controls than children with narcolepsy. It is interesting that the polysomnography results did not show a significant difference in total sleep time between the two groups. As previously mentioned, actigraphy monitors estimate sleep-wake patterns based on movement which can lead to the actigraphy measurement overestimating wake after sleep onset and underestimating total sleep time relative to PSG. It is therefore possible that the children with narcolepsy were more restless during their sleep than the healthy controls and this led the actigraphy software to score more time asleep as 'wake' and this lead to the significant difference in total sleep time in the actigraphy results but not in the PSG results. Future studies should consider video recording during polysomnography and actigraphy recordings as this would reveal if children with narcolepsy are more restless when asleep than healthy children.

Actigraphy is a non-invasive method of measuring sleep in children in their own environments over a number of nights. As the actigraphy results are based on a 5 nights of sleep data, they are likely to be more representative of the child's typical sleep than the one night of sleep recorded using polysomnography. However, the actigraphy sleep variables are also calculated based on the times the child was reported to be in and out of bed. These times are reported by parents in the sleep diary. Therefore if inaccurate information is provided by the parents, the overall actigraphy results may be inaccurate.

6.8.7 Conclusion

The actigraphy results suggest that children with narcolepsy have more disturbed night time sleep compared to healthy controls. This is in line with the polysomnography results reported in section 6.3.3.

6.9 Summary of the Chapter

This is the first study to conduct unattended home sleep studies in children with narcolepsy and to establish the agreement between polysomnography and actigraphy measures of sleep in children with narcolepsy. The polysomnography and actigraphy results presented in this Chapter support the hypothesis that children with narcolepsy have more disturbed sleep comparted to controls due to spending significantly more time awake after sleep onset. As only two children with narcolepsy were not treated with medication at the time of the study, it may be concluded that sleep disturbance persists even when the children are treated with stimulant and antidepressant medications.

The results showed that there were significant positive correlations between polysomnography and actigraphy measurements of total sleep time and wake after sleep onset when the data from children with narcolepsy and health controls were combined. However, actigraphy tends to overestimate wake after sleep onset compared to gold standard polysomnography and may be less reliable at estimating sleep-wake patterns in children with narcolepsy than in healthy controls due to their significantly disturbed nocturnal sleep.

Chapter 7 Characterisation of daytime sleep and physical activity in children with narcolepsy

7.1 Daytime sleep in children with narcolepsy

7.1.1 Introduction

In Chapter 6, the overnight sleep of children with and without narcolepsy was measured using The Child Sleep Habits Questionnaire, polysomnography and actigraphy. The results showed that the children with narcolepsy had significantly greater disturbance in sleep, spent more time awake after sleep onset and had reduced sleep efficiency (measured by actigraphy) compared to the children without narcolepsy. As only two children with narcolepsy were not treated with medication at the time of the study, it may be concluded that sleep disturbance persists even when the children are treated with stimulant and antidepressant medications. As discussed in Chapter 6, it is possible that the medications are having an effect on overnight sleep quality and resulting in the children with narcolepsy spending more time awake after sleep onset compared to controls.

In addition to stimulant medication, planned daytime naps are often recommended for the management of disrupted sleep and excessive daytime sleepiness in children with narcolepsy (Elphick et al., 2017). One of the aims of The Paediatric Narcolepsy Project was to investigate what proportion of the children with narcolepsy included in this study nap during the day and to investigate the average frequency and length of the naps.

It was hypothesised that napping would not be observed in the healthy controls and that the majority of children with narcolepsy would nap because of their excessive daytime sleepiness and because planned naps are often recommended as part of their treatment plan. It was hypothesised that the frequency and the length of naps would vary between children because symptom severity and willingness to nap is known to vary between children.

7.1.2 Daytime sleepiness

As described in Chapter 4, The Paediatric Daytime Sleepiness Questionnaire (Drake et al., 2003) was used to measure and compare daytime sleepiness in the children with narcolepsy and the healthy controls. Children were asked to complete this

questionnaire and higher scores indicated greater levels of sleepiness. Three children with narcolepsy did not complete the questionnaire due to time constraints. The results show that children with narcolepsy reported that they are significantly more sleepy during the day than the children without narcolepsy (see Table 7.1).

Table 7.1 The Paediatric Daytime Sleepiness Questionnaire data

Measurement	Narcolepsy *M* ± *SD* (*n* = 20)	Control *M* ± *SD* (*n* = 21)	df	*t*	*p* value	Cohen's *d*
The Paediatric Daytime Sleepiness Questionnaire Score	17.00 ± 5.94	10.14 ± 3.71	39	4.46	<.001	1.39

Notes. M = Mean, SD = Standard deviation.

7.1.3 Daytime sleep measured by actigraphy

Daytime sleep in children with narcolepsy and healthy controls was measured using actigraphy and sleep diaries. The same sample of children that were included in the overnight sleep actigraphy analysis (described in Chapter 6), were included in the daytime sleep analysis described in this Chapter. The sample included 20 children with narcolepsy and 20 healthy controls. These children had 5 consecutive days and nights of actigraphy wear time, where at least one night was a weekend night (Friday or Saturday). 18 out of the 20 children with narcolepsy were treated with medication. Six of the children with narcolepsy and five of the healthy controls wore the actigraphy monitor during the school holidays. All of the other children wore the actigraphy monitor during school term time.

During the week that the children were wearing the actigraphy monitor, parents were asked to note down any naps their child had during the day in the sleep diary provided. The parents were asked to provide information about the time the child started to fall asleep, the time the child woke up and whether this was a typical day of naps for their child. If it was not a typical day of naps, the parents were asked to provide a reason why. This allowed the researcher to determine whether the 5 days

that the child was wearing the actigraphy monitor were likely to be representative of a typical week for the child. As described in Chapter 6, the information provided by the parents was used by the researcher to manually enter the daytime sleep times ('time in bed' and 'time out of bed') within Actilife's sleep analysis tool (ActiGraph, Pensacola, Florida, USA) (see section 6.8.2). Figure 7.1 shows an example of a graph produced by the sleep analysis software within Actilife when daytime sleep and overnight sleep periods have been manually entered by the researcher. The graph displays the actigraphy data of a 15 year old female with narcolepsy collected across 8 days and 8 nights in this study. These are the same data used as an example in Chapter 6 (see Figure 6.1), however the graph now shows additional periods of sleep during the day highlighted in pink. The green lines represent the period of time scored as sleep by the Sadeh sleep scoring algorithm (Sadeh, 2011). The blue lines represent activity counts.

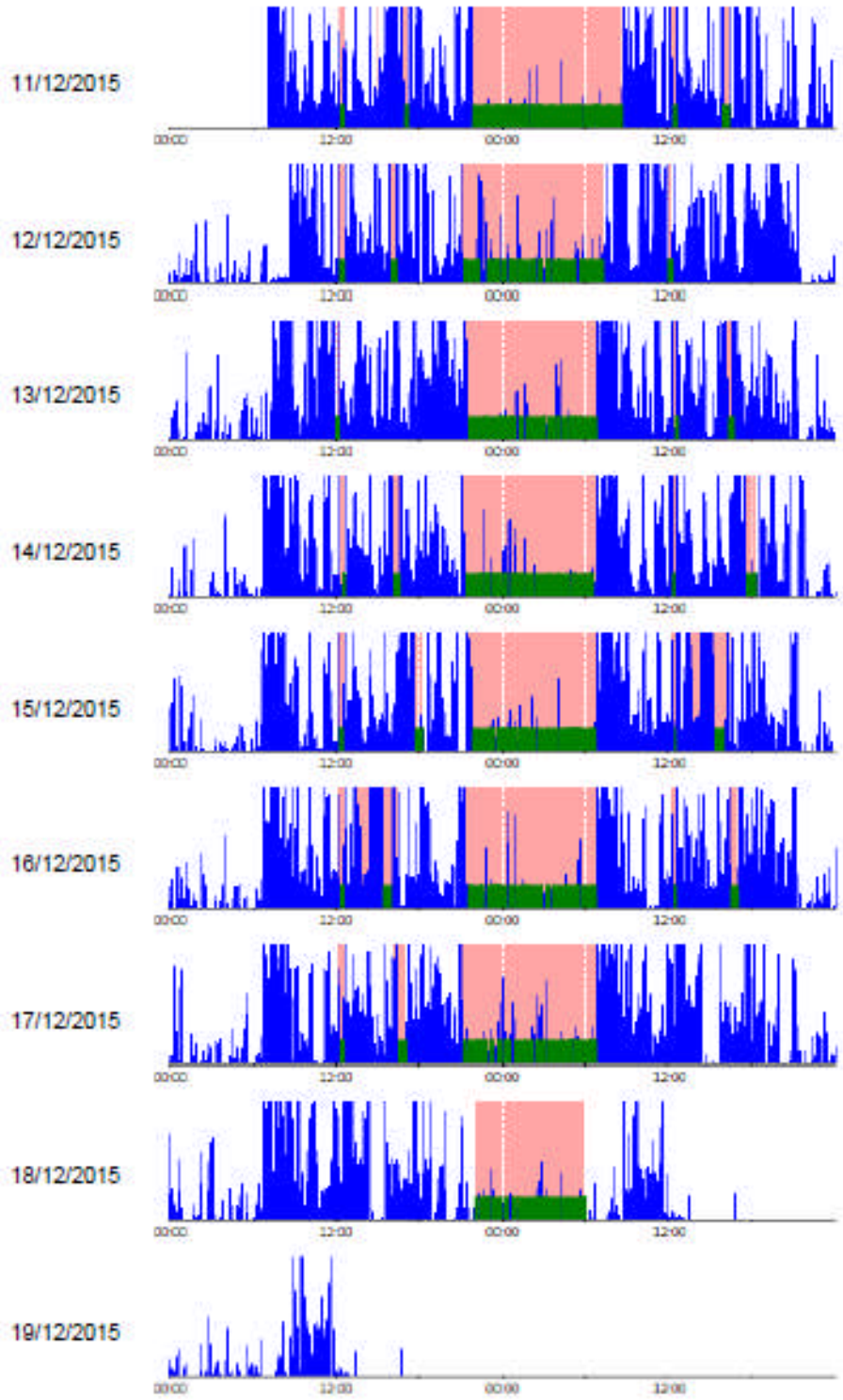

Figure 7.1 Graph displaying the actigraphy data collected from a 15 year old female with narcolepsy across 8 days and 8 nights. Daytime and overnight sleep periods are highlighted in pink.

The outcomes of interest from the actigraphy data and the sleep diaries were the number of naps per day, the total time in bed during the day (minutes), the total sleep time during the day (minutes) and the total number of naps over 5 days. Descriptive statistics for these measures are reported in Table 7.2. Sleep variables such as sleep onset latency, sleep efficiency, wake after sleep onset, number of awakenings and the length of awakenings were not calculated for daytime naps because there were no control data available to compare these outcomes to (only one healthy child napped).

7.1.4 Daytime sleep results

The results show that during the five consecutive days of actigraphy wear time, all children with narcolepsy napped (n = 20) and one child without narcolepsy had three naps over three days (one per day). The child without narcolepsy reported that the naps were due to having late nights. Due to the lack of children in the control group who napped, Table 7.2 displays the daytime sleep results for the children with narcolepsy only. The results show that on average, children with narcolepsy had two naps per day (range 1-4) and 6 naps across five days (range 2-13). The results also show that on average, children with narcolepsy spent more ‘time in bed’ (44 minutes) during the day than time asleep during the day (17 minutes).

Table 7.2 Daytime sleep data

Measurement	Narcolepsy *M* ± *SD* (*n* = 20)	Range	Median
Number of naps per day	1.80 ± 0.89	1-4	2
Total time in bed during the day (minutes)	44.20 ± 21.64	15-101	44.29
Total sleep time during the day (TST) (minutes)	17.40 ± 18.17	0-84	13.93
Total number of naps over 5 days	6.15 ± 3.18	2-13	5.50

Notes. M = Mean, SD = Standard deviation.

7.1.5 Summary of findings

7.1.5.1 The Paediatric Daytime Sleepiness Questionnaire

- The Paediatric Daytime Sleepiness Questionnaire was completed by 20 children with narcolepsy and 21 children without narcolepsy. 18 out of the 20 children with narcolepsy were treated with medication.
- Children with narcolepsy reported that they were significantly more sleepy during the day than children without narcolepsy (p = <.001).

7.1.5.2 Daytime sleep measured by actigraphy

- 20 children with narcolepsy were included in this analysis. 18 of the 20 children with narcolepsy were treated with medication.
- The results show that during the five consecutive days of actigraphy wear time, all children with narcolepsy napped (n = 20) and one child without narcolepsy had three naps over three days (one per day). The child without narcolepsy reported that the naps were due to having late nights.
- On average, children with narcolepsy had two naps per day (range 1-4).

- On average, children with narcolepsy had 6 naps across five days (range 2-13).
- On average, children with narcolepsy spent more 'time in bed' (44 minutes) during the day than time asleep during the day (17 minutes).

7.1.6 Discussion

The aim of this study was to investigate what proportion of the children nap during the day and to investigate the average frequency and length of the naps.

The Paediatric Daytime Sleepiness Questionnaire results show that children with narcolepsy reported that they are significantly more sleepy during the day than healthy controls. 18 out of the 20 children with narcolepsy included in this analysis were treated with medication and the majority were taking medication to treat both excessive daytime sleepiness and cataplexy (see Chapter 5 section 5.1.1). The results indicate that the medications used to manage daytime sleepiness in children with narcolepsy do not eliminate daytime sleepiness or improve daytime sleepiness to the point that children with narcolepsy experience typical levels.

As expected, the actigraphy and sleep diary results show that majority of healthy controls did not nap during the day. One child without narcolepsy reported having three naps across three days (one per day) due to having late nights. The results supported the hypothesis that the majority of children with narcolepsy nap during the day. This study found that all 20 of the children with narcolepsy napped during the day but the frequency and length of the naps varied between children. It is likely that many of the children with narcolepsy had been advised to take planned naps during the day as part of their treatment plan. On average children with narcolepsy had two naps per day and the average time spent asleep during the day was 17 minutes. The total minutes in bed and total sleep time during the day varied between children. The results suggest that naps are a necessary part of children with narcolepsy's treatment plan (even when they are treated with medication) and they may help the children to manage the effects of their disturbed night time sleep. It appears that some children with narcolepsy require a lot more sleep during the day than other children with narcolepsy (range 0-84 minutes).

It is interesting that according to the actigraphy data, children with narcolepsy spent more time in bed during the day than the time they spent asleep. Total time in bed during the day was calculated using the 'time in bed' and 'time out of bed' provided

by the parents in the sleep diary. As naps occurred during the day, many children did not nap in their own bed and instead napped in a variety of places: on the sofa, in the car, in their nap room at school, on the bus or on other forms of public transport. It may therefore have been more difficult for parents to accurately report the time the child started to fall asleep and wake up, especially if the child was at school (14 children with narcolepsy and 15 children without narcolepsy wore the actigraphy monitor during school term time). This may have led to the total 'time in bed' being over estimated based on the information provided by the parents. Another possibility is that the actigraphy monitors were over estimating wake after sleep onset because the children with narcolepsy were restless during their nap. As described in Chapter 6, actigraphy provides an estimate of sleep-wake patterns based on movement and the actigraphy monitors used in this study were found to overestimate wake after sleep onset relative to PSG (see section 6.7.5). The actigraphy results must therefore be interpreted with caution, especially as polysomnography recordings were not conducting during the children's naps and therefore the agreement between the two measures cannot be established for this analysis. However, if the results are accurate they suggest that children with narcolepsy are being given periods of time to nap during the day but they may be resting or doing something else rather than sleeping during these times. Some parents, especially of older children, may be unaware if a child has slept when they said they were going for a nap. It is common for children with narcolepsy to be resistant to taking planned naps as this can mean missing out on school and home life. Educating children with narcolepsy and their parents about good sleep hygiene is important for increasing the benefits of sleeping during the day in this population. For example, children with narcolepsy should be encouraged to only spend time in bed during the day when they are planning to sleep and to remove all electronic devices from the bedroom or nap room. This may help the children with narcolepsy to fall asleep faster and get good quality sleep during their nap, which may lead to increased alertness during the day.

7.1.7 Conclusion

The results suggest that the children with narcolepsy are significantly more sleepy during the day than children without narcolepsy even though the majority of the children with narcolepsy were treated with stimulant medication. All children with narcolepsy included in this analysis napped during the day and the frequency and length of the naps varied between children. It is not clear why the children with narcolepsy vary in their need for sleep during the day but it is possible that this is associated with the quality of their overnight sleep or their daytime physical activity levels. The relationships between these variables are explored in section 7.3. The results suggest that the medications used to treat excessive daytime sleepiness in children with narcolepsy do not remove the need for the children to nap during the day. This research suggests that daytime naps may play a crucial role in the management of excessive daytime sleepiness and disturbed overnight sleep in children with narcolepsy.

7.2 Physical activity

7.2.1 Introduction

In addition to planned naps, another common behavioural strategy for the management of narcolepsy symptoms in children is encouraging daily physical activity. Daily physical activity is often recommended as it may increase alertness, lead to weight loss and lead to improvements in the overall well-being and health of children with narcolepsy. It is also possible that physical activity could improve overnight sleep efficiency in children with narcolepsy. The aim of this study was to investigate how the levels of physical activity in children with narcolepsy compare with that of healthy controls. It was hypothesised that when awake, children with narcolepsy would be significantly less active throughout the day compared to matched controls. This may be associated with their excessive daytime sleepiness.

7.2.2 Physical activity data analysis

As described in Chapter 4, the data scoring tool within Actilife (ActiGraph, Pensacola, Florida, USA) was used to score the daytime physical activity data (see section 4.8.3). For this analysis only, sleep periods (naps during the day and overnight sleep) were marked as ‘non-wear’ time with the wear time validation tool and were excluded from the actigraphy analysis. The aim was to look at the physical activity levels of children with narcolepsy and children without narcolepsy when both groups were awake. If sleep periods had not been excluded from this analysis, daytime naps would be classified as sedentary time by the Actilife software and would have increased the amount of time the children with narcolepsy appeared to be sedentary when in fact they were asleep. As described in Chapter 4, The Actilife software (ActiGraph, Pensacola, Florida, USA) breaks down the proportion of time (total epochs) within each dataset the participant spent in different categories of intensity using ‘cut points’. The cut points are displayed in Chapter 4 and they categorize the data collected from the wGT3X-BT monitors (known as counts) into different intensity categories (sedentary, light, moderate, vigorous) (see section 4.8.3).

The daytime physical activity outcomes of interest were:

- Percentage time sedentary
- Percentage time in light activity
- Percentage time in moderate activity
- Percentage time in vigorous activity
- Overall physical activity (vector magnitude counts per minute).

Percentage time in each level of physical activity was calculated by the time in a particular level of activity divided by the total wear time, multiplied by 100. Overall physical activity was measured by vector magnitude (VM) counts per minute (CPM). Vector magnitude is the square root of the sum of the squares of each axis of data. Overall physical activity was determined as the total count of activity (VM) divided by the total duration of wear time to determine counts per minute (CPM). Vector magnitude counts per minute is the appropriate measure of overall physical activity because the actigraphy monitors were worn on the wrist.

Based on existing literature, the data were checked to ensure all children included in the daytime physical activity analysis had worn the actigraphy device for at least 600 minutes (10hrs) per day.

7.2.3 Physical activity results

As described in Chapter 6, 20 children with narcolepsy and 20 healthy controls were included in the actigraphy analysis. Physical activity data consisted of a mean value based on five consecutive days, where at least one of days was a weekend day (Friday or Saturday). Overnight and daytime sleep periods were excluded from this analysis. Table 7.3 displays the results of the actigraphy analysis for daytime physical activity levels in children with and without narcolepsy. There was no significant difference in the percentage of time spent in light physical activity when awake between the two groups (p = .09). Healthy children spent a significantly greater percentage of their time in moderate physical activity when awake than children with narcolepsy (p = .002). The results show that none of the children spent any time in vigorous physical activity whilst wearing the actigraphy monitor.

Children with narcolepsy were significantly less active overall (measured by vector magnitude counts per minute) than children without narcolepsy when awake (p = .001).

Table 7.3 Actigraphy data

Measurement	Narcolepsy *M* ± *SD* (*n* = 20)	Control *M* ± *SD* (*n* = 20)	*p* value	Cohen's *d* *or 'r'*
Sedentary (%)	37.20 ± 11.01	27.75 ± 8.41	.003[b]*	*r* = -.46
Light (%)	15.95 ± 2.76	14.95 ± 1.85	.09[b]	*r* = -.27
Moderate (%)	46.35 ± 11.79	57.35 ± 9.48	.002[a]*	*d* = 1.03
Vigorous (%)	00.00 ± 00.00	00.00 ± 00.00		
Overall physical activity (counts per minute)	2653.59 ± 892.68	3436.41 ± 791.59	.001[a]*	*d* = .93

Note. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.01) (0.05/4 = 0.01). M = Mean, SD= Standard deviation.

[a] Independent *t*-test

[b] Mann-Whitney *U* test.

7.2.4 Summary of findings

- 20 children with narcolepsy and 20 healthy children were included in this analysis. 18 of the 20 children with narcolepsy were treated with medication.
- The results show that the children with narcolepsy spent a significantly greater percentage of their time sedentary when awake than children without narcolepsy (p = .003).
- There was no significant difference in the percentage of time spent in light physical activity when awake between the two groups (p = .09).
- Healthy children spent a significantly greater percentage of their time in moderate physical activity when awake than children with narcolepsy (p = .002).

- The results show that none of the children spent any time in vigorous physical activity whilst wearing the actigraphy monitor.
- Children with narcolepsy were significantly less active overall (measured by vector magnitude counts per minute) than children without narcolepsy when awake (p = .001).

7.2.5 Discussion

The aim of this study was to use actigraphy to investigate how the levels of physical activity in children with narcolepsy compare with that of healthy controls. It was hypothesised that when awake, children with narcolepsy would be significantly less active throughout the day compared to children without narcolepsy.

The actigraphy data supported the hypothesis that children with narcolepsy are significant less physically active than children without narcolepsy when awake. Daytime and overnight sleep periods were removed from this analysis to ensure that a direct comparison between the two groups could be made when the children were awake. Children with narcolepsy spent more time sedentary and less time in moderate physical activity than children without narcolepsy. There were no significant differences found between the two groups for the percentage of time spent in light or vigorous activity.

A possible reason why none of the children were shown to spend any time in vigorous activity is if the watch had been taken off for P.E classes in school or extra-circular sports activities. It is highly likely that the actigraphy monitor needed to be removed for sports such as rugby and gymnastics as wearing the monitor could cause injury to the child or others. The child was also asked to remove the actigraphy monitor for any water based activities such as swimming as it is not fully waterproof and therefore cannot be submerged in water. It is therefore possible that vigorous physical activity was taking place in both groups but that this could not be monitored using the actigraphy devices in this study. The parents were asked to note down when the watch was removed and the reason why. Many parents reported that their child had removed the actigraphy monitor for sports activities in order to comply with their school rules. It was not possible to analyse the amount of physical activity the children completed during these activities. Future research should use

actigraphy devices that are fully water proof and more discrete so that it may be safe for children to wear the device during sport activities.

14 children with narcolepsy and 15 children without narcolepsy wore the actigraphy monitor during school term time. The results are therefore more representative of children's activity levels when at school rather than when at home. However, all children wore the device for at least one weekend day so the results should be reasonably representative of a typical week for the children.

There are a number of possible explanations as to why the children with narcolepsy are less physically active when awake compared to children without narcolepsy. The disturbed overnight sleep of children with narcolepsy may lead to excessive daytime sleepiness. Excessive daytime sleepiness may lead to lack of motivation to engage in physical activity or children may worry about the knock on effects of doing too much physical activity on their ability to function afterwards and therefore avoid physical activity. Children with cataplexy may avoid participating in sports activities in order to avoid an injury or embarrassment if a cataplexy attack is triggered.

7.2.6 Conclusion

The results show that when awake, children with narcolepsy spent a significantly lower percentage of their time physically active than children without narcolepsy. Given the importance of physical activity for health, it is possible that the lower levels of physical activity may contribute to weight gain, sleepiness during the day and poor overnight sleep in children with narcolepsy. It is also possible that sleepiness during the day and poor overnight sleep lead to reduced physical activity. The relationships between overnight sleep, daytime naps and physical activity in children with narcolepsy are described in section 7.3 below.

7.3 Associations between overnight sleep, daytime sleep and physical activity

Chapter 6 and sections 7.1 and 7.2 of this Chapter describe the overnight sleep, daytime sleep and physical activity of children with narcolepsy and healthy controls. One of the aims of The Paediatric Narcolepsy Project was to investigate the relationships between sleep efficiency (measured by polysomnography (PSG)), time spent asleep during the day (measured by actigraphy) and physical activity (measured by actigraphy) in children with and without narcolepsy. 40 children were included in this analysis (children with narcolepsy $n = 20$, healthy controls, $n = 20$). Sleep efficiency is calculated by the child's total sleep time divided by the total time spent in bed and the polysomnography measurement of sleep efficiency was based on one night of recording. Daytime sleep and physical activity data collected using actigraphy consisted of a mean value based on five consecutive days, where at least one of days was a weekend day (Friday or Saturday).

Physical activity data were normally distributed, whereas sleep efficiency measured by PSG and total sleep time during the day data were not normally distributed. Therefore, the relationships between the variables were evaluated by Spearman's correlations. Three correlations were performed to investigate the relationship between sleep efficiency, time spent asleep during the day and physical activity, therefore the Bonferroni-adjusted significance level was $p <. 01$ (0.05/3 = 0.02). There was a significant negative correlation between age and physical activity, r_s (38) = -.51, $p = .001$ (as age increases, physical activity decreases) (see Figure 7.2). Therefore partial correlations controlling for age were performed when investigating the relationships between physical activity and sleep.

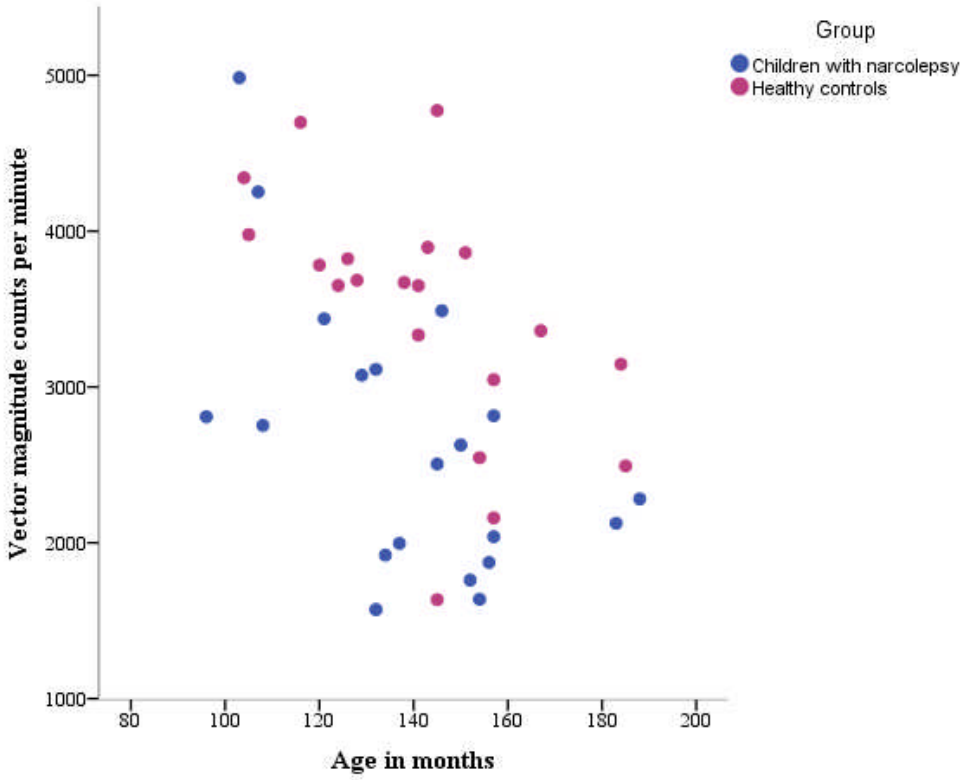

Figure 7.2 A scatterplot of the correlation between age in months and overall physical activity counts (measured by actigraphy-vector magnitude counts per minute) in children with narcolepsy and healthy controls (n = 40), r_s = -.51, p = .001.

7.3.1 Association between sleep efficiency and daytime sleep

The aim was to investigate whether there was a relationship between sleep efficiency and the time spent asleep in the day. In order to address this aim, sleep efficiency as measured by polysomnography was correlated with total sleep time during the day. For this analysis, only children with narcolepsy were included (n = 20) because all of the children with narcolepsy napped during the day and only one child from the control group napped. The hypothesis was that there will be a negative correlation between sleep efficiency and total sleep time during the day.

There was no significant correlation found between sleep efficiency measured by polysomnography and total sleep time during the day in children with narcolepsy, r_s (13) = .12, p = .71 (see Figure 7.3).

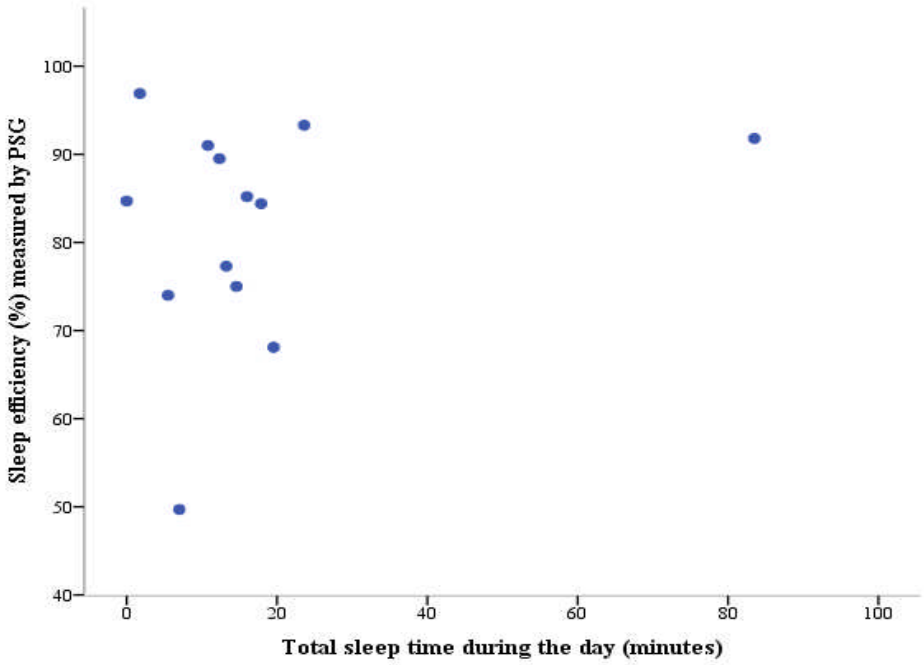

Figure 7.3 A scatterplot of the relationship between sleep efficiency (%) measured by polysomnography and total sleep time during the day (minutes) in children with narcolepsy (n = 20), r_s = .12, p = .71.

7.3.2 Association between sleep efficiency and physical activity

The aim was to investigate whether there was a relationship between sleep efficiency and daytime physical activity in children with narcolepsy and healthy controls (n = 40). In order to address this aim, sleep efficiency as measured by polysomnography was correlated with overall physical activity counts (measured by actigraphy-vector magnitude counts per minute). The hypothesis was that there will be a positive correlation between sleep efficiency and daytime physical activity.

There was a significant negative correlation between age and overall physical activity counts (r_s = -.51, p = .001), therefore a partial correlation was run to determine the relationship between sleep efficiency and overall physical activity counts, whilst controlling for age. There was a significant positive partial correlation between sleep efficiency measured by polysomnography and overall physical activity counts, whilst controlling for age, r_s (29) = .44, p = .01. Figure 7.5 displays the scatterplot for the partial correlation. The scatterplot was produced using unstandardized residuals and higher values indicate greater sleep efficiency and greater physical activity.

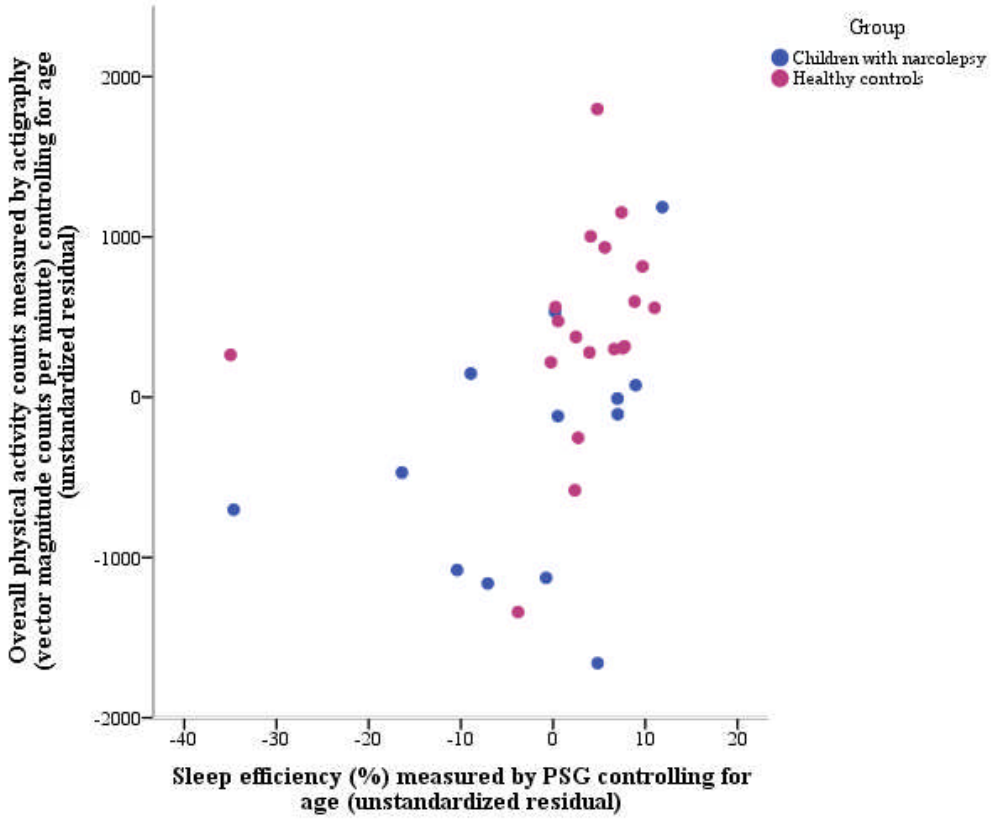

Figure 7.4 A scatterplot of the partial correlation between overall physical activity counts (measured by actigraphy-vector magnitude counts per minute) and sleep efficiency (%) measured by polysomnography (controlling for age) in children with narcolepsy and healthy controls (n = 40), r_s (29) = .44, p = .01.

7.3.3 The association between physical activity and daytime sleep

The aim was to investigate whether there was a relationship between daytime physical activity and the time spent asleep during the day in children with narcolepsy (n = 20). In order to address this aim, overall physical activity counts (measure by vector magnitude counts per minute) was correlated with total sleep time during the day. The hypothesis was that there will be a negative correlation between the time spent asleep during the day and physical activity.

There was a significant negative correlation between age and overall physical activity counts (r_s = -.51, p = .001), therefore a partial correlation was run to determine the relationship between overall physical activity counts and the time spent asleep during the day, whilst controlling for age. There was no significant correlation found between physical activity counts and time spent asleep in the day in children with narcolepsy, whilst controlling for age, r_s (17) = -.03, p = .90. Figure 7.7 displays the scatterplot for the partial correlation. The scatterplot was produced using unstandardized residuals and higher values indicate greater total sleep time during the day and greater physical activity.

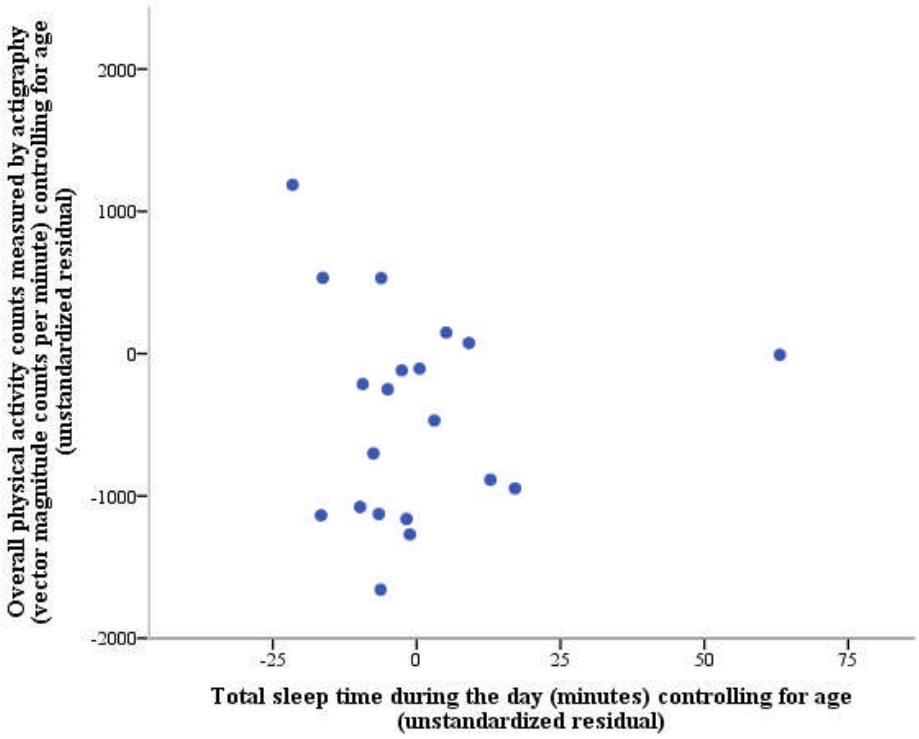

Figure 7.5 A scatterplot of the partial correlation between overall physical activity counts (measured by actigraphy-vector magnitude counts per minute) and total sleep time during the day (minutes) in children with narcolepsy (n = 20), r_s (17) = -.03, p = .90.

7.3.4 Summary of findings

Spearman's correlations revealed:

- There was no significant correlation found between sleep efficiency measured by polysomnography and total sleep time during the day in children with narcolepsy, r_s (13) = .12, p = .71.
- There was a significant positive partial correlation between sleep efficiency measured by polysomnography and overall physical activity counts in children with narcolepsy and healthy controls, whilst controlling for age, r_s (29) = .44, p = .01.
- There was no significant correlation found between overall physical activity counts and time spent asleep in the day in children with narcolepsy, whilst controlling for age, r_s (20) = -.03, p = .90.

7.3.5 Discussion

This is the first study to investigate the relationships between sleep efficiency (measured by polysomnography), time spent asleep during the day (measured by actigraphy) and physical activity (measured by actigraphy) in children with and without narcolepsy. The results showed significant positive partial correlations between sleep efficiency measured by polysomnography and actigraphy and overall physical activity counts in children with narcolepsy and healthy controls, whilst controlling for age. The results suggest that sleep efficiency may be associated with daytime physical activity in children with and without narcolepsy. However, as this is a correlational analysis it is not possible to infer causality. For example, reduced daytime activity could lead to poorer sleep efficiency or poor sleep efficiency could cause the child to be more tired and therefore lead to reduced daytime activity. A intervention study investigating the effects of an intervention designed to improve overnight sleep efficiency in children with narcolepsy (for example a behavioural sleep intervention) would provide information about the causal relationship between overnight sleep efficiency, total sleep time during the day and overall physical activity in children with narcolepsy. If for example, overnight sleep efficiency in children with narcolepsy improved following an intervention and this led to increased physical activity and reduced time spent asleep during the day, the direction of the relationship between these variables becomes clearer (poor sleep efficiency leads to increased total sleep time during the day and reduced physical activity).

7.4 Summary of the Chapter

The results described in this Chapter show that all of the children with narcolepsy included in this study nap during the day, even though 18 out of 20 of the children were being treated with medication. On average children with narcolepsy have two naps per day, which last less than 20 minutes on average. The results also show that children with narcolepsy are less physically active than healthy controls when awake. This is interesting given that the majority of children with narcolepsy were treated with stimulant medication. A significant positive relationship was found between sleep efficiency and physical activity. It is important to investigate whether the disturbed overnight sleep, daytime sleepiness and reduced physical activity of

children with narcolepsy are associated with their cognitive function and psychosocial well-being.

Chapter 8 Cognitive function in children with narcolepsy

8.1 Introduction

As described in Chapter 3, one of the aims of The Paediatric Narcolepsy Project was to investigate how cognitive function in children with narcolepsy compares with that of gender and age matched healthy controls. The aim was to assess the children with narcolepsy and the healthy controls at their optimal performance. In order to do this, the children with narcolepsy were asked to take their medication and nap as usual during the testing session. To ensure that the children felt alert throughout the testing session, the researcher used the Stanford Sleepiness Scale (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973) to measure the children's current level of sleepiness before each task began. If a child rated him/herself as a '4' on the scale or higher ('somewhat foggy', 'foggy', 'sleepy' or 'sleep onset soon'), the researcher asked the child if they would like to nap, take a break and checked with the parents if they were due medication (this only occurred when testing the children with narcolepsy). It is therefore assumed that all of the children were feeling alert during the testing session. The majority of the participants completed the tasks in the early afternoon.

Based on the previous literature summarised in Chapter 2, it was hypothesised that children with narcolepsy (even those who are medicated) will have normal full scale I.Q's (within the average range) but they will have significantly impaired attention and executive functions compared to healthy controls.

8.2 Results

8.2.1 Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II) (Wechsler, 2011)

As described in Chapter 4, the vocabulary and matrix reasoning subtests of the WASI-II were administered (see section 4.8.4). The Full Scale IQ-2 Subtests (FSIQ-2) score provides a general estimate of cognitive functioning based on the results of the vocabulary and matrix reasoning subtests. According to the WASI-II manual, full scale I.Q scores can be classified as follows:

- 130 and above = Very superior
- 120 - 129 = Superior
- 110 - 119 = High average
- 90 - 109 = Average
- 80 - 89 = Low average
- 70 - 79 = Borderline
- 69 and below = Extremely low

As mentioned in Chapter 5, two of the children in the control group were excluded from all of the analyses in this thesis (see section 5.1). The first child was excluded because they had a diagnosis of dyslexia. The second child was excluded because their Full Scale IQ-2 Subtests (FSIQ-2) score was 76. As two children from the control group met the exclusion criteria, there were 23 children with narcolepsy and 21 healthy controls included in this analysis.

The FSIQ-2 data was normally distributed and therefore the comparison between the two groups was performed using an independent *t*-test. Table 8.1 displays the WASI-II data. The results show that there was no significant difference in FSIQ-2 score between the two groups and that the mean I.Q for both groups was within the average range. The results suggest that the children with narcolepsy and the healthy controls were adequately matched for I.Q.

Table 8.1 WASI-II data

Measurement	Narcolepsy $M \pm SD$ (n = 23)	Control $M \pm SD$ (n = 21)	p value	Cohen's d
FSIQ-2 score	102.74 ± 16.70	100.57 ± 14.64	.65	.14

Notes. M = Mean, SD = Standard deviation.

8.2.2 The Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, 2017)

As described in Chapter 4, the children with narcolepsy and the healthy controls were asked to complete seven CANTAB tests. The tests objectively measured their executive function and neurocognitive performance. All of the tasks are described in detail in Chapter 4 (see section 4.8.4). 23 children with narcolepsy and 21 healthy controls are included in this analysis. One child with narcolepsy completed the CANTAB battery 7 months after the researcher's visit to their home. This was due to the CANTAB license expiring during the research visit. A time was arranged for the child to complete the battery at the Narcolepsy UK conference which both the researcher, the child and their family were attending. The child was still the same age (13 years old) and taking the same medication as when the researcher visited the family at home, therefore the child's data was included in the analysis.

The results of the seven CANTAB tests are described below. For normally distributed variables, comparisons between the two groups were performed using independent two-tailed *t*-tests and mean scores are reported. For non-normally distributed data, Mann-Whitney *U* tests were performed and median scores are reported. Bonferroni-adjusted significance levels were calculated for each CANTAB task:

- MOT task analysis = 0.05/2 = 0.025
- RTI task analysis = 0.05/6 = 0.042
- SSP task analysis = 0.05/4 = 0.013
- SOC task analysis = 0.05/9 = 0.006

- IED task analysis = 0.05/4 = 0.013
- SWM task analysis = 0.05/3 = 0.016
- PAL task analysis = 0.05/2 = 0.025

The majority of the results are displayed using grouped scatterplots and identical values are stacked so that each individual score can be seen.

8.2.2.1 Motor Screening Test (MOT)

The MOT was administered to familiarise participants with the touch screen interface and to measure speed and accuracy. Participants touched a series of 10 flashing crosses shown in different locations on the screen (see Chapter 4 section 4.8.4).

The main outcomes of interest and the results for MOT are described below:

Total correct: The total number of correct responses made by the participant over the 10 assessed trials in the test. A higher score is better. The results showed that all of the children with narcolepsy and all of the healthy controls correctly responded to the 10 crosses (100% correct).

Mean error: This is a measurement of the accuracy of the participant's pointing. It measures the mean distance between the centre of the cross and the location the participant touched on the screen. The distance is measured in pixel units and a lower score is better. The MOT mean error data was normally distributed and therefore an independent two-tailed *t*-test was performed. There was no significant difference in mean error between the narcolepsy group (M = 13.18, SD = 2.90) and the control group (M = 12.98, SD = 1.86), t (42) = .28, p = .78, d =.08. Figure 8.1 indicates that the children with narcolepsy were more variable than the healthy controls.

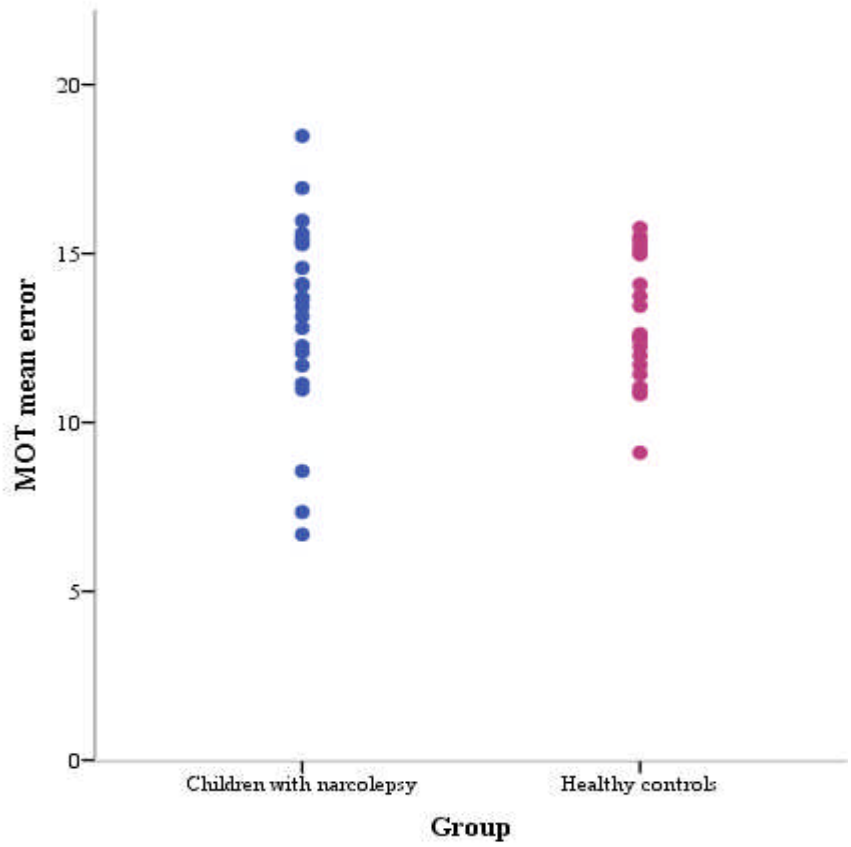

Figure 8.1 MOT mean error

MOT latency: This is the time taken for the participant to touch the cross after it appeared on the screen (reaction time for correct responses only). Reaction time is measured in milliseconds and a shorter reaction time is better (assuming accuracy is unaffected). MOT latency data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was a no significant difference between the reaction time for correct responses (MOT latency) in the narcolepsy group (*Mdn* = 705.70) and the control group (*Mdn* = 586.00), *U* = 164, *z* = -1.82, *p* = .07, *r* = -.27. Figure 8.2 indicates that the children with narcolepsy were also more variable than the healthy controls as a group.

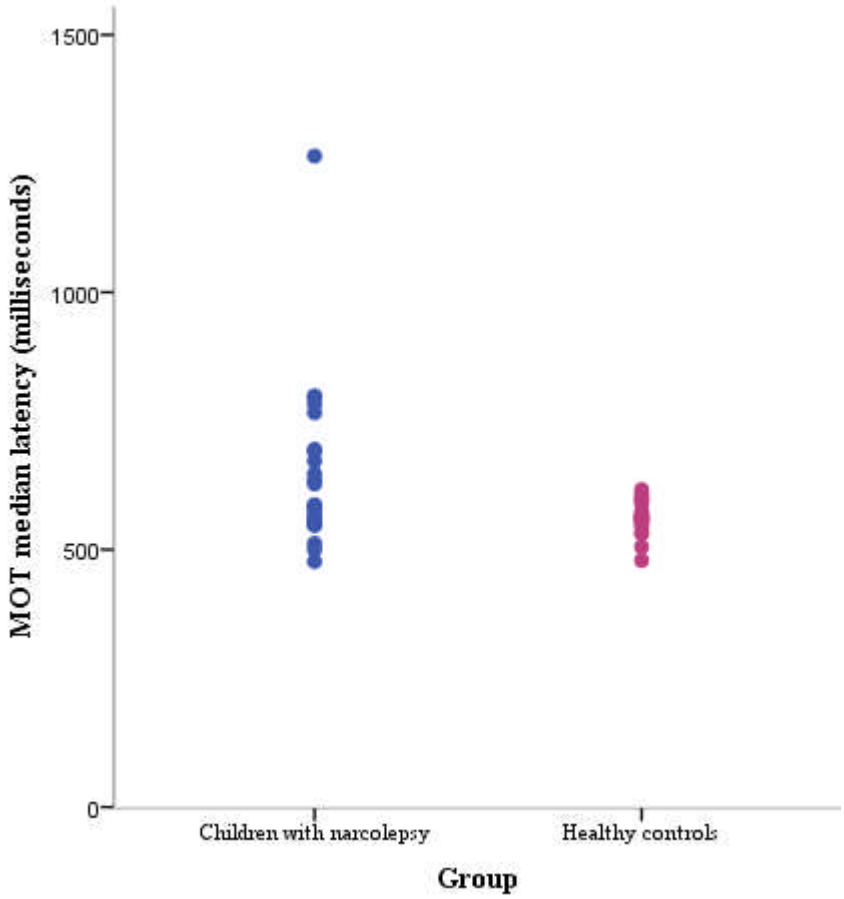

Figure 8.2 MOT median latency (milliseconds)

8.2.2.2 Reaction Time (RTI)

RTI is a measure of a participants speed of response to a visual target where the stimulus is either predictable (simple reaction time) or unpredictable (choice reaction time) (see Chapter 4 section 4.8.4).

The main outcomes of interest and the results for RTI are described below:

Simple reaction time: The speed with which the participant releases the press pad button in response to the onset of a stimulus in a single location. This is measured in milliseconds and lower is better. Simple reaction time data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the simple reaction time in the narcolepsy group (*Mdn* = 297.13) and the control group (*Mdn* = 281.78), *U* = 209, *z* = -.76, *p* = .45, *r* = -.11. Figure 8.3 indicates that the children with narcolepsy were more variable in simple reaction time than the healthy controls as a group.

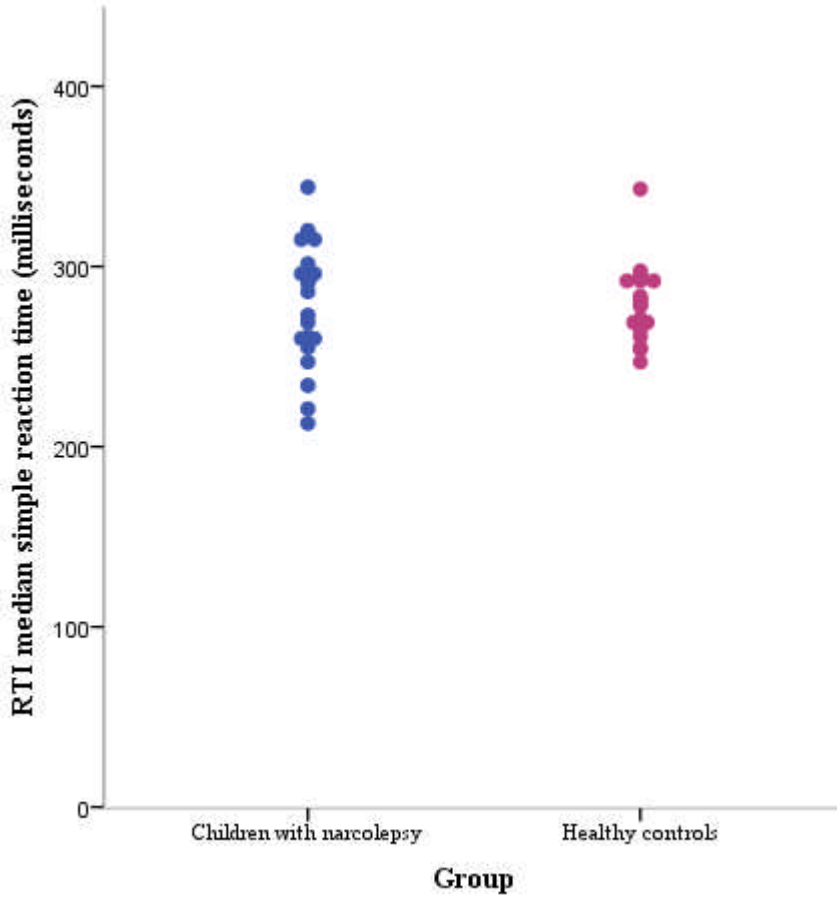

Figure 8.3 RTI median simple reaction time (milliseconds)

Simple movement time: This is the time taken to touch the stimulus after the press pad has been released in trials where the stimuli appear in one location only. This is measured in milliseconds and lower is better. Simple movement time data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the simple movement time in the narcolepsy group (*Mdn* = 272.78) and the control group (*Mdn* = 285.00), *U* = 258, *z* = .39, *p* = .70, *r* = .06. Figure 8.4 indicates that the children with narcolepsy were more variable in simple movement time than the healthy controls as a group.

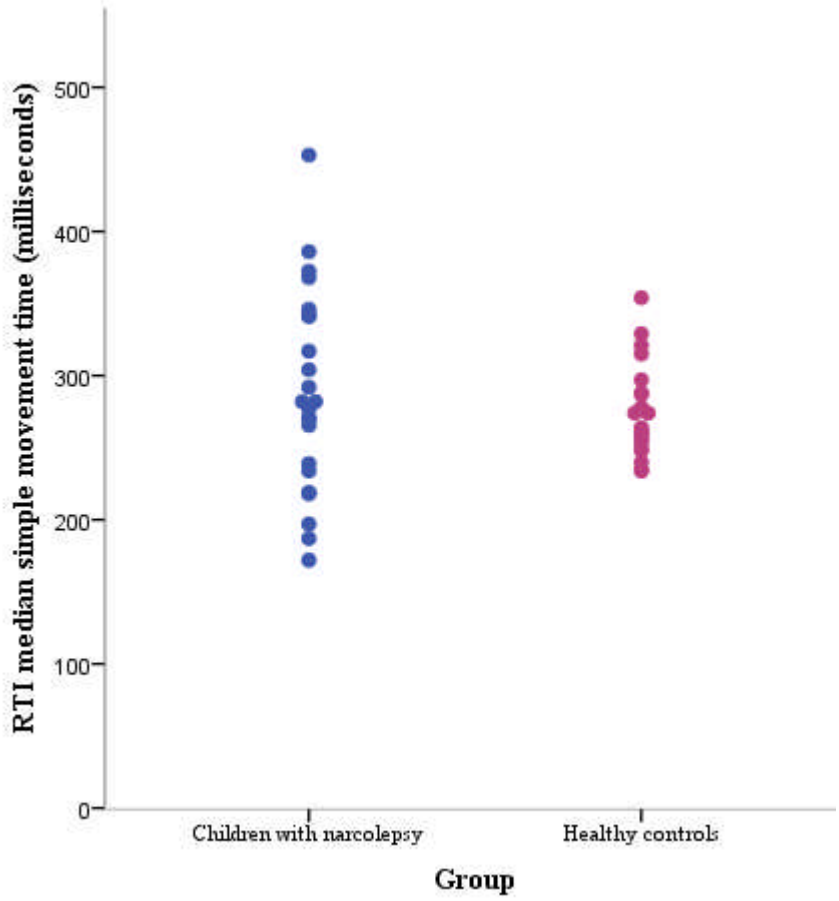

Figure 8.4 RTI median simple movement time (milliseconds)

Five choice reaction time: The speed with which the participant releases the press pad button in response to the onset of a stimulus in any one of five locations. This is measured in milliseconds and lower is better. The five choice reaction time data was normally distributed and therefore an independent two-tailed *t*-test was performed. There was no significant difference between the five choice reaction time in the narcolepsy group (M = 322.42, SD = 52.62) and the control group (M = 309.20, SD = 38.23), t (42) = .95, p = .35, d = .27 (see Figure 8.5).

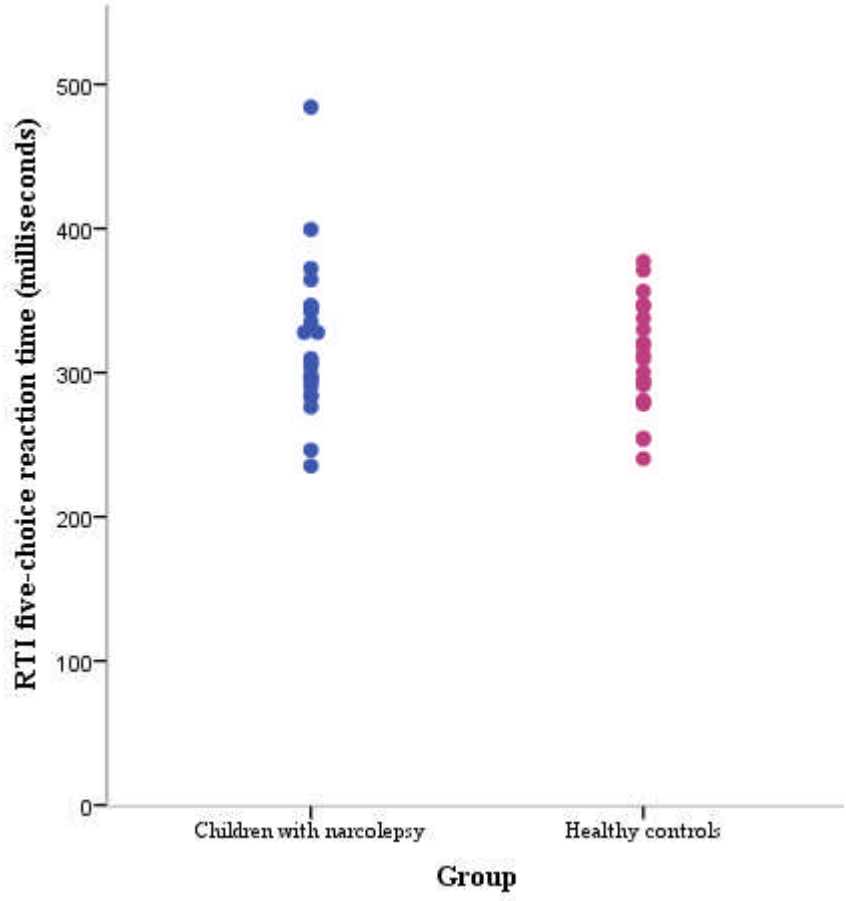

Figure 8.5 RTI five choice reaction time (milliseconds)

Five choice movement time: This is the time taken to touch the stimulus after the press pad has been released in trials where the stimuli appear in one of five possible locations. This is measured in milliseconds and lower is better. The five choice movement time data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the five choice movement time in the narcolepsy group (*Mdn* = 292.86) and the control group (*Mdn* = 279.13), *U* = 180, *z* = -1.45, *p* = .15, *r* = -.22. Figure 8.6 indicates that the children with narcolepsy were more variable in five choice movement time than the healthy controls group.

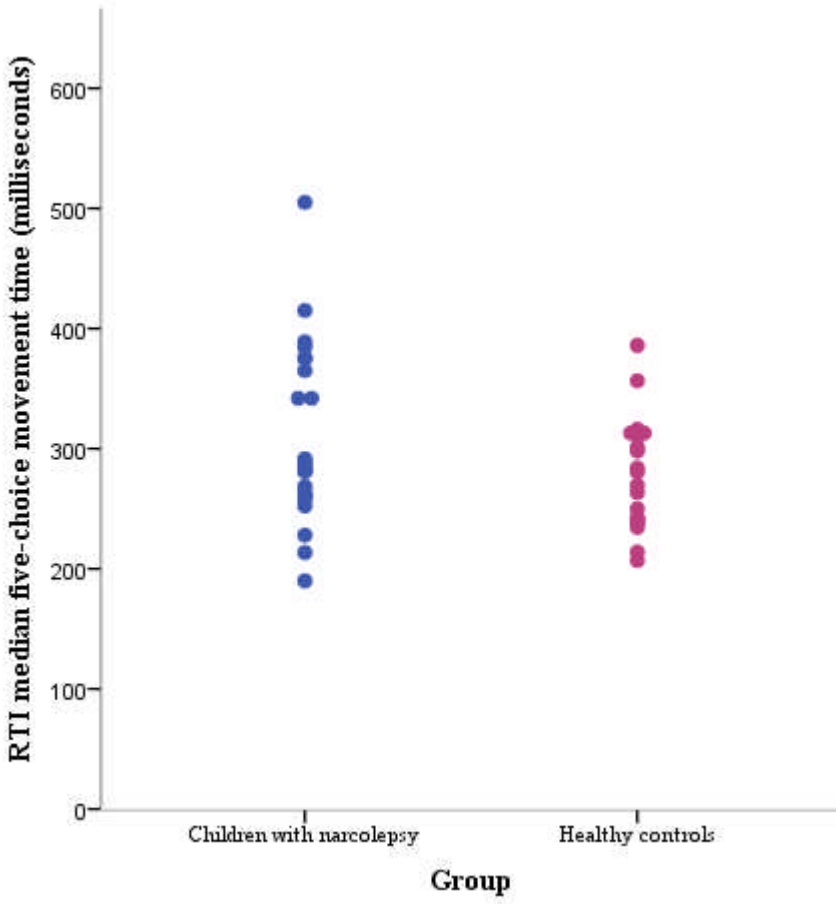

Figure 8.6 RTI median five choice movement time (milliseconds)

Simple accuracy score: This is the total number of trials where the response is recorded as correct where the stimuli appear in one location only. Higher is better. The simple accuracy score data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the simple accuracy score in the narcolepsy group (*Mdn* = 9.00) and the control group (*Mdn* = 9.00), *U* = 283, *z* = 1.12, *p* = .26, *r* = .17 (see Figure 8.7).

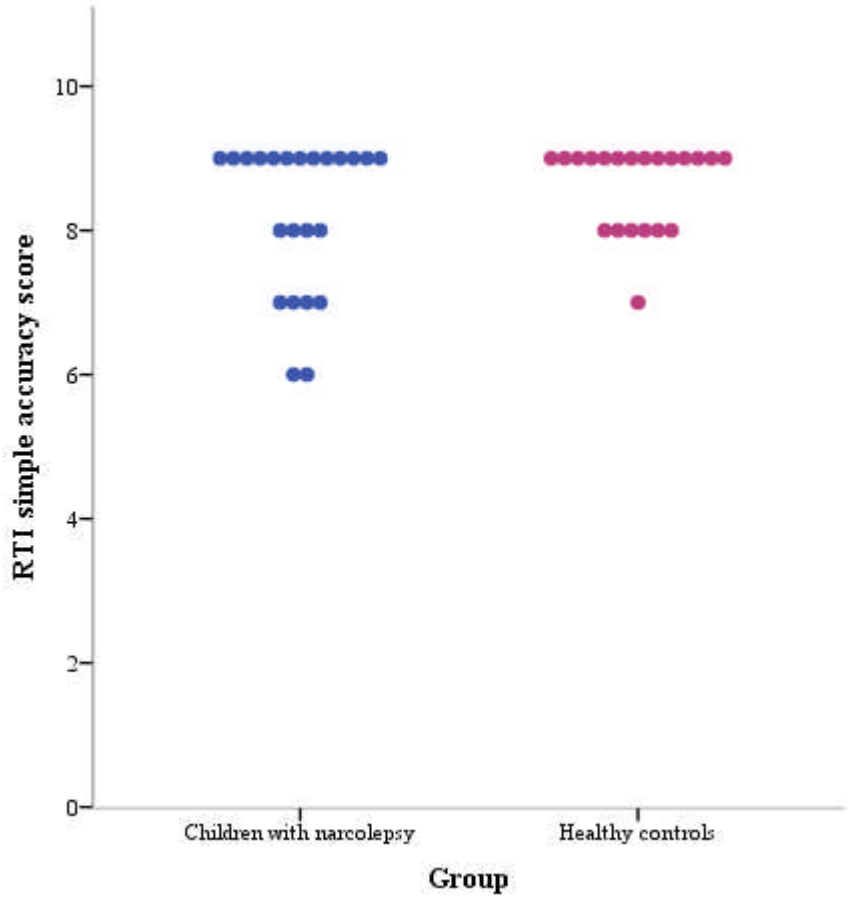

Figure 8.7 RTI simple accuracy score

Five choice accuracy score: This is the total number of trials where the response is recorded as correct where the stimuli appear in one location of five locations. Higher is better. The five choice accuracy score data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the five choice accuracy score in the narcolepsy group (*Mdn* = 8.00) and the control group (*Mdn* = 8.00), $U = 248$, $z = .22$, $p = .83$, $r = .03$ (see Figure 8.8).

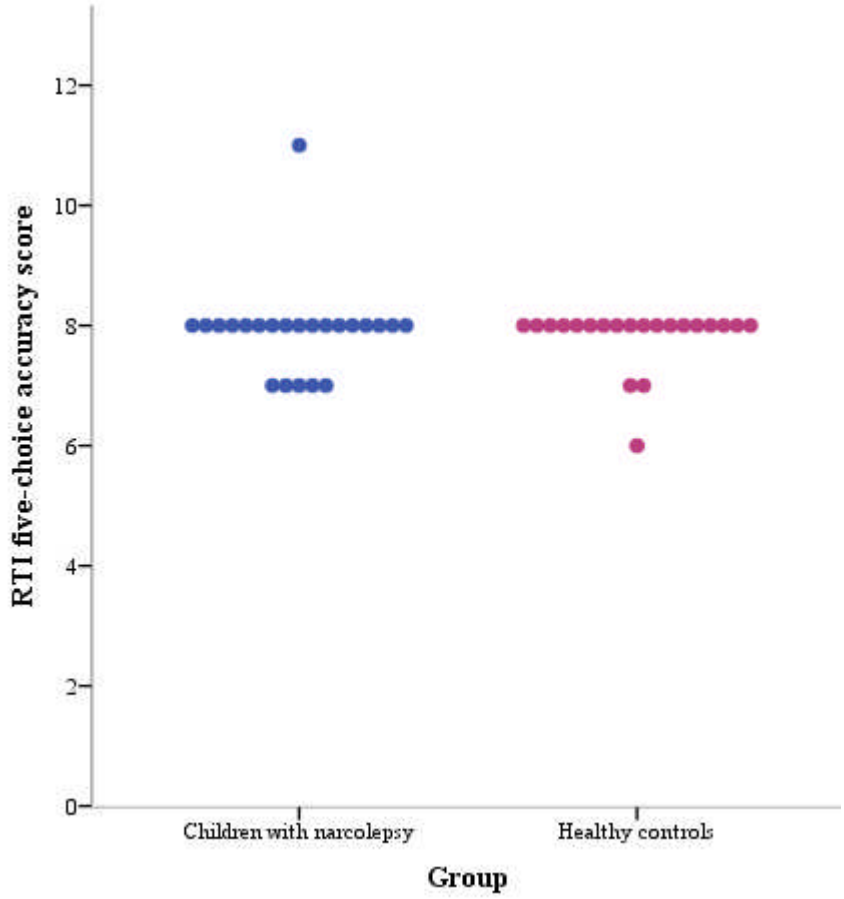

Figure 8.8 RTI five choice accuracy score

8.2.2.3 Spatial Span (SSP)

SSP is a test of working memory capacity (see Chapter 4 section 4.8.4).

The main outcomes of interest and the results for SSP are described below:

Span length: This is the longest sequence successfully recalled by the participant. The participant has three attempts at each level. The maximum possible score is 9 and a higher score is better. The span length data was normally distributed and therefore an independent two-tailed *t*-test was performed. There was no significant difference in span length between the narcolepsy group (M = 6.17, SD = 1.53) and the control group (M = 6.19, SD = 1.40), t (42) = -.04, p = .97, d = <.001 (see Figure 8.9).

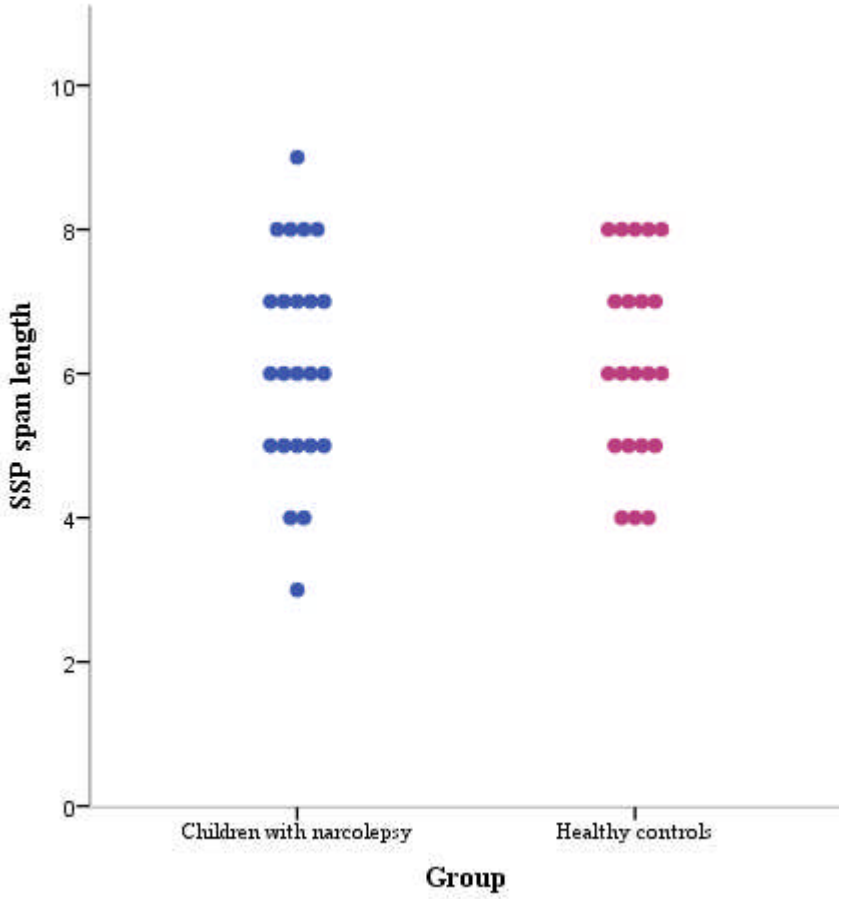

Figure 8.9 SSP span length

Number of attempts: This measure reports the total number of attempts that the participant made across all spans. Lower is better. The span length data was normally distributed and therefore an independent two-tailed *t*-test was performed. There was no significant difference in the number of attempts made across all spans between the narcolepsy group (M = 9.57, SD = 2.37) and the control group (M = 9.90, SD = 2.32), t (42) = -.48, p = .63, d = .14 (see Figure 8.10).

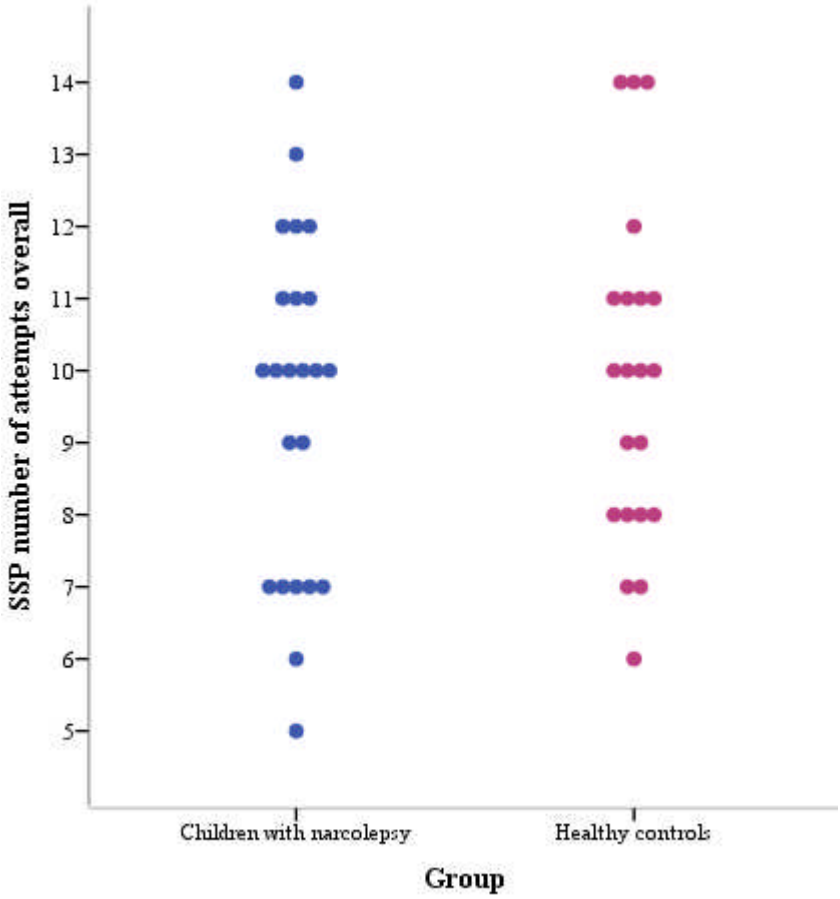

Figure 8.10 SSP number of attempts made across all spans.

Total errors: This is defined as the number of times the participant selected an incorrect box. The maximum score is 97 and a lower score is better. The total errors data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the total errors in the narcolepsy group (*Mdn* = 8.00) and the control group (*Mdn* = 8.00), *U* = 275, *z* = .79, *p* = .43, *r* = .12 (see Figure 8.11).

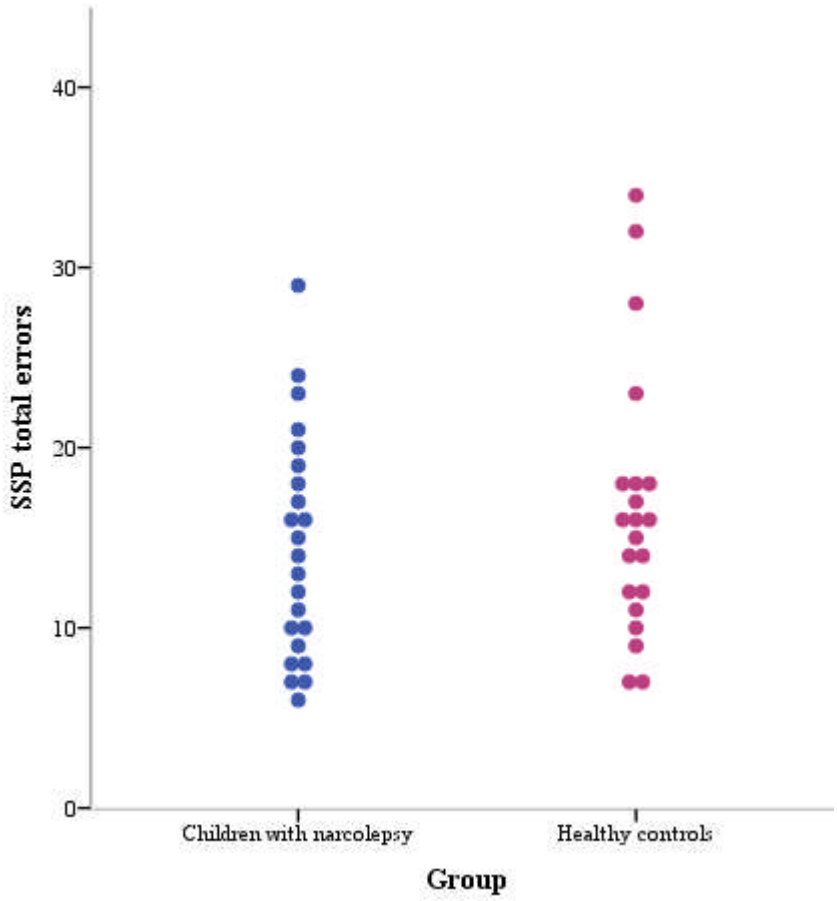

Figure 8.11 SSP total errors

Total usage errors: This measure reports the number of times the participant selected a box not in the sequence being recalled. The maximum score is 39 and a lower score is better. The total usage error data was normally distributed and therefore an independent two-tailed *t*-test was performed. There was no significant difference in the total usage errors between the narcolepsy group (M = 2.22, SD = 1.54) and the control group (M = 2.43, SD = 1.57), t (42) = -.45, p = .65, d = .14 (see Figure 8.12).

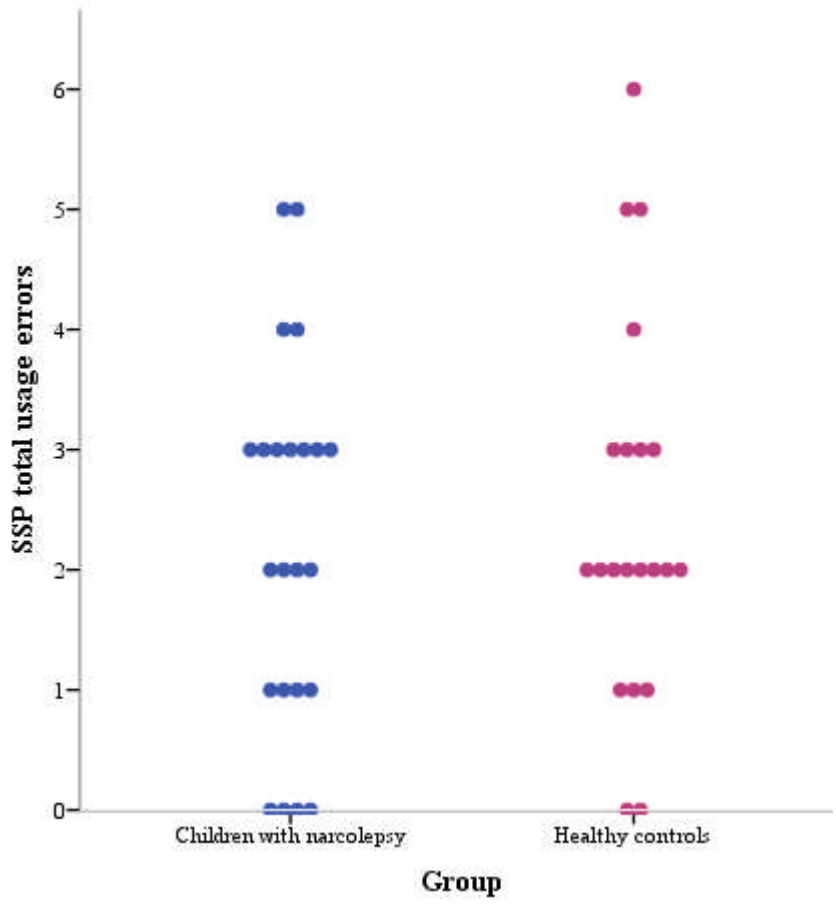

Figure 8.12 SSP total usage errors

8.2.2.4 Stockings of Cambridge (SOC)

SOC is a test of executive function, planning and spatial working memory (see Chapter 4 section 4.8.4).

The main outcomes of interest and the results for SOC are described below:

Problems solved in minimum number of moves: This is the fundamental measure, recording the number of occasions upon which the participant has successfully completed a test problem in the minimum possible number of moves. A higher score is better. The problems solved in minimum number of moves data was normally distributed and therefore an independent two-tailed *t*-test was performed. There was no significant difference in the problems solved in minimum number of moves between the narcolepsy group (M = 7.91, SD = 2.04) and the control group (M = 8.24, SD = 1.67), t (42) = -.57, p = .57, d = .18.

Mean moves (2, 3, 4 and 5 move problems): The mean number of moves required by the participant to solve 2, 3, 4 and 5 move problems. A lower score indicates better performance. The variables were not normally distributed and therefore Mann-Whitney *U* tests were performed. The results are displayed in Figure 8.13.

2 moves

There was no significant difference between the moves required to solve a 2 move problem in the narcolepsy group (*Mdn* = 2.00) and the control group (*Mdn* = 2.00), *U* = 253, *z* = 1.05, *p* = .30, *r* = .16.

3 moves

There was no significant difference between the moves required to solve a 3 move problem in the narcolepsy group (*Mdn* = 3.00) and the control group (*Mdn* = 3.00), *U* = 213, *z* = -.80, *p* = .43, *r* = .12.

4 moves

There was no significant difference between the moves required to solve a 4 move problem in the narcolepsy group (*Mdn* = 5.25) and the control group (*Mdn* = 6.50), *U* = 311.50, *z* = 1.66, *p* = .10, *r* = .25.

5 moves

There was no significant difference between the moves required to solve a 5 move problem in the narcolepsy group (*Mdn* = 7.00) and the control group (*Mdn* = 6.75), *U* = 238, *z* = -.08, *p* = .93, *r* = -.01.

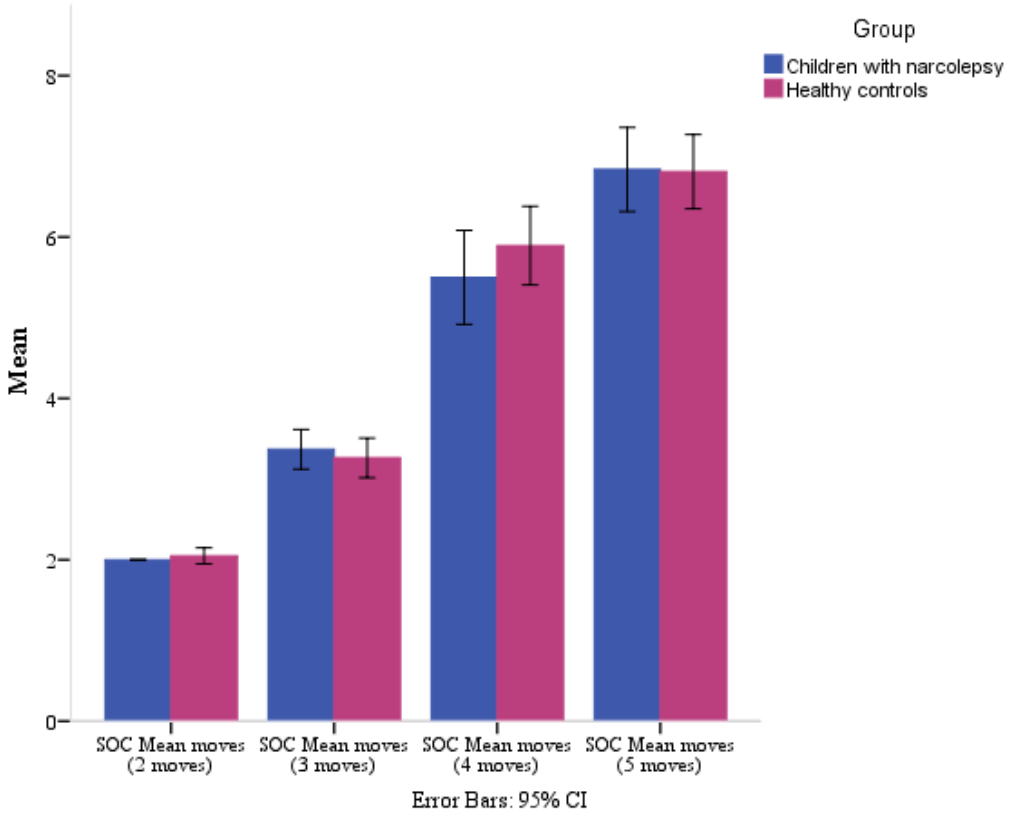

Figure 8.13 SOC mean moves required to solve 2, 3, 4 and 5 move problems

Initial thinking time (2, 3, 4 and 5 move problems): The participants are encouraged to plan their moves before actually enacting the solution to the problem. This measures gives an indication of the time taken to plan the problem solution. The variables were not normally distributed and therefore Mann-Whitney *U* tests were performed. The results are displayed in Figure 8.14.

Initial thinking time for a 2 move problem

There was no significant difference between the initial thinking time for a 2 move problem in the narcolepsy group (*Mdn* = 1819.00) and the control group (*Mdn* = 1767.00), *U* = 251, *z* = .22, *p* = .82, *r* = .03.

Initial thinking time for a 3 move problem

There was no significant difference between the initial thinking time for a 3 move problem in the narcolepsy group (*Mdn* = 4648.00) and the control group (*Mdn* = 4105.50), *U* = 200, *z* = -.98, *p* = .33, *r* = -.15.

Initial thinking time for a 4 move problem

There was no significant difference between the initial thinking time for a 4 move problem in the narcolepsy group (*Mdn* = 5009.00) and the control group (*Mdn* = 7586.00), *U* = 270, *z* = .67, *p* = .50, *r* = .10.

Initial thinking time for a 5 move problem

There was no significant difference between the initial thinking time for a 5 move problem in the narcolepsy group (*Mdn* = 4196.75) and the control group (*Mdn* = 6742.25), *U* = 327, *z* = 2.01, *p* = .05, *r* = .30.

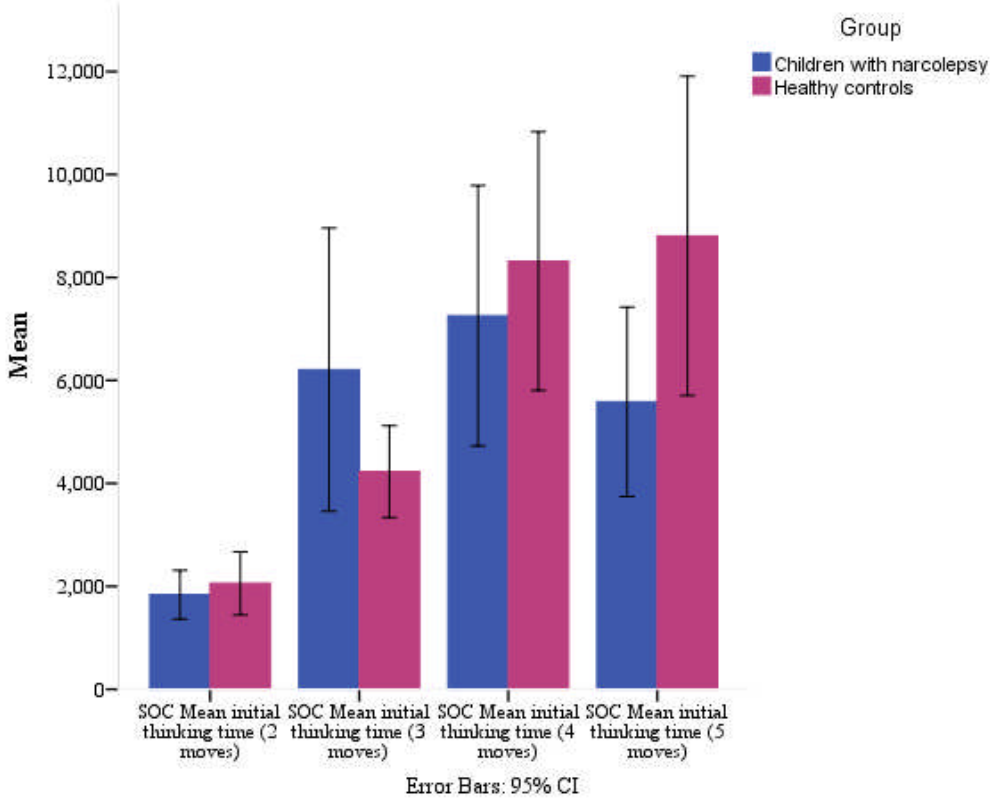

Figure 8.14 SOC initial thinking time (milliseconds) for 2, 3, 4 and 5 move problems.

8.2.2.5 Intra-Dimensional/Extra-dimensional Set Shift (IED)

IED is a test of rule acquisition, reversal learning and attentional set shifting (see Chapter 4 section 4.8.4).

The main outcomes of interest and the results for IED are described below:

Stages completed: This is the total number of stages the participant completed successfully. There are 9 stages in total. The data were not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the stages completed in the narcolepsy group (*Mdn* = 9.00) and the control group (*Mdn* = 9.00), *U* = 246.50, *z* = .17, *p* = .87, *r* = .03.

Total errors (adjusted): This is a measure of the participant's efficiency in attempting the test. Although a participant may pass all nine stages, a substantial number of errors may be made in doing so. It is crucial to note that participants failing at any stage of the test by definition have had less opportunity to make errors. Therefore, this adjusted score is calculated by adding 25 for each stage not attempted due to failure. This value of 25 is used since participants must complete 50 trials to fail a stage and half of these could be correct by chance alone. Lower is better. The total errors (adjusted) data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the total errors (adjusted) in the narcolepsy group (*Mdn* = 13.00) and the control group (*Mdn* = 13.00), *U* = 250.50, *z* = .21, *p* = .83, *r* = .03 (see Figure 8.15).

Pre ED errors: This measure records the number of errors made prior to the extra-dimensional shift of the task. Errors are defined as instances when the participant fails to select the stimulus that is compatible with the current rule. Lower is better. The pre ED error data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the pre ED errors in the narcolepsy group (*Mdn* = 8.00) and the control group (*Mdn* = 8.00), *U* = 252.50, *z* = .26, *p* = .79, *r* = .04 (see Figure 8.15).

EDS errors: Errors made in the extra-dimensional stage of the task are labelled EDS errors, as they have been committed at the stage where the participant is required to make an extra-dimensional shift. Errors committed at the reversal stage following the EDS stage are not included. Lower is better. The EDS error data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There

was no significant difference between the EDS errors in the narcolepsy group (*Mdn* = 2.00) and the control group (*Mdn* = 3.00), *U* = 226.50, *z* = -.36, *p* = .72, *r* = .05 (see Figure 8.15).

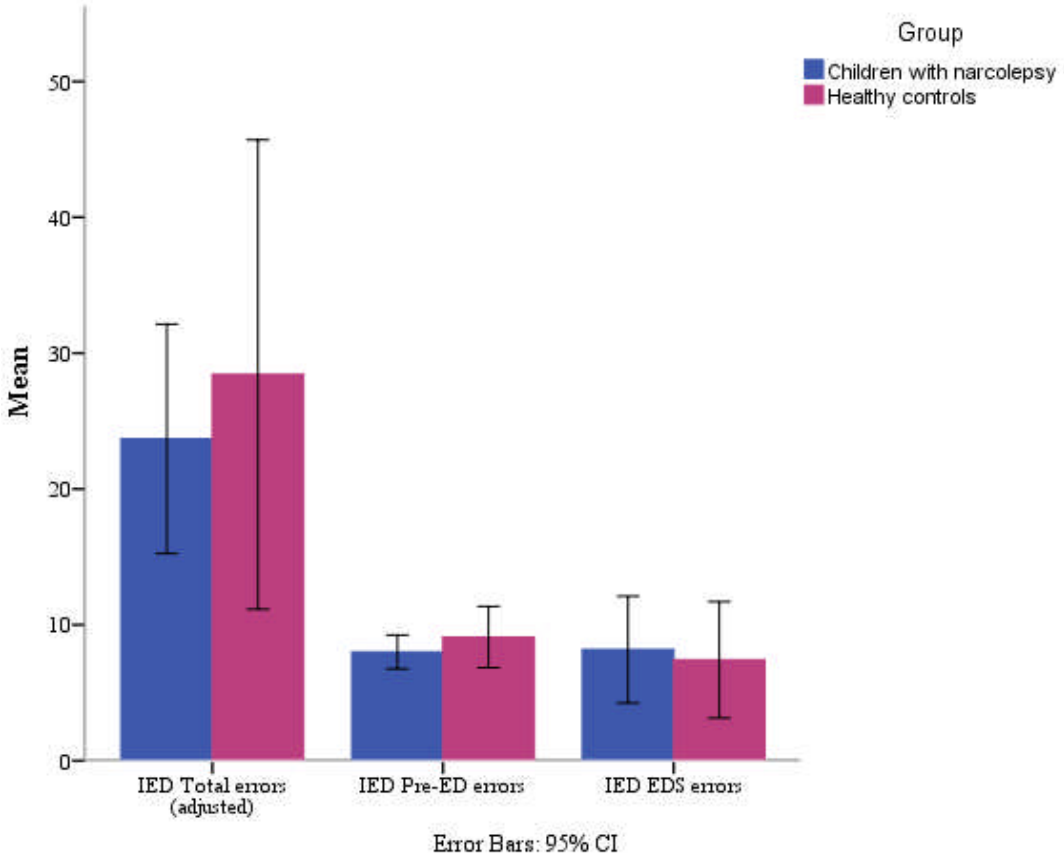

Figure 8.15 Mean IED errors: Total errors (adjusted), Pre-ED errors, EDS errors.

8.2.2.6 Spatial Working Memory (SWM)

SWM measures the ability to retain spatial information and manipulate it in working memory (see Chapter 4 section 4.8.4).

The main outcomes of interest and results for SWM are described below:

Between errors: Between errors are defined as times the participant revisits a box in which a token has previously been found. This is calculated for all trials of four or more tokens only. Lower is better. The between errors data was normally distributed

and therefore an independent two-tailed *t*-test was performed. There was no significant difference in the SWM between errors between the narcolepsy group (*M* = 36.30, *SD* = 18.90) and the control group (*M* = 37.38, *SD* = 16.21), *t* (42) = -.20, *p* = .84, *d* = .06 (see Figure 8.16).

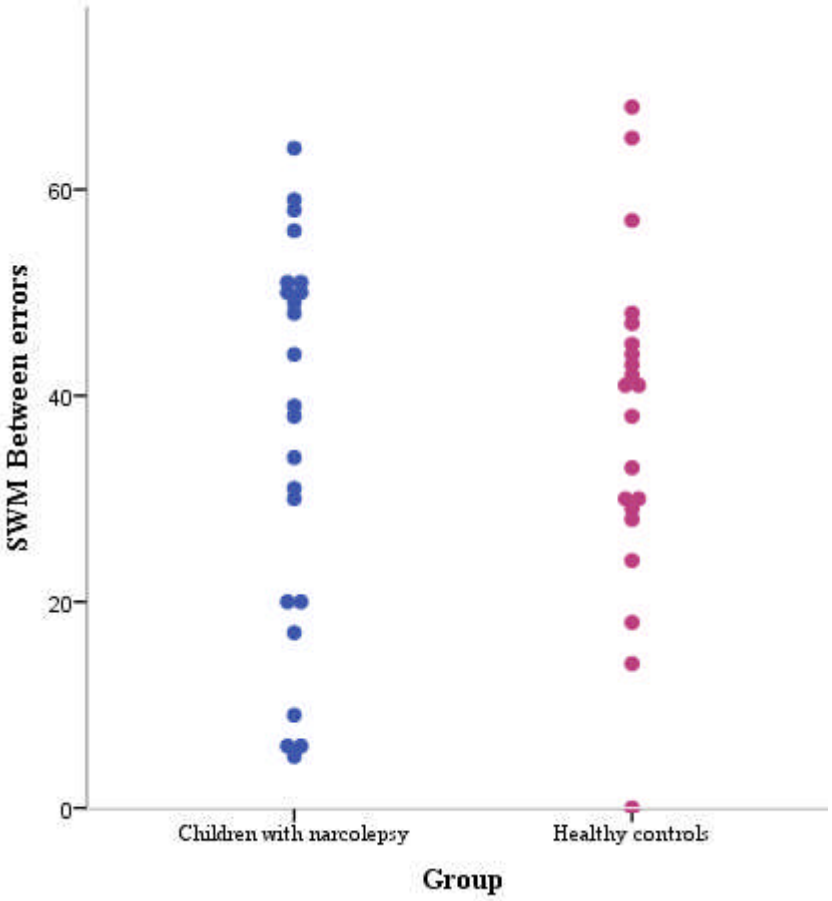

Figure 8.16 SWM between errors

Within errors: Within errors are defined as the number of errors made within a search, i.e., the number of times a participant revisits a box already found to be empty during the same search. This is calculated for all trials of four or more tokens only. Lower is better. The within errors data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the SWM within errors in the narcolepsy group (*Mdn* = 00.00) and the control group (*Mdn* = 00.00), *U* = 238, *z* = -.09, *p* = .93, *r* = -0.01 (see Figure 8.17)

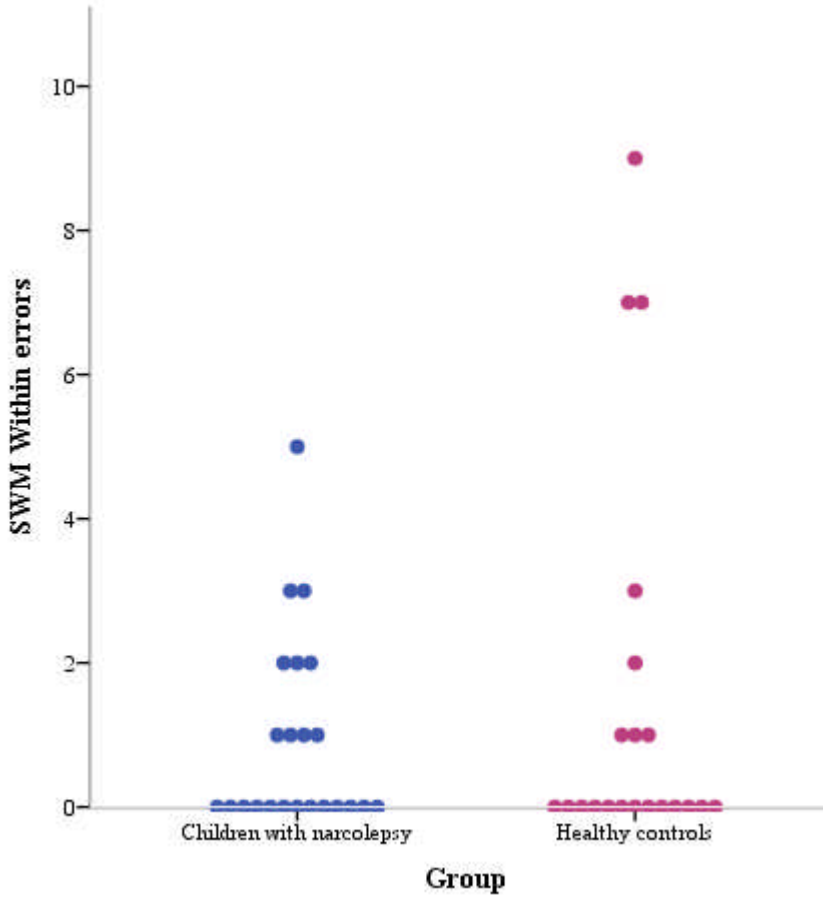

Figure 8.17 SWM within errors

Strategy: It is suggested that an efficient strategy for completing this task is to follow a predetermined sequence by beginning with a specific box and then, once a blue token has been found, to return to that box to start the new search sequence. An estimate of the use of this strategy is obtained by counting the number of times the participant begins a new search with a different box for 6 and 8 box problems only. A high score represents poor use of this strategy and a low score equates to effective use. The strategy data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the SWM strategy in the narcolepsy group (*Mdn* = 34.00) and the control group (*Mdn* = 36.00), $U = 295$, $z = 1.26$, $p = .21$, $r = 0.19$ (see Figure 8.18).

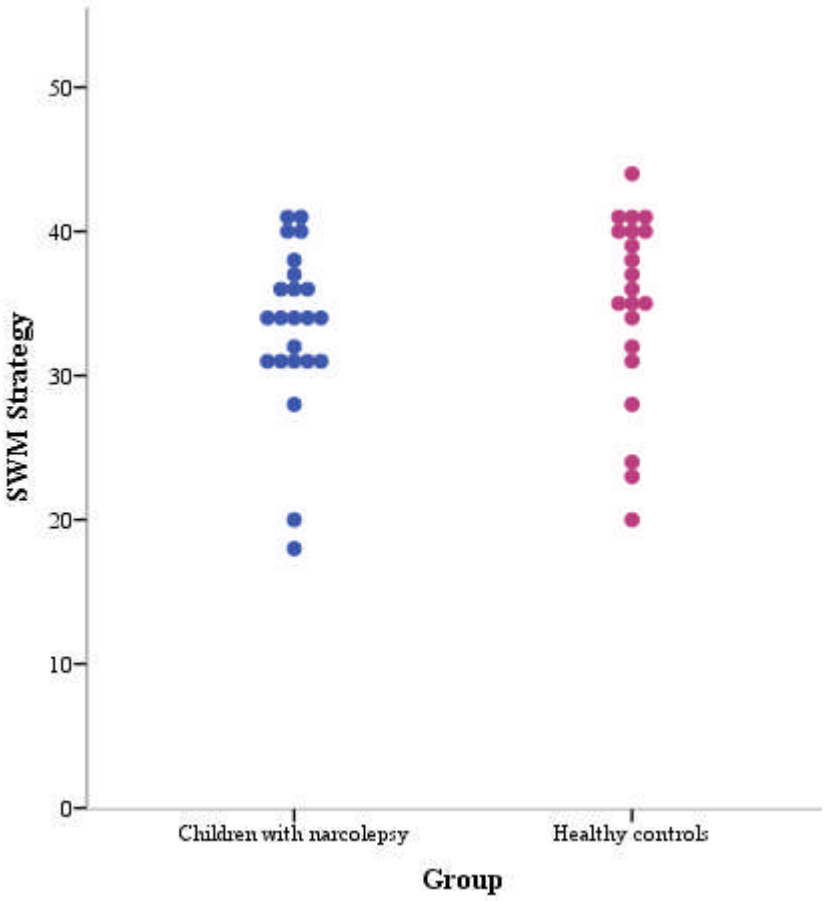

Figure 8.18 SWM strategy

8.2.2.7 Paired Associates Learning (PAL)

PAL assesses visual associative learning and memory (see Chapter 4 section 4.8.4).

The main outcomes of interest and the results for PAL are described below:

Stages completed: This is a key indicator of the participants overall success, recording how many stages were successfully completed. A higher score is better. All the children in both groups completed all eight stages.

First trial memory score: This measure is the number of patterns correctly located after the first trial, summed across the stages completed (range 0-26, with 26 meaning all the patterns were correctly located for all stages first time). Higher is better. The first trial memory score data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between

the first trial memory score in the narcolepsy group (*Mdn* = 22.00) and the control group (*Mdn* = 22.00), *U* = 294.50, *z* = 1.25, *p* = .21, *r* = 0.19 (see Figure 8.19).

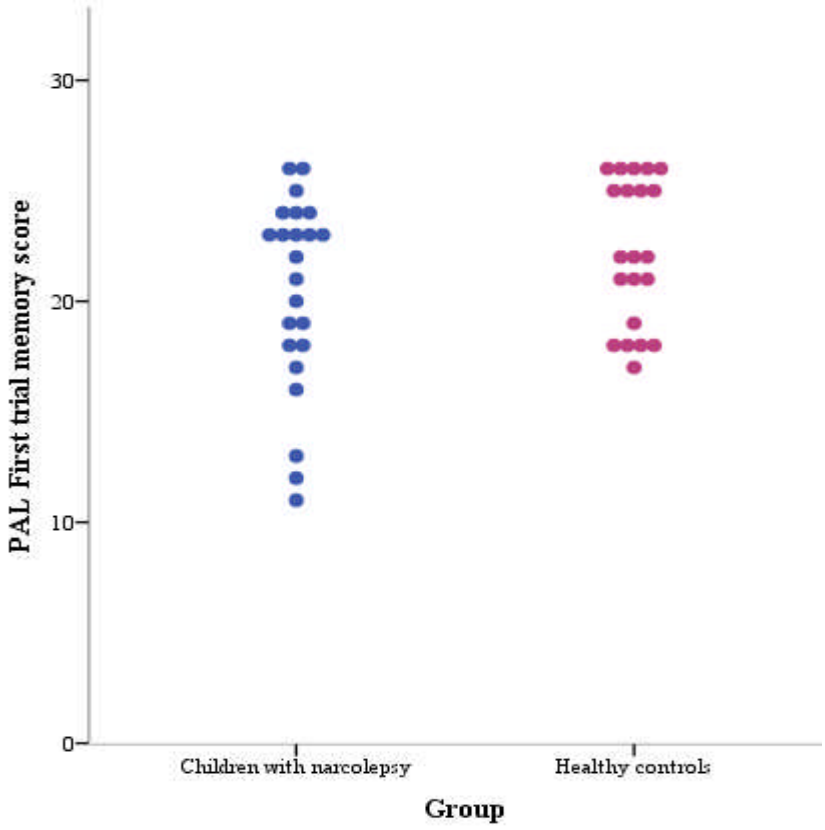

Figure 8.19 PAL First trial memory score

Total errors (adjusted): This measure reports the total number of errors across all assessed problems and all stages, with an adjustment for each stage not attempted due to previous failure. Lower is better. The total errors (adjusted) data was not normally distributed and therefore a Mann-Whitney *U* test was performed. There was no significant difference between the total errors (adjusted) in the narcolepsy group (*Mdn* = 4.00) and the control group (*Mdn* = 4.00), *U* = 197, *z* = -1.05, *p* = .29, *r* = 0.16 (see Figure 8.20).

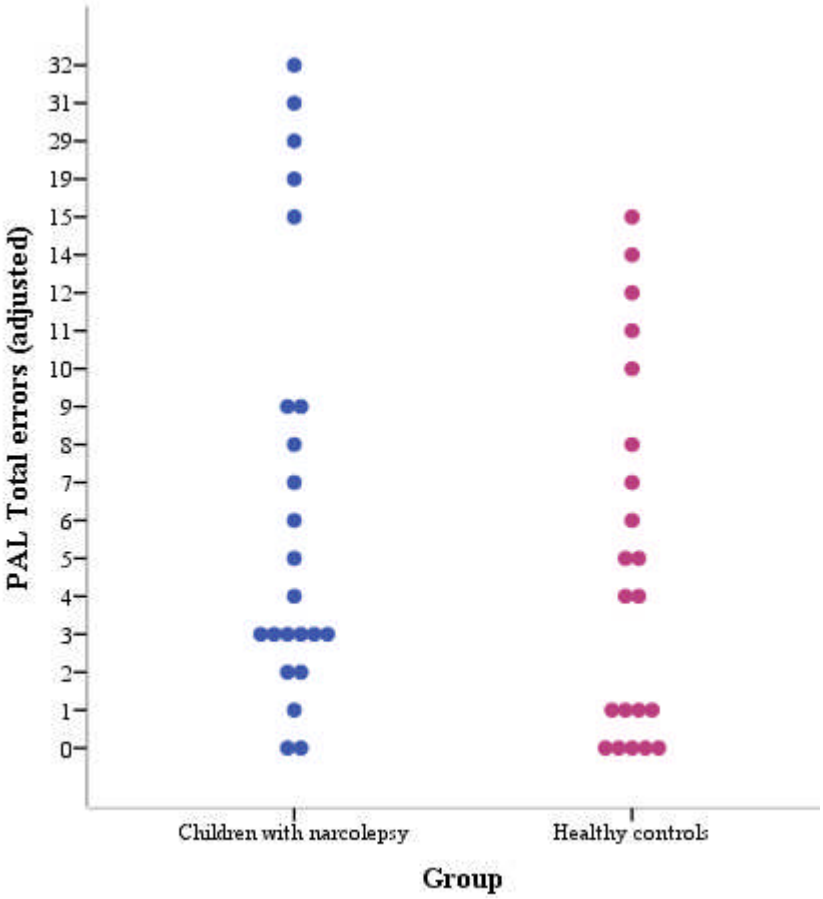

Figure 8.20 PAL total errors (adjusted)

8.2.3 Wechsler Individual Achievement Tests-Second Edition (WIAT-2) (Wechsler, 2002)

Numerical and written language attainment were assessed using the following two measures from the WIAT-2 battery.

8.2.3.1 Numerical operations

The numerical operations task assesses number discrimination, addition, subtraction, division, multiplication and calculating percentages. The data was normally distributed and therefore an independent two-tailed *t*-test was performed. Table 8.2 displays the numerical operations data. The results show that there was no significant difference in numerical attainment between the two groups. The mean scores are within the average range for both groups.

Table 8.2 Numerical operations data

Measurement	Narcolepsy $M \pm SD$ (n = 23)	Control $M \pm SD$ (n = 21)	p value	Cohen's d
Numerical operations standard score	104.14 ± 20.34	104.76 ± 18.58	.92	.03

Notes. M = Mean, SD= Standard deviation.

8.2.3.2 Spelling

The spelling task assesses the ability to spell dictated letters, letter blends and words. Three children with narcolepsy did not complete this task. One child became poorly during the testing session so did not proceed and two children did not complete the task due to time constraints. The data was normally distributed and therefore an independent two-tailed *t*-test was performed. Table 8.3 displays the spelling data. The results show that there was no significant difference in written language attainment between the two groups. The mean scores are within the average range for both groups.

Table 8.3 Spelling data

Measurement	Narcolepsy *M* ± *SD* (*n* = 20)	Control *M* ± *SD* (*n* = 21)	*p* value	Cohen's *d*
Spelling standard score	103.75 ± 10.83	101.57 ± 13.30	.57	.18

Notes. M = Mean, SD= Standard deviation.

8.2.4 Test of Word Reading Efficiency-Second Edition (TOWRE-2) (Torgesen et al., 2012)

The Test of Word Reading Efficiency–Second Edition (TOWRE–2) is a measure of an individual's ability to pronounce printed words (sight word efficiency) and phonemically regular non-words (phonemic decoding efficiency) accurately and fluently. The data was normally distributed and therefore independent two-tailed *t*-tests were performed. Table 8.4 displays the TOWRE 2 data. The Bonferroni-adjusted significance level was $p <. 016$ (0.05/3 = 0.016). The results show that there was no significant difference in word reading efficiency between the two groups. The mean scores are within the average range for both groups.

Table 8.4 TOWRE 2 data

Measurement	Narcolepsy *M* ± *SD* (*n* = 23)	Control *M* ± *SD* (*n* = 21)	*p* value	Cohen's *d*
Sight word efficiency standard score	96.04 ± 11.96	96.81 ± 12.22	.84	.06
Phonemic decoding efficiency standard score	103.61 ± 11.52	105.10 ± 12.08	.68	.13
Total word reading efficiency index (TWRE)	99.87 ± 11.23	101.05 ± 14.64	.74	.09

Notes. M = Mean, SD= Standard deviation.

8.2.5 Working Memory Test Battery for Children (WMTB-C) (Pickering & Gathercole, 2001)

Digit recall and backwards digit recall were administered to measure verbal working memory. As the variables were non-normally distributed Mann-Whitney *U* tests were performed for the group comparisons. Table 8.5 displays the results. The Bonferroni-adjusted significance level was $p <$. 013 (0.05/4 = 0.013). The results show that there was no significant difference in working memory performance between the two groups. The mean scores are within the average range for both groups.

Table 8.5 WMTB-C data (digit recall and backwards digit recall)

Measurement	Narcolepsy *M* ± *SD* (*n* = 23)	Control *M* ± *SD* (*n* = 21)	*p* value	*r*
Digit recall standard score	101.44 ± 11.61	101.29 ± 18.83	.85	.03
Digit recall span score	5.83 ± 1.07	5.48 ± 1.21	.21	-.19
Backwards digit recall standard score	92.87 ± 14.88	101.48 ± 16.99	.12	.23
Backwards digit recall span score	3.70 ± 1.15	4.00 ± 1.00	.52	.10

Notes. M = Mean, SD = Standard deviation.

8.3 Summary of findings

I.Q

- The results show that there was no significant difference in FSIQ-2 score between the two groups. This suggests that the children with narcolepsy and the healthy controls were adequately matched for I.Q.

CANTAB

- There were no significant differences between the two groups were found on the CANTAB tasks.
- The grouped scatterplots revealed that there was greater variability between the children with narcolepsy on tasks such as MOT and RTI than between the healthy controls.

Academic attainment

- No significant differences were found between the two groups for the measures of numerical attainment, written language attainment, word reading and working memory.

8.4 Discussion

The aim of this study was to assess and compare cognitive function in children with narcolepsy and healthy controls. The results supported the hypothesis that the children with narcolepsy would have I.Q's within the average range, as the mean I.Q in the narcolepsy group was 102.74. The results suggest that the children with narcolepsy do not have an impairment in general cognitive functioning and that because there was no significant difference in FSIQ-2 score between the two groups, the groups were adequately matched on I.Q. The results also showed that there was no significant difference between the two groups on the measures of academic attainment which included: numerical operations, spelling, word reading and working memory. The mean scores for these measures were within the average range for both groups of children.

The results do not support the hypothesis that the children with narcolepsy would have significantly impaired attention and executive functions compared to healthy controls. The results suggest that medicated children with narcolepsy do not have significantly impaired attention and executive functions compared to healthy controls. However, the grouped scatterplots suggest that the children with narcolepsy are more variable compared to the healthy controls. This may mean that cognitive performance is affected in different ways for each child with narcolepsy and this may be related to the severity of their symptoms and how effective their treatment plan is.

The results do not support the findings of the systematic review in Chapter 2, which found that narcolepsy puts children and adolescents at particular risk of cognitive impairment in at least one domain (e.g. decision making, verbal I.Q, performance I.Q). The results of the current study suggest that the children with narcolepsy included in this study do not have significantly impaired cognitive function compared to healthy controls when tested at their optimal performance and in optimal conditions. There are a number of possible reasons for the discrepancy between the results of the systematic review and the results reported in this Chapter which include differences in the sample recruited, the measurements, the study design and the testing conditions.

Sample

One possible explanation for the discrepancy is that in the current study 21 out of 23 children with narcolepsy were treated with medication at the time of participation. The systematic review included five studies that examined cognitive function in school age-children with narcolepsy. Two of these studies reported that none of the children were taking medication at the time of the study (Avis et al., 2014; Posar et al., 2014) and three reported that some of the participating children were taking medication at the time of the study (Dorris et al., 2008; Lecendreux et al., 2015; Stores et al., 2006). It is likely that the stimulant medications (such as modafinil and methylphenidate) taken by the children in this study, not only have an effect on reducing daytime sleepiness, but also have an effect on cognitive processes such as the ability to concentrate, focus and memorise information. Modafinil and methylphenidate are considered pharmacological neuroenhancement agents and are popular amongst people trying to improve their performance on cognitive tasks (Bisagno, González, & Urbano, 2016). It is therefore reasonable to suppose that the medications used to treat the children with narcolepsy included in this study had some effect on their cognitive performance. It is possible that the impairments found in decision making (Avis et al. 2015), attention, and impulsivity (Lecendreux et al. 2015) in untreated children with narcolepsy in the systematic review were not present in this study because the children with narcolepsy were receiving optimal treatment at the time of the study.

Measurements

As discussed in Chapter 2, two studies assessed academic performance (reading, writing and maths) according to teacher and family reports (Posar et al., 2014; Stores et al., 2006). It was found that seven out of 13 children with narcolepsy had failed academically (Posar et al., 2014) and that teachers rated children with narcolepsy as having significantly more educational difficulties than children without narcolepsy (problems with learning, not reaching academic potential, not working hard enough and being difficult to teach) (Stores et al., 2006). In the current study the standardised Wechsler Individual Achievement Test-Second Edition (WIAT-2) was chosen to assess numerical and language attainment rather than teacher and family reports in order to provide a more accurate and reliable assessment of ability and allow for direct comparison between the participating

children and between studies. In the current study no significant differences were found in numerical or language attainment between the two groups. It is possible that parent and teacher reports reviewed in Chapter 2 overestimated the academic difficulties faced by children with narcolepsy. Mixed-methods research is needed to better understand how academic performance is affected in children with narcolepsy so that qualitative data (for example interviews with children, parent and teachers) can be used to support quantitative results (standardised assessments of academic attainment).

Design

In the systematic review two studies investigated cognitive function in school age children using a standardized measure of intelligence (The Wechsler Intelligence Scale for Children) alongside one or more additional measures of working memory, non-verbal reasoning, attention, alertness or problem solving. Overall, the results of these studies showed that the children with narcolepsy had an I.Q within the average range (with the exception of one child (Posar et al., 2014)), however clinically significant discrepancies between verbal I.Q and performance I.Q were reported in both studies (Dorris et al., 2008; Posar et al., 2014). However, these two studies were limited by a lack of a control group and/or a comparison group (Dorris et al., 2008; Posar et al., 2014). This is a key limitation because it is not possible to compare the cognitive profiles of children with narcolepsy to that of healthy matched controls. It is possible that the uneven cognitive profiles reported in the studies are also observed in typically developing children. In the current study, the vocabulary and matrix reasoning subtests of the WASI-II were administered to estimate the general cognitive function (I.Q) of the children with narcolepsy and the healthy controls. The results showed that there was no significant difference in FSIQ-2 score between the two groups and that the mean I.Q for both groups was within the average range. Unfortunately only two subtests of the WASI-II were administered in this study (due to time limitations) which can provide a FSIQ-2 score but does not yield a verbal I.Q score or a performance I.Q score. Therefore the results of this study cannot be directly compared to the finding of the systematic review that uneven cognitive profiles are frequently observed in children with narcolepsy. Future research investigating cognitive function in children with narcolepsy should include a full battery of a standardised intelligence test in order to yield a FSIQ-2 score, a verbal I.Q score and a performance I.Q score so that the

results can be compared with the findings of Dorris et al. (2008) and Posar et al. (2014).

Testing conditions

As previously mentioned, all of the children in the current study were asked to rate their level of sleepiness on the Stanford Sleepiness Scale before a cognitive task commenced, to ensure that they were alert enough to complete the task to the best of their ability. Although this is a subjective measure of sleepiness, it provided some indication about how the child was feeling and whether the testing session should continue. Children were only tested if they reported that they were feeling alert. The children with narcolepsy were also asked to nap at their usual time to ensure that they were tested at their optimal performance. The studies reviewed in Chapter 2 did not include any objective or subjective measures of alertness and sleepiness during testing so it is not clear whether participants were performing at an optimal level during the assessments. It is therefore possible that in the current study the children with narcolepsy performed better than they would have done on a typical day at school where they would have to deal with multiple competing demands. The testing session took place in a quiet room in their home, which may have helped the child to maintain their concentration. The testing also took place during a weekend when the child may have been more relaxed and rested than they would be on a usual school day. Testing conditions may therefore be another possible explanation for the discrepancies between the current results and the result of the systematic review.

The results suggest that when children with narcolepsy are treated with medication (and/or naps) and are tested in optimal conditions, their cognitive performance is similar to that of healthy controls. Whereas the results of the systematic review in Chapter 2 suggest narcolepsy puts children and adolescents at particular risk of cognitive impairment in at least one domain (e.g. decision making, verbal I.Q, performance I.Q). Possible explanations for the discrepancies in the results have been discussed.

8.5 Conclusion

The results suggest that the children with narcolepsy included in this study do not have significantly impaired cognitive function and that their cognitive performance is similar to that of the healthy matched controls. As already discussed, this may be

due to the children having effective treatment plans which include stimulant medication and daytime naps. The results are encouraging and indicate that when children are tested in optimal conditions their cognitive performance is not impaired. However, the results also revealed that there was greater variability between the children with narcolepsy on tasks such as the CANTAB MOT and the CANTAB RTI than between the healthy controls. It is possible that the symptoms of narcolepsy (such as poor sleep efficiency) are associated with performance on the cognitive tasks. For example, as sleep efficiency increases, performance on cognitive tasks may improve. Given these observations, educational authorities may wish to consider providing appropriate support for children with narcolepsy at school, especially during examinations, so that their examination results are a fair appraisal of the their ability and potential.

Chapter 9 Psychosocial well-being in children with narcolepsy

9.1 Introduction

As described in Chapter 3, one of the aims of The Paediatric Narcolepsy Project was to investigate how psychosocial well-being in children with narcolepsy compares with that of gender and aged matched healthy controls. The literature reviewed in Chapter 2 showed that children with narcolepsy are at risk of emotional problems including depression, anxiety and low self-esteem which may consequently lead to poorer quality of life (Dorris et al., 2008; Inocente et al., 2014; Inocente. et al., 2014; Karjalainen et al., 2014; Lecendreux et al., 2015; Stores et al., 2006). In order to further investigate psychosocial well-being in children with narcolepsy, in the current study three self-report measures were chosen to measure psychosocial well-being, health-related quality of life and strengths and difficulties in the children with narcolepsy and the healthy controls. Wherever possible, the children did not complete the questionnaires in front of their parents, siblings or friends so that they could respond openly. Parents were also asked to complete two questionnaires about their child's health-related quality of life and their child's strengths and difficulties. The parents were also asked not to complete the questionnaires in front of their child to encourage openness. Based on the previous literature summarised in Chapter 2, it was hypothesised that children with narcolepsy will be significantly more likely to report feelings of depression, anxiety and anger than healthy controls. It was also hypothesised that children with narcolepsy will report more disruptive behaviours, lower self-esteem and poorer health-related quality of life than healthy controls.

9.2 Results

9.2.1 Statistical analysis

All variables were inspected visually for potential outliers and normality was assessed using the Shapiro-Wilk test prior to running any analysis. For normally distributed variables, comparisons between the two groups were performed using independent two-tailed *t*-tests and for non-normally distributed data Mann-Whitney *U* tests were used.

9.2.2 The Beck Youth Inventories-Second Edition for Children and Adolescents (Beck et al., 2005)

As described in Chapter 4, The Beck Youth Inventories was used to assess symptoms of depression, anxiety, anger, disruptive behaviour and self-concept in the children with narcolepsy and the healthy controls (see section 4.8.5.1). The Beck Youth Inventories are 5 self-report scales:

- **Beck Self-Concept Inventory for Youth (BSCI-Y)**- The items explore self-perceptions, such as competence and positive self-worth.
- **Beck Anxiety Inventory for Youth (BAI-Y)-** The items reflect children's fears, worries and physiological symptoms associated with anxiety.
- **Beck Depression Inventory for Youth (BDI-Y)**- The items reflect the respondent's negative thoughts about themselves or their lives, feelings or sadness and physiological indications of depression.
- **Beck Anger Inventory for Youth (BANI-Y)-** The items include perceptions of mistreatment, negative thoughts about others, feelings of anger and physiological arousal.
- **Beck Disruptive Behaviour for Youth (BDBI-Y)**- Behaviours and attitudes associated with conduct disorder and oppositional-defiant behaviour are included in this inventory.

Total raw scores were calculated from the children's responses and were converted to standardized scores (*T* scores) using the child's age and gender and the table provided in the manual (see section 4.8.5.1). For the depression, anxiety, anger and disruptive behaviour inventories, the higher the *T* score, the higher the distress the youth is reporting. For the self-concept inventory, a higher score indicates a more positive self-concept. According to The Beck Youth Inventories manual, The *T* scores for the depression, anxiety, anger and disruptive behaviour inventories can be interpreted as follows:

- *T* = 70 + = Extremely elevated
- *T* = 60-69 = Moderately elevated
- *T* = 55-59 = Mildly elevated
- *T* = <55 = Average

T scores for the self-concept inventory can be interpreted as follows:

- *T* = >55 = Above average
- *T* = 45-55 = Average
- *T* = 40-44 = Lower than average
- *T* = <40 = Much lower than average

23 children with narcolepsy and 21 healthy controls were included in this analysis. The mean *T* scores and standard deviations for each inventory are displayed in Table 9.1. The Bonferroni-adjusted significance level was $p <. 01$ (0.05/5 = 0.01). The results show that children with narcolepsy scored significantly higher on the anger and disruptive behaviour inventories than the healthy controls. The mean *T* scores for the four inventories were in the average range (<55) in both the narcolepsy group and the control group.

Anxiety T scores

In the narcolepsy group, there were three children in the 'mildly elevated' range, one child in the 'moderately elevated' range and one child in the 'extremely elevated' range. In the control group, there was one child in the 'moderately elevated' range.

Depression T scores

In the narcolepsy group, there was one child in the 'moderately elevated' range. In the control group, there was one child in the 'mildly elevated' range.

Anger T scores

In the narcolepsy group, there was one child in the 'mildly elevated' range, three children in the 'moderately elevated' range and one child in the 'extremely elevated' range. In the control group, there was one child in the 'mildly elevated' range.

Disruptive behaviour T scores

In the narcolepsy group, there were two children in the 'mildly elevated' range, one child in the 'moderately elevated' range and one child in the 'extremely elevated' range. In the control group, all children were within the average range.

Self-concept

There was no significant difference found between the two groups in the scores on the self-concept inventory. The mean *T* scores for the self-concept inventory where

within the average range (45-55) in both the narcolepsy group and the control group. In the narcolepsy group, there were three children in the 'lower than average' range and four children in the 'much lower than average' range. In the control group, there were two children in the 'lower than average' range and one child in the 'much lower than average' range.

Table 9.1 Beck Youth Inventories data

Measurement	Narcolepsy *M* ± *SD* (*n* = 23)	Control *M* ± *SD* (*n* = 21)	*p* value	Cohen's *d* or '*r*'
Beck Self-Concept Inventory for Youth (BSCI-Y) *T* score	48.39 ± 7.88	51.24 ± 6.88	.21[a]	*d* = .39
Beck Anxiety Inventory for Youth (BAI-Y) *T* score	49.48 ± 8.54	43.24 ± 5.62	.01[a]	*d* = .86
Beck Depression Inventory for Youth (BDI-Y) *T* score	45.91 ± 5.95	42.00 ± 5.85	.03[a]	*d* = .66
Beck Anger Inventory for Youth (BANI-Y) *T* score	48.52 ± 9.56	40.48 ± 6.35	.002[a]*	*d* = .99
Beck Disruptive Behaviour for Youth (BDBI-Y) *T* score	47.65 ± 8.23	40.81 ± 3.67	.001[b]*	*r* = -.48

Notes. Significant results after correcting for multiple comparisons are indicated by an asterisk ($p < .01$) (0.05/5 = 0.01).

M = Mean, SD = Standard deviation.

[a] Independent *t*-test

[b] Mann-Whitney *U* test.

9.2.3 Paediatric Quality of life Inventory (PedsQL) (Varni et al., 1999)

The PedsQL 4.0 generic core scales (Varni et al., 1999) were used to measure and compare health-related quality of life in the children with narcolepsy and the healthy controls (see section 4.8.5.1).

Age-appropriate versions of the inventory (8-12 years and 13-18 years) were administered. Parents were asked to complete a version of the questionnaire which corresponded to the version completed by their child. Each inventory is composed of 23 items comprising 4 dimensions: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items). The procedure for scoring the data is described in detail in Chapter 4 (see section 4.8.5.1). The main outcome measure is the total scale score. The total scale score is the sum of all the items (max score 2300) divided by the number of items answered on all the scales (23 if all items have been answered). Higher scores indicate better health-related quality of life.

20 children with narcolepsy and 21 healthy controls completed the Paediatric Quality of Life Inventory. Three children with narcolepsy and three parents of a child with narcolepsy did not complete the measure due to time constraints. The PedsQL data was normally distributed and therefore independent two-tailed *t*-tests were performed for group comparisons. The Bonferroni-adjusted significance level was $p <. 025$ (0.05/2 = 0.025). The results are displayed in Table 9.2 and show that children with narcolepsy reported significantly lower health-related quality of life compared to the healthy controls. The results also show that the parents of the children with narcolepsy reported that their children's health-related quality of life was significantly lower than that reported by parents of the healthy children. In the narcolepsy group, the parent-report mean total scale score was lower than the child self-report mean total scale score, indicating that parents rated their child's health-related quality of life as poorer than the children rated their own health-related quality of life.

Table 9.2 Paediatric Quality of life Inventory data

Measurement	Narcolepsy *M* ± *SD* (*n* = 20)	Control *M* ± *SD* (*n* = 21)	*p* value	Cohen's *d*
PedsQL child self-report total scale score	63.64 ± 15.09	84.88 ± 11.05	<.001*	.85
PedsQL parent proxy report total scale score	50.54 ± 15.62	86.90 ± 6.86	<.001*	3.01

Note. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.025) (0.05/2 = 0.025). M = Mean, SD = Standard deviation.

9.2.4 The Strengths and Difficulties Questionnaire (SDQ) (Goodman et al., 1998)

As described in Chapter 4, the SDQ was used to measure and compare the psychosocial well-being of the children with narcolepsy and the healthy controls (see section 4.8.5.1). Children aged 11 years or older were asked to complete the self-report questionnaire (suitable for 11-17 year olds) and all parents were asked to complete the version suitable for parents of 4-17 year olds.

All versions of the SDQ contain 25 items on psychological attributes which comprise the following 5 scales:

- Emotional problems scale
- Conduct problems scale
- Hyperactivity scale
- Peer problems scale
- Prosocial scale

An impact supplement was also included with each questionnaire which asks the child/parent whether they think that they/their child has difficulties in one or more of the following area: emotions, concentration or being able to get on with other people. The participant can respond 'no', 'yes-minor difficulties', 'yes-definite difficulties' or 'yes-severe difficulties'. If they mark 'yes', they are asked to respond

to four further items about chronicity, distress, social impairment, and burden to others (Goodman et al., 1998).

A total difficulties score is generated by summing scores from all the scales except the prosocial scale. The scores can range from 0-40 and a higher score represents more total difficulties. An impact score ranging from 0 to 10 is generated by summing items on overall distress and impairment. The impact score is automatically 0 if the participant did not perceive themselves (child version) or their child (parent version) as having any emotional or behavioural difficulties because they are not asked to complete the additional four items on distress or impairment. A higher score represents a larger impact. More detailed information about scoring The SDQ is provided in Chapter 4 (see section 4.8.5.1).

In this study, 15 children with narcolepsy were aged 11 years or older and completed the self-report version of the SDQ. 14 healthy children were aged 11 years or older and also completed the self-report version of the SDQ. The Bonferroni-adjusted significance level was $p <. 007$ (0.05/7 = 0.007). The results of the child self-report version of the SDQ are displayed in Table 9.3. No significant differences were found between the two groups after correcting for multiple comparisons.

Table 9.3 The Strength and Difficulties Questionnaire data (children aged 11 years or older)

Measurement	Narcolepsy *M* ± *SD* (*n* = 15)	Control *M* ± *SD* (*n* = 14)	*p* value	Cohen's *d* or '*r*'
SDQ Total difficulties score	12.13 ± 6.03	7.86 ± 3.84	.03[a]	*d* = .84
SDQ Emotional problems score	2.80 ± 2.48	1.57 ± 1.55	.13[a]	*d* = .59
SDQ Conduct problems score	2.67 ± 2.02	1.36 ± 1.08	.04[a]	*d* = .81
SDQ Hyperactivity score	5.00 ± 3.00	3.64 ± 1.74	.15[a]	*d* = .55
SDQ Peer problems score	1.67 ± 1.63	1.29 ± 1.49	.45[b]	*r* = -.15
SDQ Prosocial score	7.40 ± 2.03	7.79 ± 1.76	.59[a]	*d* = .21
SDQ Impact score	0.92 ± 1.66	0.07 ± 0.27	.08[b]	*r* = -.44

Note. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.007) (0.05/7 = 0.007). M = Mean, SD= Standard deviation.

[a] Independent *t*-test

[b] Mann-Whitney *U* test.

21 parents of the children with narcolepsy and 21 parents of the healthy children completed the SDQ parent proxy report. Two parents of children with narcolepsy did not complete the SDQ parent proxy report due to time constraints. The results of the parent version of the SDQ are displayed in Table 9.4. The results show that the parents of children with narcolepsy reported that their children had significantly more total difficulties than the parents of healthy children. The mean impact score was also significantly higher in the narcolepsy group than the control group.

Table 9.4 The Strengths and Difficulties Questionnaire data (parent proxy report)

Measurement	Narcolepsy *M* ± *SD* (*n* = 21)	Control *M* ± *SD* (*n* = 21)	*p* value	Cohen's *d* or '*r*'
SDQ Total difficulties score	12.48 ± 5.89	7.38 ± 4.65	.003[a]*	*d* = .96
SDQ Emotional problems score	3.24 ± 2.93	1.24 ± 1.76	.01[b]	*r* = -.42
SDQ Conduct problems score	2.48 ± 1.94	1.52 ± 1.50	.08[a]	*d* = .55
SDQ Hyperactivity score	4.00 ± 2.57	3.62 ± 2.69	.60[b]	*r* = -.08
SDQ Peer problems score	2.76 ± 2.41	1.00 ± 1.26	.01[b]	*r* = -.41
SDQ Prosocial score	7.24 ± 1.76	8.52 ± 1.50	.01[b]	*r* = .39
SDQ Impact score	3.26 ± 2.79	0.05 ± 0.22	<.001[b]*	*r* = -.78

Note. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.007) (0.05/7 = 0.007). M = Mean, SD= Standard deviation.

[a] Independent *t*-test [b] Mann-Whitney *U* test.

9.3 Summary of findings

Beck Youth Inventories

- The results show that the children with narcolepsy scored significantly higher on the anger and disruptive behaviour inventories than the healthy controls. The mean *T* scores were in the average range (<55) for the four inventories in both the narcolepsy group and the control group.
- There was no significant difference found between the two groups in the scores on the self-concept inventory. The mean *T* scores for the self-concept inventory were within the average range (45-55) in both the narcolepsy group and the control group.
- A greater number of children with narcolepsy were in the mildly, moderately and extremely elevated range on the anxiety, anger and disruptive behaviour inventories than healthy children.
- A greater number of children with narcolepsy were in the 'lower than average' range and the 'much lower than average' range on the self-concept inventory than the healthy children.

PedsQL

- The results show that the children with narcolepsy reported significantly lower health-related quality of life compared to the healthy controls.
- The results also show that the parents of children with narcolepsy reported that their child's health-related quality of life was significantly lower compared to reports from parents of the healthy children.
- In the narcolepsy group, the parent-report mean total scale score was lower than the child self-report mean total scale score, indicating that parents rated their child's health-related quality of life as poorer than the children rated their own health-related quality of life.

SDQ

- Child self-report: There were no significant differences found between the two groups on the SDQ scales or on the impact supplement after correcting for multiple comparisons.
- Parent proxy report: The results show that the parents of children with narcolepsy reported that their children had significantly more total difficulties than the parents of the healthy children. The mean impact score was also significantly higher in the narcolepsy group than the control group.

9.4 Discussion

The aim of this study was to assess and compare psychosocial well-being in children with narcolepsy and healthy controls. The results supported the hypothesis that children with narcolepsy would be significantly more likely to report feelings of anger than healthy controls. The results also supported the hypothesis that children with narcolepsy would report more disruptive behaviours and poorer quality of life than healthy controls. The results of this study are in line with the findings of the systematic review in Chapter 2, which found that children with narcolepsy are at risk of emotional problems which may consequently lead to poorer quality of life.

The systematic review also found that children with narcolepsy were at risk of lower self-esteem. The results of this study do not support the findings of the review or the hypothesis that children with narcolepsy would have lower self-esteem than the healthy controls. There was no significant difference found in self-concept scores on The Beck Self-Concept Inventory between the two groups, indicating that the children with narcolepsy still have feelings of competence and positive self-worth. In order to correct for multiple comparisons the Bonferroni-adjusted significance level was $p < .01$ (0.05/5 = 0.01). Although the children with narcolepsy scored higher numerically on the Beck depression and anxiety inventories the group differences were not significant after correcting for multiple comparisons (depression = $p = .03$, $d = .66$) (anxiety = $p = .01$, $d = .86$).

Although the children with narcolepsy scored significantly higher on the anger and disruptive behaviour Beck Youth Inventories than the healthy controls, the mean *T* scores were within the average range. This suggests that not all of the children with narcolepsy have clinically significant symptoms of anger and disruptive behaviour.

However, as highlighted in section 9.2.2, a greater number of children with narcolepsy were in the mildly, moderately and extremely elevated range on the anxiety, anger and disruptive behaviour inventories than healthy children. Additionally, a greater number of children with narcolepsy were in the 'lower than average' range and the 'much lower than average' range on the self-concept inventory than the healthy children. It is important to understand whether sleep efficiency, total sleep time during the day or physical activity are associated with symptoms of anger and disruptive behaviour in children with narcolepsy. These relationships are explored in Chapter 10.

The PedsQL was completed by both the children and the parents. The results from the child-self report questionnaire and the parent proxy report were consistent and showed that even though the majority of children with narcolepsy were treated with medication they had poorer health-related quality than the healthy controls. It is interesting that the parents of the children with narcolepsy rated their child's health-related quality of life as poorer than the children rated their own health-related quality of life. This may be because the parents are more aware of the wider impact of narcolepsy on the child's physical, emotional and social functioning and the impact on their own life. The mean age of the children with narcolepsy included in this study was 11 years old and therefore many children have had the condition since being very young and do not remember life before they had narcolepsy. On the other hand, as the children with narcolepsy do not rate their quality of life to be as poor as their parents do, this may indicate that the children with narcolepsy do not think the condition has too much of a negative effect on their life at home and at school.

Varni, Limbers, and Burwinkle (2007) used the PedsQL to compare generic health-related quality of life across ten chronic disease clusters and 33 disease categories/severities from the perspectives of paediatric patients and parents. The results showed that pediatric patients with diabetes, gastrointestinal conditions, cardiac conditions, asthma, obesity, end stage renal disease, psychiatric disorders, cancer, rheumatologic conditions, and cerebral palsy self-reported more impaired overall health-related quality of life than healthy children, with medium to large effect sizes (Varni et al., 2007). The results described in this Chapter show that the mean PedsQL child self-report total scale score in the narcolepsy group was 63.64, which is similar to the mean total scale score reported by children with psychiatric disorders (66.90) in the study by Varni et al. (2007). The children with psychiatric disorders were diagnosed with either

attention-deficit hyperactivity disorder, disruptive behavior disorders, anxiety disorders, mood disorders and pervasive developmental disorders. The mean PedsQL parent-report total scale score in the narcolepsy group was 50.54 and this is similar to the mean total scale score reported by parents of children with cerebral palsy (52.28) in the study by Varni et al. (2007). These comparisons help give the PedsQL results context and highlights that the health-related quality of life of children with narcolepsy included in the current study is similar to that of children with psychiatric disorders and cerebral palsy.

Similarly, the SDQ was completed by both the children (aged 11 or older) and the parents. The results from the child-self report questionnaire and the parent proxy report were not consistent. The child self-report results showed no significant differences between the two groups on the SDQ scales or on the impact supplement after correcting for multiple comparisons. Parents of the children with narcolepsy reported that their children had significantly more total difficulties than the parents of the healthy children. The mean impact score was also significantly higher in the narcolepsy group than the control group.

It is interesting that the parents of the children with narcolepsy reported that their children had difficulties on more of the SDQ scales than the children themselves reported. The children with narcolepsy did not feel that their difficulties had an impact on their emotions, concentration or being able to get on with other people, whereas the parents impact score was significantly higher than in the control group. The results indicate that the children with narcolepsy do not feel that their difficulties have an impact on their emotions, concentration or relationships, whereas their parents think they do. However, it is important to note that only a subsample of children aged 11 years and older completed the child self-report version of the SDQ, therefore the child self-report and parent-reports are not directly comparable. The analysis was also conducted including only the children aged 11 years and older and their parents (excluding parents of children under the age of 11 years old) and the results remained unchanged. Future research should aim to establish the agreement between child self-report and parent-report measures of psychosocial well-being.

The results discussed in Chapter 8 suggest that when children with narcolepsy are treated with medication and/or naps and are tested in optimal conditions, their cognitive performance is broadly similar to that of healthy controls. It is important to

note that even though 21 out of the 23 children with narcolepsy were treated with medication at the time of participating in this study, their psychosocial well-being and health-related quality of life was significantly poorer than that of the healthy controls. It is possible that the children with narcolepsy devote the majority of their energy to performing well in school, at the cost of their psychosocial well-being. As previously mentioned, the semi-structure interviews will provide more information about how the child balances life at school and at home. As discussed in Chapter 8, many of the children with narcolepsy included in this study were treated with stimulant medications such as modafinil and methylphenidate. Although these medications are known to have an effect on reducing daytime sleepiness they can also have side effects in both children and adults. The medications can cause anxiety, agitation, psychosis, hallucinations and excitement (NHS choices, 2016). It is therefore possible that the children with narcolepsy scored higher than healthy controls on the anxiety, depression, anger and disruptive behaviour Beck Youth Inventories due to some of the side effects of their medication. It may be that the medication remediates cognitive deficit but not impairments in psychosocial well-being.

9.5 Conclusion

The results suggest that the children with narcolepsy included in this study experienced more symptoms of anger and disruptive behaviour than the healthy controls and that the severity of these symptoms varied between children. The children with narcolepsy also reported poorer health-related quality of life than the healthy controls. Although the drivers of psychosocial impairments in narcolepsy are not yet understood, parents, teachers and clinicians should be aware that narcolepsy is associated with poor psychosocial well-being, even when the child is treated with medication and daytime naps. Given these observations, health care professionals may wish to carefully monitor children with narcolepsy and report any negative side effects of medication used to treat the condition. Children with narcolepsy with clinically significant psychological symptoms may benefit from access to psychological services that can provide appropriate support when necessary.

Chapter 10
The relationships between sleep, physical activity and psychosocial well-being in children with narcolepsy and healthy controls

10.1 Introduction

The previous Chapters in this thesis have described overnight sleep (Chapter 6), daytime sleep (Chapter 7), physical activity (Chapter 7), cognitive function (Chapter 8) and psychosocial well-being (Chapter 9) in children with narcolepsy and healthy controls. As described in Chapter 3, one of the aims of The Paediatric Narcolepsy Project was to investigate whether any observed case-control differences in cognitive function and psychosocial well-being are associated with overnight sleep efficiency, total sleep time during the day or physical activity.

A hypothesis driven approach was used to select which variables would be included in the correlation analyses in this Chapter. In order to reduce the risk of type I error, variables were included in Chapter 10 if a significant difference was found between the children with narcolepsy and the healthy controls (after correcting for multiple comparisons). This hypothesis driven approach was chosen because including all of the 40 measures of cognitive function (described in Chapter 8) and all of the 21 measures of psychosocial well-being (described in Chapter 9) in the correlation analyses in this Chapter would dramatically increase the risk of type I error (as discussed in Chapter 4 see section 4.9). Due to the relatively small sample included in the study, the non-normally distributed data and the lack of highly correlated measures it was not considered appropriate to form composite measures for the analyses in the thesis.

Significant group differences were found for the following six variables (after correcting for multiple comparisons): Beck Youth Anger Inventory score, Beck Youth Disruptive Behaviour Inventory score, PedsQL child self-report total scale score, PedsQL parent proxy report total scale score, SDQ parent proxy report total difficulties score and SDQ parent proxy report impact score. The relationships between these six variables and sleep efficiency measured by PSG, total sleep time during the day and overall physical activity were examined. Relationships between unresolved symptoms related to sleep and activity levels and psychosocial function

may suggest targets for behavioural or pharmacological interventions aimed at optimising outcomes.

In Chapter 7, the relationships between sleep efficiency, total sleep time during the day and physical activity in children with narcolepsy and healthy controls were investigated (see section 7.3). Sleep efficiency was measured by polysomnography (PSG) (1 night of recording) and actigraphy (5 nights of recording). Total sleep time during the day was measured by actigraphy (5 days of recording) and overall physical activity was measured by actigraphy over 5 days (vector magnitude counts per minute). Significant positive partial correlations were found between sleep efficiency (measured by PSG and actigraphy) and overall physical activity in children with narcolepsy and healthy controls, whilst controlling for age. The results indicate that the participants with higher sleep efficiency also tended to exhibit higher levels of physical activity (and vice versa).

In this Chapter sleep efficiency measured by polysomnography (PSG), total sleep time during the day and overall physical activity were included in the correlation analysis. Given the moderate-to-strong correlation between polysomnography and actigraphy (see Chapter 7 section 7.3) the polysomnography measure of sleep efficiency was primarily used in the analyses in this chapter in order to reduce the number of correlations performed. Where significant correlations were found between sleep efficiency and psychosocial well-being outcomes, the correlations were also performed using sleep efficiency measured by actigraphy. The actigraphy data consisted of a mean value based on five consecutive nights (sleep efficiency) or days (total sleep time during the day and physical activity), where at least one of nights/days was a weekend night/day (Friday or Saturday). To control for multiple comparisons Bonferroni corrections were applied and the Bonferroni-adjusted significance level was $p <. 02$ ($0.05/3 = 0.02$).

The first hypothesis was that a significant positive association between sleep efficiency (measured by polysomnography and actigraphy) and psychosocial well-being outcomes would be observed (as sleep efficiency increases, psychosocial well-being increases). This hypothesis is based on the literature discussed in Chapter 1, which highlights the importance of sleep for psychological well-being (see section 1.8.3).

The second hypothesis was that a significant association between total sleep time during the day (measured by actigraphy) and psychosocial well-being outcomes would be observed. This hypothesis is also based on the literature discussed in Chapter 1 (see section 1.8.3).

The third hypothesis was that a significant positive association between overall physical activity (measured by actigraphy) and psychosocial well-being outcomes would be observed (as overall physical activity increases, psychosocial well-being increases). This hypothesis is based on previous literature suggesting that exercise and physical activity are associated with better quality of life and health outcomes (Penedo & Dahn, 2005; Pretty, Peacock, Hine, Sellens, South, & Griffin, 2007; Steptoe & Butler, 1996).

10.2 The relationships between overnight sleep, daytime sleep, physical activity and psychosocial well-being in children with narcolepsy and healthy controls

All variables were inspected visually for potential outliers and normality was assessed using the Shapiro-Wilk test prior to running any analysis. The Bonferroni-adjusted significance level was $p <. 01$ (0.05/3 = 0.02). Sleep efficiency measured by PSG, daytime sleep measured by actigraphy and the majority of the psychosocial well-being measures were not normally distributed, therefore relationships between sleep, physical activity and psychosocial well-being were assessed using non-parametric Spearman's correlation coefficients (r_s). Age significantly correlated with physical activity, therefore the correlations performed to assess the relationships with this variable were partial, controlling for age. Raw scores rather than standard scores were included in the correlation analyses.

The results are displayed in the tables below. Each variable was correlated with sleep efficiency measured by PSG, total sleep time during the day and overall physical activity. To control for multiple comparisons, Bonferroni corrections were applied. The Bonferroni-adjusted significance level was $p <. 02$ (0.05/3 = 0.02) and significant results after correcting for multiple comparisons are indicated by an asterisk. Scatterplots are included with all significant correlations. The strength of the Spearman's correlations can be interpreted as follows: correlation coefficients of

0.1-0.3 are considered ‘weak’, correlation coefficients of 0.4-0.6 are considered ‘moderate’ and correlation coefficients of 0.7-0.9 are considered ‘strong’.

Beck Youth Anger

Table 10.1 shows that there were no significant correlations found between overnight sleep efficiency measured by PSG, time spent asleep during the day, overall physical activity and Beck Anger Inventory scores.

Table 10.1 Spearman’s correlation matrix of the relationships between sleep efficiency, total sleep time during the day, overall physical activity and Beck Anger Inventory scores.

Measurement	Overnight sleep efficiency measured by PSG	Total sleep time during the day measured by actigraphy	Overall physical activity (vector magnitude counts per minute)
Beck Anger Inventory for Youth (BANI-Y) raw score	r_s = -.34, p = .05 df = 34	r_s = .15, p = .52 df = 18	r_s = -.37, p = .02 df = 37

Notes. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.007) (0.05/3 = 0.02).

Beck Youth Disruptive Behaviour

Table 10.2 shows that a significant negative partial correlation was found between overall physical activity measured by actigraphy (vector magnitude counts per minute) and Beck Disruptive Behaviour Inventory for Youth raw scores, whilst controlling for age. As physical activity increases, disruptive behaviour scores decrease, r_s (37) = -.57, p = <.001 (see Figure 10.1). The scatterplot was produced using unstandardized residuals and higher values indicate greater physical activity and higher disruptive behaviour scores.

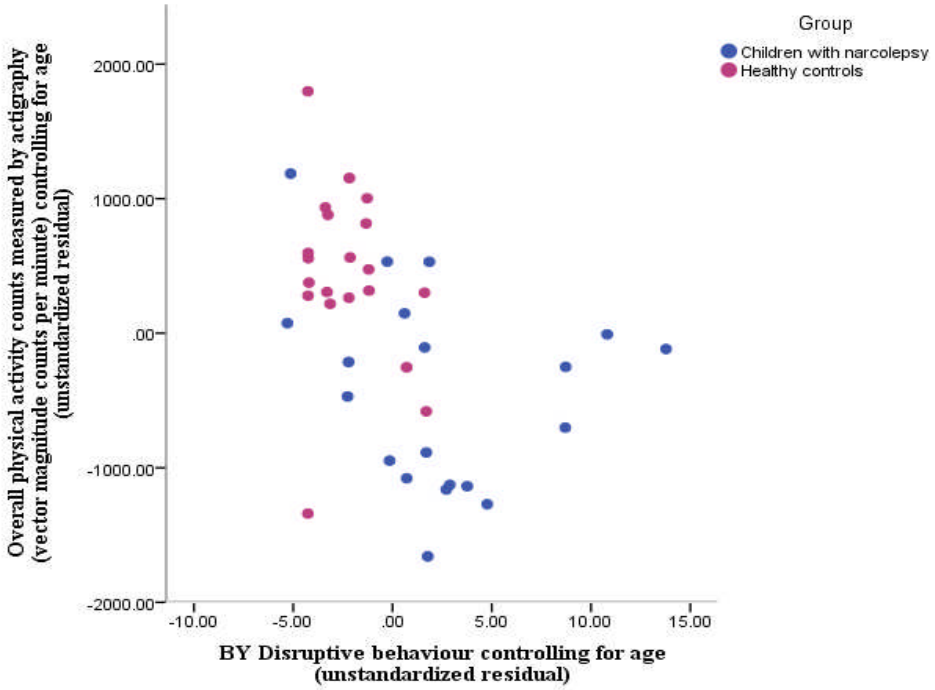

Figure 10.1 A scatterplot of the partial correlation between overall physical activity counts (measured by actigraphy-vector magnitude counts per minute) and Beck Disruptive Behaviour Inventory for Youth raw scores in children with narcolepsy and healthy controls, r_s (37) = -.57, p = <.001.

There were no significant correlations found between overnight sleep efficiency measured by PSG, time spent asleep during the day and Beck Disruptive Behaviour Inventory scores.

Table 10.2 Spearman's correlation matrix of the relationships between sleep efficiency, total sleep time during the day, overall physical activity and Beck Disruptive Behaviour Inventory scores.

Measurement	Overnight sleep efficiency measured by PSG	Total sleep time during the day measured by actigraphy	Overall physical activity (vector magnitude counts per minute)
Beck Disruptive Behaviour for Youth (BDBI-Y) raw score	r_s = -.39, p = .02 df = 34	r_s = .08, p = .75 df = 18	r_s = -.57, p = <.001* df = 37

Notes. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.007) (0.05/3 = 0.02).

PedsQL Child-self report

Table 10.3 shows that a significant positive partial correlation was found between overall physical activity measured by actigraphy (vector magnitude counts per minute) and PedsQL child self-report total scale score, whilst controlling for age. As physical activity increases, child self-report health-related quality of life scores increase (higher scores indicate better health-related quality of life), r_s (35) = .44, p = .01 (see Figure 10.2). The scatterplot was produced using unstandardized residuals and higher values indicate greater physical activity and higher child self-report health-related quality of life.

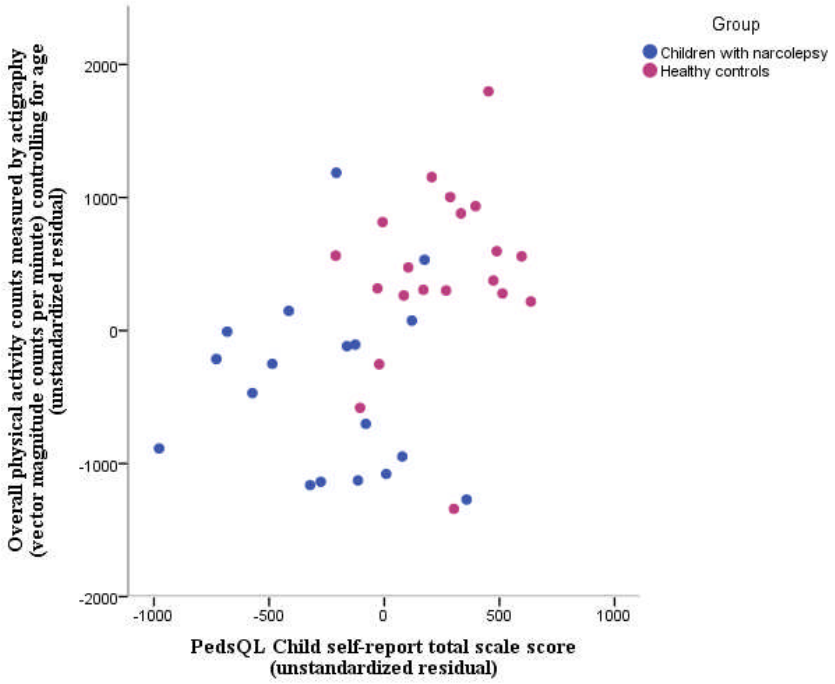

Figure 10.2 A scatterplot of the partial correlation between overall physical activity counts (measured by actigraphy-vector magnitude counts per minute) and PedsQL Child self-report total scale scores in children with narcolepsy and healthy controls r_s (35) = .44, p = .01.

There were no significant correlations found between overnight sleep efficiency measured by PSG, time spent asleep during the day and Child self-report total scale scores.

Table 10.3 Spearman's correlation matrix of the relationships between sleep efficiency, total sleep time during the day, overall physical activity and Beck Disruptive Behaviour Inventory scores.

Measurement	Overnight sleep efficiency measured by PSG	Total sleep time during the day measured by actigraphy	Overall physical activity (vector magnitude counts per minute)
PedsQL child self-report total scale score	r_s = .32, p = .08 df = 32	r_s = -.17, p = .49 df = 16	r_s = .44, p = .01* df = 35

Notes. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.007) (0.05/3 = 0.02).

PedsQL Parent proxy report

Table 10.4 shows that a significant positive correlation was found between sleep efficiency measured by PSG and PedsQL parent proxy report total scale score. As sleep efficiency increases, parent proxy report health-related quality of life scores increase (higher scores indicate better health-related quality of life), r_s (32) = .45, p = .01 (see Figure 10.3).

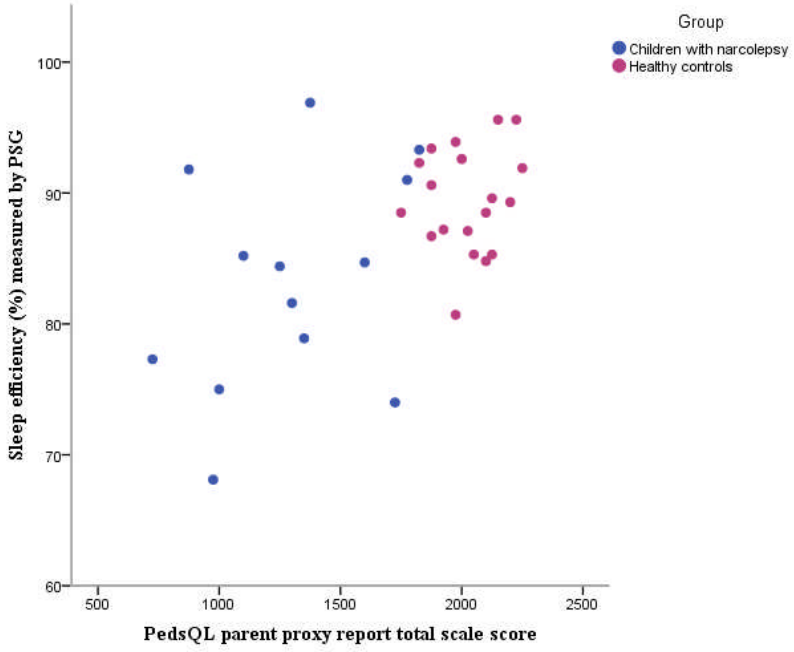

Figure 10.3 A scatterplot of the correlation between sleep efficiency (%) measured by PSG and PedsQL parent proxy report total scale scores in children with narcolepsy and healthy controls r_s (32) = .45, p = .01.

A significant positive correlation was also found between sleep efficiency measured by actigraphy and PedsQL parent proxy total scale score. As sleep efficiency increases, parent proxy report health-related quality of life scores increase (higher scores indicate better quality of life) r_s (36) = .59, p = <.001 (see Figure 10.4).

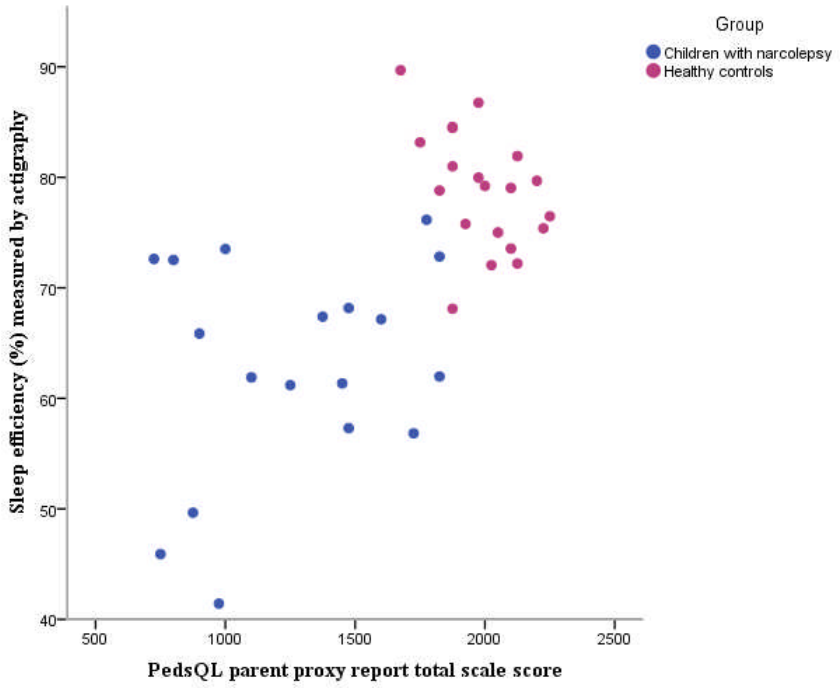

Figure 10.4 A scatterplot of the correlation between sleep efficiency (%) measured by actigraphy and PedsQL parent proxy report total scale scores in children with narcolepsy and healthy controls, r_s (36) = .59, p = <.001.

Table 10.4 also shows that a significant positive partial correlation was found between overall physical activity measured by actigraphy (vector magnitude counts per minute) and PedsQL parent proxy report total scale score, whilst controlling for age. As physical activity increases, parent proxy report health-related quality of life scores increase (higher scores indicate better health-related quality of life), r_s (35) = .57, p = <.001 (see Figure 10.5). The scatterplot was produced using unstandardized residuals and higher values indicate greater physical activity and higher parent proxy report health-related quality of life.

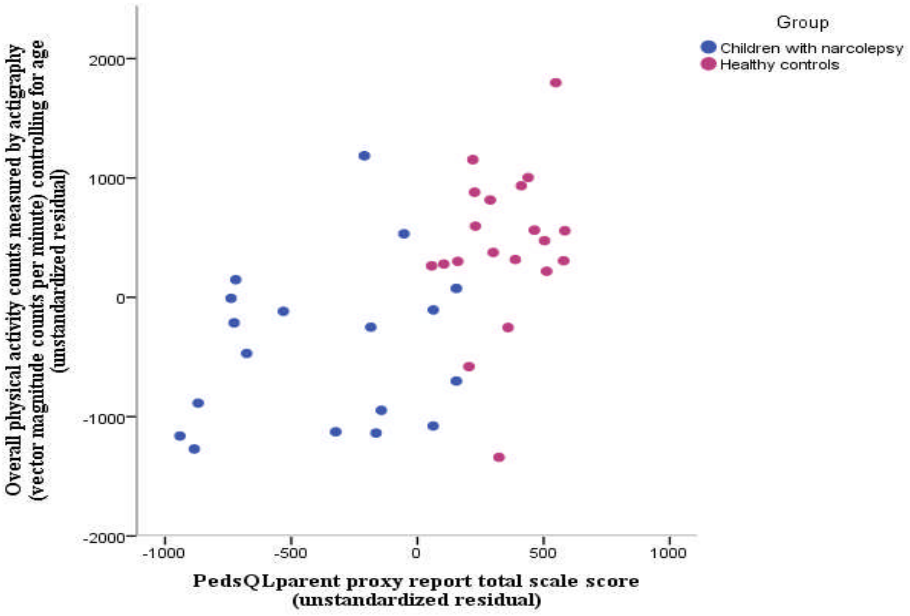

Figure 10.5 A scatterplot of the correlation between overall physical activity counts (measured by actigraphy-vector magnitude counts per minute) and PedsQL parent proxy report total scale scores in children with narcolepsy and healthy controls, r_s (35) = .57, p = <.001.

No significant correlation was found between total sleep time during the day and PedsQL parent proxy report total scale scores.

Table 10.4 Spearman's correlation matrix of the relationships between sleep efficiency, total sleep time during the day, overall physical activity and PedsQL parent proxy report total scale score.

Measurement	Overnight sleep efficiency measured by PSG	Total sleep time during the day measured by actigraphy	Overall physical activity (vector magnitude counts per minute)
PedsQL parent proxy report total scale score	r_s = .45, p = .01* df = 32	r_s = -.45, p = .06 df = 16	r_s = .57, p = <.001* df = 35

Notes. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.007) (0.05/3 = 0.02).

SDQ Parent report total difficulties

Table 10.5 shows that there were no significant correlations found between overnight sleep efficiency measured by PSG, time spent asleep during the day, overall physical activity and SDQ parent report total difficulties scores.

Table 10.5 Spearman's correlation matrix of the relationships between sleep efficiency, total sleep time during the day, overall physical activity and SDQ parent total difficulties score

Measurement	Overnight sleep efficiency measured by PSG	Total sleep time during the day measured by actigraphy	Overall physical activity (vector magnitude counts per minute)
Parent SDQ Total difficulties score	r_s = -.18, p = .30 df = 33	r_s = .49, p = .04 df = 15	r_s = -.34, p = .04 df = 35

Notes. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.007) (0.05/3 = 0.02).

SDQ Parent impact score

Table 10.6 shows that a significant negative partial correlation was found between overall physical activity measured by actigraphy (vector magnitude counts per minute) and parent-report SDQ impact scores. As physical activity increases, parent-report SDQ impact scores decrease, r_s (33) = -.56, p = <.001 (see Figure 10.6). The scatterplot was produced using unstandardized residuals and higher values indicate greater physical activity and higher SDQ parent proxy impact scores.

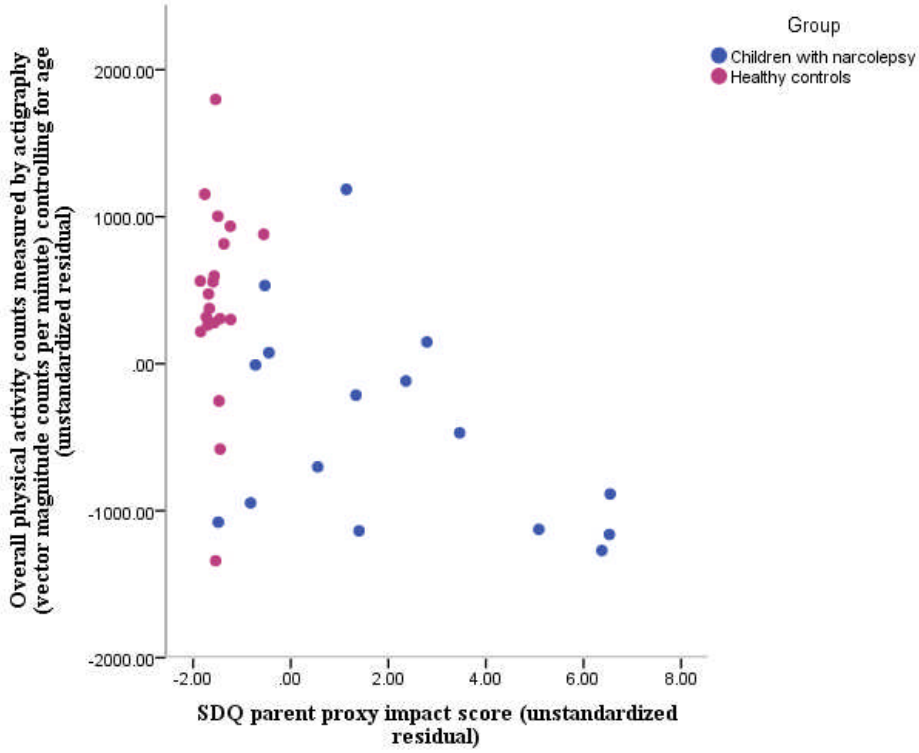

Figure 10.6 A scatterplot of the correlation between overall physical activity counts (measured by actigraphy-vector magnitude counts per minute) and SDQ parent proxy impact scores in children with narcolepsy and healthy controls, r_s (36) = -.59, p = <.001.

No significant correlations found between overnight sleep efficiency measured by PSG, time spent asleep during the day and SDQ parent report impact scores.

Table 10.6 Spearman's correlation matrix of the relationships between sleep efficiency, total sleep time during the day, overall physical activity and SDQ parent total impact score.

Measurement	Overnight sleep efficiency measured by PSG	Total sleep time during the day measured by actigraphy	Overall physical activity (vector magnitude counts per minute)
Parent SDQ Impact score	r_s = -.35, p = .04 df = 32	r_s = .16, p = .55 df = 14	r_s = -.56, p = <.001* df = 33

Notes. Significant results after correcting for multiple comparisons are indicated by an asterisk (p <.007) (0.05/3 = 0.02).

10.3 Summary of findings

The main findings from the significant correlations were:

- As physical activity increases, Beck Youth Inventories disruptive behaviour scores decrease.
- As physical activity increases, child-self report health-related quality of life scores increase (higher scores indicate better health-related quality of life) (measured by the PedsQL).
- As sleep efficiency and physical activity increases, parent proxy report health-related quality of life scores increase (higher scores indicate better health-related quality of life) (measured by the PedsQL).
- As physical activity increases, parent-report SDQ impact scores decrease.

10.4 Discussion

The aim of this study was to investigate whether overnight sleep efficiency, total sleep time during the day and physical activity during the day are associated with psychosocial well-being in children with narcolepsy and gender and age matched healthy controls.

It is important to note that all the correlation coefficients were moderately strong and therefore a lack of strong correlational relationships were found in the current

study. It is also probable that there are unknown factors affecting cognitive performance and psychosocial well-being in addition to sleep efficiency, total sleep time during the day and physical activity in children with narcolepsy and healthy controls.

10.4.1 Sleep efficiency

The first hypothesis that there would be a significant positive relationship between sleep efficiency (measured by polysomnography) and psychosocial well-being outcomes (as sleep efficiency increases, psychosocial well-being increases). The results show that as sleep efficiency increases, health-related quality of life scores increase (as rated by parents) (higher scores indicate better health-related quality of life). The correlations coefficients were all moderately strong.

Despite the fact that 21 out of the 23 children with narcolepsy included in this study were treated with medication, their sleep efficiency was still poorer than that of healthy controls (see Chapter 6). The results suggest that interventions aiming to improve sleep in children with narcolepsy may be beneficial and enable the children to have greater health-related quality of life. The results in Chapter 6 suggest that the medications used to treat the symptoms of narcolepsy do not fully resolve sleep difficulties in children with narcolepsy and therefore alternative treatment approaches should be explored. Behavioural interventions focus on teaching families about good bedtime routines that can help to improve sleep. In addition to the effect their neurological sleep disorder has on sleep, children with narcolepsy may have poor sleep hygiene and bed time routines which contribute to spending more time awake after sleep onset. Teaching children techniques to self-settle back to sleep and teaching parents about how to deal with their child's disturbed overnight sleep may have beneficial effects on both the child and the parents' sleep quality. Behavioural sleep interventions have been shown to be effective in improving sleep in other clinical populations such as children with attention deficit hyperactivity disorder (ADHD) and children with other neurodevelopmental disorders (Hiscock et al., 2015; Johnson, Turner, Foldes, Brooks, Kronk, & Wiggs, 2013; Montgomery, Stores, & Wiggs, 2004; Sciberras et al., 2017).

10.4.2 Total sleep time during the day

The second hypothesis that there would be a significant relationship between total sleep time during the day (measured by actigraphy) and psychosocial well-being outcomes was not supported by the results. Future intervention studies should recruit a large sample of children with narcolepsy to investigate the impact of sleep duration during the day and compare the impact of planned vs unplanned naps in order to better understand the relationship between daytime sleep and psychosocial well-being in children with narcolepsy.

10.4.3 Physical activity

The results supported the third hypothesis that there would be a significant association between overall physical activity (measured by actigraphy) and psychosocial well-being outcomes (as overall physical activity increases, psychosocial well-being increases). The results show that as physical activity increases, Beck Youth disruptive behaviour scores decrease and parent-report SDQ impact scores decrease. The results also show that as physical activity increases, self-report and parent-report health-related quality of life increases.

The results suggest that physical activity is associated with psychosocial well-being in children with narcolepsy and healthy controls. The results should be considered in the design of interventional studies which aim to increase physical activity in children with narcolepsy and investigate whether this leads to improvements in their sleep efficiency and psychosocial well-being. It may be beneficial for clinicians to recommend regular physical activity in the treatment of paediatric narcolepsy, in addition to daytime naps.

10.5 General discussion

The data presented in this thesis demonstrates a lack of strong relationships between sleep, physical activity and psychosocial well-being in a group of children with narcolepsy and healthy matched controls. This may be due to the relatively small sample size that could be achieved within the time frame and budget of this project. Future studies should aim to recruit larger numbers of children with narcolepsy when investigating relationships between sleep, physical activity, cognitive function and psychosocial well-being in children with narcolepsy. Given the sample size and

the moderate strength of the observed associations, the results should be considered in the context of hypothesis generation and informing the design of future interventions programmes rather than as conclusive evidence of the mechanistic drivers of psychosocial impairment in clinically managed narcolepsy.

10.6 Conclusion

The main findings from this study are that physical activity and sleep efficiency are statistically associated with psychosocial well-being in children with narcolepsy and healthy controls. As discussed in Chapter 2, longitudinal research is needed to follow up children with narcolepsy to provide insights into how cognitive and psychological difficulties change over the lifespan. Longitudinal data is critical to understanding the relationship between sleep and physical activity and cognitive and psychological outcomes in children with narcolepsy. Understanding how sleep and physical activity affect cognitive and psychosocial outcomes in this population may inform the design of effective interventions to improve cognitive functioning and psychosocial well-being in children with narcolepsy.

Chapter 11 General discussion

11.1 Introduction

Narcolepsy is a lifelong neurological sleep disorder characterised by excessive daytime sleepiness and attacks of muscle weakness triggered by emotions (cataplexy). In 2010, alarms were raised about an increase in the incidence rate of narcolepsy diagnosis in children. Subsequent research has confirmed a causal link between the use of the Pandemrix H1N1 influenza vaccine and cases of narcolepsy in children. Despite the rise in cases, there is limited research investigating the clinical characterisation and functional impact of paediatric narcolepsy. To address this gap in the literature, a case-control study entitled 'The Paediatric Narcolepsy Project' was designed to characterise, compare and explore the relationships between sleep, physical activity, cognitive function and psychological well-being in children with narcolepsy and healthy controls.

The debilitating symptoms of narcolepsy are described in Chapter 1 and the results of a systematic review investigating cognitive function and psychosocial well-being in school-age narcolepsy are described in Chapter 2. The results of the systematic review indicate that school-age children with narcolepsy are at significant risk of cognitive and psychosocial impairment. The overall aim of this thesis was to clarify whether any particular clinical symptom of narcolepsy (for example disturbed overnight sleep) or any observed change in behaviour (for example reduced daytime physical activity) is associated with cognitive and psychological difficulties in children with narcolepsy.

In order to address this research question, 23 children with narcolepsy and 23 gender, age, I.Q and socioeconomic status (SES) matched healthy controls were recruited from across the UK and the ROI. The researcher visited the children in their homes over two days and the children underwent standardized neuropsychological assessment, a full polysomnography recording and were asked to wear an activity monitor for 8 days and 8 nights to monitor their physical activity levels and daytime sleep. 21 out of the 23 children with narcolepsy were treated with medication at the time of the study.

11.2 Summary of the key findings in relation to the research questions

The study presented in this thesis has addressed seven key research questions. The research questions, their associated hypotheses, the methodology and a summary of the results are outlined below.

1. **How does overnight sleep in children with narcolepsy compare with that of gender and age matched healthy controls?**

   This research question was addressed in Chapter 6. Based on the literature reviewed in Chapter 1, it was hypothesised that children with narcolepsy would have significantly poorer sleep efficiency, significantly shorter sleep onset latency and spend significantly more time awake after sleep onset compared to matched controls. It was also hypothesised that children with narcolepsy would spend significantly more time in sleep stages N1 and N2 and have more arousals per hour than matched controls.

   The sleep of the children with narcolepsy and healthy controls was measured objectively using home polysomnography (1 night of recording) and actigraphy (5 nights of recording). Parents were also asked to complete The Child Sleep Habits Questionnaire (CSHQ) which can be used to identify both behaviourally based and medically based sleep problems in school-aged children.

   The polysomnography results supported the hypotheses that children with narcolepsy would spend significantly more time awake after sleep onset. The results also show that the children with narcolepsy spent significantly more of their sleep in stage N3 sleep than healthy controls. The hypotheses that children with narcolepsy would have significantly poorer sleep efficiency, shorter sleep onset latency, spend more time in N2 sleep and have more arousals per hour than the matched controls were not supported by the polysomnography results. The results show that children with narcolepsy spent significantly less of their sleep in stage N2 sleep compared to healthy

controls. In line with the polysomnography findings, The CSHQ results indicated that the children with narcolepsy have significantly more disturbed sleep than healthy controls (as reported by parents).

The actigraphy data supported the hypotheses that children with narcolepsy would have significantly poorer sleep efficiency and spend significantly more time awake after sleep onset compared to matched controls. The actigraphy data did not support the hypothesis that children with narcolepsy would have shorter sleep onset latency and more awakenings than healthy controls. However, the actigraphy results did show that the awakenings of children with narcolepsy were significantly longer than the awakenings of the controls. The actigraphy results also show that total sleep time was significantly greater in healthy controls than children with narcolepsy.

This was the first study to assess the agreement between polysomnography (PSG) and actigraphy measures of sleep in children with narcolepsy. When the data from children with narcolepsy and the healthy children were combined, the results show that there were significant moderate-to-strong positive correlations between PSG and actigraphy measures for total sleep time (strong correlation) and wake after sleep onset (moderate correlation). Moderate correlations were also found for sleep efficiency and sleep onset latency but they were not statistically significant after correcting for multiple comparisons. However, when the groups were considered separately, the strength of the correlations reduced in the narcolepsy group but not in the control group. The results suggest that actigraphy may be less reliable at estimating sleep-wake patterns in children with narcolepsy than in healthy controls. The results show that actigraphy tends to overestimate wake after sleep onset compared to gold standard polysomnography. Actigraphy may be less reliable in children with narcolepsy because the children with narcolepsy have more disturbed overnight sleep and are more restless when asleep than healthy controls. Actigraphy may over estimate wake after sleep onset in this population because the software scores movement during the night as ‘wake’ when in fact the child is asleep but moving around and therefore the actigraphy results may underestimate sleep efficiency in children with

narcolepsy. However, the results from the gold standard polysomnography measurement of sleep in children with narcolepsy also show that children with narcolepsy have significantly more wake after sleep onset compared to the healthy controls, which gives more confidence in the actigraphy findings.

This is the first study to conduct unattended home sleep studies in children with narcolepsy. The results of the home polysomnography and actigraphy recordings suggest that children with narcolepsy have more disturbed overnight sleep compared to healthy controls, even when the majority of the children with narcolepsy included in this study were treated with medication.

2. **How does daytime sleep in children with narcolepsy compare with that of gender and age matched healthy controls? What proportion of children with narcolepsy nap during the day? What is the average frequency and length of the naps?**

This research question was addressed in Chapter 7. It was hypothesised that the healthy controls would not nap and that the majority of children with narcolepsy would nap because of their excessive daytime sleepiness and because planned naps are often recommended as part of their treatment plan. It was hypothesised that the frequency and the length of naps would vary between children because symptom severity and willingness to nap is known to vary between children.

Daytime sleep in children with narcolepsy and healthy controls was measured using actigraphy and sleep diaries. The results show that during the five consecutive days of actigraphy wear time, all children with narcolepsy napped (n = 20) and one child without narcolepsy had three naps over three days (one per day). The child without narcolepsy reported that the naps were due to having late nights. The results show that on average, children with narcolepsy had two naps per day (range 1-4) and 6 naps across five days (range 2-13). The results also show that on average, children with narcolepsy spent more ‘time in bed’ (44 minutes) during the day than time asleep during the day (17 minutes).

The results suggest that the medications used to treat excessive daytime sleepiness in children with narcolepsy do not remove the need for the children to nap during the day. These results suggest that daytime naps may play a crucial role in the management of excessive daytime sleepiness and disturbed overnight sleep in children with narcolepsy.

3. **How do daytime physical activity levels in children with narcolepsy compare with that of gender and age matched healthy controls?**

This research question was addressed in Chapter 7. It was hypothesised that when awake, children with narcolepsy would be significantly less active throughout the day compared to matched controls.

Actigraphy was used to measure physical activity in children with narcolepsy and healthy controls. There was no significant difference in the percentage of time spent in light physical activity when awake between the two groups. Healthy children spent a significantly greater percentage of their time in moderate physical activity when awake than children with narcolepsy. The results show that none of the children spent any time in vigorous physical activity whilst wearing the actigraphy monitor but this may have been due to the children removing the devices when participating in vigorous sport. Children with narcolepsy were significantly less active overall than healthy controls when awake.

4. **What is the relationship between overnight sleep efficiency, time spent asleep during the day and physical activity in children with narcolepsy and healthy controls?**

This research question was addressed in Chapter 7. The first hypothesis was that there will be a negative correlation between sleep efficiency and total sleep time during the day (as sleep efficiency increases, total sleep time during the day decreases). The second hypothesis was that there will be a

positive correlation between sleep efficiency and daytime physical activity (as sleep efficiency increases, daytime physical activity increases). The third hypothesis was that there will be a negative correlation between the time spent asleep during the day and physical activity (as total sleep time during the day increases, physical activity decreases).

The results showed that there were significant positive partial correlations between sleep efficiency (measured by polysomnography and actigraphy) and overall physical activity in children with narcolepsy and healthy controls, whilst controlling for age. The results suggest that sleep efficiency may be associated with physical activity in children with and without narcolepsy. However, as this is a correlational analysis it is not possible to infer causality. There were no significant correlations found between sleep efficiency (measured by polysomnography and actigraphy) and total sleep time during the day in children with narcolepsy. There was no significant correlation found between overall physical activity counts and time spent asleep in the day in children with narcolepsy

5. **How does cognitive function in children with narcolepsy compare with that of gender and age matched healthy controls?**

This research question was addressed in Chapter 8. Based on the previous literature summarised in Chapter 2, it was hypothesised that children with narcolepsy (even those who are clinically managed and medicated) would have normal full scale I.Q's (within the average range) but they would have significantly impaired attention and executive functions compared to healthy controls.

A battery of standardized age appropriate assessments was chosen to describe and compare cognitive function in children with narcolepsy and healthy controls.

The results supported the hypothesis that the children with narcolepsy would have I.Q's within the average range, as the mean I.Q in the narcolepsy group

was 102.74. The results show that there was no significant difference between the two groups on the measures of academic attainment which included: numerical operations, spelling, word reading and working memory. The mean scores for these measures were within the average range for both groups of children.

The results did not support the hypothesis that the children with narcolepsy (treated with medication) would have significantly impaired attention and executive functions compared to healthy controls. The results suggest that medicated children with narcolepsy do not have significantly impaired attention and executive functions compared to healthy controls. However, the grouped scatterplots presented in Chapter 8 suggest that the children with narcolepsy are more variable compared to the healthy controls. This may mean that cognitive performance is affected in different ways for each child with narcolepsy and this may be related to the severity of their symptoms (excessive daytime sleepiness) and how effective their treatment plan is.

6. **How does psychosocial well-being in school-age children with narcolepsy compare with that of gender and aged matched healthy controls?**

This research question was addressed in Chapter 9. Based on the previous literature summarised in Chapter 2, it was hypothesised that children with narcolepsy would be significantly more likely to report feelings of depression, anxiety and anger than healthy controls. It was also hypothesised that children with narcolepsy would report more disruptive behaviours, lower self-esteem and poorer health-related quality of life than healthy controls.

Three self-report measures were chosen to measure psychosocial well-being, health-related quality of life and strengths and difficulties in the children with narcolepsy and the healthy controls.

The results showed that children with narcolepsy reported significantly more feelings of anger and more disruptive behaviour than healthy controls. The results supported the hypothesis that children with narcolepsy would report

poorer quality of life than healthy controls. The results of this study are in line with the findings of the systematic review in Chapter 2, which found that children with narcolepsy are at risk of emotional problems including depression and anxiety which may consequently lead to poorer quality of life.

7. Are any observed case-control differences in cognitive function and psychosocial well-being associated with sleep efficiency, total sleep time during the day and physical activity?

Based on the previous literature summarised in Chapter 1 (see section 1.8.2, 1.8.3 and 1.8.4), it was hypothesised that any observed difficulties in cognitive function or psychosocial well-being would be associated with poor sleep efficiency, total sleep time during day (Pilcher & Huffcutt, 1996; Philibert, 2005; Durmer & Dinges, 2005; Lim & Dinges, 2010) and lower levels of physical activity (Coe, Pivarnik, Womack, Reeves, & Malina, 2006; Hillman, Erickson, & Kramer, 2008; Trudeau & Shephard, 2008).

Significant group differences were found for the following six variables (after correcting for multiple comparisons): Beck Youth Anger Inventory score, Beck Youth Disruptive Behaviour Inventory score, PedsQL child self-report total scale score, PedsQL parent proxy report total scale score, SDQ parent proxy report total difficulties score and SDQ parent proxy report impact score. The relationships between these six variables and sleep efficiency measured by PSG, total sleep time during the day and overall physical activity were examined.

The results showed that sleep efficiency positively correlated with physical activity and health-related quality of life in children with narcolepsy and controls. Physical activity positively correlated with health-related quality of life and negatively correlated with disruptive behaviour in children with narcolepsy and controls. There were no significant correlations found between total sleep time during the day and psychosocial well-being in children with narcolepsy.

11.3 Strengths of the research

This thesis has answered important clinical and research questions about how sleep, physical activity, cognitive function and psychosocial well-being differs between children with narcolepsy and gender, age, I.Q and socioeconomic status (SES) matched healthy controls. To the researcher's knowledge, this is also the first study to investigate the relationships between sleep, physical activity and psychosocial well-being in children with narcolepsy. The study has contributed to knowledge by providing useful insights into the relationship between sleep efficiency and physical activity and psychosocial well-being in children with narcolepsy and the results may have implications for clinical management protocols. The results will inform the design of intervention studies aiming to investigate whether improving sleep efficiency and increasing physical activity in children with narcolepsy enables the children to have better psychosocial well-being.

Although The Paediatric Narcolepsy Project was run on a very limited budget and time scale, the study makes a significant contribution to the literature related to paediatric narcolepsy and improves on the studies described in Chapter 2 in the following ways:

- 23 healthy controls matched on age, gender, socioeconomic status (SES) and I.Q were recruited and included in the study. Only four of the eight studies reviewed in Chapter 2 included a control group.

- Children with narcolepsy are a relatively rare and hard to reach population. 23 children with narcolepsy and their families were recruited from across the UK and the ROI in this study. As the families were recruited through charities rather than from one narcolepsy clinic in the UK, the participants are likely to be representative of the wider population of families with narcolepsy. This may mean that the results have greater generalisability to the wider population of children with narcolepsy.

- The aim of the study was to compare children with narcolepsy to healthy controls when the children were following their usual routine, so that the results are more representative of how the children are on a day to day basis.

Therefore, all children with narcolepsy who met the inclusion criteria for the study were recruited for the study, regardless of whether they were treated with medication. The results of this study provide a useful insight into the sleep, physical activity, cognitive function and psychosocial well-being of children with narcolepsy when they are following their usual treatment plan.

- Standardized age appropriate assessment tools were carefully chosen to measure cognitive function and psychosocial well-being in children with narcolepsy and healthy controls. A wide range of tools were chosen to measure many areas of cognitive function and psychosocial well-being. These tools were also chosen to be suitable for repeat testing at a longitudinal follow up visit.

- To the researcher's knowledge, this was the first study to conduct home polysomnography recordings in children with narcolepsy. This research has shown that conducting unattended home sleep studies to measure sleep architecture in children with narcolepsy and healthy controls for research purposes is feasible and is tolerated by the majority of children. It is reasonable to suppose that sleep recorded in the home environment is likely to be more representative of a child's typical sleep quality than when recorded in a sleep laboratory. Therefore the polysomnography results presented in Chapter 6 may be more representative of typical sleep in children with narcolepsy than if the children's sleep had been recorded in a laboratory.

- This study also used actigraphy to measure sleep and daytime activity in children with narcolepsy and healthy controls over 8 days and 8 nights in their natural environment. This is the first study to document and compare sleep and physical activity in children with narcolepsy and healthy controls from the UK and the ROI. The results provide an insight into the daily routines of children with narcolepsy (how much time they spend asleep during the day and how physically active they are).

- This is the first study to compare polysomnography and actigraphy measures of sleep in children with narcolepsy. The results showed that there were significant positive correlations between polysomnography and actigraphy measurements of sleep for total sleep time and wake after sleep onset when the data from children with narcolepsy and healthy controls were combined. However, when the groups were considered separately, the strength of the correlations reduced in the narcolepsy group but not in the control group. The results suggest that actigraphy may be less reliable at estimating sleep-wake patterns in children with narcolepsy than in healthy controls. This may be because the children with narcolepsy have more disturbed overnight sleep and are more restless when asleep than healthy controls. Actigraphy may over estimate wake after sleep onset in this population because the software scores movement during the night as 'wake' when in fact the child is asleep but moving around and therefore actigraphy results may underestimate sleep efficiency in children with narcolepsy. The results provide a useful insight into the strengths and limitations of using actigraphy to measure sleep are in children with narcolepsy and healthy controls. These results may inform the design of future research studies aiming to measure sleep in children with narcolepsy and healthy controls.

11.4 Clinical implications

The results of this thesis have implications for self-care and clinical management in children with narcolepsy.

The results suggest that the children with narcolepsy included in this study experienced more symptoms of anger and more disruptive behaviour than the healthy controls. The children with narcolepsy also reported poorer health-related quality of life than the healthy controls. Parents, teachers and clinicians should be aware that narcolepsy is associated with poorer health-related quality of life, even when the child is treated with medication and daytime naps. Given these observations, health care professionals may wish to carefully monitor children with narcolepsy and report any negative side effects of mediation used to treat the

condition. Children with narcolepsy with clinically significant psychological symptoms may benefit from access to psychological services that can provide appropriate support when necessary.

The results also suggest that sleep efficiency and physical activity are positively associated with psychosocial well-being in children with narcolepsy and healthy controls. The findings suggest that children with greater sleep efficiency and those who participate in higher levels of physical activity have better psychosocial well-being and health-related quality of life. It is therefore important for clinicians to closely monitor children with narcolepsy who have poor sleep efficiency and those who participate in low levels of physical activity. It may be beneficial for clinicians to recommend regular physical activity in the treatment of paediatric narcolepsy, in addition to daytime naps. These findings have highlighted the importance of sleep and physical activity for psychosocial well-being in children.

The results also suggest that the children with narcolepsy included in this study do not have significantly impaired cognitive function compared to that of the healthy matched controls. As discussed in Chapter 8, this may be due to the children having effective treatment plans which include stimulant medication and daytime naps. The results indicate that when children with narcolepsy are tested in optimal conditions their cognitive performance is not impaired. Given these observations, educational authorities may wish to consider providing appropriate support for children with narcolepsy at school, especially during examinations, so that their examination results are a fair appraisal of the their ability and potential.

11.5 Limitations of the research

The limitations of the current study are discussed below.

- The unattended home polysomnography recordings took place on one night only and therefore the sleep measured by polysomnography may not be representative of a typical night's sleep for the child. The child's sleep may have been affected by a 'first night' effect from wearing the invasive polysomnography equipment or there may be night to night variation in the sleep of children with narcolepsy that could not be captured by one night of polysomnography recording. Ideally, an adaptation night where the child

wears the equipment for one night before the main polysomnography recording would have been included in the study but this was deemed unfeasible given the burden to participants and the time and cost limitations of the project. As an alternative, actigraphy was used to measure the sleep of the children over 8 nights.

- It could be considered a limitation that the children with narcolepsy included in the study were treated with a variety of different medications. This makes it difficult to assess if and how different medications are affecting sleep, physical activity, cognitive function and psychosocial well-being in the children with narcolepsy. Future studies should aim to recruit a larger sample of children with narcolepsy so that the comparisons can be made between outcomes of larger groups of children treated with different medications (for example children with narcolepsy treated with sodium oxybate vs children with narcolepsy treated with methylphenidate). This will provide more insight into the effects of different medications on the outcomes measured in this project.

- Five of the children in the control group were siblings of a child with narcolepsy, which could be considered a limitation of the current study. As mentioned in Chapter 5, since the recruitment stage of this project in 2014 and 2015, there has been some published evidence to suggest that there may be a “narcolepsy spectrum disorder” in family members of patients with type 1 narcolepsy (Wang, Yan, Han, Lin, & Mignot, 2017). In the study, 378 parents of children with narcolepsy underwent HLA typing, polysomnography, multiple sleep latency test (MSLT) and questionnaire evaluations. Wang et al. (2017) found that in parents of children with cataplexy, 0.8% had narcolepsy with cataplexy and an equivalent or larger number (0.5-1.6%) had mild type 1 narcolepsy due to hypocretin deficiency. The authors suggest that mild symptomatology may explain why the parents of children with narcolepsy are rarely diagnosed in sleep centres (Wang et al., 2017). Based on this recent publication, the data collected from the five siblings of a child with narcolepsy were looked at in detail before deciding whether or not to include the siblings as part of the healthy control group in

the analyses in the thesis. The sibling data did not differ significantly from the healthy control data and therefore the sibling data were included in the analyses in this thesis. For completeness, the analyses described in Chapters 6, 7, 8 and 9 were also conducted with siblings excluded. The overall pattern of case-control differences were unaffected by the exclusion.

- The data presented in this thesis demonstrates a lack of strong relationships between sleep, physical activity and psychosocial well-being in a group of children with narcolepsy and healthy matched controls. This may be due to the relatively small sample size that could be achieved within the time frame and budget of this project. Future studies should aim to recruit larger numbers of children with narcolepsy when investigating relationships between sleep, physical activity, cognitive function and psychosocial well-being in children with narcolepsy. It is also likely that other factors that were not measured in this project such as diet and motivation may contribute to associations between sleep, physical activity, cognitive function and psychosocial well-being in children with narcolepsy.

- The chapters in this thesis have described and compared overnight sleep (Chapter 6), daytime sleep (Chapter 7), physical activity (Chapter 7), cognitive function (Chapter 8) and psychosocial well-being (Chapter 9) in children with narcolepsy and healthy controls. Consequently multiple comparisons have been performed in each Chapter which increases the risk of type I error (concluding that a significant difference is present when it is not). In order to reduce the risk of type I error, Bonferroni corrections for multiple testing were applied throughout the thesis. Additionally, many of the group comparisons in this thesis were performed using non-parametric statistical tests because these tests do not require the assumption of normality to be met. Non-parametric statistical tests are more conservative than parametric analyses and therefore there is less likelihood of type I error and reaching incorrect conclusions (Nahm, 2016).

  It is important to note some of the limitations of applying Bonferroni corrections to analyses. Despite the widespread use of the Bonferroni

method, there has been continuing controversy regarding its use (Armstrong, 2014). One of the main criticisms of the Bonferroni method is that it is overly conservative (Perneger, 1998) and increases the likelihood of type II error (Garamszegi, 2006), such that real differences may not be detected (Armstrong, 2014). The interpretation of result depends on the number of other tests performed, so that as the number of tests increase, the value of the adjusted *p* that has to be achieved to consider a result significant decreases markedly, lowering the power of a test (Armstrong, 2014). Perneger (1998) highlighted that type II errors are no less false than type I errors and states that simply describing what tests of significance have been performed, and why, is generally the best way of dealing with multiple comparisons. Nakagawa (2004) recommends reporting effect sizes for all group comparisons along with exact *p* values. This enables the readers to evaluate the importance of the findings. Based on this recommendation, in this thesis effect sizes for all group comparisons were reported along with exact *p* values.

- It could be considered a limitation that the current study was not pre-registered before the data was collected. Pre-registration involves publishing the research plan (including sample size, methodology, plan for data analysis) prior to the actual implementation of the research project and the plans are peer reviewed before data collection. Preregistration promotes transparency and openness and protects researchers from suspicions of p-hacking. P-hacking is a type of bias which occurs when researchers collect or select data or statistical analyses until nonsignificant results become significant (Head, Holman, Lanfear, Kahn & Jennions, 2015). Although this study was not pre-registered, the following steps recommended by Head et al. (2015) were taken: effect sizes for all group comparisons were reported along with exact *p* values, Dr Ruth Kingshott (who scored the polysomnography data) was blind to whether the data was from a child with narcolepsy or a healthy control and an a priori power analysis was performed to determine the minimum sample size required in this study.

11.6 Implications for future research

As a result of the findings of the current study, a number of directions for future research have been identified and are discussed below.

- Longitudinal research is needed to follow up children with narcolepsy to provide insight into how sleep, physical activity, cognitive function and psychosocial well-being change over the lifespan. Collecting longitudinal data will improve understanding about non-interventional change and interventional studies will elucidate the causal relationship between sleep and physical activity and cognitive and psychological outcomes in children with narcolepsy. The researcher has been awarded a Wellcome Trust ISSF Early Career Researcher Fellowship to conduct the first ever longitudinal follow up study of children with narcolepsy. During this fellowship, the researcher will collect follow up data on cognitive function, psychosocial well-being, physical activity and sleep in the same population of children with narcolepsy and healthy controls two years after their baseline data was collected. It is important to investigate whether the baseline measures of nocturnal sleep and physical activity are related to cognitive and psychosocial outcomes at follow up. For example, it is important to understand whether the children who experience the most disturbed night time sleep or have more sedentary behaviour at baseline have poorer cognitive and psychosocial outcomes at the two year follow up. If this is found to be the case, these factors are modifiable with interventions. For example, a behavioural sleep intervention or an exercise intervention may lead to changes in nocturnal sleep which consequently may improve cognitive and psychosocial outcomes. The efficacy of these interventions should be evaluated using randomised controlled trials.

- Intervention studies are also required to establish the causal relationship between sleep, physical activity, cognitive function and psychosocial well-being in children with narcolepsy. The results of the current study suggest that as sleep efficiency increases, physical activity increases (and vice versa). Given that the results also indicate that sleep efficiency and physical activity

are associated psychosocial well-being in children with narcolepsy, it may be beneficial to test the feasibility and efficacy of behavioural sleep interventions for improving sleep efficiency in children with narcolepsy. Interventions should aim to improve sleep in children with narcolepsy so that the children can have better psychosocial well-being. As previously discussed, the results reported in Chapter 6 suggest that the medications used to treat the symptoms of narcolepsy do not improve sleep efficiency. In addition to the effect their neurological sleep disorder has on sleep efficiency, children with narcolepsy may have poor sleep hygiene and bed time routines which contribute to spending more time awake after sleep onset. Behavioural sleep interventions may therefore be beneficial for children with narcolepsy. Interventions could also aim to increase physical activity in children with narcolepsy, which may have a positive impact on sleep efficiency and psychosocial well-being outcomes.

- In order to better understand the effects of different medications on the sleep quality of children with narcolepsy, a UK wide study should be conducted to analyse and compare the results of polysomnography recordings conducted in sleep clinics with children with narcolepsy before and after the children start taking new medications. This would enable the comparison of sleep in treatment naive children with narcolepsy and sleep in children with narcolepsy who are taking medication. If certain medications are found to have a negative impact on sleep efficiency, this could inform clinical decision making about the most appropriate treatment plans for children with narcolepsy. Randomised controlled trials are also required to determine which medication or combinations of medications provide optimal clinical benefits for children with narcolepsy.

11.7 Overall conclusion

The Paediatric Narcolepsy Project is a case-control study designed to characterise, compare and explore the relationships between sleep, physical activity, cognitive function and psychosocial well-being in children with narcolepsy and gender, age, I.Q and socioeconomic status (SES) matched healthy controls. The aim of the study was to compare children with narcolepsy to healthy controls when the children were

following their usual routine, so that the results are more representative of how the children are on a day to day basis. Therefore 21 out of the 23 children with narcolepsy were treated with medication at the time of the study.

The results show that the children with narcolepsy had more sleep disturbance, spent more time asleep during the day and were less active when awake than controls. Children with narcolepsy reported more feelings of anger and more disruptive behaviour than controls. Children with narcolepsy also showed poorer health-related quality of life than controls. There were no significant differences found in cognitive performance between the two groups, suggesting that well-managed children with narcolepsy do not have significantly impaired cognitive function. Sleep efficiency positively correlated with physical activity and health-related quality of life in children with narcolepsy and controls. Physical activity positively correlated with health-related quality of life and negatively correlated with disruptive behaviour in children with narcolepsy and controls.

These findings will inform the design of intervention studies that aim to optimise the clinical management of paediatric narcolepsy. Longitudinal research is needed to better understand the causal relationship between sleep, physical activity, cognitive function and psychosocial well-being in children with narcolepsy. Future research should aim to investigate the feasibility and efficacy of non-pharmacological interventions (such as a behavioural sleep intervention or an exercise intervention) in combination with pharmacological treatment for optimising outcomes in paediatric narcolepsy.

Chapter 12 References

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