AN EXAMINATION OF THE NATURE OF SLEEP FRAGMENTATION IN CHILDREN WITH UPPER AIRWAY OBSTRUCTION

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i. Abstract

An examination of the nature of sleep fragmentation in children with upper airway obstruction.

Introduction – Sleep related upper airway obstruction (UAO) in children disrupts breathing in sleep, resulting in sleep fragmentation and subsequent neurocognitive and behavioural deficits. Unfortunately the nature of this fragmentation in children is poorly understood and a universally accepted, clinically valid, measure of sleep fragmentation has been elusive. This limits our ability to accurately determine and measure the consequences of sleep fragmentation on a child's development due to UAO, as well as the success of any treatment administered.

General Aims - The aim of the current study was to (i) examine the nature of sleep fragmentation in children with upper airway obstruction and (ii) to develop a new sleep fragmentation index for use in paediatric clinical populations with upper airway obstruction. When this study began no such index existed that was widely accepted and utilized. A range of sleep fragmentation measures already trialed in children with upper airway obstruction were reviewed to identify problems and limitations with current and previous methods of measuring sleep fragmentation in these children. An attempt was also made to identify other possible additional factors that mediate sleep fragmentation so as to develop a workable and generally applicable sleep fragmentation index for children with upper airway obstruction.

Methods – We performed a series of analyses on sleep and neurocognitive data from children with upper airway obstruction to identify and quantify neural activity associated with sleep fragmentation. We then used these measures and other mediating factors to create a composite measure of sleep fragmentation in children.

Results – We found that children with upper airway obstruction had characteristically altered neural activity as measured by electroencephalogram (e.g. changes in sleep spindle density,

decreased alpha and sigma power around spontaneous arousals from sleep). They also had an altered movement distribution in sleep (increased exponential distribution coefficient when sleep runs between movements are modeled on a survival curve), when compared to normal controls. The studies also demonstrated the potential ability of a composite measure of such sleep fragmentation markers and mediating vulnerability factors to more accurately and usefully quantify the negative impacts of upper airway obstruction.

Conclusions - Sleep fragmentation is a significant consequence of UAO in children, however the current measure of UAO severity is insufficient for determining the overall impact on a child's development. As this study demonstrates, the impact of sleep fragmentation is dependent on a complicated set of variables including: age, health factors (e.g. BMI), exposure time, disease severity (e.g. AHI), genetics, trait-like factors, social factors (e.g. SES) and family history. The arousals, or disruptions to sleep, are also altered in children with UAO compared to normal controls. We therefore propose a composite measure of these important factors as a more accurate tool for determining the impact of sleep fragmentation and overall severity of UAO in children.

ii. Signed Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis (as listed below) resides with the copyright holders of those works.

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iv. Publications

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v. *Style and Referencing Format of Jointly Authored Papers, Documents and Unpublished Manuscripts*

The manuscript style and referencing format for chapters 1,2,3,5,7 and 8 are that prescribed by the journal Sleep Medicine.

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vi. Abbreviations

α	*Alpha Wave Form In EEG (~ 9 – 12 Hz)*
ACPT	Auditory Continuous Performance Test
Adolescents	12-18 Years Old
AHI	Apnoea-Hypopnea Index
ANOVA	One Way Analysis Of Variance
ArtotI	Total Arousal Index
BMI	Body Mass Index
C	Control
CA	Central Apnoea
CBCL	Child Behaviour Check-List
Children	4-11 Years Old
CPRS	Conner's Parents Rating Scale
CRS-R	Conner's Rating Scale – Revised (Conners 1997)
DAS	Differential Abilities Scale
DBP	Diastolic Blood Pressure;
DS	Daytime Sleepiness
DTVMI	The Developmental Test Of Visual-Motor Integration
EMG (SM)	Electromyogram (Submental) – Chin Electrode Measuring Local Muscle Activity
ESS	Epworth Sleepiness Scales. A Subjective Measure Of Daytime Sleepiness
GDSVD - s	The Gordon Diagnostic System Vigilance And Distractibility Subtests (Gordon 1983)
Infants	1-3 Year Old
MAP	Mean Arterial Pressure
MDI	Mental Development Index

ME	Movement Events
MSLT	Multiple Sleep Latency Test. An Objective Measure Of Daytime Sleepiness
nCPAP	Nasal Continuous Positive Airway Pressure
NEPSY	Neuropsychological Developmental Assessment (Korkman 2001)
NIPPV	Nocturnal Non-Invasive Positive Pressure Ventilation
NN	SFI Calculated Using A Neural Network Approach To Complicated To Be Summarized In This Paper
ns	Not Significant
nt	Night Of Study Including Clinical PSG
OA	Obstructive Apnoea
OAI	Obstructive Apnoea Index
OSAS	Obstructive Sleep Apnea Syndrome
OSLER	Oxford Sleep Resistance Test. An Objective Measure Of Daytime Sleepiness
PeS	Esophageal Pressure Monitoring
PLMI	Periodic Limb Movement Index
PS	Primary Snoring
R/K	Remember/Know (R/K) Procedure (Tulving 1985)
RAI	Respiratory Arousal Index
REM	Sleep Stage REM (Rapid Eye Movement)
S1, S2, S3, S4	Sleep Stage 1, 2, 3 And 4 Respectively
SAI	Spontaneous Arousal Index
SaO_2	Arterial Oxyhaemoglobin Saturation
SBP	Systolic Blood Pressure
SPT	Sleep Period Total
TAC	Thoracoabdominal Asynchrony
TCAoSAS	Subjects From The Tucson Children's Assessment Of Sleep Apnoea Study (Mulvaney 2005)

TST	Total Sleep Time (In Hours)
TWT	Total Wake Time In Hours
Ua	Unattended In Home PSG
WASI	The Wechsler Abbreviated Scales Of Intelligence
WCST- 64	The Wisconsin Card Sorting Test-64 Card Version
WISC-III	Wechsler Intelligence Scale For Children-Third Edition
wk	Weeks
WPPSI-R	Wechsler Pre-School And Primary Scale Of Intelligence–Revised
WRAML	Wide Range Assessment Of Memory And Learning

CHAPTER 1

Introduction to Sleep and Sleep Disorders in Children

1.1. SLEEP

Sleep is characterized as a naturally recurring state of reduced or absent consciousness, reduced or suspended sensory activity and relative inactivity of voluntary muscles. The nature of sleep is not a homogenous state but rather follows a progression of distinct sleep stages that are repeated in cycles across the course of the night. The two main stages of sleep are known as rapid eye movement sleep (REM sleep), which is famously associated with dreaming, and non-rapid eye movement sleep (NREM Sleep) (Aserinsky 1953). The overall structure and pattern of these sleep stages and their cyclical nature is referred to as the sleep architecture. The research behind the discovery and definition of sleep architecture will be reviewed later in this chapter.

Sleep in children and adults is made up of four distinct sleep stages : NREM sleep stages 1, 2, and slow wave sleep (known variously as stage N3, SWS, NREM stages 3 and 4 – see chapter 3 for a more comprehensive review of the history of sleep stage nomenclature) and REM sleep.

Sleep Architecture

Sleep architecture represents the cyclical pattern of sleep as it shifts between the different sleep stages, typically moving from awake through lighter sleep stages (NREM sleep stage 1 and 2 sleep) to deeper, slow-wave sleep followed by REM sleep. There are generally four or five sleep cycles during a night and each lasts from 90 to 120 minutes with the cycles lengthening as the night progresses. With aging the amount of particular sleep stages and the quality of sleep changes. Slow-wave sleep decreases and lighter NREM sleep stages increase.

The Transition to Sleep

During the earliest phases of sleep, there is still a relatively high level of alertness and awake-like behavior in the brain. As viewed by brain imaging techniques like the electroencephalogram (EEG),

the brain is seen to produce high frequency synchronized activity known as beta waves. These waves have a relatively low amplitude and a relatively high frequency (>16Hz) when compared to most brain activity in sleep. As the brain begins to relax and move closer to the sleep state, slower waves known as alpha waves (typically about 9-12Hz although this does vary between individuals and across age) are produced, particularly over the occipital regions. During this stage, still classed as wake, the individual may experience unusual and often extremely vivid sensations known as hypnagogic hallucinations. Common examples of these phenomena include an individual having the sensation of falling or hearing the persons own name called out. Another very common event as the individual transitions to sleep is known as a myoclonic jerk which is characterized as a sudden limb or whole body twitch associated with an increase in awareness. These movements, also known as hypnic myoclonia are caused by the motor areas of the brain being spontaneously stimulated as the brain transitions to sleep (Dagnino *et al*., 1969).

NREM Sleep Stage 1

Non-REM Stage 1 sleep is the "lightest" sleep stage with the lowest awakening threshold. The sleeping individual can experience a drift between conscious awareness and unconsciousness or dreaming but can still be easily woken. The sleeping individual's eye movement become rhythmic and body movements reduce in frequency and intensity. As mentioned above, it is common to continue to have sudden jerky movement of the legs or other muscle groups in this stage but will likely remain outside of awareness. Non-REM Stage 1 sleep is sometimes considered a transition period between wakefulness and sleep and not an actual sleep stage. In Stage 1, the brain produces moderate to high amplitude theta waves (of approximately 4-9Hz). This sleep stage typically lasts only a brief period with most NREM stage 1 sleep bouts lasting less than 5 minutes. It is commonly found that if someone is awoken during this sleep stage, that they report that they had not been asleep.

NREM Sleep Stage 2

Non-REM stage 2 sleep is the second lightest stage of sleep. This sleep stage is characterized on the EEG by low to medium amplitude theta (4-9Hz) and delta (0.5-4Hz) band activity and the presence of bursts of rhythmic cortical activity known as sleep spindles found in the sigma frequency range (around 12-16Hz). In this sleep stage, body temperature starts to decrease and heart rate begins to slow. Around 50 percent of time spent sleeping is spent in stage 2 sleep although this is highly variable between individuals and also varies across the lifespan. During this sleep stage, eye movements are greatly reduced.

Slow Wave Sleep

Following NREM stage 2 sleep, a person with normal sleep architecture will tend to transition from the lighter stage of sleep to deeper sleep stages. These deeper sleep stages are known as NREM stages 3 and 4 or N3 or slow wave sleep (SWS) depending on which staging guidelines are being used. The brain waves associated with this stage of sleep are slower, low frequency, high amplitude waves, known as delta waves (0.5-4Hz).

During stage 3 sleep, slow brain waves known as delta waves begin to emerge. By stage 4, the waves are almost exclusively delta and thus this stage is sometimes also referred to as delta sleep. The ability to wake someone during this deepest of sleep stages can prove difficult and individuals woken during these SWS stages report feeling groggy and disoriented for several minutes. Non-REM stages 3 and 4 are believed to play an important role in reducing the feeling of subjective sleepiness that increases with time awake.

Rapid Eye Movement Sleep (REM Sleep)

Rapid eye movement sleep (REM sleep) is the sleep stage in which most dreaming occurs. REM sleep typically begins about 90 minutes after initial sleep onset, with the first sleep cycle having a

shorter phase of REM sleep. Toward morning, the time spent in REM sleep increases as the deeper NREM sleep stages decrease. REM sleep was once commonly referred to as paradoxical sleep because it was noticed that while the brain and some other physiological systems had increased metabolic activity while the skeletal muscles in particular had noticeably reduced tone. REM sleep has several other distinct characteristics. Principally respiration becomes irregular and shallow, eye movements increase in speed and frequency and the heart rate and blood pressure generally increase and males of sufficient age and development may develop erections. REM sleep accounts for about 30 percent of sleep in children and decreases slowly in proportion with aging.

1.2. POLYSOMNOGRAPHY

Polysomnography (PSG), also often known as a sleep study, is a multi-channel, continuous physiological monitoring method used in the study of sleep and as a diagnostic tool in sleep medicine. The PSG originally only utilised EEG, electro-occulography (EOG; eye activity) and electromyography measurements (EMG; muscle activity) but, as time went on, various other physiological measures including respiratory and cardiovascular channels were added. In 1968, Rechtschaffen and Kales (commonly referred to as R & K) published a manual that became the world-standard in sleep study performance and sleep EEG interpretation using PSG (Rechtschaffen & Kales 1968). Such standardization and setting of minimal criteria (1 or 2 channel EEG, 2 EOGs and chin EMG) enabled an improved objective comparison of human sleep analysis between sleep researchers (Rechtschaffen & Kales 1968). This basic set of rules for sleep staging remained almost unchanged for the next 30 years.

In 1972, a research group from Stanford University devised a highly influential set of rules that standardized how abnormal respiratory events during sleep should be described and evaluated. It was this research that introduced the terms apnoea and hypopnoeas and the minimum criteria for scoring such events. For example, the events were to be at least 10 seconds in duration and have an associated 4% desaturation in peripheral oxygen (SpO_2) and/or 3 second cortical arousal (Guilleminault *et al*., 1976). These rules were revised and refined with revisions in 1996 to account for children having sleep studies with a further major review in 1999 (ATS 1996; American Academy of Sleep Medicine Task Force 1999).

In 1992, a group of prominent sleep researchers produced a paper on the standardized scoring of cortical arousals and other sleep disruption that was then added to the rules developed by R & K

(Bonnet *et al*., 1993). Movement disorders in sleep and their standardized measurement and analysis were also added to list of rules governing sleep studies with a major task-force review of the evidence producing "The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Leg Syndrome Group (IRLSSG)" (Zucconi *et al*., 2006).

Today, modern polysomnographic analysis consists of four main components: (1) sleep staging, (2) arousal scoring, (3) abnormal respiratory event scoring and (4) movements/behaviour scoring.

(1) Sleep staging in adults and children is primarily based on three electrophysiological signals – the EEG, chin muscle tone (sub mental EMG) and eye movements. The polysomnogram recording is divided up into discrete 30 second epochs of either awake, REM sleep, NREM sleep (sub-stages 1- 4), or removed as artefact based on the combined characteristics of the three signals outlined above with behavioural observations used as supporting evidence.

(2) Arousal scoring mainly utilizes the EEG but also uses changes in other signals and behavioural observations as supporting evidence in certain circumstances. Arousals may be scored as cortical or sub-cortical and can be further categorized according to their association with other events that occur in sleep (e.g. limb movements)

(3) Abnormal respiratory event scoring is mainly based on recordings of respiratory effort and airflow flow parameters. Respiratory events of sleep are normally divided into hypopnoea (partial reduction in respiratory flow) and apnoea (complete cessation of respiratory flow) with further sub-division into central, obstructive, mixed or unknown, dependent on the suspected cause of flow reduction. The definition of each of these respiratory events will also be reviewed later in this document.

(4) Movement and other behaviour scoring generally utilize all available information from physiological measures but often focus on electromyography variables.

1.3. PAEDIATRIC SLEEP ANALYSIS

It is recognized that paediatric sleep is significantly different from that of adults (Grigg-Damberger, *et al*. 2007). The important differences include the length of sleep, which is longer compared to adults, and sleep architecture which results in a different sleep stage pattern in comparison to adults (Grigg-Damberger *et al*. 2007). Children also have a higher arousal threshold in sleep when compared to adults in the same sleep stage at the same time of night (Marcus 1998). Furthermore, children have different electrophysiological signal ranges with an increased EEG amplitude (particularly in the deepest sleep stages; i.e. NREM sleep stages 3 & 4), increased respiratory rate and increased electro-cardiogram (ECG) beat rate compared to adults. Despite these and many other important differences between adult's and children's sleep, paediatric sleep laboratories often only crudely adjusted their accepted adult polysomnographic analysis standards for use in children. This, once again produced a lack of consistency in the analysis of sleep in children between laboratories and a low level of sensitivity and specificity for the PSG in children with a range of sleep disorders (Aurora 2011).

1.4. SLEEP FUNCTION

Despite nearly half of childhood and a great deal of our adult lives being spent sleeping, the exact nature and functions of sleep are yet to be elucidated. However, several theories for the functional significance of sleep have been proposed.(Sejnowski, 2000; Rauchs *et al*., 2005) Sleep has alternately been proposed to have the function of (a) cellular repair (Savage & West 2007), (b)

conservation of resources (Baker 1985), (c) restoration of cellular energy supplies (Montgomery-Downs & Gozal 2006), (d) offline memory reprocessing (Hasselmo 1999; Rauchs *et al*., 2005), and (e) resetting homeostatic systems that become deregulated during wakefulness such as the synaptic homeostasis hypothesis (Tononi & Cirelli 2006) where the plastic neural processes occurring during wakefulness are believed to result in increased synaptic strength in neural circuits. The role of sleep, then is to downscale synaptic strength to a lower baseline level that is of assistance for learning processes and memory formation. However, the various functions of sleep as outlined above are certainly not mutually exclusive. A full exploration of the potential functions of sleep is beyond the scope of this text but it is at least clear that sleep is suspected to be important in general mental and physical wellbeing and functioning.

1.5. SLEEP DISORDERS

If sleep is disrupted, it could disrupt the protective and regenerative processes outlined above that occur mostly or exclusively in sleep. Today, there are many known diseases that can disrupt sleep. A common sleep disrupting disorder, and the focus of this thesis, is a sleep related breathing disorder known as upper airway obstruction (UAO).

Upper Airway Obstruction (UAO) in children

Upper airway obstruction is a spectrum of sleep related breathing disorders (see Figure 1.1). Upper airway obstruction is characterized by varying degrees of upper airway collapse and associated hypoxia, hypercapnia, cortical arousal and snoring during sleep. This sleep-related disorder is common among children (Marcus et al. 2012, Mindell & Owens 2003).

Prevalence of Upper Airway Obstruction in children

It has been estimated that more than a quarter of people will suffer from some degree of UAO at some time during their childhood (Marcus et al. 2012, Mindell & Owens 2003). Snoring is the cardinal symptom of UAO and epidemiological studies suggest that between 1.5 to 27.6% of children will snore at any one time, depending on the definition and data collection techniques (Marcus et al. 2012).

The most severe form of UAO is obstructive sleep apnoea syndrome (OSAS). Children with OSAS have periodic episodes of total upper airway occlusion during sleep which disrupts airflow for short periods. This can cause significant episodic hypoxia and sleep disturbances (ATS 1996; Marcus 2001). Around 1-4% of children are thought to have OSAS at any one time (Marcus 2001; Lumeng & Chervin 2008).

At the other end of the UAO spectrum is primary snoring (PS). Primary snoring is defined as snoring in the absence of significant blood gas exchange abnormalities or overt sleep disturbance (Mindell & Owens 2003). Exact prevalence levels of PS are not known but estimates range as high as 25% for children having PS at some time during their childhood (Guilleminault *et al*. 1982; Ferreira *et al*. 2000; O'Brien & Gozal 2002).

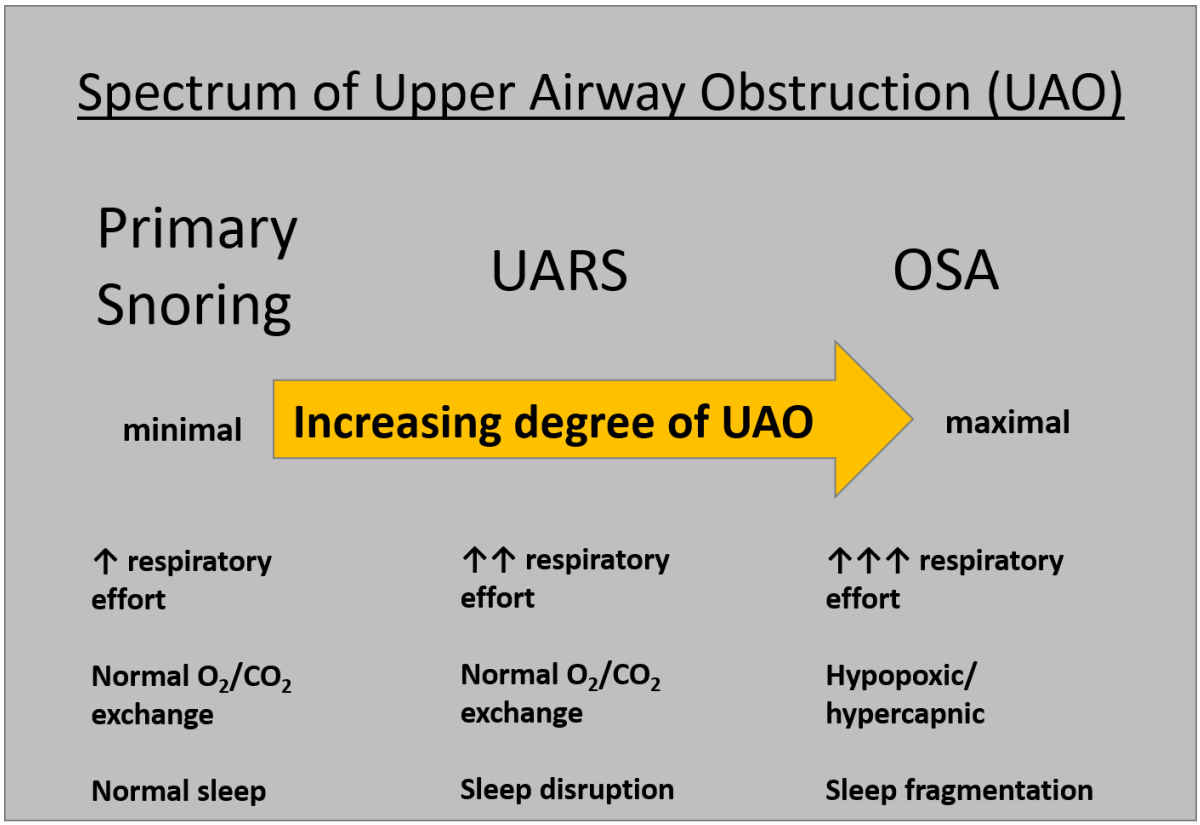

Figure 1.1 Spectrum of Upper Airway Obstruction (UAO).

As the degree of UAO increases, so does the severity of symptoms exhibited by the patient.

UARS = Upper Airway Resistance Syndrome; OSA = Obstructive Sleep Apnoea.

The Incomplete Story of Hypoxia as the Pathophysiological Mechanism of Upper Airway Obstruction

It had been proposed that the cognitive deficits seen in children with severe OSAS are the result of repeated episodic hypoxia (a defining feature of this condition) which causes neuronal damage to the prefrontal cortex which in turn leads to reduced performance on neurocognitive tests.(Beebe & Gozal 2002)

Adult OSAS subjects have demonstrated reduced executive functioning such as in planning ability and sustained attention which are controlled by the prefrontal cortex (Jones & Harrison 2001). Gozal and colleagues demonstrated that in a rat model repeated bouts of hypoxia could account for damage to the prefrontal cortex (Barry *et al*. 2003).

Until quite recently PS was considered to be benign (Brooks, 1993). However, with more detailed and specifically targeted studies, results have demonstrated that primary snorers exhibit some of the same neurocognitive and behavioural deficits as seen in children with OSAS (Guilleminault *et al*. 1982; O'Brien, *et al*. 2004). This is despite the fact that primary snorers, by definition have normal blood oxygen saturation levels while sleeping. This raises the issue of what other pathophysiological mechanisms may be responsible for the neurocognitive and behavioral decrements observed in UAO.

Although many of the details are unclear, it is now well established that at least some part of the learning process occurs during sleep (Hars, et al. 1985; Berry & Gleeson 1997). Studies have shown that performance on tests of skill acquisition continue to improve for up to four days following training if there is sleep between training, testing and retesting (Hars, et al. 1985). This improvement in performance was seen whether or not further training took place.

Sleep fragmentation, or disruption to the sleeping process, is believed to underlie the pathophysiology of neurocognitive deficits associated with UAO. Sleep fragmentation has been

defined variously as sleep disturbance (Stepanski 1984), arousal from sleep (ASDA 1992), awakening from sleep or some variant employing changes in EEG frequency and muscle activity that indicate a more wake-like state (Martin et al 1997). For the purposes of this study**, sleep fragmentation is defined as the disruption of normal sleeping processes that result in intrusions of wake-like behavior into periods of sleep.**

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CHAPTER 2

A Review of Clinical Sleep Fragmentation Indices in Children with Upper Airway Obstruction

2.1. INTRODUCTION

2.1.1. SLEEP FRAGMENTATION IN CHILDREN

Sleep fragmentation in children with UAO is believed to occur as a result of the body's protective response to potentially adverse or threatening physiological conditions. For example arousals are triggered by the mechanoreceptors response to increased respiratory effort associated with a blocked upper airway. The resultant arousal increases muscle tone and activity, restoring airway patency and overcoming airway occlusion but without fully waking the sleeping individual.

There have been many attempts at quantifying sleep fragmentation in children. In general these have been unsuccessful and have shown poor correlations to important daytime outcomes such as behavior, cognition and general quality of life. Some measures have shown correlations with the aforementioned outcomes but they have so far either been impractical for use in clinical settings or have been too complicated, slow, expensive or require equipment or skills that are not normally available in a sleep laboratory.(e.g. (De Groote et al. 2002)) Currently, there is no one validated sleep fragmentation index (SFI) with wide acceptance in the paediatric clinical sleep analysis community. Some of the fragmentation measures that are in use were originally designed for other reasons, to diagnose other conditions or have not been validated in a paediatric population. For example, a measure of sleep disturbance that has been adopted by some when assessing paediatric UAO is movement time as indicated by the number of scored movement (artefact) epochs (see chapter 3 and chapter 5 for a fuller definition and explanation of this sleep staging component). A movement epoch is defined as a thirty second epoch of sleep that has the majority of the period obscured by movement artefact. Movement epochs are a relic of analogue physiological measurements in sleep studies and were never intended as a representative measure of a person's movement during a sleep study. Not surprisingly then, movement measured

in this way is poorly correlated with sleep fragmentation severity. My project will therefore address this apparent void and attempt to develop a widely accessible and applicable validated SFI for use in paediatric sleep analysis.

The primary difficulty when attempting to quantify sleep fragmentation in children is that children often have a smaller arousal response than adults to stimuli during sleep and it is suspected that children with UAO have a blunted reflex response (Guilleminault & Poyares 2002). This raises the question as to whether children with UAO actually have sleep fragmentation, that is, do they have wake intrusions into sleep or are their sleep-protective mechanisms so effective that they do not. There are four main arguments as to why it likely that children with UAO do have sleep fragmentation:

1) Children with a mild form of UAO have no associated hypoxia but still exhibit behaviours that could potentially disrupt sleep (such as flow limitation and snoring) have similar neurocognitive and behavioural deficits to those with severe blood-gas abnormalities (Blunden, et al. 2000, Kohler et al. 2008). In order for this finding to be explained without sleep fragmentation, a third factor common to both severe and mild forms of UAO would need to be proposed. Potential candidates that have been proposed have been obesity (Bhattacharjee et al. 2010), socioeconomic status (Tarasiuk et al 2007) and parental education (Mitchell and Kelly, 2005). However, Kohler et al (2008) demonstrated that children with mild UAO still had similar deficits to those with a moderate to severe form of the disease even when such factors were taken into account. Therefore the mysterious third factor awaits elucidation and the simpler explanation is the best current available option.

2) Children with non-respiratory sleep disorders that have no associated hypoxia (Beebe 2006) but are known to have sleep disturbing events, such as eczema have shown similar deficits to those with UAO (Camfferman et al. 2005).

3) In adults, sleep fragmentation due to UAO has been linked to hypertension, excessive daytime somnolence, reduced neurocognitive function and increased mood problems (Gotfried 1984; Stepanski et al., 1984; Baker 1985; Berry & Gleeson 1997; Martin et al. 1997; Bennett 1998; Smith et al. 1999; Engleman et al. 2000; Jones & Harrison 2001; Mateika & Mitru 2001; Beebe & Gozal 2002; Stepanski 2002a; Stepanski 2002b; Halasz et al., 2004). Sleep disorders in children have been less widely studied than in adults. However, it has been clearly demonstrated that the effects of sleep fragmentation in children are not always the same as that for adults. Children tend to have a higher arousal threshold than adults and they may also have a stronger drive to maintain sleep architecture (Brooks 1993). Thus sleep fragmentation in children is different to that of adults and may also be more subtle in appearance which may subsequently make it more difficult to detect and measure (De Groote et al., 2002; Pepin et al. 2005). However, as stated earlier, most current sleep fragmentation indices were originally designed to measure fragmentation in adults. Therefore, a sleep fragmentation index designed specifically for children is required in order to properly understand and quantify the problem.

4) It has been demonstrated that even mild UAO contributes to increased morbidity in children (Blunden, *et al*., 2000; Beebe 2006). Chronic UAO in children is believed to primarily result in a range of neurobehavioral deficits. These include hyperactivity, inattention, learning difficulties, reduced social competence, increased problematic behaviour, lower IQ and decreased school performance (Bonnet 1989; Bennett *et al*. 1998;

Blunden, *et al*. 2000; O'Brien *et al* 2004; Beebe 2006). Some studies indicate that some of the impacts on health caused by UAO in children may be irreversible.(Kohler, *et al*. 2009) This may be due to critical periods in brain development that, if disturbed by sleep fragmentation, will be sub-optimal and cannot later be completely recovered, even with reversal of the underlying condition (Kohler, *et al*. 2009). There are a number of plausible physiological mechanisms by which sleep fragmentation, associated with UAO, could explain these changes: One potential mechanism involves the combination of two theories behind the function of sleep; (1) being primarily for cellular repair and (2) being a method of conservation of resources (Baker 1985; Savage & West 2007). In support of this, Bonnet and colleagues found that sleep fragmentation attenuated the normal metabolic reduction found in consolidated sleep (Bonnet et al. 1991) and so it is proposed that increased cellular metabolism during sleep could lead to negative daytime sequelae via any or all of the following pathways:

(a) Oxidative stress: Cellular metabolism, although essential to survival, can cause damage to physiological systems via the production of damaging waste products such as free radicals (Martin, Wraith *et al*. 1997). Increased overall metabolism could cause increased damage and hence reduced functional performance of neurons, endothelial cells and other cellular systems in the body.

(b) Alternately, it has been shown that cellular damage caused by metabolism is repaired during the lower metabolic period of sleep - largely during slow wave sleep.(Tononi & Cirelli 2006) It has been shown in recent studies that sleep fragmentation can lead to a reduction in the amount of slow wave sleep (O'Brien & Gozal 2002) The reduction of this crucial sleep stage may reduce or interfere

with normal cellular repair processes resulting in adverse neurobehavioural sequelae.

Another suggested function of sleep mentioned earlier was that it may facilitate the restoration of cellular energy supplies that are depleted by daytime activities (Montgomery-Downs & Gozal 2006). Increased cellular metabolism during fragmented sleep could deplete cellular energy stores further and result in reduced cellular energy levels and hence reduced neural performance during waking hours.

An alternative and perhaps more likely additional proposed mechanism of negative sequelae due to sleep fragmentation is related to the theory that the main role of sleep is offline memory reprocessing (Stickgold 2008). This approach to the function of sleep produces two potential mechanisms for the effects of sleep fragmentation:

(a) It is known that sleep fragmentation can cause sympatho-excitation (Martin, Wraith *et al*. 1997) Sympatho-excitation refers to the process of up-regulating of the autonomic nervous system with preference of the sympathetic component over the parasympathetic component. This process triggers a stress response that increases the production of glucocorticoids (Martin, Wraith *et al*. 1997). The increase in circulating stress hormones reduces neurogenesis (the growth of new neurons - Martin, Wraith *et al*. 1997). Neurogenesis and the formation of new neural pathways is thought to be one of the fundamental mechanisms for learning and longer term memory storage in children. Thus a reduction in new neurons and/or neuronal connections being formed could account at least partly for reduced learning and memory performance is sleep fragmented patients.

(b) The reactivation hypothesis has also been proposed (Buzsaki 1998). In this theory it is suggested that memory traces are replayed (reactivated) during sleep and physical associations strengthened between neurons are linked to the trace. The synchronized firing of neural populations in the cortex seen in sleep is thought to reflect the consolidation of associations between and within memory traces (Gais *et al.,* 2008). Sleep fragmentation in the form of cortical arousals desynchronizes neural firing, returning the cortex briefly to awake-like behaviour. Disruption of coherent neural behaviour through sleep fragmenting events is believed to be a pathway by which sleep fragmentation leads to neurobehavioural deficits. Children have a higher level of neocortical neural coherence in sleep when compared to adults as evidenced by the power (amplitude) of coherent waveforms in their EEG (Grigg-Damberger *et al*., 2007). If the reactivation hypothesis is correct, sleep fragmentation that disrupts this normal coherent behaviour of neural groups is potentially more damaging in children than in adults.

Therefore, for the purposes of the document and studies outlined within, the compelling evidence cited earlier and the plausible mechanisms outlined above, it will be assumed that children with UAO do have sleep fragmentation to some degree and that children with normal sleep do not. It is also likely this fragmentation is different compared to that observed in adults, as indicated by the current methods for determining sleep fragmentation severity in adults, showing no difference between child groups.

Limitations on the use of sleep fragmentation measures in children

A limitation on the investigation of the prevalence and impacts of sleep fragmentation in paediatric patients with UAO has been the lack of standardized and verified sleep fragmentation indices designed for use in children. While some progress has been made, especially over the last ten

years, no single clinical measure of sleep fragmentation has been produced that can be generally applied to the full range of UAO patients. Instead, a plethora of indices of fragmentation have been produced and trialed. Those indices developed have usually fallen into one of two broad categories: measures based on (a) cortical neural activity, usually derived mainly from the EEG and (b) measures based on sub-cortical nervous system activation caused by sleep fragmenting events (*e.g.* autonomic measures).

A second limitation on the investigation of sleep fragmentation in children with UAO has been the focus on indices derived from respiratory measures. However, many children with UAO do not have frank respiratory events that can be recognized under current guidelines. A generally applicable index would need to be based on measures other than those derived from the measurement of standard respiratory events. Therefore the following review was composed to summarise existing sleep fragmentation indices derived from non-respiratory measures and to highlight their limitations.

2.2. AIMS OF THE REVIEW

The aims of this review are three-fold:

1) To review the range of sleep fragmentation measures already trialed in children with UAO.

2) To identify problems and limitations with current and previous methods of measuring sleep fragmentation in children with UAO.

3) To identify the possible components of a workable and generally applicable sleep fragmentation index for children with UAO and other sleep disrupting diseases.

2.3. SLEEP FRAGMENTATION INDICES DERIVED FROM MEASURES OF CORTICAL NEURAL ACTIVATION

2.3.1. EEG SYNCHRONY

During sleep, large populations of cortical neurons fire in synchrony causing a characteristic oscillating electromagnetic field measurable at the scalp. An indirect measure of this cortical neural activity can be taken via the electroencephalogram (EEG). The EEG is a standard measure during overnight polysomnography which is conducted for the clinical evaluation of sleep disorders. The EEG is measured by applying sensitive electrodes to the scalp and amplifying the tiny electric field changes that are detected. Disruptions to sleep continuity result in characteristic changes in the EEG pattern. Arousals in the cortex are initially manifested by rapid increases in the frequency and amplitude of the EEG. Sustained cortical arousals generate desynchrony in the EEG with an eventual return to awake-like neural behaviour. Measuring changes in EEG synchrony during sleep has been one of the fundamental methods used to identify sleep-fragmenting events. Usually these changes have been scored visually according to standardized rules (Rechtschaffen & Kales 1968). More recently, attempts have been made to automate the process using computerized systems (Bennett 1998). In contrast to the synchronized EEG of sleep, the EEG of an awake cortex appears highly desynchronized and tends to have a lower amplitude signal.

2.3.2. AWAKENINGS

A simple, clear and intuitive indication that sleep is being fragmented is if the subject awakens during the sleep period. Measures of waking rate in the sleep period as a measure of sleep fragmentation in adults has been utilized for several decades (Stepanski *et al*., 1984). Using

awakenings as an arousal measure has some significant advantages but equally important drawbacks.

Awakenings are easy to measure

Although some sleep stages can occasionally be mistaken for awake, additional measures performed in standard clinical sleep assessments make scoring periods of awake reasonably reliable. Identifying wake and sleep epochs has high inter-rater reliability so an index based on awakenings is unlikely to be inaccurate. (Stepanski *et al*., 1984) To ascertain if someone is awake also requires little specialized equipment or training and can be calculated easily and automatically as part of a normal clinical report.

Awakenings may underestimate fragmentation

One benefit of indices derived from awakenings is that arousals that wake the subject are, by definition, of the most severe nature. This type of measure is unlikely to overestimate the level of sleep fragmentation of a subject. However, studies utilizing wake time or periodicity as a measure for sleep fragmentation found poor correlations between such measures and relevant sequelae in children with UAO (Scholle & Zwacka 2001). Findings also indicate that smaller arousals that do not cause full awakenings may be more relevant and that indices of awakening were underestimating fragmentation levels (Guilleminault & Poyares 2002).

Awakenings Number and Awakenings Index

Results of studies using awakenings as a measure of sleep fragmentation in children with UAO have been highly varied and inconsistent. One study found that total awakenings were different between children with PS or very mild OSAS and normal controls, with the UAO group having more such arousals.(Blunden *et al*. 2000) However, the number of awakenings in all groups was very low and not corrected for total sleep time, potential confounding the findings. More recent studies by

the same group in subjects with a similar severity of UAO found no such differences when total sleep time was taken into account (Kohler, *et al*. 2009). In contrast, Bhattacharjee and colleagues found that habitual snorers with more severe UAO had fewer awakenings than habitual snorers with milder symptoms (Bhattacharjee, *et al*. 2009). Scholle and Zwacka found no difference between awakenings in children with UAO and controls (Scholle & Zwacka 2001) and this finding was replicated by Montgomery_Downs *et al*., (2005). Such contradictory and unreliable results indicate that such indices are not suitable alone for assessing sleep fragmentation in children with UAO.

2.3.3. ASDA STANDARD AROUSALS

In 1992 the American Sleep Disorders Association (ASDA) developed standard criteria for identifying and scoring cortical arousals as measured in clinical PSGs (Bonnet *et al*., 1992). They decided to define an arousal (which are referred to in this document as standard arousals) as occurring when (a) During NREM sleep stages, there is a visually discernable return to alpha (9-12Hz) or theta (3-9Hz) frequencies in any of the EEG channels for a least 3 seconds or (b) During the REM sleep stage, there is a similar EEG change with a corresponding increase in sub-mental EMG (also for at least 3 seconds) (Bonnet *et al*.,1992). To be scored, standard arousals need to have a minimum duration of 3 seconds. If an arousal is longer than 15 seconds in any one epoch it is scored as an awakening according to normal clinical protocols (Rechtschaffen & Kales1968). Standard cortical arousals have been found to be weakly associated with many daytime performance and quality of life indicators in adults (Mood, IQ, objective and subjective sleepiness such as the Epworth sleepiness score or ESS and the multiple sleep latency test or MSLT respectively) but these results have been inconsistent (Stepanski *et al*., 1984, Bonnet, 1989, Cheshire *et al*., 1992,). In one prospective study, 29 adult patients with UAO were assessed via

standard PSG to determine the relationship between mood, neurocognitive performance and objective and subjective daytime sleepiness with apnoea-hypopnea index (AHI), sleep fragmentation and hypoxemia. Neurocognitive performance correlated with the degree of sleep fragmentation as measured by cortical arousals. Multiple regression analysis revealed that the frequency of arousals was one of the variables most strongly associated with cognitive deficits. However it is interesting to note that objective daytime sleepiness was not significantly associated with any of the PSG derived variables (Chervin *et al*. 2014, Cheshire *et al*.,1992).

Arousal Length

Standards for scoring arousal lengths have been dictated primarily by technical limitations and not by any underlying physiological principles. The minimum arousal duration for clinical assessment was set at 3 seconds (Bonnet *et al*., 1992). This was not because arousals less than 3 seconds were necessarily of no consequence but because this length was a convenient compromise between ease of scoring and accuracy of reporting (Bonnet *et al*., 1992). It is possible that this arbitrary decision has impacted on the reliability and relevance of arousals as a measure of sleep fragmentation.

Total Arousals

Studies using a total arousal index (TAI, which includes respiratory, spontaneous, limb movement, sub-cortical, external, movement and others) as a measure of sleep fragmentation have produced inconsistent results. Kaemingk (2003) found no difference between the TAI of primary school aged children with mild OSAS (AHI<5) and those with more severe OSAS (AHI >5).

However, Scholle and Zwacka (2001) found that children and adolescents with untreated OSAS had higher TAI than when they were treated (a variety of treatment options employed as

appropriate) and also higher than matched normal controls. As TAI includes respiratory arousals (RA) and about half of all respiratory events with children include an arousal this latter result is not surprising. However, the above result is unlikely to be replicated in children with more mild forms of upper airway obstruction such as PS that have few if any associated scored events and so much fewer respiratory arousals.

Spontaneous Arousals

Spontaneous arousals (SA) are arousals generated spontaneously and not the result of other specific events (*e.g.* respiratory events, external noises etc.). Bhattacharjee and colleagues found that habitual snorers with more severe UAO had no difference in spontaneous arousal index) when compared to habitual snorers with more mild symptoms (Bhattacharjee, *et al*. 2009). These finding were confirmed by Kohler (2009) and Montgomery-Downs (2005) with no difference in SAI or number of spontaneous arousals between children with UAO and normal controls. Another study found that children with UAO have more spontaneous arousals than normal controls (O'Brien, Mervis *et al*. 2004). These various findings are perhaps somewhat surprising as the evidence to date is that children with UAO will have a dampened arousal response as an adaption to chronic sleep disruption and have fewer spontaneous arousals than normal children (O'Brien, Tauman *et al*. 2004). Some other researchers have also confirmed this more conventional outcome.(O'Brien, Tauman *et al*. 2004) With this range of sometimes contradictory findings, it is clear that spontaneous arousals alone cannot be used to measure sleep fragmentation.

Respiratory Arousals

Respiratory arousals (RA) are standardly defined as EEG arousals that are closely associated with a respiratory event. Such arousals are found to be different between groups of children with varying

UAO symptom severity and thus would appear an ideal measure of sleep fragmentation. Several studies have confirmed that children with more severe UAO have higher numbers of RA (O'Brien, Tauman *et al*. 2004, Kohler *et al*. 2009, Bhattacharjee, *et al*. 2009). However, RA have a number of important limitations in such applications. One is that UAO severity groups are often defined post hoc by the number of respiratory events noted in a PSG so group differences are assured. A second is that, in children only about half of all respiratory events are associated with an EEG arousal, limiting its accuracy as an SFI. A third issue of concern is that children with mild UAO may not have many discreet scored events or associated arousals. In fact one study found no correlation between RAI and neurocognitive measures (including intelligence, verbal and nonverbal reasoning ability, attention, executive functioning, memory, processing speed, and visual-motor skill) in children with mild UAO (Calhoun, *et al*. 2009). Considering the critical limitations of RA, any SFI based on RA will have similarly limited utlitity and applicability.

2.3.4. THE SLEEP PRESSURE SCORE

As neither spontaneous nor respiratory arousals alone are adequate for a general SFI, a combination of these measures might more accurately indicate SF levels. The sleep pressure score incorporates spontaneous arousals and respiratory arousals as well as an appreciation of their interaction (O'Brien *et al*. 2004). The sleep pressure score (SPS) is based on the theory that individuals with elevated respiratory arousals will have an impaired arousal response and so a reduced spontaneous arousal level. The SPS had a number of advantages over other measures of sleep fragmentation. The SPS was developed for children with UAO and looks not only at the arousals caused by UAO on the night of measurement but also the chronic effects of repeated sleep disturbance through its theoretical calculation of impairment of spontaneous arousals. O'Brien and colleagues, who developed the SPS found reasonable correlations between the SPS

and disease severity (AHI) but this is expected considering that the index is defined using RA that correlate strongly with AHI.(O'Brien, Tauman *et al*. 2004) They also found decreased scores in children in the group with high SPS scores in measures of memory, language abilities, verbal abilities, and some visuo-spatial functions when compared to children in the group with low SPS scores (O'Brien, Tauman *et al*. 2004). A rebuttal paper was released soon after these finding were published criticizing the assumptions underlying the development of the index, pointing out a level of autocorrelation (Sotos 2005). Furthermore, recent studies of children with UAO have not replicated these results (Foster, *et al*. 2008). As with respiratory arousals alone, the SPS is also not applicable to all subjects as many children do not have discrete respiratory events associated EEG arousals (Guilleminault and Poyares 2002).

2.3.5. MICROAROUSALS

Children often have a smaller arousal response than adults to stimuli during sleep and it is suspected that children with UAO have a blunted reflex response (Guilleminault & Poyares 2002). To address this issue it was proposed that indices based on smaller more subtle EEG changes as indicators of SF might hold the key to measuring sleep fragmentation in children with UAO. Microarousals are similar to the standard ASDA arousals but with a shorter duration. Microarousals of various durations have been trialed including 0.5 seconds to 3.0 seconds (Martin, Engleman *et al*. 1997). The standard arousal minimum duration of 3 seconds was an arbitrary limit determined primarily by equipment limitations and has no validated physiological basis (Himanen & Hasan 2000). Realizing this lack of scientific rigor, researchers trialed ever shorter durations to discover the shortest duration arousal with significant physiological consequences. Several limitations of scoring and using shorter duration arousals have subsequently been uncovered.

Inter-Scorer Variability

A major limitation with microarousals is that as the required duration of EEG disruption decreases, the difficulty in reliably visually identifying these transient events increases (Martin, Engleman *et al*. 1997, Poyares *et al*., 2002). When tested, inter-scorer variability for short duration arousals was unacceptably high for most clinical applications. One study in adults with UAO found no extra utility in employing microarousals over standard arousals when detecting UAO events (Martin, Engleman *et al*. 1997).

Score Reliability

A second problem with short-duration arousal scoring is that even normal subjects can produce a very wide range of scores for an overnight PSG. This and inter-scorer variability factor has led to a wide variety of results for studies incorporating microarousals. Daurat and colleges found that microarousals were correlated to spatial and temporal learning but not to executive function or subjective or objective sleepiness in adults with and without UAO (Daurat *et al*. 2008).

Time and Cost

As yet, no reliable automatic method has been developed to score microarousals. This has meant that microarousals must be scored visually, by a human scorer. Due to the factors mentioned above this process is time consuming and labor-intensive. Consequently, scoring of microarousals is slow and expensive. Therefore, scoring microarousals is not practical for many clinical applications where limited financial resources and high time pressure for results are important considerations.

Microarousal Index

The microarousal index has not been extensively studied as a marker of sleep fragmentation in children with UAO. Supplemental oxygen during sleep is sometimes used as a temporary treatment in children with OSAS associated with significant hypoxemia. However, supplemental oxygen may also blunt hypoxic ventilatory drive and ultimately worsen ventilation. One study found that microarousals were reduced in children with OSAS when treated with supplemental oxygen.(Aljadeff *et al*. 1996) The results of this study indicate that some of the sleep fragmentation in children with OSAS is due to oxygen desaturation. It is unclear whether children with these milder forms of the disease would still show increased microarousals. Current research does not support the use of cortical arousals, visually scored, as an adequate measure of sleep fragmentation in children with UAO no matter the duration or underlying cause.

2.3.6. SPECTRAL ANALYSIS

Due to the shortcomings of using visual scoring of cortical arousals associated with UAO to adequately measure sleep fragmentation, other techniques utilizing digital signal processing have been trialed. Electroencephalographic recordings of sleeping subjects show that there is increased synchronization of neural firing in certain neuronal groups in the brain. This kind of neural activity is not apparent in the awake brain. In sleep, cortical neurons show a relatively constant oscillation of membrane potential of less than 1Hz during sleep, overlaid with shorter periods of a variety of other low frequency synchronized neural activity.

Other neural populations show different characteristic synchronized firing patterns that are reflected in the EEG. For example, thalamacortical neurons have a characteristic synchronized firing frequency in sleep of around 0.5 – 3.5 Hz. This type of neuronal activity is seen mainly in slow wave sleep (SWS). Thalamacortical neural activity has been linked to memory function. Several

other frequency components are apparent in the EEG relating to other neural populations or sleep stages.

Such studies have often utilized a mathematical transformation of the EEG signal known as the Fast Fourier Transform. This process divides the signal into its various sine-wave components of differing frequencies. The spectral power in a particular frequency band is then used as an estimate of the synchronized neural firing at that frequency.

Some studies in adults have applied an automatic classification method of short epochs of sleep by FFT of the EEG in patients with UAO which proved to be useful in the diagnosis of a disturbed sleep structure.(Penzel & Petzold 1989) Other researchers have found the inter- and intra-subject variability of values produced by such spectral methods too high to make the approach useful clinically. (Nieuwenhuijs, *et al*. 2002)

Only a few studies have performed power spectral analysis on the EEG of sleep of children with UAO. The results of such studies have been inconsistent. Guilleminault and colleges found correlations between a spectral power measure and other markers of sleep fragmentation such as standard arousals, esophageal pressure changes and heart rate changes in children and infants (Guilleminault & Poyares 2002). Unfortunately, the measure was not compared to daytime functional outcomes.(Guilleminault & Poyares 2002) A more recent study found no relationship between UAO disease severity in children and a wide variety of spectral measures averaged over sleep stage and time of night (Yang 2010).Though some results are promising using spectral analysis techniques, further research is required in specifically adapting them to children with the range of UAO and developing simpler measures that are appropriate to the level of mathematical expertise seen in clinical settings.

2.3.7. SLEEP CONTINUITY

It has been proposed that it is not the arousals themselves that are crucial in determining sleep quality but rather the inter-arousal period (Bonnet 1989). It may be that certain neural processes in sleep must be uninterrupted for certain periods in order to function properly. One study found that the only independent sleep stage-related variable that distinguished between UAO children and controls was mean duration of NREM Sleep stage 2 sleep.(Guilleminault & Poyares 2002) This suggests that the distribution of sleep fragmenting events as well as the absolute number of such events is important when looking to measure sleep fragmentation impact. A number of studies have utilized inter-arousal period as a marker of sleep fragmentation. The obvious problem with such a devise is how to apply it given that some periods of the night will be fragmented in normal sleepers and some epochs undisturbed in disrupted sleepers. Simple measures of mean inter-arousal (spontaneous arousal) period did not show significant correlations with daytime outcomes (see chapter 5).

Survival Curve Analysis

One solution to the problem of measuring sleep continuity has been the application of survival-curve analysis to contiguous epochs of sleep. Log-linear and multistate survival analysis models have been used to quantify the frequency and hazard rates of transitioning between wakefulness and some sleep stages. A study of adults using log-linear models showed that subjects with UAO had more wake-to-NREM sleep and NREM sleep-to-wake transitions, compared with subjects without UAO.(Swihart, *et al*. 2008) The same study demonstrated that multistate survival models indicated subjects with UAO transitioned more quickly from wake-to-NREM sleep and NREM sleep-to-wake than did subjects without UAO. These measures have repeatedly produced very promising results in adults with sleep disordered breathing (Norman, *et al*., 2006). The indices have

shown the ability to clearly discriminate between groups of different disease severity even when these severity differences are quite small (*i.e*. between mild and moderate disease levels) (Norman, *et al*. 2006). Recent studies in children using the same techniques have not yielded the same results with no difference found even between control subjects and the most severe UAO group (Foster, *et al*. 2008).

2.3.8. EEG AND SNORING

Snoring is a well-known indicator of partially obstructed airways. One study investigated snoring associated arousals as a measure of sleep fragmentation and found it weakly associated with neurocognitive performance in infants (Montgomery-Downs & Gozal 2006). One problem with snoring as an index is deriving a reliable and meaningful standard measure. Snoring is not a single well defined event but a range of similar noises made when sleeping from some form of obstruction and can vary widely in volume and tone.

2.4. SLEEP FRAGMENTATION INDICES DERIVED FROM MEASURES OF SUB-CORTICAL ACTIVATION

The autonomic nervous system critically maintains heart rate and blood pressure in response to stimuli of all kinds. When sleeping, autonomic arousals serve to activate a protective response known as the orienting reflex. This response helps protect against potentially dangerous stimuli during sleep (*e.g.* occlusion of the airway). The orienting reflex has been shown not to readily habituate to recurrent arousing stimuli. This fact has led some researchers to postulate that such sub-cortical arousals are more reliable indicators of arousal than those based on cortical activity. (Pepin, *et al*. 2005)

2.4.1. MOVEMENT

As sleep involves the reduction, and in REM sleep an almost complete cessation, of skeletal muscle activity, measures of movement are thought to indicate disruption of the sleep process. As part of the arousal process with UAO events, a movement or position change may occur. Many UAO events are terminated by arousal and movement.

Standard Movement Measures

One issue with movement measures is that there is, as yet no standardized measure. In a standard clinical PSG there exist several types of recorded movement. Movement may be scored from direct observation, via EMG analysis or other movement sensors. Actigraphy has been trialed with limited success with one study finding no difference between actigraphy measures in children with UAO

and controls. Another study of children and adolescents found that actigraphy only correlated fairly with AI and would not be suitable alone as a measure of sleep fragmentation in children with UAO.(O'Driscoll, *et al*. 2009)

Movement Arousals

Movement arousals are defined in various ways. One of the most common definitions used is an increase in activation of tibialis anterior EMG for greater than 3 seconds and an associated increase in some other polysomnographic variable (e.g. heart rate) (Scholle & Zwacka. 2001). One study of children with obstructive sleep apnea syndrome showed that despite no significant disturbance of sleep macrostructure (that is seen in adult OSAS patients) the microstructure of sleep (EEG arousals and movement) is changed. There is also a high coincidence between EEG arousals and movement arousals (Scholle & Zwacka. 2001). Scholle and Zwacka (2001) concluded that the evaluation of arousals and especially the analysis of movement arousals is helpful to estimate treatment effect in OSAS patients.

2.4.2. HEART RATE CHANGES

The variability of beat-to-beat time is believed to reflect the balance between the two branches of the autonomic nervous system that both innervate the heart. High frequency changes (fast changes of the systems innervated by the autonomic nervous system) are due to parasympathetic activation. Low frequency (slow) changes are attributed to sympathetic nervous system activation. Arousals from sleep are assumed to increase sympathetic while decreasing parasympathetic activity. Mietus and colleges found that people with sleep apnoea could be distinguished by heart rate variability(HRV) from people whose sleep was not disturbed by such events (Mietus *et al*., 2000). Correlations of HRV measures with event or disease severity or other fragmentation

markers were not tested. However, the technical difficulties and time required to perform HRV analysis preclude its use in a clinical setting and a full review of HRV studies is beyond the scope of this review. A simple surrogate measure of autonomic changes is heart rate HR and HR change. One study in children with UAO found that significant HR changes could be seen after and before respiratory events when compared to baseline HR (O'Driscoll, *et al*. 2009).

2.4.3. BLOOD PRESSURE CHANGES

Blood pressure (BP) is lower when asleep than when awake. Blood pressure is known to increase with increasing arousal level. Transient blood pressure rise has been demonstrated to occur at the termination of UAO events in adults such as apnoeas and have been associated with other sleep fragmentation markers such as sleep stage changes. Conversely, Loredo and colleges found that BP dips were higher in less disrupted adult sleepers though these correlations were quite weak (Loredo *et al*., 1999).

Adults with UAO may have hundreds of respiratory events per night, the majority of these events, if not all, are associated with measurable transient blood-pressure increases. It has been proposed that this may result in sustained blood pressure increases. Blood pressure is difficult to measure directly in sleeping patients. The usual "cuff' method can only practically provide periodic or averaged measures. The process is disruptive and can itself result in sleep disruption. Consequently, Morrell and colleges proposed measuring waking blood pressure as a measure of prior sleep disruption. They did not find correlations with other more commonly cited fragmentation measures such as AHI, AI or their own SFI derivation based on sleep stage changes except a weak correlation in the non-diseased group, obviously limiting the index's applicability for clinical use (Morrell 2000)

Due to technical limitations, few studies of continuous blood pressure monitoring in sleeping children have been performed. One study that did perform this measure in children found significant changes pre to post respiratory event indicating that BP changes are occurring at such times.(O'Driscoll, *et al*. 2009). However, the process is quite disruptive and itself is known to cause sleep fragmentation, making it a poor candidate for generating an accurate SFI.

2.4.4. PULSE TRANSIT TIME CHANGES

Pulse transit time can be employed as is a measure of transient blood pressure changes. It is a less intrusive measure than some other blood pressure measures that can themselves be a cause of sleep disruption. Pulse transit time has an added advantage of being derivable from existing common PSG components (i.e. the ECG and pulse oximeter). Pulse Transit Times is the time it takes a pulse wave to travel between two arterial sites. The speed at which this wave travels is proportional to the instantaneous blood pressure. Increased blood pressure causes vascular tone to increase thus wave speed to increase and the PTT decreases and vice versa. (Smith, *et al*. 1999)

Pulse transit time allows for a faster sampling frequency than more traditional blood pressure measures. PTT gives a measure of blood pressure change for each pulse rather than a maximum of one per several minutes for the 'cuff' method. The technique can also qualitatively distinguish between some UAO event types.

However, PTT does have limitations as a research or clinical tool in measuring sleep fragmentation. The measure is highly sensitive to movement and artefact-prone limiting its usefulness in clinical setting where movement often accompanies a fragmenting event. PTT is also difficult to calibrate restricting its usefulness as a quantitative measures (Poyares *et al*., 2002). Finally, PTT readings are difficult to interpret in REM sleep when a large proportion of UAO events occur due to a naturally higher level of cardiovascular variability.

Results from studies utilizing PTT as a measure of sleep fragmentation have been mixed. Poyares and colleges found that in adults, sensitivity of PTT to recognize respiratory events was 90.7 but specificity was only 21.9%. These results preclude the use of PTT by itself as a measure of sleep fragmentation. Additionally, respiratory events induce activation with positive PTT response but without arousal in only 14% of cases indicating little value for all the added expense and complication (Poyares *et al*., 2002). Another study found that there was no significant difference between the respiratory disturbance index (RDI) with or without PTT analysis however this same study showed that PTT can improve the detection of respiratory arousals, autonomic arousals and microarousals when used in conjunction with more traditional methods such as visual EEG inspection in some subjects (Pepin, *et al*. 2005).

2.5. DISCUSSION

2.5.1. SUMMARY

The results of the literature review can be summarised as follows;

a) No currently tested single clinical measure of sleep fragmentation derived from an overnight PSG is adequate to characterise the sleep problems seen in children with UAO.
b) Several measures of sleep fragmentation derived from the PSG have shown significant but low or inconsistent correlations with a range of "daytime deficits". Some of the more promising measures included cortical arousals, movement measures, autonomic measures and sleep continuity measures.
c) The "daytime deficits" themselves associated with UAO in children are not well defined but are known to differ from those seen in adults.
d) What is still required is a generally applicable and clinically meaningful sleep fragmentation index that can be applied to children across a range of UAO severity.
e) Such an index should correlate with measures of the disease burden of children with UAO

2.5.2. FUTURE DIRECTIONS FOR PERFORMANCE AND ANALYIS OF PSGS IN CHILDREN

Standard Scoring Methods

A major problem, even long after standard PSG scoring methods were introduced is that many studies are not easily comparable due to non-standard scoring criteria being applied. This is particularly true for infant and paediatric studies where no commonly accepted PSG performance

or scoring criteria are routinely applied. For indices of fragmentation to be meaningfully assessed, standard scoring criteria, particularly in the case of children need to be decided on and rigorously applied. Furthermore, the issues surrounding the historical and seemingly arbitrary nature of sleep scoring rules, derived mostly from a limited consensus, such as the division of sleep into 30 (or 20) second epochs are well known among sleep researchers. In future, the effects of such an artificial division of sleep on calculations of sleep quality will need to be factored in or a better alternate system applied.

Standardized Daytime Functional Comparisons

If research into sleep fragmentation and its effects is to move forward it seems essential to have standard measures of known neurobehavioural and health impacts of sleep fragmentation determined. Such measures would need to be applicable across a wide age range, disease type and severity range, be readily measured in a normal clinical setting and not be excessively expensive, slow or labour intensive. A wide variety of neurobehavioural tests have been employed in studies aiming to test the functional outcomes of disrupted sleep. This fact often makes them difficult to compare in detail. What is required for future research is a standardized set of neurobehavioural tests that can be applied when assessing daytime performance. This will allow for easier comparison of existing proposed indices and also quick assessment of any new proposed method.

Most of the neurobehavioural testing is looking at the cumulative effects of chronic sleep fragmentation and other associated morbidities over months or years. Most of the indices themselves are based on a single, specific night of sleep and so is questionably representational. In order to overcome this limitation, future research should also look at the acute effects of sleep fragmentation. This could be accomplished by using an overnight learning task and correlating

sleep fragmentation measures with results. This approach would allow a more detailed examination of the effect of various fragmentary events instead of their averaged effect over time which is obviously susceptible to many more confounding factors

It has also been proposed that subjective disease burden measures could be used in conjunction with objective measures to compare sleep disease severity indices (Conners *et al*., 1997, Burckhardt & Anderson 2003).

Total Sleep Time

An important problem with almost all current approaches to formulating indices of sleep fragmentation is that the measure is averaged over the total sleep time of the subject or even occasionally the total time spent in bed (TTIB). This process appears logical at first glance as a simple arousal count would be biased with regard to the duration of that person's sleep on the night (or nights) in question. However, sleep duration is not an independent variable that will simply normalize results. Sleep duration can be influenced by sleep quality on the test night or on previous nights. If sleep quality is influenced by fragmentation levels then sleep duration is partly dependent on sleep fragmentation and should not be used to make results more easily comparable. Sleep duration, sleep latency and sleep efficiency are also partly determined by behavioural factors. As sleep fragmentation is known to influence neurobehavioural function, TST and TTIB cannot be considered independent variables to normalize index results.

For future SFIs to be more accurate, different normalizing variables will need to be utilized or effects of sleep quality and neurobehavioural function will need to be factored into TST or TTIB calculations.

A further problem with averaging fragmentation levels over the night is that such calculations miss the potential differential effects of a fragmentation event occurring in different sleep stages, at different times of night or at different durations from sleep onset.

2.5.3. FUTURE DIRECTIONS FOR INVESTIGATING UNDERLYING MECHANISMS OF SLEEP FRAGMENTATION IN CHILDREN WITH UAO

Autonomic Measures

Studies have shown that chronic sympathoexcitation may be important in explaining morbidities associated with UAO (Martin, Wraith *et al*. 1997). However many of the autonomic measures do not allow for easy examination of the sympathetic nervous system independent of parasympathetic activity. One potential measure of autonomic activity that is known to be independent of parasympathetic contribution is skin conductivity or Galvanic Skin Response (GSR). The advantages of GSR measurement include that it is simple, inexpensive and can therefore be easily incorporated into a PSG. The drawbacks are that the measurement process is susceptible to artefact caused by sweating, electromagnetic radiation and movement. Further research into improving the process needs to occur before it could become a standard diagnostic tool including reliability, artefact limitation and rejection and also signal interpretation.

EEG Measures

Many studies have investigated the power spectrum of the EEG with cortical arousals and sleep disordered breathing events in adults. What is still unclear is what is happening to the EEG during

potentially sleep fragmenting events such as movements, standard and sub-cortical arousals, sleep stage changes etc in children who are under-represented in these studies.

Sleep spindles have long been recognized as a common transitory component of a normal sleep EEG. They are a marker of NREM sleep stage 2 and also often occur in response to potentially arousing stimuli. Recent interest in spindles has been in investigating their function. It is believed that spindles are involved in the consolidation of declarative and episodic memories via the interaction of the hippocampal and neocortical neurons. Although their exact role in this procedure is not entirely clear and beyond the scope of this review, it has been demonstrated that sleep spindle density is associated with neurocognitive performance in children (Chatburn *et al*., 2013). Several studies in adult subjects have found very strong correlations between spindle density and neurobehavioral performance although results from studies using adult and child subjects have often been contradictory (Gibbs & Gibbs 1962; Fogel, Nader *et al*. 2007, Fogel, Smith *et al*. 2010). This may be partly due to the differences in spindles between children and adults such as the predominance of frontal and asymmetrical spindles production in younger subjects that is not seen in adults. There are also a number of other difficulties when attempting to use spindles as a marker of sleep fragmentation. These include; (a) the difficulty in discriminating between spindles that are in response to stimuli and those that do not represent a sleep fragmenting event and (b) the variability in spindle numbers between and within subjects which can often be very large.(Fogel, Nader *et al*. 2007)

2.5.4. AIMS OF THIS STUDY

The main aims of the study are to produce a sleep fragmentation index that is generally applicable to children with a range of UAO. It is required that the index:

1) can discriminate between children with and without UAO.

2) correlates with objective neurocognitive and subjective quality of life measures seen in children with UAO.
3) can identify children that would benefit from treatment of their UAO.

This will be attempted using the following general methods

Identification of indirect sleep fragmentation measures

Indirect measures of sleep fragmentation are those that influence an individual's arousability and susceptibility to the deleterious effects of sleep fragmentation. Recent studies have suggested that there are trait factors determining arousability in individuals and susceptibility to sleep deprivation that are stable over time (Nobile, *et al*. 2000; Killgore, *et al*. 2007). These studies suggest that if an SFI is to correlate with daytime neurobehavioural outcomes, a measure of the individual's susceptibility to arousal would need to be factored into the arousal-level calculations. This idea is further explored in chapter 4 and 5. An example of such a sleep variable is sleep spindles. As outlined earlier, spindles have been identified as a part of the sleep consolidation process, related to arousability and arousals and also form a part of the memory consolidation and learning processes of sleep, thus making them a good candidate for an indirect measure of sleep fragmentation susceptibility. Spindles are further explored in chapter 4.

Adaptation of Adult Indices

One way that the main aim will be pursued will be via the adaptation of indices that have proven successful in adults but with alteration for use in children.

An example of this process are measures of movement distribution used as a marker of sleep fragmentation. Bennet and colleges (1998) found strong correlations between a movement-based index and daytime sleepiness measures in adults. The study used a computer-based analysis of

video images of sleeping subjects to derive the index. While being reasonably cost efficient, the time and technical requirements would be beyond the scope of many laboratories. While simple movement measures in children were ineffective in measuring sleep fragmentation, the distribution of movements across a PSG studies carried out by the author have shown significant differences between groups based on UAO severity. The method is cheaper and simpler than that used in adults (Coussens *et al*., 2014) and shows more promise in children than other trialed measures of movement such as actigraphy (O'Driscoll *et al*., 2009). This process is outlined in more detail in chapter 5.

Novel Combinations

There are many separate contributing components to the causes and effects of sleep fragmentation (Cheshire *et al*., 1992). A generally applicable SFI will, by necessity, incorporate several sleep related measures (Blunden & Beebe 2006). It may be that what is required is a novel combination of several existing indices in order to accurately describe the complexity of the fragmentation event and its effect. A number of such indices already exist such as the Sleep Pressure Score and RCREC (Respiratory cycle-related EEG changes-Chervin *et al*., 2004). Furthermore, there are numerous confounding and interacting factors associated with any clinical presentation of sleep fragmentation. The most obvious examples of confounders are hypoxia and obesity often associated with the range of upper airway obstruction. Any useful sleep fragmentation index will have to be able to account for such associations. These ideas are explored in chapter 7.

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CHAPTER 3

General Methods

3.1. SUBJECTS

As part of a larger study using a prospective repeated measures design, overnight polysomnography (PSG) in children with upper airways obstruction (UAO) awaiting adenotonsillectomy at baseline and at six months following surgery was performed. Non-snoring control children matched for age and gender underwent PSG at the same time points. Children with UAO were those with a history of frequent snoring who were scheduled for adenotonsillectomy for suspected obstructive sleep apnoea as diagnosed by an experienced paediatric otorhinolaryngologist at the Adelaide Women's and Children's Hospital. All children were aged between 3 and 12.9 years of age at baseline. Children were excluded if they had undergone previous ear, nose or throat or craniofacial surgery, had a medical condition (other than UAO) associated with hypoxia or sleep fragmentation or were taking medication known to affect sleep or cardiorespiratory physiology. Control children were recruited through the recommendation of parents of the participating UAO children and from advertisements in local newspapers and schools. The same exclusion criteria were applied to controls with the additional requirement that they did not snore on more than two nights per week as confirmed by parental report. This study was approved by the Women's and Children's Hospital Human Ethics Committee. Parental consent and child assent was obtained from all participants.

3.2. OVERNIGHT POLYSOMNOGRAPHY

Overnight PSG was conducted without sedation or reported sleep deprivation and began close to each child's usual bedtime with a parent present throughout the procedure. Polysomnography was only performed if children reported as well on the night and free of any recent illness including respiratory infection. The following parameters were measured and recorded continuously using a commercially available computerized PSG system (Compumedics S-Series Sleep System, Melbourne, Australia): electroencephalogram (EEG; C3-A2 or C4-A1), left and right electrooculogram (EOG), sub-mental and diaphragmatic electromyogram (EMG) with skin surface electrodes, leg movements by piezoelectric motion detection, heart rate by electrocardiogram (ECG), oro-nasal airflow by thermistor and nasal pressure, respiratory movements of the chest and abdominal wall using uncalibrated respiratory inductive plethysmography (RIP), arterial oxygen saturation (SpO_2) by pulse oximetry (Nellcor N-595; 2-3 second averaging time) and transcutaneous CO_2 ($TcCO_2$) using a heated (43^oC) transcutaneous electrode (TINA, Radiometer Pacific). All data were digitized and stored for subsequent analysis. Each child was monitored continuously overnight via infrared camera by a pediatric sleep technician who also documented observations of sleep behavior including the presence or absence of snoring. Height and weight were measured on the night of PSG and established growth charts corrected for age and gender were used to determine body mass index (BMI) z-scores (Bellizzi and Dietz, 1999).

Sleep stages were scored visually in 30s epochs by a single trained technician (SC) according to the standardized EEG, EOG and EMG criteria of Rechtschaffen and Kales (1969). Stage 3 and 4 NREM sleep were combined as slow wave sleep (SWS). Epochs were scored as movement if the EEG and EOG signals were obscured for $\geq$ 50% of the epoch by muscle tension or artefact

associated with movement of the subject ((Rechtschaffen & Kales 1968). Movement time was scored as a separate category and was not included in either sleep or awake time. Awake time refers to time spent awake during the recording period after initial sleep onset.

Respiratory variables were scored according to standard guidelines recommended for paediatric sleep studies (ATS, 1996) other than the modification for a 3% SpO_2 desaturation threshold rather than the recommended 4%. The obstructive apnea/hypopnea index (OAHI) was calculated as the total number of obstructive apneas, mixed apneas and obstructive hypopnoea divided by the total sleep time and expressed as the number of events per hour of sleep. An OAHI ≥ 1 was considered indicative of UAO. The central apnea hypopnea index (CAHI) was calculated as the total number of central apneas and central hypopneas divided by the total sleep time and expressed as the number of events per hour of sleep. The total apnea and hypopnea index (AHI) was calculated as the total number of all respiratory events divided by the total sleep time and expressed as the number of events per hour of sleep.

Cortical arousals were scored according to the criteria of the American Sleep Disorders Task Force (Bonnet, 1992). The total arousal index (AI) represents all arousals combined (excluding arousals caused by external stimuli) expressed as the number of arousal per hour of sleep. The spontaneous arousal index (SAI) represents the total number of spontaneous arousals per hour of sleep. The respiratory arousal index (RAI) represents the total number of respiratory arousals per hour of sleep.

Periodic limb movements (PLM) were scored using standard criteria (Bonnet *et al*.,1993). The PLM index (PLMI) was calculated as the number of PLMS per hour of sleep.

3.3. DATA ANALYSIS

3.3.1. PSG DATA ANALYSIS

The guidelines of Rechtschaffen and Kales (1969) were meant specifically as a reference method but unintentionally became a global gold standard. The rules were never validated and many were derived from no more than convention and consensus decisions (Himanen & Hasan 2000). The R&K rules were routinely utilized for the scoring of recordings of abnormal sleep in the clinical setting for which it was not designed (Rechtschaffen & Kales 1968). In practice, the rules are frequently ignored, misinterpreted and distorted (personal communication) leading to poor inter - rater reliability (Rosenberg & Van Hout 2013).

It has long been recognized that children's sleep is different from that of adults. Paediatric sleep laboratories tended to simply adjust their accepted adult polysomnographic analysis standards for use in children. This, once again, leads to a lack of consistency in the analysis of sleep in children between laboratories. To the best of our knowledge, at the time of production, no other systematic review of the rules of analysis (known as scoring) of paediatric sleep studies existed. We produced the following document, utilizing the major technical references and personal communications with experienced sleep technicians:

3.4. STANDARD RESEARCH SCORING RULES FOR PAEDIATRIC SLEEP STUDIES

Scott Coussens, Mark Kohler and Yvonne Pamula

3.4.1. SLEEP STAGE SCORING

NREM Stage 1 – (Set Rules)

Any epoch containing >15 seconds of the following –

- Low voltage EEG with theta prominence (relative to the characteristic EEG waveforms of the current subject) [1]
- A low frequency "rolling" EOG [1,9&3]
- No REMs, K-complexes or sleep spindles [1&9]
- Tonic EMG(SM) lower than relaxed wakefulness for the current subject [1&3]
- Additionally, there must be < 15 seconds of alpha activity (relative to the characteristic EEG waveforms of the current subject) [1]

NREM Stage 1 – (Supporting Evidence)

Any epoch containing >15 seconds of the following –

- > 15 seconds of Hypnogogic Theta or Vertex sharp waves [3 &9]
- No blink artefacts and a flatter, quieter EOG relative to the subjects waking level [3]

NREM Stage 2 – (Set Rules)

Any sleep epoch containing > 15 seconds of the following –

- A higher density of Sleep spindles or K-complexes (relative to the characteristic phasic EEG behaviour of the current subject) [1]
- Medium level voltage EEG with mixed frequency, higher than NREM S1 (relative to the characteristic EEG waveforms of the current subject) [1]

NREM Stage 2 – (Supporting Evidence)

Any sleep epoch containing > 15 seconds of the following –

- EOG reflecting EEG to some degree [3]
- A corrected delta activity level < 60% - see appendix 1 for corrected delta definition [7]

NREM Stage 3 – (Set Rules)

Any sleep epoch containing > 15 seconds of the following

- High voltage EEG with low delta (<2Hz) prominence (relative to the characteristic EEG waveforms of the current subject) [1]

NREM Stage 3 – (Supporting Evidence)

Any sleep epoch containing > 15 seconds of the following-

- A corrected delta activity level > or = 60% but < 70% [7]
- EOG reflecting EEG to a relatively higher degree when compared to that seen in the subjects NREM S2 sleep [3]

NREM Stage 4 – (Set Rules)

Any sleep epoch containing > 15 seconds of the following –

- Highest voltage EEG with delta (<2Hz) prominence (relative to the characteristic EEG waveforms of the current subject) [1]

NREM Stage 4 – (Supporting Evidence)

Any sleep epoch containing > 15 seconds of the following –

- A corrected delta activity level > or = 70% [7]
- EOG reflecting EEG to a relatively higher degree when compared to that seen in the subjects NREM S3 sleep [3]

REM – (Set Rules)

Any epoch containing >15 seconds of the following –

- Relatively low voltage EEG with theta prominence [1] and relatively higher alpha than other sleep stages.[1&3]
- REMS present in the EOG [1]
- Sawtooth waveform [1]

REM– (Supporting Evidence)

Any sleep epoch containing > 15 seconds of the following –

- Low EEG reflection in the EOG when compared to that seen in the subject's NREM sleep stages [3]

- Lower K-complex and/or sleep spindle density than that in the subject's NREM stage 2 [1&9]
- Tonic EMG(SM) lower than other sleep stages for the current subject [1&9]
- If REM onset or termination is unclear then the transition point will be when 2 of the relevant traces (EEG and 1 or more of the following EOG, EMG(SM), ECG, Resp. Bands) reflect REM activity [3&7]

Movement

Any sleep epoch containing > 15 seconds of obscured EEG and concurrent movement evidence on 2 or more independent channels [1 & 2]

- However, movement epochs are not scored when the preceding epochs are scored as Awake. In the case that an epoch that would otherwise be scored as movement is preceded by an epoch of wake, the former is also scored as wake [2&7]
- Movement epochs are not to be treated as sleep epochs for the purposes of Arousal or Respiratory Event scoring except when scoring PMCAs or PSCAs and when all other conditions for scoring these events is met

Awake – (Set Rules)

- Any epoch that does not meet the sleep stage criteria for any stage will be scored as Awake [1 & 9]

Awake – (Supporting Evidence)

- If there are more than 3 epochs of what would otherwise be scored as movement in a row then all such epochs are scored as Awake.[7]

Unknown

- This stage classification will not be used unless the EEGs are absent and other signals do not allow for scoring [2]

Artefact

- Any epoch with the EEG obscured for >15 seconds by hardware events [3]

Dealing with "Long Arousals"

- When arousals with a duration longer than 15 seconds are encountered and the epoch cannot be otherwise scored as "Awake" or "Movement" then the epoch is staged based on the previous epoch scoring and the arousal is marked as normal.

3.4.2. AROUSAL SCORING

Movement Time

- Movement Time will be scored in any sleep epoch (as pH Distal on ECG trace) when there is evidence of movement on any 2 or more independent traces for > or = 3 seconds

- If 2 Movement Time events are separated by < 3 seconds then the events are to combined into one event

Cortical Spontaneous Arousal (Spontaneous)

- Transient change in EEG frequency and/or amplitude for at least 3 seconds duration but no greater than 1 minute in length [5]
- With a clear, concurrent increase in EMG (Sub-Mental) for arousals scored in REM. The EMG(SM) increase must be for at least 0.5 seconds [5]
- With a clear, concurrent increase in 1 or more independent PSG channels for arousals scored for EEG frequency slowing, theta bursts or very high frequency power increases (>30Hz) [5 & 7]
- No arousal will be scored if the arousal onset in question occurs within 10 seconds of the termination of any prior scored arousal [14]

Sub-Cortical Spontaneous Arousal (Sub-Cortical)

- Concurrent, transient increase in 2 or more independent PSG traces other than and not including the EEG for at least 3 seconds duration but no greater than 1 minute in length [4][4&5]
- With a clear, concurrent increase in EMG (Sub-Mental) for arousals scored in REM [4]
- No arousal will be scored if the arousal onset in question occurs within 10 seconds of the termination of any prior scored arousal [14]

Respiratory Arousal (Respiratory)

- Starting concurrent with or within two breaths of the termination of a scored Respiratory Event [4]
- Transient change in EEG frequency and/or amplitude for at least 3 seconds duration but no greater than 1 minute in length [4]
- With a clear, concurrent increase in EMG (Sub-Mental) for arousals scored in REM (No arousals are to be scored if the EMG(SM) signal is very poor or absent) [4]
- With a clear, concurrent increase in 1 or more additional independent PSG channels for arousals scored for EEG frequency slowing, theta bursts or very high frequency power increases (>30Hz) [5 & 7]
- No arousal will be scored if the arousal onset in question occurs within 10 seconds of the termination of any prior scored arousal [14]

Periodic Leg Movement Arousal (PLMA)

- The arousal must occur within 2 seconds of PLM element termination and within 3 seconds of PLM element onset to be associated with the element in question [10]
- Transient change in EEG frequency and/or amplitude for at least 3 seconds duration but no greater than 1 minute in length [6,5,4 &2]
- With a clear, concurrent increase in EMG (Sub-Mental) for arousals scored in REM. The EMG(SM) increase must be for at least 0.5 seconds [6,5,4 &2]
- With a clear, concurrent increase in 1 or more independent PSG channels for arousals scored for EEG frequency slowing, theta bursts or very high frequency power increases (>30Hz) [5 & 7]

- No arousal will be scored if the arousal onset in question occurs within 10 seconds of the termination of any prior scored arousal [14]

Technician-Caused Arousal (Scored as Resp. Event – TECH)

- Starting concurrent with or within 30 seconds of a recorded event by any person other than the subject that would likely cause arousal[4&7]
- Transient change in EEG frequency and/or amplitude for at least 3 seconds duration but no greater than 1 minute in length [4&7]
- With a clear, concurrent increase in EMG (Sub-Mental) for arousals scored in REM. The EMG(SM) increase must be for at least 0.5 seconds. [4&7]
- With a clear, concurrent increase in 1 or more independent PSG channels for arousals scored for EEG frequency slowing, theta bursts or very high frequency power increases (>30Hz) [5 & 7]
- No arousal will be scored if the arousal onset in question occurs within 10 seconds of the termination of any prior scored arousal [14]

Sub-Cortical Respiratory Arousal (SCRA)

- Starting concurrent with or within two breaths of the termination of a scored Respiratory Event [4]
- Concurrent, transient increase in 2 or more independent PSG traces other than and not including the EEG for at least 3 seconds duration but no greater than 1 minute in length [4 & 5]
- With a clear, concurrent increase in EMG (Sub-Mental) for arousals scored in REM [4]

- No arousal will be scored if the arousal onset in question occurs within 10 seconds of the termination of any prior scored arousal [14]

Spindles in Arousals

If what would otherwise be scored as an arousal occurs at the same time as a spindle then –

- If the spindle is continuous with the onset or termination of the arousal then the spindle is not counted as part of that arousal [5]
- If the spindle occurs during an arousal then the spindle will be counted as part of the arousal only if both of the surrounding arousal components independently meet the criteria for being scored as an arousal

3.4.3. RESPIRATORY EVENT SCORING

Central Apnoea – (Set Rules)

An event will be scored in a sleep epoch as a central apnoea when there is:

- A reduction in airflow to < 20% of local baseline level on what appears to be a reliable trace (Air Flow or Thermistor) for at least the duration of two breaths based on the local average for that subject [2,8, 17 & 4]

AND

- A cessation of breathing effort as indicated by the thoracic and abdominal band traces (where these traces are deemed to be reliable) for at least the duration of two breaths based on the local average for that subject [2 & 4]

AND

- No movement just prior to or overlapping the beginning of the event [2 & 7]

AND

- A minimum of a 3% reduction in baseline SpO_2 and/or associated arousal within two breaths of the event termination and/or if the event duration is >=20 seconds. [2, 17, 4 & 8]
- The event is to be marked from the end or reduction of airflow to the base of the upswing associated with the next breath on what is deemed to be a reliable airflow trace [2 & 7]
- If what would otherwise be scored as a central apnoea directly follows a sigh then the event will only be scored if the signals used to determine the event are stabilized prior to event onset (e.g. SpO_2)

Central Hypopnea – (Set Rules)

An event will be scored in a sleep epoch as a central hypopnea when there is:

- A reduction in airflow to < 50% of local baseline level but greater than 20% of local baseline level on what appears to be a reliable trace (Air Flow or Thermistor) for at least two respiratory cycles based on the local baseline [2,8, 17 & 4]

AND

- A reduction in breathing effort as indicated by the thoracic and abdominal band traces (where these traces are deemed to be reliable) to <50% of local baseline level [2 & 4]

AND

- No movement just prior to or overlapping the beginning of the event [2 & 7]

AND

- A minimum of a 3% reduction in baseline SpO_2 and/or associated arousal within two breaths of the event termination. [2, 17 & 4]

AND

- A lack of any visible phase difference between abdominal and thoracic band traces

- The event is to be marked from the end or reduction of airflow to the base of the upswing associated with the next breath on what is deemed to be a reliable airflow trace [2 & 7]

Central Hypopnea – (Supporting Evidence)

- The event may be accompanied by a reduction in EMG(DM) activity

Obstructive Apnoea – (Set Rules)

An event will be scored in a sleep epoch as an obstructive apnoea when there is:

- An 80% or greater reduction in airflow from the local baseline level on what appears to be a reliable trace (Air Flow and/or Thermistor with scoring from both traces being preferable) for at least two respiratory cycles based on the local baseline [2,8,4, 12 & 13]

AND

- A continuation or apparent increase in breathing effort as indicated by the thoracic and abdominal band traces and/or EMG(IC) (where these traces are deemed to be reliable) [2 & 4]

AND

- A lack of movement just prior to or overlapping the beginning of the event
- An obstructive event should also contain breathing paradox or a least a change in phase between the thoracic and abdominal bands [2 & 4]
- The event is to be marked from the point where the abdominal and thoracic bands go out of phase (peak or trough) to the point where they are in phase again. If this is not possible due to poor effort traces then the event is to be marked from the end or reduction of airflow

to the base of the upswing associated with the next breath on what is deemed to be a reliable airflow trace [2 & 7]

Obstructive Apnoea – (Supporting Evidence)

- The event will often be accompanied by a reduction in SpO_2 and or arousal
- The event may be indicated by a flattening of a breathing effort trace rather than directly identifiable paradox or phase change
- The event may also be indicated by an apparent flow limitation in the Airflow trace

Obstructive Hypopnea – (Set Rules)

An event will be scored in a sleep epoch as a obstructive hypopnea when there is :

- At least a 50% (but no more than 80%) reduction in airflow from the local baseline level on what appears to be a reliable Thermistor trace **or** a clear change in what is deemed to be a reliable nasal pressure trace for at least two respiratory cycles based on the local baseline [2, 12, 13 & 4]

AND

- A continuation or apparent increase in breathing effort as indicated by the thoracic and abdominal band traces and or EMG(IC) (where these traces are deemed to be reliable) [2 & 4]

AND

- No movement just prior to or overlapping the beginning of the event [2 & 7]

AND

- A minimum of a 3% reduction in baseline SpO_2 and/or associated arousal within two breaths of the event termination. [2,18, 17 & 4]
- The event is to be marked from the end or reduction of airflow to the base of the upswing associated with the next breath on what is deemed to be a reliable airflow trace. If this is not possible due to poor traces then the event is to be marked from the point where the abdominal and thoracic bands go out of phase (peak or trough) to the point where they are in phase again. [2 & 7]

Obstructive Hypopnea – (Supporting Evidence)

- An obstructive event often contains breathing paradox or a least a change in phase between the thoracic and abdominal bands and/or an apparent flow limitation in the Airflow trace [2 & 4]

Mixed Apnoea – (Set Rules)

An event will be scored in a sleep epoch as a mixed apnoea when there is:

- A reduction in airflow to < 20% of local baseline level on what appears to be a reliable trace (Airflow or Thermistor) for at least two respiratory cycles based on the local baseline [2,8 & 4]

AND

- A cessation of breathing effort as indicated by the thoracic and abdominal band traces (where these traces are deemed to be reliable) followed by, or following a continuation or apparent increase in breathing effort as indicated by the thoracic and abdominal band traces and or EMG(IC) (where these traces are deemed to be reliable) with the obstructive

component also containing breathing paradox or a least a change in phase between the thoracic and abdominal bands [2,4 & 7]

AND

- No movement just prior to or overlapping the beginning of the event [2 & 7]

AND

- A minimum of a 3% reduction in baseline SpO_2 and/or associated arousal within two breaths of the event termination. [2, 17 & 4]
- The event is to be marked from the end or reduction of airflow to the base of the upswing associated with the next breath on what is deemed to be a reliable airflow trace. If this is not possible due to poor effort traces then the event is to be marked from the end or reduction of airflow to where the abdominal and thoracic bands are in phase again [2 & 7]

Inspiratory Flow Reduction Event (IFRE) – (Set Rules)

An event will be scored in a sleep epoch as an IFRE when there is : [12]

- At least a 50% reduction in airflow from the local baseline level on what appears to be a reliable Thermistor trace **or** at least a 20% reduction in airflow from the local baseline on what is deemed to be a reliable airflow trace (with scoring from both being preferable) for at least two respiratory cycles based on the local baseline [11,12, 16 & 13]

AND

- A sustained or increased breathing effort as indicated by the thoracic and abdominal band traces and or EMG(DM) (where these traces are deemed to be reliable) [4]

AND

- No movement just prior to or overlapping the beginning of the event [4]

AND

- No associated respiratory arousal [4]

AND

- No more than a 2% reduction in baseline SpO_2 and/or associated arousal within two breaths of the event termination [4]
- The event is to be marked from the start of the increase in effort to the start of the arousal associated with the event [4]

Post Movement Central Apnoea – (Set Rules)

An event will be scored in a sleep epoch as a post-movement central apnoea when, directly following a movement there is:

- A reduction in airflow of > 80% of the local baseline level on what appears to be a reliable trace (Air Flow or Thermistor) for at least the duration of two breaths based on the local average for that subject [2,8 & 4]

AND

- A cessation of breathing effort as indicated by the thoracic and abdominal band traces (where these traces are deemed to be reliable) for at least the duration of two breaths based on the local average for that subject [2, 18 & 4]

AND

- A minimum of a 3% reduction in baseline SpO_2 (provided the baseline has returned to normal following any movement artifact and/or associated arousal within two breaths of the event termination and/or if the event duration is >=20 seconds. [2, 4, 17 & 8]
- The event is to be marked from the end or reduction of airflow to the base of the upswing associated with the next breath on what is deemed to be a reliable airflow trace

Respiratory Paradox – (Set Rules)

An event will be scored in a sleep epoch as respiratory paradox when there is:

- Breathing paradox or a least a 25% (1/4 wavelength) change in phase between the thoracic and abdominal bands (where these traces are deemed to be reliable) for at least the duration of two breaths based on the local average for that subject [2, 18 & 4]

AND

- No associated arousal and/or SpO_2 decrease

Post Sigh Central Apnoea – (Set Rules)

An event will be scored in a sleep epoch as a post-sigh central apnoea when, directly following a sigh there is:

- A reduction in airflow of > 80% of the local baseline level on what appears to be a reliable trace (Air Flow) for at least the duration of two breaths based on the local average for that subject [2,8 & 4]

AND

- A cessation of breathing effort as indicated by the thoracic and abdominal band traces (where these traces are deemed to be reliable) for at least the duration of two breaths based on the local average for that subject [2, 18 & 4]

AND

- A minimum of a 3% reduction in baseline SpO_2 (provided the baseline has returned to normal following any dip or artifact prior to event onset) and/or associated arousal within two breaths of the event termination and/or if the event duration is >=20 seconds. [2, 4, 17 & 8]

- The event is to be marked from the end or reduction of airflow to the base of the upswing associated with the next breath on what is deemed to be a reliable airflow trace [4]

3.4.4. PERIODIC LEG MOVEMENT SCORING

- Each PLM element will consist of a transient burst of activity in the Leg EMG trace (L Leg EMG, R Leg EMG or L&R Leg EMG) [6&2]
- Each PLM element will be between 0.5 and 5 seconds in duration [6&2]
- Each PLM element will have between 15 and 90 seconds interval between the termination of the first element and the start of the next PLM element in series (unless it is the final PLM element in that series) [6&2]
- A PLM series will only be scored if there are at least 4 elements in a row [6&2]
- If the PLM element directly follows the termination of a respiratory event then it is to be scored PLMI [10]
- No PLMs are to be scored in NREM stage 1, wake or REM stages [10]
- No PLMs are to be scored in Movement Epochs unless the PLM occurs before the movement which defined the epoch [10]
- No PLMs are to be scored directly following the termination of a scored arousal [10]
- Each element must have a minimum amplitude of at least 25% of the maximum recorded reaction derived from the smaller of the two calibration signals of the leg movements prior to sleep onset [10]. If both of the calibration signals contain clipping then the minimum amplitude required for scoring a PLM element is 25% of the maximum bandwidth of the signal

3.4.5. SIGNAL ARTEFACT SCORING

$TcCO_2$ Artefact

- $TcCO_2$ values will be marked as artefact if sudden changes are simultaneous with movement as indicated by 1 or more reliable movement-indicating traces (EMG(legs) , O_2 waveform, EEG(artefact), EMG(SM), Position) [2&7]
- The Artefact will be scored from the point where the $TcCO_2$ value changes by 3 mmHg from the local baseline level due to movement. The artefact will terminate when the $TcCO_2$ returns to within 3 mmHg of the previous level or when it is evident that a new set-point has been reached.
- Periods where the $TcCO_2$ is being calibrated, is detached or being reapplied until the values stabilize for 3 consecutive epochs should also be marked as artefact.

SpO_2 Artefact

- SpO_2 values will be marked as artefact if sudden changes, > 3% are temporally associated with movement as indicated by 2 or more reliable movement-indicating traces (EMG(legs) , EEG(artefact), EMG(SM), Position) and the O2 waveform is desynchronized [2&7]
- The artefact will be scored from the point where the SpO_2 value changes by 2% from the local baseline level due to movement. [7] The artefact will terminate when the SpO_2 returns to within 2% of the previous level or when it is evident that a new set-point has been reached.

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3.6. APPENDIX 1

Corrected delta refers to the proportion of the EEG signal that is delta, as indicated by Fast Fourier Transform signal decomposition minus the proportion of the signal indicated as artefact and is calculated as follows:

Corrected Delta % = (((Original Delta %) / (100 – Artefact %)) x 100)

3.6.1. NEUROCOGNITIVE ASSESSMENT

Neurocognitive assessment was completed by a trained examiner who was blinded to the clinical status of the child. The assessment was conducted over 2-3 hours with a planned 10-15 minute break. Assessment was conducted in the same order for each child and comprised of the 5th edition of the Stanford Binet Intelligence Scale (Roid 2003) and the NEPSY (Korkman *et al*., 1998) – a developmental neuropsychological assessment.

Stanford Binet Intelligence Scale

The Stanford Binet Intelligence Scale (SB5 - 5th edition; Roid, 2003) was selected for use in the present study because it provided the most up to date normative data and well defined factor structure and sensitivity over the 3-12 year age range at the time of the study. The Stanford Binet Intelligence Scale is an individually administered assessment of intelligence and cognitive abilities. The test is designed for individuals aged 2 years and above and, for children in this study, took 60 to 90 minutes to complete. The reliability of The Stanford Binet Intelligence Scale has been tested utilizing a variey of methods including test-retest stability, and inter-scorer agreement. On average, the IQ scores for this scale are found to be quite adequately stable across time with the median inter-scorer correlation found to be 0.90 (Janzen 2003). Content validity has been confirmed based on professional assessment (Bain & Allin, 2005).

A global measure of intellectual ability is provided by the Full Scale IQ (FSIQ) score, which is derived from the sum of all tasks. The Verbal (VIQ) and Nonverbal IQ (NVIQ) scores are composites of the skills required to solve tasks in the 5 verbal and 5 nonverbal subtests respectfully. Fluid Reasoning (FR) examines the ability to reason from the specific to the general (inductive reasoning) or, given more general information, infer a specific conclusion or implication (deductive reasoning), using information that is novel to the individual. Knowledge (KN) refers to a

person's accumulated fund of general information acquired from their surrounding environment and experiences, and thus in contrast to FR represents the crystallized dimension of intelligence. An individual's numerical problem solving skills, facility with numbers and understanding of mathematical concepts is determined by the Quantitative Reasoning domain (QR). The assessment of Visual-Spatial Processing (VS) measures the ability to determine patterns and relationships from visual objects, describe spatial orientations, and apply inductive type reasoning skills to visual information. Finally, Working Memory (WM), a subcomponent of tasks more generally described as *executive functions* and also highly interrelated with general memory function, assesses the facility in which information stored in short-term memory is inspected, organized and manipulated in order to produce a solution to a given problem.

A Developmental NEuroPSYchological Assessment

The NEPSY (Korkman *et al*.,1998) provides a comprehensive stand-alone battery of neuropsychological assessments for children aged 3-12 years. Very few such assessments exist and none other than the NEPSY allows for assessment of children as young as 3 years. Recently the NEPSY has been successfully used to assess children with SDB (Gottlieb 2004; O'Brien 2004). The authors recommended order of subtest administration was preserved in this study (Korkman *et al*.,1998). Re-test reliability and validity of NEPSY indices has been confirmed in a variety of children (Schmitt *et al.* 2004).The duration of the core NEPSY assessment ranged from 45-60 minutes.

The NEPSY consists of a series of interactive subtests, the scores which combine to provide an indication of a child's ability in each of five functional domains: attention/executive functions; language development; sensorimotor functions; visuospatial Processing; and memory and learning. The attention/executive domain provides an assessment of the interaction of attention with

executive functions and provides a measure inhibition, monitoring and self-regulation, selective and sustained attention, non-verbal problem solving, figural fluency, vigilance, and establishment, maintenance and change of a response set. The Language domain provides an assessment of components thought to be critical for oral and written language development. Language components assessed by the NEPSY include phonological processing, naming, receptive language comprehension, and ability to name and accomplish speeded naming. The Sensorimotor domain assesses the ability to process basic tactile information, imitation of hand positions, ability to produce repetitive finger movements and rhythmic hand movements in an ordered sequence, and the speed and precision for which a pencil is used. The Visuospatial domain assesses the ability to visually synthesize elements into a meaningful whole, to judge an objects orientation and location in space and to judge the relative location and direction of such objects, to copy or reproduce a model from subcomponents of the original, to mentally rotate an object, to interpret symbolic representations of space and location, and non-verbal problem solving. The Memory domain assesses immediate and delayed declarative memory for verbal and nonverbal information.

3.6.2. STATISTICAL ANALYSIS

One-way ANOVA was used to compare continuous demographic data, while χ^2 tests or Kruskal-Wallis test were used to test for group differences in frequency of ordinal and nominal demographic data. Repeated measures ANCOVA, covarying for significant group differences in demographic variables, was used to assess group differences, changes across assessment times and interactions of group by assessment for PSG results and cognitive performance. Assumptions of normality were valid for all PSG variables with the exception of periodic limb movement index (PLMI), respiratory arousal index(RAI), frequency of SpO_2 desaturations ≥ 3%/ hr TST, percentage of sleep time with SpO_2 < 95%, $TcCO_2$ > 50 mmHg, OAHI, CAHI and AHI. Inverse transformation [1/(x + 1)] and square root transform [√x] was performed where appropriate for these variables to

correct skewness. Post hoc testing was conducted using planned means comparisons with Bonferroni adjustment for multiple comparisons. All *p* values reported are 2-tailed, with statistical significance determined at $\alpha = 0.05$. Data is presented as mean ± standard deviation unless otherwise stated.

Selected data collected during the study outlined above was used in experiments that form chapters 4, 6 - 11 of this thesis.

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RESULTS

CHAPTER 4

Sleep Spindle Activity and Cognitive Performance in Healthy Children

Contextual Statement

The following chapter is a published paper entitled "Sleep Spindle Activity and Cognitive Performance in Healthy Children" (Alex Chatburn, Scott Coussens, Kurt Lushington, Declan Kennedy, Mathias Baumert, and Mark Kohler, Sleep 36, no. 2 (2013): 237-243).

It focuses on a common element of EEGs in sleeping children known as sleep spindles. Spindles have been postulated by some researchers to indicate or to be directly involved in sleep fragmentation. It was found that certain measures of EEG spindle activity did show correlations with neurocognitive performance in healthy children. Further investigations into whether similar correlations are seen in children with UAO are ongoing but at the time of completing this study they were yet to be finalized and so are not included in detail in the chapters that proceed this one.

Statement of Authorship

Title of Paper	Sleep spindle activity and cognitive performance in healthy children.
Publication Status	✓ Published ○ Accepted for Publication ○ Submitted for Publication ○ Publication Style
Publication Details	Chatburn A, Coussens S, Lushington K, Kennedy D, Baumert M, Kohler M. Sleep spindle activity and cognitive performance in healthy children. Sleep. 2013 Feb 1;36(2):237-43.

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author	Alex Chatburn		
Contribution to the Paper	Assisted in the analysis of the data and prepared the manuscript for publication.		
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Contribution to the Paper	Conceived, designed the study and assisted with the analysis of the data and preparation of the manuscript for publication.		
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Name of Co-Author	Mark Kohler
Contribution to the Paper	Conceived, designed and executed the study and the analysis of the data and preparation of the manuscript for publication.
Signature	Date 28/1/14

Chatburn, A., Coussens, S., Lushington, K., Kennedy, D., Baumert, M. & Kohler, M. (2013). Sleep spindle activity and cognitive performance in healthy children. *Sleep, 36*(2), 237-243

CHAPTER 5

EEG Changes Accompanying Spontaneous Arousals during Sleep Correlate with Neurocognitive Performance in Children with Upper Airway Obstruction

Contextual Statement

Preliminary results from this experiment were presented in poster and short talk format and published as an abstract (S.Coussens, M.Kohler, M.Baumert, J.Martin, D.Kennedy, K.Lushington, D.Saint and Y.Pamula (2011). ”EEG spectral changes associated with spontaneous arousals in children with upper airway obstruction”. Journal of Sleep Research, 20(suppl. 1), p52.) for the 2011 Australasian Sleep Association Annual Scientific Meeting in Adelaide, Australia. Following the investigation into spindles and their relationship to cognitive functioning in children, it was thought that smaller scale elements of the EEG related to arousals and arousal suppression (of which spindles are one) might further elucidate the role of sleep fragmentation with UAO in neurocognitive deficits.

Statement of Authorship

Title of Paper	EEG Changes Accompanying Spontaneous Arousals During Sleep Correlate with Neurocognitive Performance in Children with Upper Airway Obstruction
Publication Status	◉ Published ◉ Accepted for Publication ◉ Submitted for Publication ◉ Publication Style
Publication Details	Scott Coussens, Mathias Baumert, Mark Kohler, James Martin, Declan Kennedy, Kurt Lushington, David Saint, Yvonne Pamula

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Scott Coussens		
Contribution to the Paper	Conceived, designed and executed the study and the analysis of the data and preparation of the manuscript for publication.		
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EEG spectral changes associated with spontaneous arousals in children with upper airway obstruction

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Background: Children with upper airway obstruction (UAO) have fragmented sleep due to the occurrence of abnormal respiratory events that are often accompanied by arousal. Sleep fragmentation has been shown to contribute to the negative sequelae seen in UAO including neurobehavioural deficits. However children with UAO do not demonstrate the same degree of sleep fragmentation as seen in adults with UAO. It has been postulated that children may be able to preserve sleep integrity by modifying their arousal response. This change in arousal response may be reflected by arousal number, arousal length or EEG spectral power associated with arousal.

Hypothesis: Children with UAO will have fewer and shorter spontaneous arousal and an altered EEG arousal spectral profile compared to normal controls.

Methods: 87 children aged 3.0 to 12.9 years underwent overnight polysomnography. Subjects were divided into three groups: non-snoring controls (n = 45), primary snorers (n = 23) and obstructive sleep apnoea (n = 19). Fast fourier transform (FFT) was performed over three time periods: during spontaneous arousal as well as the 10 seconds prior to and following each arousal. Mean relative power was calculated for the following frequency bands: delta: 0.5-4.5 Hz; theta: 4.5-9Hz; alpha: 9-12 Hz; sigma: 12- 15 Hz and beta: 15-30Hz.

Results: There was no difference in arousal frequency between groups but children with UAO had arousals of shorter duration ($p<0.01$). Children with UAO displayed lower power in the alpha band pre- and post-arousal and lower sigma power post-arousal compared to control children($p<0.05$). Children with UAO also had significantly reduced sigma and beta power during arousal ($p<0.05$).

Conclusion: Children with UAO showed altered neural activity during spontaneous arousal, in particular a decrease in higher frequency EEG power. This difference in EEG spectral profile associated with arousal could be used in the development of a sleep fragmentation index.

5.1. INTRODUCTION

As has been discussed in previous chapters of this document, upper airway obstruction (UAO) is a common sleep disorder in children and varies along a continuum from primary snoring (PS) to obstructive sleep apnoea syndrome (OSAS). Primary snoring is the mildest form and is characterized by frequent snoring without ventilatory abnormalities or obvious sleep disruption. Estimates suggest it affects 5-15% of children.(Lumeng & Chervin 2008; Bixler *et al*., 2009) The more severe form of UAO, OSAS, is characterized by periodic airway occlusion, hypoxia and sleep fragmentation and is seen in approximately 1-4% of children.(Lumeng & Chervin 2008; Bixler *et al*., 2009) It has been shown that even mild UAO is associated with neurocognitive deficits, impacting in particular memory, learning, attention, executive functioning and cognitive capacity. (Beebe & Gozal 2002; Kohler, *et al*. 2009) Despite the relatively high prevalence of UAO, a previous report by this research group suggested that less than 20% of potentially affected children are clinically evaluated in the community.(Blunden, *et al*. 2000) Thus, UAO is both common and under-diagnosed as well as having a potentially significant negative impact on learning and behaviour.

It has been proposed that neural cells in the prefrontal cortex are adversely affected by repeated hypoxia.(Gozal, *et al*. 2001) The pre-frontal cortex is thought to have a major role in controlling executive functions such as attention and decision making and damage to this area may therefore explain the cognitive and social deficits seen in children with OSAS (Beebe & Gozal 2002; Gozal, *et al*. 2004).

A limitation of this hypothesis, that the accumulated effects of chronic nocturnal hypoxia cause the deficits seen in people with UAO, is that cognitive and other functional deficits are still seen in children who have disturbed sleep without hypoxia such as those with primary snoring (PS) which by definition have no gas exchange abnormalities (Ali, *et al*. 1993; Blunden *et al*. 2000; Gozal &

Pope 2001; Bourke *et al*. 2011). This has led researchers to speculate on the potentially greater importance of the fragmentation of normal nocturnal neural processes in explaining deficits seen in a range of chronic sleep disorders (Bonnet 1993; Stepanski 2002; Montgomery-Downs & Gozal 2006). However, the exact mechanism by which sleep fragmentation might lead to neurocognitive and other functional deficits is yet to be satisfactorily clarified (Stepanski 2002; Hornyak *et al*. 2005; Montgomery-Downs & Gozal 2006). It has been suggested that chronic sleep fragmentation can result in altered cortical neural activity (Hornyak, *et al*. 2005) and altered cortical responses to sleep fragmenting events such as abnormal respiratory events (Bandla & Gozal 2000; Gozal & Kheirandish 2006). It is widely believed that children with UAO have a reduced number of spontaneous cortical arousals in sleep (Gozal, *et al*. 2004). It has been suggested that this may be an adaptive response to increased sleep disturbance, with increased respiratory insults leading to a decrease in responsiveness in order to preserve sleep structure (Tauman *et al*. 2004; Hornyak *et al*. 2005). If so, children with UAO will have altered neural activity during sleep and around or during challenges to that sleep (Bandla & Gozal 2000).

Different synchronized firing frequencies of cortical activity in sleep are associated with cognitive performance and suggests that sleep specific neural processes and structures are involved in learning and memory consolidation (Bodizs *et al*. 2005). Thus, altered neural activity caused by adaptation to chronic UAO may help preserve sleep integrity but may also come at a cognitive cost.

A common way of measuring neural activity during sleep is by examining the power spectrum of the electroencephalogram (EEG). Several studies have shown that there are consistently identifiable spectral changes in the EEG around sleep disrupting events that are characteristic of children with UAO (Bandla & Gozal 2000; Shouldice *et al*. 2004). However, results of such analysis over the night or from large segments of sleep EEG have not shown consistent spectral correlations with neurocognitive performance. Yang and colleagues found no differences between the EEG power spectra of children with sleep disordered breathing and normal controls across the

night, in any hour of the night or in any sleep stage (Yang 2010). In contrast, Bodizs *et al*. (2005) found strong correlations between sigma and delta frequency power in sleep and general intelligence in healthy young adults.

However, several studies have shown that there are consistent spectral changes in the EEG , over shorter durations, around and during sleep disrupting events that are characteristic of children with UAO such as an increase in low frequency EEG power (Poyares *et al*. 2002; Chervin *et al*., 2004).

We therefore hypothesized that children with upper airway obstruction would:

(1) have an altered cortical arousal response when compared to normal children as measured by common polysomnographic metrics and that this alteration would be proportional to disease severity.

(2) have reduced alpha and beta band spectral power, prior to and post arousal (reflecting a dampened arousal response).

(3) have increased sigma production (spindle frequency) as an adaptive change to help consolidate sleep and reduce the impact of sleep disruption on the cortex (spindles have been proposed to have a sleep preserving effect).

(4) have reduced performance on neurocognitive tests when compared to normal controls.

(5) show a correlation between neurocognitive performance and EEG spectral changes associated with cortical arousals.

As not all children with upper airway obstruction have discrete and identifiable respiratory events or respiratory arousals but all do have spontaneous arousals, we have decided on the latter as a target for analysis of spectral differences in children with UAO.

5.2. METHODS

This study conformed to principles outlined in the Declaration of Helsinki (1964) and was approved by the Women's and Children's Hospital (WCH) Human Ethics Committee. Parental consent and child assent was obtained from all participants.

5.2.1. SUBJECTS & PROCEDURE

Forty four children (22 males) with sleep-related upper airway obstruction (UAO) and 48 control children (22 males) took part in this study which included a single night of laboratory based polysomnography and a neurocognitive and behavioural battery (See chapter 3 of this document for a more thorough description of subject characteristics including inclusion and exclusion criteria and procedural details). Two UAO subjects and 3 control children were excluded from analysis due to technical problems with their PSG signal recordings which were of insufficient quality for the detailed analysis this study required. Children with UAO were frequent snorers, scheduled for adenotonsillectomy. Polysomnographic recordings were scored according to standardized criteria (see chapter 3).

5.2.2. EEG SIGNAL PROCESSING

The EEGs were sampled at a frequency of 250 Hz. All spontaneous arousals were visually scored on the C3-A1 (or C4-A2 when C3-A1 was deficient) derivation and exported using Profusion 2 software (Compumedics Pty Ltd Australia) in EDF format. Each arousal, as well as the 10 seconds immediately preceding and following the arousal were then individually displayed using a custom built interface (Matlab USA). Several other corresponding PSG traces were also displayed

simultaneously to aid in recognition of artefact (in descending order of display); C4-A1, EOG, EMG(SM), ECG and Leg EMG. For each scored arousal the Matlab interface prompted the user (a trained paediatric sleep technician) to choose from the following three options; (1) select the arousal for further analysis using the C3-A2 derivation, (2) select the arousal for further analysis using the C4-A1 if the C3-A2 was deemed not suitable (see below) or (3) reject the candidate arousal from further analysis. Arousals were considered unsuitable and rejected if they contained movement, signal clipping, signal loss or were otherwise not useable (e.g. there was less than 10 seconds of recorded sleep following the event). In total, 5718 spontaneous arousals were scored in all PSGs combined. After initial screening for suitability, 4419 arousals were retained for further analysis.

For the arousals that met selection criteria, the 10 s immediately prior to the arousal onset and the 10 s immediately after the arousal end (as determined by visual scoring) were then subjected to individual spectral analysis. A period of 10 seconds pre and post arousal was chosen as this duration has been successfully utilized in studies performing similar analyses (Bandla and Gozal 2000). Fast Fourier Transform (FFT) was performed repeatedly on consecutive time windows of 1024 samples after applying the Blackman-Harris Window function.(Harris 1978) For each window the absolute and relative power within the following frequency bands was calculated delta: 0.5-4.5 Hz; theta: 4.5-9Hz; alpha: 9-12 Hz; sigma: 12- 15 Hz and beta: 15-30Hz. Subsequently, the relative power within these bands was averaged for each of the three time periods separately. Relative EEG spectral power was chosen for further statistical analysis due to its lower variance than absolute power and relative EEG power measures in sleep have been previously shown to be correlated to neurocognitive performance measures in adolescents and adults (Tarokh, Carskadon *et al*. 2010).

5.2.3. NEUROCOGNITIVE TESTING

Neurocognitive testing was completed by a trained examiner who was blinded to the clinical status of the child. The assessment was conducted over 2-3 hours with a planned 10-15 minute break. Assessment was conducted in the same order for each child and comprised the 5th edition of the Stanford Binet Intelligence Scale (SB5, Roid 2003). The following 8 scores derived from components of these tests were used to assess correlations between spectral measures and neurocognitive function as these have previously been shown by our group to be correlated with sleep disturbance in children: (Kohler, Lushington *et al.* 2009)

(1) Full Scale IQ (FSIQ): A global measure of intellectual ability derived from the sum of all tasks.

(2) The Verbal (VIQ): the composite of scores of tests of skills required to solve tasks in the 5 verbal subtests

(3) Nonverbal IQ (NVIQ): the composite of scores of tests of skills required to solve tasks in the 5 nonverbal subtests.

(4) Fluid Reasoning (FR): examines the ability to reason from the specific to the general (inductive reasoning) or, given more general information, infer a specific conclusion or implication (deductive reasoning), using information that is novel to the individual.

(5) Knowledge (KN): refers to a person's accumulated fund of general information acquired from their surrounding environment and experiences, and thus in contrast to FR represents the crystallized dimension of intelligence.

(6) Quantitative Reasoning (QR): A measure of an individual's numerical problem solving skills, facility with numbers and understanding of mathematical concepts.

(7) Visual-Spatial Processing (VS): a measure of the ability to determine patterns and relationships from visual objects, describe spatial orientations, and apply inductive type reasoning skills to visual information.

(8) Working Memory (WM): a subcomponent of tasks more generally described as executive functions and also highly interrelated with general memory function, assesses the facility in which information stored in short-term memory is inspected, organized and manipulated in order to produce a solution to a given problem.

5.2.4. STATISTICS

For statistical analysis between groups for demographic, polysomnographic, and neuropsychological testing variables, a one way Analysis of Variance (ANOVA) test was used ($p<0.05$). Post hoc testing was conducted using planned means comparisons with Tukey's Honestly Significant Difference (HSD) method for multiple comparisons.

When testing for correlations between the various sleep fragmentation measures and neurocognitive performance results, Pearson's r method was employed ($p<0.05$) for parametric variables and Spearman's Rho test ($p<0.05$) for non-parametric as appropriate. Kolmogorov-Smirnov statistic, with a Lilliefors significance level was used in testing the normality of variables. Assumptions of normality were valid for all PSG variables with the exception of PLMI, RAI, frequency of SpO_2 desaturations ≥ 3%/ hr TST, percentage of sleep time with SpO_2 < 95%, $TcCO_2$ > 50 mmHg, OAHI and AHI. Inverse transformation [1/(x + 1)] and square-root transformation [$\sqrt{x}$] were applied as appropriate for these variables to correct skewness. All *p* values reported are 2-tailed, with statistical significance determined at $\alpha = 0.05$ unless otherwise specifically stated. Data are presented as mean ± standard deviation unless stated otherwise.

5.3. RESULTS

5.3.1. SUBJECTS

Demographic characteristics for the 87 children are presented in Table 5.1. Children with UAO were divided into two groups based on the degree of sleep-related UAO seen during overnight polysomnography: primary snorers (OAHI < 1, N = 23) and those with obstructive sleep apnoea syndrome (OAHI $\geq$ 1, N = 19). Children with OSAS had a greater BMI compared to controls (p <0.05). Control children had a significantly higher SES score than children in the PS or OSA groups (p <0.001). There were no other significant differences in demographic variables between the three groups. Due to these findings BMI z-score and SES were entered as covariates in statistical analyses where appropriate.

5.3.2. POLYSOMNOGRAPHY

Polysomnographic data are presented in Table 5.2. There were no significant differences between the three groups with respect to total sleep time, the percentage of time spent in all sleep stages, REM sleep latency, spontaneous arousal index, sleep efficiency, wake time after sleep onset (WASO), number of awakenings per hour, stage shifts per hour or PLM index. As expected children with OSAS had a higher OAHI, AHI, a higher number of SpO_2 dips ≥ 3%, a lower SpO_2 nadir and a higher respiratory arousal index compared to both primary snorers and controls (p <0.001).

5.3.3. NEUROPSYCHOLOGICAL TESTING

Neuropsychological test results are presented in table 5.3 below. Control subjects had higher scores than OSAS subjects in all domains tested other than Quantitative Reasoning ($0.05 > p > 0.01$) The control subjects also had higher scores than the primary snoring group in all domains other than Fluid Reasoning, Quantitative Reasoning and Working Memory ($0.05 > p > 0.01$).

Table 5.1 Subject demographic data for control (C), primary snoring (PS) and obstructive sleep apnoea syndrome (OSAS) children.

	C	PS	OSAS	Post Hoc (ANOVA)
N	45	23	19	n/a
Gender, (% male)	45.7	59.1	64.7	ns
SES	1027.8 ± 84.1	937.8 ± 93.3	952.7 ± 85.1	C > OSAS*** C > PS***
Age (years)	7.6 ± 2.6	6.4 + 2.2	7.0 + 3.1	ns
BMI z-score	0.3 ± 0.8	0.5 ± 1.2	1.2 ± 1.5	OSAS > C*

(*p < 0.05, ***p<0.001)

Table 5.2 Polysomnography results for control (C), primary snoring (PS) and obstructive sleep apnoea syndrome (OSAS) children.

	C	PS	OSAS	Post Hoc (ANOVA)
Total Sleep Time (min)	447.5 ± 35.8	439.8 ± 50.8	427.5 ± 47.8	ns
Stage 1 (% TST)	3.2 ± 1.9	2.6 ± 2.0	3.4 ± 2.1	ns
Stage 2 (% TST)	44.7 ± 5.7	43.6 ± 5.6	41.9 ± 5.1	ns
SWS (% TST)	31.8 ± 5.4	35.0 ± 7.1	33.2 ± 4.8	ns
REM (% TST)	20.3 ± 4.1	18.8 ± 5.2	21.5 ± 5.1	ns
REM latency (min)	119.9 ± 58.6	96.1 ± 49.2	128.5 ± 59.7	ns
OAHI[1]	0.2 ± 0.2	0.3 ± 0.3	11.1 ± 11.4	**OSAS>PS*** OSAS>C***
AHI[1]	1.4 ± 1.2	1.3 ± 0.8	14.3 ± 12.7	**OSAS>PS*** OSAS>C***
SpO_2 Nadir	93.1 ± 1.8	93.0 ± 1.5	85.7 ± 7.0	**OSAS>PS*** OSAS>C***
SpO_2 > 3% dips / hr TST	6.5 ± 6.4	6.2 ± 4.3	78.4 ± 83.6	**OSAS>PS*** OSAS>C***
RAI[1]	0.5 ± 0.5	0.6 ± 0.7	6.2 ± 4.6	**OSAS>PS*** OSAS>C***
SAI	9.4 ± 2.9	8.7 ± 2.7	8.0 ± 2.6	ns
Sleep Efficiency	81.5 ± 6.9	81.6 ± 7.4	80.4 ± 8.7	ns
WASO (min)	41.1 ± 29.1	42.7 ± 35.3	54.6 ± 46.1	ns
Awakenings/ hour TST	0.8 ± 0.5	0.8 ± 0.7	0.9 ± 0.6	ns
Stage shifts/ hour TST	12.2 ± 2.9	12.9 ± 2.8	12.8 ± 3.0	ns
PLM/ hour TST	4.6 ± 7.0	7.7 ± 10.7	4.6 ± 5.9	ns

TST = total sleep time; REM = rapid eye movement sleep; SWS = Slow wave sleep; WASO = wake time after sleep onset; PLMI = periodic limb movement index; SAI = spontaneous arousal index; RAI = respiratory arousal index; AHI
= obstructive apnea/hypopnea index; CAHI = central apnea/hypopnea index; AHI = apnea/ hypopnea index. [1]Analysis performed using transformed values. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, ns not significant

Table 5.3 Mean neurocognitive test results and between group comparisons for control (C), primary snoring (PS) and obstructive sleep apnoea syndrome (OSAS) children.

	C	PS	OSAS	Post Hoc (ANOVA)
Non Verbal IQ	109.3 ± 12.9	100.7 ± 13.2	98.3 ± 13.8	**C > PS*** **C>OSAS***
Verbal IQ	110.5 ± 10.9	100.9 ± 11.1	98.5 ± 12.0	**C > PS**** **C>OSAS *****
Full Scale IQ	110.2 ± 11.6	100.8 ± 10.9	98.2 ± 12.3	**C > PS**** **C>OSAS ****
Fluid Reasoning	110.8 ± 14.6	102.7 ± 14.1	95.5 ± 15.6	**C>OSAS *****
Knowledge	103.7 ± 10.0	93.9 ± 10.9	93.9 ± 10.3	**C > PS**** **C>OSAS ****
Quantitative Reasoning	109.0 ± 14.2	103.7 ± 13.4	107.1 ± 13.0	ns
Visual Spatial Skills	109.2 ± 11.9	100.0 ± 15.2	95.1 ± 13.1	**C > PS*** **C>OSAS *****
Working Memory	112.3 ± 14.5	104.3 ± 11.1	101.7 ± 14.6	**C>OSAS***
Attention and Executive Function	114.6 ± 10.9	103.7 ± 12.8	100.1 ± 16.8	**C > PS**** **C>OSAS *****
Language	111.3 ± 16.4	96.6 ± 15.5	97.2 ± 17.0	**C > PS**** **C>OSAS ****

*p < 0.05, ** p < 0.01,***p<0.001, IQ Intelligence Quotient.

5.3.4. SPONTANEOUS AROUSAL DURATION

Spontaneous arousal duration results are summarized in table 5.4. The control group had longer arousals than the OSAS group in NREM stage 2 sleep (p<0.05) and slow wave sleep (SWS, p<0.01). No other differences in arousal duration were seen between groups.

5.3.5. MEAN SPECTRAL POWER ASSOCIATED WITH SPONTANEOUS AROUSALS

In NREM stage 2 sleep control subjects had a higher proportion of power in the alpha band, pre arousal than either the PS or OSAS groups (p <0.05, Figure 5.1). Control subjects also had higher sigma (Figure 5.2) and beta (Figure 5.3) power during arousal than the OSAS group (p <0.05). Finally, control subjects had increased alpha (Figure 5.1) and sigma (Figure 5.2) power following arousal than the OSAS group (p <0.05). There were no differences in spectral power between groups in the delta (Figure 5.4) and theta power bands (Figure 5.5).

In REM sleep (results not shown), there were no differences between groups in spectral power prior to, following or during spontaneous arousals found.

In SWS (results not shown), the PS group had higher power in the alpha and sigma range prior to an arousal than subjects in the OSAS group (p <0.05). We also found that control subjects had higher beta power during arousals than the OSAS group (p <0.01).

Table 5.4 Mean duration (in seconds) of spontaneous arousals and comparisons between control (C), primary snoring (PS) and obstructive sleep apnoea syndrome (OSAS) groups

Group (Sleep Stage)	C	PS	OSAS	Post Hoc (ANOVA)
NREM Stage 2	6.87 ± 0.81	6.52 ± 1.02	6.23 ± 1.05	**C > OSAS***
REM	7.21 ± 1.76	6.32 ± 1.36	6.79 ± 1.85	ns
SWS	7.04 ± 1.51	6.29 ± 1.0	6.01 ± 1.24	**C > OSAS****

(*p < 0.05, ** p < 0.01, SWS Slow Wave Sleep, REM Rapid Eye Movement)

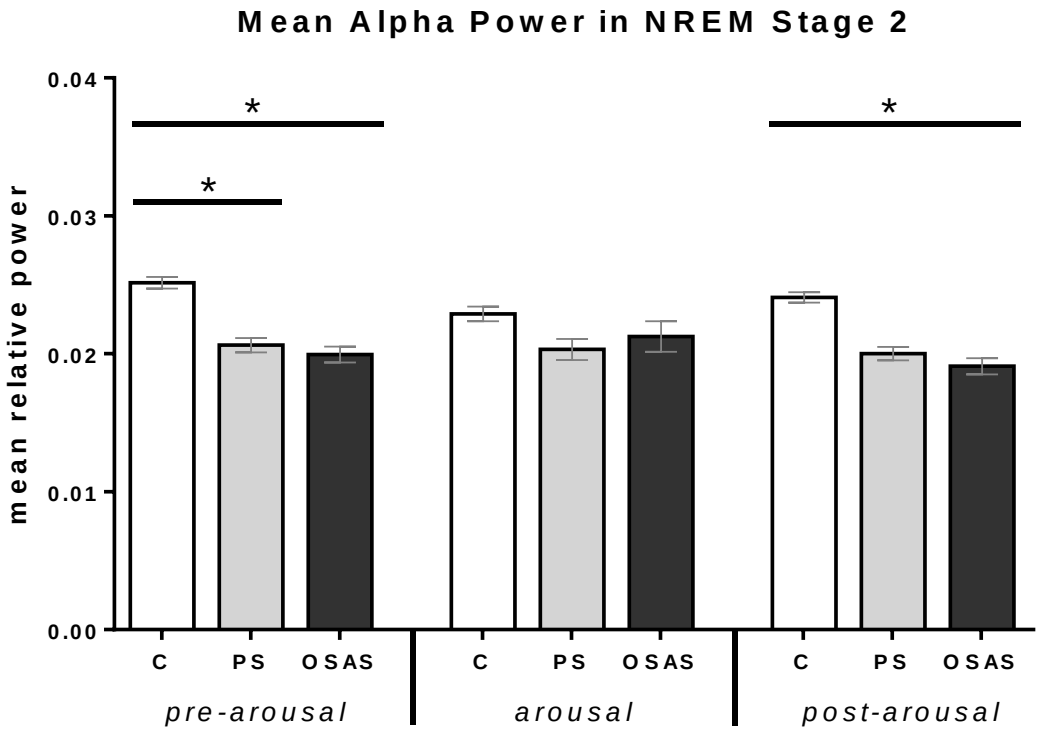

Figure 5.1: Group mean relative **alpha** power in NREM stage 2 for prior to, following or during spontaneous arousals (* = p<0.05).

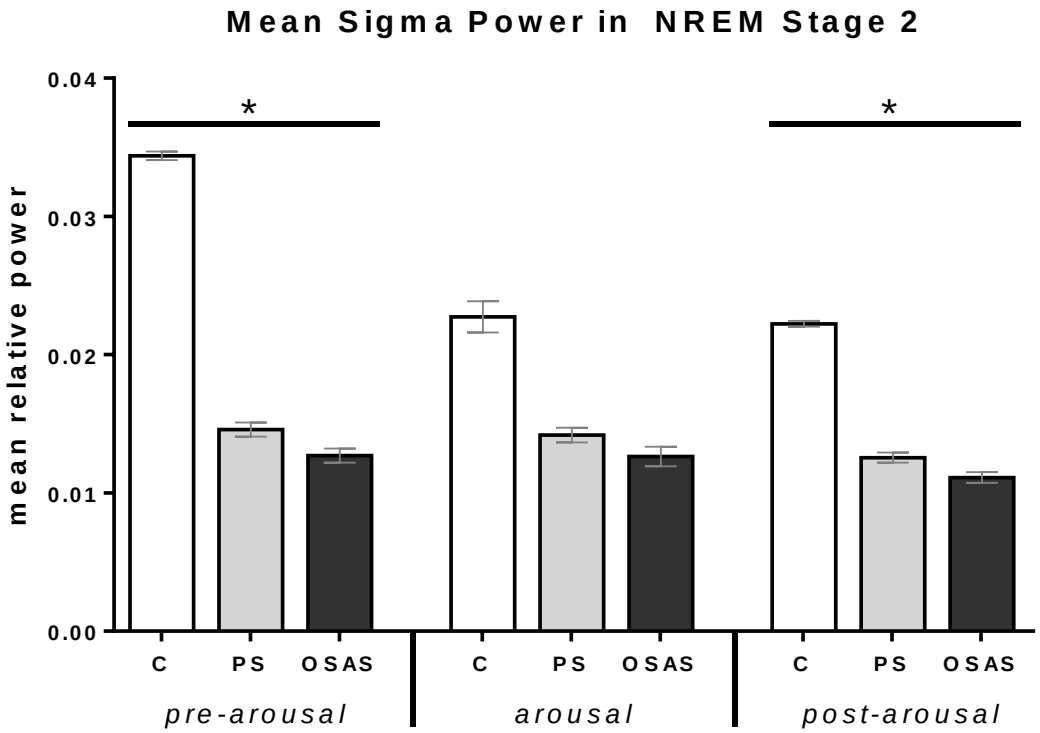

Figure 5.2: Group mean relative **sigma** power in NREM stage 2 for prior to, following or during spontaneous arousals (* = $p<0.05$)

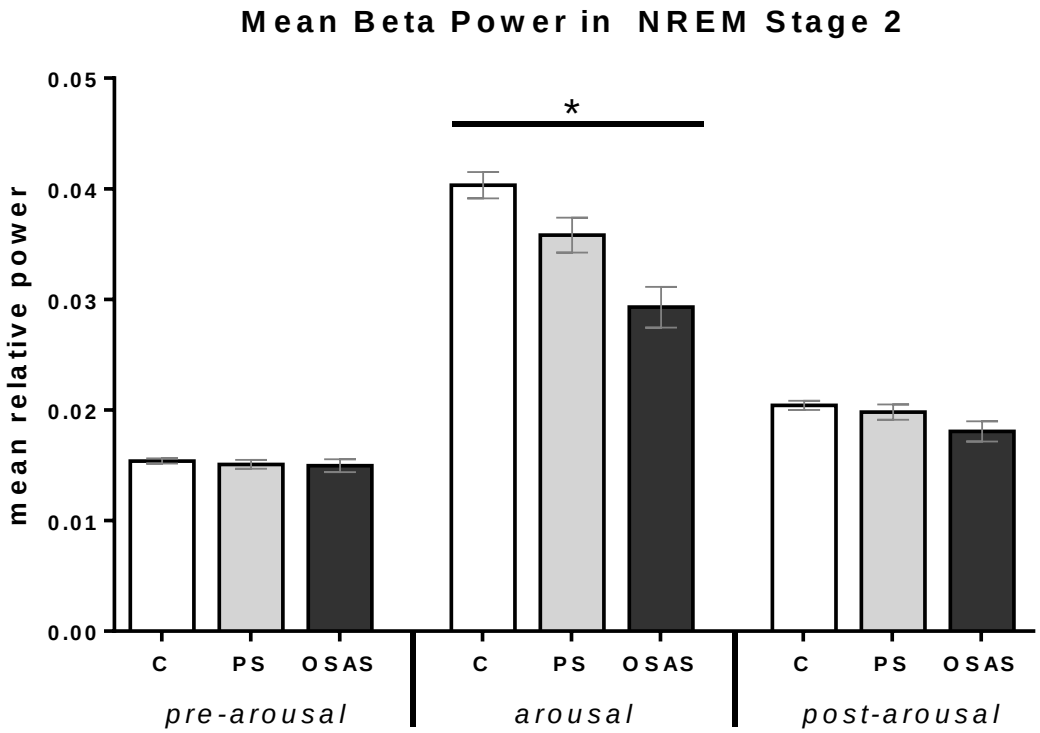

Figure 5.3: Group mean relative **beta** power in NREM stage 2 for prior to, following or during spontaneous arousals (* = $p<0.05$)

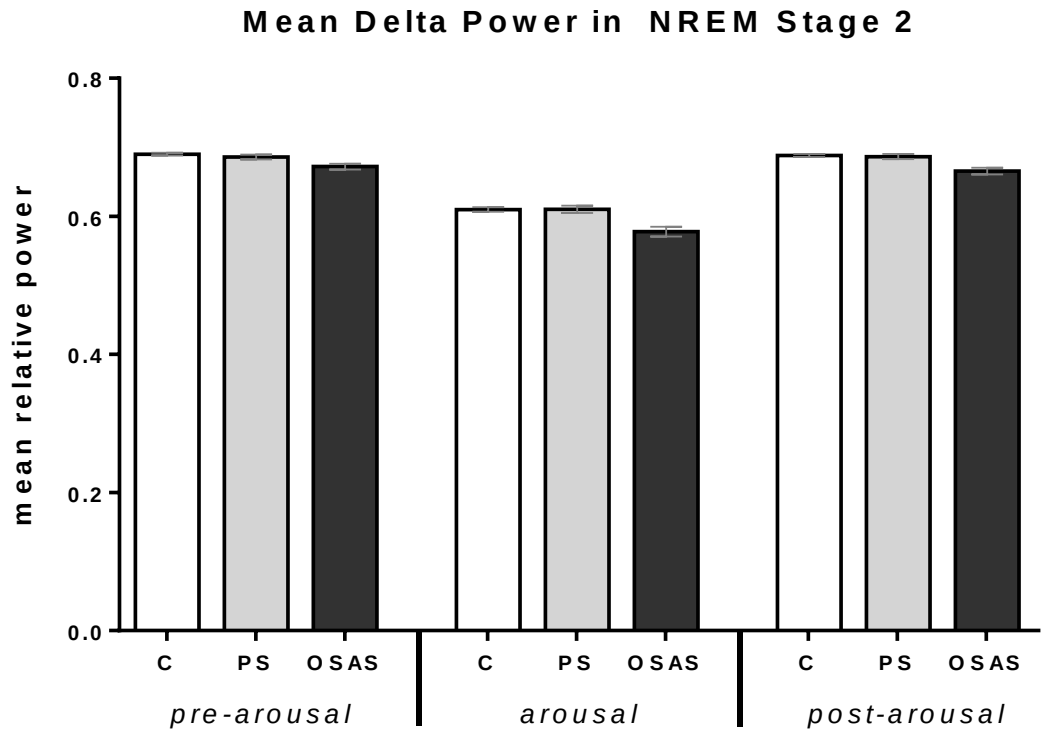

Figure 5.4: Group mean relative d**elta** power in NREM stage 2 for prior to, following or during spontaneous arousals

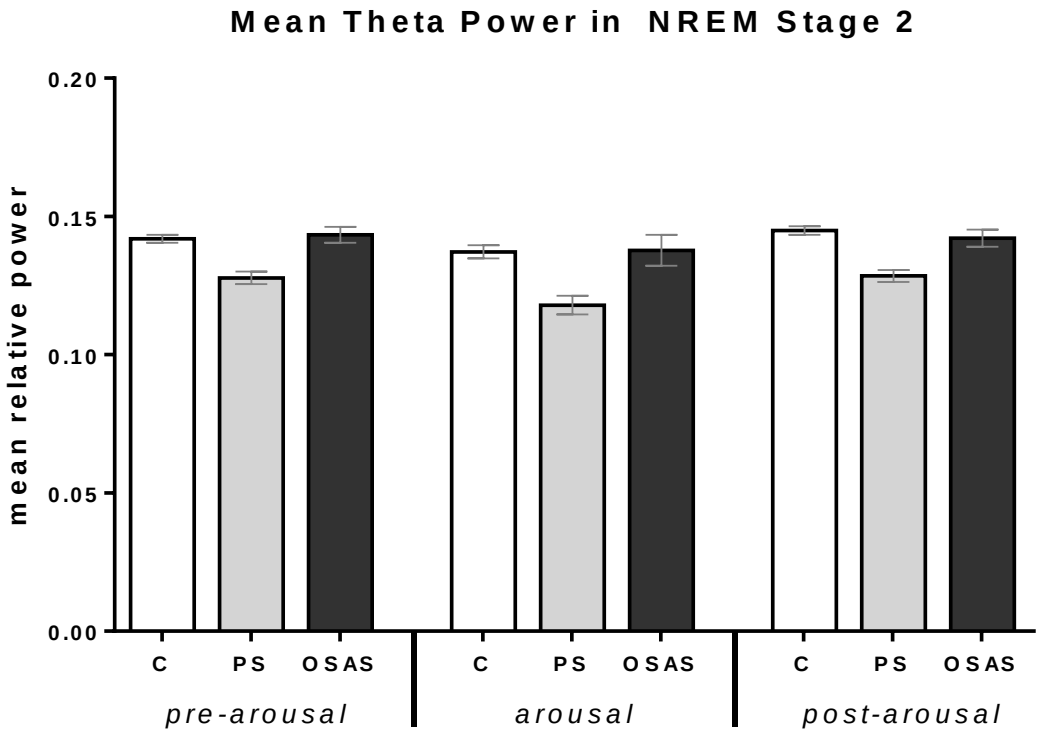

Figure 5.5: Group Mean Relative **Theta** Power in NREM stage 2 for prior to, following or during spontaneous arousals

5.3.6. RELATIVE CHANGE IN SPECTRAL EEG POWER WITH SPONTANEOUS AROUSAL ONSET

The relative change in spectral EEG power with arousals was calculated by subtracting the arousal mean power for a particular spectral band from the corresponding mean pre-arousal power. The results are summarized in Table 5.5.

Briefly, in NREM stage 2 sleep, the mean EEG power change between pre arousal and during arousal was greater in the control group than that seen in the PS or OSAS groups for the beta band ($p<0.01$, $p<0.005$ respectively). This result indicates that the control group had a larger increase in beta power from baseline (pre arousal period) to arousal than the other two groups. No other significant differences in mean power changes were seen between groups for NREM stage 2 sleep.

In REM sleep, the OSAS group had larger decreases in mean EEG power during an arousal than the control subjects in the theta ($p<0.05$) and alpha ($p<0.05$) bands. No other significant differences in mean power changes were seen between groups for REM sleep.

In SWS mean EEG power increase between pre arousal and arousal in the control group was greater than that seen in the OSAS group for the beta band ($p<0.05$). No other significant differences in mean power changes were seen between groups for SWS.

Table 5.5 Mean relative change (difference) in spectral power with spontaneous arousal onset observed between the different disease groups. PS = primary snorers; OSAS = Obstructive sleep apnoea syndrome. RP = Relative Power.

		Control	*PS*	*OSAS*	*Post Hoc (ANOVA)*
Sleep Stage	**Frequency Band**	**Mean difference in relative spectral power (arousal RP – prearousal RP)**			**Tahane**
NREM (Stage 2)	Delta	-0.080 + 0.060	-0.084 + 0.051	-0.094 + 0.071	ns
	Theta	0.002 + 0.047	0/001 + 0.048	0.009 + 0.058	ns
	Alpha	-0.003 + 0.015	0.0001 + 0.011	0.001 + 0.010	ns
	Sigma	-0.003 + 0.012	-0.002 + 0.013	-0.004 + 0.008	ns
	Beta	0.026 + 0.026	0.023 + 0.020	0.010 + 0.013	**C > OSAS**** **C > PS***
REM	Delta	-0.090 + 0.059	-0.084 + 0.097	-0.090 + 0.075	ns
	Theta	-0.063 + 0.035	-0.065 + 0.058	-0.089 + 0.041	**OSAS > C***
	Alpha	-0.001 +0.011	0.003 + 0.011	-0.005 + 0.006	**OSAS > C*****
	Sigma	0.004 + 0.006	0.005 + 0.006	0.004 + 0.012	ns
	Beta	0.031 + 0.030	0.024 + 0.022	0.029 + 0.037	ns
NREM (SWS)	Delta	-0.066 + 0.189	-0.029 + 0.175	-0.097 + 0.188	ns
	Theta	0.039 + 0.130	0.011 + 0.104	0.038 + 0.172	ns
	Alpha	-0.0001 + 0.017	0.003 + 0.028	0.001 + 0.016	ns
	Sigma	-0.0003 + 0.015	-0.001 + 0.018	0.002 + 0.011	ns
	Beta	0014 + 0.034	0.008 +0.022	0.003 + 0.015	**C > OSAS***

(* $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$

5.3.7. CORRELATIONS BETWEEN NEUROPSYCHOLOGICAL PERFORMANCE AND SPECTRAL POWER

No significant correlations were found between neurocognitive measures and mean relative EEG power prior to, following or during spontaneous arousals in NREM stage 2 sleep, REM sleep or for SWS for all groups combined except for VIQ which correlated positively with delta band power during arousals in REM sleep (p <0.05, r=0.23).

The groups were then examined separately for correlations between neuropsychological test results and mean spectral EEG power.

5.3.8. CORRELATIONS BETWEEN NEUROCOGNITIVE PERFORMANCE AND EEG POWER WITH SPONTANEOUS AROUSALS FOR THE CONTROL GROUP

Results for NREM stage 2 sleep were as follows: It was found that there were significant negative correlations between EEG power in the beta band during arousal and knowledge (KN) (p <0.05, r=-0.30). Pre arousal beta power was positively correlated with working memory (WM) (p <0.05, r=-0.3).

Results for REM sleep were as follows: It was found that there were significant positive correlations between power in the delta band during arousal and verbal IQ (VIQ, p <0.05, r=-0.30). Post arousal theta power was positively correlated with Visuo-spatial reasoning (VS, p <0.05, r=-0.31).

Results for SWS were as follows: Pre arousal alpha power was positively correlated with quantitative reasoning subtest results (QR, p <0.05, r=0.30). Post arousal beta power was negatively correlated with KN (p <0.05, r=-0.42).

5.3.9. CORRELATIONS BETWEEN NEUROCOGNITIVE PERFORMANCE AND EEG POWER WITH SPONTANEOUS AROUSALS FOR THE PRIMARY SNORING GROUP

Results for NREM stage 2 sleep were as follows *(see Table 5.6 at the end of this chapter)***:** It was found that there were significant positive correlations between power in the theta band during arousal and KN subtest results, Pre arousal sigma power was negatively correlated with VIQ, full scale IQ (FSIQ), QR and VS scores. Post arousal alpha and beta power were negatively correlated with VS.

Results for REM sleep were as follows *(see Table 5.7 at the end of this chapter)***:** It was found that there were significant negative correlations between power in the theta band during arousal and NVIQ. Pre arousal theta power was negatively correlated with fluid reasoning (FR) and working memory (WM). Pre arousal alpha power was negatively correlated with non-verbal IQ, NVIQ, FSIQ, FR and WM scores. Pre arousal sigma power was negatively correlated with NVIQ, FSIQ, QR and language (L) scores. Post arousal theta power was negatively correlated with FR. Post arousal alpha power was negatively correlated with NVIQ and VS. There were no significant findings for correlations between the beta power band and IQ test results.

Results for SWS were as follows *(see table 5.8 at the end of this chapter):* Pre arousal delta power was positively correlated with KN. Post arousal delta and alpha power was positively correlated with VS.

5.3.10. CORRELATIONS BETWEEN NEUROCOGNITIVE PERFORMANCE AND EEG POWER WITH SPONTANEOUS AROUSALS FOR THE OSAS GROUP

Results for NREM stage 2 sleep were as follows *(see table 5.9 at the end of this chapter)***:** Pre arousal delta power was positively correlated with FR and QR. Pre arousal theta power was negatively correlated with VS. Pre arousal alpha power was negatively correlated with NVIQ and QR. Post arousal delta power was positively correlated with QR.

Results for REM were as follows *(see Table 5.10 at the end of this chapter)*: Pre arousal theta power was positively correlated with L. Post arousal delta power was positively correlated with QR. Post arousal beta power was negatively correlated with KN.

Results for SWS were as follows *(see Table 5.11):* There were significant positive correlations between power in the delta band during arousal and AE. There were also highly significant positive correlations between power in the theta band during arousal and NVIQ and QR. Pre arousal delta power was positively correlated with KN. Post arousal delta power was positively correlated with QR.

5.4. DISCUSSION

The main findings of this study are as follows: (1) Children with UAO had an altered spontaneous arousal response when compared to normal control children. (2) Control subjects had a higher level of alpha activity preceding arousal than either PS or OSAS subjects in NREM stage 2 sleep. (3) Control subjects had higher beta power in response to arousals than OSAS subjects in NREM stage 2. (4) Control subjects had higher sigma power in response to arousals than OSAS subjects in NREM stage 2. (5) Children with UAO had reduced performance on neurocognitive tests when compared to normal controls. (6) Correlations were found between some measures of neurocognition and some EEG spectral measures of spontaneous cortical arousals in children with UAO.

5.4.1. SPONTANEOUS AROUSAL ALTERATION IN CHILDREN WITH UAO AS MEASURED BY COMMON POLYSOMNOGRAPHIC METRICS

As has been previously published by this group, we found that children with UAO did not have significantly reduced numbers of spontaneous arousals when compared to matched controls (Kohler *et al*., 2009). This is in contrast to the finding of O'Brien *et al.* (2004). However, the current study showed that spontaneous arousals were shorter in the OSAS group when compared to controls suggesting the occurrence of an arousal dampening process in response to chronic sleep disturbance. The finding of this study also confirms the previous findings of our group.(Kohler *et al*. 2009)

It was hypothesised that this alteration in arousal duration would be proportionate to disease severity (i.e. the worse the disease severity the greater the dampening and thus the shorter the mean arousal duration) but though the results did trend in this direction, with the mean duration of spontaneous arousals in the PS group being between the OSAS and C groups, the association did not reach statistical significance.

5.4.2. SPONTANEOUS AROUSAL ALTERATION IN CHILDREN WITH UAO AS DETERMINED BY SPECTRAL ANALYSIS

During spontaneous cortical arousal, children with UAO did have a dampening of higher EEG frequencies in some sleep stages. An adaptive change in the arousal response in the two UAO groups due to the increased level of chronic sleep disruption could explain this observation; dampening higher frequency arousal responses may help to maintain sleep structure in the face of UAO. Arousal duration results further support this assertion, with control subjects having longer arousals than those in the OSAS group.

These results also indicate a possible dose response between the degree of sleep disturbance and the extent of the dampening process. Specifically, the greater the sleep disturbance the higher the maximum frequency of synchronized neural oscillations and the larger the frequency range that is affected.

The PS group did not show the same degree of alteration in arousal response that was seen in the OSAS group. As predicted, the PS group did have different arousal characteristics when compared

to both the OSAS group and normal controls such as the alpha band changes pre-arousal in SWS and NREM stage 2 sleep.

Children with UAO did not have a measured increase in sigma frequency production with spontaneous arousal which is contrary to our hypothesis. Instead they had a decreased relative sigma power with arousal when compared to the control group.

There may be a number of reasons why the expected increase in power was not seen. One explanation is that there may have been an increase in absolute power in the sigma frequency range but with changes in the spectral profile with arousal, a relative decrease could be detected. Another possible reason for decreased sigma power is that the band overlaps with other high frequency bands that are decreased in power in children with UAO and may not reflect sleep-preserving spindle activity but simply high frequency alpha or low end beta decreases.

5.4.3. SPONTANEOUS AROUSAL ALTERATION IN CHILDREN WITH UAO AND NEUROCOGNITIVE PERFORMANCE

Many studies have demonstrated individually, the links between (a) various measures of synchronized neuronal oscillations of the cortex in sleep (e.g. relative spectral power of the EEG), (b) sleep quality, (c) the activity of particular corresponding neurological structures and (d) neurocognitive performance while awake. We surmised that sleep disruption must alter at least one and therefore all of these four interacting factors.

A neuronal structure that could potentially be disrupted by the adaptation process outlined earlier is the cortico-thalama-cortical neuronal reticular loop. These neurons are thought to be involved in transferring short-term memories in the hippocampus to a longer term store.(Nolan, Malleret *et al*. 2004) These networks have also been implicated in the development of attention in infants.(Orekhova *et al*. 2006) They have a characteristic synchronized firing frequency in sleep in the theta range of around 4.5 – 9 Hz.(Buzsaki & Draguhn 2004)

Another neural group, within the cortico – cortical neurons are proposed by some researchers to be involved in the consolidation and integration of procedural knowledge and general cortical development.(Sankupellay *et al*. 2011) These neuronal structures have a usual synchronized firing frequency in sleep in the alpha range of around 9 -12 Hz. This frequency band is also thought to indicate the process of waking and therefore the termination of sleep processes (Ferrara *et al*. 1999).

Reticular neurons of the hippocampus are thought to be involved in episodic memory consolidation and are also thought to help promote sleep depth and help stop outside stimuli impacting on the

cortex.(Buzsaki & Draguhn 2004) These neurons have a typical firing frequency in the spindle frequency or sigma range of around 12 – 15 Hz.

Finally, the delta frequency range (0.5 – 4.5 Hz) is thought to help promote sleep-based neural homeostasis, is a marker of development and is also important in the processes of long term memory consolidation and regulation of other synchronized neural activity in sleep.(Atlas Task Force 1993; Benoit *et al*. 2000; Sankupellay *et al*. 2011)

In this study, the general trend in the IQ correlations with frequency bands within groups was towards more low frequency power and less high frequency power around and during arousals being beneficial to neurocognitive performance. This result may seem counterintuitive when compared to power differences between groups where the control group tended to have greater high frequency power surrounding arousals than the children with UAO. However if one considers the change in EEG frequency distribution in children with UAO as an adaptive response to preserve sleep then it is clear that those subjects with UAO that did not adapt as well lost sleep and suffered the neurocognitive consequences.

For instance, we found that children with UAO suppress alpha-range neural activity in the 15 seconds prior to spontaneous arousals when compared to controls. It can be reasonably assumed that some level of alpha suppression is occurring in these children in response to a variety of sleep disrupting events. As outlined earlier, alpha activity in sleep has been linked to general development and procedural knowledge consolidation. Alpha activity has also been linked to normal REM sleep process and many researchers have demonstrated the negative consequences of disruption to that stage. Some researchers have further proposed that alpha activity inhibits the areas of the cortex that are not currently in use. An example of such inhibition is seen in the visual cortex, where when a person lays quietly with their eyes closed they generate a high amplitude alpha wave that is characteristically seen in occipital EEG leads. An alternative theory states that alpha activity in sleep facilitates general neural network coordination and memory consolidation.

We would therefore expect that children with UAO and therefore reduced alpha activity in sleep would have deficits in general cognitive performance. This result is exactly what is seen with broad intelligence scores and memory test results in children with UAO being significantly reduced and negatively correlated with alpha band production prior to arousals in REM sleep (PS group) and NREM stage 2 sleep (OSAS group).

5.5. CONCLUSION

Our study demonstrates the utility of FFT measures of the EEG in clinical assessment of children with UAO and possibly other sleep-disrupting chronic conditions such as eczema. Specifically, it shows that EEG spectral measures in response to arousal in sleep could be utilized in developing a sleep fragmentation index that is correlated to known cognitive deficits of children with UAO. A limitation of the study is that spontaneous arousals are only a very broadly defined and therefore a rather varied phenomenon. For instance, it is likely that some spontaneous arousals in children with UAO are actually due to a respiratory disturbance but that the respiratory event cannot be scored for technical reasons relating to scoring rules and definitions. It is also possible that some spontaneous arousals are due to an undetected external source given the limitations of monitoring. A more controlled and uniform arousal candidate (perhaps experimentally induced via sub-threshold auditory tones) would need to be assessed to further develop the spectral measures for clinical diagnostic use.

Further research utilizing other disease and age groups is required to develop a clinically practical and more widely applicable tool. The possibility also exists to combine this measure with other measures of sleep disturbance to produce more accurate screening and diagnostic tools than currently exist.

Table 5.6 Correlations between neurocognitive testing results and Mean Relative Power Pre Post and During Spontaneous Arousals in NREM Stage 2 in the primary snorers (PS) group Ar = Arousal. Pre = Pre arousal. Post = post arousal. ns is recorded where the result does not reach significance ($p<0.05$)

NREM S2 PS		**Delta**			**Theta**			**Alpha**			**Sigma**			**Beta**		
		pre	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***
VIQ	*r*	ns	ns	ns	ns	ns	ns	ns	ns	ns	**-0.432**	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns	ns	ns	**0.045**	ns	ns	ns	ns	ns
FSIQ	*r*	ns	ns	ns	ns	ns	ns	ns	ns	ns	**-0.449**	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns	ns	ns	**0.036**	ns	ns	ns	ns	ns
KN	*r*	ns	ns	ns	ns	**0.515**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	**0.014**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
QR	*r*	ns	ns	ns	ns	ns	ns	ns	ns	ns	**-0.423**	ns	**-0.456**	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns	ns	ns	**0.050**	ns	**0.033**	ns	ns	ns
VS	*r*	ns	ns	ns	ns	ns	ns	ns	ns	**-0.591**	**-0.462**	ns	**-0.489**	ns	ns	**-0.427**
	p	ns	ns	ns	ns	ns	ns	ns	ns	**0.004**	**0.030**	ns	**0.021**	ns	ns	**0.048**

Table 5.7 Correlations between neurocognitive testing results and Mean Relative Power Pre, Post and During Spontaneous Arousals in REM in the Primary Snorers (PS) group**.** Ar = Arousal. Pre = Pre arousal. Post = post arousal. ns is recorded where the result does not reach significance ($p<0.05$)

REM PS		Delta			Theta			Alpha			Sigma			Beta		
		pre	*ar*	*post*	*pre*	*ar*	*post*	*pre*	*ar*	*post*	*pre*	*ar*	*post*	*pre*	*ar*	*post*
NVIQ	*r*	ns	ns	ns	ns	**-0.464**	ns	**-0.567**	ns	**-0.498**	**-0.520**	ns	ns	**-0.448**	ns	ns
	p	ns	ns	ns	ns	**0.034**	ns	**0.007**	ns	**0.022**	**0.016**	ns	ns	**0.042**	ns	ns
FSIQ	*r*	ns	ns	ns	ns	ns	ns	**-0.558**	ns	ns	**-0.512**	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	**0.009**	ns	ns	**0.018**	ns	ns	ns	ns	ns
FR	*r*	ns	ns	ns	**-0.532**	ns	**-0.479**	**-0.519**	ns	ns	ns	ns	ns	**-0.439**	ns	ns
	p	ns	ns	ns	**0.013**	ns	**0.028**	**0.016**	ns	ns	ns	ns	ns	**0.046**	ns	ns
QR	*r*	ns	ns	ns	ns	ns	ns	ns	ns	ns	**-0.442**	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns	ns	ns	**0.045**	ns	ns	ns	ns	ns
VS	*r*	ns	ns	ns	ns	ns	ns	ns	ns	**-0.523**	ns	ns	ns	**-0.463**	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns	ns	**0.015**	ns	ns	ns	**0.034**	ns	ns
WM	*r*	ns	ns	ns	**-0.565**	ns	ns	**-0.474**	ns	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	**0.008**	ns	ns	**0.030**	ns	ns	ns	ns	ns	ns	ns	ns
L	*r*	ns	ns	ns	ns	ns	ns	ns	ns	ns	**-0.461**	ns	ns	**-0.508**	ns	ns
	p	ns	ns	ns	ns	ns	ns	ns	ns	ns	**0.036**	ns	ns	**0.019**	ns	ns

Table 5.8 Correlations between neurocognitive testing results and Mean Relative Power in Frequency Bands Around and During Spontaneous Arousals in SWS in the Primary Snorers (PS) group. Ar = Arousal. Pre = Pre arousal. Post = post arousal. ns is recorded where the result does not reach significance ($p<0.05$)

SWS PS		Delta			Theta			Alpha			Sigma			Beta		
		pre	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***
KN	*r*	**0.471**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	p	**0.027**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
VS	*r*	ns	ns	**0.472**	ns	ns	ns	ns	ns	**0.439**	ns	ns	ns	ns	ns	ns
	p	ns	ns	**0.027**	ns	ns	ns	ns	ns	**0.041**	ns	ns	ns	ns	ns	ns

Table 5.9 Correlations between neurocognitive testing results and Mean Relative Power Pre, Post and During Spontaneous Arousals in Stage 2 NREM in the OSAS group**.** Ar = Arousal. Pre = Pre arousal. Post = post arousal. ns is recorded where the result does not reach significance ($p<0.05$)

S2 NREM OSAS		**Delta**			**Theta**			**Alpha**			**Sigma**			**Beta**		
		pre	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***
NVIQ	*r*	ns	ns	ns	ns	ns	ns	**-0.496**	ns	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	ns	ns	**0.036**	ns	ns	ns	ns	ns	ns	ns	ns
FR	*r*	**0.491**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	p	**0.046**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
QR	*r*	**0.679**	ns	**0.534**	ns	ns	ns	**-0.489**	ns	ns	ns	ns	ns	ns	ns	ns
	p	**0.003**	ns	**0.027**	ns	ns	ns	**0.039**	ns	ns	ns	ns	ns	ns	ns	ns
VS	*r*	ns	ns	ns	**-0.477**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	**0.050**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Table 5.10 Correlations between neurocognitive testing results and Mean Relative Power Pre, Post and During Spontaneous Arousals in REM in the OSAS group. Ar = Arousal. Pre = Pre arousal. Post = post arousal. ns is recorded where the result does not reach significance ($p<0.05$)

REM OSAS		Delta			Theta			Alpha			Sigma			Beta		
		pre	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***
KN	*r*	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	**-0.491**
	p	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	**0.045**
QR	*r*	ns	ns	**0.660**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	**0.004**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
L	*r*	ns	ns	ns	**0.483**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	**0.050**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Table 5.11 Correlations between neurocognitive testing results and Mean Relative Power in Frequency Bands pre, post and During Spontaneous Arousals in SWS in the OSAS group**.** Ar = Arousal. Pre = Pre arousal. Post = post arousal. ns is recorded where the result does not reach significance (p<0.05)

SWS OSAS		**Delta**			**Theta**			**Alpha**			**Sigma**			**Beta**		
		pre	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***	***pre***	***ar***	***post***
NVIQ	*r*	ns	ns	ns	ns	**0.590**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	ns	ns	**0.016**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
KN	*r*	**0.543**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	p	**0.030**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
QR	*r*	ns	ns	**0.734**	ns	**0.728**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
	p	ns	ns	**0.001**	ns	**0.001**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
AE	*r*	ns	**0.520**	ns	ns	ns	ns	Ns	ns	ns	ns	ns	ns	ns	ns	ns
	p	ns	**0.039**	ns	ns	ns	ns	Ns	ns	ns	ns	ns	ns	ns	ns	ns

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CHAPTER 6

Movement in Sleep

Contextual Statement

The following chapter is a manuscript published in the journal SLEEP - Coussens, S., Baumert, M., Kohler, M., Martin, J., Kennedy, D., Lushington, K., & Pamula, Y. (2014). Movement Distribution: A New Measure of Sleep Fragmentation in Children with Upper Airway Obstruction. Sleep. Children with UAO have been shown in the previous chapter to have altered arousal supression. The technique employed would not necessarily be a useful clinical tool due to the analytical expertise and time required to produce the results. In the following chapter an attempt is made to produce a more practical method of measuring this altered arousal pattern using movement as the sleep fragmentation marker.

Statement of Authorship

Title of Paper	Movement Distribution: A New Measure of Sleep Fragmentation in Children with Upper Airway Obstruction
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Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

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Contribution to the Paper	Conceived, designed and executed the study and the analysis of the data and preparation of the manuscript for publication.		
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CHAPTER 7

Towards a Composite Index of Upper Airway Obstruction Severity in Children

Contextual statement

It was the aim of this series of studies (see chapters 4-6) to develop a measure of sleep fragmentation that would be clinically useful and applicable, technically feasible and correlate with important outcomes of children with UAO.

The following chapter, in manuscript format, combines the findings and implications of preceding chapters by demonstrating the construction and utility of a composite index of sleep-related upper airway obstruction severity. This is achieved via the combination of sleep fragmentation measures, respiratory function data and other relevant clinical information in children with upper airway obstruction into a single index that reflects the disease severity as experienced by the prospective patient and its subjective and objective impact of the disease on their health and wellbeing.

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Author Contributions

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A Composite Index of Sleep Fragmentation Measures in Children with Upper Airway Obstruction

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7.1. ABSTRACT

Sleep fragmentation (SF) has been linked to a myriad of cognitive, behavioural and health problems in children and adults. Upper airway obstruction (UAO) is known to cause SF. The measurement of SF in children with UAO has yet to be accurately formulated. As previous chapters have alluded to, several inherent problems contribute to the resolution of this, including 1) the variable nature, symptoms and severity of the disease, 2) the variable nature of the adaptive responses to the disease, 3) the variable developmental changes occurring in the subjects and 4) the variable nature of the fragmentation of sleep caused by the measurement of sleep variables in standard clinical polysomnograms (PSG). We hypothesized that a combined (or composite) index of various known and novel indices of SF as well as demographic and clinical variables would more accurately measure the disruption of sleep in children with UAO.

In this experiment, as part of a larger study exploring the effects of adenotonsillectomy, the data from 44 primary school aged children with suspected upper airway obstruction was utilized. Correlations and interactions of known SF measures were used to build a composite SF index. We then compared this composite index to other individual indices for its ability to estimate UAO disease severity by examining correlations with subjective and objective outcome measures.

The derived composite indices were found to more strongly correlate to outcomes measures than any of the trialed fragmentation indices alone ($p < 0.05$).

This finding shows that a composite index may be a useful approach in modeling disease pathology risk in children with UAO. It appears particularly useful in identifying children with what are traditionally considered mild symptoms that are at an increased risk of negative sequalae.

7.2. INTRODUCTION

7.2.1. LIMITATIONS OF SLEEP FRAGMENTATION AS AN EXPLANANTION OF NEUROCOGNITIVE AND BEHAVIOURAL DEFICITS IN CHILDREN WITH UAO

Sleep fragmentation (SF) in children with upper airway obstruction (UAO) has been consistently linked to the cognitive and behavioural deficits (Achenbach *et al*., 1991; Brooks 1993; Beebe & Gozal 2002; Blunden *et al*., 2000; Ferreira *et al*., 2000; Kaemingk *et al*., 2003; Beebe *et al*., 2004; O'Brien, Mervis *et al*., 2004; Beebe 2006; Bhattacharjee *et al*., 2009). However, results from a large array of experiments consistently demonstrate that any single measure of sleep fragmentation in children with UAO accounts for only a small proportion in the variance of scores on tests of cognition and behaviour (Blunden *et al*., 2000, Kaemingk *et al*., 2003, O'Brien, Mervis *et al*., 2004). It is likely that such deficits are actually the result of the combination and interaction of many factors that include but are not limited to sleep fragmentation. (Gozal & Kheirandish 2006). These other factors include; the presence or absence of chronic hypoxia (Barry *et al*., 2003, Beebe & Gozal 2002, Gozal & Kheirandish 2006, Blunden & Beebe 2006), other respiratory factors e.g. work of breathing (Brown 2008), inflammatory processes resulting from UAO (Tauman *et al*., 2004; Gozal & Kheirandish 2006), genetic (or trait) characteristics (Brooks 1993, Killgore *et al*., 2007), UAO disease severity (Engelman 2000; Beebe & Gozal 2002; Gozal & Kheirandish 2006), duration of exposure (Blunden & Beebe 2006), anatomical factors (Brooks 1993), environmental and socio-economic factors (Achenbach 1991; Gozal & Kheirandish 2006), demographic factors (Grigg-

Damberger *et al*., 2007) and co-morbidities such as obesity (Kohler *et al*., 2009) and PLMS (Blunden & Beebe 2006).

7.2.2. INDICES OF UPPER AIRWAY OBSTRUCTION DISEASE SEVERITY IN CHILDREN

Upper airway obstruction in children is almost exclusively defined in the clinical context by a single polysomnogram-derived index, the respiratory disturbance index (RDI). Diagnosis of obstructive sleep apnoea syndrome in children requires an obstructive RDI > 1 (a minimum of at least 1 obstructive apnea, obstructive hypopnea, mixed hypopnea or RERA per hour of sleep, Iber 2007). However, RDI is an incomplete measure of UAO disease severity in children, correlating poorly with important daytime outcomes such as neurocognitive dysfunction and behavioural deficits, reduced school performance and reduced overall quality of life (Kohler *et al*., 2009).

7.2.3. COMPOSITE INDICES

Due to the comparative failure of researchers to identify any single PSG variable or other clinical factor that correlates with (and explains) the daytime outcomes associated with UAO in children, models of the morbidity due to UAO have been proposed that incorporate multiple and varied physiological, demographic and clinical factors. For instance, Gozal and Kheirandish (2006) have developed a triple risk model proposing oxidative-inflammatory mechanisms as mediating the morbid consequences of UAO in children with UAO that incorporates a dose-dependent disease severity factor, an environmental factor and a genetic susceptibility factor. The model was not developed into an applicable algorithm for use in a clinical setting.

Some researchers, however have investigated the potential of mathematically combining promising individual sleep fragmentation measures and other measures that each alone explains only a small part of the deficits seen in children in order to amplify the diagnostic power of the metric (Balakrishnan *et al*., 2012; Gozal & Kheirandish 2006; O'Brien, Tauman 2004 Brown *et al*., 2008).

The basic assumption behind this technique is that the any individual factor of a particular size does have a proportionate individual impact but that the factors also interact with one another giving a cumulative and possibly amplified effect. For example, O'Brien, Tauman *et al.* (2004) developed a composite fragmentation measure derived from arousal type scores termed the sleep pressure score independent of direct respiratory measures and hypoxemia. The SPS correlated with cognitive and behavioral morbidity in 199 snoring children who underwent neurobehavioral testing following an overnight PSG. Children with higher SPS were significantly more likely to have deficits in memory, language abilities, verbal abilities, and some visuospatial functions than were children with lower SPS (O'Brien 2008). However, there were critcisms of the basic assumptions of the methodology of the SPS and it has not been widely adopted (Sotos 2005).

In adults, the sleep apnoea severity index (SASI) was developed to address the complex nature of sleep apnoea and the factors that influence the impact of the disease over time (Balakrishnan *et al*., 2012). The proposed model of sleep apnoea disease severity had three main factors; physical severity index, the functional severity index and the polysomnographic severity index (see figure 11.1).

The Physical Severity Index

The physical severity index (PSI) was a score based on physical characteristics, specifically body mass index (BMI) and a score for redundant pharyngeal mucosa size. In children across an age range, BMI scores are not easily comparable. An index component that accounts for the age-

related changes might be more applicable in children with UAO (e.g. a BMI z score). Also, the measurement of redundant pharyngeal mucosa is difficult in children and has other methodological issues (Piccirillo 1998). However, Grigg-Damberger (2007) proposed that age was the most significant individual factor in determining sleep variables and response to sleep disturbing events in children. This kind of information is also routinely collected as a part of a normal clinical paediatric PSG. In this study we combined age and BMI z score for a physical severity index value.

The Functional Severity Index

The functional severity index (FSI) of the SASI was a score derived from the Epworth Sleepiness Scale. This score would not be appropriate for use in children as the scale was designed and validated for adults (Johns 1991) and sleepiness is often not a symptom of UAO in younger children, contrary to findings in adults (Chervin *et al*., 2006). A possible alternative functional severity measure to the ESS could be a measure of the degree of adaptation to the disease seen, thus indicating indirectly the level of disease impact on physiology. One possible approach is to measure sleep arousal remodeling. For instance, Norman *et al*. (2007) demonstrated that it was the distribution of sleep fragmenting events rather than the number of events that was important in estimating disease severity. A number of measures of exposure to sleep fragmenting events using techniques adapted from Norman *et al* (2007) were developed. One such measure was based on a surrogate measure of movement derived from the SpO_2 plesthmography trace and the other on a novel movement measure using multiple PSG traces (Coussens *et al*., 2013).

The Polysomnographic Severity Index

The polysomnographic severity index (PSGSI) of the Piccirillo *et al.* (1998) study was derived directly from the apnoea hypopnea index (AHI) and SpO_2 nadir. In order to develop a PSGSI for children with a range of UAO severity, a wide range of PSG measures needed to be included so that the more varied and subtle events (when compared to those of adults) seen in children's sleep studies could be included .

Measures of Hypoxemia

Many studies have linked hypoxemia to cognitive deficits (Engleman *et al*., 2000). Historically, the repeated arterial oxygen desaturation during sleep that are a cardinal feature of the more severe forms of UAO were believed to be the main cause of the cognitive impairment and other morbidities seen in these people (Gozal & Kheirandish 2006). Engelman (2000) showed significant but weak associations between a cognitive 'intellectual ability' score and the minimum oxygen saturation ($r = 0.15$, $p<0.05$). However, as UAO encompasses a range of severity that includes PS that occurs, by definition, without gas exchange abnormalities but still results in reduced neurobehavioural functioning, hypoxia must be only a partial explanation for such performance reductions (Blunden *et al*., 2000 Ferreira *et al*., 2000). In the current study, the measure utilized for hypoxemia was the number of desaturations greater than or equal to 3% rectified for total sleep time as this was easily measured and widely assumed to be one of the most significant features of any nocturnal oxygen saturation profile (Iber 2007) and the format of the index fit inclusion in the alogirithm.

Measures of Sleep Fragmentation

It has been widely demonstrated that there are numerous individual measures of sleep disturbance that correlate weekly with important daytime outcomes like IQ and quality of life (QOL). It has been

proposed that movement may be an important but under recognized and underutilized marker of sleep fragmentation (Coussens *et al*., 2013). However, O'Driscoll *et al.*(2006) recently showed that actigraphy on its own has limited usefulness as a screening tool for use in children with sleep disordered breathing.

In the current study, a measure of sleep fragmentation based on a novel measure of PSG derived movement was developed and used to generate a component of the two composite indices.

Another commonly used measure of sleep disruption is cortical arousal. Children have relatively few awakenings during sleep when compared to adults. This is possibly due to increased dampening of arousal mechanisms during childhood (Gozal & Kheirandish 2006). Children also have reduced arousals in sleep when compared to adults supporting this explanation. As arousals are less common in children, a measure of their frequency is likely of more importance when assessing sleep fragmentation via polysomnography as they would consequently be indicative of a higher level of sleep disturbance when compared to a similar arousal in adults.

Respiratory Measures

Many studies have shown that cognitive performance in adult OSAS subjects broadly worsen with increasing disease severity (Engleman *et al*., 2000). However, Mateika and Mitru (2001) demonstrated that this relationship may not be a simple linear one with their finding that autonomic nervous system changes associated with snoring subjects were very different in subjects with and without apnoea, implying different pathological mechanisms.

7.2.4. OUTCOME MEASURES OF DISEASE BURDEN

An obvious difficulty when testing a new measure of disease severity is the problem of what to compare the measure to, given that what one would ideally compare it to is the "true" disease severity level which is exactly what is being ascertained in the first place. One of the possible solutions to this apparent paradox is to use a subjective measure of disease burden as a surrogate measure of severity. This process however, requires the assumption that the more severe a disease, the greater its impact will be on the patient's quality of life. It also ignores subjective information reported by the patient (or parent/caregiver) especially if it contradicts objective evidence. However, if a patient feels that a disease has a high burden on their life, then in many important ways it does. In this study, we therefore used a measure known as "Quality of Life" which measures perceived quality of life of an individual (by their caregiver) on several scales of life function and achievement and combines the measures into a single variable (Overall Quality of Life – OQOL, Lima *et al*., 2008). See Table7.1 for an example of the types of individual items within each conceptual category in the original 20 item QOL scale (Franco *et al*., 2000).

An objective measure of disease burden was also employed in this study. In the Balakrishnan *et al.* (2012) study, AHI was chosen as a simple marker of objective disease severity and hence disease burden. In this study, AHI was also used as such a measure.

7.2.5. HYPOTHESES

Therefore we hypothesized the following;

(1) An index of combined indices (which we will term the Total Sleep Disturbance Index or TSDI) could be derived from regularly collected PSG measures that would better correlate with identified important subjective outcome scores (Quality of Life) and objective severity measures (SpO_2 nadir) in children with UAO than any single PSG measure alone.

(2) An index of combined indices (which we will term the Composite Upper airway obstruction Disease Severity Index for Children or CUDSIC) could be derived from regularly collected PSG measures and clinical and/or demographic variables and functional measures that would better correlate with identified important subjective outcome scores (Quality of Life) and objective severity measures (SpO2 nadir) in children with UAO than any of the component factors alone.

7.3. METHODS

This study was approved by the Women's and Children's Hospital (WCH) Human Ethics Committee. Parental consent and child assent was obtained from all participants.

7.3.1. SUBJECTS

The data from PSG and neurobehavioural testing of forty four children with sleep-related upper airway obstruction (UAO) was utilized for this study. Children with UAO were those with a history of frequent snoring who were scheduled for adenotonsillectomy for suspected obstructive sleep apnoea as diagnosed by an experienced paediatric otorhinolaryngologist at the WCH. Children were excluded if they spoke English as a second language, had undergone previous ENT or craniofacial surgery, had a medical condition (other than UAO) associated with hypoxia or sleep fragmentation or were taking medication known to affect sleep, cardiorespiratory physiology or neuropsychological performance. Children with neurological, psychological, cognitive or behavioural problems were also excluded. The sample was further restricted to children aged between 3.0-12.9 years to facilitate neuropsychological testing and to avoid the potential effects of late pubertal developmental changes on sleep physiology and upper airway dynamics.

Socioeconomic status (SES) was determined for each child using the Australian Bureau of Statistics' Index of Relative Socio-economic Advantage/Disadvantage 2006 national census data. A higher score on this index indicates increased income and occupational skills and/or training within the geographical area of residence (collection district), with a national population mean of 1000 and standard deviation of 100.

7.3.2. OVERNIGHT POLYSOMNOGRAPHY

Subjects underwent a single polysomnographic assessment. Overnight PSG was conducted without sedation or sleep deprivation and began close to each child's usual bedtime with a parent present throughout the procedure. Polysomnography was only performed if children were well on the night and free of any recent illness including respiratory infection. The following standard parameters were measured and recorded continuously using a commercially available computerized PSG system (Compumedics S-Series Sleep System, Melbourne, Australia): electroencephalogram (EEG; C3-A2 or C4-A1), left and right electrooculogram (EOG), sub-mental and diaphragmatic electromyogram (EMG) with skin surface electrodes, leg movements by piezoelectric motion detection, heart rate by electrocardiogram (ECG), oro-nasal airflow by thermistor and nasal pressure, respiratory movements of the chest and abdominal wall using uncalibrated respiratory inductive plethysmography (RIP), arterial oxygen saturation (SpO_2) by pulse oximetry (Nellcor N200; 2-3 second averaging time) and transcutaneous CO_2 ($TcCO_2$) using a heated (43^{o}C) transcutaneous electrode (TINA, Radiometer Pacific). All data were digitized and stored for subsequent analysis. Each child was monitored continuously overnight via infrared camera by a pediatric sleep technician who also documented observations of sleep behavior including the presence or absence of snoring. Height and weight were measured on the night of PSG and established growth charts corrected for age and gender were used to determine body mass index (BMI) z-scores (ref).

Sleep stages were visually scored in 30-second epochs according to the standardized EEG, EOG and EMG criteria of Rechtschaffen and Kales (Rechtschaffen & Kales, 1968). Stage 3 and 4 NREM sleep were combined as slow wave sleep (SWS). Movement time (>50% of an epoch obscured by movement artefact) was scored as a separate category and was not included in either

sleep or awake time. Awake time refers to time spent awake during the recording period after initial sleep onset.

Respiratory variables were scored according to modified guidelines (see chapter 3) recommended for pediatric sleep studies (ATS, 1996). The obstructive apnea/hypopnea index (OAHI) was calculated as the total number of obstructive apneas, mixed apneas and obstructive hyperpnoea divided by the total sleep time and expressed as the number of events per hour of sleep. An OAHI ≥ 1 was considered indicative of OSAS. The central apnea hypopnea index (CAHI) was calculated as the total number of central apneas and central hypopneas divided by the total sleep time and expressed as the number of events per hour of sleep. The total apnea and hypopnea index (AHI) was calculated as the total number of all respiratory events divided by the total sleep time and expressed as the number of events per hour of sleep.

Cortical arousals were scored according to the criteria of the American Sleep Disorders Task Force (Bonnet 1992). The total arousal index (ArTotI) represents all arousals combined (excluding arousals caused by external stimuli) expressed as the number of arousals per hour of sleep. The spontaneous arousal index (SAI) represents the total number of spontaneous arousals per hour of sleep. The respiratory arousal index (RAI) represents the total number of respiratory arousals per hour of sleep.

Periodic limb movements (PLM) were scored using standard criteria (Ref). The PLM index was calculated at the number of PLM events per hour of NREM sleep.

7.3.3. OUTCOME MEASURES OF DISEASE BURDEN

The subjective outcome measure selected for this study was overall quality of life (OQOL) which is a composite score of elements of the OSA-18 scale. The OSA-18 is an 18-item questionnaire for children with OSAS that uses a Likert scoring system to rate 5 subscales that are considered to be essential components in determining quality of life in children with OSA (Franco *et al*., 2000). The 5 sub-scales are sleep disturbance, physical symptoms, emotional symptoms, daytime function, and caregiver concerns. Figure 7.2 contains a more detailed summary of the subscale components. A combined score of all 5 sub-scale scores (OQOL) is then calculated and converted to a categorical scale that ranges from 10 (no negative impact on quality of life) to 1 (major negative impact, Franco *et al*., 2000). A OQOL score less than or equal to 5 is considered abnormal (Franco *et al*., 2000). The Cronbach's alpha (a measure of test reliability) for the OSA18 has been determined to be ≥ 0.70 for the total OSA-18 score and for all but 1 of the domains in both general population and disease groups (Bannink *et al*. 2011). The discriminative validity of the domains sleep disturbance, physical suffering, caregiver concerns, and total OSA-18 score have been found to be significantly different between the general population and various disease groups (Bannink *et al.* 2011).

As for the Balakrishnanm *et al.* (2012) study, the objective outcome measure selected for this study was the SpO_2 nadir (%) value recorded during sleep in the overnight polysomnography determined not to be artefact by an experienced technician.

7.3.4. MOVEMENT ANALYSIS

A novel movement measure termed the movement event (ME) developed by the author were used for this study (Coussens *et al*., 2013). We scored an ME when there was simultaneous evidence of movement on two or more independent channels > 3 seconds in duration. Additionally, Movement

Events separated by less than 0.5 seconds were combined. A Movement event index (MEI) was calculated by dividing the number of movement events scored by the TST in hours. A measure of movement event distribution was then calculated using the method outlined in Coussens (2013) to give the movement event distribution exponent (MEx).

7.3.5. POLYSOMNOGRAPHIC SEVERITY INDEX – THE TOTAL SLEEP DISTURBANCE INDEX

The total sleep disturbance index was a simply derived measure of the total amount of sleep fragmentation that occurs during a recording of a PSG excluding when possible that disturbance caused by external influences.

The total sleep disturbance index was calculated simply as follows;

$$TSDI = [(RDI) + (DI) + (ArTotI) + (PLMI) + (MEI) + (AwI) + (SSI)]$$

The TSDI was simply the sum of the respiratory disturbance index (RDI: total number of respiratory events rectified for total sleep time (TST)), the SpO_2 desaturation index (DI: total number of desaturations greater than or equal to 3% SpO_2 rectified for total sleep time (TST)), the total arousal index (ArTotI), the periodic limb movement index (PLMI), The movement event index (MEI), the awakening index (number of awakenings in the sleep period rectified for total sleep time, AwI) and the sleep stage index (SSI: total number of sleep stage shifts in the sleep period rectified for TST). This compound measure was developed as it was predicted that the combined number (sum) of sleep disrupting events, while not necessarily interacting or being dependent on one another and

despite often being normal events would by cumulative impact negatively correlate with functional outcomes thus the higher the TSDI score the worse the sleep fragmentation by all causes.

The polysomnographic severity index (PSGSI) was calculated as follows;

PSGSI = (TSDI / Age)

This arrangement was chosen as the PSGSI value increases as sleep disruption increases and age decreases. This is because it was known that levels of disease burden are rated by physicians as more severe in younger subjects as evident from lower threshold values for equivalent diagnoses in children when compared to adults. For example, if a child of 5 years old has an AHI of 10 events per hour, disease severity would be rated as severe whereas it is possible for a 15 year old subject, validly scored under adult rules to have the same AHI of 10 and be considered only mild.

7.3.6. FUNCTIONAL SEVERITY INDEX WITH SLEEP CONTINUITY ANALYSIS.

The functional severity index (FSI) scores were calculated using survival curve analysis of the distribution of scored sleep movement events (as a measure of physical adaptation to UAO, Coussens *et al*., 2013) was calculated by initially exporting the acquired sleep data for the appropriate channels to XML format for further processing in MATLAB (Mathworks, USA). Using custom made software, time intervals between consecutive movement events were extracted for each sleep study. Subsequently, survival curves were constructed based on empirical cumulative distribution functions and exponential regression functions fitted. . Assumptions of normality were

not valid for survival curve exponent values and a square root transform [$\sqrt{x}$] was used to correct for skewness. For a more detailed explanation of the methods involved in performing survival curve analysis see Norman *et al.* (2006) and Coussens *et al.* (2013). The FSI was calculated as follows;

FSI = $\sqrt{x}$ (where x = Movement Event Distribution Exponent, MEx)

7.3.7. PHYSICAL SEVERITY INDEX

The physical severity index (PSI) was derived from BMI (z-scores) and age (in years) measures as follows

$$PSI = [(Age) \times (Mod\ BMIz)]$$

This arrangement, known as an interaction variable was chosen as the PSI value increases as age increases and BMI z values become more extreme. It was known that extreme BMI scores are associated with disturbed sleep in children (Gozal and Kheirandish 2006). It is also known that sleep disturbance due to elevated BMI has greater impact in older subjects compared to younger ones (Kohler *et al*., 2009)

7.3.8. COMPOSITE UPPER (AIRWAY OBSTRUCTION) DISEASE SEVERITY INDEX (FOR) CHILDREN (CUDSIC)

The CUDSIC was similar to the sleep apnoea severity index (SASI) but modified for use in children with UAO (see Figure 11.3). The CUDSIC was calculated as follows;

$$CUDSIC = [((PSGSI) \times (FSI)) + (PSI)]$$

The CUDSIC was developed as a mixed model of interacting and additive variables based on a simplified version of the SASI model.

7.3.9. STATISTICS

For correlation calculations between the various sleep fragmentation measures, Spearman's rho method was employed with statistical significance set at $p<0.05$. Kolmogorov-Smirnov statistic, with a Lilliefors significance level were used in testing the normality of variables. Assumptions of normality were valid for all PSG variables with the exception of PLMI, RAI, frequency of SpO_2 desaturations ≥ 3%/ hr TST, percentage of sleep time with SaO_2 < 95%, $TcCO_2$ > 50 mmHg, OAHI and AHI. Inverse transformation [1/(x + 1)] were required for these variables to correct skewness. Post hoc testing was conducted using planned means comparisons with Tukey's Honestly Significant Difference (HSD) method for multiple comparisons. All *p* values reported are 2-tailed, with statistical significance determined at $\alpha = 0.05$. Data are presented as mean ± standard deviation unless stated otherwise.

7.4. RESULTS

7.4.1. SUBJECTS

Forty four children with a range of sleep-related upper airway obstruction (UAO) took part in this study. Biophysical characteristics for the 44 children are presented in Table 7.2.

7.4.2. POLYSOMNOGRAPHY

Polysomnographic variable data for mean, standard deviation, range, minimum value and maximum value for the 44 children with UAO are presented in Table 7.3.

7.4.3. NEUROPSYCHOLOGICAL TESTING

The distribution of overall quality of life (OQOL) score calculated from the Quality of Life (QOL) survey results for 42 of the 44 children with UAO are presented in Figure 7.4. Two subjects failed to complete the survey adequately and were removed from analysis. The median value (value with equivalent numbers of subjects higher and lower) was 6, the mode (most common value) was 7, the score range was 7 with a minimum of 3 (high negative impact of OSAS on QOL) and a maximum of 10 (no negative impact from OSAS on QOL).

7.4.4. MOVEMENT MEASURES

The distribution of scores for movement distribution exponent (MEx) analysis are presented in Figure 7.4. The mean value for MEx was 0.97 + 0.10. The distribution of MEx values was skewed

so a square-root transformed version of the variable was used in further analysis and model construction.

7.4.5. TOTAL SLEEP DISTURBANCE INDEX

In support of hypothesis 1, the TSDI correlated negatively ($p<0.05$) with subjective disease severity (OQOL) whereas the components of TSDI did not (see Table 7.3). The TSDI also correlated significantly with objective disease severity (SpO_2 nadir) as did several of the other variables ($p<0.05$).

7.4.6. CUDSIC

The results for calculating the CUDSIC measure are summarized in table 7.5. As can be seen in Table 7.5, CUDSIC correlates strongly with measures of subjective and objective disease severity ($P<0.001$). It is further apparent that CUDSIC correlates more strongly with these variables than any of the component indices alone, confirming hypothesis two and furthermore confirming the utility of the composite approach to disease severity modeling.

7.5. DISCUSSION

The current standard clinical measure used to indicate UAO disease severity in children is the respiratory disturbance index (RDI) which is the rate of sleep disturbing respiratory events (apnoeas, hypopneas and RERAs) per hour of total sleep time. However, some children with milder forms of UAO do not show many discrete "scorable" events and consequently have low RDIs despite having other symptoms of the disease (eg. snoring) and similar neurocognitive and behavioural deficits (Kohler *et al*., 2009). It has been proposed that these children have deficits due to other forms of sleep process disturbance, namely sleep fragmentation. (Gozal & Kheirandish. 2006)

The findings of this study show that the answer is more complicated than this simplified model. RDI is inadequate for an accurate assessment of disease severity and burden and often is not sufficient for clinicians who need to make decisions regarding therapeutic intervention with significant associated costs to the medical system and real risks to the patient. Similarly, as has been consistently demonstrated, no single sleep fragmentation index explains a large proportion of the variance in subjective and objective outcomes for children with UAO.

Despite these findings, RDI and several previously identified SFIs have some demonstrated predictive worth. In adults, RDI has been associated with hypertension and other markers of reduced cardiovascular health (Balakrishnan *et al.* 2012) as well as impacts on mood and cognitive function (Gozal *et al.*2008). In children with UAO, disease-precursor cardiovascular changes are seen (Kabir *et al*. 2010). There is growing evidence that those with an elevated RDI also show deficits in neurocognitive performance, increased behavioral impairment, reduced school performance (Gozal *et al*.1998; Blunden *et al*., 2000; Lewin *et al*. 2002; O'Brien & Gozal 2002) and

increased reporting of problematic behaviors (Blunden *et al*., 2000; Lewin *et al*., 2002; O'Brien, Tauman, *et al*. 2004) .

Furthermore, commonly used subjective measures (often completed by parents or other caregivers) of disease burden also do not reflect the full impact of UAO on children with communication difficulties inherent in dealing with paediatric patients and a physical disconnect between the sufferer and person reporting the suffering.

As there are numerous variables that partly correlate with subjective and objective measures of disease severity and burden, it follows that an index of such should incorporate a number of pertinent parameters in such a way as to amplify their predictive effect. Several recent studies have utilized this approach of combining indices using relatively simple mathematical data manipulation. For example, a 2009 study in children with dysphagia created and used a composite index they termed the Swallow Risk Index (SRI, Omari *et al*., 2011). They combined various measured factors by a simple process of amplification whereby index components were multiplied together if they were positively correlated to the same outcome(s) and divided if correlating negatively with the same outcome(s). This simple technique was similar to that employed in the current study and has similarly proved itself a potentially useful approach. Another study, mentioned earlier in this study, developed the sleep apnoea severity index (SASI), a similar composite measure of various clinical and measured components but using a far more complex and robust modeling technique (Balakrishnan *et al*., 2012). The components rather than their mathematical interaction was adapted for use in the current study.

The results demonstrate that hypothesis one is plausible. A composite measure of upper airway obstruction disease severity was derived from simple sleep fragmentation and respiratory indices of children with UAO that correlated with a subjective outcome measure (OQOL). This measure (TSDI) did indeed correlate with OQOL better than any component fragmentation or respiratory

index. The TSDI also correlated well with an objective disease severity measure but not more strongly than the component measures. This is strong evidence for the potential usefulness of the approach but also highlights the weakness of the study; that the subject groups were too small and on average at the milder end of the disease severity range. Future work should see the consolidation of larger subject groups with a wider range of UAO disease severity.

Hypothesis two was that an index of combined measures could be derived from a wider range of sleep and other subject variables (PSG variables, clinical observations, demographic variables and functional measures) that would better correlate with outcome scores in children with UAO than any of the component measures alone. Again, this study's findings demonstrate that this is a plausible and promising approach to diagnosing and characterizing upper airway obstruction and its impact in children. The composite score we derived (CUDSIC) did more strongly correlate with objective and subjective measures of disease severity than any single component index alone.

Limitations

A limitation of the current study has been its design with small sample size and cross-sectional configuration that limits the power and ability to determine causation. Larger groups with a greater number of a wider variety of experimental and demographic measures would allow a more accurate determination of the important factors in determining UAO severity.

A further limitation is the lack of direct measures of genetic markers and other more invasively determined physiological indicators of disease severity and/or susceptibility.

Conclusion

Upper airway obstruction in children is a complex, multifaceted disease with both subjective and objective components with many environmental, genetic and epigenetic contributors. It is clear from the results of this study that any useful measure of UAO disease severity and its subsequent

impact on sufferers will need to take into account the range of contributing factors and their interactions. To date, researchers have focused on objective measures, specifically, the RDI. Although the RDI does have a clear diagnostic value, particularly in severe cases of UAO in children, the results of this study suggest that a composite index may be more useful in determining the need for treatment in borderline cases. Further studies are required to examine the usefulness of such indices in predicting and assessing therapeutic effects and disease development over childhood and into adulthood.

7.6. FIGURES AND TABLES

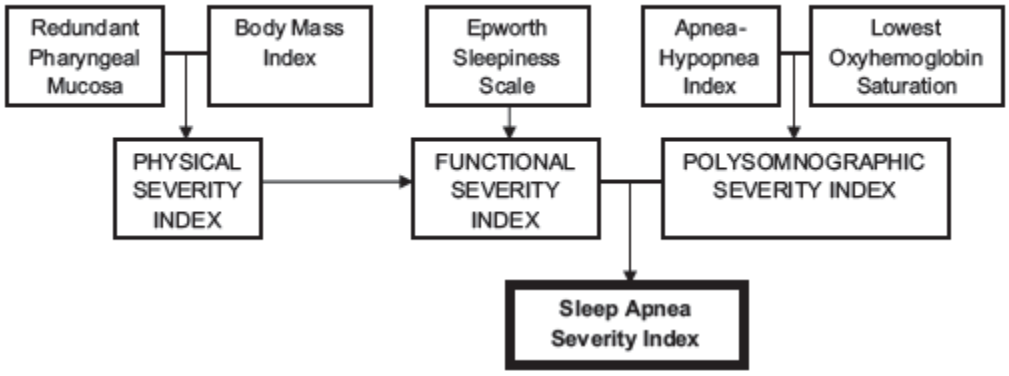

Figure 1. Schematic derivation of the Sleep Apnea Severity Index (SASI) and Modified Sleep Apnea Severity Index. The scoring algorithm was generated through a conjunctive consolidation process. Modified SASI uses tonsil size in place of SASI's redundant pharyngeal mucosa element.

Figure 7.1: The Sleep Apnoea Severity Index. (from Balakrishnan 2012)

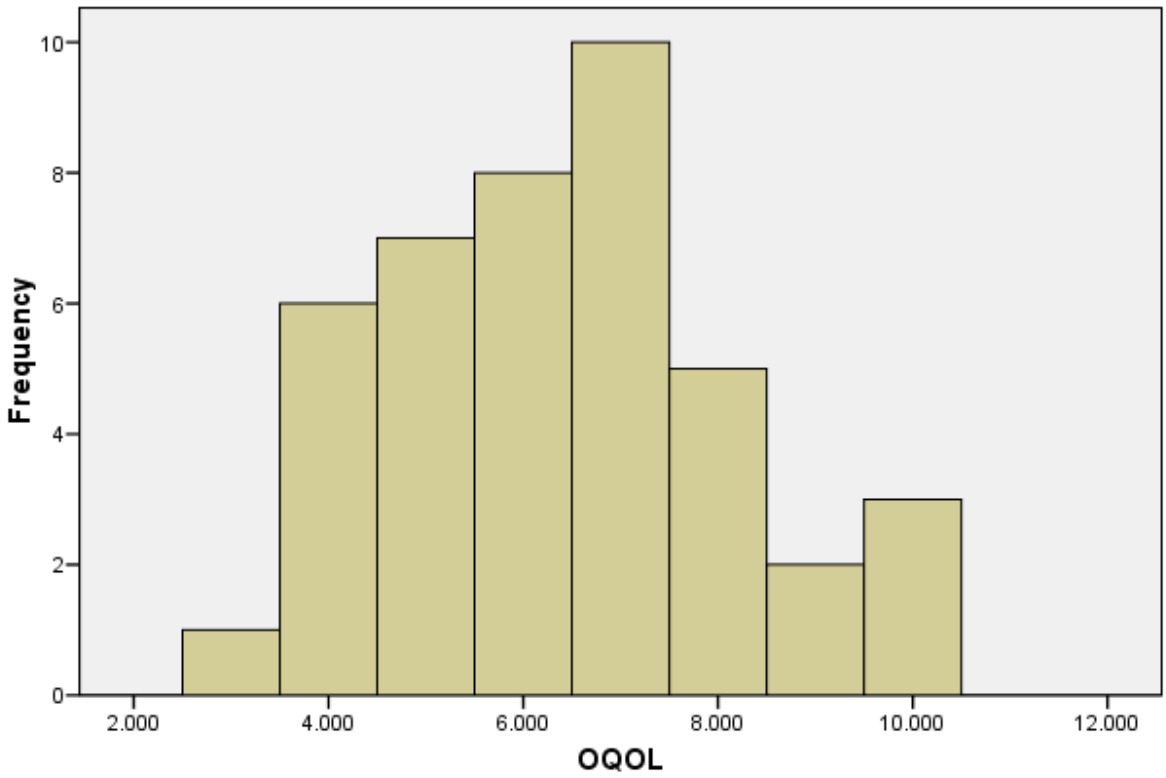

Figure 7.2 Quality of Life (OSA-18) Survey Overall Quality of Life score (OQOL) Results

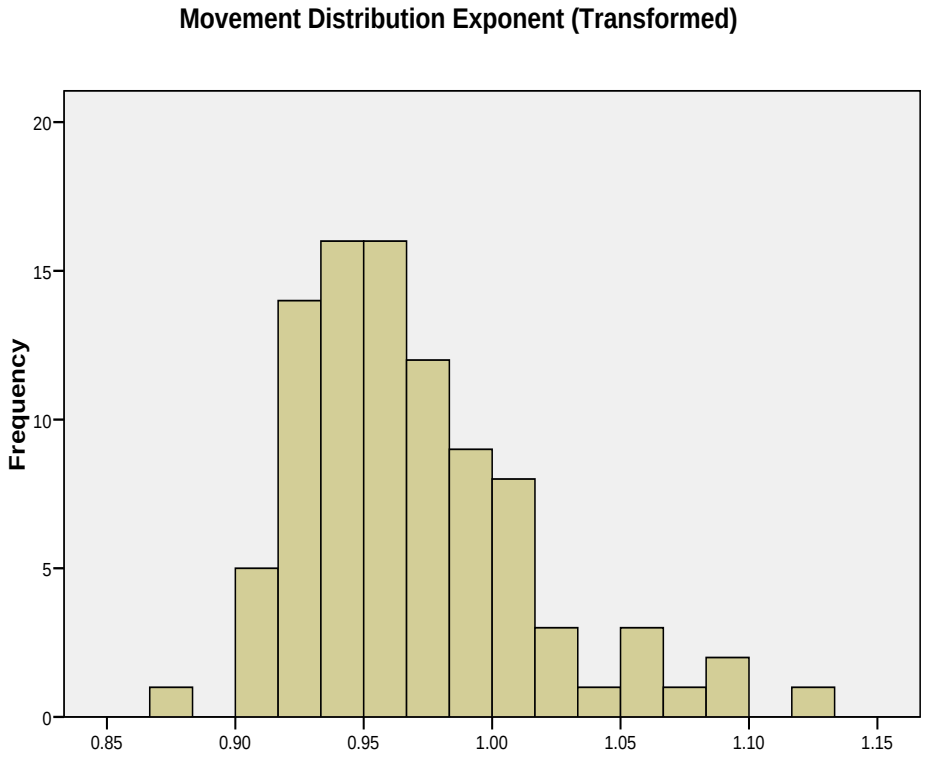

Figure 7.3 The Composite Upper Airway Obstruction Disease Severity Index for Children (CUDSIC).

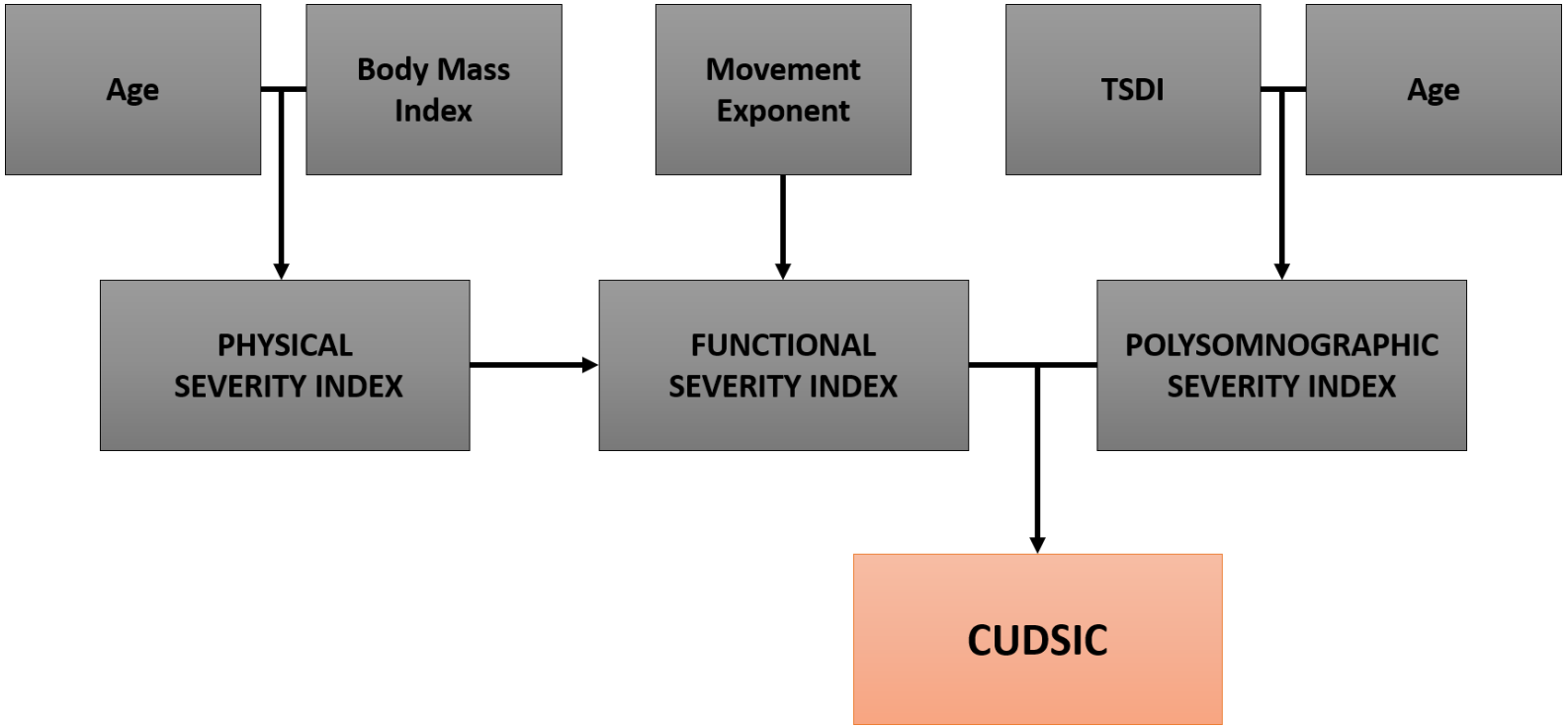

Figure 7.4 The Composite Upper Airway Obstruction Disease Severity Index for Children (CUDSIC).

Table 7.1 Quality of Life Scale (OSA-18) with 20 original conceptual categories and scale items **(**adapted from Franco 2000).

Item	Subscale	Content
1	Sleep disturbance	Loud snoring
2	Sleep disturbance	Breath holding spells or pauses in breathing at night
3	Sleep disturbance	Choking or gasping sounds while asleep
4	Sleep disturbance	Restless sleep or frequent awakenings from sleep
5	Physical symptoms	Mouth breathing because of nasal obstruction
6	Physical symptoms	Frequent colds or upper respiratory infections
7	Physical symptoms	Nasal discharge or runny nose
8	Physical symptoms	Difficulty swallowing foods
9	Emotional distress	Mood swings or temper tantrums
10	Emotional distress	Aggressive or hyperactive behavior
11	Emotional distress	Discipline problems
12	Emotional distress	Problems getting along with other children
13	Daytime function	Excessive daytime drowsiness or sleepiness
14	Daytime function	Poor attention span or concentration
15	Daytime function	Difficulty getting out of bed in the morning
16	Daytime function	School or learning problems
17	Caregiver concerns	Worrying about child's general health because of above problems
18	Caregiver concerns	Concern that child is not getting enough air at night
19	Caregiver concerns	Inability to perform daily activities because of above problems
20	Caregiver concerns	Frustration because of above problems

Parents rated symptom frequency during the previous 4 weeks using a 7-point ordinal scale of (1) none of the time, (2) hardly any of the time, (3) a little of the time, (4) some of the time, (5) a good bit of the time, (6) most of the time, and (7) all of the time.

Table 7.2 Mean subject biophysical characteristics for UAO children at polysomnography.

	Mean	S.D	Range	Minimum	Maximum
N	44	n/a	n/a	n/a	n/a
Age (years)	6.59	2.58	9.79	3.08	12.87
Gender, N (% male)	28(64)	n/a	n/a	n/a	n/a
BMI z-score	0.84	1.32	6.12	-2.67	3.45

BMI= body mass index (kg/m^2) , n = number of subjects, S.D = standard deviation, UAO = upper airway obstruction

Table 7.3 Polysomnography results for a single night polysomnography in children with UAO

	Mean	S.D.	Range	Minimum	Maximum
Total Sleep	436.70	49.26	239.50	318.00	557.50
Stage 1 (%TST)	0.03	0.02	0.10	0.00	0.10
Stage 2 (%TST)	42.45	5.42	22.51	30.87	53.38
SWS (%TST)	149.51	28.63	103.50	102.00	205.50
REM (% TST)	20.31	5.32	24.17	10.14	34.31
REM latency	108.36	54.67	241.00	15.00	256.00
OAHI[1]	5.82	10.17	49.76	0.00	49.76
CAI	2.31	3.29	17.75	0.00	17.75
AHI[1]	7.40	12.03	55.14	0.00	55.14
RAI[1]	3.81	6.17	33.94	0.00	33.94
SAI	8.51	2.60	11.66	4.50	16.15
Sleep Efficiency	81.65	7.95	27.20	67.20	94.40
WASO (min)	45.34	40.07	164.50	0.00	164.50
WASO (% TST)	0.11	0.1	0.44	0.00	0.44

TST = total sleep time; REM = rapid eye movement sleep; SWS = Slow wave sleep; WASO = wake time after sleep onset; PLMI = periodic limb movement index; SAI = spontaneous arousal index; RAI = respiratory arousal index; OAHI = obstructive apnea/hypopnea index; CAHI = central apnea/hypopnea index; AHI = apnea/ hypopnea index. [1]Analysis performed using transformed values.

Table 7.4 Mean Values for Total Sleep Disturbance Index (TSDI) and component indices and correlations with Subjective Disease Severity (Quality of Life (OQOL)) and Objective Disease Severity (O2 nadir during sleep).

Measure	N	Mean	S.D		Correlation with Overall Quality of Life (OQOL)	Correlation with O2 nadir
RDI - Respiratory Disturbance Index (/hr TST)	44	8.13	12.52	rho	-0.24	-0.78
				p	0.13	< 0.00001
MEI - Movement Episode Index (/hr TST)	44	11.63	5.22	rho	-0.27	-0.22
				p	0.08	0.15
SSI - Sleep Stage Index (/hr TST)	44	12.92	2.82	rho	-0.17	-0.11
				p	0.28	0.49
TAI - Total Arousal Index (/hr TST)	44	0.24	0.12	rho	-0.1	-0.50
				p	0.52	< 0.001
AWI - Awakenings Index (/hr TST)	44	0.79	0.67	rho	-0.03	-0.10
				p	0.83	0.52
PLMI - Periodic Limb Movement Index (/hr NREM ST)	44	6.7	9	rho	0.09	0.09
				p	0.58	0.54
ODI - Oxygen Desaturation Index (3% or greater desaturations /hr TST)	42	6.26	11.22	rho	-0.25	-0.82
				p	0.11	<0.00005
TSDI - Total Sleep Disturbance Index	44	60.18	32.99	rho	-0.31	-0.59
				p	0.04	<0.00005

p<0.05, TST = total sleep time in hours

Table 7.5 Mean Values for Composite Upper airway disease Disturbance of Sleep Index for Children (CUDSIC) and component indices and correlations with Objective Disease Severity (Apnoea/Hypopnoea Index and O2 desaturation index during sleep) and Subjective Disease Severity (Quality of Life – QOL)

Variable	N	Range	Minimum	Maximum	Mean	SE	SD	Correlations with Outcome Measures		
								AHI	SpO2I	OQOL
CUDSIC	44.00	7.39	2.13	9.52	4.36	0.23	1.55	0.584***	0.546***	-0.632***
FSI	44.00	0.25	0.88	1.13	0.98	0.01	0.06	0.328*	0.337*	-0.337*
PSI	44.00	23.65	0.03	23.68	8.34	1.00	6.64	0.303*	0.246	-0.182
PSGSI	44.00	36.29	3.56	39.84	10.72	1.07	7.08	0.489**	0.528***	-0.518**

*P<0.05, **P<0.01,***P<0.001, FSI = Functional severity index, PSI = Physical severity index, PSGSI = Polysomnographic severity index

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DISCUSSION

CHAPTER 8

Conclusion and Future work

8.1. OVERVIEW

Sleep disordered breathing (SDB) is common in children. Common symptoms are a degree of upper airway obstruction leading to snoring, sleep disturbance and intermittent hypoxia (Mindel & Owens 2003). Children with SDB also have reduced neurocognitive performance and increased problematic behaviour (Kohler *et al*., 2009, Lima *et al*., 2008). Some researchers have proposed that hypoxia is the main cause of the neurocognitive deficits in children with SDB (Beebe & Gozal 2002). Beebe and Gozal (2002) proposed a model whereby neural cells, particularly in the prefrontal cortex (PFC), were adversely affected by the repeated hypoxic exposure in patients with a severe form of SDB, obstructive sleep apnoea syndrome (OSAS). The PFC is believed to control executive functions such as attention to tasks and division of attention between tasks. Reduced attentional capacity or control was then proposed to lead to reduced neurocognitive performance in children with OSAS. (Beebe & Gozal 2002)

Hypoxia is present in severe sleep disorders such as OSAS (Bandla 2000). Recent work has shown that children with more mild forms of SDB, such as habitual snoring in the absence of hypoxia, also exhibit neurocognitive deficits. Such children make up the bulk of those with SDB. Children at the mild end of the SDB range often have PSG results within the normal range and are therefore not treated.

Recent studies have proposed that arousals due to SDB may contribute significantly to neurocognitive deficits (Tauman *et al*., 2004). The disruption to the normal neuronal processes during sleep rather than hypoxia may be the major cause of neurobehavioural deficits in children with milder SDB. It is known that some part of the learning process occurs in sleep with, for example, objective performance on some kinds of newly learned tasks improved by sleep within a

short temporal window of 48 to 96 hours (Huber *et al*. 2004). This is true if training continues or not during the intervening waking periods.

Electroencephalographic recording of sleeping subjects show that there is increased synchronization of neural firing in certain neuronal groups of the brain which is very different from waking brain behaviour. Cortical neurons show a relatively constant oscillation of membrane potential of less than 1Hz during sleep. These slow frequency oscillations propagate through the cortex, at once organizing and generating the other synchronized neural behaviours that are seen in sleep.

The aims of the study was to produce a sleep fragmentation index that was generally applicable to children with a range of UAO and had the following properties:

1) it could discriminate between children with and without UAO.

2) it would correlate with objective neurocognitive and subjective quality of life measures seen in children with UAO.

3) it could identify children that would benefit from treatment of their UAO.

8.2. SUMMARY OF FINDINGS

From **Chapters 1 and 2** of this study program it can be concluded that:

1) There is no clinically valid measure of sleep fragmentation derived from an overnight PSG that:
    a) consistently correlates with neurocognitive and other deficits seen in children with UAO
    b) or consistently identifies children with (particularly mild) UAO from those without UAO.
2) Several measures of sleep fragmentation derived from the PSG have shown significant but low or inconsistent correlations with a range of "daytime deficits" Some of the more promising measures included cortical arousals, movement measures, autonomic measures and certain sleep stage changes.
3) The "daytime deficits" associated with UAO in children are not well defined but are known to differ from those seen in adults.
4) We still require a clinically viable sleep fragmentation index that can be applied to children across a range of UAO severity.

C**hapters 4, 5 and 6** demonstrated that:

1) **Children with UAO have altered EEG activity when asleep compared to normal control subjects.** Spindle frequency was higher in children with UAO. This demonstrated a difference between children with and without UAO that was linked both to sleep fragmentation (indirectly) and the cognitive processes of sleep.

2) **Children with UAO had an altered spontaneous arousal response when compared to normal control children,** *i.e.*:

   a) Children with UAO had lower levels of higher frequency EEG activity preceding and following spontaneous arousal in sleep compared to control subjects in certain stages of sleep. This result demonstrates that children with UAO have an increased arousal suppression mechanism that exists outside the bounds of the arousal event itself and

   b) Children with UAO's performance on neurocognitive tests correlated with the alpha frequency EEG spectral measures of spontaneous arousals in sleep.

   Combined, these findings show that children with UAO have altered sleep, in response to chronic sleep fragmentation. This is likely to cause much of the neurocognitive deficit seen in this group.

3) **Children with UAO had altered movements in sleep when compared to normal control children.** Children with UAO had a similar number of movements to children without UAO, however their distribution was altered; greater numbers of extreme long and short contiguous sleep periods. This finding indicates that subcortical structures of the central nervous system are altered, or abnormal, in chronic UAO sufferers.

Finally**, Chapter 7** demonstrated that it is possible to use and combine several indices of sleep fragmentation and other vulnerability indicators in children with UAO to better describe the disease and its impact.

8.3. LIMITATIONS

One of the limiting factors in this study was the small test groups that hindered the measurement of small effect sizes. A second limiting factor was that the data that was used in the studies that formed the components of the current research program were generated from a larger cross-sectional study that was not purpose-designed for characterizing sleep fragmentation in children with UAO. A third limitation is that the PSG as currently conceived has a significant and individually variable impact on sleep quality. Further research should include more specifically designed prospective studies of sleep disturbance with experimental fragmentation, overnight learning measures and other neurocognitive impact determination and deliberately reduced external impact on sleep quality.

8.4. FUTURE WORK

8.4.1. NOVEL COMBINATIONS OF KNOWN FACTORS

As outlined earlier, there are many separate but interacting factors that contribute to and mediate the impact of sleep fragmentation in children with UAO. Future work will need to include factors that have been identified but are yet to be incorporated into a diagnostic sleep model.

As far back as the early 1990s, studies have shown the frequency of breathing irregularities, the extent of sleep fragmentation and the extent of nocturnal hypoxemia were important factors in determining daytime function in patients with UAO. It was even recognized that all of these various factors needed to be considered when deciding treatment options (Cheshire *et al*., 1992). However, research into measurement reliability and repeatability needs to be performed to narrow down the potential range of sleep measures considered for inclusion in a novel model or algorithm. Measures could be usefully excluded based on their night to night variability value which has the added advantage of perhaps reducing the amount of contradictory findings in future sleep research.

Physiological Factors

Sleepiness as well as hypoxemia have been shown to separately contribute to cognitive deficits associated with UAO by experimental sleep fragmentation in normal adults that produced deficits on attention-biased scores (Engleman *et al*., 2000). Gozal and Kheirandish (2006) showed that oxidative stress and inflammation responses in children who snore are important pathways to the pathogenesis and end-organ morbidity of the disease. The hypothetical working model they proposed was a three factor description that incorporated both dose-dependent disease severity components, as well as environmental and genetic elements of susceptibility (Gozal & Kheirandish

2006). O'Brien *et al*. (2004) found that the measure “sleep pressure” (derived from sleep arousal measures) correlates with deficits in neurobehavioral daytime functions in children with UAO that is independent of respiratory disturbance and hypoxemia and indicates a significant role for disrupted sleep homeostasis in pediatric UAO. Such measures should now be integrated with sleep fragmentation and other factors to produce a more accurate and more widely applicable measure of disease burden in children with UAO.

Severity Factors

It has been demonstrated that nocturnal cardiovascular and autonomic function may be uniquely different in non-apnoeic snoring individuals when compared to snorers with apnoea (Mateika & Mitru 2001). This finding indicates that a generally applicable sleep fragmentation disease burden measure must still take into account a subject’s AHI or similar measure of apnoeic disease severity but also that the relationship between AHI and outcomes will not be a simple linear one.

Psychological Factors

According to Eysenck's theory of Introversion-Extroversion (I-E), introverts demonstrate higher levels of basal activity within the reticular-thalamic-cortical loop with a higher measured tonic cortical awake arousal level than extraverts with higher extraversion status being associated with greater declines in speed of responding and more frequent attentional lapses following sleep loss (Killgore *et al*., 2007). These findings suggest that individual differences in the trait of extraversion/intreversion confer some vulnerability or resilience (respectively) to the adverse effects of sleep loss on attention and vigilance (KIllgore *et al*., 2007).

A generally applicable SFI will incorporate many of these factors. A novel combination of several existing indices is required to accurately describe the complexity of the fragmentation event and its effect.

8.4.2. NOVEL MEASURES

Swihart (2008) found that log-linear and multistate analysis of the sleep hypnogram identifies differences in sleep structure that are not evident with conventional sleep-stage scoring-based measures. Novel approaches, incorporating different measurement techniques and eqipment as well as novel or more advanced mathmatical modelling are obviously required to overcome existing diagnostic limitations. Some examples of novel approaches are outlined below.

Sleep Spindles

Incorporation of sleep associated EEG derived measures such as spindles may improve trait assessment of subjects. For instance, Gibbs and Gibbs (1962) found that extreme spindles in children (that is, sleep spindles that are of higher amplitude and frequency than in normal subjects) correlated with “mental retardation”.

Disease Burden and Resiliency

The magnitude and reversibility of cognitive and other quality-of-life deficits associated with UAO in children should be of the upmost importance to clinicians and researchers. Impairment effect sizes (ESs) from studies of cognitive performance in adults with UAO suggests that deficits broadly worsen with disease severity, with large average deficit values for attentional and executive cognitive scores, and moderate values for memory-related performance scores (Engleman *et al*., 2000). The reversibility of cognitive deficits has also been investigated with measures of cognitive enhancements following CPAP showing only small improvements (Engleman *et al*., 2000).

Esophageal Pressure Monitoring

Esophageal pressure monitoring (PeS) measures the internal pressure in the esophagus and is considered the 'gold standard' for measuring events of increased respiratory effort but due to expense and patient comfort considerations it is rarely used in the paediatric clinical setting. Increased respiratory effort is one of the main arousal triggers in UAO. Esophageal pressure monitoring is performed during polysomnography using a thin, water-filled catheter inserted in the esophagus, connected to an external pressure transducer or more recently, a solid state transducer. The application of PeS can be uncomfortable and often distressing for children and their parents. PeS has also been shown to cause significant sleep disruption in adults which obviously limits its potential use as a measure of SF (Chervin & Aldrich 1997). However, more recent studies by the same author found that the use of PeS in children during PSG was associated with sleep disturbance of such a minor nature that the potential clinical significance was dubious (Chervin *et al*., 2012). The study did find decrements in total recording time, total sleep time, sleep efficiency, percent N2, and percent REM sleep, and with increases in latency to REM sleep, latency to persistent sleep, and percent N3 sleep but were all considered by the author to be largely clinically irrelevant. There are less disruptive substitutes which are far easier to incorporate into a normal sleep study setting such as the suprasternal notch movement monitor and the standard sub-mental EMG. One study found that esophageal pressure changes were associated with characteristic EEG spectral power changes that may indicate small scale sleep fragmentation but this approach needs further investigation (Black *et al*., 2000).

8.4.3. AUTOMATION

Finally, the Holy Grail of sleep fragmentation research, and the focus of this thesis, is the development of an index that can be automatically produced and incorporated into standard sleep

analysis software as a simply interpretable clinical tool (Brown et al., 2002). We require a simple, automatically generated number that indicates how much sleep fragmentation has occured and what effect it is likely to have, on its own and in conjunction with the other identified interacting factors. As the understanding of sleep fragmentation increases, there will potentially be an increased number of variables of an increased complexity incorporated into an SFI, leading to increased work and expense associated with sleep analysis. Depending on how labor intensive or difficult the measures are to calculate, such a sleep measure may be practically unfeasible. The obvious solution to save time and money would be to automate the process and save on the most expensive component of human sleep analysis: labor.

8.4.4. CONCLUSION

The data presented in this thesis indicates that sleep fragmentation associated with UAO in children plays a large role in the cognitive and behavioural deficits observed with this disease. The results have also shown that the impact of UAO is dependent on the interaction between various factors including; age, health factors (e.g. BMI) exposure time, disease severity (e.g. AHI), social factors (e.g. SES) and history. This suggests that any approach to dealing with UAO in children must be multi-factorial.

Currently the severity of disease (AHI) is the strongest, single determining factor on whether a child receives treatment for their UAO. This excludes many children in the mild spectrum that may benefit from treatment. A sleep fragmentation index or composite measure, such as those suggested in this thesis, may be a better indicator of disease impact and thus the qualification of treatment. These findings provide a direction for the future development of diagnostic tests and interventions for the treatment of UAO in children.

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Appendices

APPENDIX I

Spindle Counting Rules

Inclusion Criteria For Candidate Spindles

Spindles will be defined as…

(a) a waveform of frequency 12-14Hz

(b) a waveform of at least 0.5 seconds in length

(c) a waveform of approximately equivalent amplitude and consistent frequency

(d) a waveform that has an approximately sinusoidal envelope

(e) waves of a narrow, conical shape.

(f) a waveform (with above-mentioned characteristics) occurring in stage 2

Exclusion Criteria For Candidate Spindles

Candidate spindles will be rejected if…

(g) they occur in the first occurrence of stage 2.

(h) the waveform is too broad and/or too flat (see examples)

(i) the waveform could otherwise be defined as vertex waves

(j) the waveform could otherwise be defined as Saw-tooth waves

(k) the waveform if of highly variable amplitude or frequency (see examples)

(l) the waveform is composed partly of a K-complex

(m) the waveform baseline is too variable (see examples)

Staging Rules

(a) Small stage disturbances of 8 epochs (90 seconds) or less are to be ignored and a stage 2 occurrence deemed to continue. The small disturbance epochs are removed from any epoch count.

(b) Stage disturbances of > 8 epochs are recognized and a new stage2 occurrence will be deemed to have started after each such disturbance

Scoring Rules

(a) "Broken Spindles" are counted as a single spindle if the interval between components is 1 second or less (see example)

Protocol

1. Generate "READ-ONLY" version of file for scoring
2. Set upper frame of Profusion2 scoring software to 30 seconds per page
3. Change both EEG channels to size "2" in the "polygraph properties" dialog box
4. Choose either central EEG (not Occipital) and use it for the whole study. EEG 1 should be chosen unless the signal-quality is very poor (as determined by a brief visual inspection)
5. Within "trace properties" dialog box (a) Set High Pass to 0.7 Hz, (b) Set Low Pass to 25 Hz and (c) Set Notch Filter to 50Hz
6. Increase the gain of the chosen EEG to 250uV
7. Record first occurrence of stage 2 as "discarded" on data sheet

8. Go to next occurrence of stage 2 and record start and end epochs according to the staging rules
9. Identify likely spindle candidates visually
10. Using the “zoom” feature, open a 2-second window over the spindle candidate
11. Within zoomed window, count the peaks as a frequency check (reject candidate spindles of <6 or >7 peaks per half-second) and apply other exclusion and inclusion criteria
12. For each confirmed spindle record “1” in the tally box of the data sheet for that stage occurrence
13. Go to instruction (8) until the end of the study.

APPENDIX II

Quality of Life Survey

OSA18-18 Survey on Quality of Life
Sleep Respiratory Disorder Assessment

Instructions. For each of the questions below, please circle the number that best describes the frequency with which each symptom or problem has occurred within the past four weeks (or since the last survey, if more recently).

	None	Almost None	Few times	Some times	Many times	Most of the time	Every times
Sleep disorders							
For the past 4 weeks, how often has your child...	1	2	3	4	5	6	7
... snored loudly?							
... held his or her breath or stopped breathing at night?	1	2	3	4	5	6	7
... choked or had difficulty breathing during sleep?	1	2	3	4	5	6	7
... had agitated sleep or woken up frequently from sleep?	1	2	3	4	5	6	7
Physical distress							
For the past 4 weeks, how often has your child...							
... mouth-breathed due to nasal obstruction?	1	2	3	4	5	6	7
... had colds or upper airway infections?	1	2	3	4	5	6	7
... had nasal secretion or runny nose?	1	2	3	4	5	6	7
... had difficulty feeding?	1	2	3	4	5	6	7
Emotional distress							
For the past 4 weeks, how often has your child...							
... had mood swings or anger episodes?	1	2	3	4	5	6	7
... behaved aggressively or hyperactively?	1	2	3	4	5	6	7
... had discipline problems?	1	2	3	4	5	6	7
Diurnal problems							
For the past 4 weeks, how often has your child...							
... been sleepy or napped excessively during the day?	1	2	3	4	5	6	7
... had difficulty focusing or paying attention?	1	2	3	4	5	6	7
... had difficulty getting up in the morning?	1	2	3	4	5	6	7
Caretaker preoccupation							
For the past 4 weeks, how often did the troubles above...							
... leave you worried about your child's overall health?	1	2	3	4	5	6	7
... lead you to believe your child was not breathing well enough?	1	2	3	4	5	6	7
... interfere with you ability to perform your daily duties?	1	2	3	4	5	6	7
... make you feel frustrated?	1	2	3	4	5	6	7

Figure 1

Above all, how would you rate your child's quality of life given the troubles mentioned above?
(Circle a number)

0	1	2	3	4	5	6	7	8	9	10
Worst quality of life possible				Average, between worst and best					Best quality of life possible	