Polysomnographic signal processing for advanced diagnostics of paediatric sleep disordered breathing

by

Sarah Anita Immanuel

B. Eng. (Electrical and Electronics Engineering),
Bharathiar University, India 1998
M. Eng. (Applied Electronics),
Bharathiar University, India 2000

Thesis submitted for the degree of

Doctor of Philosophy

in

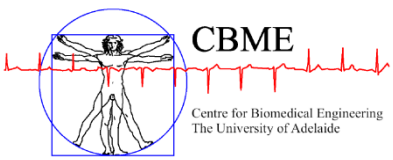
Electrical and Electronic Engineering,
Faculty of Engineering, Computer and Mathematical Sciences
The University of Adelaide, Australia

December 2014

Supervisors:

Assoc Prof Mathias Baumert, School of Electrical & Electronic Engineering

Assoc Prof David Saint, School of Medical Sciences



Contents

This page intentionally left blank

Abstract

Sleep disordered breathing (SDB) is a highly prevalent but an under-diagnosed disease especially in children. Childhood SDB is characterised by an increased work of breathing, restless night sleep and excessive daytime sleepiness and has been associated with neurocognitive impairment, behavioural disturbances and early cardiovascular changes that may predispose them to an increased risk of developing cardiovascular diseases. Thus there is an increasing need for the investigation and management of childhood SDB, so as to instigate early and appropriate treatment. Polysomnography (PSG) is the reference test for diagnosis of SDB and to measure the effectiveness of treatment. During PSG, a number of physiological signals including electrocardiogram (ECG), electroencephalogram (EEG), electromyogram (EMG) and respiration are recorded during an overnight sleep and then manually scored for sleep/wake stages, cardio-respiratory events, arousals, periodic limb movement etc. Indices commonly used to assess SDB severity are the obstructive apnea/hypopnea index (OAHI) and the respiratory disturbance index (RDI) and these reflect the average number of obstructive events and/or arousals per hour of sleep.

Signal processing approaches have been developed to perform automated detection and quantification of cardio-respiratory events based on analysis of EEG, respiratory, ECG, oximetry and airflow signals acquired during overnight PSG. These methods automate the application of standard scoring criterion on corresponding signals and thus aim to overcome the limitations of manual PSG scoring. However, the diagnostic criterion in current clinical guidelines may under-estimate the severity of SDB when children exhibit partial obstructive hypoventilation-a pattern of SDB commonly seen in children, where even in the absence of frank apnea or arousal, there might be underlying manifestations indicating SDB pathology. Thus it is important to investigate sleep periods free of frank events, i.e. scored event free (SEF) periods in children suspected for SDB and compare them to healthy controls. This would shed light on altered physiological measures, if any, in children with SDB that are subtle yet persistent and prolonged. With this as a focus of this Thesis, signal processing methods

were developed and applied on respiratory, EEG and ECG signals to investigate SEF periods of sleep in children. In the studies conducted thoracoabdominal asynchrony (TAA), respiratory timing and their variability, respiratory waveform regularity, respiratory cycle related EEG changes (RCREC) and heartbeat related evoked potentials (HEP) were the measures quantified and investigated within specific sleep stages in both study groups. To analyse the impact of SDB on breathing mechanics, respiratory timing and their variability were quantified. Inspiratory and expiratory timing were found to be significantly elevated in children with SDB. Secondly, to quantify the impact of SDB on the breathing movements, TAA was estimated using a novel Hilbert transform based approach and respiratory waveform regularity was measured using a wavelet based low-frequency estimation approach. Breathing waveform regularity and TAA were influenced by sleep stages. The level of asynchrony was found to be significantly elevated in children with SDB and also breaths immediately before apnea/hypopneas were associated with a high degree of variability in both TAA and respiratory timing. Further, to investigate the impact of SDB on breathing phase dependent EEG responses that might be indicative of subtle cortical arousals, RCREC were quantified using normalised EEG power changes and symbolic dynamics based EEG fluctuations. In children with SDB, the earlier approach revealed higher overall and frequency band specific RCREC during REM and the later showed altered respiratory phase-related reduction in EEG variability during the expiratory phase. Finally, to elucidate the impact of SDB on visceral cortical processing of intrinsic stimuli, HEP were quantified and analysed. Importantly, this study provides the first evidence for the existence of HEP during sleep in children. Sleep stage specific HEP were observed and the potentials were found to be attenuated in children with SDB compared to healthy controls. Importantly, associations between HEP and daytime behavioural scores were observed. Thus, this Thesis provides a summary of studies based on signal processing of pediatric sleep data that led to significant findings emphasising the impact of childhood SDB on cortical and respiratory measures and the effect of surgical intervention on normalising the parameters.

Thesis Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, 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. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree. 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. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time. The author(s) acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

Sarah Immanuel……..... Date……

Acknowledgements

I express my gratitude and heartfelt thanks to my supervisor Assoc Prof Mathias Baumert for his guidance, encouragement and continued support throughout my candidature. His insight and ideas were a great resource that helped me move forward throughout my candidature. Working with him has broadened my knowledge in biomedical signal processing, built my confidence as a researcher and has made my PhD journey a pleasant and interesting one. I thank my co-supervisor Assoc Prof David Saint for his support and guidance in every stage of my candidature. The encouraging attitude of my supervisors and the confidence they had in me was a huge inspiration all along. I thank my co-investigators Dr Yvonne Pamula, Dr Declan Kennedy, Dr James Martin (Women's and Children's Hospital, Adelaide) and Dr Mark Kohler (University of South Australia, Adelaide) for providing me with the data, helping me with interpretation of results and strengthening the findings with their vast knowledge in paediatric sleep research. Working with them and co-authoring articles provided an unique learning experience. I would like to thank A/Prof Eugene Nalivaiko (School of Biomedical Sciences and Pharmacy, University of Newcastle) for his valuable inputs and suggestions. I thank the Head of School Assoc Prof Cheng Chew Lim, Dr Said Al-Sarawi and Dr Brian Ng for their support. A special thanks to all my friends and colleagues from the School of Electrical & Electronic Engineering: Dr Muammar Muhammad Kabir (currently at Oregon Health and Science University, Portland) Dr Muhammad Asraful Hasan, Dr Ali Karami, Mrs Zhara Shaterian, Mrs Fatima ElHamad, Mr Sam Darvishi, Dr Syed Mostafa Rahimi Azghadi and Mr Mostafa Numan for their collegiality and encouragement throughout my candidature. I am grateful to Ms Rose-Marie Descalzi, Ms Ivana Rebellato, Ms Jodie Schluter, Ms Deborach Koch, Mr Greg Pullman and Mr Stephen Guest at School of Electrical & Electronic Engineering for their assistance in administrative work during my candidature. I would also like to thank Mr David Bowler and other IT support and technical officers for their timely technical support. I gratefully acknowledge the School of Electrical & Electronic Engineering at the University of Adelaide and the Walter and Dorothy Duncan Trust Fund for their financial support and travel grants. I would also like to thank Australian

Research Council for its support in the research studies presented in this Thesis (grant # DP 110102049). I would like to take the opportunity to extend my deepest gratitude to all my family members, friends and colleagues who were always there with a helping hand in time of need. I am greatly indebted to my husband and my loving children for their understanding, support, patience and co-operation without which my dream to do a PhD would not have come true. My special thanks to my parents for their prayers, encouragement and motivation. Above all, I thank the ALMIGHTY for his abundant grace and blessings that fills me with an inner strength and takes me forward in every step of my life.

Thesis convention

The following conventions have been adopted in this Thesis:

1. **Spelling.** Australian English spelling conventions have been used, as defined in the Macquarie English Dictionary, A. Delbridge (Ed.), Macquarie Library, North Ryde, NSW, Australia, 2001.

2.Typesetting. This document was compiled using Microsoft Word 2010.

3.Mathematics. MATLAB code was written using MATLAB Version R2010b; URL: http://www.mathworks.com.

4. Referencing. The Harvard style has been adopted for referencing.

Publications arising from this Thesis

Journal Articles

IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., KABIR, M. M., SAINT, D. A. & BAUMERT, M. 2012. Respiratory timing and variability during sleep in children with sleep-disordered breathing. *Journal of Applied Physiology,* 113**,** 1635-1642.

IMMANUEL, S. A., KOHLER, M., MARTIN, J., KENNEDY, D., PAMULA, Y., KABIR, M. M., SAINT, D. A. & BAUMERT, M. 2014. Increased thoracoabdominal asynchrony during breathing periods free of discretely scored obstructive events in children with upper airway obstruction. *Sleep and Breathing***,** DOI 10.1007/s11325-014-0963-3.

IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., SAINT, D. A. & BAUMERT, M. 2014. Respiratory Cycle-Related Electroencephalographic Changes during Sleep in Healthy Children and in Children with Sleep Disordered Breathing. *Sleep,* 37**,** 1353-1361.

IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., NALIVAIKO, E., SAINT, D. A. & BAUMERT, M. 2014. Heartbeat evoked potentials during sleep and daytime behavior in children with sleep disordered breathing. *American Journal of Respiratory and Critical Care Medicine*, 190, 1149-1157.

Conference Articles

IMMANUEL, S. A., KOHLER, M., PAMULA, Y., KABIR, M. M., SAINT, D. A. & BAUMERT, M. 2012. Thoraco-abdominal asynchrony in children during quiet sleep using Hilbert transform, *Proceedings of the 34th IEEE Engineering in Medicine and Biology Society*, San Diego, USA, pp. 3448-3451.

IMMANUEL, S. A., PAMULA, Y., KOHLER, M., KABIR, M. M., SAINT D. A. & BAUMERT, M. 2013. Characterizing Respiratory Waveform Regularity and Associated Thoraco-

abdominal Asynchrony during Sleep using Respiratory Inductive Plethysmography, *Eighth International Conference on Intelligent Sensors, Sensor Networks and Information Processing*, Melbourne, Australia, pp. 329-332.

IMMANUEL, S. A., KOHLER, M., PAMULA, Y., KABIR, M. M., SAINT D. A. & BAUMERT, M. 2013. Increased variability in respiratory parameters heralds obstructive events in children with sleep disordered breathing, *Proceedings of the 35th IEEE Engineering in Medicine and Biology Society*, Osaka, Japan, pp. 2024-2027.

IMMANUEL, S. A., KOHLER, M., KABIR, M. M., SAINT D. A. & BAUMERT, M. 2014. Symbolic dynamics of respiratory cycle related sleep EEG in children with sleep disordered breathing, *Proceedings of the 36th IEEE Engineering in Medicine and Biology Society,* Chicago, USA, pp. 6016-6019.

KABIR, M. M., **IMMANUEL, S. A**., TAFRESHI, R., SAINT D. A. & BAUMERT, M. 2014. Effect of resistive inspiratory and expiratory loading on cardio-respiratory interaction in healthy subjects, *Proceedings of the 36th IEEE Engineering in Medicine and Biology Society,* Chicago, USA, pp. 710-713.

Chapter 1

Introduction

Respiratory disorders during sleep are of importance during childhood. Scientific evaluation of sleep to understand its effect on cardio-pulmonary functioning is made possible through polysomnographic (PSG) studies. Standard diagnostic criteria applied on PSG-derived physiological signals to assess the quality of sleep may underestimate the severity of SDB in children. Hence signal processing and analysis of PSG signals within event free sleep periods that are free of frank obstructions is important in understanding the pathophysiology of paediatric SDB. With this as the objective, several research questions were formulated and addressed. This chapter presents an Introduction and background towards the studies presented in this Thesis.

1.1 Introduction

Control of breathing involves a complex network of neurons in the brainstem responding to stimuli from chemoreceptors, mechanoreceptors, and higher cortical inputs. Changes in breathing during sleep are a reflection of changes in metabolic demand, direct postural effects on breathing mechanics, as well as the state of the brain. Sleep significantly modifies breathing behavior, particularly with respect to central respiratory control, respiratory muscle activity, and respiratory mechanics (Krimsky and Leiter, 2005, McNicholas, 1997). In addition to respiratory parameters like respiratory rate, tidal volume, respiratory asynchrony, functional residual capacity, minute ventilation etc., several other physiological and neurological features such as upper airway resistance, heart rate, blood pressure, muscle tone, metabolic rate, level of consciousness, sensory activity, cortical processing of stimuli are also influenced by different stages of sleep (Henke et al., 1991, Douglas et al., 1982, Coenen, 2012). Sleep proceeds in cycles of two major states, the non-rapid eye movement (NREM) and REM sleep and NREM includes stages 1, 2 and slow wave sleep (SWS), which is stages 3 and 4 together. The alternation between non-REM and REM sleep is the outcome of a balanced action based on the cyclic function of brainstem structures. The modulating effects of sleep on breathing differ markedly between these two major sleep states (Phillipson and Bowes, 1986).

In addition to the normal physiological changes during sleep, sleep disordered breathing (SDB), a pathological condition characterised by complete or partial cessation of breathing due to upper airway obstruction (UAO), causes abnormal ventilatory, cardio-vascular and cortical responses. Obvious symptoms include varied degrees of snoring, restless sleep and daytime sleepiness (Dempsey et al., 2010). Repeated occurrence of partial UAO, termed obstructive sleep apnea syndrome (OSAS) is a common manifestation of SDB and is estimated to occur in 1-4% of children (Lumeng 2008). OSAS in children is associated with adverse cardiovascular, neurocognitive and behavioural consequences (Blunden et al., 2001, Kohler et al., 2010). The pathogenesis of OSAS in children is multifactorial and is very different from adults, especially the sleep structure, respiratory patterns, duration/termination of

obstructions and the daytime symptoms (Marcus, 2001). Hence data from studies on adults with SDB cannot be extrapolated to make inferences in children with SDB (Scholle and Zwacka, 2001).

Several signal processing approaches have been reported in literature, investigating the physiological changes, together with the pathology of sleep disturbances in adults, but comparatively little is reported in children. Processing of physiological signals and deriving sleep stage specific indices and markers based on cardio-respiratory and cortical changes are essential to gain insight into childhood SDB. The following sections provide an overview of the field of knowledge within the foci of this Thesis - obtain diagnostic markers by investigating respiratory timing and its variability, thoracoabdominal asynchrony (TAA), respiratory cycle related electroencephalographic changes (RCREC) and heartbeat evoked electroencephalographic (EEG) potentials in children with SDB.

1.1.1 Contextual statement

Sleep is a naturally recurring state of rest for the mind and body that alters consciousness and inhibits sensory activity. Both rapid eye movement (REM) sleep and non-REM sleep influence autonomic nervous system functions such as body temperature, breathing rate, heart dynamics, EEG rhythms and blood pressure (McCarley, 2007). Compared to non-REM sleep, REM sleep is shown to be associated with reduced intercostal and upper airway muscle tone, variable tidal volume, erratic breathing and decreased ventilatory drive (Hudgel et al., 1984, Douglas et al., 1982). Hence, in this Thesis, a **sleep stage based analysis** of the nocturnal physiological signals was employed and it is highly beneficial in having a better understanding of the underlying phenomenon.

Studies have investigated respiratory mechanics and brain activation associated with sleep related respiratory loads by quantifying changes in EEG spectra, blood oxygen levels and airflow signals before, during and after obstructive apneas/hypopneas, but such approaches still remain linked to visually identified and scored respiratory events on the polysomnograms (PSG). (Rees et al., 1995, Bandla and Gozal, 2000, Richard et

al.,1980). However, children with SDB present a pattern of partial obstructive hypoventilation in the absence of significant oxygen desaturation or arousals and apneas are not always terminated with cortical arousal as they have elevated arousal thresholds (Rosen et al., 1992, Rosen, 1999, Dempsey et al., 2010). Thus it is very important to investigate sleep periods free of frank respiratory events, i.e. scored event free (SEF) periods of sleep in children suspected for SDB and compare them to healthy controls. Thus, the studies reported in this Thesis were focussed on evaluating of respiratory and neural function in children with SDB during **sleep periods that do not contain discrete respiratory events that qualified to be scored according to PSG scoring criteria**.

Sleep-induced partial obstruction of the upper airway, often exaggerated due to adenotonsillar hypertrophy, is the most common form of SDB and is treated with adenotonsillectomy (Bhattacharjee et al., 2010, Marcus et al., 2013). With studies showing impact of SDB on cardio-respiratory outcomes, cognition and behavior in children, the studies presented in this Thesis were conducted on **PSG data both at baseline and after adenotonsillectomy** to understand if the surgical procedure that relieved upper airway obstruction and normalised the PSG findings had similar effects on the parameters that were investigated in the study group.

Thus, the rationale behind the studies formulated and presented in the Thesis was to develop an understanding of how SDB impacts cardio-respiratory parameters and brain information processing in children, especially during periods of sleep during which scorable obvious or frank manifestations of airway obstruction are absent. This way, the subtle yet persistent impact of upper airway obstruction on respiratory mechanics and respiration related cognitive potentials may be identified. With substantial evidence for cognitive and behavioral deficits in children with SDB being available (Amin et al., 2002, Bourke et al., 2011, Kohler et al., 2010, Marcus et al., 1998), investigating these respiratory and cardiac related brain potentials during sleep is significant in the pathophysiology of SDB. Importantly, by comparing sleep data between baseline study and the follow-up, it could be tested if surgical intervention in these children normalises the impact of SDB. This would suggest beneficial effects of

treatment. With this background, several key research questions were formulated as summarised below.

1.1.2 Key questions addressed

• Does upper airway obstruction affect the mean respiratory rate, respiratory variability and thoracoabdominal asynchrony in children with sleep disordered breathing?

• Can thoraco-abdominal asynchrony be quantified by a robust waveform independent method? Is there a sleep stage effect on TAA?

• Are sleep stage specific TAA altered in the children with SDB during SEF sleep? Can TAA be used as a marker for determining the severity of airway obstruction? Does adenotonsillectomy normalise TAA levels in children with SDB?

• Are there quantifiable frequency band specific respiratory cycle related EEG changes in children and are they higher in an SDB group? Does adenotonsillectomy normalise this phenomenon? Does sleep stage influence RCREC?

• Can cortical processing of intrinsic stimuli during sleep be quantified in children using heartbeat evoked potentials? Are the cortical heartbeat-evoked potential measures associated with daytime behavioural measures in children?

• Is there a sleep stage effect on the quantified potentials and are they different between the study groups? If so, does surgical intervention normalise the differences in heartbeat evoked potentials between the groups?

1.1.3 Data

The data and findings reported in this Thesis are based on retrospective analyses of a larger study that was approved by the Women's and Children's Health Network Human Research Ethics Committee, South Australia, with parental consent and child assent obtained from all participants. Fifty-three healthy children and fifty-four children with SDB were enrolled. Among the healthy children (controls), none were

reported to snore regularly or were taking medication that would affect sleep architecture or cardiovascular physiology. The children with SDB were those who had a history of frequent snoring and were scheduled for adenotonsillectomy for suspected SDB, as diagnosed by an experienced paediatric otorhinolaryngologist at the Adelaide Women's and Children's Hospital. Children were excluded if they had undergone previous ear, nose, throat or craniofacial surgery; had a medical condition (other than SDB) associated with hypoxia or sleep fragmentation; or were taking medication known to affect sleep or cardiorespiratory physiology. Both groups underwent overnight PSG to evaluate sleep and breathing parameters. Children with SDB had two PSGs; one before and one after surgical intervention (adenotonsillectomy) while control children had two PSGs at the same time points. The PSG data for 13 of the 53 control children and 4 of the 54 children with SDB were excluded due to poor signal quality. Of the remaining 50 children with SDB, a further 10 were excluded due to significantly greater age and lower socioeconomic status compared to control children.

1.2 Respiration

Respiration coordinates gas exchange between the human body and the atmosphere and is associated with repeated involuntary inspiratory and expiratory phases, involving the thoracic cavity, intercostal muscles and the diaphragm.

1.2.1 Respiratory timing and variability

Age, gender, and body mass index (BMI) influence respiratory patterns. Compared to wakefulness, respiratory control and muscle activity are different during sleep. The control of diaphragm, genioglossus and the intercostal muscles are distinct between REM and non-REM sleep (Grace et al., 2013). Increase in upper-airway resistance, reduction in functional residual capacity, fall in inspiratory drive and tonic inhibition of skeletal muscles is associated with sleep stages and is exaggerated during REM sleep (Fraigne and Orem, 2011). Ventilatory changes during sleep have also been investigated in adolescents, where minute ventilation, inspiratory timing, and

respiratory frequency (fR) were shown to differ significantly between NREM and REM sleep (Tabachnik et al., 1981). Comparatively, little is known about ventilation during sleep in younger children. Sleep-stage effects on breathing rate and its regularity in healthy children and the effect of sleep on interbreath variability in children undergoing PSG for suspected OSA have been demonstrated (Elder et al., 2012). In children with SDB, abnormal ventilatory responses caused by repeated partial or complete closure of the upper airway may alter both respiratory timing and respiratory variability, the assessment of which would provide an indirect indication towards adenotonsillar hypertrophy and respiratory phase specific resistive loading, flow limitation and airway closure (Schneider et al., 2009). Also, the effect of adenotonsillectomy on the timing parameters would give an indication if surgery normalises breathing parameters.

Interpretation of various timing and volume components of the natural breathing signal during sleep is feasible with an external device such as the respiratory inductive plethysmograph (RIP) (Fiamma et al., 2007). Polysomnographic sleep studies include two RIP channels extracting the ribcage (RC) and the abdominal (ABD) breathing movements. The first study presented in Chapter 2 therefore analysed the mean and variability of a range of breathing parameters derived from RIP such as inspiratory time (Ti), expiratory time (Te), inspiratory duty cycle (Ti/(Ti+Te)) and respiratory frequency (fR) in children with SDB and in healthy controls during periods of sleep free of apnoea and hypopneas. We hypothesized that (1) breathing patterns in children with SDB would differ from normal controls even during apneic-free periods of breathing; (2) ventilatory parameters would be influenced by sleep stage, and (3) in children with SDB, surgical treatment by adenotonsillectomy would normalize breathing patterns. Thus, the specific aims of this study were to (a) compare respiratory timing and variability between children with SDB and healthy controls, (b) investigate the effects of sleep stage on these respiratory parameters, and (c) evaluate the effect of surgical treatment (adenotonsillectomy) for SDB on the parameters.

1.2.2 Thoracoabdominal asynchrony

During normal breathing, a small and stable phase difference between ribcage (RC) and abdominal (ABD) movement can be observed resulting in a slight asynchrony between the two breathing movements. This thoracoabdominal asynchrony (TAA) is distinctly different between wakefulness and sleep and is influenced by a range of factors including chest wall dynamics, airway resistance, and respiratory muscle activity (Hudgel et al., 1984). Children with OSAS have been shown to have a narrower and more collapsible airway with increased upper airway resistance (Loughlin et al., 1994, Arens and Marcus, 2004) and the greater respiratory effort required to overcome this resistance can be indirectly quantified by measuring the temporal coordination of thoracic and abdominal movements. Sivan et al. reported an association between phase differences of thoraco-abdominal movements and the severity of SDB in children with augmented TAA during episodes of acute upper airway obstruction (UAO) (Sivan et al., 1990, Sivan et al., 1991). In these studies that evaluated respiratory asynchrony, TAA assessment was based on the width of the Lissajous figure obtained by plotting the movement of the ribcage against the movement of the abdomen, also called Konno Mead plots. A significant shortcoming of this method is that it presumes strictly sinusoidal waveforms and given our current understanding of the non-sinusoidal nature of respiratory waveforms, is prone to errors in the determination of the loop width. To demonstrate this, an example plot of RC and ABD signal of an individual breath and the corresponding Konno Mead plot are shown in Figure 1.

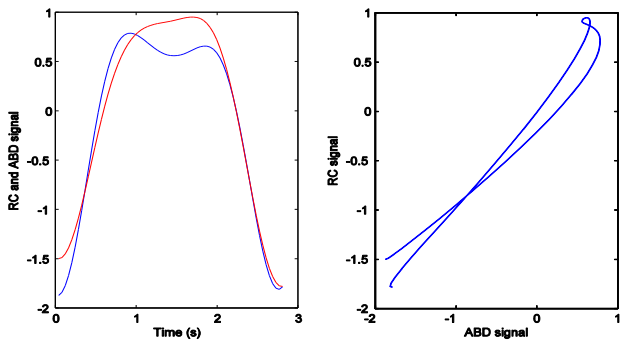
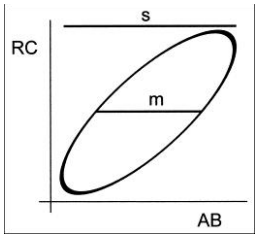


Figure 1. Example plot of ribcage and abdominal respiratory signals (left) and their corresponding Konno-Mead plots (right) obtained from real data

Theoretically, calculation of phase angle based on the Konno Mead loops (plot of RC signal vs. ABD) involves precise measurement of the loop widths as shown below:



where phase angle Φ = sin-1 (m/s)

However, as can be seen from the real data, the respiratory waveforms are non-sinusoidal and their Konno Mead loops assumes different shapes, which makes automated calculation of loop widths 'm' and 's' very difficult and highly error prone. Evaluating respiratory cycles based on these loops would turn out to be unreliable. We therefore developed a robust, waveform independent TAA estimation method that is based on computing instantaneous phases of RC and ABD signals, using the Hilbert transform approach. This method was employed to quantify TAA derived from paediatric polysomnography (PSG) where an elevated asynchrony is considered an indicator of obstructive sleep apnea (OSA).

Hilbert transform based TAA estimation

The Hilbert transform gives the instantaneous amplitude and phase of a signal $x(t)$ via construction of an analytical signal $\zeta(t)$ which is a complex function of time (Gabor, 1946) defined as

$$\zeta(t) = x(t) + j\tilde{x}(t) = Ae^{j\phi(t)}, \quad (1)$$

where $\tilde{x}(t)$ is the Hilbert transform of $x(t)$. The instantaneous amplitude and phase are given by

$$A(t) = \sqrt{\left(x^2(t) + \tilde{x}^2(t)\right)} \quad (2)$$

$$\phi(t) = \arctan \frac{\tilde{x}(t)}{x(t)} \quad (3)$$

Given two signals $x_1(t)$ and $x_2(t)$, the relative phase between the two signals can be obtained (Rosenblum and Kurths, 1998) via their Hilbert transforms $\tilde{x}_1(t)$ and $\tilde{x}_2(t)$ as

$$\phi_1(t) - \phi_2(t) = \arctan \left[\frac{x_1(t)\tilde{x}_2(t) - x_2(t)\tilde{x}_1(t)}{x_1(t)x_2(t) + \tilde{x}_1(t)\tilde{x}_2(t)} \right] \quad (4)$$

Although TAA was proposed as a tool to assess UAO it did not attain universal acceptance in PSG scoring rules (Iber et al., 2007), where the severity of UAO is assessed based on the frequency of obstructive events associated with either oxygen desaturation and/or cortical arousal. Studies during the last decade have shown that the correlation between PSG defined obstructive indices and morbidity outcomes of children with OSAS are weak (Marcus et al., 2012). Given the limitation of conventional TAA estimation methods we sought to employ the robust TAA estimation approach based on Hilbert transform to quantify chest and abdominal wall mechanics and derive a marker for the assessment of severity of airway obstruction in children.

An obstructed airway leads to increased respiratory effort, which may be manifested as asynchronous or paradoxical inward motion of the ribcage (Sackner et al., 1984, Hammer and Newth, 2009). The severity of OSA as indicated by the frequency of obstructive events (OAHI) might be reflected in the level of asynchrony (TAA) that persists even in apnea free sleep. In addition to the OAHI index, we also sought to evaluate the association between TAA and two other indicators of UAO related sleep disruption – the pulse wave transit time (PTT) and power spectral analysis of the sleep EEG (Katz et al., 2003, Yang et al., 2012).

The study presented in Chapter 3 was therefore aimed at evaluating the RC and ABD breathing movements during sleep using improved signal analysis methodology based on Hilbert transform in order to (a) compare TAA between periods of sleep, free of frank apnea/hypopnea and during discrete obstructive episodes in children with SDB, (b) compare TAA between healthy controls and children with SDB during SEF periods

of breathing in sleep and (c) evaluate the effect of surgical treatment (adenotonsillectomy) for UAO on TAA. We hypothesised that (1) TAA would be influenced by sleep stage (Appendix A1); (2) children with SDB would exhibit elevated level of TAA compared to healthy controls, and (3) in children with SDB, surgical treatment by adenotonsillectomy would normalize TAA. Application of TAA estimation method to test these hypotheses was the focus of the article in Chapter 3.

To evaluate cortical and sub-cortical indicators of sleep disruption throughout SEF periods, relative EEG power in theta, delta and alpha bands and pulse transit time (PTT) were also measured.

1.2.3 Respiratory waveform variability

Compared to wakefulness, respiratory muscle activity and respiratory control are different during sleep with each stage of sleep having a distinct set of physiological functions (Parmeggiani, 1982, Villa et al., 2000). Also, the control of diaphragm, genioglossus and the intercostal muscles are distinct between REM and non-REM sleep (Wiegand et al., 1991). Although RIP and other non-invasive techniques are routinely employed during PSG to monitor respiratory effort (Guilleminault et al., 2001, Masa et al., 2003), quantitative analysis of respiratory variability and ribcage/abdominal volume changes recorded by such techniques during normal breathing periods have not been rigorously performed and described, especially in children. Respiratory effort during sleep, influenced by the control of diaphragm, genioglossus and the intercostal muscles, vary with sleep stages (Tabachnik et al., 1981). Altered respiratory effort that affects the tidal volume is a polysomnographic observation and is associated with intra-thoracic pressure swings (Pitson et al., 1995). We were interested to quantify respiratory regularity as reflected on the amplitude levels of the RC movement signal that would provide an indirect measure of changes in respiratory effort. Amplitude modulations of the breathing signal at one or more frequencies much lower than the respiratory frequencies would provide an indication towards the regularity of breathing. Due to the non-stationary nature of such amplitude modulated breathing signals we choose a wavelet based approach over

conventional spectral analysis methods to obtain a more precise estimate of their low-frequency energy.

Low frequency energy estimation using continuous wavelet transforms

The application of the continuous wavelet transform to non-stationary signals allows a time-frequency representation of the components of the signal (Louis et al., 1997). Given a signal $x(t)$, its continuous wavelet transform $X(\tau, a)$ is defined for each dilation a and translation τ of the mother wavelet function $\psi(t)$ as

$$X(\tau, a) = \frac{1}{|a|}\int x(t)\psi^*\left(\frac{t-\tau}{a}\right)dt \,. \qquad (1)$$

The normalized total energy, $E\psi$, of the wavelet transform $X(t,j)$ is given by

$$E_\psi = \frac{\sum_{j=1}^{J}\sum_{t=1}^{N}|X(t,j)|^2}{\|x\|_2^2} \qquad (2)$$

and the normalized energy of the wavelet transform across low frequency scales j_1 to j_2 at each time, $E_{\psi,j}(t)$ is given by

$$E_{\psi,j}(t) = \frac{\sum_{j=j_1}^{j_2}|X(t,j)|^2}{\|x\|_2^2}, \qquad (3)$$

where $\|x\|_2^2$ is the L_2 norm of the signal. The low frequency energy (LFE) content is expressed as a percentage of the total energy of the wavelet transform, giving a quantitative measure of the respiratory waveform regularity as

$$\frac{E_{\psi,j}}{E_\psi} * 100\% \,. \qquad (4)$$

In the study presented in Appendix A2, we employed the above approach to investigate respiratory regularity in different stages of sleep using a Daubechies (db8) wavelet based LFE estimation and to see if they are temporally associated with the coordination between ribcage (RC) and abdominal (ABD) which was quantified using

the Hilbert transform based TAA estimation method (section 1.2.2). Also, in children with SDB, respiratory timing, respiratory variability and thoracoabdominal asynchrony associated with breaths before the onset of obstructive apnea/hypopneas were investigated and presented in Appendix A3.

1.3 Electroencephalography

The collective electrical activity of the cerebral cortex is usually referred to as the EEG rhythm because the measured signal often exhibits oscillatory, repetitive behaviour. The joint activity of millions of cortical neurons produces an electric field, which is sufficiently strong to be measured on the scalp.

1.3.1 EEG Rhythms

The diversity of EEG rhythms is enormous and depends among many other things on the mental state of the subject, level of attentiveness, wakefulness or depth of sleep. The rhythms are characterised by their frequency range and amplitude. EEG rhythms are conventionally classified based on a set of frequency bands. Large amplitude delta (0.5 to 4 Hz) activity is largely observed during sleep especially during SWS along with theta (4 to 7 Hz) and relatively smaller levels of alpha (8 to 12) Hz, sigma (12 to 15 Hz) and beta (15 to 30 Hz) activity. Generally high frequency low amplitude rhythms reflect an active brain associated with dream or REM sleep, while low frequency high amplitude rhythms reflect drowsiness or non-dreaming sleep states (Nir et al., 2013). Though the meaning of different brain rhythms and their correlates to behaviour and mental state are largely unexplained, the quantification of overall and frequency-band specific EEG rhythms have proved to be extremely useful in clinical research (Mezzanotte et al., 1996, Campbell et al., 2011).

1.3.2 Cortical Arousals

Compared to wakefulness, sleep is perceived as a state with reduced responsiveness to environmental stimuli. Although sleep is characterized by decreased conscious perception, the human brain is active during sleep and controls autonomic, metabolic and hormonal changes within the body and controls behavioural responses to external

stimuli (Vandekerckhove and Cluydts, 2010). These tasks are accomplished through a gradual partial activation of the brain that is confined to some cerebral areas (Ujszászi and Halász, 1988). Such activation is also stimulated by the arousal system. An arousal is an abrupt change in the pattern of brain wave activity that reflects an elevation of vigilance level due to arousal stimuli. Arousal during sleep represents a shift from deep to light non-REM sleep or from sleep to wakefulness.

Clinical scoring of arousals during NREM stages are based on indications on the EEG showing abrupt shift of frequencies including alpha, theta and/or frequencies greater than 16 Hz (but not spindles) that lasts at least 3s, with at least 10s of stable sleep preceding the change. Scoring of arousal during REM requires a concurrent increase in submental EMG lasting at least 1s (Iber et al., 2007). Unlike these clear-cut arousals, which have enough activating strength to change the level of vigilance on a macro-scale, there are a range of partial arousal responses with EEG manifestations different from classical arousals, termed microarousals (Martin et al., 1997). These microarousals, graded in different levels are associated with cardiac, respiratory or somatic modifications without an overt EEG response and hence remain undetected using classical visual analysis of EEG (Halász et al., 2004). Sub-cortical or autonomic arousals are subtle microarousals that are characterised by autonomic stimulation such as increase in heart rate or rise in blood pressure but without shifts in EEG frequencies (Marcus et al., 1998). In children with SDB, who exhibit partial obstruction and hence, hypoventilate for longer sleep periods, these microarousals could be a nocturnal response to upper airway resistance causing brief shifts in sleep stages. Such recurrent changes in cortical state result in restless sleep or sleep fragmentation. The frequency of microarousals during sleep has been shown to predict daytime sleepiness in children (Chervin et al., 2005). Quantification of microarousals could thus be clinically used to assess the level of sleep fragmentation. However, obtaining markers that reflect these low intensity brain activations are a challenge.

1.3.3 Respiratory cycle related EEG changes (RCREC)

Since the level of airway resistance, flow limitation and airway occlusions are linked to the phase of respiration, it could be hypothesised that the microarousals are too

subtle to be visually scored on the EEG could occur on a breath by breath basis and be influenced by the respiratory phase during sleep, especially in children with SDB, who as such have elevated arousal thresholds. To test this hypothesis, an analytical approach towards the quantification of respiratory cycle related EEG changes (RCREC) was developed by Chervin et al (Chervin et al., 2004). This approach is based on measuring subtle changes in cortical activity that occurs phase-locked with respiration. An example trace of respiratory cycles and corresponding raw EEG (early/late inspiration and expiration) are shown in Figure 2. By averaging the EEG power within the four segments over several respiratory cycles and computing the maximal change between them, respiratory cycle related changes in EEG power, i.e. REREC is quantified.

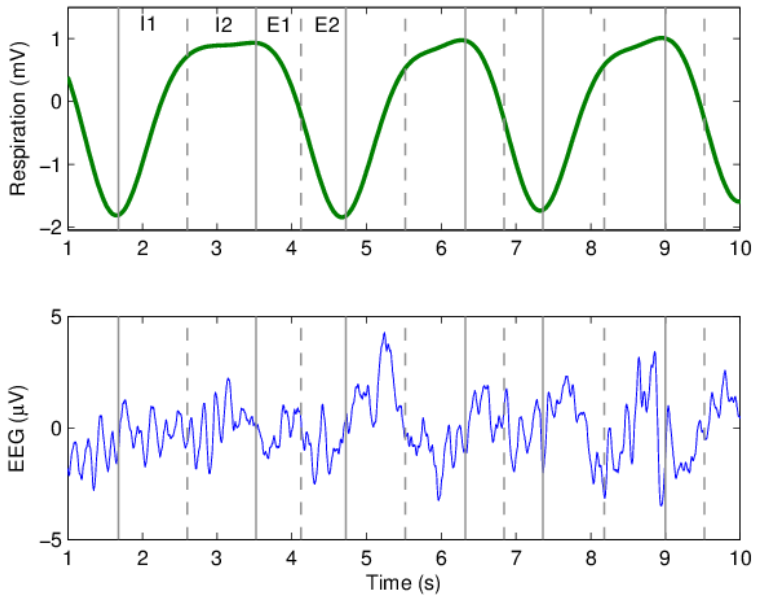


Figure 2. Example plot showing respiratory cycles over 10s (top panel) each segmented into early inspiration (I1), late inspiration (I2), early expiration (E1) and late expiration (E2) and the corresponding time aligned EEG signal (bottom panel).

In the study presented in Chapter 4, we sought to corroborate the findings of Chervin et al. in our sleep dataset of normal children and children with SDB. We investigated sleep periods free of scored apnea/hypopneas, arousals, or artifacts over the entire night duration to find (a) if frequency and sleep stage-specific RCREC existed in normal children and if they are reproducible (b) if the magnitude of RCREC in children with

SDB differ significantly from that of healthy children, and (c) if so, whether that difference diminished after the children with SDB underwent adenotonsillectomy.

Further, to expand on our findings on phase-locking between EEG fluctuations and respiratory cycle, we hypothesized that complexity analysis of respiratory cycle related EEG using non-linear methods may reveal further links between breathing and cortical activity. We adopted a novel approach for characterizing and recognizing temporal patterns of respiratory cycle related EEG changes based on symbolic dynamics (SD) that transforms a given time series into short frequency deterministic patterns, usually 3 words long, and evaluates their rate of occurrence, thus quantifying the variability in the time series (Porta et al., 2007). Electroencephalographic signals time-locked with respiratory cycles were extracted and transformed into a sequence of symbols [0, 1, 2, 3]. The transformation rule was based on the quartiles of their amplitude distribution (Cysarz et al., 2013). From the resulting sequence, symbols from within each of the six respiratory segments were extracted and patterns of length m = 3 were constructed. Each frequency deterministic pattern was grouped into one of 4 categories: 0V, 1V, 2LV and 2UV and the percentage of their occurrences were compared. The study on Appendix A4 presents the details of the methodology and the findings.

1.3.4 Heartbeat evoked potentials

Event-related potentials (ERP) represent sensory and cognitive cortical processing of stimuli and reflect the underlying state of the central nervous system. Event-related potentials consist of a series of negative- and positive-going components grouped as short or long latency potentials and are elicited with auditory, visual or somato-sensory stimuli. Components of ERP reflecting active attention responses to applied stimuli differ between wakefulness and sleep (Atienza et al., 2001, Webster and Colrain, 1998, Sallinen et al., 1996). It is found that wakefulness responses appear to be preserved in a rudimentary form during REM sleep and ERP responses during NREM differ from those during REM.

Event related brain potentials to sensory stimuli have been observed in healthy adults and children, where ERP studies during sleep have focused on cortical responses to

external, artificially induced stimuli. These stimuli may disrupt sleep homeostasis and hence do not explain visceral information processing during sleep. We therefore utilized the heartbeat as a source of visceroceptive ERP. Studies in adults have demonstrated that attention and cardiac awareness are reflected in the amplitude of heartbeat evoked potentials (HEP) and in conditions where interoceptive awareness is reduced, such as depression, the HEP amplitude is reduced. It has been postulated that HEP arises from the cyclical mechanical impact of the heart on the chest wall, resulting in neuronal signals via somato-sensory pathways and via visceral pathways to the frontal cortical areas (Kern et al., 2013). With the afferent cardiac pathway being primarily responsible for the perception of cardiac symptoms (Foreman, 1999) and studies demonstrating correlation between HEP and interoceptive awareness and perception, it has been argued that HEPs provide an indirect measure of afferent signals arriving at the cortex that are crucial for cardiac control (Leopold and Schandry, 2001).

There is substantial evidence for cognitive and behavioral deficits and an increased risk of developing cardiovascular morbidities in children with SDB and hence, an impaired cardiac perception may be important in the pathophysiology. We therefore measured HEP during sleep using our dataset of overnight PSG in both groups. An R-peak aligned ensemble averaging approach provided a temporal representation of the cortical activation pattern and enabled the distinction between the specific cardiac cycle relevant EEG response and the irrelevant background ongoing EEG activity unrelated to the heartbeat stimulus.

In the study presented in Chapter 5, we studied sleep periods free of scored apnea/hypopneas, arousals or artifacts during the entire night to extract cardiac cycle related EEG signals and test whether (a) HEP exist during sleep and if they differ between sleep stages and (b) if the magnitude and latency of HEP in children with SDB differ significantly from healthy children (c) if so, whether the difference is still present after the children with SDB underwent adenotonsillectomy. We also explored the relationship between HEP and daytime behavior measures based on their child behavior checklist scores.

1.4 Statement of Original contribution

This Thesis includes four original journal articles in Chapters 2 3 4 and 5 and five conference papers in Appendices A1 to A5, all arising from the studies conducted towards the Thesis. The methodology of each study presented in this Thesis, both as Chapters and as Appendices, largely consisted of employing advanced signal processing algorithms which were developed solely by the author using the MATLAB signal processing toolbox and the codes are provided in section Appendix B. Formulation of a hypothesis towards each study, development of appropriate methodology towards testing the hypothesis and a large part of statistical analysis involved in each study were original contributions of the author.

Chapter 2

Respiratory timing and variability during sleep in children with sleep-disordered breathing

IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., KABIR, M. M., SAINT, D. A. & BAUMERT, M. 2012. Respiratory timing and variability during sleep in children with sleep-disordered breathing. *Journal of Applied Physiology,* 113**,** 1635-1642.

Statement of Authorship

Title of Paper	Respiratory timing and variability during sleep in children with sleep-disordered breathing
Publication Status	⊙ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
Publication Details	IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., KABIR, M. M., SAINT, D. A. & BAUMERT, M. 2012. Respiratory timing and variability during sleep in children with sleep-disordered breathing. Journal of Applied Physiology, 113, 1635-1642.

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)	Sarah Immanuel		
Contribution to the Paper	Study design, Data Analysis, Interpretation of data and results, Preparation and revision of manuscript		
Signature		Date	14/08/14

Name of Co-Author	Yvonne Pamula		
Contribution to the Paper	Interpretation of results, Preparation and critical revision of manuscript		
Signature		Date	8/08/2014

Name of Co-Author	James Martin		
Contribution to the Paper	Interpretation of results, Preparation and revision of manuscript		
Signature		Date	8/8/2014

Name of Co-Author	Declan Kennedy		
Contribution to the Paper	Interpretation of results, Preparation and revision of manuscript		
Signature		Date	8/8/14

Statement of Authorship

Title of Paper	Respiratory timing and variability during sleep in children with sleep-disordered breathing
Publication Status	⊙ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
Publication Details	IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., KABIR, M. M., SAINT, D. A. & BAUMERT, M. 2012. Respiratory timing and variability during sleep in children with sleep-disordered breathing. Journal of Applied Physiology, 113, 1635-1642.

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 Co-Author	Mark Kohler		
Contribution to the Paper	Data collection, Data Analysis, revision of manuscript		
Signature		Date	8/8/14

Name of Co-Author	Muammar Kabir		
Contribution to the Paper	Data Analysis, Preparation of manuscript		
Signature		Date	12/8/14

Name of Co-Author	David Saint		
Contribution to the Paper	Interpretation of results, revision of manuscript		
Signature		Date	18/08/2014

Name of Co-Author	Mathias Baumert		
Contribution to the Paper	Study design, Data Analysis, Interpretation of results, Preparation and revision of manuscript		
Signature		Date	18/08/2014

Immanuel, S.A., Pamula, Y., Kohler, M., Martin, J., Kennedy, D., Kabir, M.M., Saint, D.A. & Baumert, M. (2012) Respiratory timing and variability during sleep in children with sleep-disordered breathing.
Journal of Applied Physiology, v. 113(10), pp. 1635-1642

This page intentionally left blank

Chapter 3

Increased thoracoabdominal asynchrony during breathing periods free of discretely scored obstructive events in children with upper airway obstruction

IMMANUEL, S. A., KOHLER, M., MARTIN, J., KENNEDY, D., PAMULA, Y., KABIR, M. M., SAINT, D. A. & BAUMERT, M. 2014. Increased thoracoabdominal asynchrony during breathing periods free of discretely scored obstructive events in children with upper airway obstruction. *Sleep and Breathing*, DOI 10.1007/s11325-014-0963-3.

Statement of Authorship

Title of Paper	Increased thoracoabdominal asynchrony during breathing periods free of discretely scored obstructive events in children with upper airway obstruction
Publication Status	⊙ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
Publication Details	IMMANUEL, S. A., KOHLER, M., MARTIN, J., KENNEDY, D., PAMULA, Y., KABIR, M. M., SAINT, D. A. & BAUMERT, M. 2014. Increased thoracoabdominal asynchrony during breathing periods free of discretely scored obstructive events in children with upper airway obstruction. Sleep and Breathing, DOI 10.1007/s11325-014-0963-3.

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)	Sarah Immanuel		
Contribution to the Paper	Study design, Data Analysis, Interpretation of data and results, Preparation and revision of manuscript		
Signature		Date	14/08/14

Name of Co-Author	Yvonne Pamula		
Contribution to the Paper	Interpretation of results, Preparation and revision of manuscript		
Signature		Date	8/08/2014

Name of Co-Author	James Martin		
Contribution to the Paper	Interpretation of results, Preparation and crevision of manuscript		
Signature		Date	8/8/2014

Name of Co-Author	Declan Kennedy		
Contribution to the Paper	Interpretation of results, Preparation and revision of manuscript		
Signature		Date	8/8/14.

Statement of Authorship

Title of Paper	Increased thoracoabdominal asynchrony during breathing periods free of discretely scored obstructive events in children with upper airway obstruction
Publication Status	⊙ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
Publication Details	IMMANUEL, S. A., KOHLER, M., MARTIN, J., KENNEDY, D., PAMULA, Y., KABIR, M. M., SAINT, D. A. & BAUMERT, M. 2014. Increased thoracoabdominal asynchrony during breathing periods free of discretely scored obstructive events in children with upper airway obstruction. Sleep and Breathing, DOI 10.1007/s11325-014-0963-3.

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 Co-Author	Mark Kohler		
Contribution to the Paper	Data collection, Data Analysis, revision of manuscript		
Signature		Date	8/8/14

Name of Co-Author	Muammar Kabir		
Contribution to the Paper	Data Analysis, Preparation of manuscript		
Signature		Date	12/8/14

Name of Co-Author	David Saint		
Contribution to the Paper	Interpretation of results, revision of manuscript		
Signature		Date	18/08/2014

Name of Co-Author	Mathias Baumert		
Contribution to the Paper	Study design, Data Analysis, Interpretation of results, Preparation and revision of manuscript		
Signature		Date	18/08/2014

Immanuel, S.A., Kohler, M., Martin, J., Kennedy, D., Pamula, Y., Kabir, M.M., Saint, D.A. & Baumert, M. (2014) Increased thoracoabdominal asynchrony during breathing periods free of discretely scored obstructive events in children with upper airway obstruction.
Sleep and Breathing, v. 19(1), pp. 65-71

Chapter 4

Respiratory Cycle-Related electroencephalographic changes during sleep in healthy children and in children with sleep disordered breathing

IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., SAINT, D. A. & BAUMERT, M. 2014. Respiratory Cycle-Related Electroencephalographic Changes during Sleep in Healthy Children and in Children with Sleep Disordered Breathing. *Sleep,* 37**,** 1353-1361.

Statement of Authorship

Title of Paper	Respiratory Cycle-Related Electroencephalographic Changes during Sleep in Healthy Children and in Children with Sleep Disordered Breathing
Publication Status	◉ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
Publication Details	IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., SAINT, D. A. & BAUMERT, M. 2014. Respiratory Cycle-Related Electroencephalographic Changes during Sleep in Healthy Children and in Children with Sleep Disordered Breathing. Sleep, 37, 1353-1361.

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)	Sarah Immanuel		
Contribution to the Paper	Conception, design, analysis, and interpretation of the data; the drafting and revision of the article and final approval of the version to be published		
Signature		Date	14/08/14

Name of Co-Author	Yvonne Pamula		
Contribution to the Paper	Critical revision of the article for important intellectual content and final approval of the version to be published		
Signature		Date	8/08/2014

Name of Co-Author	James Martin		
Contribution to the Paper	Revision of the article for intellectual content and final approval of the version to be published		
Signature		Date	8/8/2014

Name of Co-Author	Declan Kennedy		
Contribution to the Paper	Revision of the article for intellectual content and final approval of the version to be published		
Signature		Date	8/8/14

Statement of Authorship

Title of Paper	Respiratory Cycle-Related Electroencephalographic Changes during Sleep in Healthy Children and in Children with Sleep Disordered Breathing
Publication Status	⦿ Published, O Accepted for Publication, O Submitted for Publication, O Publication style
Publication Details	IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., SAINT, D. A. & BAUMERT, M. 2014. Respiratory Cycle-Related Electroencephalographic Changes during Sleep in Healthy Children and in Children with Sleep Disordered Breathing. Sleep, 37, 1353-1361.

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 Co-Author	Mark Kohler		
Contribution to the Paper	Collection of data, drafting and critical revision of the article and final approval of the version to be published.		
Signature		Date	8/8/14

Name of Co-Author	David Saint		
Contribution to the Paper	Revision of the article for important intellectual content and final approval of the version to be published		
Signature		Date	18/08/2014

Name of Co-Author	Mathias Baumert		
Contribution to the Paper	Conception, design, analysis, and interpretation of the data; the drafting and revision of the article and final approval of the version to be published		
Signature		Date	18/01/2014

Name of Co-Author			
Contribution to the Paper			
Signature		Date	

Immanuel, S.A., Pamula, Y., Kohler, M., Martin, J., Kennedy, D., Saint, D.A. & Baumert, M. (2014) Respiratory cycle-related electroencephalographic changes during sleep in healthy children and in children with sleep disordered breathing.
Sleep, v. 37(8), pp. 1353-1361

Chapter 5

Heartbeat evoked potentials during sleep and daytime behavior in children with sleep disordered breathing

IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., NALIVAIKO, E., SAINT, D. A. & BAUMERT, M. Heartbeat evoked potentials during sleep and daytime behavior in children with sleep disordered breathing *American Journal of Respiratory and Critical Care Medicine,* 190**,** 1149-1157.

Statement of Authorship

Title of Paper	Heartbeat evoked potentials during sleep and daytime behavior in children with sleep disordered breathing
Publication Status	◉ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
Publication Details	IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., NALIVAIKO, E., SAINT, D. A. & BAUMERT, M. Heartbeat evoked potentials during sleep and daytime behavior in children with sleep disordered breathing (Revised and resubmitted to AJRCCM).

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)	Sarah Immanuel		
Contribution to the Paper	Conception, design, analysis, and interpretation of the data; the drafting and revision of the article and final approval of the version to be published		
Signature		Date	14/08/14

Name of Co-Author	Yvonne Pamula		
Contribution to the Paper	Critical revision of the article for important intellectual content and final approval of the version to be published		
Signature		Date	8/08/2014

Name of Co-Author	James Martin		
Contribution to the Paper	Revision of the article for intellectual content and final approval of the version to be published.		
Signature		Date	8/8/2014

Name of Co-Author	Declan Kennedy		
Contribution to the Paper	Revision of the article for intellectual content and final approval of the version to be published.		
Signature		Date	8/8/14

Statement of Authorship

Title of Paper	Heartbeat evoked potentials during sleep and daytime behavior in children with sleep disordered breathing
Publication Status	◉ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
Publication Details	IMMANUEL, S. A., PAMULA, Y., KOHLER, M., MARTIN, J., KENNEDY, D., NALIVAIKO, E., SAINT, D. A. & BAUMERT, M. Heartbeat evoked potentials during sleep and daytime behavior in children with sleep disordered breathing. (Revised and resubmitted to AJRCCM).

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 Co-Author	Mark Kohler		
Contribution to the Paper	Collection of data, data analysis, interpretation of results, drafting and critical revision of the article and final approval of the version to be published.		
Signature		Date	14/8/14

Name of Co-Author	David Saint		
Contribution to the Paper	Revision of the article for intellectual content and final approval of the version to be published		
Signature		Date	16/08/2014

Name of Co-Author	Eugene Nalivaiko		
Contribution to the Paper	Revision of the article for important intellectual content, and final approval of the version to be published		
Signature		Date	10 August 2014

Name of Co-Author	Mathias Baumert		
Contribution to the Paper	Conception, design, analysis, and interpretation of the data; the drafting and revision of the article and final approval of the version to be published		
Signature		Date	19/08/2014

Immanuel, S.A., Pamula, Y., Kohler, M., Martin, J., Kennedy, D., Nalivaiko, E., Saint, D.A. & Baumert, M. (2014) Heartbeat evoked potentials during sleep and daytime behavior in children with sleep-disordered breathing.
American Journal of Respiratory and Critical Care Medicine, v. 190(10), pp. 1149-1157

Chapter 6

Conclusion and future work

Conclusion and future work

The motivation behind the studies presented in this Thesis was to develop and apply signal processing techniques to look beyond the obvious manifestations reflected on the PSG indices that describe the severity of sleep disturbance. This Thesis has proposed signal processing methods that could be applied to respiratory, EEG and ECG signals to derive markers that reflect the impact of upper airway obstruction on respiratory mechanics and cortical processing. In the studies conducted, altered physiological measures that were subtle yet persistent were identified in children with SDB compared to healthy controls. This Chapter summarizes the key findings of this Thesis and discusses possible future directions for further research towards understanding the pathophysiology of childhood SDB.

Breathing through a partially obstructed upper airway demands a greater respiratory effort to maintain airflow, and this alters both respiratory timing and respiratory variability. The article in Chapter 2 analysed respiratory parameters across sleep stages in children with SDB before and after their treatment. Compared to healthy controls, children with SDB had significantly prolonged inspiration and expiration and slower respiratory rates during non-apneic sleep, indicative of continuous partial obstruction of the upper airway. Adenotonsillectomy appears to have reduced this effect in SDB children, as was evidenced by normalized respiratory timing and breathing rate, suggesting the benefit of surgical treatment. Compared to studies on adult subjects, little is known about ventilation during sleep in children. Thus, the results of the presented study have provided a documentation of parameters related to inspiratory and expiratory flow limitation in children.

To add evidence towards the notion of a prolonged partial upper airway obstruction in these children with SDB, we sought to quantify their thoraco abdominal asynchrony (TAA) which would be an indirect measure of the respiratory effort to overcome the increased pharyngeal resistance. A robust waveform independent TAA estimation method using Hilbert transform is proposed in this Thesis. This method, validated using simulated signals was then applied to RIP signals of PSG data to quantify TAA. Sleep stages were found to significantly influence TAA (Appendix A1). The article in

Chapter 3 presents the study, where sleep stage specific TAA were compared between the study groups. The SDB group were found to have an increased thoraco-abdominal asynchrony (TAA) during sleep periods free of apneas and hypopneas in all sleep stages analysed, which supported the notion of persistent partial obstruction as evidenced by the findings in Chapter 2. Further, in children with SDB, breaths immediately before obstructive apnea/hypopneas were associated with a high degree of variability in respiratory timing and TAA. This is presented in Appendix A3.

The impact of airway obstruction on sleep physiology is not restricted to respiratory mechanics. Changes in blood pressure, heart rate, cortical activity, blood oxygen levels are common during episodes of central or obstructive apnea. Having demonstrated altered respiratory parameters in SDB children during SEF sleep, we sought to investigate respiration-related cortical changes, if any. The study presented in Chapter 4 involved quantification of respiration-related EEG changes using a differential approach based on measuring subtle changes in cortical activity that occurs phase-locked with respiration, termed respiratory cycle related EEG changes (RCREC). A higher RCREC in children with SDB compared to the controls, both on the overall EEG and in specific EEG frequency bands were observed predominantly in REM sleep. This difference reduced after adenotonsillectomy. RCREC may represent numerous micro-arousals in response to labored breathing that is well known to occur in children with SDB, who hypoventilate for most of the sleep periods outside of traditionally scored periods of apnea/hypopnea and arousals. Also complexity analysis of respiratory cycle related EEG using non-linear methods was performed using a novel approach for characterizing and recognizing temporal patterns based on symbolic dynamics which suggested that EEG dynamics in SDB children are altered across all stages of sleep (Appendix A4).

With findings suggesting differences between the control and SDB group in respiratory parameters and respiratory phase related cortical activity, our interest was directed towards evaluating cortical processing of cardiac information during sleep. The study presented in Chapter 5 aimed at probing cortical information processing of cardiac afferents in our study groups based on heartbeat as markers. This study has provided the first demonstration of cortical processing of visceral stimuli, evoked by the

heartbeat during sleep. Importantly, HEP were found to be attenuated in children with SDB, indicating increased sensory gating of cardiac information via afferent inputs reaching the cortex. Also, significant associations between HEP and daytime behavioral scores were observed. It is known that children with SDB have neurocognitive and behavior deficits and that their brain responsiveness to external respiratory loading is impaired. The finding from our study however has shown differences in cortical processing of intrinsic naturally occurring heartbeat stimuli and in particular during periods of sleep free of frank obstructions or arousals. With the severity of SDB in our study group being primarily mild to moderate, this abnormality in central processing of information and its association with behavioural deficits is of importance in clinical diagnosis and treatment. The TAA and RCREC measures evaluated in the previous studies that indicated elevated levels of prolonged partial obstruction and respiration linked microarousals in children with SDB, did not show any significant associations with their behavioural scores.

During pre-adolescent age in children, which is crucial for their brain maturation/ development, it is critical that their cortical functioning and executive skills are intact - the quality of night sleep plays a major role on their cognitive development and daytime functioning. Poorly treated OSA results in behavioural problems, cardiovascular consequences and neuropsychological dysfunctions. In this Thesis, robust signal processing techniques were applied to PSG data of children with primarily mild to moderate SDB. Major findings from all our studies provide strong evidence towards the notion that there are differences or deficits in these children compared to healthy controls and that they are not always reflected on their clinical sleep scorings. Altered respiratory mechanics and differences in respiratory and cardiac related cortical activity have been demonstrated in our findings. Clinical assessment of visual scoring might thus be underestimating the pathology of SDB in children.

6.1 Limitations

Inductive plethysmography, a widely used non-obtrusive technique was used as the source of respiratory signal, which however, was uncalibrated and this restricted our

initial analyses from extending to respiratory volume based parameters. Circadian influences on the parameters measured were not considered, though the time of night during which sleep is investigated is thought to influence cardio-respiratory physiology. However, a sleep stage based analysis has been performed on all the studies reported in this Thesis. The study cohort span a relatively wide age range of 3 to 13 years with the SDB severity ranging from mild to moderate. It is unclear whether the observed differences between these children with SDB and the healthy controls were restricted to the restive loading of their upper airway, or if there are broader influences originating from the central neuronal processing controlling their respiratory mechanisms.

6.2 Future Directions

In this Thesis we have investigated RIP channels from polysomnographic data in children and observed that respiratory timings and TAA could serve as indirect indicators of upper airway obstruction. These measures could serve as markers in long-term home monitoring devices to evaluate sleep, especially in children. In addition, it would be interesting to further investigate the physiological significance of these changes in respiratory parameters and whether they form a part of cyclic regulation during sleep.

Respiratory phase-locked EEG fluctuations have been demonstrated in our study and are speculated to represent numerous microarousals during sleep. Though the physiological basis of RCREC remains largely unknown, the findings are suggestive of differences in cortical activity to respiratory afferent information. Longitudinal studies could be conducted to extend these investigations on RCREC in sleep/wake states, age effect, post-treatment changes etc along with its association with daytime cognition and behavioural measures in children with moderate to severe SDB.

Heartbeat evoked potentials have been demonstrated in both NREM and REM sleep. These potentials can be easily measured in the sleep laboratory using standard PSG. The measure could be used as a tool to assess interoceptive information processing during sleep. Also, HEP could be a promising measure towards assessing cortical function deficit in children. It would be interesting to investigate HEP during

wakefulness, HEP in different brain regions and further probe its association with cortical impairment in children with different levels of SDB severity. Also, multichannel EEG, ECG studies would enable quantitative analysis of early and late HEP components by employing effective field artifact removal.

Future studies towards strengthening this area of research have been planned, including (i) extension of the presented methodologies in infant and adult data sets (ii) analysis larger data sets of children with SDB with different severity levels forming subgroups (iii) design of comprehensive EEG analysis using multichannel acquisition facilities to probe more into cortical functioning in children during sleep, which plays a very important role in their brain development and daytime functioning. Also, the findings in this Thesis have provides an opportunity for our further work towards systematic examination of the clinical utility in these developed techniques. This would supplement existing conventional PSG evaluation methods and impart earlier and better diagnostic approaches towards SDB in children.

6.3 Closing statement

This Chapter summarised the major findings and conclusions of this Thesis accompanied by recommendations for future work. This Thesis has made a number of contributions towards understanding aspects of sleep physiology in healthy children and sleep pathophysiology in children with SDB by investigating respiratory and cardio-respiratory-related cortical measures especially in sleep periods that are clinically considered quiet or event-free breathing periods. All works presented herein are unique and original, laying groundwork for future clinical research applications in pediatric SDB.

Appendix A

Conference papers

A.1 Thoraco-Abdominal Asynchrony in Children during Quiet Sleep using Hilbert Transform

IMMANUEL, S. A., KOHLER, M., PAMULA, Y., KABIR, M. M., SAINT, D. A. & BAUMERT, M. 2012. Thoraco-abdominal asynchrony in children during quiet sleep using Hilbert transform, *Proceedings of the 34th IEEE Engineering in Medicine and Biology Society*, San Diego, USA, pp. 3448-3451.

Immanuel, S.A., Kohler, M., Pamula, Y., Kabir, M.M., Saint, D.A. & Baumert, M. (2012) Thoraco-abdominal asynchrony in children during quiet sleep using Hilbert Transformation.
Presented at: 34th Annual International Conference of the IEEE EMBS, San Diego, California, 28 August-1 September

A.2 Characterizing Ventilatory Fluctuations and Associated Thoraco-abdominal Asynchrony during Sleep using Respiratory Inductive Plethysmography

IMMANUEL, S. A., PAMULA, Y., KOHLER, M., KABIR, M. M., SAINT D. A. & BAUMERT, M. 2013. Characterizing Respiratory Waveform Regularity and Associated Thoraco-abdominal Asynchrony during Sleep using Respiratory Inductive Plethysmography, *Eighth International Conference on Intelligent Sensors, Sensor Networks and Information Processing*, Melbourne, Australia, pp. 329-332.

Immanuel, S.A., Pamula, Y., Kohler, M., Saint, D.A. & Baumert, M. (2013) Charaterizing respiratory waveform regularity and associated thoraco-abdominal asynchrony during sleep using respiratory inductive plethysmography.
Presented at: Eighth International Conference on Intelligent Sensors, Sensor Networks and Information Processing, *IEEE ISSNIP Melbourne, Victoria, 2-5 April*

A.3 Increased variability in respiratory parameters heralds obstructive events in children with sleep disordered breathing

IMMANUEL, S. A., KOHLER, M., PAMULA, Y., KABIR, M. M., SAINT D. A. & BAUMERT, M. 2013. Increased variability in respiratory parameters heralds obstructive events in children with sleep disordered breathing, *Proceedings of the 35th IEEE Engineering in Medicine and Biology Society*, Osaka, Japan, pp. 2024-2027.

Immanuel, S.A., Kohler, M., Pamula, Y., Kabir, M.M., Saint, D.A. & Baumert, M. (2013) Increased variability in respiratory parameters heralds obstructive events in children with sleep disordered breathing.
Presented at: 35th Annual International Conference of the *IEEE EMBS, Osaka, Japan, 3-5 July*

A.4 Symbolic dynamics of respiratory cycle related sleep EEG in children with sleep disordered breathing

IMMANUEL, S. A., KOHLER, M., KABIR, M. M., SAINT D. A. & BAUMERT, M. 2014. Symbolic dynamics of respiratory cycle related sleep EEG in children with sleep disordered breathing, *Proceedings of the 36th IEEE Engineering in Medicine and Biology Society,* Chicago, USA, pp. 6016-6019.

Immanuel, S.A., Kohler, M., Kabir, M.M., Saint, D.A. & Baumert, M. (2014) Symbolic dynamics of respiratory cycle related sleep EEG in children with sleep disordered breathing.
Presented at: 36th Annual International Conference of the *IEEE, Chicago, Illinois, 36-30 August*

A.5 Effect of resistive inspiratory and expiratory loading on cardio-respiratory interaction in healthy subjects

KABIR, M. M., **IMMANUEL, S. A**., TAFRESHI, R., SAINT D. A. & BAUMERT, M. 2014. Effect of resistive inspiratory and expiratory loading on cardio-respiratory interaction in healthy subjects, *Proceedings of the 36th IEEE Engineering in Medicine and Biology Society,* Chicago, USA, pp. 710-713.

.

Kabir, M.M., Immanuel, S.A., Tafreshi, R., Saint, D.A. & Baumert, M. (2014) Effect of resistive inspiratory and expiratory loading on cardio-respiratory interaction in healthy subjects. *Presented at:* 36th Annual International Conference of the *IEEE, Chicago, Illinois, 36-30 August*

Appendix B

Matlab codes

B.1 Respiratory timing and variability

```
%Load ribcage and abdomen channels of RIP from PSG data along with their sampling frequencies
        ribcage= [];  ribcage=load ('Data\ribcagedata_',name,'.txt');
        abdomen= [];  abdomen=load ('Data\abdomendata_',name,'.txt');
%Load sleepstage scoring information (scored every 30s)
        sleepstage = [];  sleepstage=load ('Data\sleepstagedata_',name,'.txt');

%%%% To extract 3min artifact free segments - Stage 2 for example
% Check if there are 6 continuous ss2 (30s) epochs by comparing the values of their locations
        locss2=find(sleepstages==2);
        j=1; ss2=0; startsample_ss2=0;
                for i=1:length(locss2)-6
                        if ((locss2(i)==locss2(i+1)-1)&& (locss2(i+1)==locss2(i+2)-1)&&
                          (locss2(i+2)==locss2(i+3)-1) &&   (locss2(i+3)==locss2(i+4)-1)  &&
                          (locss2(i+4)==locss2(i+5)-1))
                          ss2(j,1)=locss2(i);   ss2(j,2)=locss2(i+5); j=j+1;
                        end
                end
%Identify start time and end time of the 3min stage2 segment and convert them into samples based on
sfreq
        startsample_ss2=(ss2(:,1)-1)*30*sfreq;endsample_ss2=ss2(:,2)*30*sfreq;
 %Extract RC and AB segments corresponding to the 3min duration i.e. 6 epochs
        j=1;rc=0;ab=0;rc1=0;ab1=0;valid_startsample_ss2=0;valid_endsample_ss2=0;
                for i=1:length(startsample_ss2)
                        if startsample_ss2 < (length(data)-4500)
                           rc=ribcage(startsample_ss2(i):endsample_ss2(i));
                           ab=abdome(startsample_ss2(i):endsample_ss2(i));
                        end
                end

%Check if there are missing samples within the 3min that were removed during artifact duration
elimination
        rc1=rc(isfinite(rc));ab1=ab(isfinite(ab));
                if length(rc)==length(rc1)
                  valid_startsample_ss2(j)=startsample_ss2(i);
                  valid_endsample_ss2(j)=endsample_ss2(i);  j=j+1;
```

```
                end
%Check for clipping in data
        j=1;u=1;unclip_startsample_ss2=0;unclip_endsample_ss2=0;
                for i=1:length(valid_startsample_ss2)
                    rc=data2(valid_startsample_ss2(i):valid_endsample_ss2(i));
                    ab=data(valid_startsample_ss2(i):valid_endsample_ss2(i));
                    loc_clip_rc=find(abs(rc)==128); loc_clip_ab=find(abs(ab)==128);
                        if isempty(loc_clip_rc)
                          unclip_startsample_ss2(j)=valid_startsample_ss2(i);
                          unclip_endsample_ss2(j)=valid_endsample_ss2(i);  j=j+1;
                        end
                end
%Check for non-overlapping consecutive 6  epochs
        s=1;k=2;j=1;nonoverlap_startsample_ss2=0;nonoverlap_endsample_ss2=0;
                while k<=length( unclip_startsample_ss2)
                        if unclip_startsample_ss2(k)-unclip_startsample_ss2(s)<4500
                        k=k+1;
                        else
                        nonoverlap_startsample_ss2(j)=unclip_startsample_ss2(s);
                        nonoverlap_endsample_ss2(j)=unclip_endsample_ss2(s); j=j+1;
                        nonoverlap_startsample_ss2(j)=unclip_startsample_ss2(k);
                        nonoverlap_endsample_ss2(j)=unclip_endsample_ss2(k); s=k; k=s+1;
                        end
                end
        Avg_Ti=0;Avg_Te=0;Avg_Ttot=0;Avg_DC=0;Avg_Resp_frqy_Ttot=0; Avg_Resp_frqy_Spec=0;
        ins_time_conc=[];exp_time_conc=[];breath_time_conc=[];duty_cycle_conc=[];
                for segment=1:nonoverlap_startsample_ss
                rc_ss2=0;rc_ss2_normalised=0;rc_ss2_standardised=0;

        rc_ss2=ribcage(nonoverlap_startsample_ss2(segment):nonoverlap_endsample_ss2(segment));

        ab_ss2=ribcage(nonoverlap_startsample_ss2(segment):nonoverlap_endsample_ss2(segment));
                end
 % Normalise and standardise the 3min artifact free respiratory signals
        mean1=mean(rc_ss2);   rc_ss2_normalised=rc_ss2-mean1;
        mean2=mean(ab_ss2);    ab_ss2_normalised=ab_ss2-mean2;
        sd_rc_ss2=std(rc_ss2_normalised); rc_ss2_standardised=rc_ss2_normalised/sd_rc_ss2;
```

```
sd_ab_ss2=std(ab_ss2_normalised); ab_ss2_standardised=ab_ss2_normalised/sd_ab_ss2;

% LPF respiratory signal fc=1Hz
rc_filter=[];    [b,a] = butter(4,(1/(sfreq/2))); rc_filter=filtfilt(b,a,rc_ss2_standardised);

%Estimate the respiratory frequency using power spectrum
Resp_frqy_Spec_current=0;
m = length(rc_ss2_filter);        % Window length
n = pow2(nextpow2(m));  % Transform length
y = fft(rc_ss2_filter,n);         % DFT
f = (0:n/2-1)*(sfreq/n);    % Frequency range
power = y.*conj(y)/n;   % Power of the DFT
loc_maxpower=find(power==max(power));
f1=f(loc_maxpower(1));
Resp_frqy_Spec(segment)=f1*60;
Resp_frqy_Spec_current=Resp_frqy_Spec(segment);% breaths per minute

%Detection of inspiratory onsets - valley points
valley=0;j=1;
        for i=2:length(rc_ss2_filter)-1
            if rc_ss2_filter(i)-rc_ss2_filter(i-1)<0 && rc_ss2_filter(i)-rc_ss2_filter(i+1)<0
&&                                  (rc_ss2_filter(i))< 0)
              valley(j)=i;j=j+1;
            end
        end
%Breath detection
f1=f(loc_maxpower(1));
Min_sample=0.5*floor(1/f1*sfreq);max_sample=1.5*floor(1/f1*sfreq);
j=1;p=0;breath_matrix_samp=0;
        for i=1:length(valley)-1
            valley1=valley(i); valley2=valley(i+1);
            if valley2-valley1 > Min_sample && valley2-valley1 < max_sample
              loc=find(rc_ss2_filter==max(rc_ss2_filter(valley1:valley2)));
              breath_matrix_samp(j,1)=valley1; breath_matrix_samp(j,2)=loc(1);
              breath_matrix_samp(j,3)=valley2;
              ins_time_samp(j)=loc(1)-valley1;
              exp_time_samp(j)=valley2-loc(1);
```

```
                    breath_time_samp(j)=valley2-valley1; j=j+1;
                end
            end
%%%%%%%%%%%%   RESIDUES
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%VALLEY TO VALLEY
% Generation of the valley matrix by storing each v-v breath as a row
        valley_matrix=0;
            for i=1:length(breath_matrix_samp)
                temp1=rc_ss2_filter(breath_matrix_samp(i,1):breath_matrix_samp(i,3));
                    for j=1:length(temp1)
                        valley_matrix(i,j)=temp1(j);
                    end
            end
%Generate an average p-p curve of all p-p breaths by averaging along columns
        allvalley_nan=0; allvalley=0;allvalley_avg=0;
            for j=1:columnlength
                    for i=1:rowlength
                        allvalley_nan(i)=valley_matrix_nan(i,j);
                    end
                allvalley=allvalley_nan(isfinite(allvalley_nan));
                allvalley_avg(j)=mean(allvalley);
            end
% create a residue matrix that contains difference between each p-p breath and the average p-p curve
            for i=1:rowlength
                    for j=1:columnlength
                    res_valley(i,j)=valley_matrix_nan(i,j)-allvalley_avg(j);
                    end
            end
        res_valley1=res_valley(isfinite(res_valley));residue_valley(segment)=mean(abs(res_valley1));
%INSPIRATION
        ins_matrix=0;
            for i=1:length(breath_matrix_samp)
                temp1=rc_ss2_filter(breath_matrix_samp(i,1):breath_matrix_samp(i,2));
                    for j=1:length(temp1)
                        ins_matrix(i,j)=temp1(j);
                    end
```

```
                end
%Generate an average insp curve of all ins breaths by averaging along  column
        allinsp_nan=0;allinsp=0;allinsp_avg=0;
                for j=1:columnlength
                        for i=1:rowlength
                            allinsp_nan(i)=ins_matrix(i,j);
                        end
                    allinsp=allinsp_nan(isfinite(allinsp_nan));
                    allinsp_avg(j)=mean(allinsp);
                end
% create a residue matrix that contains difference between each p-p breath % and the average p-p
curve
                for i=1:rowlength
                        for j=1:columnlength
                            res_insp(i,j)=ins_matrix_nan(i,j)-allinsp_avg(j);
                        end
                end
res_insp1=res_insp(isfinite(res_insp));residue_insp(segment)=mean(abs(res_insp1));

%EXPIRATION
        exp_matrix=0;
                for i=1:length(breath_matrix_samp)
                    temp1=rc_ss2_filter(breath_matrix_samp(i,2):breath_matrix_samp(i,3));
                        for j=1:length(temp1)
                            exp_matrix(i,j)=temp1(j);
                        end
                end

% Similarly generate an average expp curve of all exp breaths by averaging along %columns
% Convert all time points in samples to seconds by dividing by sampling  frequency
        Avg_SD_Ti=0;Avg_SD_Te=0;Avg_SD_Ttot=0;Avg_SD_DC=0;Resp_frqy_Ttot_current=0;
% Output measures
        Ins_time=ins_time_samp/sfreq;Ti=mean(ins_time);SD_Ti=std(ins_time);
        Avg_Ti=Avg_Ti+Ti;Avg_SD_Ti=Avg_SD_Ti+SD_Ti;
        exp_time=exp_time_samp/sfreq;Te=mean(exp_time);SD_Te=std(exp_time);
        Avg_Te=Avg_Te+Te;Avg_SD_Te=Avg_SD_Te+SD_Te;
```

```
        breath_time=breath_time_samp/sfreq;Ttot=mean(breath_time);
        SD_Ttot=std(breath_time);Avg_Ttot=Avg_Ttot+Ttot;Avg_SD_Ttot=Avg_SD_Ttot+SD_Ttot;
        duty_cycle=ins_time./breath_time;DC=mean(duty_cycle);SD_DC=std(duty_cycle);
        Avg_DC=Avg_DC+DC;Avg_SD_DC=Avg_SD_DC+SD_DC;
        Resp_frqy_Ttot(segment)=60/mean(breath_time);Resp_frqy_Ttot_current=Resp_frqy_Ttot(seg
ment);
        Residue_valley=mean(residue_valley);
        Residue_expiration=mean(residue_exp);
        Residue_inspiration=mean(residue_insp);
```

B.2 TAA estimation

```
clear all; close all; clc
%Load ribcage and abdomen channels of RIP from PSG data along with their sampling frequencies
        ribcage= [];  ribcage=load ('Data\ribcagedata_',name,'.txt');
        abdomen= [];  abdomen=load ('Data\abdomendata_',name,'.txt');
%Load sleepstage scoring information (scored every 30s)
        sleepstage = [];  sleepstage=load ('Data\sleepstagedata_',name,'.txt');
%Load sleep position scoring information (scored every 30s)
        postion = [];  position=load ('Data\positiondata_',name,'.txt');

% Normalise and standardise the signals
        mean1=mean(rc_ss2);   rc_ss2_normalised=rc_ss2-mean1;
        mean2=mean(ab_ss2);    ab_ss2_normalised=ab_ss2-mean2;
        sd_rc_ss2=std(rc_ss2_normalised); rc_ss2_standardised=rc_ss2_normalised/sd_rc_ss2;
        sd_ab_ss2=std(ab_ss2_normalised); ab_ss2_standardised=ab_ss2_normalised/sd_ab_ss2;

% LPF respiratory signal fc=1Hz
        rc_filter=[];
        [b,a] = butter(4,(1/(sfreq/2)));
        rc_filter=filtfilt(b,a,rc_ss2_standardised); ab_filter=filtfilt(b,a,ab_ss2_standardised);
% To check for unchanged positional scores throughout the 30sec epoch
        position_array=posit(((stage-1)*30)+1:(stage*30));
        position_array=position_array';
        position_1=zeros(1,length(position_array));%Supine
```

```
position_1(1,:)=1;
        if isequal(position_array,position_1)
          count_p1=count_p1+1;

%TAA using XOR Method
        for i=1:length(rc_ss2)
            if rc_ss2(i)>=0
               rc_binary(i)=1;
            else
              rc_binary(i)=0;
            end
        end
% Similarly for ABD signal

output=xor(rc_binary,ab_binary);
index_TAA_XOR=(sum(output)/length(output))*180/pi;

 %TAA_Hilbert transformation
r_ss0_hil=imag(hilbert(r_ss0)); a_ss0_hil=imag(hilbert(a_ss0));
d=atan((abs(( r_ss0_hil.*a_ss0)-(r_ss0.*a_ss0_hil))./((r_ss0.*a_ss0)+(r_ss0_hil.*a_ss0_hil)));
        for i=1:length(d)
            if d(i)<0
              d1(i)=d(i)+pi;
            else
             d1(i)=d(i);
            end
        end
index_TAA_hilbert=(sum(d1)/length( d1))*180/pi;
%Slope of Lissajou's loops
g1=0;g2=0;f=0;
[p,S]=polyfit(ab_ss2,rc_ss2,1);
f=polyval(p,ab_ss2,S);
g1=diff(f);g2=diff(ab_ss2);
g=g1/g2;
g_degree=(atan(g))*180/pi;
Index_slope_of_loops = g_degree;
```

B.3 LFE estimation

```
%Extract event free, non-overlapping 3min RC RIP signal and check for %clipping in data (shown in
section A1)
% Normalise and standardise the signals

%Compute cwt of the 3 minute segments
        c=0;scale_range=[1:900];
        c = cwt(rc_ss2,scale_range,'db8');% 'sym8'
        figure, S = wscalogram('image',c);
        [rct1,colct1]=size(c);

%Normalised total overall energy of the wavelet transform
        i=0;j=0;temp=0; %sumrow7=[];
            for i=1:rct1
                    for j=1:colct1
                        temp=temp+((abs(c(i,j))).^2);
                    end
            end
        overall_energy=temp/(norm(rc_ss2)).^2;
        overall(segment)=overall_energy;

            for i=1:rct1
                temp=0;
                    for j=1:colct1
                        temp=temp+((abs(c(i,j))).^2);
                    end
                sumrow(i)=temp/(norm(rc_ss2)).^2;
            end
        sumcol=[];temp=0;
            for j=1:colct1
                temp=0;
                    for i=1:rct1
                        temp=temp+((abs(c(i,j))).^2);
                    end
            sumcol(j)=temp/(norm(rc_ss2)).^2;
            end
```

```
%Dividing frequencies into bands and finding the corresponding scales
        freq=scal2frq(scale_range,'db8',1/sfreq);
        freq_min=min(freq);freq_max=max(freq);
        f_range1=[freq_max  3];s_range1=[1 5];
        f_range2=[3  2];s_range2=[6 8];
        f_range3=[2  1];s_range3=[9 16];
        f_range4=[1  0.1];s_range4=[17 166];
        f_range5=[0.1  0.05];s_range5=[167 333];
        f_range6=[0.05  0.02];s_range6=[334 835];
        f_range7=[0.02  freq_min];s_range7=[836 900];

%Normalized energy of the wavelet transform across low frequency scales
%s_range7
        i=0;j=0; sumrow1=[];
                for i=s_range7(1):s_range7(2)
                    temp=0;
                        for j=1:colct1
                            temp=temp+((abs(c(i,j))).^2);
                        end
                    sumrow1(i)=temp/(norm(rc_ss2)).^2;
                end
                total_energy1=sum(sumrow1);

%LFE as a percentage of overall energy
        total_energy1_per=sum(sumrow1)*100/overall_energy;
        energy1(segment)=total_energy1;
        energy1_per(segment)=total_energy1_per;

%Percentage LFE of all 3min SEF epochs averaged
%Similar computations done on other frequency scales
%Above steps repeated on SEF 3 min segments of other sleep stages
```

B.4 PTT estimation

```
%Load ECG channel of RIP from PSG data along with its sampling frequency
        ecg= [];  ecg=load ('Data\ecgdata_',name,'.txt');
%Load pulse oximetry channel from PSG data along with its sampling frequency
        Oxywave = [];  Oxywave=load ('Data\Oxywave_',name,'.txt');
%Load sleepstage scoring information (scored every 30s)
        sleepstage = [];  sleepstage=load ('Data\sleepstagedata_',name,'.txt');
%Load sleep position scoring information (scored every 30s)
        postion = [];  position=load ('Data\positiondata_',name,'.txt');

%Load RR interval information and extract R peaks
        rpeakdata=load(rr);
        rpeak=rpeakdata(:,1);rrinterval=rpeakdata(:,2);
        rpeak_samples=rpeak*500;%fs for ECG = 500 Hz
        [rows,columns]=size(ecg);
        rpeak_points=zeros(rows,1);

            for i=1:length(rpeak_samples)
                rpeak_points(floor(rpeak_samples(i)))=1;
            end

%Extract SEF 30s epochs within specific sleep stage
%Normalise and standardise the 30s epochs of ECG and Oxywave signals
%LPF Oxywave and its derivative using FIR windowing method - cut off of fc Hz

        oxy_filter=[];
        [b,a] = butter(4,(30/(sfreq8/2)));
        oxy_filter=filtfilt(b,a,oxy_standardised);

        oxy_filter_slope=diff(oxy_filter);
        oxy_filter2=[];     [b,a] = butter(4,(5/(sfreq8/2)));
        oxy_filter2=filtfilt(b,a,oxy_filter_slope);

% finding steepest slope points as peaks on d/dt waveform
        j1=1;peak_oxy=[];
```

```
        for i=2:length(oxy_filter2)-1
            if (oxy_filter2(i)>oxy_filter2(i-1))&&(oxy_filter2(i)>oxy_filter2(i+1))
                if oxy_filter2(i)>0.3*max(oxy_filter2)
                peak_oxy(j1)=i;j1=j1+1;
                end
            end
        end
    j2=1; peak_rr=[];
        for i=1:length(rpeak_points)
            if rpeak_points(i)>0
              peak_rr(j2)=i;j2=j2+1;
            end
        end
%Compute PTT - difference between R peak and steepest slope on Oxywave
    [r1,c1]=size(peak_ecg_slope); [r2,c2]=size(peak_rr);
    ptt=[]; j=1;
        if (min(peak_oxy-peak_rr(1)))<0
            for i=1:min(length(peak_rr),length(peak_oxy))-1
                if peak_oxy(i+1)-peak_rr(i)>0 && peak_oxy(i+1)-peak_rr(i)<400
                   ptt(j)=peak_oxy(i+1)-peak_rr(i);j=j+1;
                end
            end
         else
            for i=1:min(length(peak_rr),length(peak_oxy))-1
                if peak_oxy(i)-peak_rr(i)>0 && peak_oxy(i)-peak_rr(i)<400
                   ptt(j)=peak_oxy(i)-peak_rr(i);j=j+1;
                end
            end
        end
```

B.5 RCREC using average EEG power

```
clear all; close all; clc
%Load ribcage and abdomen channels of RIP from PSG data along with their sampling frequencies
        ribcage= [];  ribcage=load ('Data\ribcagedata_',name,'.txt');
        abdomen= [];  abdomen=load ('Data\abdomendata_',name,'.txt');
%Load EEG channel of RIP from PSG data along with the sampling frequency
        eeg= [];  eeg=load ('Data\eegdata_',name,'.txt');
%Load sleepstage scoring information (scored every 30s)
        sleepstage = [];  sleepstage=load ('Data\sleepstagedata_',name,'.txt');


%EEG HPF filtering - wc=0.1 Hz
        eeg_ss2_filter=[];
        [b,a] = butter(4,(0.1/(sfreq5/2)),'high'); [H,w]=freqz(b,a);
        eeg_ss2_filter=filtfilt(b,a,eeg_ss2_standardised); f=w.*250/2/pi;
% Delta frqy - low pass filter upto 4 Hz
        Wp1 = 4; Ws1 = 5;Wp_normalised=Wp1/(sfreq5/2); Ws_normalised=Ws1/(sfreq5/2);
        Rp = 0.5; Rs = 60;
        [n,W] = ellipord(Wp_normalised,Ws_normalised,Rp,Rs);
        [b1,a1] = ellip(n,Rp,Rs,W);%[H,wd]=freqz(b1,a1);fd=wd.*250/2/pi;%figure(),
plot(fd,20*log10(abs(H)))

% Theta - band pass 4 to 8 Hz
        Wp1 = [4 8];Ws1 = [3 8.5];Rp1 = 0.5;Rs1 = 30;
        Wp_normalised=Wp1/(sfreq5/2);       Ws_normalised=Ws1/(sfreq5/2);
        [n,W] = ellipord(Wp_normalised,Ws_normalised,Rp1,Rs1)
        [b2,a2] = ellip(n,Rp1,Rs1,W);%[H,wt]=freqz(b2,a2);ft=wt.*250/2/pi;%figure(),
plot(ft,20*log10(abs(H)))

% Alpha band pass - 8 to 12 Hz
% Sigma band pass - 12 to 15 Hz
% Beta band pass – 15 to 30 Hz

%Filtering EEG through the filter bank
        eeg_delta=filtfilt(b1,a1,eeg_ss2_filter);eeg_theta=filtfilt(b2,a2,eeg_ss2_filter); %Alpha, sigma
and beta
        [row,col]=size(breath_matrix_samp);
```

```
        rowcount=rowcount+row;
        midinsp=(floor((breath_matrix_samp(i5,2)-
breath_matrix_samp(i5,1))/2)+breath_matrix_samp(i5,1));
        midexp=(floor((breath_matrix_samp(i5,3)-
breath_matrix_samp(i5,2))/2)+breath_matrix_samp(i5,2));

%Compute EEG power within full breath and within each respiratory segment
        rc_breath=rc_filter(breath_matrix_samp(i5,1):breath_matrix_samp(i5,3));

%%%%%%%%%%%%%%%%%%%% OVERALL EEG
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%Full breath
        eeg_breath=eeg_ss2_filter(((breath_matrix_samp(i5,1)-
1)*10)+1:breath_matrix_samp(i5,3)*10);
        P_eeg_breath=sum(eeg_breath.^2)/length(eeg_breath);

%Inspiration1
        eeg_ins1=eeg_ss2_filter(((breath_matrix_samp(i5,1))*10)+1:midinsp*10);
        P_eeg_ins1=sum(eeg_ins1.^2)/length(eeg_ins1);
%Inspiration2
        eeg_ins2=eeg_ss2_filter(((midinsp)*10)+1:breath_matrix_samp(i5,2)*10);
        P_eeg_ins2=sum(eeg_ins2.^2)/length(eeg_ins2);
%Expiration1
        eeg_exp1=eeg_ss2_filter(((breath_matrix_samp(i5,2))*10)+1:midexp*10);
        P_eeg_exp1=sum(eeg_exp1.^2)/length(eeg_exp1);
%Expiration2
        eeg_exp2=eeg_ss2_filter(((midexp)*10)+1:breath_matrix_samp(i5,3)*10);
        P_eeg_exp2=sum(eeg_exp2.^2)/length(eeg_exp2);


        Pout_eeg=[P_eeg_ins1 P_eeg_ins2 P_eeg_exp1 P_eeg_ep2];

%Normalised using EEG power of the full breath
        P_eeg_ins1_normalised=(P_eeg_ins1/P_eeg_breath)-1;
        P_eeg_ins2_normalised=(P_eeg_ins2/P_eeg_breath)-1;
        P_eeg_exp1_normalised=(P_eeg_exp1/P_eeg_breath)-1;
        P_eeg_exp2_normalised=(P_eeg_exp2/P_eeg_breath)-1;
```

```
%RCREC - overall EEG

A=max(P_eeg_ins1_normalised,P_eeg_ins2_normalised,P_eeg_exp1_normalised,P_eeg_exp2_normalised);
B=min(P_eeg_ins1_normalised,P_eeg_ins2_normalised,P_eeg_exp1_normalised,P_eeg_exp2_normalised);
RCREC_eeg=A-B;

%%%%%%%%%%%%%%%%%% DELTA BAND  %%%%%%%%%%
        eeg_delta_breath=eeg_delta(((breath_matrix_samp(i5,1)-1)*10)+1:breath_matrix_samp(i5,3)*10);
        Pdelta_eeg_breath=sum(eeg_delta_breath.^2)/length(eeg_delta_breath);
        P_eeg_delta_ins1=sum(eeg_delta_ins1.^2)/length(eeg_delta_ins1);
        P_eeg_delta_ins2=sum(eeg_delta_ins2.^2)/length(eeg_delta_ins2);
        P_eeg_delta_exp1=sum(eeg_delta_exp1.^2)/length(eeg_delta_exp1);
        P_eeg_delta_exp2=sum(eeg_delta_exp2.^2)/length(eeg_delta_exp2);

% Compute normalised segmental EEG power based on Pdelta_eeg_breath
 % RCREC - Delta band
C=max(P_eeg_delta_ins1_normalised,P_eeg_delta_ins2_normalised,P_eeg_delta_exp1_normalised,P_eeg_delta_exp2_normalised);
D=min(P_eeg_delta_ins1_normalised,P_eeg_delta_ins2_normalised,P_eeg_delta_exp1_normalised,P_eeg_delta_exp2_normalised);
RCREC_eeg_delta=C-D;

% similarly compute RCREC_eeg_theta, RCREC_eeg_alpha, RCREC_eeg_sigma, RCREC_eeg_beta
```

B.6 RCREC using symbolic dynamics

```
clear all; close all; clc
%Load ribcage and abdomen channels of RIP from PSG data along with their sampling frequencies
        ribcage= [];  ribcage=load ('Data\ribcagedata_',name,'.txt');
        abdomen= [];  abdomen=load ('Data\abdomendata_',name,'.txt');
%Load EEG channel of RIP from PSG data along with the sampling frequency
        eeg= [];  eeg=load ('Data\eegdata_',name,'.txt');
%Load sleepstage scoring information (scored every 30s)
        sleepstage = [];  sleepstage=load ('Data\sleepstagedata_',name,'.txt');
% A given EEG segment is converted into a sequence of symbols based on the
% amplitudes of the samples
%Words of length m=3 are formed and are grouped into one of four groups 0V,
%1LV, 2LV and 2UV based on the relative change between the three samples

%%%%%%%%% MIN-MAX METHOD %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
        level=6;
        size1=(max(eeg)-min(eeg))/level;
        for i7=1:length(eeg)
                if (eeg(i7)>(level-1)*size1) && (eeg(i7)<= max(eeg))
                  S1_eeg(i7)=level-1;
                end
                if (eeg(i7)< 5*size1)&& (eeg(i7)>=4*size1)
                  S1_eeg(i7)=4;
                end
                if (eeg(i7)< 4*size1)&& (eeg(i7)>=3*size1)
                  S1_eeg(i7)=3;
                end
                if (eeg(i7)< 3*size1)&& (eeg(i7)>=2*size1)
                  S1_eeg(i7)=2;
                end
                if (eeg(i7)< 2*size1)&& (eeg(i7)>=1*size1)
                  S1_eeg(i7)=1;
                end
                if (eeg(i7)< 1*size1)
                  S1_eeg(i7)=0;
```

```
                end
        end

%%%%%% QUARTILE METHOD %%%%%%%%%%%%%%
        y = sort(eeg);
        Q(1) = median(y(find(y<median(y))));
        Q(2) = median(y);
        Q(3) = median(y(find(y>median(y))));
        S1_eeg=[];
        for i=1:length(eeg)
                if eeg(i)<Q(1)
                   S1_eeg(i)=3;
                end
                if (eeg(i)<=Q(2))&& (eeg(i)>=Q(1))
                  S1_eeg(i)=2;
                end
                if (eeg(i)<=Q(3))&& (eeg(i)>=Q(2))
                   S1_eeg(i)=0;
                end
                if (eeg(i)>Q(3))
                   S1_eeg(i)=1;
end
end

%Computing the occurance of 0V,1V, 2LV and 2UV within the symbolic sequences
%corresponding to each respiratory segment based on words of length m=3

m=3;k1=1;k2=1;k3=1;k4=1;VNo=[];Vone=[];VtwoL=[]; VtwoU=[];
ly1=length(S1_eeg);
        for j=1:ly1-(m-1)
            temp3=S1_eeg(j:1:j+(m-1))';   a=(temp3);
            %a=[2 2 2];
            a1=a(1);a2=a(2);a3=a(3);
                if a1==a2 && a2==a3
                   VNo(k1,:)=a;k1=k1+1;
                end
```

```
    %a=[3 3 2];
    a1=a(1);a2=a(2);a3=a(3);
        if (a1==a2 && a2~=a3) ||  (a2==a3 && a3~=a1)
            Vone(k2,:)=a;k2=k2+1;
        end
    %a=[1 2 3];
    a1=a(1);a2=a(2);a3=a(3);
        if (a1>a2 && a2>a3) || (a1<a2 && a2<a3)
           VtwoL(k3,:)=a;k3=k3+1;
        end
    %a=[2 3 2];
    a1=a(1);a2=a(2);a3=a(3);
        if (a1>a2 && a2<a3) || (a1<a2 && a2>a3)
           VtwoU(k4,:)=a;k4=k4+1;
        end
end
pVNo=(k1-1)/(ly1-(m-1));   pVone=(k2-1)/(ly1-(m-1));
pVtwoL=(k3-1)/(ly1-(m-1)); pVtwoU=(k4-1)/(ly1-(m-1));

p1=[pVNo pVone pVtwoL pVtwoU];p2=p1(find(p1~=0));
p1per=p1*100; peonsym = pec(S1_eeg',3,1);
dirPE=pec(eeg,3,1);
```

B.7 Heartbeat evoked potentials

```
clear all; close all; clc
%Load EEG channel of RIP from PSG data along with the sampling frequency
        eeg= [];  eeg=load ('Data\eegdata_',name,'.txt');
%Load ECG channel of RIP from PSG data along with its sampling frequency
        ecg= [];  ecg=load ('Data\ecgdata_',name,'.txt');
%Load sleepstage scoring information (scored every 30s)
        sleepstage = [];  sleepstage=load ('Data\sleepstagedata_',name,'.txt');
%Load RR interval information and extract R peaks
        rpeakdata=load(rr);
        rpeak=rpeakdata(:,1);rrinterval=rpeakdata(:,2);
        rpeak_samples=rpeak*500;%fs for ECG = 500 Hz
        [rows,columns]=size(ecg);
        rpeak_points=zeros(rows,1);

            for i=1:length(rpeak_samples)
                rpeak_points(floor(rpeak_samples(i)))=1;
            end
        j2=1; peak_rr=[];
            for i=1:length(rpeak_points)
                    if rpeak_points(i)>0
                      peak_rr(j2)=i;j2=j2+1;
                    end
            end
%Extract sleep stage specific SEF EEG and ECG epochs
        j2=1; peak_rr=[];
            for i=1:length(rpeak_points)
                    if rpeak_points(i)>0
                      peak_rr(j2)=i;j2=j2+1;
                    end
            end
        i6=1; eeg_cycle_array=[];ecg_cycle_array=[];
        for stage=1:length(sleepstages)
            if sleepstages(stage)==2%3 or 4 (SWS), 5(REM)
            eeg_ss21=data2(l:k);eeg_ss2=eeg_ss21(isfinite(eeg_ss21));
```

```
                    if (length(eeg_ss2)==length(eeg_ss21))

%cardiac cycle detection within 30s epoch
        j=1;p=0;cycle_matrix_samp=[];
                for i2=1:length(peak_rr)-1
                peak_rr1=peak_rr(i2);peak_rr2=peak_rr(i2+1);
                loc=floor((peak_rr2- peak_rr1)/2)+ peak_rr1;
                cycle_matrix_samp(j,1)=peak_rr1; cycle_matrix_samp(j,2)=loc(1);
                cycle_matrix_samp(j,3)=peak_rr2; j=j+1;
                end
%extraction of R to R-60s from ECG and the corresponding EEG
        [row,col]=size(cycle_matrix_samp);
                if row>0
                for i5=1:row
                rowcount=rowcount+row;
                eeg_cycle=eeg_ss2 (cycle_matrix_samp(i5,1):cycle_matrix_samp(i5,3)-15);%15
                samples - 60ms
                ecg_cycle=ecg_ss2 ((cycle_matrix_samp(i5,1)*2):(cycle_matrix_samp(i5,3)*2)-30);
                eeg_cycle_array{i6}=eeg_cycle;%accumulated array
                ecg_cycle_array{i6}=ecg_cycle; i6=i6+1;
        end
end

%Ensemble averaging of R peak aligned EEG
        [r,c]=size(eeg_cycle_array);temp6=[];temp5=[];
                for i7=1:c
                temp6=eeg_cycle_array{1,i7};
                temp5(i7)=length(temp6);
                end
        maxlength=max(temp5);
        eeg_cycle_arrayforav_ss2=zeros(c,maxlength);
        eeg_cycle_arrayforav_ss2(:,:)=NaN;

                for i8=1:c
                temp7=eeg_cycle_array(1,i8);
                [r1,c1]=size(temp7{1,1});
```

```
                eeg_cycle_arrayforav_ss2(i8,(1:r1))=(temp7{1,1})';
                end
        eeg_cycle_arraymean=nanmean(eeg_cycle_arrayforav_ss2);

%Ensemble averaging of R peak aligned ECG
        [r,c]=size(ecg_cycle_array);temp6=[];temp5=[];
                for i7=1:c
                temp6=ecg_cycle_array{1,i7};
                temp5(i7)=length(temp6);
                end

        maxlength=max(temp5);
        ecg_cycle_arrayforav_ss2=zeros(c,maxlength);
        ecg_cycle_arrayforav_ss2(:,:)=NaN;
                for i8=1:c
                temp7=ecg_cycle_array(1,i8);
                [r1,c1]=size(temp7{1,1});
                ecg_cycle_arrayforav_ss2(i8,(1:r1))=(temp7{1,1})';
                end
ecg_cycle_arraymean=nanmean(ecg_cycle_arrayforav_ss2);
```

This page intentionally left blank

References

AMIN, R. S., KIMBALL, T. R., BEAN, J. A., JEFFRIES, J. L., WILLGING, J. P., COTTON, R. T., WITT, S. A., GLASCOCK, B. J. & DANIELS, S. R. 2002. Left ventricular hypertrophy and abnormal ventricular geometry in children and adolescents with obstructive sleep apnea. *American journal of respiratory and critical care medicine,* 165**,** 1395-1399.

ARENS, R. & MARCUS, C. L. 2004. Pathophysiology of upper airway obstruction: a developmental perspective. *Sleep,* 27, 997-1019.

ATIENZA, M., CANTERO, J. L. & ESCERA, C. 2001. Auditory information processing during human sleep as revealed by event-related brain potentials. *Clinical neurophysiology,* 112, 2031-2045.

BANDLA, H. P. & GOZAL, D. 2000. Dynamic changes in EEG spectra during obstructive apnea in children. *Pediatric pulmonology,* 29, 359-365.

BHATTACHARJEE, R., KHEIRANDISH-GOZAL, L., SPRUYT, K., MITCHELL, R. B., PROMCHIARAK, J., SIMAKAJORNBOON, N., KADITIS, A. G., SPLAINGARD, D., SPLAINGARD, M. & BROOKS, L. J. 2010. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *American Journal of Respiratory and Critical Care Medicine,* 182, 676-683.

BLUNDEN, S., LUSHINGTON, K. & KENNEDY, D. 2001. Cognitive and behavioural performance in children with sleep-related obstructive breathing disorders. *Sleep Medicine Reviews,* 5, 447-461.

BOURKE, R., YANG J. S, JACKMAN A. R., KILLEDAR, A., NIXON, G. M, DAVEY, M. J, WALKER, A. M., TRINDER, J., HORNE, R. S. 2011. Cognitive and academic functions are impaired in children with all severities of sleep-disordered breathing. *Sleep medicine* 12, 489-496.

CAMPBELL, I. G., DARCHIA, N., HIGGINS, L. M., DYKAN, I. V., DAVIS, N. M., DE BIE, E. & FEINBERG, I. 2011. Adolescent changes in homeostatic regulation of EEG activity in the delta and theta frequency bands during NREM sleep. *Sleep,* 34, 83.

CHERVIN, R. D., BURNS, J. W. & RUZICKA, D. L. 2005. Electroencephalographic changes during respiratory cycles predict sleepiness in sleep apnea. *American Journal of Respiratory and Critical Care Medicine,* 171, 652-658.

CHERVIN, R. D., BURNS, J. W., SUBOTIC, N. S., ROUSSI, C., THELEN, B. & RUZICKA, D. L. 2004. Method for detection of respiratory cycle-related EEG changes in sleep-disordered breathing. *SLEEP,* 27, 110-115.

COENEN, A. 2012. Modelling of auditory evoked potentials of human sleep–wake states. *International Journal of Psychophysiology,* 85, 37-40.

CYSARZ, D., PORTA, A., MONTANO, N., LEEUWEN, P., KURTHS, J. & WESSEL, N. 2013. Quantifying heart rate dynamics using different approaches of symbolic dynamics. *Eur. Phys. J.: Spec. Top,* 222, 487-500.

DEMPSEY, J. A., VEASEY, S. C., MORGAN, B. J. & O'DONNELL, C. P. 2010. Pathophysiology of sleep apnea. *Physiological reviews,* 90, 47-112.

DOUGLAS, N., WHITE, D., PICKETT, C., WEIL, J. & ZWILLICH, C. 1982. Respiration during sleep in normal man. *Thorax,* 37, 840.

ELDER, D., LARSEN, P., CAMPBELL, A. & GALLETLY, D. 2012. Cardioventilatory coupling and inter-breath variability in children referred for polysomnography. *Respiratory Physiology & Neurobiology,* 181, 1-7.

FIAMMA, M. N., SAMARA, Z., BACONNIER, P., SIMILOWSKI, T. & STRAUS, C. 2007. Respiratory inductive plethysmography to assess respiratory variability and complexity in humans. *Respiratory physiology & neurobiology,* 156, 234-239.

FOREMAN, R. 1999. Mechanisms of cardiac pain. *Annual review of physiology,* 61, 143-167.

FRAIGNE, J. J. & OREM, J. M. 2011. Respiration during REM sleep and its regulation. *Rapid Eye Movement Sleep: Regulation and Function*.

GABOR, D. 1946. Theory of communication. Part 1: The analysis of information. *Journal of the Institution of Electrical Engineers-Part III: Radio and Communication Engineering,* 93, 429-441.

GRACE, K. P., HUGHES, S. W. & HORNER, R. L. 2013. Identification of the mechanism mediating genioglossus muscle suppression in REM sleep. *American Journal of Respiratory and Critical Care Medicine,* 187, 311-319.

GUILLEMINAULT, C., POYARES, D., PALOMBINI, L., KOESTER, U., PELIN, Z. & BLACK, J. 2001. Variability of respiratory effort in relation to sleep stages in normal controls and upper airway resistance syndrome patients. *Sleep Medicine,* 2, 397-405.

HALÁSZ, P., TERZANO, M., PARRINO, L. & BÓDIZS, R. 2004. The nature of arousal in sleep. *Journal of sleep research,* 13, 1-23.

HAMMER, J. & NEWTH, C. 2009. Assessment of thoraco-abdominal asynchrony. *Paediatric Respiratory Reviews,* 10, 75-80.

HENKE, K., DEMPSEY, J., BADR, M., KOWITZ, J. & SKATRUD, J. 1991. Effect of sleep-induced increases in upper airway resistance on respiratory muscle activity. *Journal of Applied Physiology,* 70, 158-168.

HUDGEL, D. W., MARTIN, R. J., JOHNSON, B. & HILL, P. 1984. Mechanics of the respiratory system and breathing pattern during sleep in normal humans. *Journal of Applied Physiology,* 56, 133-137.

IBER, C., ANCOLI-ISRAEL, S., CHESSON, A. L. & QUAN, S. F. 2007. *The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications*, American Academy of Sleep Medicine.

KATZ, E. S., LUTZ, J., BLACK, C. & MARCUS, C. L. 2003. Pulse transit time as a measure of arousal and respiratory effort in children with sleep-disordered breathing. *Pediatric research,* 53, 580-588.

KERN, M., AERTSEN, A., SCHULZE-BONHAGE, A. & BALL, T. 2013. Heart cycle-related effects on event-related potentials, spectral power changes, and connectivity patterns in the human ECoG. *NeuroImage,* 81, 178-190.

KOHLER, M. J., LUSHINGTON, K. & KENNEDY, J. D. 2010. Neurocognitive performance and behavior before and after treatment for sleep-disordered breathing in children. *Nature and science of sleep,* 2, 159.

KRIMSKY, W. R. & LEITER, J. C. Year. Physiology of breathing and respiratory control during sleep. *In:* Seminars in respiratory and critical care medicine, 2005. Copyright© 2005 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA., 5-12.

LEOPOLD, C. & SCHANDRY, R. 2001. The heartbeat-evoked brain potential in patients suffering from diabetic neuropathy and in healthy control persons. *Clinical neurophysiology,* 112, 674-682.

LOUGHLIN, G. M., SMITH, P. L. & SCHWARTZ, A. R. 1994. Upper airway collapsibility in children with obstructive sleep apnea syndrome. *Journal of Applied Physiology*, 77, 918-924.

LOUIS, A. K., MAAß, P. & RIEDER, A. 1997. *Wavelets*, Wiley.

LUMENG, J. C., and CHERVIN, R.D. 2008. Epidemiology of pediatric obstructive sleep apnea. Proceedings of the American Thoracic Society, 5, 242-252.

MARCUS, C. L. 2001. Sleep-disordered breathing in children. *American Journal of Respiratory and Critical Care Medicine,* 164, 16-30.

MARCUS, C. L., BROOKS, L. J., WARD, S. D., DRAPER, K. A., GOZAL, D., HALBOWER, A. C., JONES, J., LEHMANN, C., SCHECHTER, M. S. & SHELDON, S. 2012. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics,* 130, e714-e755.

MARCUS, C. L., GREENE, M. G. & CARROLL, J. L. 1998. Blood pressure in children with obstructive sleep apnea. *American journal of respiratory and critical care medicine,* 157, 1098-1103.

MARCUS, C. L., MOORE, R. H., ROSEN, C. L., GIORDANI, B., GARETZ, S. L., TAYLOR, H. G., MITCHELL, R. B., AMIN, R., KATZ, E. S. & ARENS, R. 2013. A randomized trial of adenotonsillectomy for childhood sleep apnea. *New England Journal of Medicine,* 368, 2366-2376.

MARTIN, S. E., ENGLEMAN, H. M., KINGSHOTT, R. N. & DOUGLAS, N. J. 1997. Microarousals in patients with sleep apnoea/hypopnoea syndrome. *Journal of sleep research,* 6, 276-280.

MASA, J., CORRAL, J., MARTIN, M., RIESCO, J., SOJO, A., HERNÁNDEZ, M. & DOUGLAS, N. 2003. Assessment of thoracoabdominal bands to detect respiratory effort-related arousal. *European Respiratory Journal,* 22, 661-667.

MCCARLEY, R. W. 2007. Neurobiology of REM and NREM sleep. *Sleep medicine,* 8, 302-330.

MCNICHOLAS, W. 1997. Impact of sleep in respiratory failure. *European Respiratory Journal,* 10, 920-933.

MEZZANOTTE, W. S., TANGEL, D. J. & WHITE, D. P. 1996. Influence of sleep onset on upper-airway muscle activity in apnea patients versus normal controls. *American Journal of Respiratory and Critical Care Medicine,* 153, 1880-1887.

NIR, Y., MASSIMINI, M., BOLY, M. & TONONI, G. 2013. Sleep and Consciousness. *Neuroimaging of Consciousness.* Springer.

PARMEGGIANI, P. 1982. Regulation of physiological functions during sleep in mammals. *Cellular and Molecular Life Sciences,* 38, 1405-1408.

PHILLIPSON, E. A. & BOWES, G. 1986. Control of breathing during sleep. *Comprehensive Physiology*.

PITSON, D., SANDELL, A. & VAN DEN HOUT, R. 1995. Use of pulse transit time as a measure of inspiratory effort in patients with obstructive sleep apnoea. *European Respiratory Journal,* 8, 1669-1674.

PORTA, A., TOBALDINI, E., GUZZETTI, S., FURLAN, R., MONTANO, N. & GNECCHI-RUSCONE, T. 2007. Assessment of cardiac autonomic modulation during graded head-up tilt by symbolic analysis of heart rate variability. *American Journal of Physiology-Heart and Circulatory Physiology,* 293, H702-H708.

REES, K., SPENCE, D., EARIS, J. E. & CALVERLEY, P. 1995. Arousal responses from apneic events during non-rapid-eye-movement sleep. *American Journal of Respiratory and Critical Care Medicine,* 152, 1016-1021.

RICHARD, J. M., BERNARD, E. P., WILLIAM, C., ORR, M. H. S. & ROBERT, M. R. 1980. Respiratory mechanics and timing during sleep in occlusive sleep apnea.

ROSEN, C. L. 1999. Clinical features of obstructive sleep apnea hypoventilation syndrome in otherwise healthy children. *Pediatric pulmonology,* 27, 403-409.

ROSEN, C. L., D'ANDREA, L. & HADDAD, G. G. 1992. Adult criteria for obstructive sleep apnea do not identify children with serious obstruction. *American Journal of Respiratory and Critical Care Medicine,* 146, 1231-1234.

ROSENBLUM, M. & KURTHS, J. 1998. Analysing synchronization phenomena from bivariate data by means of the Hilbert transform. *Nonlinear analysis of physiological data*, 91-99.

SACKNER, M., GONZALEZ, H., RODRIGUEZ, M., BELSITO, A., SACKNER, D. & GRENVIK, S. 1984. Assessment of asynchronous and paradoxic motion between rib cage

and abdomen in normal subjects and in patients with chronic obstructive pulmonary disease. *The American review of respiratory disease,* 130, 588.

SALLINEN, M., KAARTINEN, J. & LYYTINEN, H. 1996. Processing of auditory stimuli during tonic and phasic periods of REM sleep as revealed by event-related brain potentials. *Journal of sleep research,* 5, 220-228.

SCHNEIDER, H., KRISHNAN, V., PICHARD, L., PATIL, S., SMITH, P. & SCHWARTZ, A. 2009. Inspiratory duty cycle responses to flow limitation predict nocturnal hypoventilation. *European Respiratory Journal,* 33, 1068-1076.

SCHOLLE, S. & ZWACKA, G. 2001. Arousals and obstructive sleep apnea syndrome in children. *Clinical neurophysiology,* 112, 984-991.

SIVAN, Y., DEAKERS, T. W. & NEWTH, C. J. L. 1990. Thoracoabdominal asynchrony in acute upper airway obstruction in small children. *American journal of respiratory and critical care medicine,* 142, 540-544.

SIVAN, Y., WARD, S. D., DEAKERS, T., KEENS, T. G. & NEWTH, C. J. L. 1991. Rib cage to abdominal asynchrony in children undergoing polygraphic sleep studies. *Pediatric pulmonology,* 11, 141-146.

TABACHNIK, E., MULLER, N. L., BRYAN, A. C. & LEVISON, H. 1981. Changes in ventilation and chest wall mechanics during sleep in normal adolescents. *Journal of Applied Physiology,* 51, 557-564.

UJSZÁSZI, J. & HALÁSZ, P. 1988. Long latency evoked potential components in human slow wave sleep. *Electroencephalography and clinical Neurophysiology,* 69, 516-522.

VANDEKERCKHOVE, M. & CLUYDTS, R. 2010. The emotional brain and sleep: an intimate relationship. *Sleep medicine reviews,* 14, 219-226.

VILLA, M. P., CALCAGNINI, G., PAGANI, J., PAGGI, B., MASSA, F. & RONCHETTI, R. 2000. Effects of sleep stage and age on short-term heart rate variability during sleep in healthy infants and children. *CHEST Journal,* 117, 460-466.

WEBSTER, K. E. & COLRAIN, I. M. 1998. Multichannel EEG analysis of respiratory evoked-potential components during wakefulness and NREM sleep. *Journal of Applied Physiology,* 85, 1727-1735.

WIEGAND, L., ZWILLICH, C. W., WIEGAND, D. & WHITE, D. P. 1991. Changes in upper airway muscle activation and ventilation during phasic REM sleep in normal men. *J Appl Physiol,* 71, 488-497.

YANG, J. S., NICHOLAS, C. L., NIXON, G. M., DAVEY, M. J., ANDERSON, V., WALKER, A. M., TRINDER, J. & HORNE, R. S. 2012. EEG spectral analysis of apnoeic events confirms visual scoring in childhood sleep disordered breathing. *Sleep and Breathing,* 16, 491-497.